Lifestyle in Cardiovascular Disease

John O. Younge

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Author	John O.Younge
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Voor de Youngeones

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Chapter 1

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General introduction

Burden of cardiovascular disease

In recent decades, cardiovascular disease (CVD) has become one of the most important medical problems worldwide.[1] Although the numbers are declining, CVD is still one of the most important causes of death, with more than 200 deaths per 100.000 individuals per year.[2] Unfortunately, the mortality rate from major cardiovascular causes (e.g. myocardial infarction, stroke or heart failure) is still increasing in low income countries (LIC)[3] (Figure 1), whereas mortality rates are decreasing in high income countries (HIC).[3] In contrast, the burden of risk factors is higher in HIC than in LIC.[3]

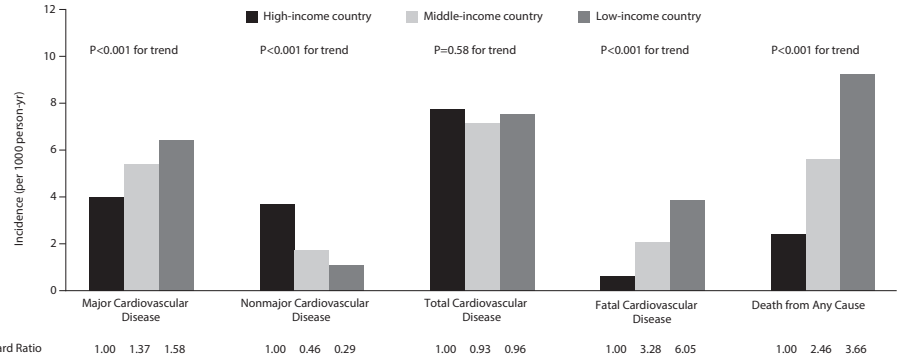

Figure 1. *Cardiovascular Disease Event Rates in High-, Middle-, and Low-Income Countries*
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Treatment strategies such as medication for hypertension, diabetes mellitus, and heart failure and progresses in invasive techniques (e.g. surgical and percutaneous) have led to lower mortality rates and prolonged survival in CVD. For instance, the introduction of the heart-lung machine has made open heart surgery possible with dramatic improved outcome in patients suffering from congenital heart disease: before the introduction survival was 15%, whereas now almost 95% of patients reach adulthood.[4,5] As a result, focus has shifted from solely survival to better management of cardiovascular morbidity and reduction of cardiovascular risk factors and more emphasis on quality of life (QoL). Individuals with CVD in middle-income (MIC) and LIC probably need more attention for risk factors to prevent a steep rise of accountable deaths in the coming decades.[3] Several international guidelines have been established to improve the awareness of healthcare professionals and politicians in both the primary and the secondary prevention setting.[6,7]

Risk factors for cardiovascular disease

After years of research, we now generally accept that lifestyle factors are the most important risk factors for the burden of CVD[8,9] and lifestyle is a target for preventive treatment strategies.[10] Lifestyle has a prominent role in health care and patient-related outcomes such as QoL, physical- and psychosocial functioning. Via promoting a healthy lifestyle in the setting of primary prevention the risk of developing CVD can be significantly reduced.

Several modifiable risk factors with a causal relation with CVD have been identified such as abdominal obesity, diabetes mellitus, hypertension, hypercholesterolemia, diminished physical activity (sedentary lifestyle), smoking, and unhealthy diet, but also non-modifiable risk factors such as age, gender, and genetic background (family history of CVD).[2,11] The role of (abdominal) obesity as a modifiable risk factor is still unclear. Several studies have shown higher survival rates of obese patients after undergoing a surgical or percutaneous intervention.[12-14] This phenomenon, referred to as the ''obesity paradox", is not yet fully understood.

In certain cases, risk factors for CVD have been clustered to identify syndromes that are metabolically linked. A well-known example is the 'Metabolic Syndrome'. This syndrome, first identified as 'Syndrome X', was described by Reaven and colleagues in 1988.[15] Over the past decades the definition of the metabolic syndrome has changed in numerous ways.[16-18] Because of the different criteria the true prevalence among individuals is not clear and has varied across studies.[19,20] To date, there is still much debate about the implementation of the metabolic syndrome in clinical care and more uniformity is needed.[21]

Some traditional risk factors are still poorly controlled for.[22] For example, high blood pressure is a growing problem in LIC and needs better clinical awareness in patients and clinicians.[23] Both men and women with a low-risk profile have a considerably longer life-expectancy.[24] It is therefore advised to motivate individuals to start off, or maintain a healthy lifestyle. This way, a low-risk profile for the development of CVD and related adverse outcomes can be maintained.

There is increased interest in the role of psychological and psychosocial risk factors in individuals with, or at risk of CVD. Both direct and indirect changes have been studied in the association between increased levels of stress and accompanied physiological changes in the human body.[25,26] One of the most important biological systems in the human stress response is the hypothalamic-pituary-adenocortical (HPA) axis. The HPA-axis stimulates the production of several (gluco)corticoids and androgens, of which cortisol is considered the most essential. Cortisol is best known for its somatic effects of the human body, such as the inhibition of inflammation and the immune response and mediating effects on metabolism.[27,28] Excess levels of cortisol are associated with an increased cardiovascular risk.[29,30]

Stress in itself may also lead to an imbalance between the sympathetic and parasympathetic system. The sympathetic nervous system is a key factor in case of acute stress.[31] Increased sympathetic activity can lead to arrhythmias and metabolic and immunological changes of the coronary vasculature.[32,33] In patients, all physiological parameters such as blood pressure, heart rate, respiration rate and brain activity can be influenced by stress and are a target of treatment.[28]

There is still further research needed in this area to understand the relation between the 'mind and the body' and their effects on the cardiovascular system.

Several psychological and psychosocial distress factors can be identified such as low socio-economic status, anxiety, major depression, and hopelessness.[34] Studies report a high incidence of these factors and are of significant importance in individuals at risk of CVD and the prognosis of patients with diagnosed CVD.[28,35-38] Psychological distress can act as a barrier in the treatment adherence and are included in the European guidelines on cardiovascular disease prevention.[7] Unfortunately, in practice, the role of physicians in assessing these distress factors is frequently limited because of their limited familiarity with these symptoms.[34] Some aspects of unhealthy lifestyle behaviors, accompanied by subclinical or chronic stress, go totally unrecognized. Possible explanations are the limited knowledge of assessing these lifestyle behaviors and their potential hazardous effects on long-term outcome. To date, most treatment recommendations for psychological and psychosocial distress are established on epidemiological studies and the prognostic implications are still under debate.[7,34] This has resulted in a low acceptance rate of lifestyle interventions that focus on behavioral changes in the setting of CVD.[39-41]

Lifestyle interventions for cardiovascular disease

To reduce cardiovascular risks it is essential to provide resources for lifestyle changes besides established medical therapy. These resources should be intertwined in the setting of primary and secondary prevention to achieve the highest effectivity in stimulating individuals to adopt healthy lifestyle behaviors.[7,42]

In recent years, cardiovascular lifestyle programs have gradually evolved from primarily educational to more multifactorial interventions to address most modifiable cardiovascular risk factors. Multifactorial lifestyle interventions have the potential to be effective in high risk populations in reducing mortality.[43] These interventions can consist of components such as education, counseling, behavioral interventions, diets and exercise programs. They have evidently resulted in lower mortality rates similar to cardiovascular preventive drug prescription.[44,45] Adherence to behavioral advice is associated with lower recurrent cardiovascular events after acute coronary syndromes and should therefore be given full attention[46] Unfortunately, it is often difficult to disentangle the true effectiveness of a lifestyle component among other modifications because they frequently occur at the same time. Additionally, lifestyle interventions suffer from patient non-compliance and studies evaluating such interventions often have high loss to follow-up that potentially affects their validity.[47]

There is increased interest in using psychological intervention programs for CVD, in which stress management and behavioral changes play an important role. These interventions are often part of a multifactorial program that may include cardiac exercise training or dietary modifications. It is therefore difficult to evaluate the specific effect of one intervention on clinically important cardiovascular outcomes. Lifestyle programs focusing on stress reduction are mainly conducted

in secondary prevention settings. Several meta-analyses support their added value with positive effects on cardiac mortality and surrogate endpoints such as depression and anxiety.[48-51]

Increased attention is also being paid to potential beneficial mind-body practices. These practices such as meditation, mindfulness training, relaxation or breathing exercises and yoga are increasingly popular in the general population and more commonly used in the western world.[52,53] Because prevention of CVD is still suboptimal, alternative interventions, such as mind-body practices, could be an option for individuals looking for adjuncts to conventional care. Mind-body practices are easy to learn, low in costs, and have almost no side-effects. As a safe adjunct to conventional care, mind-body practices have been found to positively affect risk factors for CVD such as diabetes, hypertension, bodyweight, depression and increased levels of stress.[54-58] However, studies conducted in primary prevention settings have shown conflicting results and mind body practices are therefore not yet commonly used in the prevention of CVD.[14,59]

As aforementioned, lifestyle interventions that focus on stress reduction show promising results in CVD. In recent years, mindfulness training has gained more attention, also in healthcare. By doing mindfulness, one is taught to live with an open and non-judgmental awareness towards all experiences within the present moment.[60,61] A healthy lifestyle is also promoted by focusing on the true needs of the body and mind.[62] Until now, mindfulness training is mainly used in healthcare as a standardized 8-week group training focusing on mindfulness-based stress reduction and mindfulness-based cognitive therapy.[61,63-65] Mindfulness training has been found to positively affect mainly psychological outcomes in patients with chronic pain, obesity, hypertension, depression, anxiety and cardiovascular disease.[66-70]

In recent years, the increased awareness of traditional risk factors has resulted in better lifestyle management of CVD. However, systematically screening for components of psychological distress, diminished quality of life and related risk factors is not yet fully integrated in clinical practice and should be acknowledged.[7,26,34] It is also important to note that effects of lifestyle interventions are most often not imminent. Current knowledge of other lifestyle interventions that focus on stress reduction and behavioral changes is still limited. We need to seek for more and better alternatives in current lifestyle management to provide tailored advice as personal interest and clinical characteristics can result in different motivations on how lifestyle is chosen and addressed.

Aim and outline of the thesis

The aim of this thesis is to gain knowledge of lifestyle behaviors, lifestyle factors and the effectiveness of lifestyle interventions in the prevention and treatment of cardiovascular disease (CVD). Our aim was to provide insight in the connection between psychological functioning and physiological outcome measures. We conducted cross-sectional studies on several modifiable cardiovascular risk-factors and clinically important objective and subjective outcomes. By performing systematic reviews and meta-analyses, we summarized evidence of lifestyle interventions, including mind-body practices, in CVD. Additionally, we aimed to assess the additional

value (effectiveness) of online mindfulness training for patients with structural heart disease under surveillance at the cardiology outpatient clinic of the Erasmus Medical Center Rotterdam. To increase the quality of future studies evaluating lifestyle interventions, we concentrated on aspects of randomized controlled designs in a methodological paper.

Part I of this thesis will focus on the association between selected characteristics of lifestyle and several objective and subjective outcome measurements. This will be discussed in four different chapters. In **Chapter 2** we focus on the additional value of biomarkers in a population of patients with congenital heart disease. We studied whether higher NT-proBNP levels are associated with certain aspects of subjective quality of life. **Chapter 3** focusses on the role of overweight and obesity on survival after a percutaneous intervention. We aim to assess a possible explanation for the obesity paradox, which is until today, not yet fully understood. **Chapter 4** reports the use of mind-body practices in a well-defined suburb of the city of Rotterdam, The Netherlands. We aimed to assess the cross-sectional association between these practices and cardiometabolic risk factors.

In **Chapter 5** we evaluate long-term cortisol levels, measured in scalp hair, and the association with several clinical characteristics of patients with structural heart disease. Additionally, we assess the effect of 12-weeks online mindfulness training on cortisol levels.

Part II aims to evaluate the additional value of lifestyle interventions in cardiovascular disease. In **Chapter 6** we systematically review the literature and pool results on the effectiveness of lifestyle interventions for hypertension in low-and middle income countries. In **Chapter 7** we summarize lifestyle interventions focusing on mind-body practices in patients with cardiac disease and their effect on several clinically relevant physiological and psychological outcome parameters.

Part III of this thesis aims to evaluate the execution and assessment of lifestyle interventions performed within a randomized design. In **Chapter 8** we describe the effectiveness of a 12-week online mindfulness training in patients with structural heart disease conducted at the cardiology outpatient clinic of the Erasmus Medical Center, Rotterdam, The Netherlands. In **Chapter 9**, we present a methodological perspective on the execution of randomized controlled trials for lifestyle interventions with the aim to provide guidance in the choice of an optimal randomized design.

Finally, in **Part IV** we will reflect on, and discuss, the most important findings of this thesis. Concluding remarks and future perspectives are provided for clinical practice and research.

References

1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2197-2223.
2. 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(3):399-410.
3. Yusuf S, Rangarajan S, Teo K, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med.* 2014;371(9):818-827.
4. Warnes CA. The adult with congenital heart disease: born to be bad? *J Am Coll Cardiol.* 2005;46(1):1-8.
5. Moons P, Bovijn L, Budts W, Belmans A, Gewillig M. Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. *Circulation.* 2010;122(22):2264-2272.
6. 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. *J Am Coll Cardiol.* 2014;63(25 Pt B):2935-2959.
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 (constituted by representatives of nine societies and by invited experts). *Eur Heart J.* 2012;33(13):1635-1701.
8. Carlsson AC, Wandell PE, Gigante B, Leander K, Hellenius ML, de Faire U. Seven modifiable lifestyle factors predict reduced risk for ischemic cardiovascular disease and all-cause mortality regardless of body mass index: a cohort study. *Int J Cardiol.* 2013;168(2):946-952.
9. O'Flaherty M, Buchan I, Capewell S. Contributions of treatment and lifestyle to declining CVD mortality: why have CVD mortality rates declined so much since the 1960s? *Heart.* 2013;99(3):159-162.
10. Organization WH. Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases. 2002;Report No. 916.
11. 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(9438):937-952.
12. Gruberg L, Mercado N, Milo S, et al. Impact of body mass index on the outcome of patients with multivessel disease randomized to either coronary artery bypass grafting or stenting in the ARTS trial: The obesity paradox II? *Am J Cardiol.* 2005;95(4):439-444.
13. Gruberg L, Weissman NJ, Waksman R, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol.* 2002;39(4):578-584.
14. Hartley L, Flowers N, Lee MS, Ernst E, Rees K. Tai chi for primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2014;4:CD010366.
15. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes.* 1988;37(12):1595-1607.
16. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation.* 2009;120(16):1640-1645.
17. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med.* 1998;15(7):539-553.
18. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. 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(25):3143-3421.
19. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care.* 2001;24(4):683-689.
20. Rantala AO, Kauma H, Lilja M, Savolainen MJ, Reunanen A, Kesaniemi YA. Prevalence of the metabolic syndrome in drug-treated hypertensive patients and control subjects. *J Intern Med.* 1999;245(2):163-174.
21. Kahn R, Buse J, Ferrannini E, Stern M, American Diabetes A, European Association for the Study of D. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2005;28(9):2289-2304.
22. 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(9859):2224-2260.

23. Pereira M, Lunet N, Azevedo A, Barros H. Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. *J Hypertens.* 2009;27(5):963-975.
24. Lloyd-Jones DM, Dyer AR, Wang R, Daviglus ML, Greenland P. Risk factor burden in middle age and lifetime risks for cardiovascular and non-cardiovascular death (Chicago Heart Association Detection Project in Industry). *Am J Cardiol.* 2007;99(4):535-540.
25. Steptoe A, Kivimaki M. Stress and cardiovascular disease. *Nat Rev Cardiol.* 2012;9(6):360-370.
26. Dimsdale JE. Psychological stress and cardiovascular disease. *J Am Coll Cardiol.* 2008;51(13):1237-1246.
27. Girod JP, Brotman DJ. Does altered glucocorticoid homeostasis increase cardiovascular risk? *Cardiovasc Res.* 2004;64(2):217-226.
28. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet.* 2007;370(9592):1089-1100.
29. Arnaldi G, Angeli A, Atkinson AB, et al. Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab.* 2003;88(12):5593-5602.
30. Manenschijn L, Schaap L, van Schoor NM, et al. High long-term cortisol levels, measured in scalp hair, are associated with a history of cardiovascular disease. *J Clin Endocrinol Metab.* 2013;98(5):2078-2083.
31. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *J Psychosom Res.* 2002;53(4):865-871.
32. Goebel MU, Mills PJ, Irwin MR, Ziegler MG. Interleukin-6 and tumor necrosis factor-alpha production after acute psychological stress, exercise, and infused isoproterenol: differential effects and pathways. *Psychosom Med.* 2000;62(4):591-598.
33. Huang QH, Takaki A, Arimura A. Central noradrenergic system modulates plasma interleukin-6 production by peripheral interleukin-1. *Am J Physiol.* 1997;273(2 Pt 2):R731-738.
34. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J Am Coll Cardiol.* 2005;45(5):637-651.
35. Hamer M, Molloy GJ, Stamatakis E. Psychological distress as a risk factor for cardiovascular events: pathophysiological and behavioral mechanisms. *J Am Coll Cardiol.* 2008;52(25):2156-2162.
36. Richardson S, Shaffer JA, Falzon L, Krupka D, Davidson KW, Edmondson D. Meta-analysis of perceived stress and its association with incident coronary heart disease. *Am J Cardiol.* 2012;110(12):1711-1716.
37. Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364(9438):953-962.
38. Figueredo VM. The time has come for physicians to take notice: the impact of psychosocial stressors on the heart. *Am J Med.* 2009;122(8):704-712.
39. Lin JS, O'Connor E, Whitlock EP, Beil TL. Behavioral counseling to promote physical activity and a healthful diet to prevent cardiovascular disease in adults: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2010;153(11):736-750.
40. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation.* 1999;99(16):2192-2217.
41. Steptoe A, Kerry S, Rink E, Hilton S. The impact of behavioral counseling on stage of change in fat intake, physical activity, and cigarette smoking in adults at increased risk of coronary heart disease. *Am J Public Health.* 2001;91(2):265-269.
42. 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(25 Pt B):2960-2984.
43. Ebrahim S, Taylor F, Ward K, Beswick A, Burke M, Davey Smith G. Multiple risk factor interventions for primary prevention of coronary heart disease. *Cochrane Database Syst Rev.* 2011(1):CD001561.
44. Franklin BA, Cushman M. Recent advances in preventive cardiology and lifestyle medicine: a themed series. *Circulation.* 2011;123(20):2274-2283.
45. Iestra JA, Kromhout D, van der Schouw YT, Grobbee DE, Boshuizen HC, van Staveren WA. Effect size estimates of lifestyle and dietary changes on all-cause mortality in coronary artery disease patients: a systematic review. *Circulation.* 2005;112(6):924-934.
46. Chow CK, Jolly S, Rao-Melacini P, Fox KA, Anand SS, Yusuf S. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. *Circulation.* 2010;121(6):750-758.
47. Hertogh EM, Schuit AJ, Peeters PH, Monninkhof EM. Noncompliance in lifestyle intervention studies: the instrumental variable method provides insight into the bias. *J Clin Epidemiol.* 2010;63(8):900-906.
48. Whalley B, Rees K, Davies P, et al. Psychological interventions for coronary heart disease. *Cochrane Database Syst Rev.* 2011(8):CD002902.

49. van Dixhoorn J, White A. Relaxation therapy for rehabilitation and prevention in ischaemic heart disease: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil.* 2005;12(3):193-202.
50. Linden W, Phillips MJ, Leclerc J. Psychological treatment of cardiac patients: a meta-analysis. *Eur Heart J.* 2007;28(24):2972-2984.
51. Dusseldorp E, van Elderen T, Maes S, Meulman J, Kraaij V. A meta-analysis of psychoeduational programs for coronary heart disease patients. *Health Psychol.* 1999;18(5):506-519.
52. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *Natl Health Stat Report.* 2008(12):1-23.
53. Prasad K, Sharma V, Lackore K, Jenkins SM, Prasad A, Sood A. Use of complementary therapies in cardiovascular disease. *Am J Cardiol.* 2013;111(3):339-345.
54. Chiesa A, Serretti A. Mindfulness-based stress reduction for stress management in healthy people: a review and meta-analysis. *J Altern Complement Med.* 2009;15(5):593-600.
55. Dod HS, Bhardwaj R, Sajja V, et al. Effect of intensive lifestyle changes on endothelial function and on inflammatory markers of atherosclerosis. *Am J Cardiol.* 2010;105(3):362-367.
56. Innes KE, Bourguignon C, Taylor AG. 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.
57. Singh S, Malhotra V, Singh KP, Madhu SV, Tandon OP. Role of yoga in modifying certain cardiovascular functions in type 2 diabetic patients. *J Assoc Physicians India.* 2004;52:203-206.
58. Xin L, Miller YD, Brown WJ. A qualitative review of the role of qigong in the management of diabetes. *J Altern Complement Med.* 2007;13(4):427-433.
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. Kabatzinn J. An Outpatient Program in Behavioral Medicine for Chronic Pain Patients Based on the Practice of Mindfulness Meditation - Theoretical Considerations and Preliminary-Results. *Gen Hosp Psychiat.* 1982;4(1):33-47.
61. Segal ZVW, J.M.G.; Teasdale, J.D. *Mindfulness-based Cognitive Therapy for Depression: A New Approach to Preventing Relapse.* New York: Guilford Press; 2002.
62. Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits. A meta-analysis. *J Psychosom Res.* 2004;57(1):35-43.
63. Kabatzinn J, Lipworth L, Burney R. The Clinical Use of Mindfulness Meditation for the Self-Regulation of Chronic Pain. *J Behav Med.* 1985;8(2):163-190.
64. Kabatzinn J. Full Catastrophe Living Using the Wisdom of Your Body and Mind to Face Stress, Pain and Illness. *Delacorte Press.* 1990:15.
65. Teasdale JD, Segal ZV, Williams JM, Ridgeway VA, Soulsby JM, Lau MA. Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *J Consult Clin Psychol.* 2000;68(4):615-623.
66. Hofmann SG, Sawyer AT, Witt AA, Oh D. The Effect of Mindfulness-Based Therapy on Anxiety and Depression: A Meta-Analytic Review. *J Consult Clin Psych.* 2010;78(2):169-183.
67. Zeidan F, Johnson SK, Gordon NS, Goolkasian P. Effects of Brief and Sham Mindfulness Meditation on Mood and Cardiovascular Variables. *J Altern Complem Med.* 2010;16(8):867-873.
68. Baer RA. Mindfulness training as a clinical intervention: A conceptual and empirical review. *Clin Psychol-Sci Pr.* 2003;10(2):125-143.
69. Ospina MB, Bond K, Karkhaneh M, et al. Meditation practices for health: state of the research. *Evid Rep Technol Assess (Full Rep).* 2007(155):1-263.
70. Olivo EL, Dodson-Lavelle B, Wren A, Fang Y, Oz MC. Feasibility and effectiveness of a brief meditation-based stress management intervention for patients diagnosed with or at risk for coronary heart disease: a pilot study. *Psychology Health & Medicine.* 2009;14(5):513-523.

Part I

Association studies

Chapter 2

Association between N-terminal pro-brain natriuretic peptide and quality of life in adult patients with congenital heart disease

Younge JO, Eindhoven JA, Utens EW, Opić P, Cuypers JA, van den Bosch AE, Witsenburg M, van Domburg RT, Hunink MG, Roos-Hesselink JW. Cardiol Young. 2015 Feb;25(2):288-94

Abstract

Aims

Advances in medical treatment have resulted in increased life expectancy in congenital heart disease. Consequently, the focus of management has shifted from reducing mortality to reducing long-term morbidity with the goal of improving quality of life. A predictor of quality of life might be N-terminal pro-brain natriuretic peptide, a well-established marker for heart failure. We aimed to determine the association between N-terminal pro-brain natriuretic peptide and quality of life in patients with congenital heart disease.

Methods

We collected blood samples from consecutive patients who were initially operated between 1968 and 1980 (47.8% women; mean age 40.2 ± 5.4 years). The 36-item Short-Form health Survey was completed to assess subjective health status as a measure of quality of life. Analysis was performed for the entire group and for subgroups defined as simple versus complex congenital heart diseases. Median N-terminal pro-brain natriuretic peptide level was 15.2 pmol/L (overall range 1.3–299.3 pmol/L). N-terminal pro-brain natriuretic peptide levels were associated with the subdomain physical functioning (β= –0.074, p=0.031). This association remained significant after adjustment for age and sex (β= –0.071, p=0.038) and after adjustment for age, sex, body mass index, left ventricular function, and renal function (β= –0.069, p=0.048). In complex congenital heart disease, the association between N-terminal pro-brain natriuretic peptide and physical functioning remained significant in multivariable analysis (β= –0.076, p=0.046). No associations were found in the simple congenital heart disease group or on the other health status subdomains.

Conclusion

In adults operated for congenital heart disease, N-terminal pro-brain natriuretic peptide is associated with the subdomain physical, primarily in the complex subgroup.

Introduction

The many advances in the medical care of patients with congenital heart disease have resulted in the past few decades have resulted in an increased survival. Owing to this, the prevalence of adults living with congenital heart disease is increasing. This population is estimated to increase by 5% per year and currently consists of more adults than children.[1] The focus of attention has shifted from pure survival to long-term morbidity (sequela), quality of life and their determinants.

Several studies have reported on the short- and long-term outcome of quality of life in congenital heart disease patients. Although some studies reported impairments of specific quality of life scales, other studies indicated that overall quality of life was comparable to that seen in the general population.[2,3] A study by Moons et al[4] showed even better scores in congenital heart disease than the general population. Diminished Quality of life has also been reported, especially in the domain of physical functioning.[5-7]

The use of biomarkers in congenital heart disease is gaining more attention with brain natriuretic peptide and N-terminal pro–B type natriuretic peptide being the most prominent biomarkers. These objective markers have shown to be of diagnostic and prognostic value as they are related to severity and prognosis in patients with heart failure due to acquired heart disease.[8-11] In two recent systematic reviews by Eindhoven et al,[12,13] an overall increase in brain natriuretic peptide levels was seen in more complex congenital heart disease. Unfortunately, the prognostic value of individual brain natriuretic peptide levels is still under debate, because differences exist between types of congenital heart disease and lack of prospective studies.

Until now, little is known about the relationship between objective measurement of brain natriuretic peptide levels and subjective measurement of quality of life in patients with congenital heart disease. Prior research on brain natriuretic peptide levels and quality of life in patients with congestive heart failure showed no correlation.[14] Hence, both markers seem to have independent value in evaluating present clinical status and in predicting long-term functioning.

In this study, our aim was to assess the cross-sectional association between N-terminal pro-brain natriuretic peptide levels and subjective quality of life as measured with the Short-Form health Survey-36, a generic health status questionnaire, in a cohort of patients with congenital heart disease.

Materials and methods

Inclusion criteria

Patients who had undergone corrective open heart surgery between 1968 and 1980 were enrolled in the study. This included all consecutive patients who underwent corrective open heart surgery for atrial septal defect, ventricular septal defect, pulmonary stenosis, tetralogy of Fallot

or transposition of the great arteries in the Erasmus Medical Center, and were younger than 15 years at the time of surgery.

Previous follow-up investigations on this cohort were undertaken in 1990/1991 and in 2000/2001. Patients' baseline characteristics, medical and psychosocial results have been reported in detail previously.[15,16]

The target population of our third follow-up, conducted in 2010 and 2011, consisted of the 412 patients who participated in the previous 2 follow-ups. We excluded 39 patients, of whom ten had died - causes: six cardiovascular, three unknown, and one accident), one had undergone heart transplantation, and 28 patients were lost to follow-up. Of the 373 eligible patients, 102 refused to participate in this third follow-up because of practical reasons, such as work, distance to hospital, resulting in a response rate of 73%.

Patients were approached uniformly and invited to visit the hospital for extensive cardiac and psychological examination. A cardiologist performed cardiac and medical examination during their visit. The health status questionnaire was completed during the hospital visit. Owing to practical reasons - work, children - 20 patients completed the questionnaires at home. If patients had trouble reading or understanding, the questionnaire was administered verbally.

Laboratory testing

After at least 30 minutes of rest, peripheral venous blood samples were obtained from all participants. Plasma and serum were separated immediately after blood sample collection and N-terminal pro-brain natriuretic peptide and creatinin levels were measured. N-terminal pro-brain natriuretic peptide levels were determined using the Elecsys system (Roche Diagnostics, Basel, Switzerland). The Elecsys system cut-off value of normal N-terminal pro-brain natriuretic peptide level is ≤ 14 pmol/L.

Subjective health status

Health status was assessed using the 36-item Short Form Health Survey.[17] The 36-item survey consists of 36 items with standardised response choices that contribute to eight health status domains, that is, physical functioning, role physical functioning, role emotional functioning, mental health, vitality, social functioning, bodily pain, and general health. Scale scores are obtained by summing the items together within a domain, dividing this outcome by the range of scores, and then transforming the raw scores to a scale from 0 to 100.[17] A higher score on the 36-item survey sub domains represents better functioning. A high score on the bodily pain scale indicates freedom from pain. Previous use of the Dutch version of the 36-item survey has shown good reliability and validity.[18]

Informed consent

The research protocol was approved by the institutional ethical committee and complies with the 1975 Declaration of Helsinki. Before participating, all patients signed informed consent.

Statistical analysis

Baseline characteristics of the study population are presented as proportions for categorical variables and as means ± standard deviations for continuous variables. Patients were analysed as a total sample and as subgroups. Patients with corrected atrial septal defect, ventricular septal defect and pulmonary stenosis were classified as simple congenital heart disease - unless they had complications such as severe ventricular dysfunction - whereas patients with tetralogy of Fallot or transposition of the great arteries (Mustard repair) were classified as moderate to complex congenital heart disease.[19] Group differences were examined using the χ^2 test (Fisher's exact test if appropriate) for nominal variables, whereas one-way ANOVA was used for continuous variables. Univariable linear regression models were used to examine the association between continuous N-terminal pro-brain natriuretic peptide levels and continuous 36-item survey scores.

Multivariable models were used to correct for potential confounder effects of N-terminal pro-brain natriuretic peptide levels, such as, age, sex, body mass index, renal function, and left ventricular function. Owing to small numbers, multivariable models for subgroups were limited to adjust for age and sex. Two-dimensional echocardiography was used to assess left ventricular function - for patients with transposition of the great arteries, this was the systemic right ventricle - with ''eyeballing", which was categorized into good, reasonable, moderate or poor functioning. All statistical analyses were performed using SPSS for Windows 20.0 (SPSS Inc., Chicago, Illinois, United States of America).

Results

Patient population

Of the 271 eligible patients in this third quality of life cohort, 20 patients had no N-terminal pro-brain natriuretic peptide measurements because of practical reasons - filled in questionnaires at home – and were excluded from further analysis. There was one patient who visited the outpatient clinic refused blood sampling. Of the remaining 250 patients, 5 questionnaires were excluded due to incomplete answers – three because of mental retardation and two refused). Therefore, the final analyses were performed on 245 patients (47.8% female; mean age 40.2 ± 5.4 years, range [30-56] years). In Table 1, the median N-terminal pro-brain natriuretic peptide and the mean 36-item survey scores are presented. Patients with complex disease were younger, had a worse left ventricular function, higher N-terminal pro-brain natriuretic peptide levels and lower 36-item survey scores on physical functioning and general health (Table 1). No residual lesions were found in the simple congenital heart disease patients. On the contrary, 20 patients with a complex malformation had residual lesions (Table 1).

Table 1. *Baseline characteristics.*

	Total sample	Simple	Moderate/Complex	
	(n=245)	(n=164)	(n= 81)	p-value
Age (years)	40.2 ± 5.4	41.0 ± 5.3	38.4 ± 5	<0.001*
Gender [female (%)]	47.8	51.2	40.7	
BMI (kg/m^2) Mean ± (SD)	25.3 ± 4.5	25.4 ± 3.5	25.2 ± 4.4	0.718
ConHD (%)				
ASD	27.8	41.5	—	
VSD	27.8	41.5	—	
PS	11.4	17.1	—	
TOF	21.2	—	64.2	
TGA	11.8	—	35.8	
Renal function [mean ± (SD)]	74.9 ± 14.7	75 ± 14.2	74.7 ± 16.0	0.902
LV function (%)**				<0.001*
good	73.2	85.4	52.3	
mildly impaired	23.8	12.6	43.2	
moderately impaired	0.4	0.7	0	
severely impaired	2.5	1.3	4.5	
Residual lesions (n)**	20	0	20	<0.001*
NT-proBNP [median (minimum-maximum)	15.2(1.3-299.3)	13.1 (1.3-116.1)	23.4(2.8-299.3)	<0.001*
SF-36 scores [mean ± (SD)]				
Physical functioning	89.3 ± 16.7	90.0 ± 16.4	86.0 ± 17.0	0.028*
Role physical functioning	89.5 ± 25.8	90.1 ± 25.8	88.4 ± 26.1	0.640
Bodily pain	84.6 ± 20.9	83.7 ± 22.1	86.5 ± 26.1	0.334
Social functioning	92.1 ± 16.4	91.3 ± 17.6	93.5 ± 13.9	0.330
Mental health	82.8 ± 14.5	83.4 ± 13.4	81.7 ± 16.5	0.386
Role emotional functioning	91.5 ± 24.3	91.1 ± 24.5	92.4 ± 23.8	0.686
Vitality	72.6 ± 19.7	72.8 ± 19.6	72.3 ± 20.1	0.869
General Health	73.0 ± 21.4	75.9 ± 22.1	67.2 ± 18.3	0.002*

ASD = atrial septal defect; BMI = body mass index; ConHD = congenital heart disease; LVF = left ventricular function; NT-proBNP = N-terminal pro-brain natriuretic peptide; PS = pulmonary stenosis; SD= standard deviation; SF-36 = 36-item Short Form Health Survey; TGA =transposition of the great arteries; TOF = tetralogy of fallot; VSD = ventricular septal defect

**Statistical significance with p ≤ 0.05*

*** Echocardiography was performed in 255/245 (92%) patients*

****Residual lesions: baffle leakage (n=1), baffle obstruction (n=8), residual ASD (n=0), residual VSD (n=0), moderate/severe tricuspid insufficiency (n=16), or moderate/severe pulmonary stenosis (n=11). If a patient had multiple residual laesions (that is, baffle obstruction and severe tricuspid insufficiency), this was counted as 1.*

N-terminal pro-brain natriuretic peptide and health status in all congenital heart disease

Univariable regression analyses with N-terminal pro-brain natriuretic peptide were executed for each of the eight health status subdomains. N-terminal pro-brain natriuretic peptide levels showed a significant inverse association with the subdomain physical functioning (β = -0.074, p = 0.031), whereas no significant association was found in the other 7 subdomains (Table 2). This association with physical functioning remained significant after adjusting for age and sex (β =

Table 2. *Association between NT-proBNP and SF-36 domains in all ConHD patients*

	Univariable analysis		Multivariable analysis**		Multivariable analysis***	
	β	p-value	β	p-value	β	p-value
SF-36 subdomains						
Physical functioning	-0.074	0.031*	-0.070	0.038*	-0.069	0.048*
Role physical functioning	0.280	0.665	0.052	0.412	0.049	0.428
Bodily pain	0.067	0.117	0.064	0.131	0.075	0.113
Social functioning	0.007	0.824	0.009	0.785	0.015	0.673
Mental health	0.018	0.536	0.019	0.644	0.010	0.774
Role emotional functioning	0.003	0.955	0.020	0.735	0.009	0.892
Vitality	0.029	0.471	0.038	0.344	0.052	0.241
General health	-0.067	0.122	-0.063	0.153	-0.049	0.311

ConHD = congenital heart disease; NT-proBNP = N-terminal pro-brain natriuretic peptide; SF-36 = 36-item Short Form Health Survey
**Statistical significance with p ≤ 0.05*
***Adjusted for age and gender*
****Adjusted for age, gender, body mass index, left ventricular function and renal function*

-0.070, p = 0.038) and age, sex, body mass index, left ventricular function and renal function (β = -0.069, p = 0.048).

Simple vs. complex congenital heart disease

In a second model, the eight health status subdomains were analysed separately for type of congenital heart disease – simple vs. complex. In univariable analysis, no association was seen between N-terminal pro-brain natriuretic peptide levels and the 8 subdomains in both the simple

Table 3. *Association between NT-proBNP and SF-36 subdomains in ConHD subgroups*

	Simple				Complex			
	Univariable analysis		Multivariable** analysis		Univariable analysis		Multivariable** analysis	
	β	p-value	β	p-value	β	p-value	β	p-value
SF-36 subdomains								
Physical functioning	0.038	0.678	0.096	0.307	–0.072	0.064	–0.076	0.046*
Role physical functioning	0.127	0.380	0.179	0.226	0.017	0.826	0.034	0.660
Bodily pain	0.038	0.762	0.095	0.452	0.064	0.133	0.060	0.158
Social functioning	0.016	0.875	0.069	0.497	–0.006	0.864	–0.004	0.901
Mental health	–0.02	0.984	0.046	0.549	0.034	0.381	0.032	0.415
Role emotional functioning	0.090	0.511	0.159	0.261	–0.030	0.672	–0.017	0.813
Vitality	0.20	0.867	0.098	0.381	0.036	0.435	0.039	0.412
General health	0.033	0.791	0.073	0.569	–0.42	0.335	–0.041	0.358

ConHD = congenital heart disease; NT-proBNP = N-terminal pro-brain natriuretic peptide; SF-36 = 36-item Short Form Health Survey
**Statistical significance with p ≤ 0.05*
***Adjusted for age and gender*

and the complex congenital heart disease groups. After adjusting for the socio-demographics age and sex, a significant inverse association with physical function was found (β = -0.076, p = 0.046; Table 3) in the complex group, whereas no significant relation was seen on the other 7 subdomains. The difference was seen in the tetralogy of Fallot subgroup as compared with the transposition of the great arteries subgroup (β = -0.090, p = 0.012 versus β = 0.002, p = 0.982, respectively). The subdomains in the simple group showed no relation with N-terminal pro-brain natriuretic peptide (Table 3).

Discussion

The relationship between biomarkers and quality of life in congenital heart disease patients is not well known. This is the first study that focused on the relationship between N-terminal pro-brain natriuretic peptide levels and quality of life in the specific population. Previous studies have mainly been conducted in patients with congestive heart failure, where N-terminal pro-brain natriuretic peptide already is an established marker of prognosis and severity of disease. Our results show that higher levels of N-terminal pro-brain natriuretic peptide are associated with lower scores on the 36-item survey on the subdomain physical functioning, but not with the other seven subjective health domains. In addition, we showed that this relation was found only in complex congenital heart disease patients, but not in simple congenital heart disease.

The general assumption that congenital heart disease patients have lower quality of life is a misconception for patients who underwent repair of their congenital heart disease. However, this is not true for patients who could only be palliated. Several studies have found an equivalent or even better subjective health status, as compared with healthy counterparts.[2-4] However, in patients who had merely palliative surgery, a diminished psychosocial outcome has been found.[20] Objective measures most often relate to severity of disease, although results differ among the various types of congenital heart disease.[6,19] However, the severity of disease does not necessarily reflect lower quality of life scores.[21] The contradictory results found on quality of life scores could be attributed to different outcomes used and methodological flaws.[22]

Some studies report that physical limitations will not be reflected on generic health status questionnaires. A study by Kamphuis et al[6] showed a weak correlation between objective physical indices and related domains of subjective health status and health-related quality of life. Limited exercise capacity usually does not hamper patients with congenital heart disease in their daily activities and rigorous activities are most often not undertaken.[23] It seems that most of the congenital heart disease patients learn to cope with their physical limitations and, if present, adapt their way of living and expectations.

It is evident that more complex congenital heart disease results in lower performance on exercise capacity.[24] Negative correlations between plasma brain natriuretic peptide levels and exercise testing have been reported. Trojnarska et al[25] showed a negative correlation between

brain natriuretic peptide and oxygen uptake during cardiopulmonary testing in a heterogeneous group of congenital heart disease patients. These results were consistent in other reports.[26,27] In addition, when a 6-minute walk test was conducted, a negative correlation between N-terminal pro-brain natriuretic peptide levels and 6-minute walking distance was observed.[28] Not all studies support these results, as in Fontan patients no direct relation was observed between brain natriuretic peptide levels and exercise capacity by peak oxygen consumption.[29,30] A possible direct association between increase in plasma brain natriuretic peptide levels and decrease in exercise capacity has never been supported by reports. Although in most congenital heart disease patients diminished physical functioning is not reflected on overall generic quality of life scores, it could be helpful to pay attention specifically to the physical functioning subscale (subdomain). Both elevated levels of brain natriuretic peptide and diminished physical functioning should trigger clinical awareness on possible early deterioration of patients' cardiac function, and further evaluation of exercise performance can be considered.

A previous study in patients with heart failure showed no relationship between N-terminal pro-brain natriuretic peptide changes over time and short-term changes in health status.[14] Furthermore, a report by Hogenhuis et al[31] demonstrated that N-terminal pro-brain natriuretic peptide levels correlate more with cardiac function than parameters that reflect physical functioning on quality of life scales. Hence, previous results on the relation between quality of life and brain natriuretic peptide are scarce. No firm conclusions can be drawn when comparing these results with other cardiac diseases.

The use of biomarkers is still limited in congenital heart disease. Whereas elevated levels of N-terminal pro-brain natriuretic peptide correlate with long-term functioning and mortality in heart failure patients, not many long-term (prospective) studies have been conducted in congenital heart disease patients. The systematic reviews by Eindhoven et al[12,13] give a clear picture of the evidence until now. The use of the biomarkers is most-often limited to short-term changes – that is peri-operative – and most studies were not designed to evaluate natriuretic peptides. Therefore, our finding that N-terminal pro-brain natriuretic peptide is related to physical functioning is of interest and a first step in this field, which has yet to be explored. It is evident that larger, prospective studies are needed to evaluate the use and predictive value of biomarkers in congenital heart disease.

A first limitation of this study is the small number of patients per diagnosis in the current study sample. Recent studies have clearly shown that N-terminal pro-brain natriuretic peptide levels differ between types of congenital heart disease.[32,33] Therefore, conclusions in subgroup analyses should be drawn with caution. A second limitation is the cross-sectional design. Prospective results, especially long-term, could give a better understanding of changes in both N-terminal pro-brain natriuretic peptide levels and quality of life in congenital heart disease patients. Third, outcomes of this cohort of relatively older patients, all operated before 1980, may not be generalizable to the current population of congenital heart disease patients undergoing cardiac surgery.

Medical treatment and support has drastically changed over the past decades with improved outcomes.

In conclusion, the current study shows an association between cross-sectionally assessed N-terminal pro-brain natriuretic peptide levels and quality of life – assessed with a generic health status questionnaire – on the subdomain physical functioning, predominantly in complex congenital heart disease patients. No association was found between N-terminal pro-brain natriuretic peptide and the seven other subdomains.

References

1. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. *N Engl J Med.* Jan 27 2000;342(4):256-263.
2. Immer FF, Althaus SM, Berdat PA, Saner H, Carrel TP. Quality of life and specific problems after cardiac surgery in adolescents and adults with congenital heart diseases. *Eur J Cardiovasc Prev Rehabil.* Apr 2005;12(2):138-143.
3. Saliba Z, Butera G, Bonnet D, et al. Quality of life and perceived health status in surviving adults with univentricular heart. *Heart.* Jul 2001;86(1):69-73.
4. Moons P, Van Deyk K, De Bleser L, et al. Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts. *Eur J Cardiovasc Prev Rehabil.* Jun 2006;13(3):407-413.
5. Jefferies JL, Noonan JA, Keller BB, Wilson JF, Griffith C, 3rd. Quality of life and social outcomes in adults with congenital heart disease living in rural areas of Kentucky. *Am J Cardiol.* Jul 15 2004;94(2):263-266.
6. Kamphuis M, Ottenkamp J, Vliegen HW, et al. Health related quality of life and health status in adult survivors with previously operated complex congenital heart disease. *Heart.* Apr 2002;87(4):356-362.
7. Simko LC, McGinnis KA. What is the perceived quality of life of adults with congenital heart disease and does it differ by anomaly? *J Cardiovasc Nurs.* May-Jun 2005;20(3):206-214.
8. Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation.* Oct 12 2004;110(15):2168-2174.
9. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J.* Oct 2003;24(19):1735-1743.
10. Januzzi JL, Jr., Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol.* Apr 15 2005;95(8):948-954.
11. Maeda K, Tsutamoto T, Wada A, et al. High levels of plasma brain natriuretic peptide and interleukin-6 after optimized treatment for heart failure are independent risk factors for morbidity and mortality in patients with congestive heart failure. *J Am Coll Cardiol.* Nov 1 2000;36(5):1587-1593.
12. Eindhoven JA, van den Bosch AE, Boersma E, Roos-Hesselink JW. The usefulness of brain natriuretic peptide in simple congenital heart disease - a systematic review. *Cardiol Young.* Sep 21 2012:1-10.
13. Eindhoven JA, van den Bosch AE, Jansen PR, Boersma E, Roos-Hesselink JW. The usefulness of brain natriuretic peptide in complex congenital heart disease: a systematic review. *J Am Coll Cardiol.* Nov 20 2012;60(21):2140-2149.
14. Luther SA, McCullough PA, Havranek EP, et al. The relationship between B-type natriuretic peptide and health status in patients with heart failure. *J Card Fail.* Aug 2005;11(6):414-421.
15. Utens EM, Verhulst FC, Erdman RA, et al. Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: a follow-up study. *J Psychosom Res.* Oct 1994;38(7):745-758.
16. van Rijen EH, Utens EM, Roos-Hesselink JW, et al. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. *Eur Heart J.* Apr 2003;24(7):673-683.
17. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* Jun 1992;30(6):473-483.
18. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol.* Nov 1998;51(11):1055-1068.
19. Warnes CA, Liberthson R, Danielson GK, et al. Task force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol.* Apr 2001;37(5):1170-1175.
20. Popelova J, Slavik Z, Skovranek J. Are cyanosed adults with congenital cardiac malformations depressed? *Cardiol Young.* Jul 2001;11(4):379-384.
21. Moons P, Van Deyk K, De Geest S, Gewillig M, Budts W. Is the severity of congenital heart disease associated with the quality of life and perceived health of adult patients? *Heart.* Sep 2005;91(9):1193-1198.
22. Moons P, Van Deyk K, Budts W, De Geest S. Caliber of quality-of-life assessments in congenital heart disease: a plea for more conceptual and methodological rigor. *Arch Pediatr Adolesc Med.* Nov 2004;158(11):1062-1069.
23. De Bleser L, Budts W, Sluysmans T, et al. Self-reported physical activities in patients after the Mustard or Senning operation: comparison with healthy control subjects. *Eur J Cardiovasc Nurs.* Sep 2007;6(3):247-251.

24. Kempny A, Dimopoulos K, Uebing A, et al. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life—single centre experience and review of published data. *Eur Heart J.* Jun 2012;33(11):1386-1396.
25. Trojnarska O, Gwizdala A, Katarzynski S, et al. The BNP concentrations and exercise capacity assessment with cardiopulmonary stress test in cyanotic adult patients with congenital heart diseases. *Int J Cardiol.* Mar 18 2010;139(3):241-247.
26. Cheung EW, Lam WW, Chiu CS, Chau AK, Cheung SC, Cheung YF. Plasma brain natriuretic peptide levels, right ventricular volume overload and exercise capacity in adolescents after surgical repair of tetralogy of Fallot. *Int J Cardiol.* Oct 1 2007;121(2):155-162.
27. Norozi K, Buchhorn R, Bartmus D, et al. Elevated brain natriuretic peptide and reduced exercise capacity in adult patients operated on for tetralogy of fallot is due to biventricular dysfunction as determined by the myocardial performance index. *Am J Cardiol.* May 1 2006;97(9):1377-1382.
28. Iversen K, Jensen AS, Jensen TV, Vejlstrup NG, Sondergaard L. Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. *Eur Heart J.* May 2010;31(9):1124-1131.
29. Lechner E, Schreier-Lechner EM, Hofer A, et al. Aminoterminal brain-type natriuretic peptide levels correlate with heart failure in patients with bidirectional Glenn anastomosis and with morbidity after the Fontan operation. *J Thorac Cardiovasc Surg.* Sep 2009;138(3):560-564.
30. Motoki N, Ohuchi H, Miyazaki A, Yamada O. Clinical profiles of adult patients with single ventricular physiology. *Circ J.* Sep 2009;73(9):1711-1716.
31. Hogenhuis J, Jaarsma T, Voors AA, Hillege HL, Lesman I, van Veldhuisen DJ. Correlates of B-type natriuretic peptide and 6-min walk in heart failure patients. *Int J Cardiol.* Mar 22 2006;108(1):63-67.
32. Eindhoven JA, van den Bosch AE, Ruys TP, et al. N-terminal proBrain Natriuretic Peptide and its Relation with Cardiac Function in Adult Patients with Congenital Heart Disease. *J Am Coll Cardiol.* Jul 20 2013.
33. Popelova J, Kotaska K, Cerny S, Prokopova M, Rubacek M. Range and distribution of NT-proBNP values in stable corrected congenital heart disease of various types. *The Canadian journal of cardiology.* Jul-Aug 2012;28(4):471-476.

Chapter 3

Obesity, health status, and 7-year mortality in percutaneous coronary intervention: in search of an explanation for the obesity paradox

Younge JO, Damen NL, van Domburg RT, Pedersen SS.
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Abstract

Background

Obesity is a growing health problem and is associated with adverse outcomes in coronary artery disease (CAD). However, recent studies have shown better survival in cardiovascular patients with overweight or obesity, which has been referred to as the "obesity paradox". As there is no clear understanding of the phenomenon, we examined the association between BMI and all-cause mortality in patients treated with percutaneous coronary intervention (PCI) at 7-years follow-up, and the potential role of health status in explaining the obesity paradox.

Methods

Consecutive PCI patients (72.5% men; mean age 62.0±11.2 years, range [27-90] years) from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry completed the 36-item Short-Form Health Survey (SF-36) to assess health status at baseline. Patients were classified into a normal weight, overweight and obesity group.

Results

The prevalence of normal weight was 34.7% (354/1019), overweight was seen in 45.9% (468/1019) of patients, and 19.3% (197/1019) was obese. After a median follow-up of 7.0 ± 1.7 years, 163 deaths (16.0%) from any cause were recorded. Cumulative hazard functions differed significantly for the obese and overweight group when compared to the normal weight group (log-rank $X^2 = 6.59$, $p<0.05$). In multivariable analysis, overweight, but not obesity, remained associated with a lower risk for all-cause mortality (HR = 0.60, 95%CI [0.42-0.86], $p = 0.005$). Additionally, after adding the 8 health status SF-36 domains to the multivariate model, the association between overweight and mortality remained unchanged.

Conclusion

In our study population overweight, but not obesity, was associated with a lower risk for 7-year mortality in PCI patients. Health status as measured with the SF-36 did not seem play a role in explaining the obesity paradox.

Introduction

Obesity is a growing epidemic, with prevalence rates in the general population ranging from 32% in men to 36% in women.[1] In coronary artery disease (CAD), obesity is prevalent in 29% of patients[2] and is associated with potential risk for cardiovascular morbidity and mortality.[3,4] However, evidence for a link between obesity and cardiovascular prognosis is based on a small number of studies, with results being mixed, as some[5] but not all studies support such a relationship.[6] Moreover, recent studies have demonstrated that there may not be a linear and straightforward relationship between overweight and obesity and mortality, as some studies show better survival in cardiovascular patients with overweight or obesity. This phenomenon is referred to as the "obesity paradox".[6-9]

In an attempt to explain the obesity paradox, studies have primarily focused on potential differences in the prescription of guideline-based medications.[2,7] A higher prevalence of invasive treatment has also been observed in obese patients with CAD[2]. Nevertheless, we still do not have a clear understanding of the obesity paradox.

Patient-reported health status might be another avenue to pursue in order to elucidate factors that may impinge on or help explain the obesity paradox. A recent systematic review demonstrated that poor health status in CAD and congestive heart failure increase the risk of mortality and hospital readmissions independent of indicators of disease severity and demographic and clinical characteristics.[10] Also a recent paper from our research group found an association between poor health status and higher mortality.[11] A paucity of studies focussed on the association between obesity and health status,[12-15] but the role of health status in the context of obesity and mortality in CAD has not yet been examined.

Hence, in the current study we examined 1) the association between BMI and all-cause mortality in patients treated with percutaneous coronary intervention (PCI) at 7-years follow-up, and 2) the potential role of health status in explaining the obesity paradox.

Methods

Study population

The study sample comprised consecutive CAD patients treated with PCI with either sirolimus-eluting stenting (SES) or bare metal stenting (BMS), between October 16, 2001 and October 15, 2002 at the Erasmus Medical Center, Rotterdam, the Netherlands, as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. The design of the RESEARCH registry has been published elsewhere.[16] In brief, the registry was designed to evaluate the efficacy and safety of SES implantation in the "real world" of interventional cardiology. Hence, no exclusion criteria were applied for patients entering the registry, and all PCI patients were eligible for enrolment regardless of anatomical or clinical presentation.[17]

At 6 months post PCI (referred to as baseline in the remainder of the paper), all living patients were asked to complete a standardized and validated health status measure. In accordance with previous studies, assessment at 6 months was chosen so as to represent patients in a stable condition, as the risk for restenosis is increased in the 0-6 months period post PCI.[18] All patients were prospectively followed-up for adverse clinical events.

Socio-demographic and clinical characteristics

Socio-demographic variables included gender and age. Clinical variables were obtained from patients' medical records at the time of the index PCI and included BMI body mass index; (i.e., weight in kilograms divided by the square of the height in meters), type of stent (SES vs. BMS implantation), multi-vessel disease (multi-vessel disease vs. single-vessel disease/no vessel disease), indication for PCI (stable angina/silent ischemia, unstable angina, or MI), cardiac history (i.e., previous myocardial infarction (MI), coronary artery bypass graft surgery (CABG), or PCI), CAD risk factors (i.e., hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, or self-reported current smoking) and prescribed cardiac discharge medications (i.e., ACE-inhibitors, beta-blockers, calcium antagonists, diuretics, oral nitrates or statins). Information on clinical variables was prospectively collected at the time of the index-PCI and recorded in our institutional database.

Health status

Health status was assessed at baseline post PCI, using the short form health survey (SF-36).[19] The SF-36 consists of 36 items that contribute to 8 health status domains (i.e., physical functioning, role physical functioning, role emotional functioning, mental health, vitality, social functioning, bodily pain, and general health). Scale scores are obtained by summing the items together within a domain, dividing this outcome by the range of scores, and then transforming the raw scores to a scale from 0 to 100.[19] A higher score on the SF-36 sub domains represents better functioning. A high score on the bodily pain scale indicates freedom from pain. The scale has good reliability with Cronbach's alpha ranging from 0.65 to 0.96 for all subscales.[20]

Endpoint

The primary endpoint was defined as all-cause mortality. Deaths (n=54) occurring between PCI and psychological assessment were excluded as an endpoint from analyses. Information on survival status was obtained from the Municipal Civil Registries in May 2009. The median follow-up period for all-cause mortality was 7.0 ± 1.7 years (range [0.8-9.4 years]). Information on survival status at follow-up was complete for 1007 patients (98.8%).

Informed consent

The study protocol was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam, and conducted according to the Helsinki Declaration.[21] Every patient provided informed consent.

Statistical analyses

Prior to statistical analyses, we dichotomized all 8 health status domains, as suggested by others, in order to enhance clinical interpretability.[22,23] The lowest tertile was used to indicate poor health status and the 2 highest tertiles to indicate good health status. Categorization of BMI was adopted from the World Health Organization and defined as normal weight: 18.5 to 24.99 kg/m², overweight: 25 to 29.99 kg/m², and obese: ≥30 kg/m².[24,25] For all analyses, normal weight was used as the reference group.

Group differences were examined using the Chi-square test (Fisher's exact test if appropriate) for nominal variables, while one-way ANOVA was used for continuous variables. Cumulative survival curves for BMI classes were constructed using the Kaplan-Meier method. The log-rank test was used to compare cumulative survival curves between groups. Univariable and multivariable Cox regression models were used to examine the effect of BMI on all-cause mortality. Covariates were forced into the model, thereby reducing the risk of overfitting.[26] In multivariable analyses, we adjusted for socio-demographic and clinical characteristics (i.e., gender, age, type of stent, multi-vessel disease, indication for PCI, cardiac history, CAD risk factors, and prescribed cardiac medications). Covariates were selected a priori based on the literature.[10,27-30] Health status was added to the final model to examine the role of health status in explaining the obesity paradox. Hazard Ratios (HRs) with their corresponding 95% confidence intervals (CIs) are reported for Cox regression analyses. All results were based on two-tailed tests and a p-value <0.05 was used to indicate statistical significance. All statistical analyses were performed using SPSS for Windows 17.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Patient characteristics

Of 1675 eligible patients treated with PCI in the study period, 54 patients died within 6 months. Of the remaining 1621 patients asked to participate in the study, 602 did not return the questionnaire at baseline (62.9% response rate). Final analyses were based on data from 1019 patients (72.5% men; mean age 62.0 ± 11.2 years, range [27-90] years). No systematic differences between participants and non participants were found on baseline characteristics, except for non participants more often having diabetes mellitus compared to participants (21.0% vs. 14.8%, p<.05).

In the current sample, the prevalence of normal weight was 34.7% (354/1019), overweight was seen in 45.9% (468/1019) of patients, whereas 19.3% (197/1019) was obese. At follow-up, 163

deaths (16.0%) from any cause were recorded. Patient baseline characteristics stratified by the 3 BMI categories are presented in Table 1. Overweight and obese patients were more likely to be younger, compared to the reference BMI group. Furthermore, obese patients were more likely to be female, smoke, have diabetes mellitus, and be prescribed diuretics.

Table 1. *Baseline characteristics for the total sample and stratified by BMI classes*[a]

	Total sample	Normal weight	Overweight	Obese	
	(n=1019)	(n=354)	(n=468)	(n=197)	p-value
Age, years, mean ± (SD)	62 ± 11.2	63 ± 11.4	63± 11.2	60 ± 10.6	0.005*
Gender, men (%)	72	70	76	68	0.005*
Body mass index (BMI), kg/m2, mean ± (SD)	27 ± 5.1	23 ± 1.4	27 ± 1.4	34 ± 7.1	<0.001*
Diabetes mellitus (%)	15	10	16	24	<0.001*
Hypertension (%)	29	32	28	25	0.24
Hypercholesterolemia(%)	59	56	59	61	0.45
Current smoker (%)	42	35	42	54	<0.001*
Family history of CAD (%)	15	14	15	17	0.60
BMI	29	28	29	32	0.49
Cardiac history[a]	59	57	59	61	0.71
Multi-vessel disease	54	52	57	53	0.44
Indication for PCI, %					0.66
Stable angina/silent ischemia	51	51	50	55	
Unstable angina	37	36	39	34	
MI	12	13	12	11	
Medication used, %					
Aspirin	95	94	95	95	0.87
ACE-inhibitors	33	31	33	38	0.20
Beta-blockers	67	66	67	68	0.88
Calcium antagonists	51	51	50	55	0.54
Diuretics	15	12	15	22	0.008*
Oral nitrates	17	18	15	19	0.41
Statins	73	73	73	72	0.96

ACE = angiotensin-converting enzyme, BMI = body mass index; CAD = coronary artery disease; MI = myocardial infarction; PCI= percutaneous coronary intervention; CABG = coronary artery bypass grafting.
**Statistical significance with p<0.05.*
[a]Previous myocardial infarction (MI), percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG).

BMI and all-cause mortality

The incidence of all-cause mortality at follow-up was 7.1% (72/1019) in the normal weight group versus 6.3% (64/1019) in the overweight group and 3.0% (31/1019) in the obesity group. Cumulative hazard functions differed significantly for the obese and overweight group when compared to the normal weight group (log-rank $X^2 = 6.59$, $p<0.05$). In univariable Cox regression analysis,

overweight was significantly associated with a cumulative decreased risk for all-cause mortality (HR = 0.71, 95%CI [0.51-0.97], p = 0.030) whereas obesity was not (HR = 0.96, 95%CI [0.64-1.42], p = 0.82) (Figure 1). After adjusting for socio-demographic and clinical characteristics, overweight remained associated with a lower risk for all-cause mortality (HR = 0.60, 95%CI [0.42-0.86], p = 0.005), whereas no association was found between obesity and mortality (HR = 0.87, 95%CI [0.55-1.37], p = 0.55) (Table 2).

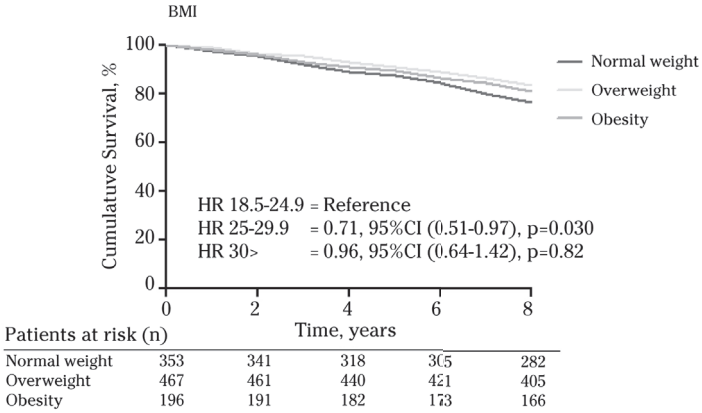

Figure 1. *Survival function stratified by BMI (unadjusted analyses)*

BMI, all-cause mortality and health status

In a final model, each of the 8 health status subdomains was added to the multivariable Cox regression analysis. After adjusting for socio-demographic, clinical characteristics, and the health status sub domains, the association between overweight and mortality remained unchanged (Table 2).

Discussion

To our knowledge, this is the first study which examined whether the paradoxical association between BMI, mortality, could be explained by health status. After a median follow-up of 7 years, overweight, but not obesity, was associated with a lower risk for all-cause mortality in patients treated with PCI, after adjusting for socio-demographic and clinical characteristics. We found no evidence that health status played a role in explaining the obesity paradox.

The results of the current study are in line with previous studies, demonstrating that overweight was associated with a decrease in mortality risk. A large meta-analysis conducted by Romero-Corral et al. selected 40 studies with a total of 250,152 patients who underwent either PCI or coronary artery bypass grafting.[31] Results showed that overweight was associated with the lowest

Table 2. *Association between BMI, health status, and all-cause mortality (adjusted analyses[a])*

	HR	95% CI	p-value
BMI (without SF-36 subdomains)			
18.5-24.9	Reference		
25-29.9	0.60	(0.42-0.86)	0.005*
30>	0.87	(0.55-1.37)	0.55
BMI (including the SF-36 subdomains)			
Physical functioning			
18.5-24.9	Reference		
25-29.9	0.59	(0.41-0.86)	0.005*
30>	0.78	(0.78-1.25)	0.30
Social functioning			
18.5-24.9	Reference		
25-29.9	0.62	(0.43-0.89)	0.009*
30>	0.85	(0.54-1.34)	0.49
Role physical functioning			
18.5-24.9	Reference		
25-29.9	0.64	(0.44-0.94)	0.024*
30>	0.89	(0.55-1.43)	0.63
Role emotional functioning			
18.5-24.9	Reference		
25-29.9	0.62	(0.42-0.91)	0.015*
30>	0.88	(0.54-1.41)	0.59
Mental health			
18.5-24.9	Reference		
25-29.9	0.59	(0.41-0.85)	0.005*
30>	0.87	(0.55-1.38)	0.56
Vitality			
18.5-24.9	Reference		
25-29.9	0.57	(0.39-0.82)	0.003*
30>	0.84	(0.53-1.33)	0.46
Bodily pain			
18.5-24.9	Reference		
25-29.9	0.62	(0.43-0.88)	0.008*
30>	0.80	(0.51-1.27)	0.35
General health			
18.5-24.9	Reference		
25-29.9	0.62	(0.43-0.89)	0.010*
30>	0.82	(0.51-1.32)	0.41

BMI= body mass index; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting.
**Statistical significance with p<0.05.*
[a]Adjusted for: sex, age, hypercholesterolemia, hypertension, diabetes mellitus, current smoker, family history of CAD, cardiac history, indication for PCI, multi-vessel disease, stent type, aspirin, ACE-inhibitors, beta-blockers, calcium antagonists, diuretics, oral nitrates, statins.

risk for total and cardiovascular mortality as compared to normal weight. In contrast to our findings, mildly obese patients also had lower mortality rates when comparing to the normal weight group. Several other studies investigated the relationship between BMI and mortality. Most of them are consistently showing an 'obesity paradox' after PCI, with better survival in obese patients.[5,6,9,32,33] However, in our PCI cohort, only overweight but not obesity was associated with lower all-cause mortality as compared to patients with a normal weight. These discrepancies may possibly be attributed to bigger sample sizes (ranging from 2,099 up to 95,435 PCI patients)[5,6,9,33] or differences in the follow-up duration, as the follow-up duration in previous studies was mainly limited to 1 year.[5,9]

In an attempt to explain the obesity paradox, previous studies in cardiac patients have mainly focused on medical factors, but results are inconclusive. For example, some studies examined the possible influence of guideline-based medication. These studies argue that higher BMI is associated with increased use of guideline-based medication, such as aspirin, B-blockers, statins and renin-angiotensin antagonists during hospitalization and at discharge. Hence, overweight and obese patients receive more optimal medical treatment, which might contribute to improved long-term outcome.[2,9] Further, more severe hypercholesterolemia and higher levels of serum low-density lipoproteins in obese patients have been examined as potential explanations for the obesity paradox.[34] Other mechanisms like plasma renin levels, increased release of inflammatory cytokines, adinopectin secretion, and physical well-being could also be part of the explanation.[35-38] However, there is still not a clear understanding of the obesity paradox.

As previously shown, health status is an important outcome measure in CAD. Schenkeveld et al. showed that poor health status is associated with adverse outcomes after PCI.[30] Moreover, a recent meta-analysis showed that poor health status is associated with higher all-cause and cardiac mortality in CAD patients.[10] These findings were confirmed in other studies in patients undergoing cardiac intervention or surgery.[30,39-41] Several studies focussed on the relation between BMI and health status, with most of them showing a negative relationship.[12-15,28,42] However, these studies were mainly focussing on heart failure patients,[12] maintenance hemodialysis patients,[13,42] or the general population but not PCI patients.[14] These studies also did not examine the role of health status as a possible explanation of the obesity paradox.

The present study did not find evidence for health status as possible explanation of the obesity paradox. There are some mechanisms which could be of importance in explaining our results. First, health status is probably a modifiable risk factor. Several mechanisms might be responsible for a connection between adverse clinical outcome and poor health status (i.e., demographical, physiological, and biomechanical mechanisms). Second, health status not only differs by level of obesity, but also by sex and age.[14] However, we adjusted for these factors in our multivariable model and no changes were observed. Finally, weight loss results in significant improvements in health status, as measured with the SF-36 and the Kellner Symptom Questionnaire.[43-45] Future studies are warranted to more precisely investigate the complex nature of the obesity paradox

and the factors that could play a role in explaining the paradox, taking both medical and psychological factors into account.

Limitations

Limitations of the current study must be acknowledged. First, data on abdominal obesity, measured by waist circumference and waist/hip ratio, were not available. A recent meta-analysis showed that central obesity was associated with higher mortality in CAD, whereas total obesity (BMI) was not.[46] Therefore, future research should focus on the different aspects of obesity, rather than total obesity alone. Second, the SF-36 is a generic measure of health status, which may be less sensitive to tap into patients' health status than the disease-specific measures used in previous studies.[10] Third, we only included patients who returned the SF-36 questionnaire. This might have influenced our results. Finally, our study population was underpowered to do sub analyses for extreme BMIs (i.e. ≤20 and ≥40). Therefore, we cannot deduce if our results show similar trends in these groups.

Conclusion

The current study showed that after a median follow-up of 7 years, overweight, but not obesity, was associated with lower mortality. In the current study health status did not seem to play a role in explaining the obesity paradox.

References

1. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA*. Jan 20 2010;303(3):235-241.
2. Steinberg BA, Cannon CP, Hernandez AF, Pan W, Peterson ED, Fonarow GC. Medical therapies and invasive treatments for coronary artery disease by body mass: the "obesity paradox" in the Get With The Guidelines database. *Am J Cardiol*. Nov 1 2007;100(9):1331-1335.
3. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol*. May 26 2009;53(21):1925-1932.
4. McGee DL, Diverse Populations C. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol*. Feb 2005;15(2):87-97.
5. Gurm HS, Brennan DM, Booth J, Tcheng JE, Lincoff AM, Topol EJ. Impact of body mass index on outcome after percutaneous coronary intervention (the obesity paradox). *Am J Cardiol*. Jul 1 2002;90(1):42-45.
6. Gruberg L, Weissman NJ, Waksman R, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol*. Feb 20 2002;39(4):578-584.
7. Gruberg L, Mercado N, Milo S, et al. Impact of body mass index on the outcome of patients with multivessel disease randomized to either coronary artery bypass grafting or stenting in the ARTS trial: The obesity paradox II? *Am J Cardiol*. Feb 15 2005;95(4):439-444.
8. Hastie CE, Padmanabhan S, Slack R, et al. Obesity paradox in a cohort of 4880 consecutive patients undergoing percutaneous coronary intervention. *Eur Heart J*. Jan 2010;31(2):222-226.
9. Lancefield T, Clark DJ, Andrianopoulos N, et al. Is there an obesity paradox after percutaneous coronary intervention in the contemporary era? An analysis from a multicenter Australian registry. *JACC Cardiovasc Interv*. Jun 2010;3(6):660-668.
10. Mommersteeg PM, Denollet J, Spertus JA, Pedersen SS. Health status as a risk factor in cardiovascular disease: a systematic review of current evidence. *Am Heart J*. Feb 2009;157(2):208-218.
11. Schenkeveld L, Magro M, Oemrawsingh RM, et al. The influence of optimal medical treatment on the 'obesity paradox', body mass index and long-term mortality in patients treated with percutaneous coronary intervention: a prospective cohort study. *BMJ Open*. 2012;2:e000535.
12. Evangelista LS, Moser DK, Westlake C, Hamilton MA, Fonarow GC, Dracup K. Impact of obesity on quality of life and depression in patients with heart failure. *Eur J Heart Fail*. Nov 2006;8(7):750-755.
13. Kalantar-Zadeh K, Kuwae N, Wu DY, et al. Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. *Am J Clin Nutr*. Feb 2006;83(2):202-210.
14. Larsson U, Karlsson J, Sullivan M. Impact of overweight and obesity on health-related quality of life—a Swedish population study. *Int J Obes Relat Metab Disord*. Mar 2002;26(3):417-424.
15. Poston WS, Haddock CK, Conard M, Spertus JA. Impact of obesity on disease-specific health status after percutaneous coronary intervention in coronary disease patients. *Int J Obes Relat Metab Disord*. Aug 2004;28(8):1011-1017.
16. Lemos PA, Lee CH, Degertekin M, et al. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *J Am Coll Cardiol*. Jun 4 2003;41(11):2093-2099.
17. Lemos PA, Serruys PW, van Domburg RT, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *Circulation*. Jan 20 2004;109(2):190-195.
18. Rumsfeld JS, Magid DJ, Plomondon ME, et al. Health-related quality of life after percutaneous coronary intervention versus coronary bypass surgery in high-risk patients with medically refractory ischemia. *J Am Coll Cardiol*. May 21 2003;41(10):1732-1738.
19. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. Jun 1992;30(6):473-483.
20. Smith HJ, Taylor R, Mitchell A. A comparison of four quality of life instruments in cardiac patients: SF-36, QLI, QLMI, and SEIQoL. *Heart*. Oct 2000;84(4):390-394.
21. Goodyear MD, Krleza-Jeric K, Lemmens T. The Declaration of Helsinki. *BMJ*. Sep 29 2007;335(7621):624-625.
22. Rumsfeld JS, Magid DJ, Plomondon ME, et al. History of depression, angina, and quality of life after acute coronary syndromes. *Am Heart J*. Mar 2003;145(3):493-499.

23. Spertus JA, Jones P, McDonell M, Fan V, Fihn SD. Health status predicts long-term outcome in outpatients with coronary disease. *Circulation.* Jul 2 2002;106(1):43-49.
24. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report. National Institutes of Health. *Obes Res.* Sep 1998;6 Suppl 2:51S-209S.
25. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser.* 2000;894:i-xii, 1-253.
26. Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. *Psychosom Med.* May-Jun 2004;66(3):411-421.
27. Freedland KE, Reese RL, Steinmeyer BC. Multivariable models in biobehavioral research. *Psychosom Med.* Feb 2009;71(2):205-216.
28. Oreopoulos A, Padwal R, McAlister FA, et al. Association between obesity and health-related quality of life in patients with coronary artery disease. *Int J Obes (Lond).* Sep 2010;34(9):1434-1441.
29. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol.* Dec 1996;49(12):1373-1379.
30. Schenkeveld L, Pedersen SS, van Nierop JW, et al. Health-related quality of life and long-term mortality in patients treated with percutaneous coronary intervention. *Am Heart J.* Mar 2010;159(3):471-476.
31. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet.* Aug 19 2006;368(9536):666-678.
32. Byrne J, Spence MS, Fretz E, et al. Body mass index, periprocedural bleeding, and outcome following percutaneous coronary intervention (from the British Columbia Cardiac Registry). *Am J Cardiol.* Feb 15 2009;103(4):507-511.
33. Minutello RM, Chou ET, Hong MK, et al. Impact of body mass index on in-hospital outcomes following percutaneous coronary intervention (report from the New York State Angioplasty Registry). *Am J Cardiol.* May 15 2004;93(10):1229-1232.
34. Rauchhaus M, Clark AL, Doehner W, et al. The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol.* Dec 3 2003;42(11):1933-1940.
35. Galal W, van Gestel YR, Hoeks SE, et al. The obesity paradox in patients with peripheral arterial disease. *Chest.* Nov 2008;134(5):925-930.
36. McCarty MF. A paradox resolved: the postprandial model of insulin resistance explains why gynoid adiposity appears to be protective. *Med Hypotheses.* Aug 2003;61(2):173-176.
37. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J.* Jul 2008;156(1):13-22.
38. Uretsky S, Messerli FH, Bangalore S, et al. Obesity paradox in patients with hypertension and coronary artery disease. *Am J Med.* Oct 2007;120(10):863-870.
39. Koch CG, Li L, Lauer M, Sabik J, Starr NJ, Blackstone EH. Effect of functional health-related quality of life on long-term survival after cardiac surgery. *Circulation.* Feb 13 2007;115(6):692-699.
40. Lenzen MJ, Scholte op Reimer WJ, Pedersen SS, et al. The additional value of patient-reported health status in predicting 1-year mortality after invasive coronary procedures: a report from the Euro Heart Survey on Coronary Revascularisation. *Heart.* Mar 2007;93(3):339-344.
41. Rumsfeld JS, MaWhinney S, McCarthy M, Jr., et al. Health-related quality of life as a predictor of mortality following coronary artery bypass graft surgery. Participants of the Department of Veterans Affairs Cooperative Study Group on Processes, Structures, and Outcomes of Care in Cardiac Surgery. *JAMA.* Apr 14 1999;281(14):1298-1303.
42. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. Association among SF36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis. *J Am Soc Nephrol.* Dec 2001;12(12):2797-2806.
43. Lavie CJ, Milani RV. Effects of cardiac rehabilitation, exercise training, and weight reduction on exercise capacity, coronary risk factors, behavioral characteristics, and quality of life in obese coronary patients. *Am J Cardiol.* Feb 15 1997;79(4):397-401.
44. Lavie CJ, Morshedi-Meibodi A, Milani RV. Impact of cardiac rehabilitation on coronary risk factors, inflammation, and the metabolic syndrome in obese coronary patients. *J Cardiometab Syndr.* Summer 2008;3(3):136-140.
45. Milani RV, Lavie CJ, Cassidy MM. Effects of cardiac rehabilitation and exercise training programs on depression in patients after major coronary events. *Am Heart J.* Oct 1996;132(4):726-732.
46. Coutinho T, Goel K, Correa de Sa D, et al. Central obesity and survival in subjects with coronary artery disease: a systematic review of the literature and collaborative analysis with individual subject data. *J Am Coll Cardiol.* May 10 2011;57(19):1877-1886.

Chapter 4

Association between mind-body practices and cardiometabolic risk factors: The Rotterdam Study

Younge JO, Leening MJG, Tiemeier H, Franco OH, Kiefte-de Jong J, Hofman A, Roos-Hesselink JW, Hunink MGM.
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Abstract

Objective

The increased popularity of mind-body practices in the general population highlights the need to explore their potential beneficial effects. We aimed to determine the cross-sectional association between mind-body practices and cardiometabolic risk factors.

Methods

This study was embedded within the population-based Rotterdam Study (visit 2009-2013) and included 2,579 participants free of cardiovascular disease. Participants were categorized if they did a form of mind-body practice based on a structured home interview. We compared individual cardiometabolic risk factors (body mass index (BMI), blood pressure, and fasting blood levels of cholesterol, triglycerides, and glucose), which were individually analyzed with linear regression. Presence of the metabolic syndrome (according to the National Cholesterol Education Program) was analyzed with logistic regression. Analyses were adjusted for age, sex, educational level, smoking, alcohol consumption, (in)activities in daily living, grief, and depressive symptoms.

Results

In our study population, 15% of the participants did a form of mind-body practice. Those who did mind-body practices had significantly lower BMI (β -0.84 kg/m^2, 95% confidence interval (CI) = -1.30;-0.38, p <.001), log-transformed triglyceride levels (β -0.02, 95%CI = -0.04;-0.001, p =.037), and log-transformed fasting glucose levels (β -0.01, 95%CI = -0.02;-0.004, p =.004). The odds-ratio for the presence of metabolic syndrome was 0.71 (95%CI = 0.54;0.95, p =.019) for individuals who do mind-body practices.

Conclusions

Individuals who do mind-body practices have a favorable cardiometabolic risk profile compared to those who do not. However, the design of our study does not allow for causal inference.

Introduction

The last decades, knowledge of modifiable cardiovascular risk factors, such as smoking, hypertension, dyslipidemia, diabetes, obesity has led to global prevention programs.[1,2] These risk factors account for >90% of the population attributable risk of acute myocardial infarction worldwide.[3] Even though the number of deaths from cardiovascular disease (CVD) decline, still in 2010 an overall death rate of 235.5 deaths per 100.000 could be attributed to CVD in the U.S.[4] Approximately 1 out of 6 die from coronary heart disease and 1 out of 19 die from stroke.[4]

Nowadays, a widespread of health care programs are implemented for the prevention and treatment of CVD. However, prevention of CVD remains suboptimal and alternative interventions should be explored. there is increased attention to other interventions and adjuncts to conventional care. Use of mind-body practices is growing in the Western world (extended to 20% of the population) and these could play a role in prevention of non-communicable disorders including CVD.[5,6]

Studies have shown the effectiveness of mind-body practices as safe adjuncts in modifying risk factors for CVD including diabetes, hypertension, body weight, depression, and post-traumatic stress[7-11] Two recent systematic reviews and meta-analyses demonstrate conflicting results in the primary prevention settings: no effects of tai chi on cardiovascular risk factors but some positive effects of yoga on blood pressure and lipid levels were demonstrated[12,13] Whether mind-body interventions could play a role in prevention of CVD is still unclear.

In this study we aimed to examine the association between individuals who do mind-body practices (including: self-prayer, meditation, yoga, breathing exercises, or any other form of mind-body related relaxation technique or practice) and the presence of cardiometabolic risk factors in a population-based cohort.

Methods

Study population

The Rotterdam Study is a population-based cohort of persons living in a well-defined suburb of the city of Rotterdam, the Netherlands. It is designed to assess determinants and consequences of chronic diseases. Over the past decades, the initial cohort has been extended twice and as of the end of 2008 the study consists of 14,926 individuals. More details on the study have been described elsewhere.[14]

For our study we included individuals examined between 2009-2013 in the third observation of the second Rotterdam Study cohort (RS-II-3) and the second observation of the third Rotterdam Study cohort (RS-III-2). Individuals who did not provide informed consent for collection of data on medical history from their treating physicians were excluded from analysis. For this study,

approval was granted by the Medical Ethics committee of the Erasmus MC and written informed consent was obtained from the participants.

Measurement of mind-body practices

During a home visit, trained interviewers questioned individuals if they did mind-body practices. The questionnaire included the following topics: ''type of mind-body practice" (eg. self-prayer (non-organizational religiosity), meditation, movement therapy (yoga, tai chi, qi-gong), breathing exercises, or any other form of mind-body related relaxation technique or practice), ''the amount of time per week spent on the mind-body practice" (0 hours, <1 hour, 1-2 hours, >2 hours) and ''the amount of years practicing". Organizational religiosity (attending religious services) was not considered a mind-body practice because of the predominant social aspect.[15]

Assessment of physical parameters

Blood samples and physical parameters were collected during a visit to the research center. BMI was calculated by weight in kilograms divided by height in meters squared. Blood pressure was measured twice at the right upper arm using a random-zero sphygmomanometer after the participant had rested for 5 minutes in the sitting position. The mean of 2 consecutive measurements was used to calculate systolic and diastolic blood pressure. Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, or the use of blood pressure lowering medication.

Laboratory works

Peripheral venous blood samples were collected at the center. Clinical chemistry measurements were done at the department of clinical chemistry of the Erasmus MC. Parameters were measured using a Roche Modular P800. Serum total cholesterol (TC) level was determined by an automated enzymatic procedure by using the CHOD-PAP reagent agent (Roche Diagnostics, Indianapolis, IN, US) and serum high-density lipoprotein cholesterol (HDL-C) level was measured with the HDL-C cholesterol plus 3rd generation assay (Roche Diagnostics, Indianapolis, IN, US). Triglycerides levels were determined by an automated enzymatic procedure by using the GPO-PAP reagent agent (Roche Diagnostics, Indianapolis, IN, US). Diabetes mellitus was defined as a fasting blood glucose exceeding 126 mg/dL, a non-fasting glucose exceeded 200 mg/dL (if fasting samples were unavailable), or use of blood glucose lowering medication.[16] Low-density lipoprotein-cholesterol (LDL-C) was calculated by the Friedewald formula (LDL-C = TC – HDL-C – (triglycerides/5)).[17]

Assessment of covariables

We used the Center for Epidemiological Studies Depression Scale (CES-D) to identify current depressive symptoms. Additionally, we report the subscales on positive and negative affect.[18] The questionnaire consists of 20-items on mood and feelings in the past week on a 4-point Likert

scale: 0 =“rarely or none of the time (0–1 day)”, 1= “some or a little of the time (1–2 days)”; 2= “occasionally or a moderate amount of the time (3–4 days)”; and 3=“most or all of time (5–7 days).” A total CES-D score is calculated by summing the scores from each item with a range of 0 to 60 points. Additionally, positive and negative affect scores can be calculated and summed as continuous variables.[19] The positive affect (happiness) comprises 4 items with a range of 0 to 12. The negative affect (depression) comprises 7 items with a range of 0 to 21. These subscales have previously been used in population-based studies.[20] We calculated the mean subscale scores for the two groups and then we tested whether adjusting for positive and negative affect separately in the multivariable models affected the results. Results were not meaningfully different. Therefore we used the total CES-D score in our multivariable analyses.

Highest education attained was recorded and categorized as ‘’primary education”, ‘’lower/ intermediate general education or lower vocational education”,‘’intermediate vocational education or higher general education”, or ‘’higher vocational education or university”. We used level of educational, because financial status was not available in app participants and education has been shown to be a good proxy for financial status in the Rotterdam Study.[21] Smoking status was categorized as never, former, and current smoker. Alcohol use was categorized as regular use (>2-3 times per week at least 1 beverage), and occasional use (< 2-4 times per month at least 1 beverage). Limitations in daily lives were documented with the activity of daily living (ADL) questionnaire.[22] Furthermore, we assessed whether grief was present with the inventory of complicated grief as a dichotomous variable.[23]

Assessment of dietary intake

To measure dietary intake we used a 389-item semi-quantitative food frequency questionnaire (FFQ) based on a FFQ that was previously validated and developed for Dutch adults.[24,25] The FFQ consisted of questions on the frequency of consumption of food items over the last month, amount and type of the food item, and how it was prepared. Standardized household measures were used to estimate portion sizes in grams per day.[26] All dietary data were converted into nutrient intakes per day using the Dutch Food Composition Table of 2006 and 2011. Next, we assessed adherence to the Dutch dietary guidelines[27] by the Dutch Healthy Diet (DHD) index, originally developed by van Lee et al.[28] The DHD-index consists of nine food components: vegetable, fruit, dietary fiber, fish, saturated fatty acids, trans fatty acids, consumption occasions with acidic drinks, foods, sodium, and alcohol. For the current study, the component ‘consumption occasions with acidic drinks and foods’ was excluded because the FFQ did not assess this specific component. The scores of the remaining 8 components of the DHD-index ranged between 0 and 10 points. All components were summed resulting in a score between 0 and 80 points with higher scores representing a higher level of adherence to the Dutch dietary guidelines.

Combined metabolic risk

To assess combined metabolic risk, participants were categorized as having the metabolic syndrome or not according to the National Cholesterol Education Program (NCEP) guidelines.[29] The presence of metabolic syndrome is defined as having 3 or more of the following 5 cardiovascular risk factors: 1) central obesity (waist circumference: men >102 cm; women >88 cm); 2) elevated triglycerides (≥150 mg/dL); 3) low HDL-C (men <40 mg/dL; women <50 mg/dL); 4) arterial hypertension (blood pressure ≥130/ ≥85 mm Hg); and 5) elevated fasting glucose (≥110 mg/dL).

Statistical analysis

Participants included in the analysis were those who completed the questionnaire and visited the research center. Furthermore, participants with a history of CVD (coronary revascularization, myocardial infarction, or stroke) were excluded from the analysis. We compared those who do mind-body practices versus those who do not (using a 1 hour/week cut-off). We present means ± SD for normally distributed characteristics and compared these by 1-way analysis of variance. We present median values (interquartile range (IQR)) for skewed data and compared these using the Mann-Whitney U test. We used Pearson's χ^2 test for categorical variables.

We conducted univariable and multivariable linear regression analyses to evaluate each metabolic risk factor separately. These analyses were performed by nested models in which we adjusted for demographics (age, sex, and educational level), current smoking, regular alcohol use, depressive symptoms (total CES-D score), grief, and disability in activities of daily living. We did not adjust for the DHD-index because this was available for only 75% of the population. Univariable and multivariable logistic regression analyses were used to analyze the association between mind-body practices and presence of metabolic syndrome. These analyses were performed by nested models in which we adjusted for demographics (age, sex, and educational level), current smoking, regular alcohol use, depressive symptoms, grief, and disability in activities of daily living.

Furthermore, we conducted test-for-trend analyses to evaluate the association between the groups who do mind-body practices (<1 hour, 1-2 hours, and >2 hours per week), or not (0 as reference group), and the presence of metabolic syndrome. Multinomial logistic regression models with zero components of metabolic syndrome as reference were constructed to examine associations between doing mind-body practices and the number of metabolic syndrome components while adjusting for age, sex, educational level, current smoking, regular alcohol use, depressive symptoms, grief, and disability in practices of daily living. A p-value less than 0.05 was considered to indicate statistical significance. All data were analyzed with IBM SPSS Statistics version 21.0 (IBM Corp., Somers, NY).

Results

Participant characteristics

Characteristics of the study population are presented in Table 1. Of the total population for analysis, 394 individuals (15.3%) did a form of mind-body practice. Most often performed was prayer (n=170, 43.1%). Other popular practices were meditation (n=97, 24.6%), movement therapies (n=57, 14.5%) and relaxation/breathing exercises (n=48, 12.2%). Compared with those who did not do mind-body practices, individuals who did a form of mind-body practice were significantly younger, more likely to be women, higher educated, and less likely to be smokers (Table 1). Moreover, persons who did mind-body practices had significantly lower BMI, SBP, DBP, levels of HDL-C, levels of triglycerides, and were less likely to have metabolic syndrome (Table 1). Participants who do mind-body practices had significantly lower levels of positive affect and reported higher levels of negative affect (Table 1).

Table 1. *Characteristics of total study population and stratified by doing vs not doing mind-body practices*

	Total (n=2579)	Mind-body practices (n=394)	No mind-body practices (n=2185)	p-value
Age, years, mean (SD)	66.2 (7.6)	64.7 (7.3)	66.4 (7.7)	<0.001
Women, (%)	57.5	65.5	56.1	<0.001
BMI, kg/m^2, mean (SD)	27.5 (4.3)	26.8 (4.3)	27.7 (4.3)	<0.001
Type of mind-body practice[a], (%)				
Prayer		43.1		
Meditation		24.6		
Movement therapy		14.5		
Relaxation/breathing exercises		12.2		
Other[b]		29.2		
Hours spent per week on mind-body practices, %				
0 hours	77.4	NA	92.7	NA
<1 hour	6.0	NA	7.3	NA
1-2 hours	7.6	43.7	NA	NA
>2 hours	9.0	56.3	NA	NA
SBP, mm Hg, mean (SD)	143 (21)	140 (22)	143 (21)	0.001
DBP, mm Hg, mean (SD)	84 (11)	83 (11)	85 (11)	0.050
HT, (%)	78.0	74.1	78.7	0.027
Use of anti-HT medication, (%)	33.3	30.7	33.8	0.13
Heart rate, mean (SD)	70 (11)	69 (10)	69 (11)	0.33
DM, (%)	11.4	8.2	11.9	0.023
Smoking, (%)				
Never	29.0	32.2	28.5	0.076
Past	54.7	55.6	54.5	0.37
Current	16.3	12.2	17.0	0.009

Table 1. *Characteristics of total study population and stratified by doing vs not doing mind-body practices (continued)*

	Total (n=2579)	Mind-body practices (n=394)	No mind-body practices (n=2185)	p-value
Regular alcohol use, (%)	58.2	57.4	58.3	0.37
Education, %				<0.001
primary education	6.7	4.8	7.0	
primary education, higher not completed or lower vocational education	19.8	16.2	20.5	
lower secondary education	20.6	17.8	21.1	
intermediate vocational education	23.7	24.4	23.6	
general secondary education	5.3	4.6	5.4	
higher vocational education	20.0	25.6	18.9	
university	3.9	6.9	3.4	
CES-D positive affect	10.5 (2.3)	10.1 (2.6)	10.6 (2.2)	<0.001
CES-D negative affect	1.1 (2.4)	1.4 (2.6)	1.0 (2.3)	0.001
CES-D Total	12.7 (5.8)	13.9 (6.2)	12.5 (5.7)	<0.001
Grief, (%)	15.2	18.0	14.7	0.051
No disability in ADL, (%)	71.8	70.1	72.1	0.22
Serum analysis				
TC, mg/dL, mean (SD)	217 (40)	216 (39)	217 (41)	0.72
HDL-C, mg/dL, median (IQR)	56 (46-68)	58 (21)	56 (22)	0.078[c]
LDL-C, mg/dL, mean (SD)	133 (37)	133 (36)	133 (37)	0.73
Triglycerides, mg/dL, median (IQR)	113 (86-153)	108 (62)	114 (69)	0.005[c]
Fasting glucose (mg/dL), median (IQR)	97 (90-106)	96 (14)	97 (16)	<0.001
DHD-Index, mean (SD)	50.7 (8.6)	52.0 (8.4)	50.4 (8.6)	0.002
Metabolic Syndrome, (%)	23.7	17.8	24.8	0.001

Abbreviations: SD, standard deviation; BMI, body mass index; NA, not applicable; SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hypertension; DM, diabetes mellitus; CES-D, Center for Epidemiological Studies Depression Scale; ADL, activities of daily living; IQR, interquartile range; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; DHD-Index, Dutch Healthy Diet Index.

[a]Some participants performed more than 1 mind-body practice (e.g. meditation and relaxation)

[b]If a participant performed a different mind-body practice, which was not a predefined option in the home-interview, this was labelled as "other".

[c]p-values calculated from on log-transformed values

Normally distributed characteristics were compared by 1-way analysis of variance. Skewed data (presented as median values and interquartile range (IQR) were compared by using the Mann-Whitney U test. Pearson's $\chi 2$ test was used for categorical variables

Mind-body practices and individual metabolic risk factors

After adjustment for age, sex, and educational level, an inverse association was seen between persons who do mind-body practices and BMI (β -0.74 kg/m^2, 95% CI: -1.20, -0.25, p .002), log-transformed triglyceride levels (β -0.02, 95% CI: -0.04, 0.00, p = .046) and log-transformed fasting glucose levels (β -0.01, 95% CI: -0.02, -0.003, p = .005) (Table 2).

In the adjusted model where current smoking, alcohol, ADL, grief, and depressive symptoms were added, the association with persons who do mind-body practices remained significant for BMI (β -0.84 kg/m^2, 95% CI: -1.30, -0.38, p < .001), log-transformed triglyceride levels (β -0.02, 95% CI: -0.04, -0.001, p = .037) and log-transformed fasting glucose levels, (β -0.01, 95% CI: -0.02, -0.004, p = .002) (Table 2).

Table 2. *Association between doing mind-body practices and cardiometabolic risk factors*[a]

	Univariable		Multivariable[b]		Multivariable[c]	
	β (95%CI)	p-value	β (95%CI)	p-value	β (95%CI)	p-value
BMI, kg/m^2	-0.88 (-1.34;-0.42)	<0.001	-0.74 (-1.20;-0.27)	0.002	-0.84 (-1.30;-0.38)	<0.001
SBP, mm Hg	-2.8 (-5.1;-0.5)	0.018	-0.3 (-2.5;17.)	0.720	-0.3 (-2.4;1.8)	0.763
DBP, mm Hg	-0.8 (-2.0;0.4)	0.187	-0.2 (-1.4;0.9)	0.692	-0.3 (-1.5;0.9)	0.611
TC, mg/dL	-0.8 (-5.1;3.5)	0.718	-3.7 (-7.9;-0.5)	0.087	-3.4 (-7.6;0.8)	0.117
HDL-C, mg/dL[d]	0.01 (-0.001;0.03)	0.078	0.001 (-0.01;0.01)	0.925	0.001 (-0.01;0.01)	0.830
LDL-C, mg/dL	-0.7 (-4.7;3.3)	0.729	-2.5 (-6.5;1.4)	0.207	-2.3 (-6.3;1.7)	0.254
Triglycerides, mg/dL[d]	-0.03 (-0.05;-0.01)	0.005	-0.02 (-0.04;0.00)	0.046	-0.02 (-0.04;-0.001)	0.037
Fasting glucose, mg/dL[d]	-0.02 (-0.02;-0.01)	<0.001	-0.01 (-0.02;-0.003)	0.005	-0.01 (-0.02;-0.004)	0.002

Abbreviations: CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a]Univariable and multivariable linear regression analyses were used to evaluate each metabolic risk factor separately
[b]Adjusted for age, sex, and educational level
[c]Adjusted for age, sex, educational level, smoking, alcohol consumption, activities of daily living, grief, and depressive symptoms
[d]Log-transformed

Mind-body practices and the metabolic syndrome

The distribution of the number of metabolic syndrome components among those who do mind-body practices and those who do not is shown in Figure 1. Adjustment for age, sex, and educational level had little effect on the association between mind-body practice and metabolic syndrome (OR =0.72, 95% CI: 0.55, 0.96, p = .023). In the adjusted model, where current smoking, alcohol use, ADL, grief, and depressive symptoms were additionally added, the association between participation in mind-body practices and metabolic syndrome remained virtually unchanged (OR 0.71, 95% CI: 0.54, 0.95, p = .019).

Trend analyses on the association between duration of practicing any form of mind-body practice and metabolic syndrome showed a significant association in univariable analysis (p =.019). The final adjusted model showed did not reach the level statistical significance (p = .097) (Table 3).

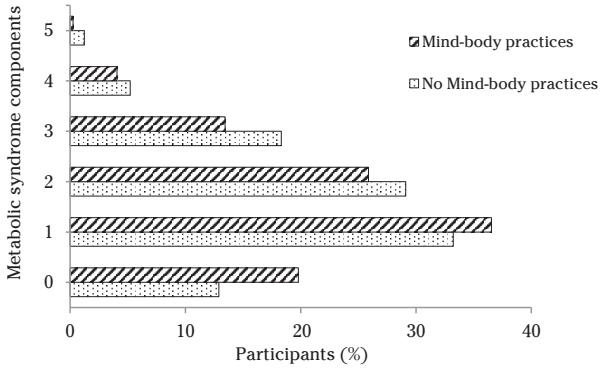

Figure 1. *Distribution of Number of Metabolic Syndrome Components*

Table 3. *Association between mind-body practices and metabolic syndrome trend analyses*[a]

	OR (95%CI)	p-value [b]
Univariable		0.019
<1 hour/week	0.88 (0.60;1.30)	
1-2 hours/week	0.74 (0.50;1.10)	
>2 hours/week	0.58 (0.40;0.84)	
Multivariable[c]		0.113
<1 hour/week	0.98 (0.66;1.45)	
1-2 hours/week	0.83 (0.56;1.23)	
>2 hours/week	0.64 (0.44;0.93)	
Multivariable[d]		0.097
<1 hour/week	0.93 (0.62;1.39)	
1-2 hours/week	0.81 (0.54;1.20)	
>2 hours/week	0.63 (0.43;0.93)	

Abbreviations: OR, odds-ratio; CI, confidence interval
[a]*Not doing a form of mind-body practice is the reference category*
[b]*logistic regression was used to obtain p-values*
[c]*Adjusted for age, sex, and educational level*
[d]*Adjusted for age, sex, educational level, smoking, alcohol consumption, activities of daily living, grief, and depressive symptoms*

The relation between mind-body practices and the number of metabolic syndrome components in a multivariable adjusted model is shown in Table 4. Doing mind-body practices (vs. not doing mind-body practices) was significantly associated with a lower prevalence of metabolic syndrome components (2 components: OR 0.67, 95% CI: 0.47, 0.94, p =.002, and 3 components: OR 0.58, 95% CI: 0.39, 0.86, p = .006.The pattern was similar for 4 components: OR 0.60, 95% CI: 0.33, 1.08, p = .090, and 5 components: OR 0.18, 95% CI: 0.02, 1.35, p = .095, although the results did not reach statistical significance due to the small number of participants in these categories (Table 4).

Table 4. *Results of multinomial logistic regression, number of metabolic syndrome Components and mind-body practices*[a]

	No mind-body practices[b]	Mind-body practices[b]	
		OR (95%CI)	p-value
Number of metabolic syndrome components			
1 vs 0	Reference	0.83 (0.60;1.15)	0.269
2 vs 0	Reference	0.67 (0.47;0.94)	0.020
3 vs 0	Reference	0.58 (0.39;0.86)	0.006
4 vs 0	Reference	0.60 (0.33;1.08)	0.090
5 vs 0	Reference	0.18 (0.02;1.35)	0.095

[a]*Not doing a form of mind-body practice is the reference category*
[b]*Adjusted for age, sex, educational level, smoking, alcohol consumption, activities of daily living, grief, and depressive symptoms*
The 5 metabolic components were: central obesity (waist circumference: men >102 cm; women >88 cm); 2) elevated triglycerides (≥150 mg/dL); 3) low HDL-C (men <40 mg/dL; women <50 mg/dL); 4) arterial hypertension (blood pressure ≥130/ ≥85 mm Hg); and 5) elevated fasting glucose (≥110 mg/dL).

Mind-body practices and Dietary Intake

Total DHD index scores were obtained from 1937 participants (75.1% of the current study population). A significant higher total DHD index score was reported by individuals performing a form of mind-body practice (52.1 versus 50.4, $p = 0.002$) (Table 1). This was mainly driven by higher scores for the mind-body practice group on the components fiber ($p < 0.001$), saturated fatty acids ($p < 0.001$), and alcohol ($p = 0.031$) (data not shown).

Discussion

In our study, doing mind body practices is inversely associated with BMI, triglycerides, and fasting glucose levels. Furthermore, doing mind-body practices is associated with a lower prevalence of metabolic syndrome components.

In our study population, 15.3% of participants did a form of mind-body practice. Within this group rates differed from 12.2% (relaxation/breathing exercises) to 43.1% (prayer). In a recent study Barnes et al.[5] showed the increased use of mind-body practices in the general population between 2002 and 2007. Most used practices were breathing exercises (12.7%) and meditation (9.4%). Furthermore, in two surveys in patients with CVD the use of mind-body practices even extended to more than 24%.[6,30] In contrast to our study, prayer was often not evaluated. We chose to include (self) prayer since it has been shown to have similar physiological effects and brain deactivation on MRI as seen in relaxation response and meditation.[31-33] The increased use of mind-body practices might be explained because they are easy to learn, side-effects or injuries are rare and even patients with limited mobility can do regular practice.[34]

As biochemical measures are probably affected by psychological stress, mind-body practices could be an effective tool to modify metabolic indices. A clear link between psychological stress and CVD has been described.[35-38] Several studies have shown beneficial results of yoga, qigong, and meditation in regulating blood-pressure, lipid levels and diabetes.[11,39-42] Unfortunately, most of these studies did not have a randomized study design and consisted of small and heterogeneous patient populations. One randomized clinical trial on transcendental meditation even presented survival benefits in African-American patients with coronary heart disease.[43] In a recent systematic review Anderson et al.[44] showed potential effectiveness of some mind-body practices on improving indicators of the metabolic syndrome. Unfortunately, the available evidence is scarce and of limited quality. Therefore, randomized clinical trials are needed to determine the effectiveness of mind-body practices in the management of metabolic syndrome and cardiovascular disease prevention. Unfortunately, due to the nature of lifestyle interventions, patients are always aware in which group they belong. Therefore, double-blind randomized clinical trials are extremely difficult in lifestyle interventions.

Mind-body medicine predates modern biomedicine and until now there is not yet a clear understanding of the underlying working mechanism. Benson and colleagues have studied the

relaxation response as a framework in mind-body medicine, which can be seen as the core component in autonomic function and physical changes.[45,46] Changes in molecular pathways provide a possible explanation of the clinical benefits found in the relaxation response.[47,48] The autonomic nervous system is a main component of the connection between the brain and the heart, demonstrated by a clear link between thoughts, emotions, and the heart.[49] An imbalance of the autonomic nervous system in increased sympathetic activity or decreased parasympathetic activity is a risk factor for cardiovascular morbidity and mortality.[49,50] A working mechanism on the effect of mind-body practices on health has been suggested to be explained by the interaction between the central nervous system, endocrine, and immune system[51] Beneficial effects are seen on the immune system and endothelial functioning.[8,52] Overall, these studies show promising results of meditation and stress reduction techniques on the body, suggesting that via these practices the mind may be able to influence health.

Some limitations of this study must be addressed. First and foremost, the design of this study is observational and cross-sectional. Therefore, no conclusions can be drawn on causality since participants were not randomized and mind-body practices were assessed at a single moment in time. Also, doing mind-body practices may reflect a more health conscious lifestyle that includes a more physically active life, healthier diet, and better adherence to medication, which are all known to directly affect levels of cardiometabolic risk factors. Therefore our findings may be subject to (residual) confounding of other lifestyle factors. Within the Rotterdam Study we did not have detailed data available on physical activity and diet for this cohort, but future follow-up observations of the Rotterdam Study cohort might give a better understanding of the relation between mind-body practices and cardiometabolic risk. A second limitation is the inclusion of religiosity (self-prayer). Although not always considered a mind-body practice, prayer is initiated by a mental action. In neuroimaging studies prayer showed similar findings as meditation and relaxation.[19-21] Third, we used a broad definition of mind-body practices and did not specify them in detail. Due to a relative small absolute number of participants involved in mind-body practices, we did not undertake further sub-analyses.

It is evident that lifestyle can affect physiological and biochemical measures. Our results indicate that mind-body practices might be of added value in the management of CVD risk. Even small beneficial changes in risk factors as observed in our study might contribute to a significant risk reduction at population level. The added value of psychosocial interventions in the context of cardiac rehabilitation has already shown some promising results.[53,54] High-quality randomized trials are needed to evaluate the effectiveness and efficacy of mind-body practices on hard cardiovascular end points.

In conclusion, we found that 15% of participants in a population-based study do mind-body practices. Mind-body practices are inversely associated with BMI, triglyceride levels, and fasting glucose levels. Furthermore, the prevalence of metabolic syndrome was lower in those who did mind-body practices. However, due to the observational and cross-sectional study design, no conclusions can be drawn on causality.

References

1. McManus B. INTERHEART: nine factors that could save your life. *Healthc Q.* 2005;8(1):28.
2. Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet.* Sep 11-17 2004;364(9438):953-962.
3. 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.* Sep 11-17 2004;364(9438):937-952.
4. 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.* Jan 21 2014;129(3):399-410.
5. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *Natl Health Stat Report.* Dec 10 2008(12):1-23.
6. Prasad K, Sharma V, Lackore K, Jenkins SM, Prasad A, Sood A. Use of complementary therapies in cardiovascular disease. *Am J Cardiol.* Feb 1 2013;111(3):339-345.
7. Chiesa A, Serretti A. Mindfulness-based stress reduction for stress management in healthy people: a review and meta-analysis. *Journal of alternative and complementary medicine (New York, N.Y.* May 2009;15(5):593-600.
8. Dod HS, Bhardwaj R, Sajja V, et al. Effect of intensive lifestyle changes on endothelial function and on inflammatory markers of atherosclerosis. *Am J Cardiol.* Feb 1 2010;105(3):362-367.
9. Innes KE, Bourguignon C, Taylor AG. Risk indices associated with the insulin resistance syndrome, cardiovascular disease, and possible protection with yoga: a systematic review. *J Am Board Fam Pract.* Nov-Dec 2005;18(6):491-519.
10. Singh S, Malhotra V, Singh KP, Madhu SV, Tandon OP. Role of yoga in modifying certain cardiovascular functions in type 2 diabetic patients. *J Assoc Physicians India.* Mar 2004;52:203-206.
11. Xin L, Miller YD, Brown WJ. A qualitative review of the role of qigong in the management of diabetes. *Journal of alternative and complementary medicine (New York, N.Y.* May 2007;13(4):427-433.
12. Hartley L, Dyakova M, Holmes J, et al. Yoga for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2014;5:CD010072.
13. Hartley L, Flowers N, Lee MS, Ernst E, Rees K. Tai chi for primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2014;4:CD010366.
14. Hofman A, Darwish Murad S, van Duijn CM, et al. The Rotterdam Study: 2014 objectives and design update. *Eur J Epidemiol.* Nov 2013;28(11):889-926.
15. Koenig H, Parkerson GR, Jr., Meador KG. Religion index for psychiatric research. *Am J Psychiatry.* Jun 1997;154(6):885-886.
16. American Diabetes A. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* Jan 2011;34 Suppl 1:S62-69.
17. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* Jun 1972;18(6):499-502.
18. Krijthe BP, Walter S, Newson RS, Hofman A, Hunink MG, Tiemeier H. Is positive affect associated with survival? A population-based study of elderly persons. *Am J Epidemiol.* Jun 1 2011;173(11):1298-1307.
19. LS R. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas.* 1977(1):385–401.
20. Ostir GV, Markides KS, Black SA, Goodwin JS. Emotional well-being predicts subsequent functional independence and survival. *J Am Geriatr Soc.* May 2000;48(5):473-478.
21. van Rossum CT, van de Mheen H, Witteman JC, Mackenbach JP, Grobbee DE. Socioeconomic status and aortic atherosclerosis in Dutch elderly people: the Rotterdam Study. *Am J Epidemiol.* Jul 15 1999;150(2):142-148.
22. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol.* Sep-Oct 1982;9(5):789-793.
23. Prigerson HG, Maciejewski PK, Reynolds CF, 3rd, et al. Inventory of Complicated Grief: a scale to measure maladaptive symptoms of loss. *Psychiatry Res.* Nov 29 1995;59(1-2):65-79.
24. Feunekes GI, Van Staveren WA, De Vries JH, Burema J, Hautvast JG. Relative and biomarker-based validity of a food-frequency questionnaire estimating intake of fats and cholesterol. *Am J Clin Nutr.* Oct 1993;58(4):489-496.
25. Goldbohm RA, van den Brandt PA, Brants HA, et al. Validation of a dietary questionnaire used in a large-scale prospective cohort study on diet and cancer. *Eur J Clin Nutr.* Apr 1994;48(4):253-265.
26. Donders-Engelen MRvdH, L.J.M.; Hulshof, K.F.A.M. Maten gewichten en codenummers. *U.R. Wageningen (Ed.)* 2003;Division of human nutrition.

27. Netherlands HCot. Guidelines for a healthy diet 2006. *Publication no. 2006/21, The Hague.* 2006.
28. van Lee L, Geelen A, van Huysduynen EJ, de Vries JH, van't Veer P, Feskens EJ. The Dutch Healthy Diet index (DHD-index): an instrument to measure adherence to the Dutch Guidelines for a Healthy Diet. *Nutr J.* 2012;11:49.
29. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The 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). *JAMA.* May 16 2001;285(19):2486-2497.
30. Yeh GY, Davis RB, Phillips RS. Use of complementary therapies in patients with cardiovascular disease. *Am J Cardiol.* Sep 1 2006;98(5):673-680.
31. Lazar SW, Bush G, Gollub RL, Fricchione GL, Khalsa G, Benson H. Functional brain mapping of the relaxation response and meditation. *Neuroreport.* May 15 2000;11(7):1581-1585.
32. Newberg A, Pourdehnad M, Alavi A, d'Aquili EG. Cerebral blood flow during meditative prayer: preliminary findings and methodological issues. *Percept Mot Skills.* Oct 2003;97(2):625-630.
33. Schjoedt U, Stodkilde-Jorgensen H, Geertz AW, Roepstorff A. Highly religious participants recruit areas of social cognition in personal prayer. *Soc Cogn Affect Neurosci.* Jun 2009;4(2):199-207.
34. Yang Y, Verkuilen J, Rosengren KS, et al. Effects of a Taiji and Qigong intervention on the antibody response to influenza vaccine in older adults. *Am J Chin Med.* 2007;35(4):597-607.
35. Richardson S, Shaffer JA, Falzon L, Krupka D, Davidson KW, Edmondson D. Meta-analysis of perceived stress and its association with incident coronary heart disease. *Am J Cardiol.* Dec 15 2012;110(12):1711-1716.
36. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J Am Coll Cardiol.* Mar 1 2005;45(5):637-651.
37. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet.* Sep 22 2007;370(9592):1089-1100.
38. Rozanski A, Bairey CN, Krantz DS, et al. Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease. *N Engl J Med.* Apr 21 1988;318(16):1005-1012.
39. Bijlani RL, Vempati RP, Yadav RK, et al. A brief but comprehensive lifestyle education program based on yoga reduces risk factors for cardiovascular disease and diabetes mellitus. *Journal of alternative and complementary medicine (New York, N.Y.* Apr 2005;11(2):267-274.
40. Ko GT, Tsang PC, Chan HC. A 10-week Tai-Chi program improved the blood pressure, lipid profile and SF-36 scores in Hong Kong Chinese women. *Med Sci Monit.* May 2006;12(5):CR196-199.
41. Tsai JC, Wang WH, Chan P, et al. The beneficial effects of Tai Chi Chuan on blood pressure and lipid profile and anxiety status in a randomized controlled trial. *Journal of alternative and complementary medicine (New York, N.Y.* Oct 2003;9(5):747-754.
42. Younge JO, Gotink RA, Baena CP, Roos-Hesselink JW, Hunink MM. Mind-body practices for patients with cardiac disease: a systematic review and meta-analysis. *Eur J Prev Cardiol.* Sep 16 2014.
43. Schneider RH, Grim CE, Rainforth MV, et al. Stress reduction in the secondary prevention of cardiovascular disease: randomized, controlled trial of transcendental meditation and health education in Blacks. *Circ Cardiovasc Qual Outcomes.* Nov 2012;5(6):750-758.
44. Anderson JG, Taylor AG. The metabolic syndrome and mind-body therapies: a systematic review. *J Nutr Metab.* 2011;2011:276419.
45. Benson H. The relaxation gesponse: its subjective and objective historical precendents and physiology. *Trends Neurosci.* 1983;6:281-284.
46. Benson H, Beary JF, Carol MP. The relaxation response. *Psychiatry.* Feb 1974;37(1):37-46.
47. Bhasin MK, Dusek JA, Chang BH, et al. Relaxation response induces temporal transcriptome changes in energy metabolism, insulin secretion and inflammatory pathways. *PLoS One.* 2013;8(5):e62817.
48. Dusek JA, Otu HH, Wohlhueter AL, et al. Genomic counter-stress changes induced by the relaxation response. *PLoS One.* 2008;3(7):e2576.
49. Emani S, Binkley PF. Mind-body medicine in chronic heart failure: a translational science challenge. *Circ Heart Fail.* Nov 2010;3(6):715-725.
50. Curtis BM, O'Keefe JH, Jr. Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. *Mayo Clin Proc.* Jan 2002;77(1):45-54.
51. Vitetta L, Anton B, Cortizo F, Sali A. Mind-body medicine: stress and its impact on overall health and longevity. *Ann N Y Acad Sci.* Dec 2005;1057:492-505.
52. Davidson RJ, Kabat-Zinn J, Schumacher J, et al. Alterations in brain and immune function produced by mindfulness meditation. *Psychosom Med.* Jul-Aug 2003;65(4):564-570.
53. Blumenthal JA, Sherwood A, Babyak MA, et al. Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: a randomized controlled trial. *JAMA.* Apr 6 2005;293(13):1626-1634.
54. Whalley B, Rees K, Davies P, et al. Psychological interventions for coronary heart disease. *Cochrane Database Syst Rev.* 2011(8):CD002902.

Chapter 5

Cortisol levels in scalp hair in patients with structural heart disease

Younge JO, Wester VL*, Rossum EFC, Gotink RA, Wery MF, Utens EMWJ, Hunink MGM, Roos-Hesselink JW.*
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**Equal contributions*

Abstract

Background

Stress is considered a modifiable risk factor for cardiovascular disease. Scalp hair analysis is a tool to assess long-term exposure to the stress hormone cortisol. We aimed to determine the association between hair cortisol concentrations (HCC) and clinical characteristics in patients with structural heart disease. Additionally, we investigated potential predictors for longitudinal change in HCC.

Methods

The study consisted of 261 patients with structural heart disease from a randomized controlled trial of mindfulness training. One sample of scalp hair was used to determine HCC both at baseline and at 12-weeks follow-up. In 151 patients HCC was available (mean age: 41.3 years, range 18-65). We investigated the association between HCC at baseline and several physiological measures (BMI, blood pressure, heart rate, respiratory rate, 6-minute walk test), as well as psychological parameters (physical and mental component summary measure (SF-36), emotional distress (HADS), and perceived stress). Additionally, we used these clinical parameters to predict HCC change over time.

Results

The median HCC was 22.3 pg/mg hair (23.5 interquartile range). In multivariable linear regression analyses an association was observed between log-transformed HCC and BMI (β 0.171, p=0.037), respiratory rate (β 0.194, p=0.016), and the physical summary score (β -0.163, p=0.054). Independent predictors of log-transformed HCC change after 12 weeks were mental summary score (β -0.200, p=0.019) and diastolic blood pressure (β -0.171, p=0.049).

Conclusions

In patients with structural heart disease a positive association exists between HCC and BMI. Mental health status may predict a change in long-term cortisol over time.

Introduction

Chronic stressors such as anxiety, depression, and hopelessness are thought to be important risk factors for cardiovascular disease (CVD).[1-5] However, little is known about the role of stressors and the human stress response in structural heart disease.

The human stress response is mainly mediated by two classes of hormones: glucocorticoids and catecholamines. Cortisol, the main glucocorticoid hormone in humans, is produced under influence of the hypothalamic-pituitary-adrenal axis (HPA-axis)[1] and affects virtually all aspects of physiology with mediating effects in inflammation, metabolism, and behavior. An extreme excess of cortisol (i.e., Cushing's syndrome) is associated with an increase of all features of the metabolic syndrome and cardiovascular disease risk.[6] In research, cortisol levels have mostly been measured in blood, saliva and urine, which reflect a time-point measurement of usually up to 24 hours of cortisol exposure. However, cortisol levels are highly variable due to acute stress, the diurnal rhythm, pulsatile secretion, and day-to-day fluctuations[7-9] Therefore, measurements in body fluids are thought to be of limited value in evaluating long-term cortisol exposure.

In the past few years, scalp hair analysis has been validated as a method to evaluate long-term cortisol levels. Scalp hair grows at a rate of approximately 1 cm per month, therefore one cm hair represents cumulative cortisol exposure of one month. This technique can be used to create retrospective timelines of cortisol exposure by separating hair samples into segments and analyzing these separately.[10,11] Hair cortisol concentrations (HCC) have been associated with a wide range of somatic and mental health outcomes.[7,12] Of note, increased HCC has been associated with cardiovascular disease,[13] metabolic syndrome[14] and obesity[15,16] and may therefore provide a novel treatment target in cardiovascular risk management.

The aim of the current study is to investigate the cross-sectional association between cortisol levels, measured in scalp hair, and several clinically relevant physical and psychological characteristics, such as: exercise tolerance, blood pressure, body mass index (BMI), NT-proBNP, perceived stress, and quality of life in patients with structural heart disease. Additionally, we investigated whether these characteristics act as predictors for cortisol change over a period of 12-weeks. We hypothesized that higher long-term cortisol levels are associated with an adverse clinical status and lower quality of life.

Methods

Setting

The current study was part of a single-center pragmatic randomized controlled trial on the effectiveness of an online mindfulness training compared to routine medical care at the outpatient cardiology clinic of the Erasmus MC, Rotterdam, The Netherlands. Ethical approval was obtained from the local Medical Ethics Committee and written consent was obtained from each par-

ticipant before baseline measurements. Randomization was performed by dedicated computer software (2:1 ratio, blocks of 12 to receive mindfulness training or usual care (UC)). The study was registered at the Dutch trial register, NTR3453, http://www.trialregister.nl.

Briefly, adult patients with structural heart disease (including cardiomyopathies (CMP), congenital (ConHD), ischemic and valvular heart disease) visiting the outpatient clinic were eligible for inclusion. In the current sub-study, hair samples were collected if there was sufficient hair at the posterior vertex (≥4 centimeter(cm)).

Study variables

In order to document and adjust for baseline levels, traditional cardiovascular risk factors and demographics were determined: age, smoking, type of structural heart disease, and employment status.

Outcome measures

Outcome measures of all patients took place at pre- (T0) and post-intervention (12 weeks online mindfulness therapy,T1).

Blood sampling laboratory tests

Peripheral venous blood samples were obtained from all patients. Levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and creatinin were measured. We used the Elecsys system (Roche Diagnostics, Basel, Switzerland) to determine the NT-proBNP levels (normal values ≤ 14pmol/L).

Hair cortisol

At T1, hair samples were taken from the study participants. The samples consisted of approximately 100-150 hairs and were taken from the posterior vertex as close to the scalp as possible. The length of the hair had to be at least 4 cm, representing the 4 months since the start of the study. The samples were cut in 2 segments (see Figure 1): the proximal 1 cm (representing mean cortisol levels in the month before the T1 visit) and a section of 1 cm at the 4th cm from the scalp (representing the cortisol levels in the month before T0). The hair sample segments were prepared according to a standardized protocol that has been described in detail.[11,17] Briefly, approximately 15 mg of hairs was weighed per hair segment, and put in a glass vial. Care was taken to make sure two hair segments did not differ in weight more than 1 mg within a subject.

After this, hair segments were finely minced using small scissors. Cortisol extraction took place in methanol, during 16 hours at 52 degrees Celsius while the samples were being gently shaken. After extraction, the methanol was transferred to clean glass tubes and evaporated under nitrogen stream. Samples were reconstituted in 250 µL of phosphate buffered saline (pH 8.0), and HCC were analyzed using a commercially available ELISA kit for cortisol in saliva (DRG Instruments GmbH, Marburg, Germany).

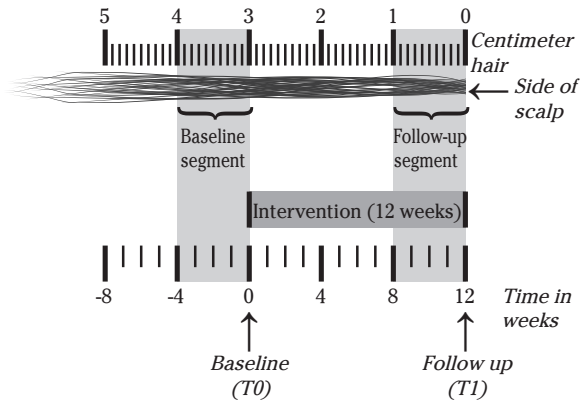

Figure 1. *Hair sample and corresponding timeline*

Clinical assessment

Physical examination included blood pressure, height, weight, respiratory rate, and heart frequency. The 6-minute walk test was used to measure overall physical fitness. The test was performed in a 20-meter-long corridor. We used colored pawns to indicate the 'start' and 'finish' marks.

Quality of Life (QoL)

To evaluate subjective health status, as a measure of quality of life, we used the Short Form Health Survey-36 (SF-36).[18] The SF-36 consist of 8 health status domains and within each domain the raw scores are summed and divided by the range of the scores. Subsequently transforming these raw scores will results in a score from 0 to 100.[18] Higher scores indicate better functioning on each subdomain. We calculated the mental component summary measure (MCS), which consisted of the subdomains: vitality, social functioning, role-emotional functioning and mental health, and we calculated the physical component summary measure (PCS), which consisted of the subdomains physical functioning, role-physical functioning, bodily pain, general health.[19]

Emotional distress

For emotional distress we used the Hospital Anxiety and Depression scale (HADS) to measure symptoms of anxiety and depression.[20] The questionnaire consist of 14-items and is divided in subscales on anxiety and depression. A 3 point Likert scale is used, with higher scores representing a greater level of emotional distress.

Stress

For the evaluation of perceived stress we used the Dutch version of the original 14 item Perceived Stress Scale (PSS).[21] This scale assesses ''the degree to which individuals appraise situations in their lives as stressful"[21] on a 5-point Likert scale, with higher scores indicating higher levels of

perceived stress (0=never, 4=very often). A total perceived stress score is generated by the sum of the individual items.

Statistical analysis

We present means ± SD for normally distributed characteristics. Non-normal distributed data were presented by median values (interquartile range (IQR)). HCC were not normally distributed and were therefore log-transformed for a normal-distribution for further statistical analyses. Associations between log-transformed HCC and patient characteristics were performed by analysis of variance and linear regression analysis.

First, we conducted linear regression analysis to evaluate the association between log-transformed HCC and age, sex, corticosteroid use, BMI, exercise tolerance, blood pressure, NT-proBNP levels, PCS, MCS, emotional distress and perceived stress. We performed multivariable linear regression analyses in which we adjusted for age, sex and BMI (model 1) and subsequently for age, sex, BMI and use of corticosteroids (model 2).

Second, we evaluated potential predictors of the change in HCC between the hair segments corresponding to baseline and 12 week follow-up. The delta of the log-transformed HCC was the dependent variable which was calculated by subtracting the cortisol level at T0 (baseline) from the T1(post-intervention) value. We conducted univariable linear regression analyses with age, sex, corticosteroid use, BMI, exercise tolerance, blood pressure, NT-proBNP levels, PCS, MCS, emotional distress, perceived stress and mindfulness training as independent variables.. Multivariable linear regression analyses were performed in which we adjusted for age, gender and treatment allocation.

All statistical tests were two-sided and a p-value less than 0.05 was considered to indicate statistical significance. Effect estimates of regression models are expressed as standardized regression coefficients. All data were analyzed with IBM SPSS Statistics version 21.0 (IBM Corp., Somers, NY).

Results

Characteristics of study participants

The main study comprised 324 participants. After 12 weeks, 261 (80%) returned for follow-up, during which 260 consented to provide a scalp hair sample (99.6%). We excluded 90 participants with a hair length of less than 4 cm. Of the 170 available scalp hair samples with sufficient length, a total of 151 cortisol levels could be measured above the detection limit in the distal segment, corresponding to the month before treatment, and these were included in the baseline analysis (Figure 2). In 141 hair samples, cortisol could be measured above the detection limit in both the distal and proximal hair segments. These samples were included in the analyses of change in HCC over time. The patient characteristics of the current study are shown in Table 1. The

majority of the 151 included study participants were female (62.9%), and the mean(SD) age was 41.3(14.2) years. More than half of the patients were diagnosed with congenital heart disease (52.3%) whereas the others had cardiomyopathy (24.5%), valvular disease (17.2%), or IHD (6.0%).

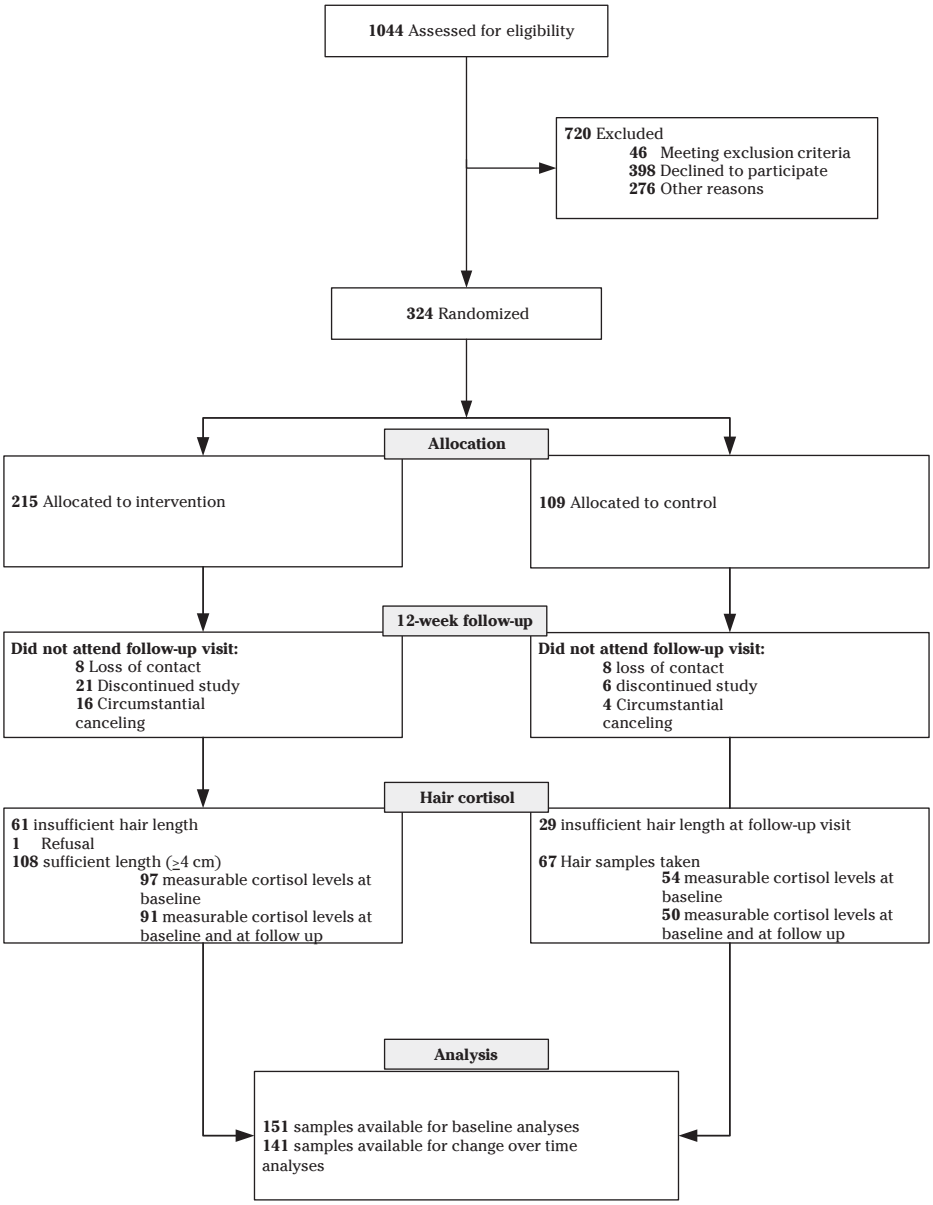

Figure 2. *Flowchart*

Table 1. *Baseline characteristics, for the total group and stratified by type of structural heart disease*

	Total Sample N=151	CONG N= 79	CMP N=37	VALV N=26	IHD N=9
Demographics					
Age (years), mean (SD)	41.3 (14.2)	35.2 (11.9)	49.1 (13.6)	44.0 (14.0)	55.3 (7.8)
Female (%)	62.9	72.2	48.6	65.4	33.3
Physiological parameters					
Heart rate (beats/min), mean (SD)	68 (11)	70 (12)	65 (9)	67 (11)	70 (11)
Systolic blood pressure (mm Hg), mean (SD)	126 (15)	124 (15)	129 (16)	129 (16)	132 (18)
Diastolic blood pressure (mm Hg), mean (SD)	78 (10)	77 (12)	80 (8)	78(10)	79 (7)
Resting respiratory rate (breaths/min), mean (SD)	15 (2)	15 (2)	15 (2)	15 (2)	16 (3)
Body mass index (kg/m^2), mean (SD)	25.5 (4.9)	25.0 (5.2)	26.5 (4.4)	24.2 (3.6)	29.2 (6.2)
Exercise tolerance					
6 minute walk test distance (meters), mean (SD)	533 (82)	538 (84)	526 (90.3)	539 (59)	506 (88)
Laboratory measurements					
NT-proBNP, median (IQR), pmol/L	16.1 (26.7)	13.8 (16.3)	40.4 (46.9)	15.1 (24.8)	12.1 (16.8)
Creatinine, median (IQR), µmol/L	75 (19)	73 (17)	75 (17)	69.5 (24)	87 (17)
Cortisol at baseline, median, (IQR), pg/mg hair	22.3 (23.5)	23.2 (26.7)	26.6 (23.6)	21.5 (26.3)	19.5 (23.3)
Previous cardiac interventions*, mean (SD)	1.5 (1.2)	1.8 (1.3)	0.8 (0.9)	1.3 (0.9)	1.9 (1.2)
ICD (%)	9.9	3.8	27.0	0	22.2
PM (%)	6.0	10.1	0	3.8	0
Hair characteristics					
Hair coloring	37.1	36.7	43.2	30.8	33.3
Hair bleaching	7.9	12.7	0	7.7	0
Use of hair products	51.0	41.8	59.5	57.7	44.4
Frequency of hair washing (>2x/week)	60.1	67.9	60.0	34.6	66.7
Current medication (%)					
Beta-blocker	33.8	22.8	48.6	30.8	77.8
Statin	14.6	1.3	16.2	23.1	100
Aspirin	14.6	10.1	13.5	11.5	66.7
Ace-inhibitor	23.8	20.3	27.0	19.2	55.6
Angiotensin II antagonist	10.6	10.1	10.8	11.5	11.1
Calcium channel blocker	6.6	1.3	8.1	15.4	22.2
Nitrate	0.7	0	0	0	11.1
Cardiac glycoside	4.0	5.1	0	7.7	0
Diuretic	11.9	7.6	10.8	15.4	44.4
Anticoagulant	29.8	22.8	18.9	50	77.8
Antidepressant	4.0	3.8	5.4	0	11.1
Tranquilizer	2.0	2.5	2.7	0	0
Other	35.8	32.9	35.1	30.8	77.8
Intoxication					
Current smoking (%)	15.9	12.6	27.0	15.4	0

Abbreviations: SD, standard deviation; NT-proBNP, N-terminal pro-brain natriuretic peptide; IQR, interquartile range; ICD, implantable cardioverter-defibrillator; PM, pacemaker
**Surgical or percutaneous interventions*

Cortisol levels stratified by structural heart disease

The distribution of the cortisol levels among the types of structural heart disease can be seen in Figure 3. Patients with CMP had the highest median HCC (median 26.8, IQR: 23.6), and valve disease the lowest (median 21.5, IQR: 26.3). Between the four groups, no significant difference was found (p= 0.944).

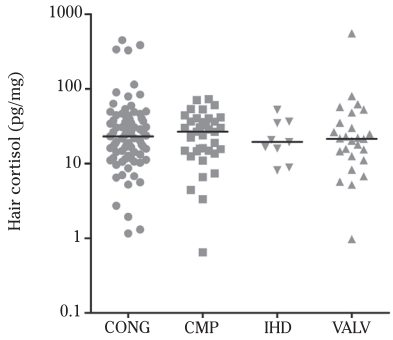

Figure 3. *Individual hair cortisol levels at baseline, stratified by structural heart disease*
Note: logarithmic scale. Horizontal lines represent medians.
Abbreviations: CONG, congenital heart disease; CMP, cardiomyopathy; IHD, ischemic heart disease; VALV, valvular heart disease.

Cortisol levels and physiological parameters (including exercise tolerance)

Table 2 shows the results of the univariable and multivariable linear regression analyses. The univariable analyses of HCC showed a positive association with BMI (estimate: 0.196, p=0.003), respiratory rate (estimate: 0.236, p=0.004) and use of corticosteroids (estimate: 0.241, p=0.003). After adjustment for age and sex, the correlation between HCC and BMI remained significant (estimate: 0.223, p=0.020). After adjustment for age, sex and BMI, the correlation between HCC and respiratory rate remained significant (estimate: 0.203, p=0.014). In the final adjusted model, when corticosteroid use was added, BMI (estimate: 0.171, p=0.037) and respiratory rate (estimate: 0.194, p=0.016) remained significant. No significant correlations were found with other physiological parameters (Table 2).

Cortisol levels and subjective parameters (perceived/emotional (dis)stress)

In table 2, the correlations between HCC and subjective outcomes can be seen. In the unadjusted model, a negative correlation was found between HCC and the PCS of the SF-36 (estimate: -0.209, p=0.010), indicating a lower self-reported physical functioning in participants with higher HCC. After adjustment for age, sex and BMI, the correlation remained significant (estimate: -0.210, p=0.013). In the fully adjusted model when age, sex, BMI and corticosteroid use were entered, a borderline significant inverse association was found on PCS (estimate: -0.163, p= 0.054). No significant associations were found between HCC and the other subjective outcomes (Table 2).

Table 2. *Correlations between patient characteristics and hair cortisol levels at baseline (n=151)*

	Univariable analysis		Multivariable model 1[a]		Multivariable model 2[b]	
	Coefficient[c]	**p-value**	**Coefficient[c]**	**p-value**	**Coefficient[c]**	**p-value**
Age	0.038	0.645	-0.025	0.767	-0.044	0.600
Sex (female vs. male)	-0.074	0.366	-0.063	0.452	-0.105	0.202
Use of corticosteroids[d]	0.241	0.003	0.223	0.005	0.223	0.005
Physiological parameters						
BMI	0.196	0.016	0.196	0.020	0.171	0.037
6 minute walk test	-0.049	0.548	-0.022	0.817	0.019	0.839
Systolic blood pressure	0.120	0.144	0.065	0.458	0.076	0.374
Diastolic blood pressure	0.124	0.129	0.080	0.347	0.097	0.240
Respiratory rate	0.236	0.004	0.203	0.014	0.194	0.016
Heart frequency	0.132	0.105	0.117	0.157	0.089	0.269
NT-ProBNP	-0.046	0.574	-0.047	0.599	-0.040	0.646
Subjective parameters						
SF-36: PCS	-0.209	0.010	-0.210	0.013	-0.163	0.054
SF-36: MCS	-0.006	0.945	-0.009	0.915	-0.013	0.875
HADS: anxiety	-0.063	0.439	-0.066	0.419	-0.049	0.539
HADS: depression	0.145	0.076	0.130	0.112	0.120	0.133
Perceived stress scale	0.031	0.710	0.037	0.656	0.030	0.709

Abbreviations: BMI, body mass index; n/a, not applicable; NT-proBNP, N-terminal pro-brain natriuretic peptide; SF-36, Short-Form Health Survey 36; PCS, physical component summary measure; MCS, mental component summary measure; HADS, Hospital Anxiety and Depression Scale.

Statistically significant associations are formatted bold.

[a]adjusted for age, sex and BMI. When age, sex or BMI was the independent variable, the multivariable model was not adjusted for it.

[b]adjusted for age, sex, BMI and corticosteroid use. When age, sex, BMI, or corticosteroids use was the independent variable, the multivariable model was not adjusted for it.

[c]standardized regression coefficient

[d]includes inhalation, nasal, systemic and topical corticosteroids

Predictors for change of cortisol levels

On average, HCC decreased in both study groups during follow-up from the hair segment corresponding to the month before treatment, to the hair segment in the last month of treatment (P<0.001, Figure 4).

Table 3 shows the results of the univariable and multivariable linear regression analyses of the association between baseline characteristics and change of HCC. Diastolic blood pressure was negatively associated with HCC (estimate: -0.181, p=0.032), indicating that HCC decreased more in individuals with higher diastolic blood pressure. After adjustment for age, sex and treatment allocation the association remained significant (estimate: -0.171, p=0.049).

Analyses in the subjective outcome parameters showed an independent association between the SF-36 MCS and HCC (estimate: -0.209, p=0.013), indicating that HCC decreased more in patients with a better MCS. After adjustment for age, sex and treatment allocation, the association was still significant (estimate: -0.200, p=0.019). No effect of mindfulness training was seen (Table 3).

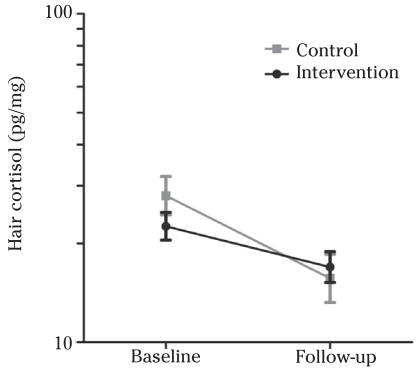

Figure 4. *Change of hair cortisol levels between baseline and 12-week follow-up*
Note: logarithmic scale. Whiskers represent standard error of the mean.

Table 3. *Correlations between patient characteristics and the change in hair cortisol levels over time (n=141)*

	Univariable analysis		Multivariable model 1[a]	
	Coefficient[b]	p-value	Coefficient[b]	p-value
Age	-0.068	0.423	-0.075	0.442
Sex (female vs. male)	-0.020	0.817	-0.028	0.745
Use of corticosteroids	-0.075	0.376	-0.072	0.400
Treatment allocation (intervention vs control)	0.158	0.062	0.156	0.066
Physiological parameters				
Body mass index	-0.107	0.208	-0.100	0.250
6 minute walk test	0.080	0.347	0.758	0.450
Systolic blood pressure	*-0.129*	*0.129*	*-0.135*	*0.125*
Diastolic blood pressure	*-0.181*	*0.032*	*-0.171*	*0.049*
Respiratory rate	*-0.063*	*0.460*	*-0.050*	*0.558*
Heart frequency	*-0.135*	*0.109*	*-0.137*	*0.108*
NT-ProBNP	*-0.057*	*0.507*	*-0.042*	*0.639*
Subjective parameters				
SF-36: PCS	*0.036*	*0.674*	*0.012*	*0.546*
SF-36: MCS	*-0.209*	*0.013*	*-0.200*	*0.019*
HADS: anxiety	0.079	0.352	0.089	0.297
HADS: depression	0.041	0.627	0.042	0.620
Perceived stress scale	0.065	0.441	0.064	0.451

Abbreviations: BMI, body mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; SF-36, Short-Form Health Survey 36; PCS, physical component summary measure; MCS, mental component summary measure; HADS, Hospital Anxiety and Depression Scale
[a]adjusted for age, sex and group allocation. If age, sex, or group allocation was the independent variable, the multivariable model was not adjusted for it
[b]standardized regression coefficient

Discussion

In this study we aimed to investigate the association between HCC and several clinical objective and subjective parameters and identify potential predictors for long-term change in cortisol levels in patients with structural heart disease. Our results showed that higher hair cortisol concentrations (HCC) were associated with higher BMI, higher respiratory rate and a lower score on the physical component summary score of the SF36. No association was found with perceived stress. After 12 weeks, lower HCC were found in the total study group. A more favorable baseline mental status (higher mental component summary score on the SF36) and higher baseline diastolic blood pressure predicted a stronger decrease in HCC after 12 weeks follow-up, whereas no significant effect of mindfulness training on the HCC was found.

In our study we used cortisol levels from hair samples, which are suitable to study effects of long-term cortisol exposure on clinical characteristics. Until now, only a few cross-sectional studies have been reported of HCC in individuals with CVD. In a recent report, Manenschijn et al.[13] showed that higher long-term cortisol levels measured in scalp hair are associated with a higher presence of CVD in an elderly population. Other studies have reported on the association between elevated cortisol levels and risk of ischemic heart disease and acute myocardial infarction.[22,23] In the present study we did not investigate cardiovascular risk but these recent studies indicate that HCC may be used to determine whether individuals are at increased risk of developing a cardiovascular related event.

Our results show a positive association between HCC and BMI, which may represent a metabolically less favorable phenotype in individuals with a higher long-term cortisol exposure. The association between cortisol and adiposity has been debated for a long time, with most studies showing a relative increase in urinary cortisol, but a decrease or unaffected cortisol in time-point measures (blood or saliva).[24] However, we and others have reported increased HCC in association with increased BMI and abdominal adiposity,[14-16,25-27] supporting the hypothesis that a slight increase in long-term cortisol exposure is associated with increased adiposity. Our results indicate that also in patients with structural heart disease long-term cortisol is associated with increased BMI, and could therefore modulate CVD risk.

In the present study no association was found between perceived stress and HCC. Interestingly, we found a borderline significant negative association on the physical component summary measure (PCS) of the SF36, whereas we did not find an association on actual physical functioning as measured with the 6MWT. This may suggest that long-term cortisol levels in the current population are affected more by physiological stress than psychological stress. Although we had no HCC levels for matched controls without structural heart disease in the present study, HCC does seem to be higher compared to our previously published healthy controls.[15] The PCS consists of several subjective components assessing physical functioning in daily life. A single objective measurement may be less sensitive in assessing the impact of physical limitation in daily life. There are limited reports that evaluate the relation between QoL physical functioning and HCC.

Feller et al.[28] found no association between HCC and the physical health score (measured with the SF-12). That study comprised of mainly older adults, whereas our population had a mean age of a little over 40 years. It is not unimaginable that limited physical functioning at younger age due to underlying structural heart disease causes more (physical or psychological) stress than it would do at an older age. In particular younger adults with complex congenital heart disease suffer from limited exercise capacity compared to their healthy counterparts.[29]

We observed a decrease in HCC after 12 weeks in both study groups. In contrast to previous studies, we did not observe a wash-out effect in the hair analysis that could limit retrospective assessment of cortisol levels.[30,31] Using the same hair sample to determine cortisol levels at T0 and T1, HCC turned out to be higher at baseline. This shows that a potential wash-out effect in the distal hair segments was not present in the current population. A decrease in HCC over time in both the mindfulness group and controls may be explained by a study effect. Patients entering the study received extra attention apart from their visit to the cardiologist. The placebo effect of the extra attention could possibly have led to less stress.

Interestingly, mental status was an independent predictor of lower cortisol levels after 12 weeks. Some reports suggest a positive relation between high cortisol levels and mental health status in individuals suffering from stressful conditions, such as depression and loneliness,[7,32,33] thus we cannot rule out a potential modifying effect on stress. However, most of these studies did not use HCC and are therefore subject to the limitations of time-point and short-term cortisol measurements.

The decrease in HCC after 12 weeks could not be explained by allocation to mindfulness training. Until now, there is only one report that has described the effect of mindfulness training on HCC. In a pilot study on smoking cessation, mindfulness training was compared with cognitive-behavioral therapy.[34] In that study, Goldberg et al. reported lower HCC in the total sample after the interventions. The investigators suggest that participation in a mindfulness training may be independently associated with lower HCC. However, almost 75% of study participants quit smoking and this may have contributed to the decrease in HCC, since smoking has been found to be associated with higher cortisol levels.[28,35] Further studies in this field have to be awaited.

Limitations of the current study must be addressed. First, the current study was a sub study of a larger randomized controlled trial and was therefore not powered to evaluate the effect of the online mindfulness training on cortisol levels. Secondly, we evaluated cortisol levels taken from hair samples at 12 weeks, which could have underestimated the full effect of the mindfulness training since the proximal hair fragment comprises the period from 8-12 weeks of treatment. Finally, all structural heart disease patients were included from the outpatient clinic of cardiology, not focusing on patients with psychological or psychiatric comorbidity. This may explain why we did not find any associations between HCC and psychological outcomes. However, we found evidence that a favorable mental status is associated with a stronger decrease in HCC. Conceivably, mental status affects the dynamic changes in long-term cortisol secretion.

The association between higher diastolic blood pressure and a stronger decrease in HCC over time is an intriguing finding. It is conceivable that a higher blood pressure, a known tissue effect of cortisol, represents a higher cortisol exposure. Furthermore, the higher diastolic blood pressure may represent a state of acute stress in part of the participants, analogous to the so-called white coat hypertension,[36] which may be reflected in HCC. However, with both explanations, one would expect a positive correlation between diastolic blood pressure and HCC at baseline, which we did not find.

Notably, participants who used corticosteroids had higher HCC. We did not have sufficient data to perform a subgroup analysis into the different exogenous corticosteroids. Most administered corticosteroids may cause a slight suppression of the HPA-axis, and would therefore be expected to lower long-term cortisol secretion.[37]. However, corticosteroids that are administered may cross-react in immunoassays such as used in the present study, and thereby erroneously increase HCC. Furthermore, patients using corticosteroids may present a subpopulation with a higher disease burden, which may in turn lead to higher endogenous cortisol production. Our results corroborate that exogenous corticosteroids are an important confounder in hair cortisol measurements, and should be taken into account in studies that use HCC.

In conclusion, our results show that long-term hair cortisol levels are associated with BMI and respiratory rate in patients with structural heart disease. Additionally, mental status was an independent predictor of change in hair cortisol levels over a period of 12 weeks.

The evaluation of HCC can provide a unique tool in the assessment of long-term cortisol levels and their changes over time in intervention studies. Further studies are needed to evaluate which interventions can modify long-term cortisol exposure. The level of HCC may provide additional information in the identification of individuals at risk of developing cardiovascular events. Therefore, long-term prospective studies are needed to evaluate the additional role of chronically elevated long-term cortisol levels in patients with regard to cardiovascular risk management, and possible (preventive) treatment strategies.

References

1. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet*. Sep 22 2007;370(9592):1089-1100.
2. Hamer M, Molloy GJ, Stamatakis E. Psychological distress as a risk factor for cardiovascular events: pathophysiological and behavioral mechanisms. *J Am Coll Cardiol*. Dec 16 2008;52(25):2156-2162.
3. Richardson S, Shaffer JA, Falzon L, Krupka D, Davidson KW, Edmondson D. Meta-analysis of perceived stress and its association with incident coronary heart disease. *Am J Cardiol*. Dec 15 2012;110(12):1711-1716.
4. Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet*. Sep 11-17 2004;364(9438):953-962.
5. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J Am Coll Cardiol*. Mar 1 2005;45(5):637-651.
6. Arnaldi G, Angeli A, Atkinson AB, et al. Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab*. Dec 2003;88(12):5593-5602.
7. Staufenbiel SM, Penninx BW, Spijker AT, Elzinga BM, van Rossum EF. Hair cortisol, stress exposure, and mental health in humans: a systematic review. *Psychoneuroendocrinology*. Aug 2013;38(8):1220-1235.
8. Wester VL, Lamberts SW, van Rossum EF. Advances in the assessment of cortisol exposure and sensitivity. *Curr Opin Endocrinol Diabetes Obes*. Aug 2014;21(4):306-311.
9. Young EA, Abelson J, Lightman SL. Cortisol pulsatility and its role in stress regulation and health. *Front Neuroendocrinol*. Jul 2004;25(2):69-76.
10. Gow R, Thomson S, Rieder M, Van Uum S, Koren G. An assessment of cortisol analysis in hair and its clinical applications. *Forensic Sci Int*. Mar 20 2010;196(1-3):32-37.
11. Manenschijn L, Koper JW, Lamberts SW, van Rossum EF. Evaluation of a method to measure long term cortisol levels. *Steroids*. Sep-Oct 2011;76(10-11):1032-1036.
12. Russell E, Koren G, Rieder M, Van Uum S. Hair cortisol as a biological marker of chronic stress: current status, future directions and unanswered questions. *Psychoneuroendocrinology*. May 2012;37(5):589-601.
13. Manenschijn L, Schaap L, van Schoor NM, et al. High long-term cortisol levels, measured in scalp hair, are associated with a history of cardiovascular disease. *J Clin Endocrinol Metab*. May 2013;98(5):2078-2083.
14. Stalder T, Kirschbaum C, Alexander N, et al. Cortisol in hair and the metabolic syndrome. *J Clin Endocrinol Metab*. Jun 2013;98(6):2573-2580.
15. Wester VL, Staufenbiel SM, Veldhorst MA, et al. Long-term cortisol levels measured in scalp hair of obese patients. *Obesity (Silver Spring)*. Sep 2014;22(9):1956-1958.
16. Chan J, Sauve B, Tokmakejian S, Koren G, Van Uum S. Measurement of cortisol and testosterone in hair of obese and non-obese human subjects. *Exp Clin Endocrinol Diabetes*. Jun 2014;122(6):356-362.
17. Sauve B, Koren G, Walsh G, Tokmakejian S, Van Uum SH. Measurement of cortisol in human hair as a biomarker of systemic exposure. *Clin Invest Med*. 2007;30(5):E183-191.
18. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. Jun 1992;30(6):473-483.
19. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. Mar 1993;31(3):247-263.
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. Jun 1983;67(6):361-370.
21. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. Dec 1983;24(4):385-396.
22. Pereg D, Gow R, Mosseri M, et al. Hair cortisol and the risk for acute myocardial infarction in adult men. *Stress*. Jan 2011;14(1):73-81.
23. Reynolds RM, Labad J, Strachan MW, et al. Elevated fasting plasma cortisol is associated with ischemic heart disease and its risk factors in people with type 2 diabetes: the Edinburgh type 2 diabetes study. *J Clin Endocrinol Metab*. Apr 2010;95(4):1602-1608.
24. Bjorntorp P, Rosmond R. Obesity and cortisol. *Nutrition*. Oct 2000;16(10):924-936.
25. Manenschijn L, van Kruysbergen RG, de Jong FH, Koper JW, van Rossum EF. Shift work at young age is associated with elevated long-term cortisol levels and body mass index. *J Clin Endocrinol Metab*. Nov 2011;96(11):E1862-1865.
26. Stalder T, Steudte S, Alexander N, et al. Cortisol in hair, body mass index and stress-related measures. *Biol Psychol*. Jul 2012;90(3):218-223.

27. Veldhorst MA, Noppe G, Jongejan MH, et al. Increased scalp hair cortisol concentrations in obese children. *J Clin Endocrinol Metab*. Jan 2014;99(1):285-290.
28. Feller S, Vigl M, Bergmann MM, Boeing H, Kirschbaum C, Stalder T. Predictors of hair cortisol concentrations in older adults. *Psychoneuroendocrinology*. Jan 2014;39:132-140.
29. Kempny A, Dimopoulos K, Uebing A, et al. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life—single centre experience and review of published data. *Eur Heart J*. Jun 2012;33(11):1386-1396.
30. Dettenborn L, Tietze A, Bruckner F, Kirschbaum C. Higher cortisol content in hair among long-term unemployed individuals compared to controls. *Psychoneuroendocrinology*. Oct 2010;35(9):1404-1409.
31. Kirschbaum C, Tietze A, Skoluda N, Dettenborn L. Hair as a retrospective calendar of cortisol production-Increased cortisol incorporation into hair in the third trimester of pregnancy. *Psychoneuroendocrinology*. Jan 2009;34(1):32-37.
32. Hackett RA, Hamer M, Endrighi R, Brydon L, Steptoe A. Loneliness and stress-related inflammatory and neuroendocrine responses in older men and women. *Psychoneuroendocrinology*. Nov 2012;37(11):1801-1809.
33. Penninx BW, Beekman AT, Bandinelli S, et al. Late-life depressive symptoms are associated with both hyperactivity and hypoactivity of the hypothalamo-pituitary-adrenal axis. *Am J Geriatr Psychiatry*. Jun 2007;15(6):522-529.
34. Goldberg SB, Manley AR, Smith SS, et al. Hair cortisol as a biomarker of stress in mindfulness training for smokers. *J Altern Complement Med*. Aug 2014;20(8):630-634.
35. Badrick E, Kirschbaum C, Kumari M. The relationship between smoking status and cortisol secretion. *J Clin Endocrinol Metab*. Mar 2007;92(3):819-824.
36. Verdecchia P, Staessen JA, White WB, Imai Y, O'Brien ET. Properly defining white coat hypertension. *Eur Heart J*. Jan 2002;23(2):106-109.
37. Bornstein SR. Predisposing factors for adrenal insufficiency. *N Engl J Med*. May 28 2009;360(22):2328-2339.

Part II

Systematic reviews of intervention studies

Chapter 6

Effects of lifestyle-related interventions on blood pressure in the low and middle income countries: systematic review and meta-analysis

Baena CP,Younge JO, Olandoski M*, Buitrago-Lopez A, Darweesh SK, Campos N, Sedaghat S, Sajjad A, van Herpt TT, Freak-Poli R, van den Hooven E, Felix JF, Faria-Neto JR, Chowdhury R, Franco OH.*

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**Equal contributions*

Abstract

Despite the overwhelming evidence supporting the effectiveness of antihypertensive medication, hypertension remains poorly controlled in low and middle income countries (LMIC). Lifestyle intervention studies reporting effects on blood pressure published from January 1977 to September 2012 were searched on various database. From the 6211 references identified 52 were included in the systematic review (12 024 participants) and 43 were included in the meta-analysis (in total 6779 participants). We calculated and pooled effect sizes in mmHg with random-effects models. We grouped interventions into behavioral counseling (1831 participants), dietary modification (1831 participants), physical activity (1014 participants) and multiple interventions (2103 participants). Subgroup analysis and meta-regression were used to evaluate origins of heterogeneity. Lifestyle interventions significantly lowered blood pressure levels in LMIC populations, including in total 6779 participants. The changes achieved in SBP (95% confidence interval) were: behavioral counseling -5.4 (-10.7, -0.0) mmHg, for dietary modification -3.5 (-5.4, -1.5) mmHg, for physical activity -11.4 (-16.0, -6.7) mmHg and for multiple interventions -6.0 (-8.9, -3.3) mmHg. The heterogeneity was high across studies and the quality was generally low. Subgroup analyses showed smaller samples reporting larger effect sizes; intervention lasting less than 6 months showed larger effect sizes and intention-to-treat analysis showed smaller effect sizes. Lifestyle interventions may be of value in preventing and reducing blood pressure in LMICs. Nevertheless, the overall quality and sample size of the studies included were low. Improvements in the size and quality of studies evaluating lifestyle interventions are required.

Introduction

Cardiovascular disease (CVD) remains the leading cause of death and disability worldwide particularly in low and middle income countries (LMIC).[1,2] Although improvements in prevention and care among high income countries have resulted in large reductions of CVD mortality in the last decade, in LMICs, the prevalence of the established CVD risk factors at all ages and the CVD disease burden are still on the rise.[3] Blood pressure remains one of the major modifiable vascular risk factors.[4] Aetiology, prevention and management of high blood pressure have been widely studied.[5,6] However, high blood pressure remains poorly controlled and the general awareness among individuals and populations with hypertension, especially in the LMICs, is considerably low.[7,8] This is of particular importance as high levels of blood pressure continues to be a top attributable cause of overall death worldwide, contributing approximately 14% of all global premature deaths.[1,9] Furthermore, 80% of the global burden of death attributable to high blood pressure occur in LMIC,[10] highlighting the urgent need for more intensive efforts to reduce the disease and mortality burden secondary to hypertension in these settings.[11]

To alleviate such overwhelming burden associated with blood pressure, effectiveness of drug therapy has been tested and demonstrated in the LMI countries. However, its availability, affordability and, therefore, adherence to treatment poses a significant challenge.[12,13] By contrast, safe, cost-effective and easily scalable lifestyle interventions are generally considered the first choice to prevent and control optimum blood pressure.[14] Despite huge potentials offered by these interventions particularly for the LMI nations, evidence to support a benefit to effectively reduce blood pressure in the LMIC is scarce and inconsistent. Currently the majority of guidelines for CVD prevention in LMICs rely on evidence gathered mainly from populations derived from high income countries. How applicable they are for the local specific populations remains unknown.[15-17]

We report a systematic review and meta-analysis to summarize and quantify the available evidence on the effects of lifestyle-related interventions conducted in the LMI countries. Additionally, we have evaluated whether the effects may vary across a wide range of study-level characteristics including ethnicity, types of interventions, geographical location and age.

Methods

Our systematic review was conducted with a predefined protocol in accordance with PRISMA guidelines and an extension of the CONSORT statement[18] to trials evaluating non pharmacological treatments.[19,20] We conducted electronic searches through Medline-Pubmed, Embase, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, Web of Science, Scopus, Scielo and LILACS (index of scientific and technical literature of Latin America and the Caribbean), searching for suitable references published between January 1977 and September,

2012 (date last time the search was run). We used combinations of Medical Subject Headings (MeSH) and free text words that included search terms related to the population (e.g. developing country or LMIC) and lifestyle interventions, which were combined with search terms related to the outcomes (e.g. blood pressure, hypertension). The detailed search strategy and countries included are presented in Appendix 1 (http://links.lww.com/HJH/A333). In order to get reports from parallel controlled studies, we sought for randomized controlled trials, clinical trials and community trials. Clinical trials and community trials were included regardless of randomization description in title and abstract. If data were unavailable, or when local libraries could not retrieve the full paper, authors were contacted by e-mail. No language restriction was applied and studies were translated by native speakers experienced in the health field. In the case of multiple publications, the most recent and complete report was included.

Study selection

Two authors independently reviewed each title and abstract to determine whether the study met the inclusion criteria. We sought for studies with a parallel controlled design evaluating nonpharmacological (e.g. dietary modifications, physical activity or educational/behavioral counseling) interventions among adult populations from LMICs, reporting blood pressure levels (both SBP and/or DBP) in mmHg at baseline and after intervention in the same sample. We excluded studies if they were: conducted solely in developed (high-income) countries according to the World Bank incoming group list used by WHO (eAppendix 1, http://links.lww.com/HJH/A333); cost-effectiveness studies; assessed effects of a pharmacological intervention; involved pregnant women; animal studies and, if the intervention lasted less than 8 weeks.[21,22] Any disagreements in article selection were solved through discussion, and if necessary, a third author was consulted to resolve disagreement. Full text articles were retrieved for the selected titles after initial appraisal. In order to find unidentified studies with the search run in databases, we checked reference lists, contacted authors directly and conducted citation tracking. Articles selected were retrieved and assessed by two independent authors to ensure they met full inclusion criteria. Any disagreements were resolved through discussion with a third independent reviewer.

Data extraction

Two independent reviewers extracted data using a predesigned data collection form on study and participant characteristics, comparison groups, outcomes, analysis and conclusions. Study characteristics recorded included: author, year of publication, geographic origin and setting of the study, design and funding source, sex of participants, ethnicity, age, duration of intervention, residence, anti-hypertensive drug treatment, comorbidities, inclusion and exclusion criteria, type and delivery of intervention, quality, intention-to-treat analysis, tests used in analysis, participants in the control and intervention group, and blood pressure measurements before and after intervention in both groups with respective variances. We translated physical activity interventions into metabolic equivalents (METs) as a covariate of interest.[23] Multiple interventions were defined as

more than one of the above interventions delivered at the same time compared to regular care or no intervention. We recorded the pre and postintervention blood pressure measurements in mmHg and the variance as SD, standard errors (SEs) or 95% confidence interval (CI) as reported. In the case of multiple publications from the same study, the most comprehensive or recent information, as appropriate, was included in the analysis. In order to avoid repeating the same control group in the analysis, if the same study presented more than one intervention arm comparing to the same control group, we only included the intervention with the largest sample in the case of diet interventions, and the highest intensity arm group in the case of physical activity. Two independent reviewers evaluated possible bias and intention to treat in individual studies according to the Cochrane Tool for Bias Assessment.[24]

Statistical Analysis

Both SBP and DBP measurements were noted as a continuous variable in mmHg. The net effect sizes were summarized as weighted mean difference between post and preintervention measurements in each trial.[25] If data were unavailable, we used standard equations (eAppendix 2, http://links.lww.com/HJH/A333) to impute the missing variance. We employed Der Simonian and Laird random effect models with a 95% CI[26] to perform the meta-analysis. A random-effects model was chosen to conservatively deal with potential heterogeneity among the studies included. Heterogeneity among studies was measured with I-squared.[25] We divided studies according to type of interventions (behavioral counseling, dietary modification, physical activity and multiple interventions). To evaluate potential differences between specific subgroups we repeated the analyses by key factors. We also conducted meta-regression (maximum likelihood method) to identify the key sources of heterogeneity.[27] Publication bias was examined by using funnel plots (plotting sample size against effect size) and nonparametric trim-and-fill methods.[28] Any potential small studies effects were investigated by Egger's test.[28] Additionally, to investigate the influence of a single study on the summary effect, we performed sensitivity analyses in the four groups of different interventions.[25] All analyses were conducted using Stata version 12.0 (StataCorp LP, College Station, Texas, United States).

Results

Identification of the relevant studies

From the initial 6211 references identified, 409 were considered potentially eligible and were retrieved. The reasons for exclusion of references to quality assessment are shown in Fig. 1. Of the 52 studies included in the systematic review, 43 were eligible for the meta-analysis including 6779 participants.

The reasons for exclusion of nine papers were the following: control group and intervention group receiving similar interventions,[29,30] interventions were at organizational level,[31] intervention

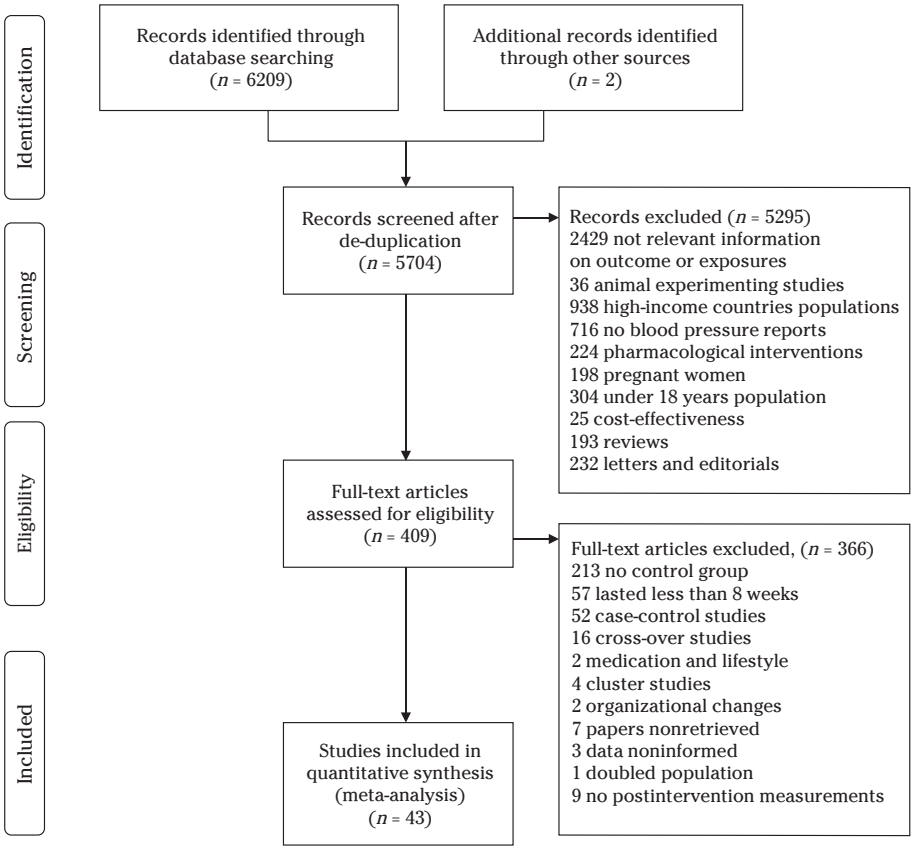


Figure 1. *Study flow diagram*

involved pharmacologic supplements or drug[32,33] with lifestyle , the results could not be pooled due to lack of variance in preintervention and postintervention[34-36] or doubled population.[37]

Since studies differed in terms of type of interventions, they were divided in 4 main groups according to delivery (e.g. physical activity, behavioural counselling, dietary modifications, and multiple interventions). The random-effect sizes and heterogeneity are shown in Fig. 2.

General characteristics of the included studies

The characteristics of the populations and interventions included in the systematic review are shown in Table 1.[29-32,34-79] The studies included in the meta-analysis involved 6779 participants (44.5% women; mean age 53.5 ± 9.5 years, range 18-80 years). The duration of the studies ranged from 2 to 30 months, with a mean duration of 5.3 ± 4.8 months. Approximately half of the studies (23 studies) reported co-morbidities and the most common were, diabetes[36,38-45] and metabolic syndrome.[46-48]

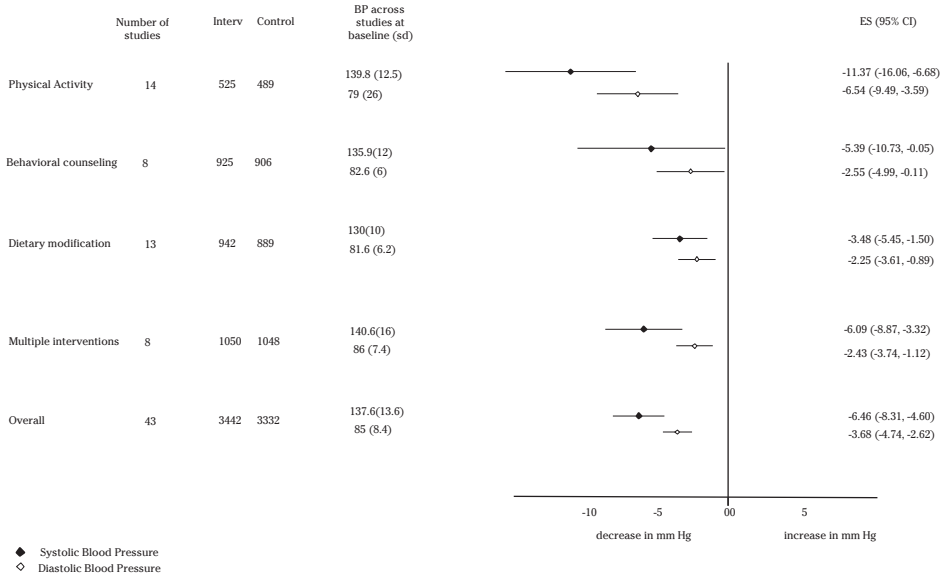


Figure 2. *Lifestyle intervention effects on blood pressure in LMIC populations*
LMIC, low and middle-income country. Heterogeneity (I^2, P value) within groups: Behavioral counseling (94.9%, P < 0.001; 90.3%, P < 0.001), Physical Activity (88.7%, P = 0.000; 89.5%, P < 0.001), Dietary Modification (64.5%, P < 0.001; 68.5%, P < 0.001), Multiple interventions (75.9%, P < 0.001; 52.9%, P = 0.038), Overall (89.0%, P < 0.001; 85.4%, P < 0.001) to systolic and diastolic pressure respectively. BP, Blood Pressure; CI, Confidence Interval 95%; ES, Effect Size; sd, Standard Deviation

Quality assessment of included studies

Evaluation of possible bias across different types of interventions showed that random sequence generation was unclear in 35.7, 60.0, 50.0 and 36.4% of studies and intention-to-treat analysis was used in 28.6, 30.0, 25.0 and 27.3% of studies in physical activity, behavioral counseling, dietary modifications and multiple interventions, respectively. Assessment of other quality criteria is presented in eFig. 1 (http://links.lww.com/HJH/A333).

Effects of various lifestyle interventions on blood pressure

Baseline mean SBP across studies for overall physical activity, behaviour counselling, dietary modifications and multiple interventions groups were 137.6 (±13.6), 139.8 (±12.5), 135.9 (±12), 130 (±10) and 140.6 (±16) mmHg, respectively. Baseline mean DBP for overall physical activity, behaviour counselling, dietary modifications and multiple interventions groups were 85 (±8.4), 79(±26), 82.6 (±6), 81.6 (±6.2) and 86 (±7.4) mmHg, respectively (Fig. 2).

The effect sizes were significant overall. When all studies were pooled irrespective of the type of intervention, the overall effect (95% CI) on SBP was -6.5 (-8.3, -4.6) mmHg and for DBP -3.7 (-4.7, -2.6) mmHg. This effect and the heterogeneity differed by type of interventions (Fig. 2). Thirty-three studies were randomized controlled trials,[39,42,44-73] two were community trials[74,79] and eight were clinical trials.[38,40,41,43,45,75-77]

Table 1. *Characteristics of trials identified*

Author	Year	Location	Type of study	*N*	Women (%)	Mean age(SD) (years)	Population baseline	Intervention	Control	Duration months
Physical Activity										
Arora *et al.* [44]	2009	India	RCT	20	40	49.6 (5.2)	Diabetes	Resistance training	Regular care	2
Barroso *et al.* [58]	2008	Brazil	RCT	35	80	66.5 (4)		Aerobic, strength and education on lifestyle	Education on lifestyle	6
Bündchen *et al.* [77]	2009	Brazil	RCT	111	66.6	58 (8.9)	BMI>30	Aerobic and resistance training	No physical activity	3
Kanegusuku *et al.* [61]	2011	Brazil	RCT	24	28	63		Resistance training	No change in lifestyle	4
Jiang *et al.* [64]	2007	China	RCT	167	70	62.11 (7.4)	Angina, MI	Aerobics and resistance	Regular care	3
Lamina *et al.* [71]	2011	Nigeria	RCT	245	0	58.63 (7.2)	Hypertension	Interval cycling training	No training	2
McCaffrey *et al.* [43]	2005	Thailand	RCT	54	65	56.7	Hypertension	Yoga	Regular care	2
de Meirelles *et al.* [40]	2009	Brazil	Clinical trial	19	63.1	49	Hypertensive, CVD, diabetes	Predominantly aerobic exercise	No physical activity	3
Monteiro *et al.* [43]	2010	Brazil	Clinical trial	22	100	61 (9.1)		Aerobics	Education on lifestyle	3.25
Terra *et al.* [38]	2008	Brazil	Clinical trial	46	100	66.8 (5.6)	Diabetes, osteoporosis, hyper cholesterol 70%.	Resistance exercise training sessions	No change lifestyle routine	3
Thomas. e*t al.* [66]	2005	China	RCT	142	45	69.1 (3.2)		Tai chi	Regular level of physical activity	12
Tsai *et al.* [55]	2003	China	RCT	23	50	49.6 (9.3)		Tai chi	Remained sedentary	3
Vianna *et al.* [75]	2011	Brazil	Clinical trial	70	65.7	69.8 (8.5)		Hydro gym, strengthening, stretching	No change in lifestyle routine	4
Wu [78]	2007	China	Clinical trial	36	100	49.7 (6.1)		Aerobics	No lifestyle change program	2
Behavioral Counseling										
Goldhaber-Fiebert *et al.*[79]	2003	Costa-Rica	RCT	61	78.6	50.8 (9.3)	Diabetes, hypertension, hypercholesterolemia	Nutrition education and walking group	Regular care	3

Table 1. *Characteristics of trials identified (continued)*

Author	Year	Location	Type of study	*N*	Women (%)	Mean age(SD) (years)	Population baseline	Intervention	Control	Duration months
Kisioglu *et al.* [34]	2003	Turkey	RCT	400	100	34.1 (8.6)		Health training and leaflets	Leaflets	6
Lee *et al.* [49]	2007	China	RCT	184	41.6	71.3 (6.4)		Walking and public health nurse support	Regular care	8
Marin *et al.* [76]	2009	Argentina	RCT	700	65.8	70 (8.3)		Supervised physical activity, dance classe, education on nutrition	Regular care	12
Muda and Kadir [59]	2006	Malaysia	Clinical trial	91	0	45 (6.8)		Advice on lifestyle and physical activity	Regular advice on lifestyle	6
Mujica *et al.* [53]	2010	Chile	Clinical trial	51	58.8	51.1 (5.3)		Nutrition education and physical activity	No lifestyle changing program	4.5
Senuzun *et al.* [52]	2004	Turkey	RCT	60	10	54.7 (7.8)	CHD	Home based exercise program with lifestyle advice	Regular care	3
Snehalatha *et al.* [63]	2008	India	RCT	232	20.7	45.9 (5.9)	Hypertension	General lifestyle advice	Standard care	30
Yen *et al.* [72]	1996	China	Community trial	359	35.8	54.5 (14.5)		General lifestyle advice	No self learning packages	2
Pazoki *et al.* [51]	2007	Iran	RCT	335	100	39.4		Physical activity and education material, home visits	Regular care	2
Dietary Modification										
Azadbakht et al. [48]	2005	Iran	RCT	55	70.6	41.2 (12.4)	MetS	DASH diet	No diet	6
Charlton *et al.* [65]	2008	South Africa	RCT	80	83.7	61.8 (6.6)		Na+ modified food plus salt replacement and fermented milk	Foods without modification	2
China Salt S.C.G. [50]	2007	China	RCT	608	56	59 (10)	Hypertension, CVD, diabetes	Salt substitution for 65% sodium, 25% potassium, 10% magnesium	Regular salt	12

Table 1. *Characteristics of trials identified (continued)*

Author	Year	Location	Type of study	*N*	Women (%)	Mean age(SD) (years)	Population baseline	Intervention	Control	Duration months
He *et al.* [69]	2006	China	Community trial	302	53.3	51.4 (9.2)	Hypertension	40g soy bean protein/day	Placebo carbohydrate	3
Hu *et al.* [37]	2009	China	RCT	192	59	59 (10)	Diabetes	Salt substitution for 65% sodium, 25% potassium, 10% magnesium	Regular salt	12
Lin *et al.* [29]	2009	China	RCT	132	65.9	34.2 (9.8)	Obesity	Very low calorie diet (450 cal/day)	Low calorie diet (800 cal/day)	3
Mark *et al.* [32]	1996	China	RCT	3318	56	54		Linxian vitamin/mineral supplement/day	Lookalike placebo	72
Mukuddem-Petersen *et al.* [62]	2007	South Africa	RCT	43	54.7	45		Walnut diet	Regular diet	2
Pereira *et al.* [56]	2005	Brazil	RCT	22	85.7	45.4 (13.2)		Salt substitution for 50%potassium	Regular salt	3
Radhakrishnan *et al.* [54]	2009	India	RCT	85	100	48 (5.4)		25g rich soy protein (75 mg powder)	Placebo of milk	6
Simão et al. [67]	2010	Brazil	RCT	30	100	45.9 (9.8)		25g/day soy protein	Regular diet	3
Sun et al. [45]	2008	China	RCT	150	28	51(1)	Diabetes, MetS	Education, dietitian consultation and low glycemic meal replacement	Education	6
Torres et al. [73]	2010	Brazil	RCT	39	90	37.9	BMI>30	Low calorie diet(800 kcal/day), high calcium intake	Low calorie diet (800 kcal/day) and low calcium intake	4
Toscani et al. [70]	2011	Brazil	RCT	26	100	29.4 (5.7)	polycystic ovary syndrome	High protein diet	Normal protein diet	2
Wu *et al.* [47]	2010	China	RCT	189	44.2	48.5 (8)	MetS	Flaxseed bread	Lifestyle counseling	3
Zhang *et al.* [46]	2011	China	RCT	202		49.8 (7.1)	MetS	Cooked brown rice	White rice	4

Table 1. *Characteristics of trials identified (continued)*

Author	Year	Location	Type of study	*N*	Women (%)	Mean age(SD) (years)	Population baseline	Intervention	Control	Duration months
Multiple Interventions										
Figar *et al.* [31]	2004	Argentina	Clinical trial	500	64.8	73	Hypertension	Education and organizational changes in the health care	Education and regular care	12
Grace *et al.* [60]	2009	South Africa	Clinical trial	122	0	41.7 (8.0)		General lifestyle advice and physical activity	Physical activity	8
Hacihasanoglu and Gozum [80]	2011	Turkey	RCT	80	51.6	58 (8.9)		General lifestyle and drug adherence adherence advice	Education on drug treatment	9
Hammad *et al.* [39]	2011	Jordan	RCT	199	64	56 (9.6)	Hypertension, diabetes	General lifestyle advice and medical adherence advice	Regular care	6
Hsieh *et al.* [74]	2008	China	Community trial	268	47.7	55.5 (11.7)		General lifestyle advice	Regular care	6
Lin *et al.* [41]	2010	China	Clinical trial	73	12.3	61.8 (10.9)	High cholesterol, hypertension, diabetes	General lifestyle advice	Regular care	3
Mendivil *et al.* [30]	2006	Colombia	RCT	75	50	51.35 (2.3)				
Metintas *et al.* [42]	2009	Turkey	RCT	498	46.2	57.112.0)	Hypertension, diabetes, CVD	Brochure and prescription of lifestyle measures	Brochure	12
Singh *et al.* [36]	1996	India	Clinical trial	463	9.5	46 (9.6)	CHD, diabetes, hypertension	Fat modified, fruit and vegetable enriched diet plus daily moderate exercise	Education	36
Singh *et al.* [57]	1993	India	RCT	621	9.5	46.3 (8.6)	CHD, diabetes, hypertension	Nutrition education and walking sessions	Education	6
Uzcategui Contreras *et al.* [35]	1999	Venezuela	Clinical trial	20	0	N.I.	Hypertension	Diet, exercise tapes, relaxation, education	Regular care	5

CHD, coronary heart disease; CVD, cardiovascular disease; MetS, metabolic syndrome; MI, myocardial infarction; N.I. noninformed; RCT, randomized controlled trial

We included 14 studies reporting physical activities interventions, involving 1014 participants (52.6% women; mean age 59.2 ± 7.5 years). The duration varied from 2 to 12 months with mean of 3.7 ± 2.3 months. The studies were conducted in Brazil,[38,40,43,58,61,75,77] China,[55,64,66] India,[44] Thailand[68] and Nigeria.[71] When pooled, physical activity interventions lowered blood pressure by -11.4 (-16.0, -6.7) mmHg for SBP and -6.5 (-9.5, -3.6) mmHg for DBP. Subgroup analysis yielded larger results from studies with sample size smaller than 100 participants versus bigger than 100 participants (Fig. 3). The differences in effect sizes for smaller samples were -4.8 (-4.9, -4.7) mmHg for SBP and -5.6 (-5.6, -5.5) mm Hg for DBP. Other key subgroups effect sizes are shown in Table 2. Meta-regression did not indicate an influence of sex, ($P > 0.05$ for both SBP and DBP). Mean age showed a borderline significant effect ($P = 0.057$) on SBP and no influence on DBP ($P > 0.05$).

We included eight studies on behavioral counseling in the meta-analysis with the total population of 1831 participants (40.3% women; mean age 53.8 ± 6.6 years). The interventions were conducted in China,[54,72,74] Turkey,[42,80] India,[63] Jordan[39] and South Africa.[60] Hypertension was reported in four studies.[39,41,42,63] Studies varied in duration from 2 to 30 months with a median of 7 months. Information available in the studies allowed subgroup analysis, which is shown in Table 3. The pooled results for behavioral counseling showed a reduction of -5.4 (-10.7, -0.0) mmHg for SBP and -2.5 (-5.0, -0.1) for DBP. Effect sizes in samples smaller than 100 participants were -5.4 (-10.7, -0.0) mm Hg and -2.5 (-5.0, -0.1) mmHg lower than bigger samples for SBP and DBP, respectively (Fig. 3). Key factor subgroup effect sizes are shown in Table 3. Mean age influenced the effect size across trials ($P = 0.03$) by 0.8 mmHg (95%CI 1.2, 0.3) decrease in SBP to 1 year increase in

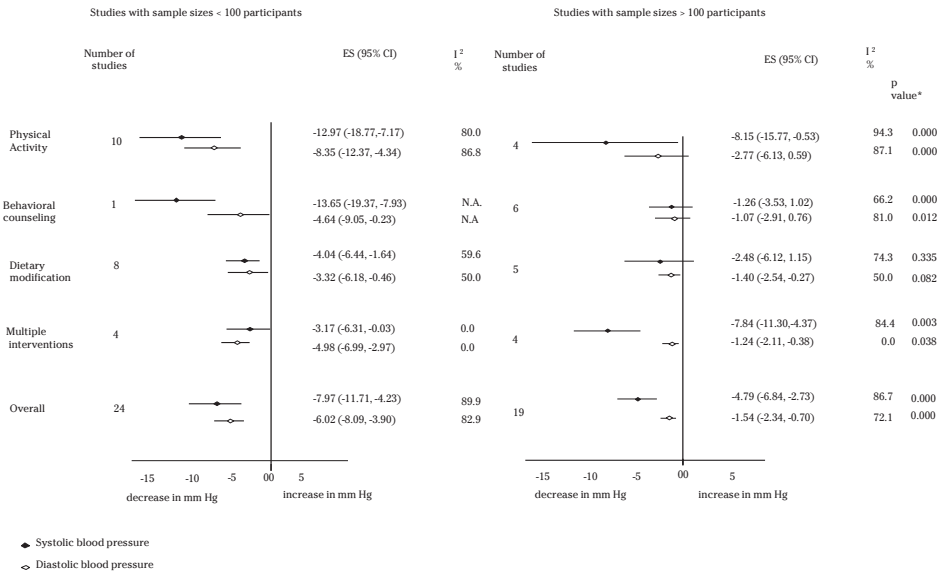


Figure 3. *Lifestyle intervention effects on blood pressure in LMIC populations by sample sizes*
*LMIC, low and middle-income country. *P-value for heterogeneity between groups.*

Table 2. *Subgroup analysis for physical activity interventions effect on blood pressure in LMICs*

	No. of studies	SBP			DBP		
		WMD	95% CI	p-value *	WMD	95% CI	p-value *
Anti-hypertensive drugs				0.378			<0.001
Yes	7	-12.13	(-18.64, -5.62)		-7.38	(-12.27, -2.5)	
No	7	-10.5	(-18.18,-2.83)		-5.2	(-8.42, -1.98)	
Ethnicity				<0.0010			0.002
Asian	6	-11.02	(-20.12, -1.93)		-6.27	(-12.07, -0.47)	
African	1	-13.09	(-13.09,-9.97)		-3.3	(-5.21, -1.39)	
South American	7	-11.82	(-11.82, -6.49)		-7.38	(-11.14, -3.63)	
Duration				<0.0010			0.177
<4 months	10	-13.8	(-19.3, -8.31)		-7.35	(-10.91, -3.78)	
4-12 months	4	-5.39	(-12.46, 1.68)		-4.61	(-10.96, 1.75)	
Sample Size				<0.0010			<0.0010
<30	5	-12	(-23.38, -0.62)		-7.48	(-13.01, -1.96)	
30-100	5	-13.28	(-20.17, -6.39)		-9.08	(-15.01, -3.14)	
>100	4	-8.15	(-15.77, -0.53)		-2.77	(-6.13, 0.59)	
Intensity METs				<0.0010			0.623
≤6 METs	9	-10.77	(-16.87, -4.66)		-6.42	(-10.64, -2.2)	
>6 METs	5	-13.11	(-19.67, -6.56)		-6.75	(-11.05, -2.45)	
Type of activity				0.088			0.001
Aerobic and resistance	7	-12.9	(-20.9, -5.44)		-8.01	(-13.04, -2.98)	
Aerobic	4	-8.52	(-14.2,-2.85)		-2.33	(-4.28, -0.37)	
Resistance	3	-13.02	(-27.25, 1.21)		-9.78	(-15.9, -3.66)	
Weekly hours				<0.0010			<0.0010
≤2 h	4	-1.89	(-4.27, 0.48)		-2.02	(-5.05, 1.05)	
2-3 h	10	-14.78	(-19.23, -10.33)		-8.43	(-12.17, -4.68)	
Co-morbidities				<0.0010			0.547
No	6	-8.75	(-16.47,-1.02)		-5.4	(-9.63,-1.17)	
Yes	8	-13.26	(-19.35,-7.16)		-7.47	(-11.89,-3.05)	
Randomization				0.068			0.001
Yes	5	-12.83	(-21.70,-3.97)		-6.18	(-12.00,-0.36)	
No	4	-13.04	(-19.93,-6.15)		-6.20	(-10.29,-2.11)	
Unclear	5	-8.38	(-15.77,-0.99)		-12.06	(-12.06,-2.61)	
Blinding outcome assessor				0.097			0.004
Yes	2	-12.62	(-33.71,8.48)		-4.61	(-12.59,3.37)	
No	2	-8.74	(-13.84,-3.63)		-2.96	(-8.17,2.26)	
Unclear	10	-11.76	(-17.53,-6.00)		-7.79	(-11.75,-3.83)	
Intention to treat				<0.001			<0.001
Yes	4	-7.74	(-16.56,1.08)		-2.33	(-5.86,1.21)	
No	10	-13.27	(-17.60,-8.95)		-8.01	(-11.51,-4.50)	

CI, confidence interval; METs, metabolic equivalent; WMD, weighted mean difference in mmHg.
**p-values for heterogeneity between groups.*

Table 3. *Subgroup analysis for behavioral counseling interventions effect on blood pressure in LMICs*

	No. of studies	SBP			DBP		
		WMD	95% CI	p-value*	WMD	95% CI	p-value*
Anti-Hypertensive drugs				<0.001			0.138
Yes	2	-9.25	(-17.25,-0.92)		-2.93	(-5.35,-0.51)	
No	5	-0.73	(-3.10,1.63)		-0.89	(-2.97,1.19)	
Duration				<0.001			<0.001
<6 months	4	-5.84	(-9.60,-2.08)		-2.81	(-5.32,-0.31)	
6-30 months	3	0.96	(-1.56,3.48)		0.22	(-0.81,1.25)	
Sample Size				0.116			0.604
<200	3	-5.12	(-14.36,4.12)		-1.84	(-4.25,0.56)	
200-498	4	-1.39	(-3.77,1.00)		-1.07	(-3.52,1.38)	
Comorbidities				0.572			0.009
No	3	-1.62	(-5.32,2.08)		-0.77	(-2.53,0.99)	
Yes	4	-3.83	(-9.02,1.36)		-1.76	(-5.00,1.48)	

CI, confidence interval; WMD, weighted mean difference in mmHg.
**p-values for heterogeneity between groups.]*

mean age, however, it did not influence DBP effects sizes ($P = 0.26$). Proportion of women did not influence SBP or DBP effect sizes ($P = 0.78$ and $P = 0.86$, respectively).

We included 13 studies reporting dietary modification in which 1831 participants were involved (53.4% women; mean age 47.3 ± 8.8 years). The studies were conducted in China,[45-47,50,69] Brazil,[56,67,70,73] South Africa,[48,62,65] India[54] and Iran.[48] Three studies enrolled only women.[46-48] Mean duration was 4.3±2.7 months. Comorbidities reported were metabolic syndrome, diabetes[45,50] and hypertension.[45,50,69] The pooled results for dietary interventions were -3.48 (-5.45,-1.50) mmHg for SBP and -2.25 (-3.61, -0.89) mmHg for DBP. Studies involving smaller samples showed larger results and the difference was -1.56 (-1.60, -1.51) mmHg for SBP and -1.92 (-1.95, -1.88) mmHg for DBP (Fig. 3) in studies involving less than 100 participants. We analyzed different types of diets and their effects on SBP and DBP: mineral replacement diets – replacing sodium by potassium - (three studies, I-squared = 0%, 59%), grains and fiber-rich diet (one study), protein-rich diets (four studies, I-squared= 73.2%, 83.6%), nuts and seed-rich diets (two studies, I-squared = 0%, 0%) and complex patterns diets (three studies, I-squared= 0%, 0%). The effects sizes are shown in Table 4.

We included eight multiple-interventions studies enrolling 2103 participants (46.3% women, mean age 53 ± 11 years). These studies were conducted in India,[57] China,[49] Costa Rica,[79] Iran,[51] Turkey,[52] Chile,[53] Malaysia,[59,76] and Argentina.[76] Coronary heart disease was reported in three studies.[36,52,79] Mean duration of the studies were 5.5 ± 3.2 months. The studies combined physical activity and diet or behavioral counseling interventions. Pooled effect sizes were -6.1 (-8.9, -3.3) mmHg for SBP and -2.4 (-3.7, -1.1) for DBP. The combination between physical activity and diet or behavioral counseling interventions did not yield significant difference in effect sizes ($P > 0.05$). In this group, results in sample sizes smaller than 100 participants differed by 4.7 (4.6,

4.7) mmHg to SBP and –3.7 (-3.7, -3.7) mmHg from the results in studies with bigger samples (Fig. 3). Information about the intensity of physical activity did not allow for transformation to METs. These findings were further investigated in various study-level subgroups (Table 5). Meta-regression analyses indicated that the proportion of women did not influence effect sizes for either SBP or DBP (meta-regression $P > 0.05$ for both measures). Mean age also did not influence effects in SBP and DBP ($P > 0.05$).

Table 4. *Subgroup analysis for dietary modifications on blood pressure in LMICs*

	No. of studies	SBP			DBP		
		WMD	95% CI	p-value*	WMD	95% CI	p-value*
Type of diet				<0.001			0.009
Mineral replacement-based	3	-6.90	(-8.6.-5.2)		-1.90	(-4.50. 0.70)	
Grains and fiber	1	-1.47	(-3.9.-1.01)		-0.10	(-1.90. 1.77)	
Protein-rich	4	0.93	(-4.6. 6.46)		-3.2	(-7.50. 1.10)	
Nuts and seeds	2	-1.57	(-4.73.1.59)		-0.49	(-2.42. 1.43)	
Complex dietary pattern	3	-3.47	(-5.45.-1.5)		-2.25	(-3.60. -0.89)	

CI, confidence interval; WMD, weighted mean difference in mmHg.
**p-values for heterogeneity between groups.*

Table 5. *Subgroup analysis for multiple interventions effect on blood pressure in LMIC*

	No. of studies	SBP			DBP		
		WMD	95% CI	p-value*	WMD	95% CI	p-value*
Delivery				0.115			0.889
Diet/Physical Activity	4	-4.79	(-8.74,-0.83)		-2.07	(-3.54,-0.61)	
Behavioral counseling/Physical Activity	4	-7.16	(-12.17,-2.15)		-2.86	(-5.4,-0.32)	
Ethnicity				<0.0010			0.225
Asian	5	-7.75	(-10.72,-4.78)		-2.22	(-3.94,-0.5)	
American	3	-1.80	(-3.01,-0.37)		-2.80	(-4.57,-1.03)	
Duration				0.007			0.639
<6 months	4	-6.22	(-12.19,-0.26)		-4.05	(-7.67,-0.42)	
6-12 months	4	-5.49	(-8.84,-2.14)		-1.70	(-2.67,-0.72)	
Co-morbidities				0.194			0.575
No	4	-6.44	(-11.95,-0.93)		-2.10	(-4.02,-0.18)	
Yes	4	-5.46	(-9.09,-1.83)		-2.93	(-5.08,-0.78)	
Blinding outcome assessor				0.738			0.504
Yes	5	-6.86	(-9.18,-4.54)		-3.34	(-5.67,-1.01)	
Unclear	3	-6.17	(-12.82,0.48)		-1.72	(-3.27,-0.17)	
Intention to treat				0.887			0.789
Yes	4	-5.79	(-9.15,-2.43)		-2.10	(-3.72,-0.49)	
No	4	-6.16	(-12.02,-0.30)		-2.89	(-5.28,-0.50)	

CI, confidence interval; WMD, weighted mean difference in mmHg.
**p-values for heterogeneity between groups.*

Discussion

Overall, we found that lifestyle interventions of any type (behavioral, physical activity or dietary interventions, given singly and in combination) significantly lowered blood pressure levels in the LMIC settings by approximately -6.5 and -3.7 mmHg for SBP and DBP, respectively. Effects ranged from -11.4 mmHg for physical activity to -3.5 mmHg in dietary modification for SBP and from -6.5 mmHg for physical activity to -2.2 mmHg for dietary modifications for DBP. Nonetheless, heterogeneity was generally high across the available studies, which was partly explained when studies were grouped according to sample size, duration of follow-up and analytical approach used.

In the current review, when assessed according to intervention type, interventions that promoted physical activity lowered SBP and DBP significantly, irrespective of antihypertensive drugs usage, ethnicity, mean age, intensity of activity and randomization of patients. Interestingly, interventions lasting 2-4 months showed a significant lowering effect on SBP and DBP than the ones lasting 4-12 months, reinforcing results in a previous meta-analysis on physical activity,[81] in which longer lasting effects were highlighted as a challenge. Physical activity interventions involving more than 100 participants did not show a significant lowering effect on DBP. Similarly, resistance exercise programs did not show a significant lowering effect on SBP and the findings of this subgroup differ from a previous meta-analysis on resistance program exercise effect on blood pressure.[82] Different inclusion criteria and our reduced number of studies in this subgroup may explain the difference in results. Additionally, interventions offering less than 2 h per week of physical activity did not show a significant effect on SBP or DBP. The large difference found between those effect sizes could be due to lower quality of those studies reporting less physical activity. These findings are in line with the first meta-analysis on the lifestyle interventions effect on blood pressure we could find[83], suggesting the difficulties of sustaining exercise routine. However, comparison of our study with other meta-analysis is impaired by the lack of other reviews focusing on low-resource-sensitive settings.

For both physical activity and behavioral counseling interventions, the effect sizes were larger in the studies that reported substantial co-morbidities, indicating that high-risk individuals may have greater benefits from the lifestyle interventions. Conversely, effects were not significant in studies reporting blinding of outcome assessors and intention-to-treat analysis, which potentially points out quality issues in this type of intervention. Behavioral counseling interventions were effective in lowering SBP and DBP in studies reporting antihypertensive drugs and in studies with follow-up from 2 to 6 months. These findings might have been driven by the nature of most of the behavioral counseling studies, which involves adherence to medication program. Furthermore, they might also indicate the challenge of sustaining a healthy lifestyle since studies with longer duration showed a significantly lower effect size as was described for physical activity interventions as well.

Studies on dietary modifications, labeled as complex dietary pattern comprised Dietary Approach to Stop Hypertension and Mediterranean diet (DASH),[84] and showed a significant lowering effect on SBP and DBP. Mineral replacement-based diets (e.g. potassium replacement) studies showed significant effect in lowering SBP, but not DBP. These two groups showed no heterogeneity even though the interventions were conducted in three different continents. These findings might indicate a consistent lowering effect of mineral replacements diets on SBP. Nuts and seed-based diets, and protein-rich diet studies did not yield significant effects both on SBP and DBP. Subgroup analysis was hampered within the dietary modifications due to reduced number of studies and the low power we found after grouping studies according to different dietary patterns. Multiple-intervention group was composed of interventions involving physical activity combined with nutrition training or behavioral counseling. There was a consistent lowering effect on SBP and DBP regardless of ethnicity, duration of the intervention, reporting of co-morbidities and intention-to-treat analysis. In studies reporting blinding of the outcome assessor, the reduction was significant for SBP and DBP, but not in studies in which there was unclear reporting of the blinding. Effects on Asian participants were greater than in South Americans and studies lasting 2-6 months showed larger effect sizes than long-term studies, especially for DBP. Multiple- intervention studies involving less than 100 participants showed no heterogeneity across them, suggesting a consistent effect from these interventions.

We observed considerable heterogeneity among the included studies which was partly explained by our subsidiary subgroup analyses involving differences in sample sizes, duration of intervention, blinding of outcome assessors and intention-to-treat analysis. On the contrary, multiple-intervention studies seemed to show the opposite effect on smaller samples, with very low heterogeneity among the smaller sample study group. This indicates a consistency in the interventions involving physical activity and nutrition training or behavioral counseling at the same time involving samples smaller than 100 participants in LMIC settings. Possible explanations for these findings could be the close supervision given to smaller samples and higher quality of reports in those interventions.

Our results somewhat differ from previous meta-analyses of the effects of lifestyle interventions on blood pressure.[22,82] We found larger effect sizes for physical activity interventions and for multiple interventions than others did. Nevertheless, we found similar larger effects in participants using antihypertensive medications in the cases of physical activity and behavioral counseling.[22,85] Our results on dietary modifications were in smaller magnitude than previously reported although, other meta-analysis showed the same direction of effect. Some differences in effect sizes might be due to different selection criteria on study designs as some other authors included crossover studies, whereas we included only parallel studies. The fact that other authors included pharmacological supplementation (e.g. potassium, magnesium, calcium and fish oil) and separated sodium-restriction diet from diet interventions, whereas we included sodium restriction on dietary interventions, might also explain different results. Additionally, our comparison with other reviews is impaired by the difference in population of interest as we focused on

LMIC populations. This might be reflected by the fact that we found very few references included in our study which were found in other meta-analysis mentioned in this discussion.

Strengths and limitations of the current study merit consideration. We were unable to evaluate the associations in the contexts of potentially important demographic information such as living in rural or urban areas and educational status, as most studies did not provide these data. Despite the considerable number of references included in this meta-analysis, there is an apparent lack of large-scale, high-quality trials in the LMICs. Nonetheless, to the best of our knowledge, this is the first quantitative synthesis of all available intervention studies based on LMICs and assessing effects of nonpharmacological lifestyle interventions on blood pressure. These effects are broadly comparable to advocated drug treatment.[86] Even though the scope of this study is to present nonpharmacological interventions as adjuvant to control blood pressure LMICs, the effects presented here are similar in magnitude to those multidrug regimen for prevention of CVD in the developing world.[87] The fact that the majority of our included studies were not included in the previous meta-analyses suggests that these populations are yet to be adequately addressed in terms of summarizing the evidence that may have help shape local vascular-preventive policies and programs. It remains unclear whether the difference in magnitude of effects between our meta-analysis and other meta-analysis of studies conducted in high-income countries, are due to quality of reports or a true different effect. Consequently, our findings reinforce the positive effects of lifestyle interventions and their significant potentials in formulating cost-beneficial preventive strategies in resource-poor countries.

In conclusion, available data indicate that lifestyle-related interventions are effective in lowering blood pressure in LMICs. The potential of cost-effective, easily scalable lifestyle interventions is attractive in resource-poor settings as a complementary approach to help shape preventive guidelines. Nonetheless, further investigations with sufficient power and scientific rigor would be required to more reliably quantify these effects.

References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet.* May 27 2006;367(9524):1747-1757.
2. Ordunez P. Cardiovascular health in the Americas: facts, priorities and the UN high-level meeting on non-communicable diseases. *MEDICC Rev.* Oct 2011;13(4):6-10.
3. Mackay J, Mensah GA, Mendis S, Greenlund K. *The atlas of heart disease and stroke.* World Health Organization; 2004.
4. 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.* Dec 15 2012;380(9859):2224-2260.
5. Guilbert J. *The world health report 2002-reducing risks, promoting healthy life.* CARFAX PUBLISHING;2003. 1357-6283.
6. Hsu C, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. *Archives of internal medicine.* 2005;165(8):923.
7. Antikainen RL, Moltchanov VA, Chukwuma C, Sr., et al. Trends in the prevalence, awareness, treatment and control of hypertension: the WHO MONICA Project. *Eur J Cardiovasc Prev Rehabil.* Feb 2006;13(1):13-29.
8. Pereira M, Lunet N, Azevedo A, Barros H. Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. *J Hypertens.* May 2009;27(5):963-975.
9. Rubinstein A, Alcocer L, Chagas A. High blood pressure in Latin America: a call to action. *Therapeutic Advances in Cardiovascular Disease.* 2009;3(4):259-285.
10. Lawes CM, Vander Hoorn S, Rodgers A, International Society of H. Global burden of blood-pressure-related disease, 2001. *Lancet.* May 3 2008;371(9623):1513-1518.
11. Danaei G, Finucane MM, Lin JK, et al. National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5· 4 million participants. *The Lancet.* 2011.
12. Mendis S, Fukino K, Cameron A, et al. The availability and affordability of selected essential medicines for chronic diseases in six low-and middle-income countries. *Bulletin of the World Health Organization.* 2007;85(4):279-288.
13. Lim SS, Gaziano TA, Gakidou E, et al. Prevention of cardiovascular disease in high-risk individuals in low-income and middle-income countries: health effects and costs. *The Lancet.* 2007;370(9604):2054-2062.
14. Mancia G, Fagard R, Narkiewicz K. List of authors Task Force members 2013: ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens.* 2013;31:1281-1357.
15. Chalmers J, MacMahon S, Mancia G, et al. 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension. Guidelines sub-committee of the World Health Organization. *Clinical and experimental hypertension (New York, NY: 1993).* 1999;21(5-6):1009.
16. Seedat YK, Rayner BL, Southern African Hypertension S. South African hypertension guideline 2011. *S Afr Med J.* Jan 2012;102(1 Pt 2):57-83.
17. Liu LS, Writing Group of Chinese Guidelines for the Management of H. [2010 Chinese guidelines for the management of hypertension]. *Zhonghua Xin Xue Guan Bing Za Zhi.* Jul 2011;39(7):579-615.
18. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMC medicine.* 2010;8(1):18.
19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine.* 2009;6(7):e1000097.
20. Boutron I, Guittet L, Estellat C, Moher D, Hrobjartsson A, Ravaud P. Reporting methods of blinding in randomized trials assessing nonpharmacological treatments. *PLoS Med.* Feb 2007;4(2):e61.
21. Fahey T, Schroeder K, Ebrahim S, Glynn L. Interventions used to improve control of blood pressure in patients with hypertension. *Cochrane database syst Rev.* 2006;4.
22. Dickinson HO, Mason JM, Nicolson DJ, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. *J Hypertens.* Feb 2006;24(2):215-233.
23. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc.* Sep 2000;32(9 Suppl):S498-504.

24. Higgins JPT, Green S, Collaboration C. *Cochrane handbook for systematic reviews of interventions*. Vol 5: Wiley Online Library; 2008.
25. Egger M, Smith GD, Altman D. *Systematic reviews in health care: meta-analysis in context*. BMJ books; 2008.
26. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials*. 1986;7(3):177-188.
27. Thompson SG, Higgins J. How should meta-regression analyses be undertaken and interpreted? *Statistics in medicine*. 2002;21(11):1559-1573.
28. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
29. Lin WY, Wu CH, Chu NF, Chang CJ. Efficacy and safety of very-low-calorie diet in Taiwanese: a multicenter randomized, controlled trial. *Nutrition*. Nov-Dec 2009;25(11-12):1129-1136.
30. Mendivil CO, Cortes E, Sierra ID, et al. Reduction of global cardiovascular risk with nutritional versus nutritional plus physical activity intervention in Colombian adults. *Eur J Cardiovasc Prev Rehabil*. Dec 2006;13(6):947-955.
31. Figar S, Waisman G, De Quiros FG, et al. Narrowing the gap in hypertension: effectiveness of a complex antihypertensive program in the elderly. *Dis Manag*. Fall 2004;7(3):235-243.
32. Mark SD, Wang W, Fraumeni JF, Jr., et al. Lowered risks of hypertension and cerebrovascular disease after vitamin/mineral supplementation: the Linxian Nutrition Intervention Trial. *Am J Epidemiol*. Apr 1 1996;143(7):658-664.
33. Lamina S, Okoye CG. Uricaemia as a cardiovascular events risk factor in hypertension: the role of interval training programme in its downregulation. *J Assoc Physicians India*. Jan 2011;59:23-28.
34. Kisioglu AN, Aslan B, Ozturk M, Aykut M, Ilhan I. Improving control of high blood pressure among middle-aged Turkish women of low socio-economic status through public health training. *Croat Med J*. Aug 2004;45(4):477-482.
35. Uzcategui Contreras D, Granadillo Vera D, Salinas PJ, Alvarez N. [A strategic family medicine model for controlling borderline and mild arterial hypertension] Modelo estrategico de medicina familiar para controlar hipertension arterial limitrofe y leve. *Aten Primaria*. Oct 31 1999;24(7):417-420.
36. Singh RB, Rastogi V, Rastogi SS, Niaz MA, Beegom R. Effect of diet and moderate exercise on central obesity and associated disturbances, myocardial infarction and mortality in patients with and without coronary artery disease. *Journal of the American College of Nutrition*. Dec 1996;15(6):592-601.
37. Hu J, Jiang X, Li N, et al. Effects of salt substitute on pulse wave analysis among individuals at high cardiovascular risk in rural China: a randomized controlled trial. *Hypertens Res*. Apr 2009;32(4):282-288.
38. Terra DF, Mota MR, Rabelo HT, et al. Reduction of arterial pressure and double product at rest after resistance exercise training in elderly hypertensive women. 2008:299-305.
39. Hammad EA, Yasein N, Tahaineh L, Albsoul-Younes AM. A randomized controlled trial to assess pharmacist- physician collaborative practice in the management of metabolic syndrome in a university medical clinic in Jordan. *J Manag Care Pharm*. May 2011;17(4):295-303.
40. de Meirelles LR, Mendes-Ribeiro AC, Mendes MA, et al. Chronic exercise reduces platelet activation in hypertension: upregulation of the L-arginine-nitric oxide pathway. *Scand J Med Sci Sports*. Feb 2009;19(1):67-74.
41. Lin HH, Tsai YF, Lin PJ, Tsay PK. Effects of a therapeutic lifestyle-change programme on cardiac risk factors after coronary artery bypass graft. *J Clin Nurs*. Jan 2010;19(1-2):60-68.
42. Metintas S, Kalyoncu C, Arikan I. Two distinct training methods for a doctrine of life with healthy heart in a low socioeconomic society model. *Int J Environ Res Public Health*. Nov 2009;6(11):2883-2897.
43. Monteiro LZ, Fiani CRV, Freitas MCFd, Zanetti ML, Foss MC. Decrease in blood pressure, body mass index and glycemia after aerobic training in elderly women with type 2 diabetes. 2010:563-570.
44. Arora E, Shenoy S, Sandhu JS. Effects of resistance training on metabolic profile of adults with type 2 diabetes. *Indian J Med Res*. May 2009;129(5):515-519.
45. Sun J, Wang Y, Chen X, et al. An integrated intervention program to control diabetes in overweight Chinese women and men with type 2 diabetes. *Asia Pac J Clin Nutr*. 2008;17(3):514-524.
46. Zhang G, Pan A, Zong G, et al. Substituting white rice with brown rice for 16 weeks does not substantially affect metabolic risk factors in middle-aged chinese men and women with diabetes or a high risk for diabetes. *J Nutr*. 2011;141(9):1685-1690.
47. Wu H, Pan A, Yu Z, et al. Lifestyle counseling and supplementation with flaxseed or walnuts influence the management of metabolic syndrome. *J Nutr*. Nov 2010;140(11):1937-1942.

48. Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi T, Azizi F. Beneficial effects of a dietary approaches to stop hypertension eating plan on features of the metabolic syndrome. *Diabetes Care.* 2005;28(12):2823-2831.
49. Lee LL, Arthur A, Avis M. Evaluating a community-based walking intervention for hypertensive older people in Taiwan: a randomized controlled trial. *Prev Med.* Feb 2007;44(2):160-166.
50. China Salt Substitute Study Collaborative G. Salt substitution: a low-cost strategy for blood pressure control among rural Chinese. A randomized, controlled trial. *J Hypertens.* Oct 2007;25(10):2011-2018.
51. Pazoki R, Nabipour I, Seyednezami N, Imami SR. Effects of a community-based healthy heart program on increasing healthy women's physical activity: a randomized controlled trial guided by Community-based Participatory Research (CBPR). *BMC Public Health.* 2007;7:216.
52. Senuzun F, Fadiloglu C, Burke LE, Payzin S. Effects of home-based cardiac exercise program on the exercise tolerance, serum lipid values and self-efficacy of coronary patients. *Eur J Cardiovasc Prev Rehabil.* 2006;13(4):640-645.
53. Mujica V, Urzua A, Leiva E, et al. Intervention with education and exercise reverses the metabolic syndrome in adults. *J Am Soc Hypertens.* May-Jun 2010;4(3):148-153.
54. Radhakrishnan G, Rashmi, Agarwal N, Vaid NB. Evaluation of isoflavone rich soy protein supplementation for postmenopausal therapy. *Pak J Nutr.* 2009;8(7):1009-1017.
55. Tsai JC, Wang WH, Chan P, et al. The beneficial effects of Tai Chi Chuan on blood pressure and lipid profile and anxiety status in a randomized controlled trial. *J Altern Complement Med.* Oct 2003;9(5):747-754.
56. Pereira MAdG, Galvão R, Zanella MT. Effects of potassium supplementation by salt on arterial blood pressure and insulin resistance in hypertensive obese patients on diuretic therapy. 2005:5-17.
57. Singh RB, Singh NK, Rastogi SS, Mani UV, Niaz MA. Effects of diet and lifestyle changes on atherosclerotic risk factors after 24 weeks on the Indian Diet Heart Study. *Am J Cardiol.* Jun 1 1993;71(15):1283-1288.
58. Barroso WKS, Jardim PCBV, Vitorino PV, Bittencourt A, Miquetichuc F. The influence of programmed physical activity on blood pressure of hypertensive elderly patients on non-pharmacological treatment. 2008:328-333.
59. Muda SH, Kadir AA. The effectiveness of physical activity counseling in Primary Care Clinic University Science Malaysia Hospital. *Int Med J.* 2006;13(4):249-253.
60. Grace JM, Wilders CJ, Strydom GL. THE EFFECT OF A PHYSICAL AND A COMBINED HEALTH PROMOTION INTERVENTION PROGRAMME ON SOME SELECTED HEALTH INDICATORS OF SOUTH AFRICAN COLLIERY EXECUTIVES. *South African Journal for Research in Sport Physical Education and Recreation.* 2009;31(1):9-18.
61. Kanegusuku H, Queiroz ACC, Chehuen MR, et al. Strength and power training did not modify cardiovascular responses to aerobic exercise in elderly subjects. 2011:864-870.
62. Mukuddem-Petersen J, Stonehouse Oosthuizen W, Jerling JC, Hanekom SM, White Z. Effects of a high walnut and high cashew nut diet on selected markers of the metabolic syndrome: A controlled feeding trial. *Br J Nutr.* 2007;97(6):1144-1153.
63. Snehalatha C, Mary S, Joshi VV, Ramachandran A. Beneficial effects of strategies for primary prevention of diabetes on cardiovascular risk factors: results of the Indian Diabetes Prevention Programme. *Diab Vasc Dis Res.* Mar 2008;5(1):25-29.
64. Jiang X, Sit JW, Wong TK. A nurse-led cardiac rehabilitation programme improves health behaviours and cardiac physiological risk parameters: evidence from Chengdu, China. *J Clin Nurs.* Oct 2007;16(10):1886-1897.
65. Charlton KE, Steyn K, Levitt NS, et al. A food-based dietary strategy lowers blood pressure in a low socio-economic setting: a randomised study in South Africa. *Public Health Nutr.* Dec 2008;11(12):1397-1406.
66. Thomas GN, Hong AW, Tomlinson B, et al. Effects of Tai Chi and resistance training on cardiovascular risk factors in elderly Chinese subjects: a 12-month longitudinal, randomized, controlled intervention study. *Clin Endocrinol (Oxf).* Dec 2005;63(6):663-669.
67. Simão ANC, Lozovoy MAB, Simão TNC, Dichi JB, Matsuo T, Dichi I. Nitric oxide enhancement and blood pressure decrease in patients with metabolic syndrome using soy protein or fish oil. 2010:540-545.
68. McCaffrey R, Ruknui P, Hatthakit U, Kasetsomboon P. The effects of yoga on hypertensive persons in Thailand. *Holist Nurs Pract.* Jul-Aug 2005;19(4):173-180.
69. He J, Gu D, Wu X, Chen J, Duan X, Whelton PK. Effect of soybean protein on blood pressure: a randomized, controlled trial. *Ann Intern Med.* Jul 5 2005;143(1):1-9.

70. Toscani MK, Mario FM, Radavelli-Bagatini S, Wiltgen D, Matos MC, Spritzer PM. Effect of high-protein or normal-protein diet on weight loss, body composition, hormone, and metabolic profile in southern Brazilian women with polycystic ovary syndrome: a randomized study. *Gynecol Endocrinol.* Nov 2011;27(11):925-930.
71. Lamina S. Comparative effect of interval and continuous training programs on serum uric acid in management of hypertension: a randomized controlled trial. *J Strength Cond Res.* Mar 2011;25(3):719-726.
72. Yen LL, Patrick WK, Chie WC. Comparison of relaxation techniques, routine blood pressure measurements, and self-learning packages in hypertension control. *Prev Med.* May-Jun 1996;25(3):339-345.
73. Torres MRSG, Francischetti EA, Genelhu V, Sanjuliani AF. Effect of a high-calcium energy-reduced diet on abdominal obesity and cardiometabolic risk factors in obese Brazilian subjects. *Int J Clin Pract.* 2010;64(8):1076-1083.
74. Hsieh YC, Hung CT, Lien LM, et al. A significant decrease in blood pressure through a family-based nutrition health education programme among community residents in Taiwan. *Public Health Nutr.* Apr 2009;12(4):570-577.
75. Vianna MV, Ali Cader S, Gomes AL, et al. Aerobic conditioning, blood pressure (BP) and body mass index (BMI) of older participants of the Brazilian Family Health Program (FHP) after 16 weeks of guided physical activity. *Arch Gerontol Geriatr.* Jan 2012;54(1):210-213.
76. Marin GH, Homar C, Niedfeld G, Matcovick G, Mamonde M. Evaluation of the state intervention project to improve quality of life and reduce the complications associated with aging: "Add health to your years". *Gaceta Sanit.* 2009;23(4):272-277.
77. Bündchen DC, Panigas CF, Dipp T, et al. Lack of influence of body mass on blood pressure reduction after exercising. 2010:678-683.
78. Wu TY, Yeh HI, Chan P, Chiou YF, Tsai JC. The effects of simple eight-week regular exercise on cardiovascular disease risk factors in middle-aged women at risk in Taiwan. *Acta Cardiol Sin.* Sep 2007;23(3):169-175.
79. Goldhaber-Fiebert JD, Goldhaber-Fiebert SN, Tristan ML, Nathan DM. Randomized controlled community-based nutrition and exercise intervention improves glycemia and cardiovascular risk factors in type 2 diabetic patients in rural Costa Rica. *Diabetes Care.* Jan 2003;26(1):24-29.
80. Hacihasanoglu R, Gozum S. The effect of patient education and home monitoring on medication compliance, hypertension management, healthy lifestyle behaviours and BMI in a primary health care setting. *J Clin Nurs.* Mar 2011;20(5-6):692-705.
81. 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.* Apr 2 2002;136(7):493-503.
82. Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension.* Oct 2005;46(4):667-675.
83. Ebrahim S, Smith GD. Lowering blood pressure: a systematic review of sustained effects of non-pharmacological interventions. *Journal of Public Health.* 1998;20(4):441-448.
84. 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. *New England Journal of Medicine.* 2001;344(1):3-10.
85. Cornelissen VA, Fagard RH, Coeckelberghs E, Vanhees L. Impact of Resistance Training on Blood Pressure and Other Cardiovascular Risk Factors A Meta-Analysis of Randomized, Controlled Trials. *Hypertension.* 2011;58(5):950-958.
86. Mah GT, Tejani AM, Musini VM. Methyldopa for primary hypertension. *Cochrane database syst rev.* 2009;4.
87. Costantino G, Ceriani E, Rusconi AM, Montano N. Prevention of cardiovascular disease with a polypill. *Lancet.* Jan 20 2007;369(9557):185-186; author reply 186.

Appendix 1.

Income groupings – WHO World Health Report 2008
(http://www.who.int/whosis/whostat/EN_WHS08_Full.pdf)

Low income

Afghanistan. Bangladesh. Benin. Burkina Faso. Burundi. Cambodia. Central African Republic. Chad. Comoros. Côte d'Ivoire. Democratic People's Republic of Korea. Democratic Republic of the Congo. Eritrea. Ethiopia. Gambia. Ghana. Guinea. Guinea-Bissau. Haiti. India. Kenya. Kyrgyzstan. Lao People's Democratic Republic. Liberia. Madagascar. Malawi. Mali. Mauritania. Mongolia. Mozambique. Myanmar. Nepal. Niger. Nigeria. Pakistan. Papua New Guinea. Rwanda. Sao Tome and Principe. Senegal. Sierra Leone. Solomon Islands. Somalia. Sudan. Tajikistan. Timor-Leste. Togo. Uganda. United Republic of Tanzania. Uzbekistan. Viet Nam. Yemen. Zambia. Zimbabwe

Lower middle income

Albania. Algeria. Angola. Armenia. Azerbaijan. Belarus. Bhutan. Bolivia. Bosnia and Herzegovina. Cameroon. Cape Verde. China. Colombia. Congo. Cuba. Djibouti. Dominican Republic. Ecuador. Egypt. El Salvador. Fiji. Georgia. Guatemala. Guyana. Honduras. Indonesia. Iran (Islamic Republic of). Iraq. Jamaica. Jordan. Kiribati. Lesotho. Maldives. Marshall Islands. Micronesia (Federated States of). Morocco. Namibia. Nicaragua. Paraguay. Peru. Philippines. Republic of Moldova. Samoa. Sri Lanka. Suriname. Swaziland. Syrian Arab Republic. Thailand. The former Yugoslav Republic of Macedonia. Tonga. Tunisia. Turkmenistan. Ukraine. Vanuatu

Upper middle income

Argentina. Belize. Botswana. Brazil. Bulgaria. Chile. Costa Rica. Croatia. Dominica. Equatorial Guinea. Gabon. Grenada. Hungary. Kazakhstan. Latvia. Lebanon. Libyan Arab Jamahiriya. Lithuania. Malaysia. Mauritius. Mexico. Montenegro. Oman. Palau. Panama. Poland. Romania. Russian Federation. Saint Kitts and Nevis. Saint Lucia. Saint Vincent and the Grenadines. Serbia. Seychelles. Slovakia. South Africa. Turkey. Uruguay. Venezuela (Bolivarian Republic of)

High income

Andorra. Antigua and Barbuda. Australia. Austria. Bahamas. Bahrain. Barbados. Belgium. Brunei Darussalam. Canada. Cyprus. Czech Republic. Denmark. Estonia. Finland. France. Germany. Greece. Iceland. Ireland. Israel. Italy. Japan. Kuwait. Luxembourg. Malta. Monaco. Netherlands. New Zealand. Norway. Portugal. Qatar. Republic of Korea. San Marino. Saudi Arabia. Singapore. Slovenia. Spain. Sweden. Switzerland. Trinidad and Tobago. United Arab Emirates. United Kingdom. United States of America Cook Islands. Nauru. Niue and Tuvalu are not categorized into income groups and are therefore excluded from the computation of aggregate indices by income group.

Appendix 2.

Methodological Supplement – Search Strategy on Pubmed

Population

(Developing Countr*[tw] OR Under Developed countr*[tiab] OR UnderDeveloped countr*[tiab]OR less Developed countr*[tiab] OR Developing nation*[tiab] OR Under Developed nation*[tiab] OR UnderDeveloped nation*[tiab] OR less Developed nation*[tiab] OR Third World*[tiab] OR low resource countr*[tiab] OR low resource nation*[tiab] OR africa[mesh] OR (africa*[tiab] NOT african americans[tiab]) OR South America[mesh] OR South America*[tiab] OR latin America*[tw] OR central America[mesh] OR ((asia[mesh] OR asia*[tiab]) NOT japan*[mesh]))

Intervention

(life style*[tw] OR lifestyl*[tw] OR diet therapy[mesh] OR Sodium Restrict*[tiab] OR salt Restrict*[tiab] OR low Sodium*[tiab] OR low salt*[tiab] OR Potassium, Diet* [tw]OR Magnesium [tw]OR Calcium [tw] OR fat Restrict*[tiab] OR low fat*[tiab] OR Carbohydrate Restrict*[tiab] OR low carb*[tiab] OR Caloric Restrict*[tw] OR Food, Formulated[tw] OR Formulated Food*[tw] OR diet[tw] OR dietary[tw] OR weight loss*[tw] OR losing weight[tw] OR Weight Reduction*[tiab] OR Disease Management*[tw] OR Exercise[mesh] OR Exercise therapy[mesh] OR Exercise test[mesh] OR Exercise Movement Techniques[mesh] OR kinesiotherap*[tw] OR Physical Endurance[mesh] OR Anaerobic*[tiab] OR aerobic*[tiab] OR Exercise*[tiab] OR Resistance Training*[tiab] OR Motor activit*[tw] OR Physical Activit*[tiab] OR Locomotor Activit*[tiab] OR social support*[tw] OR Social Network*[tiab] OR Tobacco Use Cessation*[tw]OR Smoking cessation*[tw] OR Alcohol Drink*[tw] OR Alcohol consum*[tw] OR Drinking Alcohol*[tw] OR Alcoholi*[tw] OR non pharmacol*[tw] OR relaxation therap*[tw] OR tai-ji [tw] OR yoga [tw])

Outcome

(Blood pressure*[tiab] OR Hypertension[mesh:noexp] OR Hypertension[tiab] OR Systolic Pressure[tiab] OR Diastolic Pressure [tiab] OR Pulse Pressure [tiab])

Study Type

(Clinical Trial[pt] OR Randomized Controlled Trial[pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR randomly [tiab] OR trial [tiab] OR groups [tiab] OR Comparative Study[pt] OR Compar*[tiab] OR Clinical Trial*[tiab] OR Evaluation Studies[pt] OR Evaluat*[tiab] OR Effectiv*[tiab] OR utilit*[tiab] OR Validation Studies[pt] OR Validat*[tiab] OR reliab*[tiab] OR relevan*[tiab]

Appendix 3.

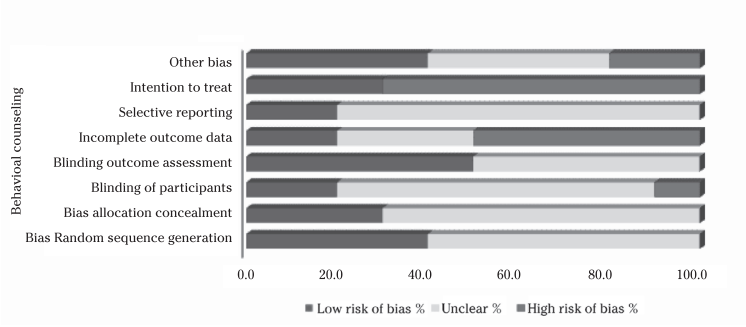
Methodological Supplement – Missing Variance imputation

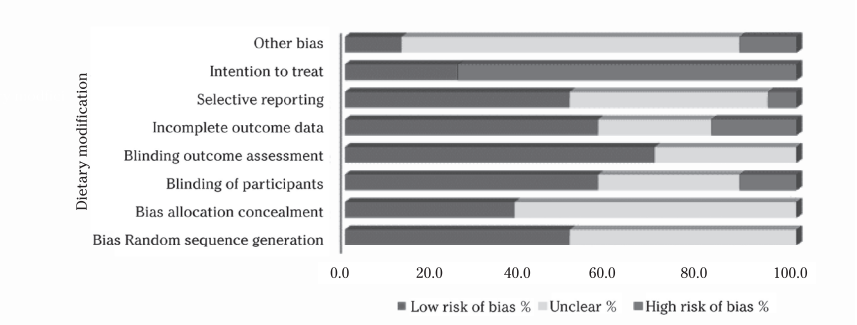
The mean difference variance estimation was calculated according different information reporting across trials and it was imputed whenever standard deviation, standard errors or confidence interval 95% was reported for baseline and/or after intervention measurements. Variance imputation to continuous variables response seems to be a field of controversy[88] but some studies have shown that different methods won't alter results of meta-analysis given the appropriate attention to each trial.[89,90] In fact, a number of meta-analysts have to deal with a trials lacking variance of effect estimates.[91]

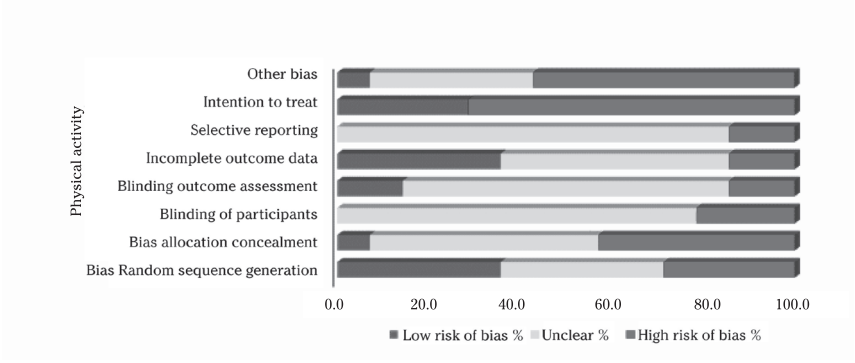
Since only 6 interventions reported variance of mean difference between pre and post intervention in each group, we imputed variance separately in each trial according to available information in each study.

When the study would inform the p value of the mean change variance we calculated the standard deviation. When the study informed t statistics of the mean change and the p value, the t statistics were used. From the sd baseline, final and change we calculated the Correlation Coefficient and used its median from the available ones. We then calculated the median from the studies that provided SD change .

We than had two datasets, one using imputation of variance with assumed correlation coefficient from studies that reported means and standard deviations for systolic and diastolic pressure at baseline (pre intervention) and final (post intervention)[88,90] and another dataset substituting missing variance information using the median of available standard deviations reported in other studies.[88] The formula used to the derive Correlation Coefficient from informed variance in other studies is shown (*Supplementary Appendix 2*). A conservative approach was used to input variance from other studies Correlation Coefficient. We analysed available sd descriptively and ranged from the median (0.53) to the maximum (0.87) according to the critical p values informed in the studies (e.g. $p<0.001$ or $p<0.05$).







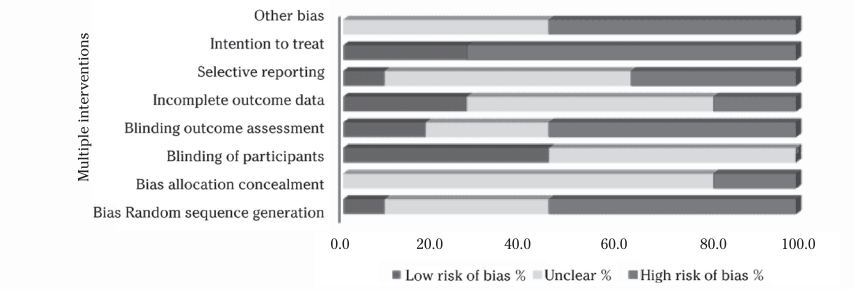


Figure 1. *Assessment of quality across included trials*

Table 1. *Equations to calculate mean difference and effect size*

Standard deviation from Standard Error	$SD = \sqrt{n}\ SE$
Standard deviation from a Confidence Interval 95%	$SD = \frac{\sqrt{n}\ (\text{upper limit} - \text{lower limit})}{3}.92$
Standard deviation of the mean change from p value or t statistics	$SD_{change} = \frac{\sqrt{n}\ Mean_{change}}{t_{n-1;\,p\ value}}$
Correlation Coefficient	$Corr = \frac{SD^2_{baseline} + SD^2_{final} - SD^2_{change}}{2\ SD_{baseline}\ \ SD_{final}}$
Standard deviation from Correlation Coefficient	$SD_{change} == \sqrt{SD^2_{baseline} + SD^2_{final} - (2\ Corr\ \ SD_{baseline}\ \ SD_{final})}$

Chapter 7

Mind-body interventions for patients with cardiac disease: a systematic review and meta-analysis

Younge JO, Gotink RA, Baena CP*, Roos-Hesselink JW, Hunink MGM.*
Eur J Prev cardiol. 2014 Sep 16
**Equal contributions*

Abstract

Background

Due to new treatment modalities in the last decades, a decline in cardiovascular deaths has been observed. There is an emerging field of secondary prevention and behavioural programs with increased interest in the use of mind-body practices. Until now, these have not been established in cardiovascular disease treatment programs.

Design

We performed a systematic review and meta-analysis of the available evidence on the effectiveness of mind-body practices for patients with diagnosed cardiac disease.

Methods

We included randomized controlled trials (RCTs), published in English, reporting mind-body practices for patients with diagnosed cardiac disease. EMBASE, MEDLINE, Pubmed, Web of Science, The Cochrane Central Register of Controlled Trials and PsycINFO were searched up to July 2013. Two reviewers independently identified studies for inclusion and extracted data on study characteristics, outcomes (Quality of Life, anxiety, depression, physical parameters and exercise tolerance) and quality assessment. Standardized effect sizes (Cohen's d) were calculated comparing the outcomes between the intervention and control group and random effects meta-analysis was conducted.

Results

We identified 11 unique RCTs with an overall low quality. The studies evaluated mindfulness based stress reduction, transcendental meditation, progressive muscle relaxation and stress management. Pooled analyses revealed effect sizes of 0.45 (95%CI 0.20-0.72) for physical quality of life, 0.68 (95%CI 0.10-1.26) for mental quality of life, 0.61 (95%CI 0.23-0.99) for depression, 0.52 (95%CI 0.26-0.78) for anxiety, 0.48 (95%CI 0.27-0.69) for systolic blood pressure and 0.36 (95%CI 0.15-0.57) for diastolic blood pressure.

Conclusions

Mind-body practices have encouraging results for patients with cardiac disease. Our review demonstrates the need for high quality studies in this field.

Introduction

Advances in medical treatment have resulted in a decline in mortality from cardiovascular disease (CVD).[1] CVD is, however, still the leading cause of death globally.[2] Furthermore, the decline in CVD mortality has led to an increase in prevalent CVD, requiring treatment and secondary prevention of more-and-more patients with documented disease. Traditionally, secondary prevention has focussed on well-established and modifiable risk factors, such as smoking, hypertension, diabetes, dyslipidaemia and physical inactivity. An emerging field is that of psychosocial risk factors (anxiety, depression, and stress) in the aetiology and prevention of CVD.[3-5]

Clinical trials studying modification of psychosocial risk factors in CVD have focused on the use of behavioural and psychological interventions in the setting of cardiac rehabilitation. Multiple studies show promising results of stress management on psychological outcomes and mind-body practices have become popular for stress reduction.[6] Commonly used in Eastern cultures for centuries, mind-body practices have more recently been making their way into Western lifestyle and clinical practice with currently almost 20% of the population routinely doing some form of mind-body practice.[7,8] Furthermore, evidence is accumulating that mind-body practices can be used as safe adjuncts to existing medical treatment and are effective in several conditions, such as insomnia, chronic pain, depression, post-traumatic stress, irritable bowel syndrome (IBS), hypertension and cardiovascular disease (CVD).[9-13]

Mind-body practices predate modern biomedicine, but there is accumulating evidence on the connection between the mind and body.[14] The encouraging results on improved psychological well-being and measurable changes in physical parameters suggest that mind-body practices can be of added value in patients with CVD. The aim of this review was to evaluate the effectiveness of meditation-based mind-body practices on quality of life, anxiety, depression, physical parameters and exercise tolerance in patients with diagnosed cardiac disease.

Methods

Search strategy

Together with a professional librarian we conducted electronic searches through Embase, Medline, Pubmed, Web of Science (WoS), The Cochrane Central Register of Controlled Trials (CENTRAL) and PsycINFO of the literature published up to 31 July 2013. We reviewed mind-body practices with the focus on meditation and relaxations in patients with diagnosed cardiac disease[15] that could be taught without external biofeedback techniques. Practices considered included: (transcendental) meditation, mindfulness meditation, autogenic training and relaxation methods. The diagnosed cardiac diseases included were: heart failure, ischemic heart disease, hypertensive heart disease, inflammatory heart disease, valvular heart disease, congenital heart disease and cardiomyopathy. The search included keywords corresponding to the mind-body

techniques and cardiac diseases. To optimize the search strategy we used synonyms including 'text words' and MeSH (Medical Subject Headings) (Appendix A, see online Supplementary material). We screened for other potentially relevant randomized controlled trials by searching through the references and citation lists from identified papers meeting our inclusion criteria.

Study selection

Two reviewers (JY and CB) independently selected all potential studies, which were identified through the results of our search strategy. Disagreements were resolved by consensus. We included relevant studies if they met the following criteria: (1) written in English, (2) study design was a randomized controlled trial (RCT), (3) study population with diagnosed cardiac disease, (4) the mind-body practice was compared to standard care, pharmacological intervention, psychological intervention, or no treatment at all, (5) at least one of the following clinically relevant outcomes was assessed - any form of Quality of life (QoL) measurement as described by Ski et al.[16] and Wenger et al.[17] including subjective health status and health-related QoL, mental health scales on anxiety or depression, physical parameters (blood pressure and heart rate), or exercise tolerance (measured by 6-minute walk test or cardiopulmonary exercise testing).

We selected studies reporting both objective and physiological outcomes, because especially in cardiac disease, the physiological parameters are good indicators of overall physical well-being. Several studies show the hypothesis and rational between mind-body interaction. We know that hypertension is one of the major risk factors of cardiovascular morbidity and mortality.[18] Prevalence of hypertension is projected to increase to about 60% in 2025.[19] Conventional medical treatment may be associated with various adverse effects,[20] especially in case of multiple drug use and treatment-resistant hypertension, which has led to investigations of the supporting role of non-pharmacological interventions.

We chose to limit our search to English written studies based on two reports, which showed no systematic bias with the use of a language restriction.[21,22]

We excluded studies if they met one of the following criteria: (1) the article was a review or meta-analysis, (2) data was from abstracts or letters, (3) studies that evaluated psychological or psychosocial interventions focussing on interactions between people, (4) studies in which the mind-body practice was not the main intervention of interest, (5) studies that evaluated stress management with a major cognitive component, (6) studies evaluating practices using an external biofeedback technique; and (7) studies that evaluated practices performed during the peri-operative phase.

Data extraction

Data from studies were extracted independently by two authors (JY and RG) using a data extraction form in accordance with the Cochrane handbook of systematic reviews.[23] The following information was obtained using this form: author, journal, year of publication, country, setting, funding, number of patients, cardiac diagnosis, mean age, gender, co-morbidity, use of medication,

type of mind-body practices, details of the practices, comparators, follow-up duration, outcome definition, unit of measurement, pre- and post-outcome measurements on exercise tolerance, QoL, anxiety, depression, blood pressure and heart rate. If more than one practices or control arm was present, we included only the mind-body practices versus the control group. Disagreements were resolved by consensus. If data were unclear or unavailable, the authors were contacted by e-mail. In case of multiple publications from one source we only included data from different papers if different outcomes were reported. Resting heart rate and blood pressure results were used and not values measured during the relaxation practice.

Quality assessment

Two reviewers (JY and RG) independently scored the methodological quality of each study by using the Cochrane Collaboration 'risk of bias' tool[23] in which the following domains are considered: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, (7) other sources of bias. The judgment is categorized as follows: A. 'Low risk' of bias B. 'High risk' of bias C. 'Unclear risk' of bias. Additionally, the heterogeneity between studies was reported, and the PRISMA statement for reporting systematic reviews and meta-analysis was used for reporting of results.[24] Disagreements were resolved by consensus. Small sample size can lead to bias but no formal agreement exists on how large the sample size of a study should be to limit the risk of bias. Consensus between JY and RG led to the cut-off point of 30 participants per study to score the study at high risk of 'other bias' due to their small sample size.

Data synthesis and analysis

To analyse the maximum treatment effect we used data of post-treatment values on the predefined outcome measurements. If multiple follow-up data were available we used the outcome assessment at the end of the intervention period in order to determine the maximum treatment effect. If multiple follow-up data were unavailable we used the data as reported. We calculated the Cohen's d effect size, comparing the intervention and control groups, of the means and confidence intervals according to the equations as shown in Appendix B (see online Supplementary Material). Data for each outcome were summarized in forest plots and random effects models were used to calculate summary estimates with 95%CI. Funnel plots were constructed to check for the presence of publication bias. Of the eight domains of the Short-Form Health Survey-36, we present the summary measures of the Physical and Mental Component Score (PCS and MCS respectively). QoL measures were grouped according to their subscale (i.e. physical, mental/emotional or other). If more than one QoL measure was reported (i.e. The Short-Form Health Survey 36 (SF-36) and the Minnesota Living With Heart Failure Questionnaire (MLWHFQ)), the SF-36 was used over the other measures in the random effects meta-analysis.

Results

Study selection

Our literature search resulted in 1487 studies, 1485 from the original search and 2 from reference lists (Figure 1). Of these, 551 studies were excluded because they were duplicates and 902 studies were excluded when title and abstract were reviewed. Of the 34 studies selected for full text review 21 were excluded for not meeting the predefined inclusion criteria (Figure 1). Finally, 13 RCTs, consisting of 11 unique studies, met our inclusion criteria and were included in this review. They were published between 1996 and 2012 and were carried out in six different countries (UK, USA, China, Brazil, India and Portugal).

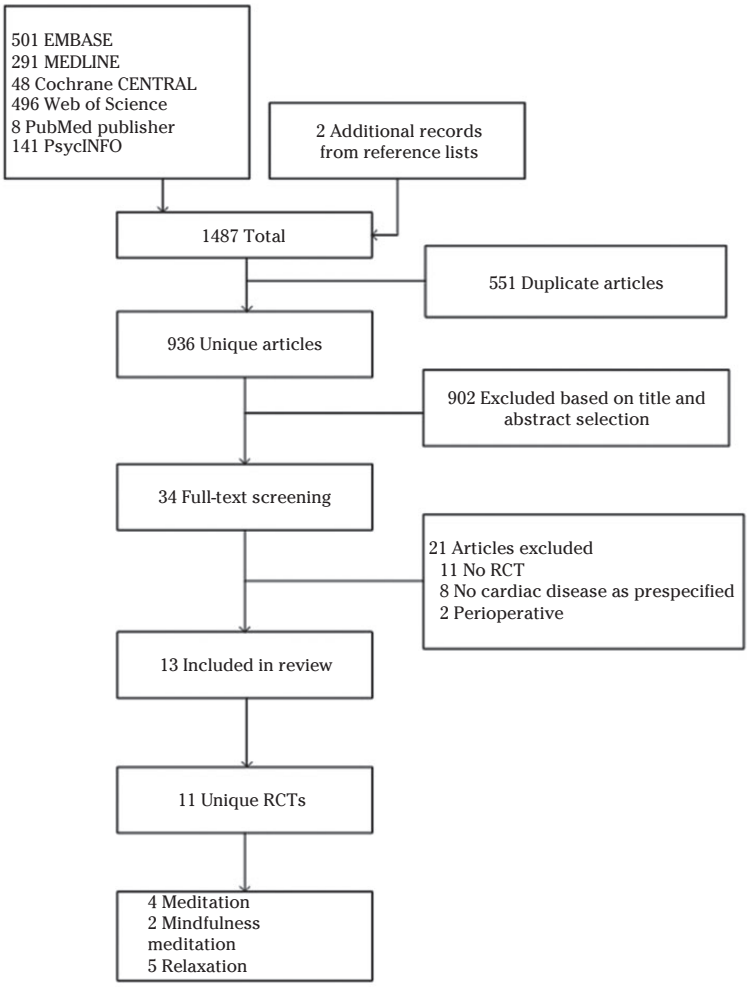


Figure 1. *Flow diagram of identified studies*

General characteristics

The characteristics of interventions and patients are presented in Table 1. The studies included 793 unique patients (46% female) with a mean age of 66 (± 11 years). The studies ranged in sample size from 18 to 201 patients. There were two cases of duplicate reports on the same patient population.[25,26] One study did not fully report their baseline characteristics.[27]

Table 1. *Study characteristics of included randomized controlled trials*

Author	Year	Study location	Cardiac diagnosis	Age (years) (mean ± SD)	Female %	N
Trzcieniecka-Green	1996	UK	AMI/CABG	60 ± 10	13	100
Wilk	2002	USA	CABG/MI/Angioplasty	63 ± NR	14	14
Tacon	2003	USA	Cardiac[a]	61 ± 9	100	18
Robert-Mccomb	2004	USA	Cardiac[a]	61 ± 8	100	18[b]
Curiati	2005	Brazil	HF	75 ± 7	74	19
Chang	2005	USA	HF	70 ± 14	0	63
Paul-Labrador	2006	USA	CAD	67 ± 14	18	103
Jayadevappa	2007	USA	HF	64 ± 11	61	23
Yu	2007	China (HK)	HF	76 ± 8	51	121
Yu	2009	China (HK)	HF	76 ± 8	51	121[b]
Neves	2009	Portugal	CAD	60 ± 15	85	81
Schneider	2012	USA	CAD	59 ± 15	43	201
Nehra	2012	India	CHD	n/a	n/a	50
All				66 ± 11	51	743[b]

AMI, acute myocardial infarction; CABG, coronary bypass artery grafting; CVD, cardiovascular disease; CAD, coronary artery disease; HF, heart failure; CHD, coronary heart disease, n/a, not available.
[a]Patients diagnosed with angina pectoris, valvular disease, hypertension or CAD
[b]743 unique patients

Patients

Most studies included patients with heart failure (n=5,)[26,28-31] or coronary artery disease (n=4).[27,32-34] One study only recruited heart failure patients after optimal medical treatment and at least two months of carvedilol therapy.[29] Two studies included patients following AMI, angioplasty or CABG, when considered in a stable condition (2-3 months post surgery or percutaneous intervention).[35,36] Two studies included various diagnoses including angina, hypertension, valve disorders and coronary artery disease.[25,37]

Interventions

The included studies compared the effects of different mind-body practices with various control interventions. The mind-body practices studied were: mindfulness-based stress reduction,[25,27,37] transcendental meditation,[30,33,34] meditation (which consisted of three components: breathing, mental repetition of a word and a guided image),[29] progressive muscle relaxation training,[26,31,36] relaxation response (which consisted of 8 different components: breathing awareness; mental

repetition of a word, sound, phrase, or prayer; mindfulness meditation; guided body scan; progressive muscle relaxation; guided countdown; autogenic and guided imagery),[28] relaxation,[32] and stress management (based on autogenic training).[35] Further details and the content of the interventions are shown in Table 2. Two studies evaluated a mind-body practice in addition to regular cardiac rehabilitation compared to cardiac rehabilitation alone.[32,36] The duration of the interventions ranged from 4 to 26 weeks. One study did not provide the duration of the intervention.[34] All, but one study[32] gave daily home exercises by audiotape or instructions. In one study the trial was conducted in two parts due to a hiatus in funding.[34]

Table 2. *Details of interventions in included studies*

Author	Year	Name	Details	Home assignments	(weeks)	Control group
Trzcieniecka-Green	1996	Stress management	Weekly sessions	Audiotape on relaxation, twice daily	10	Waiting list
Wilk	2002	Progressive muscle relaxation (+ Cardiac rehabilitation)	50 minute weekly sessions	Audiotape on PMR	4	Cardiac rehabilitation
Tacon	2003	Mindfulness based stress reduction	Two-hour weekly sessions	Audiotape, daily	8	Waiting list
Robert-Mccomb	2004	Mindfulness based stress reduction	Two-hour weekly sessions	Audiotape, daily	8	Waiting list
Curiati	2005	Meditation	Two classes 1 hour introduction	Audiotape	12	Weekly talks
Chang	2005	Relaxation response	Weekly 90 min group sessions	Audiotape	15	Usual care
Paul-Labrador	2006	Transcendental meditation	Introduction week, one month of biweekly meetings, weekly thereafter	Daily home assingments	16	Health education
Jayadevappa	2007	Transcendental meditation	Seven days introduction, 3 months biweekly meetings, 3 months monthly meetings	Twice daily, 20 minutes of TM	26	Health education
Yu	2007	Progressive muscle releaxation (grade 2)	One-hour weekly sessions, biweekly phone calls, skill revision at 4 weeks	Audiotape	14	Attention control (phone calls)
Yu	2009	Progressive muscle releaxation (grade 2)	One-hour weekly sessions, biweekly phone calls, skill revision at 4 weeks	Audiotape	14	Attention control (grade 2) (phone calls)
Neves	2009	Relaxation (+ Cardiac rehabilitation)	3 one-hour weekly sessions after cardiac rehabilitation session	None	10	Cardiac rehabilitation
Schneider	2012	Transcendental meditation	Introduction week, 1 month weekly meetings, 2 months biweekly meetings, monthly meetings thereafter	Twice daily, 20 minutes of TM	n/a	Health education
Nehra	2012	Mindfulness based stress reduction	Eight weekly individual 150 minute sessions and one 7 hour weekend sessions and extended MBCT	Yes	10-17	Usual care

PMR, progressive muscle relaxation; TM, transcendental meditation; MBCT, mindfulness-based cognitive therapy.

Control intervention

The control interventions used were: waiting list,[25,35,37] usual care (in which the patients were expected to solely attend the two moments of study outcome assessment and were not invited to group sessions),[27,28] attention control (extra attention by phone calls to balance the effect of the extra attention which patients received in the PMRT training).[13,26,1] Some studies made comparisons with an active intervention, such as health education,[30,33,34] or cardiac rehabilitation.[32,36] One study had weekly talks on stress management.[29] The study by Chang et al.[28] used two control groups (education and usual care) of which we present only the usual care.

Risk of bias

The risk of bias of included studies is shown in Table 3. Due to the nature of the intervention, none of the studies was able to blind the participants and personnel teaching the intervention. Blinding of the outcome assessor is possible and was included in the 'Risk of bias' table. Furthermore, the presence of small groups often made the risk of other bias inevitable.

Table 3. *Risk of bias in included studies*

	Random sequence generation	Allocation concealment	Blinding of patient	Blinding of personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Other bias
Trzcieniecka-Green (1996)	?	?	-	-	?	-	+	?
Wilk (2002)	?	?	-	-	-	?	-	-
Tacon (2003)	?	?	-	-	?	+	-	-
Robert-McComb (2004)	?	?	-	-	?	+	-	-
Curiati (2005)	?	?	-	-	?	+	+	-
Chang (2005)	+	?	-	-	?	+	+	-
Paul-Labrador (2006)	+	+	-	-	+	+	+	?
Jayadevappa (2007)	+	+	-	-	+	+	+	-
Yu (2007)	+	?	-	-	+	-	?	+
Neves (2009)	?	?	-	-	?	+	+	?
Yu (2009)	+	?	-	-	+	-	?	+
Schneider (2012)	?	+	-	-	+	?	+	-
Nehra (2012)	+	?	-	-	?	+	-	-

Unknown risk	?
Low risk	+
High risk	-

Random sequence generation

Five studies reported which randomization procedure was used.[26-28,30,31,33] The other studies did not provide enough information to judge which randomization procedure was used and were classified as 'Unclear risk'.

Allocation concealment

Only three studies reported allocation concealment.[30,33,34] Most studies failed to state clearly how randomization had been achieved and were judged as 'Unclear risk'.

Blinding of participants, personnel and outcome assessment

The outcome assessor was blinded in 5 studies.[26,30,31,33,34] In one study the outcome assessor was also the instructor of the intervention making blinding to the outcome impossible.[36] In the other studies the assessment procedure of the outcome was unclear.

Addressing incomplete outcome data

Almost all studies reported missing data whereas three studies did not.[26,31,35] Eight studies reported adequate information about how many participants had withdrawn after having consented to participate.

Selective reporting

Most studies reported outcomes which were predefined in the methods section and were thus judged as low risk of selective reporting bias. In three studies the risk of selective reporting was considered high since some of the outcomes mentioned in the methods section were not reported.[25,27,37] Furthermore, one study failed to provide enough statistical data (i.e. standard deviations were missing).[36]

Other bias

We considered other sources of bias to be present if the study included a small sample size ($n < 30$), was reported to be underpowered, or minimal or no group comparison at baseline was reported. Almost all studies had a small sample size. Only four studies included 100 or more patients.[26,31,33,35]

Heterogeneity across studies

Overall, based on the clinical diversity of the included patients in the studies (Table 1), the methodological diversity in study design and risk of bias (Table 3), and the statistical heterogeneity of outcomes reported, we conclude there is significant heterogeneity across studies.

Table 4. *Type of outcome in included studies (methods)*

Author	Year	Outcome	Type of scale	Moment of assessment
Trzcieniecka-Green	1996	Qol, anxiety, depression	GWB, HADS	Baseline, week 10, week 26
Wilk	2002	Anxiety, DBP, SBP	STAI	Baseline, week 4
Tacon	2003	Anxiety	STAI	Baseline, week 8
Robert-Mccomb	2004	QoL, exercise tolerance	SF-36	Baseline, week 8
Curiati	2005	QoL, exercise tolerance, DBP, SBP, HR	MLWHFQ, VO2Max	Baseline, week 14
Chang	2005	Qol, exercise tolerance	MLWHFQ, VO2Max	Baseline, week 15-19
Paul-Labrador	2006	Anxiety, depression, SBP, DBP	STAI, CESD	Baseline, week 16
Jayadevappa	2007	Qol, depression, exercise tolerance	SF-36, MLWHFQ, QWB, CESD, 6MWT	Baseline, week 12, week 26
Yu	2007	Anxiety, depression	HADS	Baseline, week 8, week 14
Yu	2009	Qol	WHOQOL-BREF-HK	Baseline, week 8, week 14
Neves	2009	SBP, DBP, HR		Baseline, week 12, week 26
Schneider	2012	Depression, SBP, DBP, HR	CESD	Baseline, week 12, every 26 weeks
Nehra	2012	Anxiety, depression	HADS	Baseline, week 10-17

QoL, quality of life; GWB, general well-being; HADS, Hospital Anxiety and Depression Scale; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; STAI, State-Trait Anxiety Inventory; SF-36, 36-item Short Form Health Survey; MLWHFQ, Minnesota Living with heart Failure Questionnaire; HRV, heart rate variability; CESD, Center for Epidemiologic Studies Depression Scale; QWB, Quality of Well Being; 6MWT, six-minute walk test; WHOQOL-BREF-HK, World Health Organization Quality of Life-BREF Hong Kong Chinese version.

Subjective outcomes

Quality of Life. Six RCTs reported quality of life outcomes assessed with five different questionnaires. Results measurements used are presented in Table 4. Pooled effect sizes of the physical QoL measures revealed an overall moderate statistically significant effect size of $d = 0.45$ (95% CI 0.18-0.72) and an overall large statistically significant effect size of d=0.68 (95%CI 0.10-1.26) for mental scores (Figure 2). The other subscales showed a small non-significant effect of $d = 0.25$ (95%CI -0.10-0.61). The results were mainly influenced by the large study of Yu et al.[26]

Depression. Depression was assessed with only two instruments: the Center for Epidemiologic Studies Depression Scale (CESD) and the Hospital Anxiety and Depression scale (HADS). Depression was reported in six studies. The study by Schneider et al.[34] consisted of repeated measurements over a period of 5.4 years. Random effects meta-analysis of the depression outcomes revealed an overall moderate statistically significant effect size of d= 0.61 (95% CI 0.23-0.99) (Figure 3). Results were heterogeneous with small effects of $d = 0.14$ in the study by Schneider et al.[34] and large effects of $d = 1.25$ in the study of Yu et al.[31] (Figure 3).

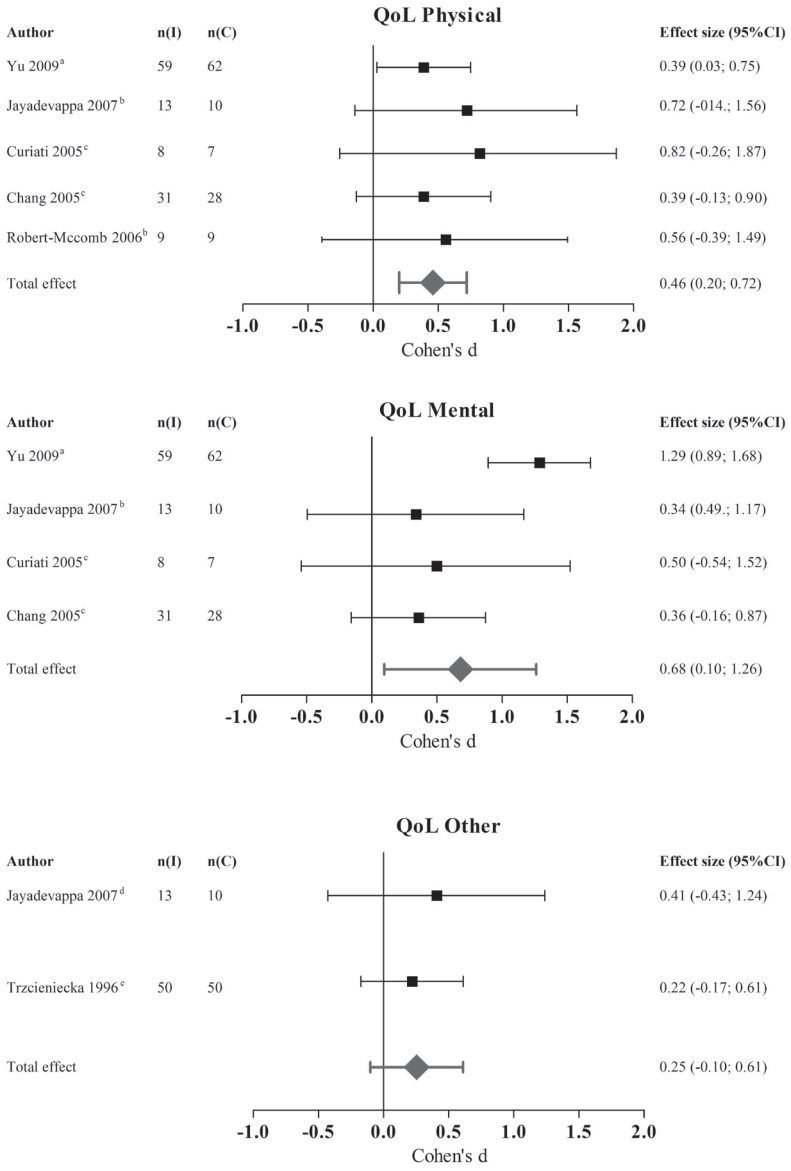


Figure 2. *Forest plot of QoL results*
CI, confidence interval; n(I), number of patients in intervention group; n(C), number of patients in control group;
[a]WHOQOL-BREF-HK, World health Organization Quality of Life Hong Kong version. [b]SF-36, Short-Form Health Survey 36.
[c]MLWHQ, Minnesota Living With Heart Failure Questionnaire. [d]QWB, Quality of Well-Being. [e]GWB, General Well-Being.

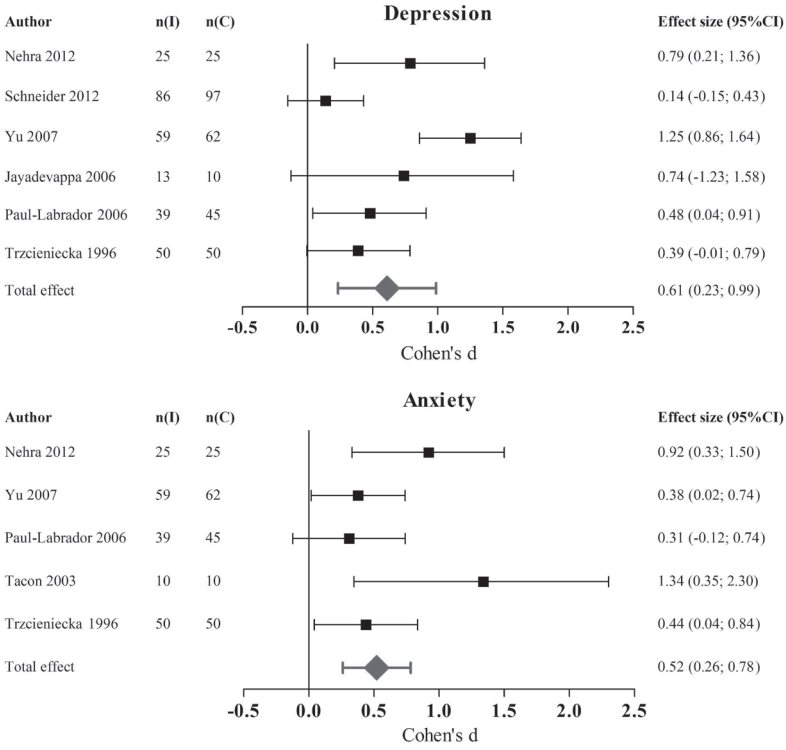


Figure 3. *Forest plots of depression and anxiety*
n(I),number of patients in intervention group; n(C), number of patients in control group; CI, confidence interval.

Anxiety. Anxiety was reported in five studies. An overall medium statistically significant effect of 0.52 (95% CI 0.26-0.78) (Figure 3). Again, results were heterogeneous with small effect sizes ranging from $d = 0.31$ in the study of Paul-Labrador et al.[33] to large effects of $d = 1.34$ in the study of Tacon et al.[37] (Figure 3).

Physiological outcomes

Resting Blood pressure. Blood pressure was reported in five RCTs. Due to missing SDs no effect size with 95% CI could be calculated for Wilk et al.[36] Effect sizes for SBP ranged from small effects of $d = 0.42$ in the study of Schneider et al.[34] to a large effect of $d = 1.10$ in the study of Curiati et al.[29] (Figure 4). The meta-analysis resulted in an overall medium statistically significant effect of d=0.48 (95% CI 0.27-0.69). Effect sizes for DBP showed a similar heterogeneous pattern with results of d ranging from 0.25 in the study by Schneider et al.[34] to 0.80 in the study by Curiati et al.[29] Random effects meta-analysis showed an overall lower, but statistically significant, effect than the SBP results (0.36, 95% CI 0.15-0.57) (Figure 4).

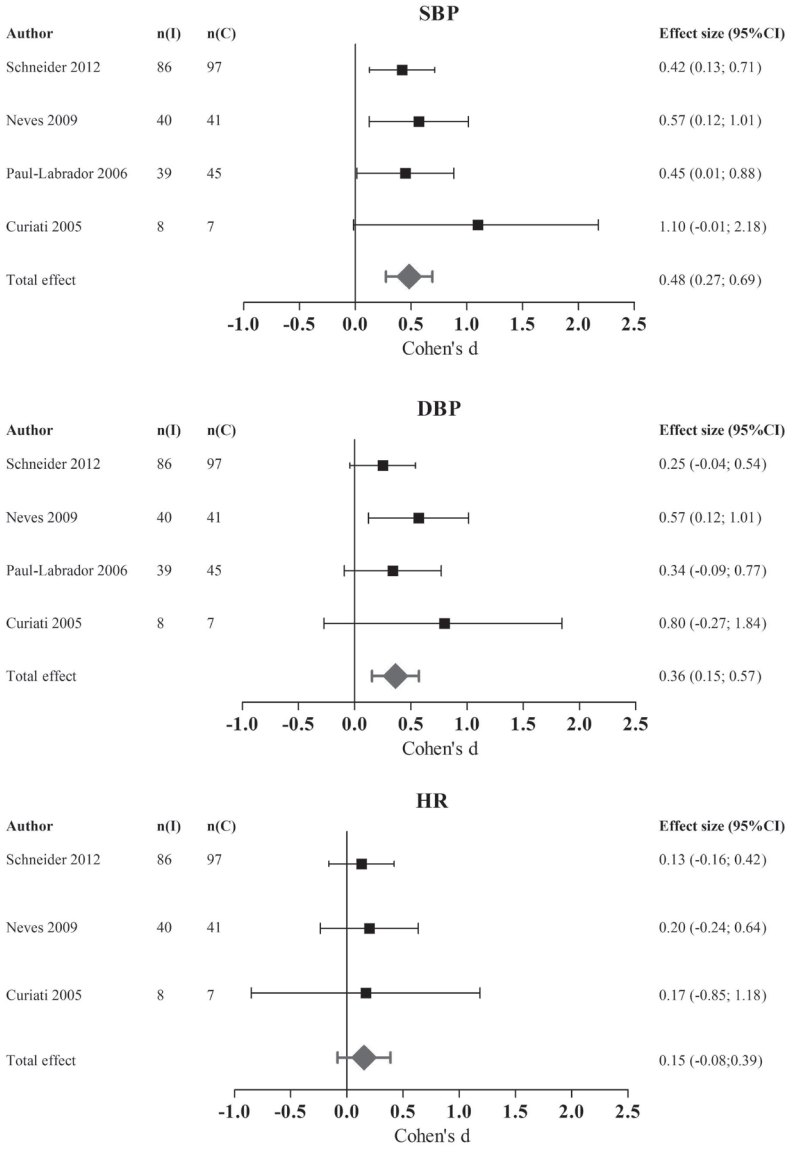


Figure 4. *Forest plots of physiological parameters*
SBP, systolic blood pressure; n(I),number of patients in intervention group; n(C), number of patients in control group; CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate.

Table 5. *Results of studies that reported exercise tolerance.*

Author	Year	Patients analyzed (n)		Effect size (95% CI)[b]	
		Intervention	Control	Exercise Tolerance	Exercise Test
Curiati	2005	8(5)[a]	7(5)[a]	0.51 (-0.75-1.77)	VO2max
Chang	2005	31	28	n/a	VO2max
Jayadevappa	2007	13	10	1.04 (0.15-1.91)	6MWT

CI, confidence interval; n/a, not available; 6MWT, six-minute walk test
[a]5 patients did VO2max testing. [b] Effect size is Cohen's d

Resting Heart rate. Four RCTs reported on resting heart rates (Figure 4). Wilk et al.[36] reported that a significant difference was found, but no effect size with 95% CI could be calculated due to missing SDs.

An overall small effect of $d = 0.15$ (95%CI -0.08-0.39) was found in random effects meta-analysis. All studies showed small effects of d ranging from 0.13 to 0.20 (Figure 4).

Exercise Tolerance. Only three studies reported exercise tolerance as outcome (Table 5).[28-30] No effect size could be calculated for Wilk et al.[36] due to missing SDs. A medium effect of $d = 0.51$ was seen for VO2 max testing, and a large effect of $d = 1.04$ was seen on the 6 minute walk test in the study of Jayadevappa et al.[30] (Table 5).

Publication bias

Funnel plots of the subjective and physiological outcomes were constructed and are shown in Appendix C (see online Supplementary Material). Overall, the funnel plots show no clear evidence of publication bias.

Discussion

The eleven unique studies in this review had an overall low quality and used a variety of outcome measurements. There was some evidence for the effectiveness of mind-body practices for patients with diagnosed cardiac disease. Promising, but heterogeneous results were seen on overall effect sizes of mental and physical QoL, anxiety, depression and blood pressure.

There are several reasons why patients engage in mind-body practices. Firstly, these therapies are easy to learn and they allow patients to take a more active role in their treatment. Secondly, most exercises can be done at home, without the help of external means. Thirdly, low emotional and physical is risk involved. Finally, the costs are relatively low.[38-40] Although mind-body practices require commitment in both adherence and time, they are becoming more-and-more popular.[7,8]

Studies on the effectiveness of mind-body practices in CVD have shown some promising results. They improved psychosocial risk factors, reduced blood pressure and even showed survival benefits.[41-44] It is hypothesized that patients with CVD are more likely to seek additional

treatment since psychological stress, whether cause or consequence, often accompanies their clinical condition.[45,46] Stress can cause an imbalance between the mind and body, and several studies suggest stress is related to CVD at several stages of the disease from the development of arteriosclerosis to acute cardiac events to chronic disease.[5,47] Furthermore, other studies have shown associations between psychosocial variables and vascular function, inflammation and increased blood clotting.[48-50] Thus, although the precise pathophysiological mechanism still needs to be unraveled, it is clear that a relationship exists between stress and CVD.

Many biological pathways have been studied that could explain the working mechanism of mind-body practices. Several studies show positive physiological effects in blood pressure, heart rate, respiration rate and oxygen consumption with mind-body practices.[10,51] Three studies showed that the autonomic nervous system releases endorphin and serotonin, which leads to counteraction of norephinephrine and activate the parasympathetic response.[10,12,51] In a small study on the effect of yoga and meditation on endothelial function, favourable changes were observed in endothelial-dependent vasodilatation in CAD patients.[44] A mechanism how mind-body practice can have influence on health is provided by research on the interaction between the central nervous system (CNS), and the endocrine, immune and peripheral autonomic nervous systems.[52] There is also evidence for a positive effect on the immune system and endothelial functioning.[51,53,54] All together, these studies show the profound effects of stress reduction and meditation techniques on the body, suggesting that the mind may be able to influence the working of the heart.

Until now, a core component in the treatment of CAD patients is cardiac rehabilitation with the components exercise training, healthy nutrition, and smoking cessation.[55] Lifestyle modification programs have shown to be of added value in treating patients with CAD.[56] These interventions have proven to be favourable for physical and psychosocial risk factors and also showed a survival advantage.[57-59] Additional stress management has been shown to have added value in cardiac rehabilitation programs.[60,61] Even though the American Heart Association (AHA) have recognized the importance of psychosocial interventions as a core component in cardiac rehabilitation programs,[62] these interventions have only been integrated in a limited number of settings. Furthermore, only 25-31% of eligible patients participate in these comprehensive programs.[63]

Some limitations of this systematic review must be addressed. Firstly, we limited our search strategy to English studies exclusively, with no consideration of studies conducted in the East - for example written in Chinese - from which mind-body practices originate. Secondly, we focused primarily one meditation-based mind-body practices which could be undertaken by patients at home without external tools. Therefore, no conclusions can be drawn on the effect of other mind-body practices in CVD.

The connection between the mind and heart is a complex phenomenon and the use of meditation-based mind-body practices is still limited in clinical practice. Clearly, the role of mind-body practices in the advanced treatment of cardiac patients still needs to be defined.

Behavioural cardiology is an emerging field that is bringing about awareness of the mind-heart connection and the management of psychosocial risk factors.[57]

However, current evidence on the efficacy and effectiveness of most mind-body practices hasn't been established due to lack of well-performed randomized clinical trials. Mind-body research has several drawbacks which can hamper the internal validity and generalizability of published studies. A paper by Caspi et al.[64] showed several important features to consider in meditation research such as monitoring, assessment procedures, integration of qualitative methods and a pragmatic design. Most of the included studies in this review failed to provide detailed information on the randomization procedure and a study protocol was often not available. Furthermore, most studies lacked power and were too small to draw firm conclusions from. Until now, there is not a clear understanding of the study design in mind-body research and future methodological studies should provide guidance.

Conclusions

In our review we showed that mind-body practices have encouraging results for patients with cardiac disease on selected QoL outcomes, anxiety, depression, and blood pressure. Due to an overall low quality of the studies no firm conclusions can be drawn. Future clinical trials should focus on using a rigorous study design in order to minimize methodological flaws and enhance their validity and generalizability.

References

1. National Heart, Lung, and Blood Institute. NHLBI Fact Book, Fiscal Year 2012, http://www.nhlbi.nih.gov/about/factbook/FactBook2012.pdf (2012, accessed 20 June 2013).
2. World Health Organization. Global status report on noncommunicable disaeses 2010, http://whqlibdoc.who.int/publications/2011/9789240686458_eng.pdf. (2011, accessed 31 July 2013.
3. Dimsdale JE. Psychological stress and cardiovascular disease. *J Am Coll Cardiol*. 2008; 51: 1237-46.
4. Hamer M, Molloy GJ and Stamatakis E. Psychological distress as a risk factor for cardiovascular events: pathophysiological and behavioral mechanisms. *J Am Coll Cardiol*. 2008; 52: 2156-62.
5. Thurston RC, Rewak M and Kubzansky LD. An anxious heart: anxiety and the onset of cardiovascular diseases. *Prog Cardiovasc Dis*. 2013; 55: 524-37.
6. Blumenthal JA, Babyak M, Wei J, et al. Usefulness of psychosocial treatment of mental stress-induced myocardial ischemia in men. *Am J Cardiol*. 2002; 89: 164-8.
7. Barnes PM, Bloom B and Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *Natl Health Stat Report*. 2008: 1-23.
8. Prasad K, Sharma V, Lackore K, Jenkins SM, Prasad A and Sood A. Use of complementary therapies in cardiovascular disease. *Am J Cardiol*. 2013; 111: 339-45.
9. Chiesa A and Serretti A. Mindfulness-based stress reduction for stress management in healthy people: a review and meta-analysis. *J Altern Complement Med*. 2009; 15: 593-600.
10. Chiesa A and Serretti A. A systematic review of neurobiological and clinical features of mindfulness meditations. *Psychol Med*. 2010; 40: 1239-52.
11. Innes KE, Selfe TK and Vishnu A. Mind-body therapies for menopausal symptoms: a systematic review. *Maturitas*. 2010; 66: 135-49.
12. Ludwig DS and Kabat-Zinn J. Mindfulness in medicine. *JAMA*. 2008; 300: 1350-2.
13. Ospina MB, Bond K, Karkhaneh M, et al. Meditation practices for health: state of the research. *Evid Rep Technol Assess (Full Rep)*. 2007: 1-263.
14. Kiecolt-Glaser JK, McGuire L, Robles TF and Glaser R. Psychoneuroimmunology and psychosomatic medicine: back to the future. *Psychosom Med*. 2002; 64: 15-28.
15. medicine NCfCaA. What is complementary and alternative medicine?
16. Ski CF and Thompson DR. Quality of life in cardiovascular disease: what is it and why and how should we measure it? *Eur J Cardiovasc Nurs*. 2010; 9: 201-2.
17. Wenger NK, Mattson ME, Furberg CD and Elinson J. Assessment of quality of life in clinical trials of cardiovascular therapies. *Am J Cardiol*. 1984; 54: 908-13.
18. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003; 289: 2560-72.
19. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK and He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005; 365: 217-23.
20. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013; 34: 2159-219.
21. Moher D, Pham B, Klassen TP, et al. What contributions do languages other than English make on the results of meta-analyses? *J Clin Epidemiol*. 2000; 53: 964-72.
22. Morrison A, Polisena J, Husereau D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care*. 2012; 28: 138-44.
23. Higgins. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011.
24. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009; 6: e1000100.
25. Robert McComb JJ, Tacon A, Randolph P and Caldera Y. A pilot study to examine the effects of a mindfulness-based stress-reduction and relaxation program on levels of stress hormones, physical functioning, and submaximal exercise responses. *J Altern Complement Med*. 2004; 10: 819-27.

26. Yu DS, Lee DT and Woo J. Improving health-related quality of life of patients with chronic heart failure: effects of relaxation therapy. *J Adv Nurs*. 2010; 66: 392-403.
27. Nehra DK, Sharma NR and Kumar P. Efficacy of MBSR program in treating Depression, Anxiety and Perceived Stress in Coronary Heart Disease Patients. *Indian Journal of Positive Psychology* 2012; 3: 91-5.
28. Chang BH, Hendricks A, Zhao Y, Rothendler JA, LoCastro JS and Slawsky MT. A relaxation response randomized trial on patients with chronic heart failure. *J Cardiopulm Rehabil*. 2005; 25: 149-57.
29. Curiati JA, Bocchi E, Freire JO, et al. Meditation reduces sympathetic activation and improves the quality of life in elderly patients with optimally treated heart failure: a prospective randomized study. *J Altern Complement Med*. 2005; 11: 465-72.
30. Jayadevappa R, Johnson JC, Bloom BS, et al. Effectiveness of transcendental meditation on functional capacity and quality of life of African Americans with congestive heart failure: a randomized control study. *Ethn Dis*. 2007; 17: 72-7.
31. Yu DS, Lee DT and Woo J. Effects of relaxation therapy on psychologic distress and symptom status in older Chinese patients with heart failure. *J Psychosom Res*. 2007; 62: 427-37.
32. Neves A, Alves AJ, Ribeiro F, Gomes JL and Oliveira J. The effect of cardiac rehabilitation with relaxation therapy on psychological, hemodynamic, and hospital admission outcome variables. *J Cardiopulm Rehabil Prev*. 2009; 29: 304-9.
33. Paul-Labrador M, Polk D, Dwyer JH, et al. Effects of a randomized controlled trial of transcendental meditation on components of the metabolic syndrome in subjects with coronary heart disease. *Arch Intern Med*. 2006; 166: 1218-24.
34. Schneider RH, Grim CE, Rainforth MV, et al. Stress reduction in the secondary prevention of cardiovascular disease: randomized, controlled trial of transcendental meditation and health education in Blacks. *Circ Cardiovasc Qual Outcomes*. 2012; 5: 750-8.
35. Trzcieniecka-Green A and Steptoe A. The effects of stress management on the quality of life of patients following acute myocardial infarction or coronary bypass surgery. *Eur Heart J*. 1996; 17: 1663-70.
36. Wilk C and Turkoski B. Progressive muscle relaxation in cardiac rehabilitation: a pilot study. *Rehabil Nurs*. 2001; 26: 238-42; discussion 43.
37. Tacon AM, McComb J, Caldera Y and Randolph P. Mindfulness meditation, anxiety reduction, and heart disease: a pilot study. *Fam Community Health*. 2003; 26: 25-33.
38. Friedman R, Sobel D, Myers P, Caudill M and Benson H. Behavioral medicine, clinical health psychology, and cost offset. *Health Psychol*. 1995; 14: 509-18.
39. Sobel DS. MSJAMA: mind matters, money matters: the cost-effectiveness of mind/body medicine. *JAMA*. 2000; 284: 1705.
40. Sobel DS. The cost-effectiveness of mind-body medicine interventions. *Prog Brain Res*. 2000; 122: 393-412.
41. Anderson JW, Liu C and Kryscio RJ. Blood pressure response to transcendental meditation: a meta-analysis. *Am J Hypertens*. 2008; 21: 310-6.
42. Barnes VA and Orme-Johnson DW. Prevention and Treatment of Cardiovascular Disease in Adolescents and Adults through the Transcendental Meditation((R)) Program: A Research Review Update. *Curr Hypertens Rev*. 2012; 8: 227-42.
43. Sullivan MJ, Wood L, Terry J, et al. The Support, Education, and Research in Chronic Heart Failure Study (SEARCH): a mindfulness-based psychoeducational intervention improves depression and clinical symptoms in patients with chronic heart failure. *Am Heart J*. 2009; 157: 84-90.
44. Sivasankaran S, Pollard-Quintner S, Sachdeva R, Pugeda J, Hoq SM and Zarich SW. The effect of a six-week program of yoga and meditation on brachial artery reactivity: do psychosocial interventions affect vascular tone? *Clin Cardiol*. 2006; 29: 393-8.
45. Leung YW, Tamim H, Stewart DE, Arthur HM and Grace SL. The prevalence and correlates of mind-body therapy practices in patients with acute coronary syndrome. *Complement Ther Med*. 2008; 16: 254-61.
46. Yeh GY, Davis RB and Phillips RS. Use of complementary therapies in patients with cardiovascular disease. *Am J Cardiol*. 2006; 98: 673-80.
47. Steptoe A and Kivimaki M. Stress and cardiovascular disease. *Nat Rev Cardiol*. 2012; 9: 360-70.
48. Ghiadoni L, Donald AE, Cropley M, et al. Mental stress induces transient endothelial dysfunction in humans. *Circulation*. 2000; 102: 2473-8.
49. Kop WJ, Krantz DS, Howell RH, et al. Effects of mental stress on coronary epicardial vasomotion and flow velocity in coronary artery disease: relationship with hemodynamic stress responses. *J Am Coll Cardiol*. 2001; 37: 1359-66.
50. von Kanel R, Mills PJ, Fainman C and Dimsdale JE. Effects of psychological stress and psychiatric disorders on blood coagulation and fibrinolysis: a biobehavioral pathway to coronary artery disease? *Psychosom Med*. 2001; 63: 531-44.
51. Dod HS, Bhardwaj R, Sajja V, et al. Effect of intensive lifestyle changes on endothelial function and on inflammatory markers of atherosclerosis. *Am J Cardiol*. 2010; 105: 362-7.
52. Vitetta L, Anton B, Cortizo F and Sali A. Mind-body medicine: stress and its impact on overall health and longevity. *Ann N Y Acad Sci*. 2005; 1057: 492-505.

53. Benson H. The relaxation response: therapeutic effect. *Science*. 1997; 278: 1694-5.
54. Davidson RJ, Kabat-Zinn J, Schumacher J, et al. Alterations in brain and immune function produced by mindfulness meditation. *Psychosom Med*. 2003; 65: 564-70.
55. Ades PA. Cardiac rehabilitation and secondary prevention of coronary heart disease. *N Engl J Med*. 2001; 345: 892-902.
56. Janssen V, De Gucht V, Dusseldorp E and Maes S. Lifestyle modification programmes for patients with coronary heart disease: a systematic review and meta-analysis of randomized controlled trials. *Eur J Prev Cardiol*. 2013; 20: 620-40.
57. Rozanski A, Blumenthal JA, Davidson KW, Saab PG and Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J Am Coll Cardiol*. 2005; 45: 637-51.
58. Goel K, Lennon RJ, Tilbury RT, Squires RW and Thomas RJ. Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. *Circulation*. 2011; 123: 2344-52.
59. Heran BS, Chen JM, Ebrahim S, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev*. 2011: CD001800.
60. Blumenthal JA, Sherwood A, Babyak MA, et al. Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: a randomized controlled trial. *JAMA*. 2005; 293: 1626-34.
61. Whalley B, Rees K, Davies P, et al. Psychological interventions for coronary heart disease. *Cochrane Database Syst Rev*. 2011: CD002902.
62. Balady GJ, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation*. 2007; 115: 2675-82.
63. Jackson L, Leclerc J, Erskine Y and Linden W. Getting the most out of cardiac rehabilitation: a review of referral and adherence predictors. *Heart*. 2005; 91: 10-4.
64. Caspi O and Burleson KO. Methodological challenges in meditation research. *Adv Mind Body Med*. 2005; 21: 4-11.

Appendix A.

Search Strategy

Embase.com

('heart disease'/exp OR 'cardiovascular disease'/de OR 'coronary artery disease'/exp OR (((heart* OR cardio* OR myocard* OR coronar* OR valvular OR cardiac) NEAR/3 (disease* OR disorder* OR failure* OR ischaem* OR ischem* OR infarct* OR attack* OR dysfunct* OR anomal* OR deficien* OR disturb* OR health)) OR cardiopath* OR cardiomyopath* OR myocardit* OR endocardit*):ab,ti) AND (meditation/de OR 'transcendental meditation'/de OR 'autogenic training'/de OR (Mindfulness* OR meditat* OR ((progressive* OR response) NEAR/3 relaxation*) OR (autogen* NEAR/3 train*)):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND [english]/lim

Medline ovidsp

(exp "heart diseases"/ OR "cardiovascular disease"/ OR (((heart* OR cardio* OR myocard* OR coronar* OR valvular OR cardiac) ADJ3 (disease* OR disorder* OR failure* OR ischaem* OR ischem* OR infarct* OR attack* OR dysfunct* OR anomal* OR deficien* OR disturb* OR health)) OR cardiopath* OR cardiomyopath* OR myocardit* OR endocardit*).ab,ti.) AND ("meditation"/ OR "Autogenic Training"/ OR (Mindfulness* OR meditat* OR ((progressive* OR response ADJ3 relaxation*) OR (autogen* ADJ3 train*)).ab,ti.) NOT (exp animals/ NOT humans/) AND English.la.

Cochrane

((((heart* OR cardio* OR myocard* OR coronar* OR valvular OR cardiac) NEAR/3 (disease* OR disorder* OR failure* OR ischaem* OR ischem* OR infarct* OR attack* OR dysfunct* OR anomal* OR deficien* OR disturb* OR health)) OR cardiopath* OR cardiomyopath* OR myocardit* OR endocardit*):ab,ti) AND ((Mindfulness* OR meditat* OR ((progressive* OR response) NEAR/3 relaxation*) OR (autogen* NEAR/3 train*)):ab,ti)

Web of Science

TS=(((((heart* OR cardio* OR myocard* OR coronar* OR valvular OR cardiac) NEAR/3 (disease* OR disorder* OR failure* OR ischaem* OR ischem* OR infarct* OR attack* OR dysfunct* OR anomal* OR deficien* OR disturb* OR health)) OR cardiopath* OR cardiomyopath* OR myocardit* OR endocardit*)) AND ((Mindfulness* OR meditat* OR ((progressive* OR response) NEAR/3 relaxation*) OR (autogen* NEAR/3 train*))) NOT ((animal* OR rats OR rat OR mouse OR mice) NOT (human* OR patient*)))

Pubmed publisher

((((heart*[tiab] OR cardio*[tiab] OR myocard*[tiab] OR coronar*[tiab] OR valvular[tiab] OR cardiac[tiab]) AND (disease*[tiab] OR disorder*[tiab] OR failure*[tiab] OR ischaem*[tiab] OR ischem*[tiab] OR infarct*[tiab] OR attack*[tiab] OR dysfunct*[tiab] OR anomal*[tiab] OR deficien*[tiab] OR disturb*[tiab] OR health[tiab])) OR cardiopath*[tiab] OR cardiomyopath*[tiab] OR myocardit*[tiab] OR endocardit*[tiab])) AND ((Mindfulness*[tiab] OR meditat*[tiab] OR progressive relaxation*[tiab] OR progressive muscle relaxation*[tiab] OR relaxation response*[tiab]) OR autogenic train*[tiab]) NOT (animals[mh] NOT humans[mh]) AND publisher[sb] AND English[la]

PsycINFO

(exp "Heart Disorders"/ OR "Cardiovascular Disorders"/ OR (((heart* OR cardio* OR myocard* OR coronar* OR valvular OR cardiac) ADJ3 (disease* OR disorder* OR failure* OR ischaem* OR ischem* OR infarct* OR attack* OR dysfunct* OR anomal* OR deficien* OR disturb* OR health)) OR cardiopath* OR cardiomyopath* OR myocardit* OR endocardit*).ab,ti.) AND ("meditation"/ OR "Autogenic Training"/ OR "Progressive Relaxation Therapy"/ OR "Mindfulness"/ OR (Mindfulness* OR meditat* OR ((progressive* OR response) ADJ3 relaxation*) OR (autogen* ADJ3 train*)).ab,ti.) NOT (exp animals/ NOT humans/) AND English.la.

Appendix B.

Equations used for quantitative measurements

Mean difference (MD) between groups

Measures where lower scores indicate better outcome

$$Mean_{post\ intervention} - Mean_{post\ control}$$

Measures where higher scores indicate better outcome

$$Mean_{post\ control} - Mean_{post\ intervention}$$

Pooled Standard deviation (SD)

$$\sqrt{((SD_{post\ intervention}\text{^}2 + SD_{post\ control}\text{^}2)/2)}$$

Cohen's d:

MD/Pooled SD

Standard error (SE) of Cohen's d:

SE=√((N1+N2/N1*N2)+(d^2/2*(N1+N2))

Standard deviation (SD) from Standard Error (SE)

$$SD = \sqrt{n} * SE$$

Standard Error from Standard Deviaton

$$SE=\sqrt{((SD_{intervention\ fup}\text{^}2/n_{fup}) + (SD_{control\ fup}\text{^}2/n_{fup})}$$

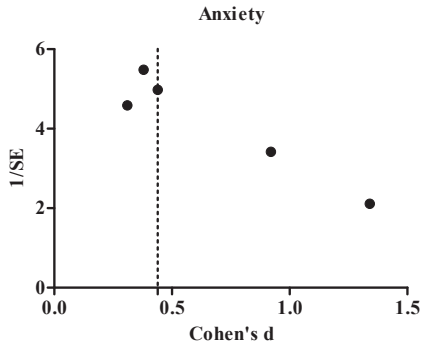
95% Confidence Interval from SE

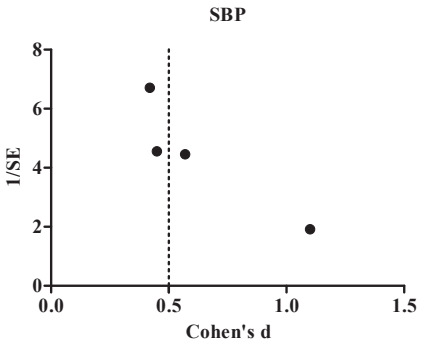
Lower limit = d - *(SE*1.96)*

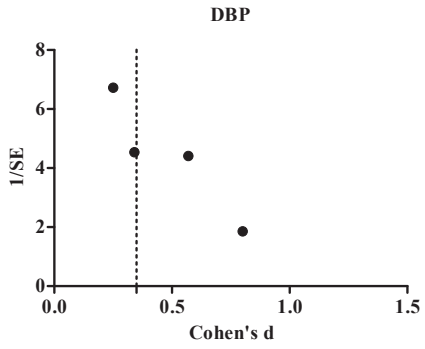
Upper limit = d + *(SE*1.96)*

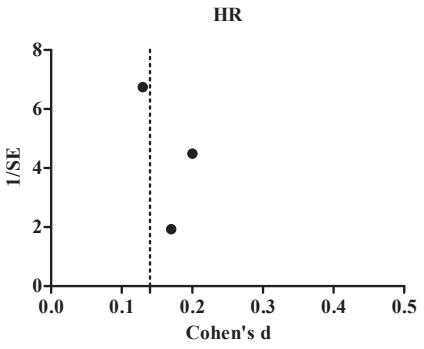
Appendix C.

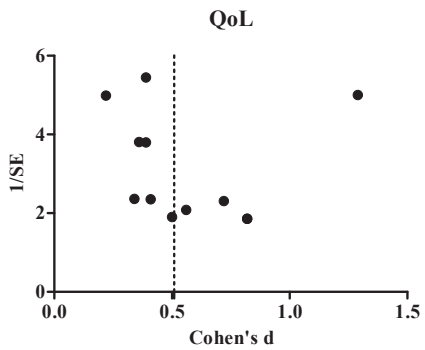
Funnel plots

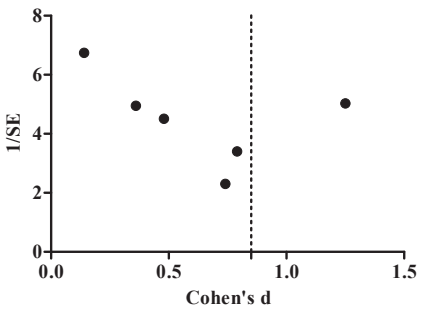












Part III

Intervention studies

Chapter 8

Mindfulness for patients with structural heart disease: a randomized controlled trial

Younge JO, Wery MF, Gotink RA, Utens EMWJ, van Rossum EFC, Michels M, Rizopoulos D, Hunink MGM, Roos-Hesselink JW, Hunink MGM*.*
Submitted
**Equal contributions*

Abstract

Objective

The objective of this study was to determine whether an online mindfulness training has beneficial physiological and psychological effects in patients with structural heart disease.

Background

Evidence is accumulating that mindfulness training has favorable effects on psychological outcomes, but studies on physiological outcomes are limited. Patients with structural heart disease have a high incidence of physiological and psychological problems and may benefit from mindfulness training.

Methods

We performed a pragmatic randomized controlled single-blind trial performed between June 2012 and April 2014 at the cardiology outpatient clinic of a tertiary center in the Netherlands. A total of 324 patients (mean age 43.2 years, 53.7% male) with structural heart disease were randomized in a 2:1 ratio (n=215, and n=109 respectively) by dedicated computer software to a 12-week online mindfulness training or usual care (UC). The primary outcome was exercise capacity measured with the 6 minute walk test (6MWT). Secondary outcomes were other physiological parameters (heart rate, blood pressure, respiratory rate, and NT-proBNP), quality of life (SF-36), perceived stress (PSS), psychological well-being (HADS), social support (PSSS12) and a composite endpoint (all-cause mortality, heart failure, symptomatic arrhythmia, cardiac surgery, and percutaneous cardiac intervention). Linear mixed models were used to evaluate differences between groups on the repeated outcome measures.

Results

Compared to UC, mindfulness showed a borderline significant improved 6MWT (effect size, meters: 13.2, 95%CI: -0.02; 26.4, p=0.050). There was also a significant lower heart rate in favor of the mindfulness group (effect size, beats per minute: -2.8, 95%CI: -5.4;-0.2, p=0.033). No significant differences were seen on subjective outcomes.

Conclusion

Mindfulness training showed a positive effect on physiological parameters, such as exercise capacity and heart rate and it might therefore be a useful adjunct to medical treatment in patients with structural heart disease.

Introduction

In recent decades, cardiovascular disease (CVD) has become the foremost cause of health burden worldwide.[1] While cardiovascular events cause significant stress,[2] chronic stressors such as anxiety and depression are themselves independent risk factors for cardiovascular morbidity and mortality.[3,4] Chronic stress can negatively affect not only quality of life, but also physiological parameters such as respiration rate, heart rate, blood pressure, inflammatory markers and brain activity.[5]

As heart rate is associated with long-term survival, patients are recommended to try reducing heart rate in the management and prevention of CVD.[6] Stress reduction in itself may also have a beneficial effect on heart rate and physical fitness. While the best approach to stress management is unclear, increased attention is now being paid to lifestyle interventions such as mindfulness therapy.[7,8] Mindfulness is described as the capacity to live with open, curious, non-judgmental awareness towards all experiences within the present moment.[9,10] Several core features, such as meditation, yoga, and cognitive assignments, can increase the ability to accept negative experience or emotions.[11] Mindfulness therapy has been found to positively affect mainly psychological outcomes in patients with chronic pain, obesity, hypertension, depression, anxiety and cardiovascular disease.[12-16]

We hypothesized that, besides these psychological effects, mindfulness therapy might also influence heart rate, breathing patterns and blood pressure. By mediating these physiological effects, it might also have a positive effect on exercise capacity and long-term outcome. In a randomized controlled trial (RCT), we therefore investigated the effectiveness of online mindfulness training on exercise capacity in patients with structural heart disease.

Methods

Study design

The current study is a single blinded, pragmatic RCT performed at the outpatient cardiology clinic of the Erasmus MC, Rotterdam, The Netherlands. Ethical approval was obtained from the Medical Ethics Committee (METC) of the Erasmus Medical Center. The study was registered at the Dutch trial register, NTR3453, http://www.trialregister.nl. Patients received written information about the study at home, 2-4 weeks prior to their scheduled visit to the cardiologist at the outpatient clinic. Full disclosure was given about the nature of the intervention.

Participants

Adult patients, between 18 and 65 years of age, with diagnosed structural heart disease (ischemic, valvular, congenital heart disease , or cardiomyopathy, were eligible for inclusion between June 2012 and April 2014. Patients were excluded based on the following criteria: (1) planned opera-

tion or percutaneous intervention within the upcoming year; (2) inability or unwillingness to give informed consent; (3) inability to understand Dutch, inability to read or write Dutch; (4) no internet access, email, or cell phone; (5) patients who did not fill out the baseline questionnaires or did not show up for the scheduled baseline tests. All participants provided written informed consent.

Intervention

All patients received usual care (UC) as provided by their treating cardiologist. The mindfulness training consisted of a 12-week structured standardized online program. Additionally, all patients received a renowned book about mindfulness to support the 12-week training.[17] The training was designed to be self-directed and to be easily accessible and engaging to a wide audience by keeping practices and lessons short. The program teaches different meditations, self-reflection, and yoga. Furthermore, it includes practical assignments and suggestions for day-to-day life. The use of breath as a reminder for present moment awareness is emphasized in all meditations. The program was divided into four components, as shown in eFigure1. During the course participants also received biweekly reminders by e-mail and standardized text messages. Adherence to the intervention was monitored by whether the questions of the online program were completed. For privacy reasons, the content of the answers remained undisclosed. Both the program and the book were provided free of charge to participating patients.

Control

The control group received UC at the outpatient clinic of the department of cardiology. We chose for a pragmatic study design without a placebo online training in order to measure effectiveness rather than efficacy.

Randomization

After written informed consent was obtained and baseline measurements were performed, patients were randomized according to a 2:1 ratio via dedicated computer software (ALEA) within blocks of 12 to receive the online Mindfulness training or UC.

Blinding

The result of the randomization procedure was sent to an independent employee of the outpatient clinic, who was neither involved in the outcome assessment nor data analyses. Subsequently, the employee contacted the participant with the result. Due to the nature of the intervention, blinding of patients was not feasible. The intervention started as soon as patients logged on to the mindfulness training website. The outcome assessors were unaware of patients' treatment allocation. Additionally, patients were instructed not to say anything about their treatment allocation, neither to study investigators nor to their cardiologist.

Outcome measures

Outcomes were measured in all patients pre- (T0) and post-intervention (12 weeks, T1).

Primary outcome measure was the 6MWT which is a measure of physical fitness. The 6MWT was performed in a 20-meter-long corridor at the Erasmus MC outpatient clinic.[18] The corridor had well-indicated 'start' and 'finish' marks with colored pawns.

Secondary outcome measures were:

Physical parameters: weight, blood pressure, respiratory rate and heart rate.

Blood sampling laboratory tests: N-terminal pro-brain natriuretic peptide (NT-proBNP, Elecsys system, Roche Diagnostics, Basel, Switzerland: normal values ≤ 14pmol/L) and creatinin were measured from peripheral venous blood samples.

Quality of Life (QoL): The Short-Form Health survey 36 (SF-36) was used to evaluate subjective health status. For each of the 8 subdomains a transformed score is generated, ranging from 0 to 100,[19] with a higher score indicating better health.[20] The subdomains were used to construct the mental component summary measure (MCS), which consists of the subdomains vitality, social functioning, role-emotional functioning and mental health, and the physical component summary (PCS) measure, which consists of the subdomains physical functioning, role physical functioning, bodily pain and general health.[21]

A Visual Analogue Scale (VAS) was used to assess subjective perceived QoL, ranging from 0 to 100, with a higher score indicating better QoL.[22]

Psychological well-being: To assess symptoms of anxiety and depression, the Hospital Anxiety and Depression scale was used. The questionnaire contains 14 items on depression and anxiety with a higher score on the 3 point Likert scale indicating a greater level of emotional distress.[23]

Stress: The Dutch version of the Perceived Stress Scale (PSS) was used to evaluate perceived stress. The scale consists of fourteen 5-point Likert scales, with a higher score indicating a higher level of stress (0=never, 4=very often). A total perceived stress score is made by summing all individual items.[24]

Social support: To evaluate perceived social support, the Dutch version of the Perceived Social Support Scale 12 Blumenthal (PSSS12) was used. The PSSS12 has 12 items with a 7-point Likert scale addressing the degree of perceived social support with a higher score indicating a greater feeling of support (1=very strongly disagree, 7= very strongly agree).[25] For the purpose of this study we used the total score.

Additional and complementary care: Participation in other mindfulness-based exercises and the use of other complementary care was monitored with a questionnaire (type, frequency, and intensity).

Composite endpoint: we used a composite endpoint of all-cause mortality, heart failure, symptomatic arrhythmia, cardiac surgery, and percutaneous cardiac intervention. Arrhythmias were defined as symptomatic if antiarrhythmic medication was prescribed, cardioversion or ablation

had been applied, or a pacemaker or intracardiac defibrillator (ICD) implantation was performed. Heart failure was defined as an event when either medication or hospitalization was necessary.

Other study parameters

In order to document baseline risk levels, traditional cardiovascular risk factors and demographics were determined: age, length, weight, smoking, type of structural heart disease, and employment status.

Quality control

The digitalization of the paper case record forms (CRFs) in the database was independently performed by 2 persons (JY and MW). After digitalization, an error rate of <0.5% was observed between JY and MW.

Sample size justification

To demonstrate an improvement of 5% in the intervention group vs 1% in the control group on the 6MWT, this study required 99 patients in the control group and 198 in the active intervention group (SD10%, alpha=0.05, power=0.90, ratio experimental to controls=2). Even if only 50% of patients in the experimental group adhere to the training, this would give us a power of 0.80 in the as-treated analysis. To account for non-adherence and loss to follow-up our aim was to randomize at least 300 patients. This number of patients is sufficient to demonstrate a smaller difference (5% in the intervention group vs 2% in the control group) in a repeated measurements analysis with a power of 75-90% (2 follow-up measurements, correlation between follow up measurements=0.70, correlation between baseline & follow-up=0.50).

Statistical analysis

Descriptive analyses were performed to describe the baseline characteristics of demographic and clinical variables stratified by treatment group. To simultaneously account for the correlation between the multiple measurements of each patient and dropout a repeated measurements analysis was performed using a multivariate linear regression model. In the mean structure of the model we included the time effect the intervention effect and their interaction, while a fully unstructured variance-covariance matrix was assumed for the error terms. Due to randomization only p-values for the interaction effect are reported.

An Intention-to-treat (ITT) analysis was performed to address whether offering a mindfulness training was effective. An as-treated (AT) analysis was performed to address whether the mindfulness training was beneficial if actually performed). In the AT, patients were considered adherent if they completed 50% or more of the exercises. Patients allocated to the UC group who sought mindfulness training on their own were excluded from the AT analysis. This way, we assessed the effectiveness of the mindfulness training if performed.

A p-value less than 0.05 was considered to be indicative of statistical significance. All data were analyzed with IBM SPSS Statistics version 21.0 (IBM Corp., Somers, NY).

Results

Patient recruitment and characteristics

A flowchart of the patients' recruitment is shown in Figure 1. Patients' baseline characteristics, stratified by mindfulness versus UC, are shown in Table 1. Crude analyses showed no statistical significant difference at T0 between the intervention and control group, which confirmed a successful randomization.

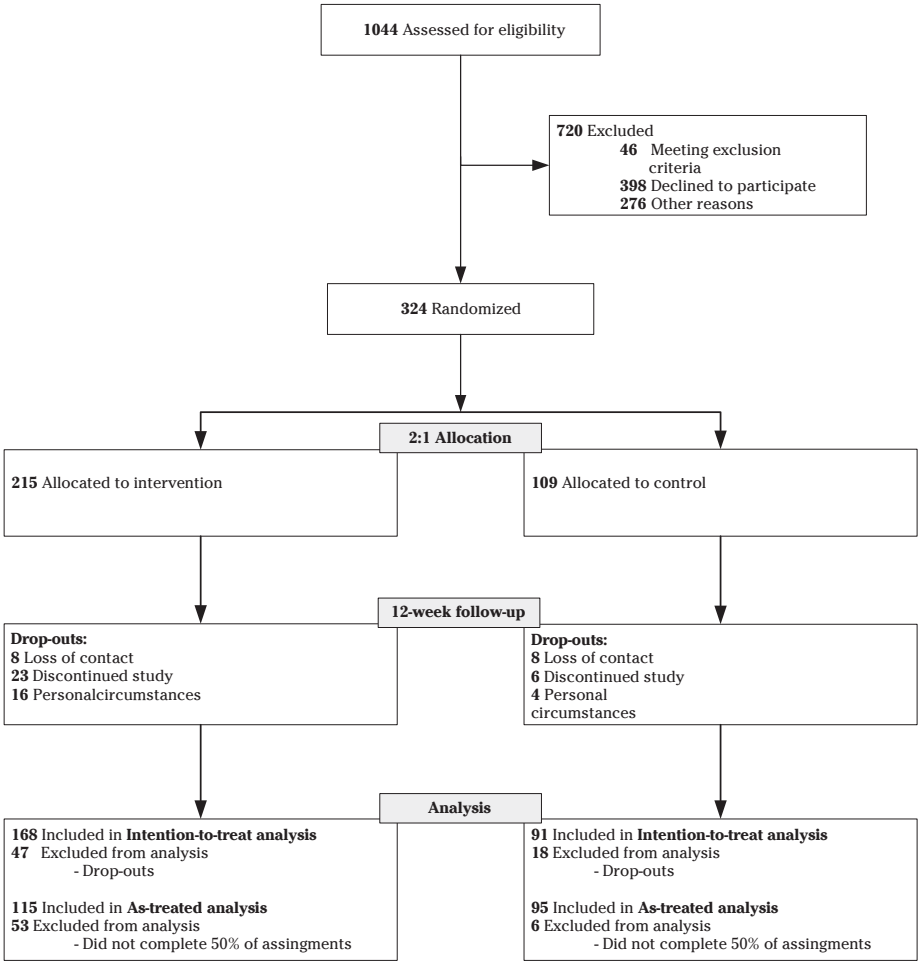


Figure 1. *Flowchart of in mindfulness training and control group*

Table 1. *Baseline characteristics of study participants*

	Mindfulness Group	Control Group
	N=215	N=109
Demographics		
Age (years), mean (SD)	43.2 (14.1)	43.2 (13.7)
Female, (%)	44.2	50.5
Physiological parameters		
Heart rate (beats/min), mean (SD)	68 (12)	69 (11)
Systolic blood pressure (mm Hg), mean (SD)	127 (16)	125 (15)
Diastolic blood pressure (mm Hg), mean (SD)	78 (11)	80 (10)
Resting respiratory rate (breaths/min), median (IQR)	15 (2)	16 (2)
Body mass index (kg/m^2), mean (SD)	25.9 (4.6)	25.7 (4.7)
Exercise tolerance		
6 minute walk test distance (meters), mean (SD)	537.5 (77.0)	539.3 (67.3)
Laboratory works		
NT-proBNP, median (IQR), pmol/L	16.7 (28.5)	18.3 (33.9)
Creatinine, median (IQR), μmol/L	79.0 (21.0)	77.0 (21.0)
Cortisol, median, (IQR), pg/mg hair[a]	-	-
Cardiac history		
Type of structural heart disease, (%)		
Congenital heart disease	41.8	42.2
Cardiomyopathy	39.5	29.4
Valvular heart disease	18.7	28.4
Number of interventions in life*, mean (SD)	1.4 (1.4)	1.4 (1.2)
Time since first intervention (years), mean (SD)	19.1 (14.0)	15.9 (11.7)
ICD, (%)	8.8	*12.8*
PM, (%)	14.0	*15.6*
Current medication (%)	70.2	*72.5*
Beta-blocker	42.8	36.7
Statin	18.6	13.8
Aspirin	16.3	13.8
Ace-inhibitor	23.3	22.0
Angiotensin II antagonist	8.8	11.9
Calcium channel blocker	9.8	6.4
Nitroglycerin	2.3	0.0
Cardiac glycoside	2.3	2.8
Diuretic	16.8	18.4
Anticoagulant	24.6	33.9
Antidepressant	5.1	2.8
Tranquilizer	1.9	1.8
Other	43.4	56.9

Table 1. *Baseline characteristics of study participants (continued)*

	Mindfulness Group	Control Group
	N=215	N=109
Intoxication, (%)		
Current smoking	14.4	18.3
Current alcohol use	62.1	55.0
Current drugs use	3.3	2.8
Work status		
Employed, (%)	68.7	67.9
Prior use of complementary therapies**, (%)	14.0	12.8

Abbreviations: SD, standard deviation; NT-proBNP, N-terminal pro-Brain Natriuretic Peptide; IQR, interquartile range; ICD, implantable cardioverter-defibrillator; PM, pacemaker.
**Include both surgical and percutaneous interventions*
***Contains yoga, meditation, mindfulness, tai chi, Qigong and acupuncture*

Safety/side effects

No major side effects were reported during the follow-up period. In 7 patients (2.2%) at baseline and 13 patients (5%) at follow-up, fatigue, dizziness, shortness of breath, or pain due to pre-existing conditions were described while performing the 6MWT.

ITT analysis

Mean scores of 6MWTs of the Mindfulness and UC group are presented in Table 2. The mindfulness group improved notably on their mean 6MWT at 12 weeks and a borderline significant improvement in favor of the mindfulness group (p=0.050).

Effect on secondary outcomes are presented in Table 2.

Physiological parameters: At follow-up, heart rate significantly decreased in the mindfulness group (p=0.033) (Table 2). Mean systolic and mean diastolic blood pressure decreased in the mindfulness and UC group, but no significant differences were found in the mixed-model analyses at 12 weeks (Table 2).

QoL: In Table 2, the 2 summary scores of the SF-36 are reported. Analyses showed no significant differences between the groups on the PSC and MSC (Table 2).

Psychological distress/well-being and social support: At 12 weeks, anxiety levels were lower in both the mindfulness and the UC group, but no significant differences were found between the groups (Table 2). Depressive symptoms decreased more in the mindfulness group, but did not reach statistical significance. At follow-up nor for perceived stress scores and neither for perceived social support a statistical significant differences was found between the groups (Table 2).

Composite endpoint: At 12-weeks, no significant differences were found on the composite endpoint.

Table 2. *Baseline scores, changes, and differences between treatment groups on physiological outcomes,intention-to-treat analyses*

Physiological outcomes	Treatment group	Delta 12-weeks[a] (mean, SD)	Estimate[b]	95% CI	p-value
6MWT, meters	Mindfulness	+10.42 (49.0)	13.2	-0.02; 26.4	0.050
	UC	-4.0 (55.6)			
Heart rate, beats/minute	Mindfulness	-2 (10.9)	-2.8	-5.4; -0.2	0.033
	UC	+0.5 (9.0)			
SBP, mmHg	Mindfulness	-4.2 (15.4)	-2.2	-6.1; 1.7	0.268
	UC	-1.9 (15.5)			
DBP, mmHg	Mindfulness	-1.9 (8.9)	1.6	-0.8; 4.0	0.186
	UC	-3.4 (10.1)			
Respiratory rate, breaths/minute*	Mindfulness	-0.5 (3.6)	-0.02	-0.04; 0.01	0.189
	UC	-0.1 (4.0)			
NT-proBNP, pmol/L*	Mindfulness	0.3 (9.7)	-0.04	-0.1; 0.04	0.333
	UC	0.0 (11.10)			
Psychological outcomes					
SF-36 subdomains					
PCS	Mindfulness	0.5 (6.3)	-0.4	-2.0; 1.3	0.668
	UC	0.7 (6.7)			
MCS	Mindfulness	0.2 (7.4)	0.74	-1.4; 2.8	0.489
	UC	1.2 (8.8)			
VAS	Mindfulness	+0.4 (10.4)	-0.4	-3.0; 2.1	0.745
	UC	+0.7 (9.3)			
HADS Anxiety	Mindfulness	-0.5 (3.2)	0.6	-0.2; 1.4	0.145
	UC	-0.9 (3.0)			
HADS Depression	Mindfulness	-0.5 (2.9)	-0.4	-1.1; 0.2	0.203
	UC	0.0 (2.3)			
PSS	Mindfulness	-2.4 (6.3)	-1.0	-2.7; 0.6	0.226
	UC	-0.9 (6.8)			
PSSS12	Mindfulness	+0.6 (7.4)	0.4	-1.6: 2.4	0.685
	UC	+0.1 (8.0)			

Abbreviations: SD, standard deviation; SE, standard error; 6MWT, six-minute walk test; UC, usual care; SBP, systolic blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; SF-36, Short Form Health survey; PCS, physical component summary measure; MCS, mental component summary measure; VAS, visual analogue scale; HADS, hospital anxiety and depression scale; PSS, perceived stress score; PSSS12, perceived social support

**Log-transformed scores*

[a]Delta value was calculated for those who attended the 12-week follow-up (eg. Follow-up value – baseline value).

[b]Linear mixed model analyses for repeated measurements for differences between treatment groups on the dependent variables (time X intervention effect)

As-treated analyses

Results of ATT-analyses are reported in Table 3.The results were comparable with the ITT analyses.

Table 3. *Baseline scores, changes, and differences between treatment groups on physiological and psychological outcomes, as-treated analyses*

	Treatment group	Delta 12-weeks[a] (mean, SD)	Estimate[b]	95% CI	p-value
6MWT, meters	Mindfulness	9.36 (35.9)	10.6	-1.7; 23.0	0.091
	UC	-1.92 (51.7)			
Heart rate,	Mindfulness	-3.07 (11.7)	-3.4	-6.3; 0.4	0.027
beats/min	UC	0.47 (9.2)			
SBP, mmHg	Mindfulness	-5.17 (14.5)	-3.8	-8.0; 0.3	0.072
	UC	-1.50 (15.5)			
DBP, mmHg	Mindfulness	-2.34 (8.9)	0.8	-1.8; 3.5	0.524
	UC	-3.39 (10.1)			
Respiratory rate,	Mindfulness	-0.67 (3.5)	-0.7	-1.8; 0.3	0.170
breaths/minute	UC	-0.11 (4.1)			
NT-proBNP, pmol/L	Mindfulness	1.03 (28.7)	-0.04	-0.2; 0.09	0.540
	UC	4.73 (21.7)			
Psychological outcomes					
SF-36 subdomains					
PCS	Mindfulness	0.7 (6.4)	0.13	-1.7; 2.0	0.893
	UC	0.4 (6.8)			
MCS	Mindfulness	-0.05 (7.5)	1.2	-1.1; 3.5	0.302
	UC	1.5 (8.9)			
VAS	Mindfulness	+0.4 (10.4)	-0.2	-3.0; 2.6	0.878
	UC	+0.7 (9.3)			
HADS Anxiety	Mindfulness	-0.5 (3.2)	0.5	-0.4; 1.4	0.267
	UC	-0.9 (3.0)			
HADS Depression	Mindfulness	-0.5 (2.9)	-0.4	-1.2; 0.3	0.267
	UC	0.0 (2.3)			
PSS	Mindfulness	-2.4 (6.3)	-1.1	-3.0; 0.8	0.244
	UC	-0.9 (6.8)			
PSSS12	Mindfulness	+0.6 (7.4)	0.5	-1.7; 2.6	0.670
	UC	+0.1 (8.0)			

Abbreviations: SD, standard deviation; SE, standard error; 6MWT, six-minute walk test; UC, usual care; SBP, systolic blood pressure; DBP, diastolic blood pressure; IQR, interquartile range; SE, standard error, NT-proBNP, N-terminal pro-brain natriuretic peptide; SF-36, Short Form Health survey; PCS, physical component summary measure; MCS, mental component summary measure; VAS, visual analogue scale; HADS, hospital anxiety and depression scale; PSS, perceived stress score; PSSS12, perceived social support

[a]*Delta value was calculated for those who attended the 12-week follow-up (eg. Follow-up value – baseline value).*

[b]*Mixed model analyses for differences between treatment groups on the dependent variables (time X intervention effect)*

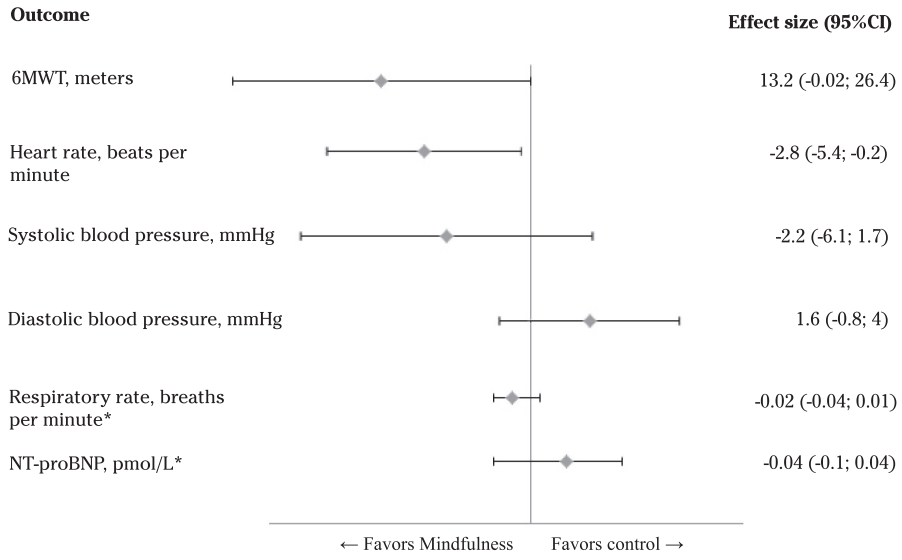


Figure 2. *Forest plot of physiological outcomes*
*Abbreviations: 6MWT, six-minute walk test; IC, confidence interval, NT-proBNP, N-terminal pro-brain natriuretic peptide; * Log-transformed scores*

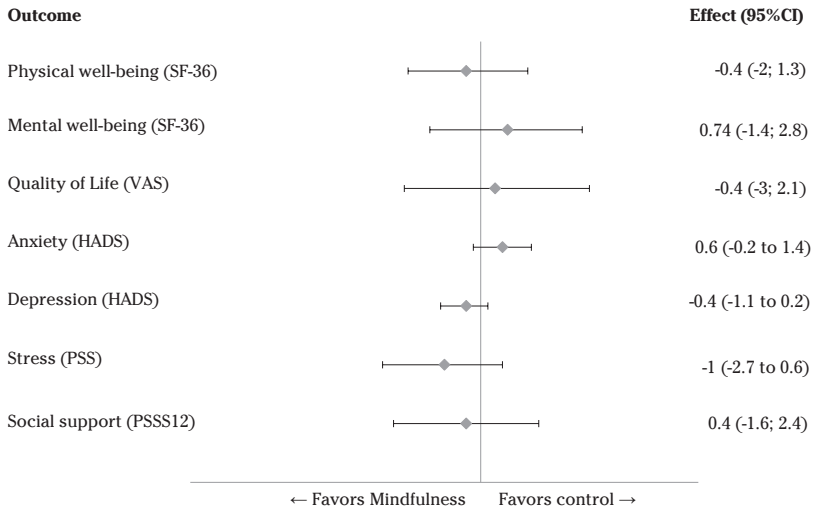


Figure 3. *Forest plot of psychological outcomes*
Abbreviations: CI, confidence interval; SF-36, Short Form Health survey; VAS, visual analogue scale; HADS, hospital anxiety and depression scale; PSS, perceived stress score; PSSS12, perceived social support

Discussion

To our knowledge, this is the first randomized trial to evaluate the effectiveness of mindfulness training in patients with structural heart disease. By taking physiological parameters as its main outcome parameter, it is also an innovative study. On the primary endpoint – exercise capacity – we found a borderline significant effect in favor of mindfulness. In the mindfulness group, the physiological parameter – heart rate – also decreased significantly. No significant improvements were found on subjective outcome measures.

Limited exercise capacity is an important predictor for outcome for cardiac disease, and several studies have reported an association with survival[26-29] Since a decrease in physical performance is also an important predictor of adverse outcomes in patients with congenital heart disease, improving physical performance may be an important target of treatment. In recent years, cardiac rehabilitation programs, many of them conducted in patients with post-myocardial infarction, have had good results on total and cardiovascular mortality.[30,31] Our results indicate that mindfulness training could be part of future treatment modalities intended to improve physical performance in structural heart disease patients. It remains to be shown whether this will also affect long-term outcome. Several epidemiological studies in patients with hypertension, acute coronary syndromes,[32] stable coronary heart disease[33] and heart failure[34] have shown that resting heart rate is a risk factor for cardiovascular and all-cause mortality. The beneficial effect of mindfulness on heart rate we found suggests that outcome was improved by this intervention.

To date, very few studies have evaluated mindfulness training in patients with cardiac disease. A pilot study that offered a brief mindfulness-based stress-reduction program to patients with, or at risk of, coronary artery disease[16,17] showed significant reductions on two psychological outcomes, depression (Cohen's d=0.54) and perceived stress (d=0.68), with moderate effect size. Unlike in our study, the participants were not randomized and the intervention was fairly short (4-weeks). Two reports of the same study population showed that mindfulness-based stress-reduction mainly improved anxiety, emotional control and coping, rather than resting-stress hormones or physical functioning.[35,36] Recently, a brief group-MBSR intervention in patients undergoing a percutaneous coronary intervention showed favorable effects on QoL.[37] Additionally, anxiety, depression, and stress appeared to be influenced positively only in the younger age group (<60 years)[37] Unlike in our study, the positive effects reported in these studies on MBSR applied mainly to psychological outcomes. A possible explanation for this difference is that we did not select patients on the basis of their underlying levels of stress, anxiety or depression. We expect to see more positive effects of mindfulness training on psychological outcomes in these patients. Also, our training was online and with no implementation of group sessions. This could have results in a less intense training regime.

The fact that we found no effect on systolic or diastolic blood pressure may be a floor effect, as our patients had regular blood pressure monitoring and (extra) medication was given when necessary. Baseline mean blood measurements of our total study population therefore showed

measurements within normal ranges for systolic blood pressure (127 mmHg) and diastolic blood pressure (79 mmHg). Previous studies, some of which showed potential benefits on blood pressure, investigated a population whose blood pressures at baseline were higher.[7,38]

Accumulating evidence suggests that mind and body do indeed shown an interaction and that physiological changes are underlain by several neuro-humoral mechanisms. For example, in an extensive study of a framework in mind-body medicine, Benson and colleagues have focused on the relaxation response as a core component in autonomic function and physical changes.[39,40] It has been shown that, through emotions and thoughts, the autonomic nervous system is key in the brain-heart connection.[41] By working through the autonomic nervous system, mind-body practices can also benefit endothelial, neuroendocrine and immune function.[42-44] However, the mechanism between the mind and body is not merely unidirectional: several levels of the neuro-axis have been found to contribute to the "top-down and bottom-up mechanisms" in mind-body practices.[45]

To date, web-based mindfulness training studies have been limited to pilot studies on stress reduction. A study by Gluck et al.[46] reported a trend in lower levels of stress. Two other studies showed not only that it was feasible to conduct online mindfulness training, but also that it was effective in reducing stress.[47,48] It is important to emphasize that their study populations consisted of healthy participants with no underlying disease and that no randomized design was used. This could have resulted in a selection bias.

Our own study used no placebo and waiting list for the control group. We considered the placebo effect of the online training to be inherent to the active intervention: the fact that the training would be implemented in real-world practice suggested that the study would measure effectiveness rather than efficacy, and that it was pragmatic rather than explanatory. Our inclusion of the placebo effect as part of the mindfulness intervention compared with UC without placebo in the control group is further justified by the fact that no competing therapy exists. No placebo online training we could think of would be likely to have a beneficial effect. As such a beneficial effect in the control group would reduce any differences in effectiveness that were measured, it would not accurately reflect what it was supposed to.

Limitations of the current study must be addressed. The first limitation is that only 80.6% (n=261) of the patients returned for follow-up. A possible explanation is the fact that the intervention was not offered in a group-based setting. However, patients who returned did not significantly differ with regard to demographic and clinical characteristics from those who did not. A second possible limitation is that the impact of online training may be lower than that of personal or group training. While this would mean that the results of mindfulness therapy may therefore be even stronger in other settings, the easy accessibility of online training may have allowed better generalizability of the results, as patients could do the training in their own environment and fit it into a busy schedule. A third limitation is that although we monitored participants' training activity, adherence was difficult to assess and control for. We had no detailed knowledge of their practice; only the completion of the online assignments was available. A fourth limitation is that

ethical considerations prevented us from blinding patients before randomization to the nature of the intervention. The control group was therefore aware that the online mindfulness training was available and that they were not receiving it. This may have resulted in a selection of patients. With regard to demographic and clinical variables, however, we found no significant difference between the mindfulness and control groups at T1. At last, our numbers did not make subgroup analysis possible. Additionally, before considering future implementation of online mindfulness training, it must be determined which content and method would be the most effective.

Conclusion

Online mindfulness training is feasible in structural heart disease and has a positive effect on exercise capacity and heart rate. The current study found no significant effect on psychological outcomes.

References

1. Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* Dec 15 2012;380(9859):2197-2223.
2. Richardson S, Shaffer JA, Falzon L, Krupka D, Davidson KW, Edmondson D. Meta-analysis of perceived stress and its association with incident coronary heart disease. *Am J Cardiol.* Dec 15 2012;110(12):1711-1716.
3. Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet.* Sep 11-17 2004;364(9438):953-962.
4. Richardson S, Shaffer JA, Falzon L, Krupka D, Davidson KW, Edmondson D. Meta-analysis of perceived stress and its association with incident coronary heart disease. *Am J Cardiol.* Dec 15 2012;110(12):1711-1716.
5. Custodis F, Gertz K, Balkaya M, et al. Heart rate contributes to the vascular effects of chronic mental stress: effects on endothelial function and ischemic brain injury in mice. *Stroke.* Jun 2011;42(6):1742-1749.
6. 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.* Jul 2012;33(13):1635-1701.
7. Abbott RA, Whear R, Rodgers LR, et al. Effectiveness of mindfulness-based stress reduction and mindfulness based cognitive therapy in vascular disease: A systematic review and meta-analysis of randomised controlled trials. *J Psychosom Res.* May 2014;76(5):341-351.
8. Goyal M, Singh S, Sibinga EM, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. *JAMA Intern Med.* Mar 2014;174(3):357-368.
9. Kabatzinn J. An Outpatient Program in Behavioral Medicine for Chronic Pain Patients Based on the Practice of Mindfulness Meditation - Theoretical Considerations and Preliminary-Results. *Gen Hosp Psychiat.* 1982;4(1):33-47.
10. Segal ZVW, J.M.G.; Teasdale, J.D. *Mindfulness-based Cognitive Therapy for Depression: A New Approach to Preventing Relapse.* New York: Guilford Press; 2002.
11. Bishop SR, Lau M, Shapiro S, et al. Mindfulness: A proposed operational definition. *Clin Psychol-Sci Pr.* Fal 2004;11(3):230-241.
12. Hofmann SG, Sawyer AT, Witt AA, Oh D. The Effect of Mindfulness-Based Therapy on Anxiety and Depression: A Meta-Analytic Review. *J Consult Clin Psych.* Apr 2010;78(2):169-183.
13. Zeidan F, Johnson SK, Gordon NS, Goolkasian P. Effects of Brief and Sham Mindfulness Meditation on Mood and Cardiovascular Variables. *J Altern Complem Med.* Aug 2010;16(8):867-873.
14. Baer RA. Mindfulness training as a clinical intervention: A conceptual and empirical review. *Clin Psychol-Sci Pr.* Sum 2003;10(2):125-143.
15. Ospina MB, Bond K, Karkhaneh M, et al. Meditation practices for health: state of the research. *Evid Rep Technol Assess (Full Rep).* Jun 2007(155):1-263.
16. Olivo EL, Dodson-Lavelle B, Wren A, Fang Y, Oz MC. Feasibility and effectiveness of a brief meditation-based stress management intervention for patients diagnosed with or at risk for coronary heart disease: a pilot study. *Psychology Health & Medicine.* Oct 2009;14(5):513-523.
17. Maex E. *Mindfulness 'in de maalstroom van je leven'.* Lannoo; 2006.
18. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* Jul 1 2002;166(1):111-117.
19. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* Jun 1992;30(6):473-483.
20. Lane DA, Lip GY, Millane TA. Quality of life in adults with congenital heart disease. *Heart.* Jul 2002;88(1):71-75.
21. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care.* Mar 1993;31(3):247-263.
22. Moons P, Van Deyk K, De Bleser L, et al. Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts. *Eur J Cardiovasc Prev Rehabil.* Jun 2006;13(3):407-413.
23. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* Jun 1983;67(6):361-370.
24. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav.* Dec 1983;24(4):385-396.
25. Pedersen SS, Spinder H, Erdman RA, Denollet J. Poor perceived social support in implantable cardioverter defibrillator (ICD) patients and their partners: cross-validation of the multidimensional scale of perceived social support. *Psychosomatics.* Sep-Oct 2009;50(5):461-467.
26. Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation.* Aug 9 2005;112(6):828-835.

27. Dimopoulos K, Okonko DO, Diller GP, et al. Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. *Circulation.* Jun 20 2006;113(24):2796-2802.
28. Inuzuka R, Diller GP, Borgia F, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. *Circulation.* Jan 17 2012;125(2):250-259.
29. Kempny A, Dimopoulos K, Alonso-Gonzalez R, et al. Six-minute walk test distance and resting oxygen saturations but not functional class predict outcome in adult patients with Eisenmenger syndrome. *Int J Cardiol.* Oct 12 2013;168(5):4784-4789.
30. Heran BS, Chen JM, Ebrahim S, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev.* 2011(7):CD001800.
31. Clark AM, Hartling L, Vandermeer B, McAlister FA. Meta-analysis: secondary prevention programs for patients with coronary artery disease. *Ann Intern Med.* Nov 1 2005;143(9):659-672.
32. Hjalmarson A, Gilpin EA, Kjekshus J, et al. Influence of heart rate on mortality after acute myocardial infarction. *Am J Cardiol.* Mar 1 1990;65(9):547-553.
33. Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. *Eur Heart J.* May 2005;26(10):967-974.
34. Gullestad L, Wikstrand J, Deedwania P, et al. What resting heart rate should one aim for when treating patients with heart failure with a beta-blocker? Experiences from the Metoprolol Controlled Release/Extended Release Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF). *J Am Coll Cardiol.* Jan 18 2005;45(2):252-259.
35. Robert McComb JJ, Tacon A, Randolph P, Caldera Y. A pilot study to examine the effects of a mindfulness-based stress-reduction and relaxation program on levels of stress hormones, physical functioning, and submaximal exercise responses. *J Altern Complement Med.* Oct 2004;10(5):819-827.
36. Tacon AM, McComb J, Caldera Y, Randolph P. Mindfulness meditation, anxiety reduction, and heart disease: a pilot study. *Fam Community Health.* Jan-Mar 2003;26(1):25-33.
37. Nyklicek I, Dijksman SC, Lenders PJ, Fonteijn WA, Koolen JJ. A brief mindfulness based intervention for increase in emotional well-being and quality of life in percutaneous coronary intervention (PCI) patients: the MindfulHeart randomized controlled trial. *J Behav Med.* Feb 2014;37(1):135-144.
38. Younge JO, Gotink RA, Baena CP, Roos-Hesselink JW, Hunink MM. Mind-body practices for patients with cardiac disease: a systematic review and meta-analysis. *Eur J Prev Cardiol.* Sep 16 2014.
39. Benson H, Beary JF, Carol MP. The relaxation response. *Psychiatry.* Feb 1974;37(1):37-46.
40. Benson H. The relaxation gesponse: its subjective and objective historical precendents and physiology. *Trends Neurosci.* 1983;6:281-284.
41. Emani S, Binkley PF. Mind-body medicine in chronic heart failure: a translational science challenge. *Circ Heart Fail.* Nov 2010;3(6):715-725.
42. Ditto B, Eclache M, Goldman N. Short-term autonomic and cardiovascular effects of mindfulness body scan meditation. *Ann Behav Med.* Dec 2006;32(3):227-234.
43. Dod HS, Bhardwaj R, Sajja V, et al. Effect of intensive lifestyle changes on endothelial function and on inflammatory markers of atherosclerosis. *Am J Cardiol.* Feb 1 2010;105(3):362-367.
44. Greeson JM. Mindfulness Research Update: 2008. *Complement Health Pract Rev.* Jan 1 2009;14(1):10-18.
45. Taylor AG, Goehler LE, Galper DI, Innes KE, Bourguignon C. Top-down and bottom-up mechanisms in mind-body medicine: development of an integrative framework for psychophysiological research. *Explore (NY).* Jan-Feb 2010;6(1):29-41.
46. Gluck TM, Maercker A. A randomized controlled pilot study of a brief web-based mindfulness training. *BMC Psychiatry.* 2011;11:175.
47. Krusche A, Cyhlarova E, King S, Williams JM. Mindfulness online: a preliminary evaluation of the feasibility of a web-based mindfulness course and the impact on stress. *BMJ Open.* 2012;2(3).
48. Morledge TJ, Allexandre D, Fox E, et al. Feasibility of an online mindfulness program for stress management—a randomized, controlled trial. *Ann Behav Med.* Oct 2013;46(2):137-148.

Appendix

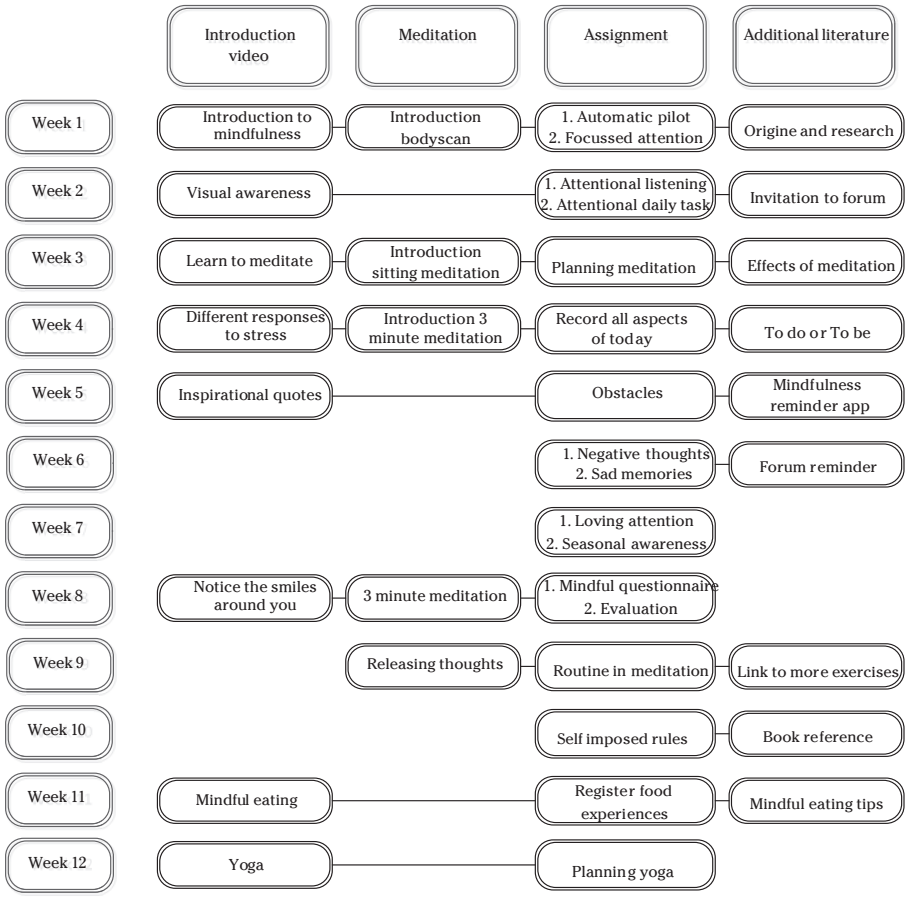


Figure 1. *Content internet-based mindfulness training*

Chapter 9

Randomized study designs for lifestyle interventions: a tutorial

Younge JO, Kouwenhoven TA, Freak-Poli R, Roos-Hesselink JW, Hunink MGM. Submitted

Introduction

Unhealthy lifestyle behaviors such as unhealthy diet, excessive energy intake, smoking, excessive alcohol use, physical inactivity, and stress can act as causal factors in the pathway of many diseases and have been identified as key modifiable risk factors.[1] Multiple interventions are being developed to help people adopt a healthier lifestyle. As with all medical interventions, lifestyle interventions should undergo rigorous evaluation to assess their effectiveness prior to widespread implementation.

There are several methods for evaluating lifestyle interventions and each has strengths and weaknesses.[2] Cohort studies and case-series may provide findings suggesting effectiveness, but drawing conclusions from such studies is limited by confounding and other forms of bias.[2] The state-of-the-art study design for the evaluation of interventions is the double-blind randomized controlled trial (RCT).[3] Considered as the foundation of evidence based medicine (EBM),[4] eligible individuals are randomly assigned to the intervention of interest or control group. The RCT is widely used to evaluate new drugs, devices, surgery or other treatment modalities. Due to randomization, confounding factors are equally distributed between groups and bias is avoided. However, randomization may not correctly account for patient preferences and non-adherence, which are important issues in lifestyle interventions that may threaten the internal and external validity of studies.[5-7]

The aim of this paper is to provide guidance in the choice of an optimal RCT design in future trials of lifestyle interventions. For the purpose of this paper, a lifestyle intervention is defined as an intervention that focuses upon improving health through one or more modifiable risk factors, which includes interventions that promote healthy nutrition, smoking cessation, moderate alcohol use, physical activity, and stress reduction.

General considerations

Objective and research question

The underlying research question of a clinical trial is inextricably linked to its design and should be relevant and feasible to answer. As for all interventions, future evaluations of lifestyle interventions should commence with a thoughtful consideration of aspects which have not yet been assessed, which do not have definitive answers and that will provide evidence that can change practice. There are several factors one must consider when developing the research question in the context of lifestyle interventions. First and foremost, you need to choose whether to assess the intervention in a controlled setting which addresses 'efficacy' vs assessing it in a real-world setting which addresses 'effectiveness'. RCTs tend to focus on efficacy rather than effectiveness, which often leads to questionable external validity[8]. Second, one needs to distinguish between evaluating offering a lifestyle intervention (with possible non-adherence) vs actual uptake of

and adherence to the intervention. Third, one needs to decide whether to evaluate specific parameters of the lifestyle intervention that may influence its effectiveness and cost, including length, frequency, and intensity of the program. An explicit statement of the study objective will lead the investigators to the identification of a clear study design.

Defining the active and control interventions

Evaluations of lifestyle interventions can be complicated by low recruitment, high rates of non-adherence, and high loss to follow-up affecting their validity.[9] To improve all three it is prudent to consider the following aspects of the active and control interventions[9,10]:

1) Target group: a primary prevention program should target the general population whereas a selective prevention program would target high risk individuals
2) Control intervention: individuals should (at least) receive, usual care[11]
3) Clinical equipoise: because of ethical considerations, randomization can only be performed if the clinical community is uncertain whether the intervention is effective and which strategy is the best choice;
4) Viability: is the lifestyle intervention implementable and affordable if shown to be effective?
5) Administration of the intervention: consider individual face-to-face coaching vs group sessions vs e-health;
6) Duration of the intervention: a long duration may lead to non-adherence and drop outs but a too short duration could lead to an ineffective intervention;
7) Intensity (workload) of the intervention: a too demanding intervention may lead to low adherence but a low intensity may lead to an ineffective intervention;
8) Run-in period: randomizing only subjects that are compliant with an initial intervention and outcome measurements may improve adherence of subjects in the trial[12];
9) Duration of enrolment: external circumstances may change over time and influence recruitment;
10) Recruitment tactics[13]: maximize recruitment in order to complete the study in a timely fashion;
11) Timeframe for follow-up measurements: both short- and long-term outcomes are important since lifestyle interventions may take time to achieve their desired effect and long-term adherence may be suboptimal;

Blinding and placebo interventions

Successful and complete blinding (that is, blinding of participants, caregivers, and outcome assessors) is often difficult and not feasible to achieve in evaluating lifestyle interventions. Participants in lifestyle interventions are actively involved in the intervention, precluding adequate blinding. For example, someone running, cycling, or practicing yoga will know that they are doing that activity. Nevertheless, sometimes it is possible to blind participants to knowledge about which trial arm is the active intervention. The active element of the intervention may in

some circumstances be hidden from the recipient by using e-health or by using special dietary products but even this can be challenging. E-health provides opportunities by offering a passive information-only module. Double blinding could be achieved in dietary interventions if foods are provided with certain elements eliminated or substituted (e.g. sugar substitute) but true blinding is only achievable with a limited number of foods.

It is difficult to distinguish the placebo effect from the actual effect of a lifestyle intervention and offering a placebo lifestyle intervention is hardly possible. Any placebo lifestyle intervention is likely to have some effect, due to non-specific therapeutic mechanisms like attention (the Hawthorne effect),[14] structure, hope and working alliance.[15-17] Thus, providing any placebo lifestyle intervention in the control group would underestimate effectiveness of the active intervention compared to what can be expected in real-world practice. Rather than trying to determine the actual effect of the intervention, it is more meaningful to consider this additional placebo effect of a lifestyle intervention as part-and-parcel of the intervention as it would be implemented in real-world practice. The control group should receive either a competing lifestyle intervention or usual care as implemented in real-world practice, which will commonly include some form of lifestyle advice provided orally during an outpatient visit or with a pamphlet or website. This implies that the study will measure effectiveness rather than efficacy and that is it pragmatic rather than explanatory. Such a pragmatic trial design sacrifices internal validity in order to achieve external validity and generalizability.[18]

Allocation concealment will prevent foreknowledge of treatment assignment both among participants and among investigators performing enrolment. Allocation concealment can easily be undertaken and prevents selection bias[19]. Blinding of the outcome assessors is more difficult but important to avoid performance and ascertainment bias.[20]

Informed consent procedure

If the active intervention is a no-risk lifestyle intervention designed to be attractive so that patients will comply and be adherent, then many patients will probably want to try it. A conventional randomized controlled trial design with full disclosure of the active intervention to all patients prior to obtaining informed consent would, according to the existing literature on lifestyle interventions, lead to several problems[21-24]: 1) slow recruitment because many patients would probably want to try the intervention rather than being randomized; 2) bias and limited generalizability due to selection of only those patients who do not care whether they receive the intervention or not and are presumably less motivated; 3) because the active intervention is attractive, patients allocated to the control group are likely to be disappointed, dissatisfied and demoralized which can lead to selective withdrawal of controls, poor response to follow-up measurements on questionnaires, non-adherence with the control intervention, and cross-over (contamination) of controls who seek the active intervention on their own elsewhere, also known as ''drop-ins''.[25] An alternative would be an informed consent procedure which does not disclose the details of the intervention. However, this may raise ethical concerns, because

withholding information about the intervention will result in an uninformed choice from the participant when entering the study.

Options for randomized designs

Parallel group RCT

The most commonly used randomized design is the parallel group design. Participants are allocated to one intervention arm for the duration of the study. This design is frequently used because of the clear temporal sequence and its simplicity (Figure 1). Eligible participants are selected based on the pre-defined inclusion and exclusion criteria. The informed consent procedure fully informs patients about the randomization process, the details of the active and control interventions, and the measurements to be performed. Participants are randomized to either the lifestyle intervention or the control group. Measurement of baseline characteristics is performed either before or immediately following the randomization process. The study is terminated after a specific period of follow-up. The outcome variables are measured in, preferably, a blinded fashion.

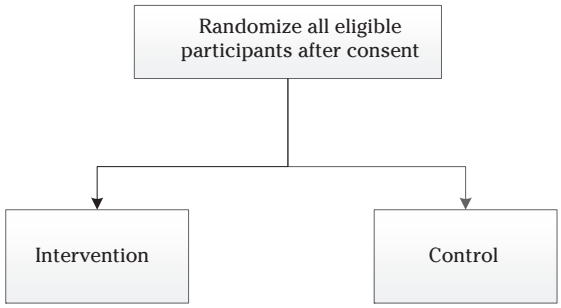


Figure 1. *Parallel group RCT*

Although the parallel group design provides an internally valid comparison, the main disadvantage is that the recruitment rate can be low because subjects may have preferences for specific lifestyle behaviors. Low recruitment rates lead to questionable generalizability (Table 1). Furthermore, if subjects participate in group sessions to learn about the lifestyle behaviour, ''contamination" may occur which may lead to correlated outcomes between subjects. Large sample sizes are needed if the primary outcome of interest has a low incidence. Additionally, the RCT may not be feasible if the outcome has a long lag time.

An example of a parallel group RCT for lifestyle is demonstrated by Estruch et al.[26] In this large multi-center study, participants at high cardiovascular risk were randomly assigned to one of three Mediterranean diets. Once randomized to one of the three diets, participants remained

Table 1. *Main features of randomized controlled trial designs for the evaluation of lifestyle interventions*

	Main design features	Advantages	Disadvantages
Parallel group (Hill 1952)	• Allocation remains unchanged throughout the duration of the study • Randomization to two or more arms (active intervention, control) • Participant is unit of randomization	• Simplicity • Universal acceptance • Clear temporal sequence • Internally valid comparison	• Double-blinding not always possible • Time consuming and expensive • Large sample size needed (in case of low incidence outcomes) • Inefficient for diseases with rare outcomes • Lifestyle interventions that have a long lag time require a long follow-up period • Often low recruitment rate • Questionable external validity and generalizability
Cross-over (Louis 1984)	• All study interventions are given to each subject in successive periods • Random allocation of intervention/control • Washout period in between study periods • Number of treatment periods may be larger than two	• Participants act as their own control • Reduces variation in response • Smaller sample size needed • More efficient • Participants receive both treatments which increases attractiveness of participating which increases recruitment rate	• Condition needs to reverse to baseline during washout period • Effects of intervention need to be reversible • Possible period effect and carry-over effect • Not appropriate for acute conditions and progressive disorders • Only intermediate endpoints • Participants serve as their own control, and no comparisons can be made if the treatment has not been received
Cluster (Donner 1981)	• 'Clusters' (groups) of individuals are randomized • Cross-sectional or cohort-type clusters can be used • Matching of clusters can increase study power • Stepped-wedge design can facilitate organization • Unit of analysis are the participants within the cluster	• Accounts for "contamination" and intra-cluster correlation between participants within a cluster • Easier to randomize groups of patients rather than individual patients • Design of choice when the intervention is at the group level or. when outcomes of participants are not independent • Social effects are included • Easier to organize	• Recruitment bias/ selection bias • Selection bias of individuals after the clusters have been randomized because treatment allocation is known • Sufficient clusters needed for adequate power • Ecological fallacy: predictor variables can be present in either the individual or at the cluster level which can lead to causal inference errors • Entire clusters, rather than individuals, may be lost to follow-up

Table 1. *Main features of randomized controlled trial designs for the evaluation of lifestyle interventions (continued)*

	Main design features	Advantages	Disadvantages
Longitudinal cohort with nested RCT	• Participants are first asked to participate in longitudinal observational cohort study, then the RCT • Other design features same as parallel group RCT	• Better reflection of real world practice • Partial (rather than full) disclosure of details of lifestyle intervention during informed consent reduces drop-ins in control arm • Participants who refuse the intervention and drop-outs are followed as part of the cohort study •	• Twice informed consent • Partial (rather than full) disclosure of details of lifestyle intervention during informed consent may increase drop-outs in active intervention arm • Other disadvantages same as parallel group RCT
Fully randomized preference design (Torgerson 1996)	• Preference recorded before randomization • Randomization and consent conducted in the usual way • Preferences taken into account during the analyses by including interaction between preference and treatment	• Advantages of 'full' randomization • Convenient way of taking preference into account	• Requires bigger sample size to analyze the interaction effect • Unethical to ignore patients' preferences when proceeding with randomization • Interaction of preference and treatment difficult to analyze
Zelen partially randomized patient preference design (Zelen 1979, 1982)	• Subjects are randomized before giving consent to participate • Single consent: Subjects in control group receive usual care; subjects in intervention group are offered the active intervention; if they refuse they receive usual care • Double consent: all subjects are asked to consent after randomization; subjects declining the active intervention are offered usual care. Subjects declining usual care are offered another treatment	• The Zelen design makes it easier for physicians to recruit patients – consent procedure is as it would be in clinical practice and physician-patient relation is not compromised • Simplification of information given to the patient (which can be seen as a disadvantage as well) • Almost all eligible participants are included • Evaluation of 'true effectiveness' as would be observed in practice • Useful for population based interventions	• Does not meet (most) ethical requirements (primarily single consent design) • Cannot be single/ double blind and is therefore an open trial • Should not be used in placebo controlled trials • Only suitable if data collection is limited to routine data • Dilution of treatment effect (can even be larger in the double consent design) if participants refuse intervention • Loss of statistical power if participants refuse intervention • Success depends on high proportion accepting the intervention • More subjects need to be randomized; loss of statistical efficiency • Treatment differences will be underestimated

Table 1. *Main features of randomized controlled trial designs for the evaluation of lifestyle interventions (continued)*

	Main design features	Advantages	Disadvantages
Wennberg partially randomized patient preference design (Wennberg 1993)	• Eligible participants are asked for consent to be randomized to a random allocation vs preference group • Participants in the preference group are offered their treatment of choice • Participants allocated to the random allocation group are randomized between active and control intervention without taking preference into account • All participants are included	• Better adherence • Reduces attrition • No bias due to refusing initial randomization • Compared to Zelen, no ethical problems concerning consent, which is asked prior to randomization • Evaluates treatment and preference effects	• Participants still need to consent for randomization • No knowledge of preference in the 2nd randomized group and how this will affect the outcomes • Unknown confounders when comparing a randomized group and preference group • No knowledge of level of preference • Patient preference known only after randomization • Large sample size needed • High costs
Rucker partially randomized patient preference design (Rucker 1989)	• Similar to Wennberg design, except participants who are randomized to the preference group after the first stage and who do not have a strong preference for a treatment, are randomized again in the second stage to active vs control intervention	• All subjects are randomized from the start • Evaluates treatment, selection and preference effects	• Only subjects that consent to be randomized enter the study • Subjects' characteristics may influence choice of treatment • Estimation of preference effect is complex
Brewin partially randomized patient preference design (Brewin 1989)	• Each eligible participant is asked for his or her preference • Randomization takes place if no strong preference exists between the intervention or the control group • Participants with a preference are given their treatment of choice	• Almost all those eligible enter the study • Preferences are taken into account in treatment allocation	• Unknown confounders in the preference group • Bigger sample size • Sample size calculation difficult • Expensive

in that arm for the duration of the study and were analysed as such using an intention-to-treat analysis. An as-treated analysis was also performed in which only participants who were adherent to the assigned diet were included.

Cross-over RCT

In a cross-over RCT, eligible subjects are initially randomly allocated to either the intervention or the control condition as in a parallel group RCT (Figure 2). After a period of time, the initial treatment is stopped, a washout period without any treatment follows, and then subjects 'cross-over' to the other treatment modality. The difference with a parallel group RCT is that all participants receive both the active and control interventions but in random order. The washout period reduces

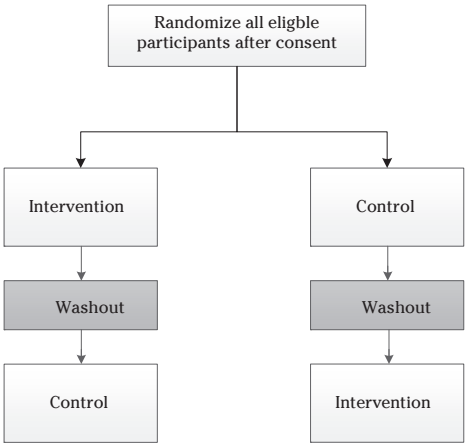


Figure 2. *Cross-over RCT*

the risk of period effects and carry-over effects: these are effects that may occur from one period to the next due to the course of the disease and due to the switch from one intervention to the other, respectively. Because subjects undergo both active and control interventions, they can serve as their own control which reduces the random variation in response between active and control arms. Cross-over trials can consist of half of the subjects when compared to the parallel group design with the same precision, which is an advantage for the feasibility and execution of the study. Furthermore, because patients receive both treatments, participation in the trial may be more attractive to them, increasing recruitment.

Cross-over RCTs can, however, only be performed under certain conditions (Table 1). First, the outcome of interest should be an intermediate outcome since after a hard outcome such as death, cross-over to the other arm of the study is impossible. Second, the effect of the behavior change needs to be reversible since a prolonged effect of the intervention can have significant carry-over effects in the subsequent control period. Because of the carry-over effect not all lifestyle interventions can be studied with this design (e.g. behavioral programs with an anticipated lasting effect such as cardiac rehabilitation would probably have significant carry-over effects). Third, there should be no difference between results from subjects who are randomized to the lifestyle intervention group and subsequently a control period from those who are randomized to first a control period and subsequently to the lifestyle intervention. All-in-all, not all conditions are amenable to be studied in a cross-over RCT. Whereas chronic conditions with measurable symptoms are well-suited for cross-over RCTs, acute or quickly progressive conditions are not because of the changes from one period to the next (period effect).

An example of a cross-over RCT is the study by Katz and colleagues[27] on subjects with overweight who were randomized to two 8-week sequences of a diet enriched with walnuts vs a diet without walnuts to evaluate the effect on flow-mediated vasodilatation. In between the

sequences, subjects had a 'washout' period of 4 weeks. The effect of eating walnuts on flow-mediated vasodilatation was assumed to be reversible within the period of 4 weeks.

Cluster RCT

Rather than randomizing individuals, groups of individuals (''clusters") are randomized to the active intervention or control treatment (Figure 3). Clusters may be families, physician practices, departments, companies or even whole towns. Eligible clusters are evaluated and informed consent is obtained from a representative for the cluster (known as the "guardian" of the cluster). Informed consent is obtained from individual participants for data collection and follow-up. The randomization procedure allocates each cluster to either the active intervention or control group. The effectiveness of the intervention is assessed and analysed at the patient-level, taking into account the intra-cluster correlation between participants within the clusters[28].

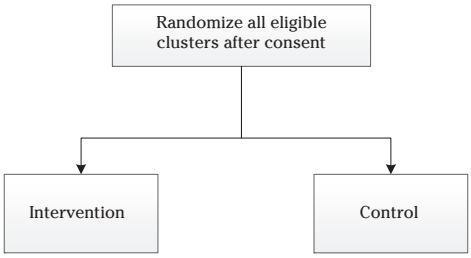


Figure 3. *Cluster RCT*

A cluster RCT is the appropriate study design to evaluate a lifestyle intervention that involves a group process. For example, an exercise program provided to a group (the cluster) uses the social interaction between participants to enhance adherence and benefit. Cluster RCTs are also useful to evaluate interventions that involve educating health care professionals which would subsequently affect an entire group of patients. For example, interventions that target physicians to adhere to new guidelines would affect all patients that are seen by the targeted physicians. Cluster RCTs can also be useful to avoid spill over effects between individuals from different arms of the study which may lead to "contamination". For example, employees in the same department in a company are likely to talk and influence each other's behaviour. Thus, if the company were to evaluate an employee lifestyle program a cluster RCT with clustering at the departmental level or at different locations of the company would be an appropriate study design. Furthermore, due to necessity, practical or ethical considerations a cluster RCT can be preferred (Table 1).

An example of a cluster RCT is provided by the Hutchinson smoking prevention project that evaluated forty Washington school districts.[29] Based on a group-randomized matched-pair design, forty 3rd grade districts were randomly assigned to control or intervention and were

followed-up until grade 12. This cluster size was sufficient to accommodate intraclass correlation. Unfortunately, this design failed to exploit the social influences of the intervention in the clusters.

A stepped-wedge cluster design may be useful when implementation of the intervention is time-consuming, resource-intensive and expensive. Such circumstances justify random allocation of clusters in a step-wise approach, which facilitates organization of the study and can even benefit trial recruitment.[30] After a control "step", clusters are allocated in random order to the intervention.[31] At the end of the study, all clusters will have a study period before and one after introducing the intervention – thus each cluster will have performed a before-after study. An example of a stepped-wedge cluster design study is provided by Lilly and colleagues[32] which evaluated the effect of telemonitoring in the intensive care unit. Clustering in this study was at the level of the intensive care unit. A limitation of their approach was the inability to blind those involved - it was obvious that the use of telemonitoring devices was implemented when the cluster was allocated to the intervention.

Longitudinal cohort study with nested RCT

The longitudinal observational cohort study with a nested RCT design has many similarities with the parallel group RCT but embeds the RCT within a cohort study (Figure 4). Eligible participants first need to give informed consent for data collection within the observational cohort study. Subsequently, participants are asked to participate in a randomized trial evaluating healthy lifestyle programs.

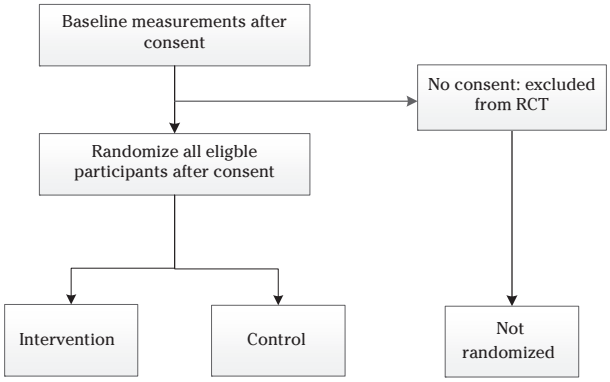


Figure 4. *Longitudinal cohort with nested RCT*

The main advantage of a nested RCT design is the available follow-up information of those who refuse the lifestyle intervention(s) or are non-adherent (Table 1). By having asked informed consent for the observational study prior to offering the active lifestyle intervention, baseline and follow-up data can be collected of all individuals, also those who refuse the intervention.

Furthermore, participants are only eligible for the nested RCT if they have complied with the observational cohort data collection which ensures that participants randomized are motivated to participate.

A case can be made to use partial rather than full disclosure of the active intervention during the informed consent procedure of the nested RCT. Details about the active intervention are then only given after treatment allocation since giving this information can be considered the educational part of the lifestyle program. Partial disclosure reduces the chance of drop-ins in the control arm but may increase the number of drop-outs in the active intervention arm (Table 1).

Preference trials and pre-randomization

Although randomization distributes characteristics of study subjects equally and thus controls for confounding, it does not take pre- and post-randomization subjects' preferences into account which may affect outcome. Preferences of participants can be an important source of bias[6]. A high dropout rate prior to randomization due to patient preference may effect generalizability of the study[5]. Especially in lifestyle interventions, preference may play an important role. If the active intervention is attractive, participants may prefer it. When randomized to the control group, this can lead to a high rate of drop-out from the study and/or a high drop-in rate (cross-over) to the active intervention, affecting the internal validity of the study. Also, if the active intervention is preferred, physicians tend to be less motivated to recruit patients for a trial that may affect their physician-patient relationship.

Several types of modified trial designs, incorporating patient preference, have been described in the literature,[6,33-37] but until now, use of preference trials is still scarce[38,39] (Table 1, Figures 5-10). In fully randomized preference trials (Figure 5) patient preferences are documented as part of the baseline data.[36] Subsequently, participants are randomized in a regular manner. In the data analysis the interaction between preference and treatment is taken into account to evaluate preference as a potential effect modifier. This 'solution' requires an increase in sample size in order to perform valid analyses of the interaction.[40]

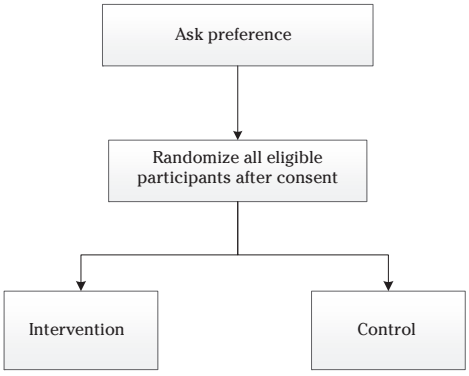


Figure 5. *Fully randomized preference design*

In partially randomized preference trials, not all groups are randomized (Table 1). In the single-consent Zelen (pre-randomization) design, participants are randomized to intervention or control groups prior to informed consent. Informed consent is asked only from patients allocated to the intervention group (Figure 6)[34] since the control group receives usual care for which informed consent is unnecessary. This design can be useful for large studies evaluating lifestyle advice for primary prevention. For example, a study evaluating a telephone consultation for smoking cessation was performed using this design.[41] Nevertheless, the single-consent Zelen design raised ethical concerns. In the double-consent Zelen design,[33] consent is asked in both groups after randomization (Figure 7). Limitations of the Zelen design include ethical concerns about absence of consent for randomization, loss of statistical power when there is a high drop-out rate in the intervention group, and problems with data collection from patients who refuse participation (Table 1).

Several other preference designs have been proposed in the literature such as the Wennberg (Figure 8), Rücker (Figure 9) and Brewin (Figure 10) designs (Table 1). The Wennberg design randomizes participants to a preference or randomization group. Those in the preference group are offered their treatment of choice, and participants in the randomization group are randomly allocated to one of two treatments.[35] Similarly, the Rucker's design starts with a randomized allocation to a random and preference group.[37] Patients in the preference group can choose their treatment. Patients without a preference and those in the random group are randomized between treatments. In contrast to Rucker's and Wennberg's design, the study design by Brewin enables all patients to choose in the first stage: they can either enter the random group (where

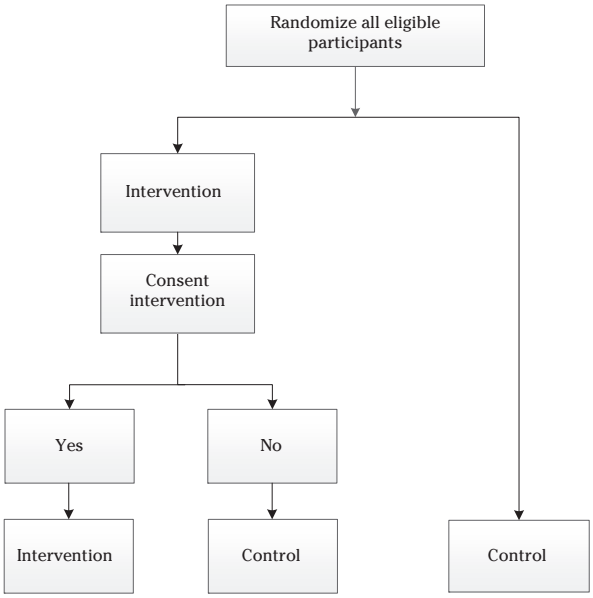


Figure 6. *Single-consent Zelen preference RCT*

randomization will allocate them to a treatment), or enter the preference group, in which they make a treatment choice themselves.[6] These designs have been used in a variety of clinical settings[38,39] and allow for the evaluation of the effect of preference on the benefit of the intervention. A disadvantage is that the results in the non-randomized groups are prone to confounding bias.[40]

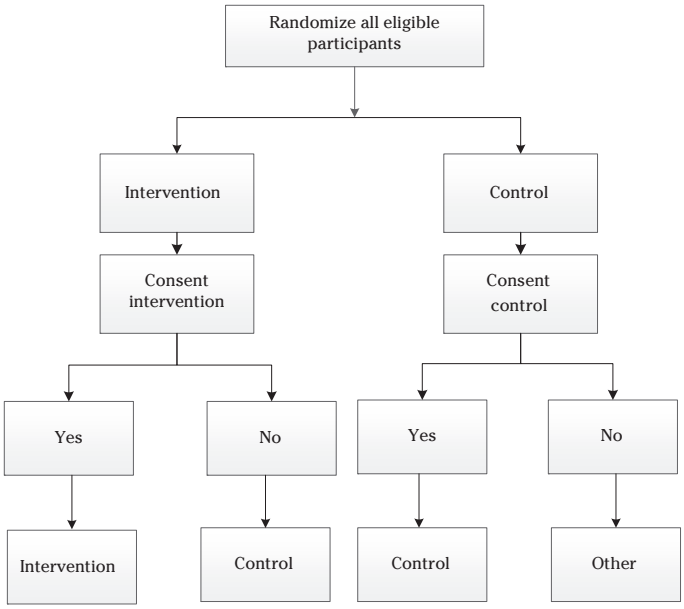


Figure 7. *Double-consent Zelen preference RCT*

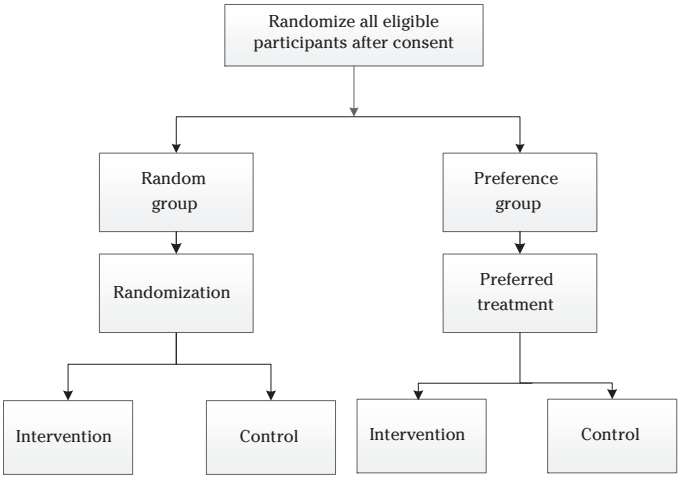


Figure 8. *Wennberg preference RCT*

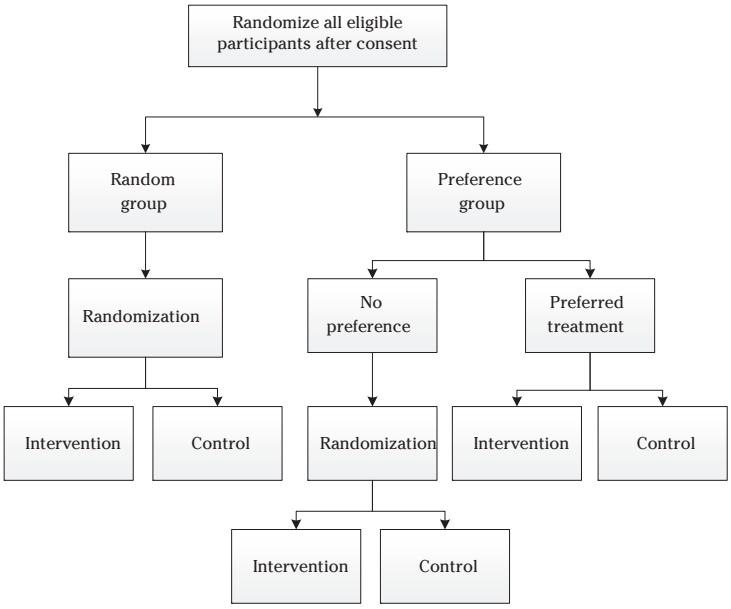


Figure 9. *Rücker preference RCT*

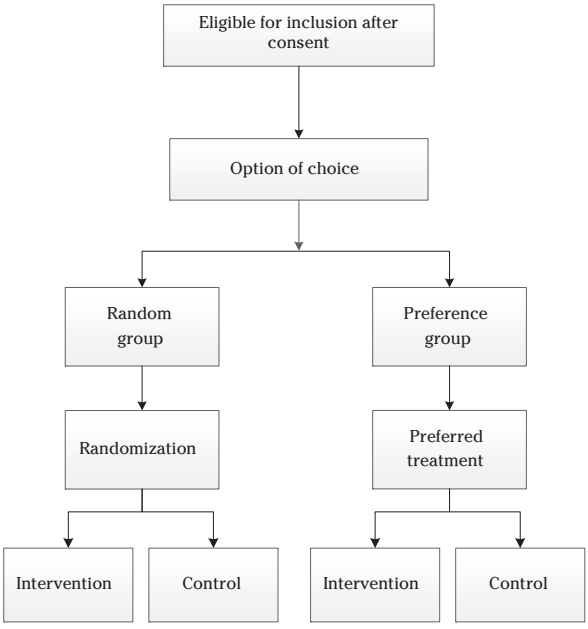


Figure 10. *Brewin preference RCT*

Discussion

This tutorial shows that difficult methodological choices have to be made to optimize the quality of an RCT evaluating the effectiveness of a lifestyle intervention. RCTs evaluating lifestyle interventions are more complex to design than RCTs evaluating medical therapy. Although RCTs are considered the cornerstone of evidence-based medicine, a straightforward parallel group randomized design will not necessarily lead to a high quality study and other randomized study designs may be a better choice.

The parallel group RCT is frequently used because of its simple design and universal acceptance. One or more interventions can easily be compared to a control intervention. Parallel group RCTs are, however, less useful in evaluating lifestyle interventions. Cross-over studies can be more efficient, because participants act as their own control, which leads to smaller required sample sizes. The biggest disadvantage of cross-over studies is that the effect of the intervention needs to be reversible. Cross-over RCTs are particularly helpful in evaluating the effect of single reversible dietary interventions on intermediate outcomes (e.g. reduced salt intake and blood pressure). A cluster design can be preferred when social influences are an important aspect (such as group exercise programs) or when the intervention is naturally performed at the group level (e.g. targeting physician practices, companies or cities). Many clusters are, however, needed to provide sufficient power and losing an entire cluster due to organizational problems can have a disastrous effect. If the drop-out rate is high and the characteristics of drop-outs is of interest (e.g. in a smoking cessation program), an RCT nested within a longitudinal cohort study is useful. Giving partial information rather than full information about the intervention may reduce drop-ins in the control group but this comes at the price of an increased drop-out rate in the active intervention group after being fully informed about the intervention. For the majority of RCT's on lifestyle-interventions, a pragmatic approach is recommended to evaluate the effectiveness of the intervention as it would be implemented in clinical practice compared to usual care as control.

Special consideration should be given to the use of patient preference in randomized trials of lifestyle interventions. There is growing interest in the understanding of treatment choices and there are both practical and ethical reasons to incorporate patient preferences in RCTs of lifestyle interventions.[42] Whether preference can lead to a better estimation of treatment effects when incorporated in the study design is still under debate and the required statistical analysis is far from straightforward.[43-45]

In the current tutorial we did not focus on several other aspects that are important in the design of an RCT, such as randomization procedures, statistical power, data analysis and reporting. Most of these aspects have been clarified extensively in the literature. In fact, the CONSORT statement has resulted in uniform and structured reporting of clinical trials and addresses these aspects.[46] It is a very helpful guide for researchers both in developing a structured protocol and in reporting the results. We welcome the fact that the CONSORT study group is expanding their

reporting guidelines to other study designs such as cluster[47] and pragmatic designs,[48] and also on the reporting of nonpharmacological interventions.[49]

In conclusion, the increased focus on healthy lifestyle behaviors has resulted in a strong demand for well-performed high quality RCTs. Evaluating lifestyle interventions calls for special considerations in designing the study which are inextricably linked to the research question. We recommend considering alternatives to the conventionally used parallel group RCT. Our discussion of several types of RCTs suitable for evaluating lifestyle interventions, including their advantages and disadvantages, provides guidance in the choice of an optimal RCT design.

References

1. Organization WH. Preventing Chronic Disease: A Vital Investment: WHO Global Report. 2005.
2. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. *PLoS Med.* Mar 11 2008;5(3):e67.
3. Lachin JM, Matts JP, Wei LJ. Randomization in clinical trials: conclusions and recommendations. *Control Clin Trials.* Dec 1988;9(4):365-374.
4. Sackett. *Evidence-Based Medicine: How to Practice and Teach EBM.* Edinburgh: Churchill Livingstone; 2000.
5. Howard L, Thornicroft G. Patient preference randomised controlled trials in mental health research. *Br J Psychiatry.* Apr 2006;188:303-304.
6. Brewin CR, Bradley C. Patient preferences and randomised clinical trials. *BMJ.* Jul 29 1989;299(6694):313-315.
7. McPherson K, Britton AR, Wennberg JE. Are randomized controlled trials controlled? Patient preferences and unblind trials. *J R Soc Med.* Dec 1997;90(12):652-656.
8. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet.* Jan 1-7 2005;365(9453):82-93.
9. Hertogh EM, Schuit AJ, Peeters PH, Monninkhof EM. Noncompliance in lifestyle intervention studies: the instrumental variable method provides insight into the bias. *J Clin Epidemiol.* Aug 2010;63(8):900-906.
10. Kendall JM. Designing a research project: randomised controlled trials and their principles. *Emerg Med J.* Mar 2003;20(2):164-168.
11. Stanley K. Design of randomized controlled trials. *Circulation.* Mar 6 2007;115(9):1164-1169.
12. Pablos-Mendez A, Barr RG, Shea S. Run-in periods in randomized trials: implications for the application of results in clinical practice. *JAMA.* Jan 21 1998;279(3):222-225.
13. Treweek S, Lockhart P, Pitkethly M, et al. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. *BMJ Open.* 2013;3(2).
14. Adair JG. The Hawthorne effect: A reconsideration of the methodological artifact. *Journal of applied psychology.* 1984;69(2):334.
15. Oken BS. Placebo effects: clinical aspects and neurobiology. *Brain : a journal of neurology.* Nov 2008;131(Pt 11):2812-2823.
16. Gerstel E, Pataky Z, Busnel C, et al. Impact of lifestyle intervention on body weight and the metabolic syndrome in home-care providers. *Diabetes & metabolism.* Feb 2013;39(1):78-84.
17. Dunn AL, Andersen RE, Jakicic JM. Lifestyle physical activity interventions. History, short- and long-term effects, and recommendations. *American journal of preventive medicine.* Nov 1998;15(4):398-412.
18. Ware JH, Hamel MB. Pragmatic trials—guides to better patient care? *N Engl J Med.* May 5 2011;364(18):1685-1687.
19. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA.* Feb 1 1995;273(5):408-412.
20. Schulz KF, Chalmers I, Grimes DA, Altman DG. Assessing the quality of randomization from reports of controlled trials published in obstetrics and gynecology journals. *JAMA.* Jul 13 1994;272(2):125-128.
21. Campbell R, Peters T, Grant C, Quilty B, Dieppe P. Adapting the randomized consent (Zelen) design for trials of behavioural interventions for chronic disease: feasibility study. *J Health Serv Res Policy.* Oct 2005;10(4):220-225.
22. Homer CS. Using the Zelen design in randomized controlled trials: debates and controversies. *J Adv Nurs.* Apr 2002;38(2):200-207.
23. Huibers MJ, Bleijenberg G, Beurskens AJ, et al. An alternative trial design to overcome validity and recruitment problems in primary care research. *Fam Pract.* Apr 2004;21(2):213-218.
24. Zelen M. Randomized consent designs for clinical trials: an update. *Stat Med.* Jun 1990;9(6):645-656.
25. Piantadosi S. *Clinical trials: a methodologic perspective.* 2005.
26. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med.* Apr 4 2013;368(14):1279-1290.
27. Katz DL, Davidhi A, Ma Y, Kavak Y, Bifulco L, Njike VY. Effects of walnuts on endothelial function in overweight adults with visceral obesity: a randomized, controlled, crossover trial. *J Am Coll Nutr.* Dec 2012;31(6):415-423.
28. Campbell MJ. Cluster randomized trials in general (family) practice research. *Stat Methods Med Res.* Apr 2000;9(2):81-94.
29. Peterson AV, Jr., Kealey KA, Mann SL, Marek PM, Sarason IG. Hutchinson Smoking Prevention Project: long-term randomized trial in school-based tobacco use prevention—results on smoking. *J Natl Cancer Inst.* Dec 20 2000;92(24):1979-1991.
30. Hutson AD, Reid ME. The utility of partial cross-over designs in early phase randomized prevention trials. *Control Clin Trials.* Oct 2004;25(5):493-501.
31. Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. *BMC Med Res Methodol.* 2006;6:54.

32. Lilly CM, Cody S, Zhao H, et al. Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. *JAMA.* Jun 1 2011;305(21):2175-2183.
33. Zelen M. Strategy and alternate randomized designs in cancer clinical trials. *Cancer Treat Rep.* May 1982;66(5):1095-1100.
34. Zelen M. A new design for randomized clinical trials. *N Engl J Med.* May 31 1979;300(22):1242-1245.
35. Wennberg JE, Barry MJ, Fowler FJ, Mulley A. Outcomes research, PORTs, and health care reform. *Ann N Y Acad Sci.* Dec 31 1993;703:52-62.
36. Torgerson DJ, Klaber-Moffett J, Russell IT. Patient preferences in randomised trials: threat or opportunity? *J Health Serv Res Policy.* Oct 1996;1(4):194-197.
37. Rucker G. A two-stage trial design for testing treatment, self-selection and treatment preference effects. *Stat Med.* Apr 1989;8(4):477-485.
38. Preference Collaborative Review G. Patients' preferences within randomised trials: systematic review and patient level meta-analysis. *BMJ.* 2008;337:a1864.
39. King M, Nazareth I, Lampe F, et al. Impact of participant and physician intervention preferences on randomized trials: a systematic review. *JAMA.* Mar 2 2005;293(9):1089-1099.
40. Halpern SD. Evaluating preference effects in partially unblinded, randomized clinical trials. *J Clin Epidemiol.* Feb 2003;56(2):109-115.
41. Zhu SH, Anderson CM, Tedeschi GJ, et al. Evidence of real-world effectiveness of a telephone quitline for smokers. *N Engl J Med.* Oct 3 2002;347(14):1087-1093.
42. Lambert MF, Wood J. Incorporating patient preferences into randomized trials. *J Clin Epidemiol.* Feb 2000;53(2):163-166.
43. Ainsworth HR, Torgerson DJ, Kang'ombe AR. Conceptual, Design, and Statistical Complications Associated with Participant Preference. *Ann Am Acad Polit Ss.* Mar 2010;628:176-188.
44. Turner RM, Walter SD, Macaskill P, McCaffery KJ, Irwig L. Sample Size and Power When Designing a Randomized Trial for the Estimation of Treatment, Selection, and Preference Effects. *Med Decis Making.* Apr 2 2014;34(6):711-719.
45. McCaffery KJ, Turner R, Macaskill P, Walter SD, Chan SF, Irwig L. Determining the impact of informed choice: separating treatment effects from the effects of choice and selection in randomized trials. *Med Decis Making.* Mar-Apr 2011;31(2):229-236.
46. Altman DG. Better reporting of randomised controlled trials: the CONSORT statement. *BMJ.* Sep 7 1996;313(7057):570-571.
47. Campbell MK, Elbourne DR, Altman DG, group C. CONSORT statement: extension to cluster randomised trials. *BMJ.* Mar 20 2004;328(7441):702-708.
48. Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ.* 2008;337:a2390.
49. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P, Group C. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med.* Feb 19 2008;148(4):295-309.

Part IV

Epilogue

Chapter 10

Summary and general discussion

Summary and general discussion

Globally, the burden of cardiovascular disease (CVD) is still increasing.[1] However, in recent decades, better treatment modalities have led to less cardiovascular related deaths. As a results of this, the focus has changed from reducing mortality to improving other clinically important outcomes such as physical functioning and quality of life. Additionally, there is increased awareness of individuals at risk of developing CVD who must be treated accordingly. This has resulted in more attention for lifestyle behaviours, lifestyle factors and lifestyle intervention strategies in the management of cardiovascular care.

In this thesis, our aim was to evaluate and provide insight in the current role of lifestyle behaviours and lifestyle factors in CVD. Additionally, we aimed to improve our knowledge of the effectiveness of selected lifestyle interventions in individuals with, or at increased risk of developing CVD. In this chapter we report the main findings of our studies and subsequently we discuss the results. We end this chapter with concluding remarks and suggestions for future research in lifestyle are made.

Main findings

Association studies

In **Chapter 2** we investigated a cohort of patients with congenital heart disease, who were operated between 1968 and 1980. For our study, they were classified as having simple (ASD, VSD, pulmonary stenosis), or complex congenital heart disease (Tetralogy Of Fallot or Transposition of The Great Arteries (Mustard repair)). We found that higher levels of NT-proBNP were associated with lower levels of quality of life, as assessed with the Short-Form health survey-36 (SF-36). This was predominantly seen in the subdomain physical functioning and more pronounced in patients with complex congenital heart disease. These results can help to trigger the awareness of physicians to use objective measurements when an evident subjective deterioration – in physical functioning – is reported by the patient. This could result in an earlier initiation of targeted treatment strategies in these patients. Important limitations of this study must be addressed. First, the sample size was small and especially in the subgroups. Second, the observed associations were weak and we must be aware of residual confounders that could have influenced the results. Our results are probably explained by the clinical characteristics of patients with complex congenital heart disease. It is evident that having a complex congenital heart disease has effects on daily functioning, especially participation in sports and other physically demanding activities. This limited exercise capacity can therefore result in a more sedentary lifestyle. Patients with complex congenital heart disease are at risk of ventricular dysfunction and consequently developing heart failure.[2]

To recognize an early clinical deterioration, there is increased interest in the use of established biomarkers, such as NT-proBNP.[2,3] The use and knowledge of NT-proBNP is still limited in patients with congenital heart disease, whereas it is a well-established biomarker in heart failure and associations with survival and quality of life have been demonstrated.[4-6] Both quality of life and NT-proBNP have potentially clinical value to guide medical treatment by the cardiologist. They can assess current clinical status (e.g. physical performance, indication of heart failure) and predict long-term functioning. To date, no correlation was seen between these two markers.[6] It is important to note that most patients with congenital heart disease learn to cope with their underlying cardiac disease and show similar quality of life results or even better when compared to age-matched controls.[7,8] The association between an objective marker, such as NT-proBNP, and subjective physical functioning, gives rise to new fields of research. Indicative lifestyle factors could serve as potential treatment targets in patients with (complex) congenital heart disease. Even though an association between subjective QoL and subjective physical functioning was seen, the conclusions should be drawn with caution. More cross-sectional and prospective studies could give a better understanding of the change of NT-proBNP levels and quality of life, because cross-sectional studies only represent a single moment in time.

In **Chapter 3** we investigated the 'obesity paradox' in a population that underwent a percutaneous coronary intervention as part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. We aimed to find an explanation for the increased survival rate as described in the obesity paradox. In our study, we investigated whether the paradox was present and if so, whether quality of life, as assessed with the SF-36, could be an explanatory factor. Poor quality of life has been shown to be associated with increased mortality in patients with cardiac disease.[9] In our study population we found that a large number of patients had either overweight or were obese (45.9%, and 19.3%, respectively). After a median follow-up of 7 years after PCI (range 0.8-9.4 years), we found that overweight, but not obesity was associated with a lower risk for all-cause mortality than those who had normal weight. When we added the subdomains of the SF-36 to the multivariable Cox-model the results did not change. Based on these findings, we conclude that quality of life did not explain the increased survival rate in the overweight group of our study.

The results of our study showed no true obesity paradox, but we did observe a higher survival rate among overweight patients after PCI compared to patients with normal weight. One hypothesis is that patients admitted with overweight are identified as individuals with an increased risk of mortality after surgical or percutaneous interventions. Because of this, they could receive more intensive counselling on lifestyle behaviors and guideline-based medication after discharge, which could have a strong impact on their survival. Thus, optimal use of medication in the overweight and obese group could be an explanatory factor in the obesity paradox.[10-12] It was noteworthy that most overweight individuals were generally younger and this could also have resulted in higher rates of survival. Hence, we adjusted for age in our multivariable analyses and it did not change the results. Even though our results show favourable effects in patients with over-

weight, it should be emphasized that an overweight lifestyle is not recommended. Overweight (including obesity) is regarded as a significant modifiable risk factor for CVD and mortality in older patients.[13] This can partly be explained by the high prevalence of concomitant significant CVD risk factors such as high blood cholesterol, diabetes, and high blood pressure.[14] Obesity increases the risks of morbidity from several other adverse health hazards such as gallbladder disease, sleep apnea, respiratory problems, stroke and cancer.[15-17] Based on the results of our study and previous reports on the obesity paradox,[18,19] we think that overweight and obesity is probably not associated with a higher mortality rate after invasive cardiovascular treatments.

In **Chapter 4** we evaluated the use of mind-body practices in individuals without diagnosed CVD living in a well-defined suburb of Rotterdam (Ommoord) and its association with cardiometabolic risk factors. Example of mind-body practices included were self-prayer, meditation, movement therapies such as yoga or tai chi, and relaxation/breathing exercises. We identified individuals who practiced regularly (>1 hour per week), and those who did not (0 hours, or <1 hour per week). Our results showed that doing a mind-body practice is fairly common in the general population with up to 15% doing at least one type of practice. This is consistent with other reports with rates up to 20% in the general population.[20] Most frequently performed were self-prayer (43.1%), meditation (24.6%), and relaxation/breathing exercises (12.2%). Those in the mind-body practice group had a favorable metabolic risk as compared to those who were not. An inverse association was seen on body mass index, triglycerides and fasting glucose levels. Additionally, we saw a lower incidence of the metabolic syndrome in the group doing mind-body practices. We conclude that mind-body practices are associated with a favourable cardiometabolic risk. Because of the cross-sectional design, no causal relationship can be determined. We need long-term follow-up studies, preferably randomized controlled trials to assess the effectiveness of mind-body practices on cardiometabolic risk factors.

The burden of CVD has resulted in an ongoing search for adjunctive treatments that may help individuals to adopt a healthy lifestyle and improve lifestyle risks factors. There is increased interest in the use of mind-body practices in cardiovascular disease.[21,22] Most mind-body practices focus on stress reduction and (in)directly promote a healthy lifestyle. Subsequently, these healthy lifestyle behaviours can potentially lower the risk of CVD and therefore have an effect on life-expectancy. Our results are in line with other studies that evaluated the beneficial effects of mind-body practices. Studies on meditation, yoga and tai-chi have shown positive effects on cardiovascular risk factors such as blood pressure and lipid levels.[23-26] However, results in the primary prevention setting are still conflicting.[27,28] We need to emphasize that most studies were of low methodological quality and were underpowered. Future studies need to address these methodological flaws so we will have conclusive answers on the effectiveness of mind-body practices in CVD. Despite these limitations, mind-body practices may hold promise for future (preventive) treatment strategies. Several pathways have been investigated that could provide insight in the beneficial effects of mind-body practices in cardiovascular disease. It is evident that the autonomic nervous system is an essential link between the brain and the heart. An im-

balance in this system is even considered a CVD risk factor (e.g. increased sympathetic activity, or decreased parasympathetic activity).[29] Benson and colleagues have proposed a framework of the influential effects of mind-body medicine on health. This framework, also known as the 'relaxation response' can be considered an anti-stress response that decreases sympathetic activation and cortical brain activation.[30,31] Moreover, studies have shown physiological changes during or after performing a form of mind-body practice such as immune and inflammatory responses, endothelial functioning, and improved cardio-vagal tone.[32-36] Unfortunately, the biological mechanisms and substrates in the context of mind-body practices are not yet fully understood and have led to a low acceptance rate in current health care.[37]

In **Chapter 5** we identified patients with diagnosed structural heart disease from a randomized controlled trial of mindfulness at the outpatient clinic of the Erasmus Medical Center, Rotterdam, The Netherlands. We evaluated whether hair cortisol levels were associated with several important clinical outcome parameters. Additionally, we investigated which parameters were independent predictors of cortisol change over a period of 12 weeks. In this study, hair samples were taken at 12-weeks follow-up to create a timeline of long-term cortisol exposure starting from baseline (week 0). Our results showed that, at baseline, negative associations were seen between cortisol levels and BMI and between cortisol levels and respiratory rate. Additionally, higher cortisol levels showed a borderline significant association with lower scores on the physical summary measure of the SF-36. When we looked at cortisol changes over time, a favourable mental status (as assessed with the SF-36) and higher diastolic blood pressure at baseline were associated with a stronger decrease in cortisol levels over a period of 12 weeks. We did not observe an effect of mindfulness training, however, the study population was not powered for this sub-analysis.

Increased levels of stress have negative effects on health and are an important target of treatment in CVD.[38-42] Cortisol is regarded as one of the most important mediators in the human stress response.[38] High levels of cortisol are associated with several indices of the metabolic syndrome and cardiovascular risk.[43,44] Cortisol may therefore be considered as a valuable marker to identify individuals at increased risk of cardiovascular disease. However, cortisol shows a diurnal variation and is directly influenced by acute stressors,[45] which makes it difficult to assess long-term cortisol exposure. New research methods have resulted in the measurement of cortisol in scalp hair and results of our study have shown its feasibility in using this as outcome measure. Recent studies have reported the association between high cortisol levels and increased cardiovascular risk.[46,47] Hair cortisol exposure may provide additional information in individuals with dysregulations in the stress response, especially over a longer period of time. We therefore need long-term prospective studies to investigate the relation of hair cortisol levels in CVD. We also need to look at potential subjective predictors of increased long-term cortisol exposure ('stress') that can trigger the awareness of physicians. In our study we did not find an association of hair cortisol concentrations and perceived stress, a self-reported chronic stress scale. Results in other studies that have investigated the association between hair cortisol concentration and perceived stress

scale were mixed.[48-50] However, mental stress has shown to be associated with higher hair cortisol concentrations.[51,52] We therefore need to investigate whether psychological and/or physiological stress are good indicators of increased long-term cortisol levels and subsequently, which subjective self-reported scales can be used. This may help future physicians to initiate (preventive) treatment strategies. Which lifestyle interventions can be used to modify long-term cortisol exposure have yet to be determined.

Systematic reviews

In **Chapter 6** we systematically searched the literature for studies on lifestyle interventions in low-and middle income countries (LMICs) and summarized the available evidence. We used a predefined protocol in accordance with preferred reporting items for systematic reviews (PRIMSA) and meta-analyses and an extension of the consolidated standards of reporting trials statement(CONSORT).[53] We found 43 studies evaluating lifestyle interventions which were divided into four groups according to their delivery (e.g. physical activity, behavioural counselling, dietary modifications, and multiple interventions). The meta-analysis showed that any form of lifestyle resulted in a significantly lower blood pressure in the LMIC setting. Physical activity resulted in the largest decrease of systolic and diastolic blood pressure, whereas dietary modifications had the lowest, but still significant decrease in SBP. We conclude that lifestyle interventions are potentially valuable in the prevention and treatment of hypertension in LMICs. However, there was a high heterogeneity between studies included in this review and overall quality of studies was low.

Low-and middle income countries (LMICs) show a different distribution of cardiovascular mortality and morbidity than high income countries.[54] Recent reports demonstrate that major cardiovascular risk factors such as diabetes mellitus, hypertension, and smoking are still poorly controlled for in LMICs.[1,54,55] Unfortunately, medical therapy is less affordable for individuals living in LMICs and the availability is often limited.[56-58] Lifestyle interventions are frequently inexpensive, but current evidence is mainly derived from studies conducted in high income countries. Whether they are applicable in the same setting in low-and middle income countries is not clear. The results of our meta-analysis will help to address this matter, because selected lifestyle interventions do show promising results in LMICs. In our meta-analyses we found similar or larger effect sizes than previous reports that addressed the effect of lifestyle interventions on blood pressure.[59-61] This might be explained by the different inclusion criteria of included study designs. The effects of dietary modifications were smaller than previously reported, but this may be explained by the fact that we did not separate sodium restriction from the dietary interventions. Future studies should investigate which lifestyle interventions have the highest potential in reducing blood pressure levels and which interventions are most feasible to conduct, especially when blood-pressure lowering medication is not an option (e.g. not available, or too costly).

Mind-body practices such as meditation, relaxation and yoga have been studied in a variety of clinical conditions, but whether mind-body practices can be of added value in patients with

diagnosed cardiac disease remains to be shown. In **Chapter 7** we present a systematic review and meta-analysis on mind-body practices focusing on meditation in patients with diagnosed cardiac disease. For this systematic review we used a predefined protocol in accordance with the Cochrane Handbook.[62] We identified mind-body practices focusing on meditation that can be easily performed at home without the use of external means. Our search strategy resulted in studies focusing on meditation, mindfulness meditation and relaxation, with studies originating from all parts of the world. For the meta-analyses, we clustered studies focusing on similar outcomes. Our results showed promising effects on the physiological outcomes systolic and diastolic blood pressure and the psychological outcomes depression, anxiety and selected quality of life outcomes. However, most of the Cohen's *d* effect sizes were moderate and studies were generally low in quality with a small sample size. We conclude that meditation based mind-body practices have encouraging results for patients with cardiac disease. Future studies are needed to eliminate most of the limitations noted in this review and to improve reporting of the results.

Due to the heterogeneity of the included studies we need to ask ourselves whether these studies are comparable. We clustered studies based on their similar focus (meditation). Our systematic reviews showed large heterogeneity in study designs (e.g. inclusion- and exclusion criteria, study population, type of intervention and moment of outcome assessment). Most of the studies consisted of small sample sizes that will inevitably lead to low statistical power and an underestimation of the true effect. Most of the limitations in **Chapter 7** are likely to occur due to the limited knowledge of the working mechanism of the treatment that is studied. Mind-body lifestyle practices are not frequently used in regular cardiovascular health care in the Western world and no consensus exists on how to address them in a cardiovascular population. Additionally, the pathophysiological mechanisms on how mind-body practices contribute to physical and mental health is still under investigation, but several frameworks have been proposed which we have addressed in **Chapter 4**. We need studies that are of high quality and methodological rigor. In addition, we need to investigate in what type of (sub)populations these practices are of added value. It can be assumed that several clinical aspects and personal interests may affect their success. Two recent meta-analyses showed notable physiological improvements in vascular patients and in various other clinical conditions.[63,64] However, they also noted the overall low quality of the published studies in this area. It is also noteworthy to address the content of the meditation protocols, because we need to ask ourselves whether predefined protocols of meditation practices can be addressed in both the general population and the clinical setting.

In our systematic reviews we mainly examined surrogate endpoints. Hard endpoints such as death, are difficult to assess in lifestyle interventions because they often require a long follow-up period and extremely large sample sizes. Nonetheless, we put emphasis on using surrogate endpoints that are clinically relevant in CVD, which can serve as treatment targets in primary and secondary prevention.

Intervention studies

In **Chapter 8** we aimed to investigate the effectiveness of an online mindfulness training in a pragmatic randomized study in patients with diagnosed structural heart disease under surveillance at the cardiology outpatient clinic of the Erasmus Medical Center, Rotterdam, the Netherlands. Our results showed that after 12 weeks, the mindfulness group had a better (borderline significant) effect on improving their exercise tolerance, as measured with the 6-minute walk test, than the control group. Additionally, we saw a significantly lower heart rate in the mindfulness group than in the control group. Interestingly, we did not find any significant difference on the psychological outcomes at follow-up. We conclude that online mindfulness training was feasible to conduct in patients with structural heart disease and has favorable effects on exercise capacity and heart rate.

Mindfulness training is a well-known mind body practice and similar practices are becoming more popular in the general population and patients with CVD.[20,22,65] Moreover, there is increased interest in the use of mindfulness training as a treatment in several clinical conditions, but it has not yet been integrated in the management of CVD. Mindfulness based stress reduction and mindfulness based cognitive therapy have shown several health benefits on a variety of clinical disorders.[63,66-68] Most of the positive effects are seen on psychological outcomes. Results on physiological outcomes are still conflicting.[63] Because of the link between the mind and the body,[37] it is not unlikely that mindfulness training may also have physiological effects. Until now, only a few studies have used online mindfulness training, whereas mindfulness training is typically addressed in a group-based or individual setting. Results of online training programs showed promising effects on stress.[69-71] However, these studies were mainly small and included healthy participants. Online training is an easy way to let patients perform mindfulness training in their own surroundings and in their own time. Whether it can result in the same effect as a group-based setting needs to be determined. Furthermore, online training is less intense than face-to-face contact, which may influence patient's motivation and compliance. However, online training may be more favorable than group-training in terms of availability, feasibility, and costs. We will need studies to determine whether this form of training provided to patients with structural heart disease is cost-effective. Future studies also need to address which patients can benefit the most from mindfulness training. We did not select on underlying psychological distress factors (e.g. high anxiety or stress levels), or physical limitations. Our results may indicate that online mindfulness training may be used in patients with limitations in physical functioning, but whether it can address clinically important physiological distress factors needs to be determined.

With regard to lifestyle interventions, several limitations have to be acknowledged that are often encountered in clinical research. The results from **Chapter 6** and **Chapter 7** also indicate that most studies on lifestyle interventions in CVD are subject to limitations and are therefore frequently of low methodological quality. In **Chapter 9** we aimed to provide guidance in the study design of randomized trials in lifestyle research. In this methodological paper we provided tools for researchers on how to choose the optimal randomized study design when assessing the

efficacy or effectiveness of a lifestyle intervention (e.g. parallel, cross-over, cluster, or preference design). In addition, we discussed the associated advantages and disadvantages of each study design. We underline various limitations that are inherent to lifestyle interventions (e.g. adherence and blinding of study participants). With this tutorial we hope to improve the overall quality of intervention studies in lifestyle research. In recent years, adherence to the CONSORT guideline have resulted in structured reporting of RCTs and is often required when studies are submitted to a journal. With our tutorial we strive towards a more informed and justified choice of which randomized design is best in different settings of lifestyle research. We hope this will result in higher quality studies,increased internal validity, and generalizability which could potentially lead to a higher rate of acceptance of lifestyle interventions in the management of CVD.

Clinical implications

Lifestyle interventions have various benefits in the setting of CVD. They are often low in costs, have limited side effects and are easy to implement by most individuals. Additionally, there are many alternatives available that can fit an individual's preference. However, lifestyle changes do require guidance within a multidisciplinary team to evaluate which approach is best for each individual to achieve a maximum response.[72] Furthermore, compliance and long-term adherence are limiting factors in the implementation of such interventions in practice.

It is noteworthy that more-and-more centers, especially those in the United States, offer mind-body practices as part of cardiac rehabilitation, CVD prevention, or wellness programs. Nevertheless, there is still resistance to the use of complementary lifestyle interventions such as mind-body practices. Unquestionably, this can be explained by the lack of well performed studies and limited knowledge of the underlying pathophysiological working mechanism. An unclear understanding of the working mechanism of an intervention calls into question the plausibility of a real effect and can denigrate a potentially effective intervention to the realm of placebo therapies. In contrast, we advocate an open mind and research of the highest scientific and ethical integrity to define the role of such interventions. This is the only way we can expand the therapeutic options for our patients and provide evidence-based care.

Future research

Lifestyle interventions focusing on exercise, nutrition, and smoking cessation have had significant contributions in the prevention and management of CVD. In particular cardiac rehabilitation has resulted in improved outcomes after invasive cardiovascular treatments (e.g. percutaneous or coronary artery bypass grafting).[73-75] However, there are other lifestyle interventions that are worth considering. Studies have addressed the effectiveness of mind-body practices, but there

is still a demand for more and higher quality reports in CVD. Most of previous studies that have evaluated mind-body practices have been conducted in heterogeneous populations and were often of low methodological quality. Nevertheless, studies have shown associations and effects on several key cardiovascular risks factors and outcomes such as blood pressure, heart rate, physiological distress factors and exercise tolerance. In one of our chapters, mindfulness training improved physical functioning in patients with structural heart disease. It may therefore be considered a good alternative treatment option when other modalities have limited effect or are less feasible as a result of personal interests or clinical motives. Future research should investigate whether mind-body practices can be applied to other clinical conditions such as patients with hypertension, or patients with coronary artery disease who often suffer from important cardiovascular risk factors such as obesity and high levels of stress. Additionally, future studies should investigate whether these lifestyle interventions are cost-effective and can be applied in countries that have limited financial and medical resources. Most studies in cardiovascular research focus on hard outcomes such as mortality. In evaluating lifestyle interventions, these outcomes often require a long follow-up time and extremely large sample sizes. Alternatively, one can consider evaluating surrogate endpoints but then the choice should focus on endpoints of significant clinical and prognostic importance. Endpoints that fulfill these criteria include: blood pressure, cardiometabolic components (e.g. LDL cholesterol), or even biomarkers such as NT-proBNP. Which populations will benefit most also needs to be further investigated. For instance, populations with high levels of stress, a high cardiometabolic risk profile, or diminished quality of life.

It should be emphasized that the evaluation and assessment of lifestyle factors are subject to limitations. Associations between risk factors and outcomes do not imply causation. Prospective longitudinal studies with analysis of repeated measures, analysis of potential confounders, propensity score matching, and randomized controlled trials, are required to distinguish true cause and effect relationships from confounding. Our results motivate new fields of study: potential new biological markers such as cortisol in hair, may help in the identification of individuals with a dysregulation in the stress response, the evaluation of subjective (psychological) functioning could help to identify patients at risk of clinical deterioration, and lifestyle interventions such as mind-body practices can be of significant clinical value in cardiovascular care.

References

1. WHO. Global Health Observatory Data Repository. http://apps.who.int/gho/data/node.main. Accessed 09-10-2014.
2. Eindhoven JA, van den Bosch AE, Jansen PR, Boersma E, Roos-Hesselink JW. The usefulness of brain natriuretic peptide in complex congenital heart disease: a systematic review. *J Am Coll Cardiol.* Nov 20 2012;60(21):2140-2149.
3. Eindhoven JA, van den Bosch AE, Boersma E, Roos-Hesselink JW. The usefulness of brain natriuretic peptide in simple congenital heart disease - a systematic review. *Cardiol Young.* Sep 21 2012:1-10.
4. Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation.* Oct 12 2004;110(15):2168-2174.
5. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J.* Oct 2003;24(19):1735-1743.
6. Luther SA, McCullough PA, Havranek EP, et al. The relationship between B-type natriuretic peptide and health status in patients with heart failure. *J Card Fail.* Aug 2005;11(6):414-421.
7. Kamphuis M, Ottenkamp J, Vliegen HW, et al. Health related quality of life and health status in adult survivors with previously operated complex congenital heart disease. *Heart.* Apr 2002;87(4):356-362.
8. Moons P, Van Deyk K, De Bleser L, et al. Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts. *Eur J Cardiovasc Prev Rehabil.* Jun 2006;13(3):407-413.
9. Mommersteeg PM, Denollet J, Spertus JA, Pedersen SS. Health status as a risk factor in cardiovascular disease: a systematic review of current evidence. *Am Heart J.* Feb 2009;157(2):208-218.
10. Gruberg L, Mercado N, Milo S, et al. Impact of body mass index on the outcome of patients with multivessel disease randomized to either coronary artery bypass grafting or stenting in the ARTS trial: The obesity paradox II? *Am J Cardiol.* Feb 15 2005;95(4):439-444.
11. Schenkeveld L, Magro M, Oemrawsingh RM, et al. The influence of optimal medical treatment on the 'obesity paradox', body mass index and long-term mortality in patients treated with percutaneous coronary intervention: a prospective cohort study. *BMJ Open.* 2012;2:e000535.
12. Steinberg BA, Cannon CP, Hernandez AF, Pan W, Peterson ED, Fonarow GC. Medical therapies and invasive treatments for coronary artery disease by body mass: the "obesity paradox" in the Get With The Guidelines database. *Am J Cardiol.* Nov 1 2007;100(9):1331-1335.
13. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med.* Oct 7 1999;341(15):1097-1105.
14. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol.* May 26 2009;53(21):1925-1932.
15. Eckel RH, York DA, Rossner S, et al. Prevention Conference VII: Obesity, a worldwide epidemic related to heart disease and stroke: executive summary. *Circulation.* Nov 2 2004;110(18):2968-2975.
16. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation.* Feb 14 2006;113(6):898-918.
17. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. *Lancet.* Aug 30 2014;384(9945):755-765.
18. Sharma A, Vallakati A, Einstein AJ, et al. Relationship of body mass index with total mortality, cardiovascular mortality, and myocardial infarction after coronary revascularization: evidence from a meta-analysis. *Mayo Clin Proc.* Aug 2014;89(8):1080-1100.
19. Del Prete JC, Bakaeen FG, Dao TK, et al. The impact of obesity on long-term survival after coronary artery bypass grafting. *The Journal of surgical research.* Sep 2010;163(1):7-11.
20. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. *Adv Data.* May 27 2004(343):1-19.
21. Prasad K, Sharma V, Lackore K, Jenkins SM, Prasad A, Sood A. Use of complementary therapies in cardiovascular disease. *Am J Cardiol.* Feb 1 2013;111(3):339-345.
22. Yeh GY, Davis RB, Phillips RS. Use of complementary therapies in patients with cardiovascular disease. *Am J Cardiol.* Sep 1 2006;98(5):673-680.
23. Anderson JW, Liu C, Kryscio RJ. Blood pressure response to transcendental meditation: a meta-analysis. *American journal of hypertension.* Mar 2008;21(3):310-316.

24. Bijlani RL, Vempati RP, Yadav RK, et al. A brief but comprehensive lifestyle education program based on yoga reduces risk factors for cardiovascular disease and diabetes mellitus. *J Altern Complement Med.* Apr 2005;11(2):267-274.
25. Ko GT, Tsang PC, Chan HC. A 10-week Tai-Chi program improved the blood pressure, lipid profile and SF-36 scores in Hong Kong Chinese women. *Med Sci Monit.* May 2006;12(5):CR196-199.
26. Tsai JC, Wang WH, Chan P, et al. The beneficial effects of Tai Chi Chuan on blood pressure and lipid profile and anxiety status in a randomized controlled trial. *J Altern Complement Med.* Oct 2003;9(5):747-754.
27. Hartley L, Dyakova M, Holmes J, et al. Yoga for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2014;5:CD010072.
28. Hartley L, Flowers N, Lee MS, Ernst E, Rees K. Tai chi for primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2014;4:CD010366.
29. Curtis BM, O'Keefe JH, Jr. Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. *Mayo Clin Proc.* Jan 2002;77(1):45-54.
30. Benson H. The relaxation response: its subjective and objective historical precedents and physiology. *Trends Neurosci.* 1983(6):281-284.
31. Benson H, Beary JF, Carol MP. The relaxation response. *Psychiatry.* Feb 1974;37(1):37-46.
32. Davidson RJ, Kabat-Zinn J, Schumacher J, et al. Alterations in brain and immune function produced by mindfulness meditation. *Psychosom Med.* Jul-Aug 2003;65(4):564-570.
33. Dod HS, Bhardwaj R, Sajja V, et al. Effect of intensive lifestyle changes on endothelial function and on inflammatory markers of atherosclerosis. *Am J Cardiol.* Feb 1 2010;105(3):362-367.
34. Jacobs GD. The physiology of mind-body interactions: the stress response and the relaxation response. *J Altern Complement Med.* 2001;7 Suppl 1:S83-92.
35. Lucini D, Covacci G, Milani R, Mela GS, Malliani A, Pagani M. A controlled study of the effects of mental relaxation on autonomic excitatory responses in healthy subjects. *Psychosom Med.* Sep-Oct 1997;59(5):541-552.
36. Vitetta L, Anton B, Cortizo F, Sali A. Mind-body medicine: stress and its impact on overall health and longevity. *Ann N Y Acad Sci.* Dec 2005;1057:492-505.
37. Taylor AG, Goehler LE, Galper DI, Innes KE, Bourguignon C. Top-down and bottom-up mechanisms in mind-body medicine: development of an integrative framework for psychophysiological research. *Explore (NY).* Jan-Feb 2010;6(1):29-41.
38. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet.* Sep 22 2007;370(9592):1089-1100.
39. Adler N, Matthews K. Health psychology: why do some people get sick and some stay well? *Annu Rev Psychol.* 1994;45:229-259.
40. Dimsdale JE. Psychological stress and cardiovascular disease. *J Am Coll Cardiol.* Apr 1 2008;51(13):1237-1246.
41. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. *JAMA.* Oct 10 2007;298(14):1685-1687.
42. Steptoe A, Kivimaki M. Stress and cardiovascular disease. *Nat Rev Cardiol.* Jun 2012;9(6):360-370.
43. Arnaldi G, Angeli A, Atkinson AB, et al. Diagnosis and complications of Cushing's syndrome: A consensus statement. *J Clin Endocr Metab.* Dec 1 2003;88(12):5593-5602.
44. Stalder T, Kirschbaum C, Alexander N, et al. Cortisol in Hair and the Metabolic Syndrome. *J Clin Endocr Metab.* Jun 2013;98(6):2573-2580.
45. Young EA, Abelson J, Lightman SL. Cortisol pulsatility and its role in stress regulation and health. *Front Neuroendocrinol.* Jul 2004;25(2):69-76.
46. Manenschijn L, Schaap L, van Schoor NM, et al. High long-term cortisol levels, measured in scalp hair, are associated with a history of cardiovascular disease. *J Clin Endocrinol Metab.* May 2013;98(5):2078-2083.
47. Pereg D, Gow R, Mosseri M, et al. Hair cortisol and the risk for acute myocardial infarction in adult men. *Stress.* Jan 2011;14(1):73-81.
48. Kalra S, Einarson A, Karaskov T, Van Uum S, Koren G. The relationship between stress and hair cortisol in healthy pregnant women. *Clin Invest Med.* 2007;30(2):E103-107.
49. Karlen J, Ludvigsson J, Frostell A, Theodorsson E, Faresjo T. Cortisol in hair measured in young adults - a biomarker of major life stressors? *BMC Clin Pathol.* 2011;11:12.
50. Van Uum SH, Sauve B, Fraser LA, Morley-Forster P, Paul TL, Koren G. Elevated content of cortisol in hair of patients with severe chronic pain: a novel biomarker for stress. *Stress.* Nov 2008;11(6):483-488.
51. Russell E, Koren G, Rieder M, Van Uum S. Hair cortisol as a biological marker of chronic stress: current status, future directions and unanswered questions. *Psychoneuroendocrinology.* May 2012;37(5):589-601.

52. Staufenbiel SM, Penninx BW, Spijker AT, Elzinga BM, van Rossum EF. Hair cortisol, stress exposure, and mental health in humans: a systematic review. *Psychoneuroendocrinology.* Aug 2013;38(8):1220-1235.
53. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med.* 2010;8:18.
54. Yusuf S, Rangarajan S, Teo K, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med.* Aug 28 2014;371(9):818-827.
55. Yusuf S, McKee M. Documenting the global burden of cardiovascular disease: a major achievement but still a work in progress. *Circulation.* Apr 8 2014;129(14):1459-1462.
56. Mendis S, Abegunde D, Yusuf S, et al. WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE). *Bull World Health Organ.* Nov 2005;83(11):820-829.
57. Quick JD, Hogerzeil HV, Velasquez G, Rago L. Twenty-five years of essential medicines. *Bull World Health Organ.* 2002;80(11):913-914.
58. Mendis S, Fukino K, Cameron A, et al. The availability and affordability of selected essential medicines for chronic diseases in six low- and middle-income countries. *Bull World Health Organ.* Apr 2007;85(4):279-288.
59. Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension.* Oct 2005;46(4):667-675.
60. Cornelissen VA, Fagard RH, Coeckelberghs E, Vanhees L. Impact of resistance training on blood pressure and other cardiovascular risk factors: a meta-analysis of randomized, controlled trials. *Hypertension.* Nov 2011;58(5):950-958.
61. Dickinson HO, Mason JM, Nicolson DJ, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. *Journal of hypertension.* Feb 2006;24(2):215-233.
62. Higgins. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011 2011.
63. Abbott RA, Whear R, Rodgers LR, et al. Effectiveness of mindfulness-based stress reduction and mindfulness based cognitive therapy in vascular disease: A systematic review and meta-analysis of randomised controlled trials. *J Psychosom Res.* May 2014;76(5):341-351.
64. Goyal M, Singh S, Sibinga EM, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. *JAMA internal medicine.* Mar 2014;174(3):357-368.
65. Wolsko PM, Eisenberg DM, Davis RB, Phillips RS. Use of Mind–Body Medical Therapies. *Journal of General Internal Medicine.* 2004;19(1):43-50.
66. Bohlmeijer E, Prenger R, Taal E, Cuijpers P. The effects of mindfulness-based stress reduction therapy on mental health of adults with a chronic medical disease: a meta-analysis. *J Psychosom Res.* Jun 2010;68(6):539-544.
67. Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits. A meta-analysis. *J Psychosom Res.* Jul 2004;57(1):35-43.
68. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *J Consult Clin Psychol.* Apr 2010;78(2):169-183.
69. Gluck TM, Maercker A. A randomized controlled pilot study of a brief web-based mindfulness training. *BMC Psychiatry.* 2011;11:175.
70. Krusche A, Cyhlarova E, King S, Williams JM. Mindfulness online: a preliminary evaluation of the feasibility of a web-based mindfulness course and the impact on stress. *BMJ Open.* 2012;2(3).
71. Morledge TJ, Allexandre D, Fox E, et al. Feasibility of an online mindfulness program for stress management—a randomized, controlled trial. *Ann Behav Med.* Oct 2013;46(2):137-148.
72. Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. *Circulation.* Feb 18 1997;95(4):1085-1090.
73. Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. *Am Heart J.* Oct 2011;162(4):571-584 e572.
74. Goel K, Lennon RJ, Tilbury RT, Squires RW, Thomas RJ. Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. *Circulation.* May 31 2011;123(21):2344-2352.
75. Pack QR, Goel K, Lahr BD, et al. Participation in cardiac rehabilitation and survival after coronary artery bypass graft surgery: a community-based study. *Circulation.* Aug 6 2013;128(6):590-597.

Nederlandse samenvatting

Samenvatting en algemene discussie

Wereldwijd neemt de last van cardiovasculaire ziekten nog steeds toe.[1] Echter, in de afgelopen decennia hebben nieuwe verbeterde behandeltechnieken geleid tot minder cardiovasculair gerelateerde sterftegevallen. Als gevolg hiervan, is de focus veranderd van het verminderen van mortaliteit in het verbeteren van andere klinisch belangrijke uitkomsten, zoals o.a. fysiek functioneren. Daarnaast is de aandacht toegenomen voor individuen die risico lopen op het ontwikkelen van cardiovasculaire ziekten en die hiervoor moeten worden behandeld. Dit heeft geleid tot meer aandacht voor leefstijl gedrag, leefstijlfactoren en leefstijlinterventie strategieën in de behandeling van cardiovasculaire zorg.

Het doel in dit proefschrift is om de rol van leefstijl gedrag en leefstijlfactoren te onderzoeken in cardiovasculaire ziekten. Daarnaast streven wij er naar om onze kennis te verbeteren van de effectiviteit van specifieke leefstijlinterventies bij individuen met een cardiovasculaire ziekte, of bij individuen met een verhoogd risico op het ontwikkelen op deze ziekte.

In dit hoofdstuk rapporteren wij de belangrijkste bevindingen van onze studies en vervolgens bespreken wij de resultaten. We eindigen dit hoofdstuk met afsluitende opmerkingen en wij geven suggesties voor toekomstig onderzoek in leefstijl.

Belangrijkste bevindingen

Associatie studies

In **Hoofdstuk 2** hebben wij een cohort van patiënten onderzocht met een congenitale hartziekte die waren geopereerd tussen 1968 en 1980. Voor onze studie werden zij geclassificeerd als een simpele (ASD, VSD, pulmonaal stenose), of complexe (Tetralogie van Fallot of Transpositie van de Grote Vaten (herstel volgens Mustard)) congenitale hartziekte. Wij vonden dat hogere waarden van NT-proBNP waren geassocieerd met een verminderde kwaliteit van leven, bepaald met de Short-Form health-survey 36 (SF-36). Dit werd voornamelijk gezien in het subdomein fysiek functioneren en was meer uitgesproken in patiënten met een complexe congenitale hartaandoening. Deze resultaten kunnen het bewustzijn van artsen stimuleren om objectieve meetmethoden te gebruiken wanneer een evidente subjectieve achteruitgang – in fysiek functioneren – wordt gerapporteerd door de patiënt. Dit kan resulteren in een vroegtijdige start van doelgerichte behandelingen van deze patiënten. Belangrijke beperkingen van deze studie moeten worden benadrukt. Ten eerste was de steekproefgrootte klein en deze heeft vooral plaats gevonden in de subgroepen. Ten tweede waren de geobserveerde associaties zwak. Wij moeten beducht zijn op confounders die de resultaten zouden kunnen hebben beïnvloed. Onze resultaten worden mogelijk verklaard door de klinische kenmerken van patiënten met een complexe congenitale hartziekte. Het is duidelijk dat een congenitale hartziekte effect heeft op het dagelijks functioneren, vooral bij deelname aan sporten of andere fysiek zware activiteiten. Dit

beperkte uithoudingsvermogen kan resulteren in een meer sedentaire leefstijl. Patiënten met een complexe congenitale hartziekte hebben een verhoogd risico op het ontwikkelen van ventrikel dysfunctie en als bijgevolg het ontwikkelen van hartfalen.[2]

Om een vroege klinische achteruitgang op te merken is er toegenomen interesse in het gebruik van gevestigde biomarkers, zoals NT-proBNP.[2,3] Het gebruik en de kennis van NT-proBNP is nog steeds beperkt bij patiënten met een congenitale hartziekte, terwijl het een gerenommeerde biomarker is in hartfalen waarbij associaties met overleving en kwaliteit van leven zijn aangetoond.[4-6] Zowel kwaliteit van leven als NT-proBNP hebben potentieel klinische waarde in medische behandelingen van cardiologen. Ze kunnen de huidige klinische toestand vaststellen (bijv. fysieke prestaties, indicatie van hartfalen), of het voorspellen van functioneren op de lange termijn. Tot op heden is er geen verband gezien tussen deze twee markers.[6] Het is belangrijk om te melden dat de meeste patiënten met een congenitale hartziekte leren omgaan met hun onderliggende hartziekte en daarbij laten zij dezelfde resultaten zien op kwaliteit van leven, of zelfs beter in vergelijking met op leeftijd gematchte controles.[7,8] De associatie tussen een objectieve marker, zoals NT-proBNP, en subjectief fysiek functioneren geeft aanleiding tot nieuwe onderzoeksgebieden. Indicatieve leefstijlfactoren zouden kunnen dienen als potentiële behandelingsdoelen voor patiënten met (complexe) congenitale hartziekten. Ook al werd er een associatie gezien tussen subjectief kwaliteit van leven en subjectief fysiek functioneren, moeten de conclusies toch met de nodige voorzichtigheid worden getrokken. Meer cross-sectionele en prospectieve studies zouden een beter begrip kunnen geven van de verandering van NT-proBNP waarden en kwaliteit van leven, omdat cross-sectionele studies eenmalig een moment in tijd voorstellen.

In **Hoofdstuk 3** hebben wij de 'obesitas paradox' onderzocht bij een populatie die een percutane coronaire interventie onderging als onderdeel van het Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) register. Wij hadden als doel een verklaring te vinden voor de verhoogde overlevingskans wat in de obesitas paradox is beschreven. In onze studie hebben wij onderzocht of deze paradox aanwezig was, en zo ja, of kwaliteit van leven, beoordeeld met de Short-Form health-survey 36 (SF-36), een mogelijke verklarende factor zou kunnen zijn. Slechte kwaliteit van leven heeft laten zien geassocieerd te zijn met toegenomen mortaliteit bij patiënten met een ziekte van het hart[9]. Wij vonden in onze studie populatie dat een groot aantal patiënten overgewicht hadden of obesitas waren (respectievelijk 45,9% en 19,3%). Na een mediane follow-up van 7 jaar na percutane coronaire interventie (bereik van 0,8-9,4 jaar), vonden wij dat overgewicht, en niet obesitas, was geassocieerd met een lager risico op totale sterfte dan degene met een normaal gewicht. Wanneer wij de subdomeinen van de SF-36 toevoegden aan het multivariabele Cox-model, veranderden de resultaten niet. Op basis van deze resultaten concluderen wij dat kwaliteit van leven niet de toegenomen overlevingskans kon verklaren bij de studiegroep met overgewicht.

De resultaten van onze studie lieten geen ware obesitas paradox zien, maar wij constateerden wel een toegenomen overlevingskans onder patiënten met overgewicht na percutane coro-

naire interventie in vergelijking met patiënten met een normaal gewicht. Een hypothese is dat patiënten met overgewicht worden geïdentificeerd als individuen met een verhoogd risico op overlijden na een chirurgische of percutane interventie. Als gevolg hiervan, zouden zij meer intensieve counseling voor leefstijl gedrag kunnen krijgen evenals voorgeschreven medicatie na ontslag, wat een belangrijk effect kan hebben op overleving. Dus, optimaal gebruik van medicatie in de groep met overgewicht of obesitas zou een verklarende factor kunnen zijn in de obesitas paradox.[10-12] Het is opvallend dat de meeste individuen met overgewicht jonger waren en dit zou kunnen leiden tot een hogere overlevingskans. Dit was de reden dat wij hebben gecorrigeerd voor leeftijd in onze multivariabele analyses en dit veranderde de resultaten niet. Ook al laten onze resultaten gunstige effecten zien bij patiënten met overgewicht, toch moet worden benadrukt dat een leefstijl met overgewicht niet is aan te bevelen. Overgewicht (inclusief obesitas) wordt beschouwd als een belangrijke beïnvloedbare risico factor voor cardiovasculaire ziekte en mortaliteit bij oudere patiënten.[13] Dat kan deels worden verklaard door de hoge prevalentie van bijkomende belangrijke cardiovasculaire risicofactoren, zoals een hoog cholesterolgehalte in het bloed, diabetes en hoge bloeddruk.[14] Obesitas verhoogt het risico op morbiditeit van verschillende andere ongunstige aandoeningen voor de gezondheid, zoals ziekten van de galblaas, slaap apneu, problemen van de luchtwegen, beroerte en kanker.[15-17] Op basis van onze resultaten, en eerdere rapportages over de obesitas paradox,[18,19] denken wij dat overgewicht en obesitas waarschijnlijk niet zijn geassocieerd met een hogere sterftekans na invasieve cardiovasculaire behandelingen.

In **Hoofdstuk 4** hebben wij het gebruik van mind-body practices onderzocht en de associatie met cardiometabole risicofactoren bij individuen zonder gediagnosticeerde cardiovasculaire ziekte die in een welomschreven voorstad leefden van Rotterdam (Ommoord). Voorbeelden van mind-body practices die waren geïncludeerd waren: zelf-gebed, meditatie, bewegingstherapieën zoals yoga of tai chi, en ontspannings/ademhalings oefeningen. Wij identificeerden individuen die regelmatig praktiseerden (>1 uur per week) en degene die dit niet deden (0 uur, of <1 uur per week). Onze resultaten lieten zien dat het doen van mind-body practices vrij gebruikelijk is bij de algemene bevolking waarbij tot 15% minimaal 1 vorm beoefent. Dit is vergelijkbaar met andere rapportages waarin percentages tot 20% in de algemene bevolking worden gemeld[20]. Het meest beoefend waren: zelf-gebed (43,1%), meditatie (24,6%) en ontspannings/ademhalingsoefeningen (12,2%). Degenen in de groep voor mind-body practices hadden een gunstiger metabool risico dan die niet in deze groep zaten. Er werd een omgekeerde associatie gezien van body mass index, tryglyceriden en nuchtere glucose waarden. Bovendien zagen wij een lagere incidentie van het metabool syndroom in de groep van mind-body practices. Wij concluderen dat mind-body practices zijn geassocieerd met een gunstiger metabool risico. Door het cross-sectionele ontwerp kan geen causale relatie worden vastgesteld. Wij hebben lange termijn follow-up studies nodig, met als voorkeur gerandomiseerde studies, om de effectiviteit van mind-body practices op cardiometabole risicofactoren vast te stellen.

De last van cardiovasculaire ziekten heeft geresulteerd in een voortdurende zoektocht naar adjuvante behandelingen die ervoor kunnen zorgen dat individuen een gezonde leefstijl aannemen en daarbij leefstijl risicofactoren verbeteren. Er is toegenomen interesse in het gebruik van mind-body practices in cardiovasculaire ziekte.[21,22] De meeste mind-body practices richten zich op het reduceren van stress en bevorderen (in)direct een gezonde leefstijl. Vervolgens kunnen deze gezonde leefstijl gedragingen potentieel het risico op cardiovasculaire ziekte verlagen en hebben derhalve ook een effect op de levensverwachting. Onze resultaten zijn in overeenstemming met andere studies die de gunstige effecten van mind-body practices hebben onderzocht. Studies naar meditatie, yoga en tai-chi hebben positieve effecten laten zien op cardiovasculaire risicofactoren, zoals bloeddruk en lipide waarden.[23-26] Echter, resultaten in de setting van primaire preventie zijn nog steeds tegenstrijdig.[27,28] We moeten benadrukken dat de meeste studies van lage en zwakke methodologische kwaliteit waren. Toekomstige studies moeten zich richten op deze methodologische gebreken zodat wij overtuigende antwoorden zullen krijgen over de effectiviteit van mind-body practices bij cardiovasculaire ziekten. Ondanks deze beperkingen hebben mind-body practices toekomstperspectief bij (preventieve) behandelingsopties. Diverse mogelijkheden zijn onderzocht die inzicht zouden kunnen bieden in de gunstige effecten van mind-body practices bij cardiovasculaire ziekten. Het is duidelijk dat het autonome zenuwstelsel een belangrijke link is tussen het brein en het hart. Een ontregeling in dit systeem wordt zelfs beschouwd als een cardiovasculaire risicofactor (bijv. een toegenomen sympathicus activiteit, of verminderde parasympatische activiteit).[29] Benson en zijn collega's hebben een kader voorgesteld voor de invloedrijke effecten van mind-body medicine op de gezondheid. Dit kader, ook wel bekend als de 'relaxatie respons'

kan worden beschouwd als een anti-stress reactie dat de sympathische activiteit en corticale hersenactiviteit vermindert.[30,31] Bovendien hebben studies fysiologische veranderingen laten zien tijdens, of na het uitvoeren van mind-body practices, zoals immuun en inflammatoire reacties, endotheliale functies en verbeterde cardiale-vagale tonus.[32-36] Helaas zijn de biologische mechanismen en de substraten van mind-body practices nog niet volledig begrepen. Dit heeft geleid tot een lage mate van acceptatie in de huidige gezondheidszorg.[37]

In **Hoofdstuk 5** hebben wij patiënten geïdentificeerd met een gediagnosticeerde structurele hartziekte van een gerandomiseerde studie naar mindfulness. Deze studie vond plaats op de polikliniek van het Erasmus Medisch Centrum in Rotterdam, Nederland. We onderzochten of haar cortisol waarden waren geassocieerd met diverse belangrijke klinische uitkomst variabelen. Verder onderzochten wij welke variabelen onafhankelijke voorspellers waren voor de verandering van cortisol waarden over een periode van 12 weken. In deze studie werden haarmonsters genomen bij de follow-up op 12 weken, om zodoende een tijdlijn te creëren van lange termijn cortisol verandering, beginnend vanaf aanvang (week 0). Onze resultaten lieten zien dat op baseline, negatieve associaties werden gezien tussen cortisol waarden en BMI en tussen cortisol waarden en ademhalingsfunctie. Bovendien lieten hogere cortisol waarden een grensgeval van significante associatie zien met lagere scores op de physical summary measure van de SF-36.

Wanneer wij keken naar de cortisol verandering over de tijd, zagen wij dat een gunstige mentale status (bepaald met de SF-36) en een hogere diastolische bloeddruk bij aanvang, waren geassocieerd met een sterkere daling van cortisol waarden over een periode van 12 weken. Wij zagen geen effect van de mindfulness training, want de studie populatie had te weinig onderscheidend vermogen (power) voor deze sub-analyse.

Toegenomen mate van stress heeft negatieve gevolgen op de gezondheid en is een belangrijk behandelingsdoel van cardiovasculaire ziekten.[38-42] Cortisol wordt beschouwd als een van de belangrijkste mediatoren in de menselijke reactie op stress.[38] Hoge waarden van cortisol zijn geassocieerd met verschillende componenten van het metabool syndroom en cardiovasculair risico.[43,44] Cortisol mag daarom worden beschouwd als een belangrijke marker om individuen te identificeren die een verhoogd cardiovasculair risico hebben. Echter, cortisol laat een dagritme zien en wordt direct beïnvloed door acute stressoren[45] wat het lastig maakt om lange termijn cortisol waarden te beoordelen. Nieuwe onderzoeksmethoden hebben geleid tot het meten van cortisol in hoofdhaar. De resultaten in onze studie hebben de haalbaarheid laten zien om dit als een uitkomstmaat te gebruiken. Recente studies hebben een associatie laten zien tussen hoge cortisol waarden en cardiovasculair risico.[46,47] Haar cortisol kan voor aanvullende informatie zorgen in individuen met verstoringen in de stress reactie, vooral over een langere tijdsperiode. Wij hebben daarom langlopende prospectieve studies nodig die de relatie onderzoeken tussen haar cortisol en cardiovasculaire ziekten. We moeten ook kijken naar potentiële subjectieve variabelen die gepaard kunnen gaan met een verhoogd lange termijn cortisol ('stress') welke kunnen resulteren in aandacht van de arts. Wij vonden in onze studie geen associatie tussen haar cortisol waarden en waargenomen stress uit een zelf gerapporteerde chronische stress schaal. Resultaten uit andere studies die de associatie tussen haar cortisol en waargenomen stress onderzochten waren gemend.[48-50] Echter, mentale stress heeft associaties laten zien met hogere levels van haar cortisol.[51,52] Wij moeten daarom onderzoeken of psychologische en/of fysiologische stress goede indicatoren zijn van lange termijn cortisol waarden en vervolgens welke subjectieve zelf gerapporteerde schalen kunnen worden gebruikt. Dit zou toekomstige artsen kunnen helpen om (preventieve) behandelingen te starten. Het moet nog worden uitgezocht welke leefstijlinterventies gebruikt kunnen worden om lange termijn cortisol waarden te veranderen.

Systematische literatuurstudies

In **Hoofdstuk 6** hebben wij systematisch de literatuur afgezocht naar studies over leefstijlinterventies in landen met lage- en middeninkomens en daarbij hebben wij het bestaande bewijs samengevat. Wij hebben hiervoor vastgestelde protocollen gebruik in overeenstemming met Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) en een uitbreiding van de Consolidated Standards of Reporting Trials Statement (CONSORT).[53] Wij vonden 43 studies die leefstijlinterventies onderzochten die vervolgens werden onderverdeeld in vier groepen volgens hun aflevering (bijv. lichamelijke activiteit, counseling van gedrag, dieet aanpas-

singen en meerdere interventies). De meta-analyse liet zien dat elke vorm van leefstijl leidde tot een significant lagere bloeddruk in landen met lage- en middeninkomens. Lichamelijke activiteit resulteerde in de grootste daling van systolische- en diastolische bloeddruk. Terwijl aanpassingen in dieet de minste daling, maar alsnog significante systolische bloeddruk daling, liet zien. Wij concluderen dat leefstijlinterventies potentieel waardevol zijn in de preventie en behandeling van hypertensie in landen met lage- en middeninkomens. Echter, er was een grote heterogeniteit tussen de geïncludeerde studies in dit overzicht en de algehele kwaliteit van de studies was laag.

Landen met lage- en middeninkomens laten meer een verschillende verdeling zien van cardiovasculaire mortaliteit en morbiditeit dan landen met een hoog inkomen.[54] Recente rapportages laten zien dat belangrijke cardiovasculaire risicofactoren, zoals diabetes mellitus, hypertensie en roken nog steeds moeilijk controleerbaar zijn in landen met lage- en middeninkomens.[1,54,55] Helaas is de medische therapie minder betaalbaar voor individuen die in landen leven met lage- en middeninkomens en bovendien is de beschikbaarheid hiervan vaak beperkt.[56-58] Leefstijlinterventies zijn vaak goedkoop, maar het huidige bewijs is voornamelijk afkomstig van studies die zijn uitgevoerd in landen met hoge inkomens. Of zij in dezelfde setting in landen met lage- en middeninkomens van toepassing zijn is niet duidelijk. Resultaten van onze meta-analyse zal helpen om deze kwestie aan te pakken, omdat geselecteerde leefstijlinterventies veelbelovende resultaten laten zien in landen met lage- en middeninkomens. Wij vonden in onze meta-analyse soortgelijke of grotere effecten dan eerdere berichtgeving die de effecten van leefstijlinterventies op bloeddruk bekeken.[59-61] Dit kan mogelijk worden verklaard door de verschillende inclusie criteria van de geselecteerde studie ontwerpen. De effecten van dieet aanpassingen waren kleiner dan eerder beschreven, maar dit kan mogelijk worden verklaard door het feit dat wij zoutbeperking niet hebben gedifferentieerd van de dieetinterventies. Toekomstige studies moeten onderzoeken welke leefstijlinterventies het hoogste potentieel hebben om de bloeddruk te verlagen en welke interventies het meest haalbaar zijn om uit te voeren, vooral als bloeddrukverlagende medicatie geen optie is (bijv. niet beschikbaar, of te duur).

Mind-body practices, zoals meditatie, ontspanning en yoga zijn onderzocht in diverse klinische omstandigheden, maar of mind-body practices van toegevoegde waarde zijn bij patiënten met een gediagnosticeerde hartziekte moet nog worden uitgezocht. In **Hoofdstuk 7** presenteren wij een systematische literatuurstudie en meta-analyse over mind-body practices die zich richten op meditatie bij patiënten met een diagnosticeerde hartziekte. Voor deze systematische literatuurstudie hebben wij gebruik gemaakt van een vooraf gedefinieerd protocol in overeenstemming met de Cochrane Handbook.[62] Wij identificeerden mind-body practices, gericht op meditatie, die gemakkelijk thuis kunnen worden uitgevoerd zonder gebruik van externe middelen. Onze zoekstrategie resulteerde in studies uit alle delen van de wereld die zich richtten op meditatie, mindfulness meditatie en ontspanning. Voor de meta-analyse bundelden wij studies met dezelfde uitkomsten. Onze resultaten lieten veelbelovende effecten zien op de fysiologische uitkomsten, de systolische en diastolische bloeddruk en de psychologische uitkomsten zoals depressie, angst en op de geselecteerde uitkomsten van kwaliteit van leven. Echter, de meeste Cohen's *d* effecten

waren matig en de studies waren in het algemeen laag van kwaliteit met een kleine studie grootte. Wij concluderen dat op meditatie gebaseerde mind-body practices bemoedigende uitkomsten hebben voor patiënten met een hartziekte. Toekomstige studies zijn nodig om de meest gemelde beperkingen in dit overzicht te elimineren en daarbij de verslaglegging van de resultaten te verbeteren.

Op basis van de heterogeniteit van de geïncludeerde studies moeten wij ons afvragen of deze studies vergelijkbaar zijn. Wij bundelden studies op basis van hun gelijkwaardige aandachtspunt (meditatie). Onze systematische literatuurstudie liet een grote mate van heterogeniteit zien in de studies (bijv. inclusie- en exclusie criteria, studie populatie, type interventie en het meetmoment van de uitkomsten). Het merendeel van de studies bestond uit een kleine studiegrootte die onvermijdelijk zal leiden tot een laag statistisch onderscheidend vermogen en een onderschatting van het werkelijke effect. De meeste beperkingen in **Hoofdstuk 7** zijn voornamelijk het gevolg van de beperkte kennis van het werkingsmechanisme van de behandeling die wordt onderzocht. Mind-body leefstijl practices worden niet vaak gebruikt in de reguliere Westerse cardiovasculaire zorg en er bestaat geen overeenstemming over de aanpak in een cardiovasculaire populatie. Bovendien wordt het werkingsmechanisme van hoe mind-body practices bijdragen aan fysieke en mentale gezondheid nog onderzocht, maar er zijn al wel enkele kaders voorgesteld die wij hebben vermeld in **Hoofdstuk 4**. Wij hebben studies nodig van hoge kwaliteit en methodologische nauwkeurigheid. Daarnaast moeten wij nagaan in welke (sub)populaties deze mind-body practices van toegevoegde waarde zijn. Het kan worden aangenomen dat verschillende klinische aspecten en persoonlijke interesses hun succes kunnen beïnvloedden. Twee recente meta-analyses lieten opmerkelijke fysiologische verbeteringen zien bij patiënten met een vasculaire aandoening en ook bij diverse andere klinische aandoeningen.[63,64] Echter, zij merkten ook op dat de algehele kwaliteit van de gepubliceerde studies laag was in dit veld. Het is ook belangrijk om de inhoud van meditatie protocollen te bekijken, omdat wij onszelf moeten afvragen of bekende protocollen in zowel de algemene bevolking, als in de klinische setting, kunnen worden gebruikt.

Wij keken in onze systematische literatuurstudies voornamelijk naar surrogaat eindpunten. Harde eindpunten, zoals de dood zijn moeilijk te beoordelen in leefstijlinterventies, omdat zij een lange follow-up en een grootte studiepopulatie vereisen. Toch leggen wij de nadruk op het gebruik van surrogaateindpunten die klinisch relevant zijn in cardiovasculaire ziekten en die kunnen dienen als behandelingsdoelen in primaire en secundaire preventie.

Interventie studies

In **Hoofdstuk 8** was ons doel om de effectiviteit van een online mindfulness training te onderzoeken in een pragmatisch gerandomiseerde studie bij patiënten met een gediagnosticeerde structurele hartziekte onder toezicht van de polikliniek cardiologie van het Erasmus Medisch Centrum Rotterdam, Nederland. Onze resultaten toonden aan dat na 12 weken de mindfulness groep een beter (grensgeval significant) effect had op het verbeteren van hun inspanningstolerantie, gemeten met de 6 minuten looptest, dan de controle groep. Daarnaast zagen wij een

significant lagere hartslag in de mindfulness groep dan in de controle groep. Het was interessant om te zien dat wij geen significant verschil zagen op de psychologische uitkomsten bij een follow-up. Wij concluderen dat online mindfulness training goed uitvoerbaar was voor patiënten met een structurele hartziekte en dat het gunstige effecten heeft op het uithoudingsvermogen en de hartslag.

Mindfulness training is een welbekende mind-body practice en vergelijkbare practices worden steeds populairder bij de algemene bevolking en bij patiënten met een cardiovasculaire ziekte.[20,22,65] Bovendien is er toegenomen interesse voor het gebruik van mindfulness training als behandeling van verschillende klinische aandoeningen,[63,66-68] maar het is nog niet geïntegreerd in de behandeling van cardiovasculaire ziekten. Mindfulness-based stress reductie en mindfulness-based cognitieve therapie hebben verschillende gezondheidsvoordelen laten zien in een variatie aan klinische aandoeningen. De meeste positieve effecten worden gezien in de psychologische uitkomsten. Resultaten op fysiologische uitkomsten zijn nog tegenstrijdig.[63] Omdat er een verband bestaat tussen het geest en het lichaam,[37] is het niet ondenkbaar dat mindfulness training ook fysiologische effecten kan hebben. Tot op heden zijn er maar een paar studies die online mindfulness training hebben onderzocht, terwijl mindfulness training vaak in een groep of individuele setting wordt aangeboden. Resultaten van online training programma's lieten veelbelovende effecten zien op stress.[69-71] Echter, deze studies waren voornamelijk klein en includeerden gezonde deelnemers. Online training is een eenvoudige manier om patiënten mindfulness te laten beoefenen in hun eigen omgeving en in hun eigen tijd. Of het kan leiden tot vergelijkbare effecten als wanneer het wordt uitgevoerd in een groep moet nog worden uitgezocht. Bovendien is online training minder intensief dan direct contact, wat mogelijk de motivatie en naleving kan beïnvloeden. Echter, online training kan gunstiger zijn dan een groep training door de beschikbaarheid, uitvoerbaarheid en kosten. Wij hebben studies nodig die uitzoeken of deze vorm van training kosteneffectief is bij patiënten met een structurele hartziekte. Toekomstige studies moeten ook nagaan welke patiënten het meeste baat kunnen hebben bij mindfulness training. Wij selecteerden niet op basis van onderliggende psychologische spanningen (bijv. hoge mate van angst of stress), of fysieke beperkingen. Onze resultaten kunnen indiceren dat online mindfulness training gebruikt zou kunnen worden in patiënten met beperkingen in fysiek functioneren, maar het moet nog worden uitgezocht of het daadwerkelijk klinisch belangrijke psychologische spanningen kan aanpakken.

Wij moeten verschillende beperkingen noemen van leefstijlinterventies die vaak worden aangetroffen in klinisch onderzoek. De resultaten in **Hoofdstuk 6** en **Hoofdstuk 7** geven aan dat de meeste leefstijl studies in cardiovasculaire ziekten meestal onderhevig zijn aan beperkingen en daarom vaak van lage methodologische kwaliteit zijn. In **Hoofdstuk 9** was ons doel om richting te geven aan de onderzoeksopzet van gerandomiseerde studies in leefstijlonderzoek. In dit methodologische artikel hebben wij getracht een leidraad te verschaffen voor onderzoekers om de beste keuze te maken in een gerandomiseerd onderzoeksopzet wanneer men de werkzaamheid en effectiviteit van leefstijlinterventies onderzoekt (bijv. parallel, cross-over,

cluster, of preferentie opzet). Daarnaast hebben wij de bijbehorende voor- en nadelen van elk onderzoeksopzet besproken. Wij benadrukken verschillende beperkingen die onlosmakelijk verbonden zijn aan leefstijlinterventies (bijv. de naleving en blindering van studie deelnemers). Met deze leidraad hopen wij de algehele kwaliteit van interventie studies in leefstijlonderzoek te verbeteren. In de afgelopen jaren heeft het naleven van de CONSORT richtlijn gezorgd voor het gestructureerd rapporteren van gerandomiseerde studies en dit is vaak vereist wanneer studies worden ingediend bij een tijdschrift. Met onze leidraad streven wij naar een meer geïnformeerde en verantwoorde keuze voor wanneer welk gerandomiseerde opzet het beste is in bepaalde omstandigheden van leefstijlonderzoek. Wij hopen dat dit zal leiden tot studies van hogere kwaliteit, hoge interne validiteit en generaliseerbaarheid die zouden kunnen leiden tot een hogere acceptatie van leefstijlinterventies in de behandeling van cardiovasculaire ziekten.

Klinische implicaties

Leefstijlinterventies hebben verschillende voordelen in de setting van cardiovasculaire ziekten. Ze zijn vaak laag in kosten, hebben weinig bijwerkingen en zijn eenvoudig uit te voeren door de meeste individuen. Bovendien zijn er veel alternatieven beschikbaar die bij ieders voorkeur kunnen passen. Echter, leefstijlveranderingen vereisen wel begeleiding binnen een multidisciplinair team om uit te zoeken welke aanpak het beste is voor ieder individu om een maximale respons te bewerkstelligen.[72] Daarnaast zijn naleving en langdurige therapietrouw beperkende factoren voor de uitvoering van dergelijke interventies in de praktijk.

Het is opmerkelijk dat meer en meer centra, vooral die in de Verenigde Staten, mind-body practices aanbieden als onderdeel van hartrevalidatie, preventie van cardiovasculaire ziekte of als welzijn programma's. Toch is er nog steeds weerstand tegen het gebruik van complementaire leefstijlinterventies, zoals mind-body practices. Dit kan zonder twijfel worden verklaard door de afwezigheid van goed uitgevoerde studies en de beperkte kennis van het onderliggende pathofysiologische werkingsmechanisme. Een onduidelijk begrip van het werkingsmechanisme van interventies zal vragen doen rijzen over de plausibiliteit van een reëel effect en kan een potentieel effectieve interventie doen afdalen tot het rijk van placebo behandelingen. Daarentegen pleiten wij juist voor een open houding en onderzoek van de hoogste wetenschappelijke en ethische integriteit om de bijdrage van dergelijke interventies te bepalen. Dit is de enige manier om behandelingsopties voor onze patiënten te kunnen uitbreiden en te zorgen voor het verschaffen van evidence-based-care.

Toekomstig onderzoek

Leefstijlinterventies die zich richten op beweging, voeding en stoppen met roken hebben een significante bijdrage geleverd aan de preventie en behandeling van cardiovasculaire ziekten. Vooral hartrevalidatie heeft geresulteerd in verbeterde uitkomsten na invasieve cardiovasculaire

behandelingen (bijv. percutane of coronaire bypass operaties).[73-75] Echter, er zijn andere leefstijlinterventies die het overwegen waard zijn. Studies hebben zich gericht op de effectiviteit van mind-body practices, maar er is nog steeds vraag naar meer en betere kwaliteit rapportages binnen cardiovasculaire ziekten. Het merendeel van eerdere studies die mind-body practices hebben onderzocht, waren uitgevoerd in heterogene populaties en waren vaak van lage methodologische kwaliteit. Desalniettemin hebben studies associaties en effecten laten zien op verschillende belangrijke cardiovasculaire risicofactoren en uitkomsten, zoals bloeddruk, hartslag, psychologische spanningsfactoren en uithoudingsvermogen. In een van onze hoofdstukken zagen wij dat mindfulness training fysiek functioneren verbeterde bij patiënten met een structurele hartziekte. Het kan daarom worden beschouwd als een goede alternatieve behandelingsoptie wanneer andere modaliteiten een beperkt effect hebben of wanneer de uitvoerbaarheid minder haalbaar is door persoonlijke interesses of klinische overwegingen. Toekomstig onderzoek moet uitzoeken of mind-body practices kunnen worden toegepast in andere klinische aandoeningen, zoals bij patiënten met hypertensie, of bij patiënten met kransslagaderlijden die vaak last hebben van belangrijke cardiovasculaire risicofactoren zoals obesitas en hoge mate van stress. Bovendien zouden toekomstige studies moeten uitzoeken of deze leefstijlinterventies kosteneffectief zijn en kunnen worden toegepast in landen die beperkte financiële en medische middelen hebben. De meeste studies in cardiovasculair onderzoek richten zich op harde uitkomsten, zoals sterfte. Wanneer dit wordt onderzocht in leefstijlinterventies zal dit leiden tot een lange follow-up duur en extreem grote onderzoeksgroepen. Als alternatief kan men surrogaateindpunten onderzoeken, maar dan moet de keuze worden gemaakt voor eindpunten die van belangrijke klinische en prognostische waarde zijn. Eindpunten die voldoen aan deze criteria zijn onder andere: bloeddruk, cardiometabole risicofactoren (bijv. LDL-cholesterol) en zelfs biomarkers, zoals NT-proBNP. Welke populaties hierbij het meeste baat zullen hebben moet ook worden onderzocht. Bijvoorbeeld: populaties met een hoge mate van stress, een hoog cardiometabool risicoprofiel, of een verlaagde kwaliteit van leven.

Het moet worden benadrukt dat het onderzoek en de beoordeling van leefstijlfactoren beperkingen heeft. Associaties tussen risicofactoren en uitkomsten impliceren geen causaliteit. Prospectieve longitudinale studies zijn nodig met analyses van herhaalde metingen, analyses van potentiele confounders, propensity score matching en gerandomiseerde gecontroleerde studies om de daadwerkelijke verbanden tussen oorzaak en effect te onderscheiden van confounders. Onze resultaten zetten aan tot nieuwe studierichtingen: potentiele nieuwe biologische markers, zoals cortisol in haar zouden kunnen helpen in het identificeren van individuen met een verstoring in de stress reactie. De evaluatie van subjectief (psychisch) functioneren kan mogelijk helpen bij het identificeren van patiënten die risico lopen op klinische achteruitgang. En leefstijlinterventies naar mind-body practices kunnen van substantiële klinische betekenis zijn in de cardiovasculaire zorg.

Referenties

1. WHO. Global Health Observatory Data Repository. http://apps.who.int/gho/data/node.main. Accessed 09-10-2014.
2. Eindhoven JA, van den Bosch AE, Jansen PR, Boersma E, Roos-Hesselink JW. The usefulness of brain natriuretic peptide in complex congenital heart disease: a systematic review. *J Am Coll Cardiol.* Nov 20 2012;60(21):2140-2149.
3. Eindhoven JA, van den Bosch AE, Boersma E, Roos-Hesselink JW. The usefulness of brain natriuretic peptide in simple congenital heart disease - a systematic review. *Cardiol Young.* Sep 21 2012:1-10.
4. Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation.* Oct 12 2004;110(15):2168-2174.
5. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J.* Oct 2003;24(19):1735-1743.
6. Luther SA, McCullough PA, Havranek EP, et al. The relationship between B-type natriuretic peptide and health status in patients with heart failure. *J Card Fail.* Aug 2005;11(6):414-421.
7. Kamphuis M, Ottenkamp J, Vliegen HW, et al. Health related quality of life and health status in adult survivors with previously operated complex congenital heart disease. *Heart.* Apr 2002;87(4):356-362.
8. Moons P, Van Deyk K, De Bleser L, et al. Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts. *Eur J Cardiovasc Prev Rehabil.* Jun 2006;13(3):407-413.
9. Mommersteeg PM, Denollet J, Spertus JA, Pedersen SS. Health status as a risk factor in cardiovascular disease: a systematic review of current evidence. *Am Heart J.* Feb 2009;157(2):208-218.
10. Gruberg L, Mercado N, Milo S, et al. Impact of body mass index on the outcome of patients with multivessel disease randomized to either coronary artery bypass grafting or stenting in the ARTS trial: The obesity paradox II? *Am J Cardiol.* Feb 15 2005;95(4):439-444.
11. Schenkeveld L, Magro M, Oemrawsingh RM, et al. The influence of optimal medical treatment on the 'obesity paradox', body mass index and long-term mortality in patients treated with percutaneous coronary intervention: a prospective cohort study. *BMJ Open.* 2012;2:e000535.
12. Steinberg BA, Cannon CP, Hernandez AF, Pan W, Peterson ED, Fonarow GC. Medical therapies and invasive treatments for coronary artery disease by body mass: the "obesity paradox" in the Get With The Guidelines database. *Am J Cardiol.* Nov 1 2007;100(9):1331-1335.
13. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med.* Oct 7 1999;341(15):1097-1105.
14. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol.* May 26 2009;53(21):1925-1932.
15. Eckel RH, York DA, Rossner S, et al. Prevention Conference VII: Obesity, a worldwide epidemic related to heart disease and stroke: executive summary. *Circulation.* Nov 2 2004;110(18):2968-2975.
16. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation.* Feb 14 2006;113(6):898-918.
17. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. *Lancet.* Aug 30 2014;384(9945):755-765.
18. Sharma A, Vallakati A, Einstein AJ, et al. Relationship of body mass index with total mortality, cardiovascular mortality, and myocardial infarction after coronary revascularization: evidence from a meta-analysis. *Mayo Clin Proc.* Aug 2014;89(8):1080-1100.
19. Del Prete JC, Bakaeen FG, Dao TK, et al. The impact of obesity on long-term survival after coronary artery bypass grafting. *The Journal of surgical research.* Sep 2010;163(1):7-11.
20. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. *Adv Data.* May 27 2004(343):1-19.
21. Prasad K, Sharma V, Lackore K, Jenkins SM, Prasad A, Sood A. Use of complementary therapies in cardiovascular disease. *Am J Cardiol.* Feb 1 2013;111(3):339-345.
22. Yeh GY, Davis RB, Phillips RS. Use of complementary therapies in patients with cardiovascular disease. *Am J Cardiol.* Sep 1 2006;98(5):673-680.
23. Anderson JW, Liu C, Kryscio RJ. Blood pressure response to transcendental meditation: a meta-analysis. *American journal of hypertension.* Mar 2008;21(3):310-316.

24. Bijlani RL, Vempati RP, Yadav RK, et al. A brief but comprehensive lifestyle education program based on yoga reduces risk factors for cardiovascular disease and diabetes mellitus. *J Altern Complement Med.* Apr 2005;11(2):267-274.
25. Ko GT, Tsang PC, Chan HC. A 10-week Tai-Chi program improved the blood pressure, lipid profile and SF-36 scores in Hong Kong Chinese women. *Med Sci Monit.* May 2006;12(5):CR196-199.
26. Tsai JC, Wang WH, Chan P, et al. The beneficial effects of Tai Chi Chuan on blood pressure and lipid profile and anxiety status in a randomized controlled trial. *J Altern Complement Med.* Oct 2003;9(5):747-754.
27. Hartley L, Dyakova M, Holmes J, et al. Yoga for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2014;5:CD010072.
28. Hartley L, Flowers N, Lee MS, Ernst E, Rees K. Tai chi for primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2014;4:CD010366.
29. Curtis BM, O'Keefe JH, Jr. Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. *Mayo Clin Proc.* Jan 2002;77(1):45-54.
30. Benson H. The relaxation response: its subjective and objective historical precedents and physiology. *Trends Neurosci.* 1983(6):281-284.
31. Benson H, Beary JF, Carol MP. The relaxation response. *Psychiatry.* Feb 1974;37(1):37-46.
32. Davidson RJ, Kabat-Zinn J, Schumacher J, et al. Alterations in brain and immune function produced by mindfulness meditation. *Psychosom Med.* Jul-Aug 2003;65(4):564-570.
33. Dod HS, Bhardwaj R, Sajja V, et al. Effect of intensive lifestyle changes on endothelial function and on inflammatory markers of atherosclerosis. *Am J Cardiol.* Feb 1 2010;105(3):362-367.
34. Jacobs GD. The physiology of mind-body interactions: the stress response and the relaxation response. *J Altern Complement Med.* 2001;7 Suppl 1:S83-92.
35. Lucini D, Covacci G, Milani R, Mela GS, Malliani A, Pagani M. A controlled study of the effects of mental relaxation on autonomic excitatory responses in healthy subjects. *Psychosom Med.* Sep-Oct 1997;59(5):541-552.
36. Vitetta L, Anton B, Cortizo F, Sali A. Mind-body medicine: stress and its impact on overall health and longevity. *Ann N Y Acad Sci.* Dec 2005;1057:492-505.
37. Taylor AG, Goehler LE, Galper DI, Innes KE, Bourguignon C. Top-down and bottom-up mechanisms in mind-body medicine: development of an integrative framework for psychophysiological research. *Explore (NY).* Jan-Feb 2010;6(1):29-41.
38. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet.* Sep 22 2007;370(9592):1089-1100.
39. Adler N, Matthews K. Health psychology: why do some people get sick and some stay well? *Annu Rev Psychol.* 1994;45:229-259.
40. Dimsdale JE. Psychological stress and cardiovascular disease. *J Am Coll Cardiol.* Apr 1 2008;51(13):1237-1246.
41. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. *JAMA.* Oct 10 2007;298(14):1685-1687.
42. Steptoe A, Kivimaki M. Stress and cardiovascular disease. *Nat Rev Cardiol.* Jun 2012;9(6):360-370.
43. Arnaldi G, Angeli A, Atkinson AB, et al. Diagnosis and complications of Cushing's syndrome: A consensus statement. *J Clin Endocr Metab.* Dec 1 2003;88(12):5593-5602.
44. Stalder T, Kirschbaum C, Alexander N, et al. Cortisol in Hair and the Metabolic Syndrome. *J Clin Endocr Metab.* Jun 2013;98(6):2573-2580.
45. Young EA, Abelson J, Lightman SL. Cortisol pulsatility and its role in stress regulation and health. *Front Neuroendocrinol.* Jul 2004;25(2):69-76.
46. Manenschijn L, Schaap L, van Schoor NM, et al. High long-term cortisol levels, measured in scalp hair, are associated with a history of cardiovascular disease. *J Clin Endocrinol Metab.* May 2013;98(5):2078-2083.
47. Pereg D, Gow R, Mosseri M, et al. Hair cortisol and the risk for acute myocardial infarction in adult men. *Stress.* Jan 2011;14(1):73-81.
48. Kalra S, Einarson A, Karaskov T, Van Uum S, Koren G. The relationship between stress and hair cortisol in healthy pregnant women. *Clin Invest Med.* 2007;30(2):E103-107.
49. Karlen J, Ludvigsson J, Frostell A, Theodorsson E, Faresjo T. Cortisol in hair measured in young adults - a biomarker of major life stressors? *BMC Clin Pathol.* 2011;11:12.
50. Van Uum SH, Sauve B, Fraser LA, Morley-Forster P, Paul TL, Koren G. Elevated content of cortisol in hair of patients with severe chronic pain: a novel biomarker for stress. *Stress.* Nov 2008;11(6):483-488.
51. Russell E, Koren G, Rieder M, Van Uum S. Hair cortisol as a biological marker of chronic stress: current status, future directions and unanswered questions. *Psychoneuroendocrinology.* May 2012;37(5):589-601.

52. Staufenbiel SM, Penninx BW, Spijker AT, Elzinga BM, van Rossum EF. Hair cortisol, stress exposure, and mental health in humans: a systematic review. *Psychoneuroendocrinology.* Aug 2013;38(8):1220-1235.
53. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med.* 2010;8:18.
54. Yusuf S, Rangarajan S, Teo K, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med.* Aug 28 2014;371(9):818-827.
55. Yusuf S, McKee M. Documenting the global burden of cardiovascular disease: a major achievement but still a work in progress. *Circulation.* Apr 8 2014;129(14):1459-1462.
56. Mendis S, Abegunde D, Yusuf S, et al. WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE). *Bull World Health Organ.* Nov 2005;83(11):820-829.
57. Quick JD, Hogerzeil HV, Velasquez G, Rago L. Twenty-five years of essential medicines. *Bull World Health Organ.* 2002;80(11):913-914.
58. Mendis S, Fukino K, Cameron A, et al. The availability and affordability of selected essential medicines for chronic diseases in six low- and middle-income countries. *Bull World Health Organ.* Apr 2007;85(4):279-288.
59. Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension.* Oct 2005;46(4):667-675.
60. Cornelissen VA, Fagard RH, Coeckelberghs E, Vanhees L. Impact of resistance training on blood pressure and other cardiovascular risk factors: a meta-analysis of randomized, controlled trials. *Hypertension.* Nov 2011;58(5):950-958.
61. Dickinson HO, Mason JM, Nicolson DJ, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. *Journal of hypertension.* Feb 2006;24(2):215-233.
62. Higgins. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011 2011.
63. Abbott RA, Whear R, Rodgers LR, et al. Effectiveness of mindfulness-based stress reduction and mindfulness based cognitive therapy in vascular disease: A systematic review and meta-analysis of randomised controlled trials. *J Psychosom Res.* May 2014;76(5):341-351.
64. Goyal M, Singh S, Sibinga EM, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. *JAMA internal medicine.* Mar 2014;174(3):357-368.
65. Wolsko PM, Eisenberg DM, Davis RB, Phillips RS. Use of Mind–Body Medical Therapies. *Journal of General Internal Medicine.* 2004;19(1):43-50.
66. Bohlmeijer E, Prenger R, Taal E, Cuijpers P. The effects of mindfulness-based stress reduction therapy on mental health of adults with a chronic medical disease: a meta-analysis. *J Psychosom Res.* Jun 2010;68(6):539-544.
67. Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits. A meta-analysis. *J Psychosom Res.* Jul 2004;57(1):35-43.
68. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *J Consult Clin Psychol.* Apr 2010;78(2):169-183.
69. Gluck TM, Maercker A. A randomized controlled pilot study of a brief web-based mindfulness training. *BMC Psychiatry.* 2011;11:175.
70. Krusche A, Cyhlarova E, King S, Williams JM. Mindfulness online: a preliminary evaluation of the feasibility of a web-based mindfulness course and the impact on stress. *BMJ Open.* 2012;2(3).
71. Morledge TJ, Allexandre D, Fox E, et al. Feasibility of an online mindfulness program for stress management—a randomized, controlled trial. *Ann Behav Med.* Oct 2013;46(2):137-148.
72. Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. *Am Heart J.* Oct 2011;162(4):571-584 e572.
73. Goel K, Lennon RJ, Tilbury RT, Squires RW, Thomas RJ. Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. *Circulation.* May 31 2011;123(21):2344-2352.
74. Pack QR, Goel K, Lahr BD, et al. Participation in cardiac rehabilitation and survival after coronary artery bypass graft surgery: a community-based study. *Circulation.* Aug 6 2013;128(6):590-597.
75. Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. *Circulation.* Feb 18 1997;95(4):1085-1090.

List of publications

1. **Younge JO**, Leening MJG, Tiemeier H, Franco OH, Kiefte-de Jong JJ, Hofman A, Roos-Hesselink JW, Hunink MGM. Association between mind-body practice and cardiometabolic risk: the Rotterdam study. Accepted for publication in *Psychosom Medicine*
2. **Younge JO**, Eindhoven JA, Utens EMWJ, Opic P, Cuypers JA, van den Bosch AE, Witsenburg M, van Domburg RT, Hunink MGM, Roos-Hesselink JW. Association between NT-proBNP and Quality of life in adult patients with congenital heart disease. *Cardiol Young*. 2015 Feb;25(2):288-94
3. **Younge JO***, Wester VL*, van Rossum EFC, Wery MF, Gotink RA, Utens EMWJ, Hunink MGM, Roos-Hesselink JW. Cortisol levels in scalp hair of patients with structural heart disease. Int J Cardiol. 2015 Feb 10
4. **Younge JO**, Gotink RA*, Baena CP*, Roos-Hesselink JW, Hunink MGM. Mind-body practices for patients with cardiac disease: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2014 Sep 16
5. Baena CP, **Younge JO***, Olandoski M*, Buitrago-Lopez A, Darweesh SK, Campos N, Sedaghat S, Sajjad A, van Herpt TT, Freak-Poli R, van den Hooven E, Felix JF, Faria-Neto JR, Chowdhury R, Franco OH. Systematic review: Effects of lifestyle-related interventions on blood pressure in the low and middle income countries. *J Hypertens*. 2014 May;32(5):961-73
6. **Younge JO**, Damen NL, van Domburg RT, Pedersen SS. Obesity, health status, and 7-year mortality in percutaneous coronary intervention: in search of an explanation for the obesity paradox. *Int J Cardiol*. 2013 Aug 20;167(4):1154-8
7. **Younge JO**, Nauta ST, Akkerhuis KM, Deckers JW, van Domburg RT. Effect of anemia on short- and long-term outcome in patients hospitalized for acute coronary syndromes. *Am J Cardiol*. 2012 Feb 15; 109(4):506-10
8. **Younge JO,** Wery MF, Gotink RA, Utens EMWJ, Michels M, Rizopoulos D, van Rossum EFC, Hunink MGM*, Roos-Hesselink JW*. Mindfulness in patients with structural heart disease: a randomized trial. *Submitted*
9. **Younge JO**, Kouwenhoven TA, Freak-Poli R, Roos-Hesselink JW, Hunink MGM. Randomized study designs for lifestyle interventions: a tutorial. *Submitted*

*Equal contributions

PhD portfolio

Name PhD student:	John Owen Younge
Erasmus MC Departments:	Cardiology and Epidemiology
Research School:	Cardiovascular Research School (COEUR), Erasmus MC
PhD period:	December 2011 - November 2014
Promotoren:	Prof.dr. M.G.M. Hunink, Prof.dr. J.W. Roos-Hesselink

I. PhD Training

	Year	Workload (ECTS)
Research skills		
Master of Science in Clinical Epidemiology Netherlands Institute for Health Sciences, Rotterdam, The Netherlands	2012-2014	70
In-depth courses		
Ercathan Masterclass	2012	0.1
Basiscursus klinisch onderzoeker (BROK)	2012	1.5
COEUR – Seminars	2012-2014	1.2
COEUR – Pathophysiology of ischemic heart disease	2012	1.5
COEUR – Clinical cardiovascular epidemiology	2012	1.5
COEUR – Arrhythmia research methodology	2012	1.5
COEUR – Intensive Care Research	2012	1.5
COEUR – Cardiovascular imaging and diagnostics	2013	1.5
COEUR – Congenital heart disease	2013	1.5
Symposia – Congresses		
Karel V symposium - Utrecht	2012	0.3
ESC congress 2013 - Amsterdam	2013	1.6
Karel V symposium - Utrecht	2014	0.3
ESC congress 2014 - Barcelona	2014	1.6

II. Teaching

Lecturing		
Presentation Workgroup complementary care: 'Mindfulness and structural heart disease'	2012	0.3
Presentation CCV Nurses: 'Congenital heart disease'	2013	0.3
Staflunch: 'Mindfulness for the heart"/ 'Chronic subdural hematoma in a patient with a prosthetic valve'	2012-2013	0.6

	Year	Workload (ECTS)
Supervising (practical) sessions		
Supervising 2nd year medical students: 'How to perform a systematic review'	2012	0.3
Teaching 1st year medical students during: 'How to read a scientific paper'	2012-2013	0.8
Teaching 4th year medical students during: 'Clinical Trials'	2012-2013	0.8
Supervising 4th year medical student master's thesis	2014	0.8
Teaching assistant at Erasmus Winter Programme Course: 'Advanced Topics in Decision Making in Medicine'	2014	0.7
Total ECTS		**88.7**

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About the author

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John Owen Younge was born on June 26, 1986 in Hoorn, the Netherlands. In 2004 he graduated from secondary school (Gymnasium, OSG, Hoorn) and enrolled in Health Policy and Management (BMG) at the Erasmus University in Rotterdam. After receiving his Bachelor 1 in 2005, he started medical school at the Erasmus University in Rotterdam from which he obtained the degree of medical doctor in 2011. Subsequently he worked on his PhD-thesis at the department of cardiology and epidemiology under the supervision of Prof.dr. MGM Hunink and Prof.dr. JW Roos-Hesselink. His work focused on ''lifestyle interventions in cardiovascular disease". He was involved in the execution of a randomized controlled trial of mindfulness training in patients with structural heart disease. In 2012 he also enrolled in a Master of Science program in Clinical Epidemiology coordinated by the Netherlands Institute of Health sciences (NIHES), Rotterdam, The Netherlands. He obtained the MSc degree in August 2014. Since November 2014 he is working as a resident (ANIOS) at the department of Internal Medicine of the Sint Franciscus Gasthuis, Rotterdam under the supervision of Drs. AP Rietveld.

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