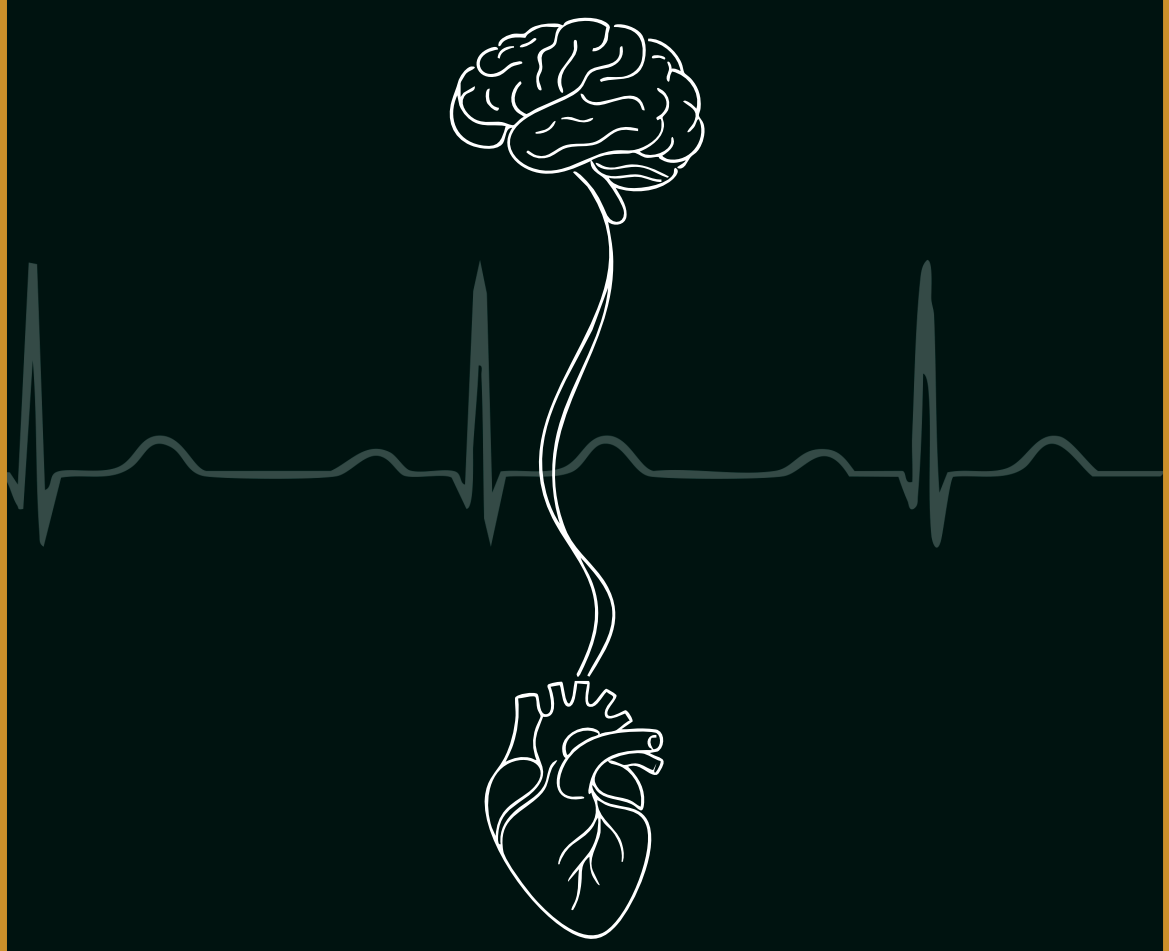
The Signals of Heart and Mind

Psychological and Autonomic Pathways in Coronary Artery Disease



Tom Roovers

The Signals of Heart and Mind
Psychological and Autonomic Pathways in Coronary Artery Disease

Tom Roovers

The Signals of Heart and Mind

Psychological and Autonomic Pathways in Coronary Artery Disease

The work presented in this dissertation was supported by the HORIZON 2020 grant awarded by the European Commission.

Autor: Tom Roovers

ISBN: 978-94-6537-125-2

Cover & layout design: Arina van Londen | Ridderprint, www.ridderprint.nl

Printing: Ridderprint | www.ridderprint.nl

The Signals of Heart and Mind

Psychological and Autonomic Pathways in Coronary Artery Disease

Proefschrift ter verkrijging van de graad van doctor aan Tilburg University

op gezag van de rector magnificus, prof. dr. W.B.H.J. van de Donk, in het openbaar te verdedigen ten overstaan van een door het college voor promoties aangewezen commissie in de Aula van de Universiteit op woensdag 15 april 2026 om 14:00 uur

door

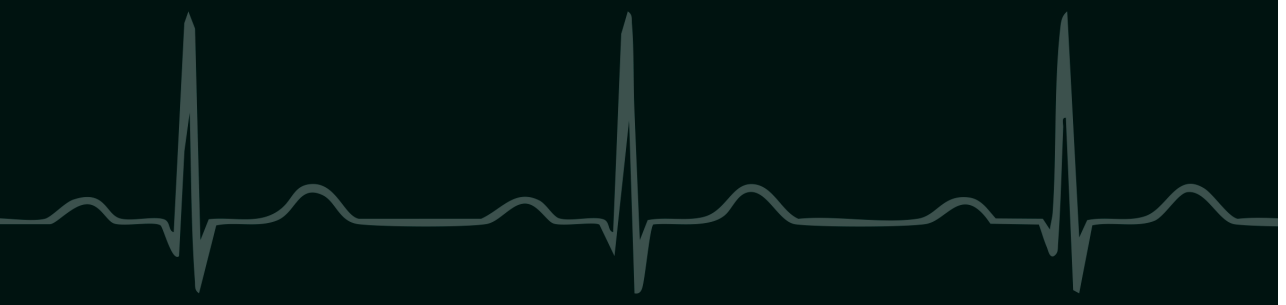
Tom Roovers,

geboren te Oosterhout

Promotores	prof. dr. W.J. Kop, Tilburg University
	prof. dr. J.W.M.G. Widdershoven, Tilburg University
Copromotores	dr. M. Habibovic, Tilburg University
	dr. I.A.C. Vermeltfoort, Instituut Verbeeten
Leden promotiecommissie	em. prof. dr. A.J.J.M. Vingerhoets, Tilburg University
	prof. dr. M.L. van der Lee, Tilburg University
	prof. dr. L.R.C. Dekker, TU Eindhoven
	dr. P.G.H.M. Raijmakers, Amsterdam UMC

TABLE OF CONTENTS

Chapter 1



General Introduction

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality worldwide [1, 2]. Among the cardiovascular diseases, coronary heart disease (CHD) is the most common [3], with 244.1 million people affected by it in 2020 globally [4]. There are several major individual and societal challenges related to CHD, including disabling symptoms, an increased risk of myocardial infarction and sudden cardiac death, and challenges related to loss of work, hospitalisation, and other health care-related costs [3]. Adequate risk assessment and timely diagnostic testing for the detection of CHD are therefore critically important. The main underlying disease process of CHD is atherosclerosis of the coronary arteries, referred to as coronary artery disease (see below for details). Before receiving a diagnosis, patients typically undergo a series of diagnostic tests. However, the psychological consequences of this diagnostic process for CHD on the patient's well-being are insufficiently understood [5]. Even less is known about the relative contributions of psychological factors and measures of the autonomic nervous system as related to CHD risk factors. Furthermore, the interplay of traditional biological risk factors for CHD and health behaviours remains unclear. This dissertation describes a series of investigations that address the extent to which psychological and behavioural interventions can be used to optimise patients' experiences during diagnostic testing for CAD, as well as their long-term clinical care. It further explores the complex associations between CAD risk factors, psychological factors, and autonomic nervous system activity.

The first section of this introduction provides an overview of cardiovascular disease, particularly CHD and its risk factors. The following sections describe the pathophysiological mechanisms of CHD and the role of the autonomic nervous system in this context. The next sections address diagnostic procedures, the most common treatments, and clinical follow-up, including health behaviour interventions. This General Introduction concludes with the aims and outline of this dissertation.

CARDIOVASCULAR DISEASES AND ISCHEMIC HEART DISEASE

Cardiovascular diseases account for up to 20.5 million deaths each year worldwide. Age-adjusted mortality rates have declined over the last decades and are expected to further decline due to improvements in prevention and treatment [2]. However, projections still estimate an increase of 90% in cardiovascular disease prevalence, accompanied by a 73.4% rise in mortality, and a 54.7% increase in disability adjusted life years in 2050, which is primarily

related to population growth and aging [1]. In addition to the significant health burden on patients and their relatives, cardiovascular diseases also bring high economic costs. Cardiovascular diseases are estimated to cost the European Union €282 billion annually, representing 11% of the EU health expenditure [3].

Among cardiovascular diseases, coronary heart disease is the most common clinical manifestation [6]. There is overlap in the terms CHD and ischemic heart disease (IHD); in general, IHD covers a broader range of clinical conditions than CHD, but the terms are often used interchangeably. In most cases, IHD is the result of (obstructive) coronary artery disease, a condition in which one or more of the main coronary arteries become narrowed or completely blocked. This narrowing of the coronary arteries is a result of the buildup of plaques in the vessel wall, a process referred to as atherosclerosis, and the disease is referred to as coronary artery disease (CAD). This narrowing reduces blood flow and impairs oxygen supply to the heart muscle. Such reductions in oxygenated blood flow are referred to as myocardial ischemia, which is why CAD is also referred to as ischemic heart disease. Other non-atherosclerotic conditions, such as coronary microvascular dysfunction and spasm of the coronary arteries, can also result in IHD [7, 8]. Myocardial ischemia may cause symptoms such as chest pain (angina pectoris), shortness of breath, fatigue, and pain in the arms, neck, jaw, or back. If left untreated, blood flow to the heart muscle can become completely obstructed, potentially resulting in the death of heart muscle cells, a condition known as myocardial infarction, popularly known as a heart attack [9].

RISK FACTORS FOR CORONARY ARTERY DISEASE

Epidemiological and clinical research has demonstrated that the risk of CAD and its adverse long-term consequences can be reduced. Several risk factors have been established, which can be classified into modifiable and non-modifiable risk factors. Non-modifiable risk factors include age, sex, ethnicity, and genetic factors. The prevalence of CAD increases after age 35, and the lifetime risk of developing CAD after age 40 for men and women is 49% and 32%, respectively [10]. This also highlights the increased risk in men compared to women. Although these factors are most predictive of CAD, they cannot be altered; therefore, the main focus for prevention has been on modifiable risk factors [11]. The American Heart Association has identified eight modifiable risk factors essential for cardiovascular health, referred to as

Life's Essential 8 [12]. These include four health behaviours (physical activity, healthy diet, smoking cessation, and sufficient sleep) and four clinical health factors (body mass index (BMI), blood pressure, cholesterol levels, and blood glucose). Global estimates suggest that a large proportion of the population does not meet the recommended guidelines [13]. Evidence suggests that 26.3% of the population does not meet the recommended levels of physical activity, and 34.1% do not adhere to a healthy diet. Nicotine exposure was present in 15.4% of individuals, while 38.4% had insufficient sleep quality. In terms of the clinical health factors, 17.3% of the population was classified as obese, 34.1% had dyslipidaemia, 12.0% were diagnosed with diabetes mellitus, and 29.4% had hypertension [13].

These modifiable risk factors should also be considered within a broader biopsychosocial framework. Good psychological health and favourable socioeconomic and social conditions can be viewed as foundational for cardiovascular health. Negative psychological factors such as stress, anxiety, and depression have consistently been shown to increase the risk of cardiovascular disease. Exposure to repeated or sustained psychological stressors and elevated levels of perceived psychological distress have been associated with poor cardiovascular prognosis [14]. In addition, levels of psychological distress and related constructs are elevated in the cardiac population, including patients with IHD. Specifically, depressive and anxiety symptoms are highly prevalent in patients with IHD, affecting approximately 31% and 33% of patients, respectively [15]. These psychological factors are also linked to higher rates of rehospitalisation, recurrent cardiac events, increased mortality risk, and reduced quality of life [16].

In addition to chronic psychological factors, acute experiences of negative emotions such as anger, anxiety, sadness, grief, and acute stress have also been associated with the onset of acute coronary syndromes and with the inducibility of myocardial ischemia [17, 18]. Patients whose cardiac event was triggered by such a negative experience appear to carry a higher psychological burden and may face an increased risk of mortality following myocardial infarction [19]. While the role of negative emotions has been extensively studied in this context, research has also shown that strong acute positive emotions, such as intense joy or excitement, can act as triggers of acute coronary syndromes [20]. However, when experienced as stable characteristics, positive psychological traits, including optimism, life satisfaction, and a sense of purpose, are associated with a lower risk of cardiovascular events, both in healthy and patient populations [21–23].

In patients with suspected or confirmed coronary artery disease, the diagnostic process itself, along with uncertainty about symptoms and potential outcomes, can further contribute to psychological distress. In addition, myocardial ischemia, for instance, may lower the threshold for experiencing negative emotions [24]. A bidirectional relationship may therefore exist in which psychological distress increases the risk of developing cardiovascular disease, and at the same time, the presence and evaluation of disease also amplify the presence and severity of psychological distress.

PHYSIOLOGICAL MECHANISMS OF ISCHEMIC HEART DISEASE

The main underlying cause of coronary artery disease, atherosclerosis, has been described above. Atherosclerosis develops through a cascade of pathophysiological processes (Figure 1) that start with endothelial dysfunction, referring to impaired functioning of the inner lining of blood vessels, vital in maintaining vascular homeostasis. Endothelial dysfunction is triggered by exposure to cardiovascular risk factors such as hypertension, hyperlipidaemia, smoking, obesity, and aging. This dysfunction can impair nitric oxide production, which impairs vasodilation and increases inflammation and vascular permeability [25]. Endothelial impairment facilitates lipid accumulation, such as LDL cholesterol, within the inner layer of the vessel wall, where it can initiate oxidative stress. This oxidative environment promotes the recruitment of immune cells, which infiltrate the vessel wall and, together with retained lipids, form the foundation of early atherosclerotic plaques [26]. The resulting chronic inflammation triggers structural changes in the vessels, known as vascular remodelling [27]. While these changes initially serve to stabilise the plaque, they can contribute to further plaque growth and instability over time. Unstable plaques are prone to rupture or erosion, exposing their contents to the bloodstream. This activates platelets and clotting factors, leading to a blood clot that can block the artery [9].

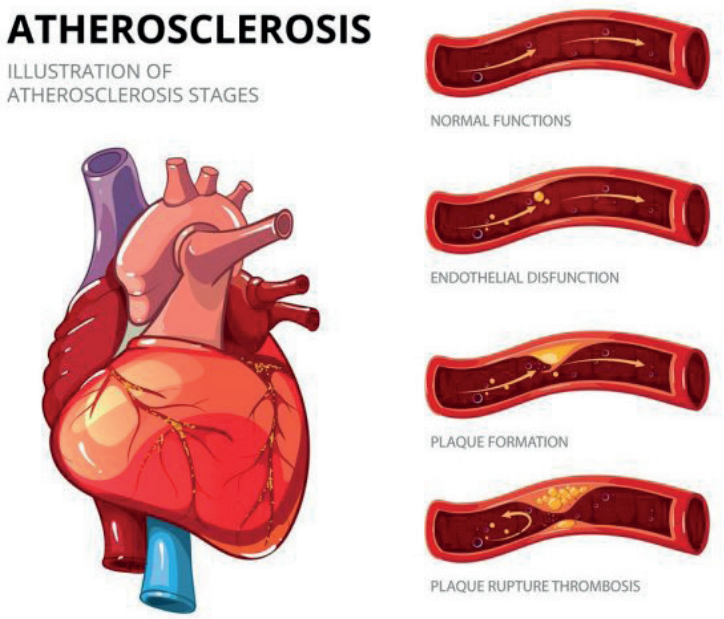


Figure 1. Visual illustration of the stages of atherosclerosis. Adapted from https://www.haymsalomonhome.com/atherosclerosis-symptoms-faqs/

THE ROLE OF THE AUTONOMIC NERVOUS SYSTEM IN CARDIOVASCULAR DISEASE

Several intrinsic mechanisms, including the autonomic nervous system, regulate the function of the cardiovascular system. The primary function of the heart is to pump oxygenated blood to the body and deoxygenated blood to the lungs. Heartbeats originate from the sinoatrial (SA) node, which intrinsically generates a heart rate of 100 to 110 beats per minute. However, there is autonomic (parasympathetically mediated) inhibition of the intrinsic SA node, resulting in resting heart rates that typically range between 60 and 100 beats per minute. To respond to the varying needs of oxygen in the body's organs, cardiac output and heart rate must be adaptable. Therefore, heart rate and contractility are modulated by the nervous system, hormones, and other factors. The autonomic nervous system plays a crucial role in controlling cardiac muscle contraction and regulating heart rate, blood pressure, and respiration. It consists of two counteracting branches: the sympathetic and parasympathetic systems. The sympathetic system, often referred to as

the fight-or-flight system, activates the body, while the parasympathetic system promotes rest and restoration. Both branches exert chronotropic (heart rate) effects on the heart by innervating the SA node and dromotropic (conduction velocity) effects through modulation of the atrioventricular (AV) node. In addition, the sympathetic system exerts positive inotropic effects, increasing contractility, whereas the parasympathetic system has minimal influence on myocardial contractility [28]. The autonomic nervous system also regulates blood pressure, primarily via the baroreflex. Pressure-sensitive baroreceptors detect changes in blood pressure and respond by inhibiting sympathetic and increasing parasympathetic activity when blood pressure rises, and vice versa when blood pressure falls [29]. Because of its crucial role in cardiovascular regulation, disruptions in the balance between the two branches of the autonomic nervous system can promote cardiac instability. A shift toward increased sympathetic activity and decreased parasympathetic tone can elevate myocardial oxygen demands [30], reduce coronary blood flow through vasoconstriction, and increase the risk of ventricular arrhythmias [31]. Low baseline parasympathetic activity predicts adverse cardiovascular outcomes, and autonomic imbalance is strongly associated with increased all-cause and cardiovascular mortality [32, 33].

Activity of the autonomic nervous system can be indexed through heart rate variability, which refers to the variation in the time intervals between successive heartbeats. Higher variability in inter-beat intervals reflects activation of the parasympathetic branch of the autonomic nervous system. Well-established measures of HRV for evaluating autonomic function include frequency domain metrics such as high-frequency (0.15 – 0.40 Hz) and low-frequency (0.04 – 0.15 Hz) power, and time domain metrics, such as the standard deviation of normal-to-normal inter-beat intervals (SDNN), and the root mean square of successive differences (RMSSD) [34]. High-frequency power and RMSSD are highly correlated and primarily reflect parasympathetic activity. In contrast, both sympathetic and parasympathetic influences contribute to low-frequency power and SDNN [35]. In this dissertation, these components of HRV will be used to investigate the association between health behaviours, psychological factors, ischemic heart disease, and autonomic nervous system activity, as well as changes in autonomic nervous system activity during behavioural interventions.

DIAGNOSTIC PROCEDURES FOR THE DETECTION OF ISCHEMIC HEART DISEASE

Several diagnostic tests are available to detect coronary artery disease, and specifically the presence and severity of coronary artery stenosis. The diagnostic process follows a structured, stepwise approach, beginning with non-invasive tests such as blood tests, resting ECG, echocardiography, and exercise testing. Based on the estimated pre-test probability of CAD from these initial evaluations, more advanced diagnostic tests may be performed [36]. Cardiac computed tomography (CT) testing provides an image of the heart and the presence of calcified plaques in the coronary arteries based on analyses of X-ray data. In addition, one of the most prominent and widely used non-invasive functional imaging tests for the detection of ischemic heart disease is myocardial perfusion imaging single-photon emission computed tomography (MPI-SPECT) [37]. In most clinical settings, this procedure consists of two phases: rest and stress. On the rest day, a radioactive tracer is injected, after which MPI-SPECT scans are performed to assess myocardial perfusion at rest. On the stress day, a cardiac stress test is conducted, either through physical exertion or pharmacologically using intravenous adenosine injection. During peak stress, a tracer is administered again, followed by another set of MPI-SPECT scans. By comparing the rest and stress images, reversible perfusion defects can be identified, which suggest myocardial ischemia, and irreversible (fixed) perfusion defects, which are indicative of a prior myocardial infarction. If MPI-SPECT suggests significant myocardial ischemia or if symptoms persist, invasive imaging can be performed using coronary angiography to visualise the coronary arteries directly using catheterisation and imaging after injection of a contrast dye into the coronary artery [36]. If severe stenosis of the coronary arteries has been established through this stepwise approach, treatment is warranted. The most common treatment is percutaneous coronary intervention (PCI), which uses an inflatable balloon to open the narrowed coronary artery, followed by placement of a vascular stent to keep it open. Another treatment option is coronary artery bypass grafting (CABG), which restores blood flow by bypassing blocked arteries using a healthy blood vessel graft. Following these treatments, patients are invited to participate in a guideline-recommended, structured cardiac rehabilitation program [38]. Cardiac rehabilitation programs include supervised exercise training, optimisation of medical treatment, risk factor management, smoking cessation, diet guidance, patient education, and psychosocial counselling. Cardiac rehabilitation is associated with a reduced risk of all-cause mortality [39]. However, although cardiac rehabilitation can

lead to meaningful improvements in health behaviours, maintaining these behavioural changes in the long term is challenging for most patients [40, 41].

TREATMENT OF ISCHEMIC HEART DISEASE, FOLLOW-UP, AND HEALTH BEHAVIOUR INTERVENTIONS

Diagnostic procedures, while essential for accurate assessment and treatment planning, can also induce psychological distress [42]. This distress may arise not only from the procedure itself, but also from possible side effects and the uncertainty of the outcome. For example, the diagnostic procedure of MPI-SPECT involves the injection of a radioactive tracer, possible side effects from the pharmacological stress test, feelings of claustrophobia while lying in the scanner, and the general stress of hospital visits [43]. Patient-centred care, which includes emotional and informational support before, during, and after the diagnostic process, may help reduce psychological distress. Research shows that patients value social and emotional support throughout their diagnosis [44], and such support is associated with improved health outcomes, greater patient satisfaction, and enhanced quality of life [45, 46]. In addition to emotional support, adequate informational support may also help alleviate distress by reducing uncertainty about the diagnostic process. Uncertainty in the face of potentially negative outcomes can make it difficult to avoid or mitigate their negative consequences. Providing information about the timing and nature of upcoming procedures enables the appropriate allocation of cognitive, affective, and behavioural resources [47]. Clear, accessible, and appropriately tailored information may therefore play a key role in reducing psychological distress during diagnostic procedures.

In addition to providing support throughout the diagnostic and treatment process, it is essential to help patients reduce the risk of readmission and mortality after discharge. Although cardiac rehabilitation encourages the adoption of a healthier lifestyle, sustaining these changes over time is challenging once supervised sessions end. Even when additional centre-based support is offered, participation rates are low because of common barriers such as time constraints or travel burden [48]. One promising solution that has gained momentum in recent years is the use of eHealth interventions, which offer the opportunity to deliver personalised support in the patient's home environment. Beyond behavioural support, eHealth platforms allow for remote monitoring of clinical risk factors such as blood pressure, heart rate, heart rate variability, and cardiac symptoms. These physiological measures

and symptom reports can provide clinicians with valuable information on patient status to detect early signs of deterioration and improve the quality and efficiency of care. In addition, they offer the potential to give patients insights into their health status and guide recovery and lifestyle adjustments. Research has shown that eHealth-based cardiac rehabilitation interventions are effective in increasing physical activity, improving quality of life, and decreasing blood pressure [40].

AIMS AND OUTLINE OF THIS DISSERTATION

The common overarching theme of this dissertation is to understand the role of physical and psychological risk factors in autonomic nervous system activity and provide support to patients with ischemic heart disease. Several integrated studies will be described, each of which targets a specific research question. In order to describe the findings of these studies, this dissertation has two parts.

Part I focuses on psychological well-being during myocardial perfusion imaging, a diagnostic procedure used for the detection of ischemic heart disease. **Chapter 2** examines the effects of two interventions designed to provide social, emotional, and informational support during the diagnostic procedure on psychological well-being. **Chapter 3** explores an innovative approach that utilises facial expressions of emotions to infer emotional states during cardiac stress testing, thereby expanding the assessments of emotional states beyond self-report data. The impact of social and emotional support on these novel measures of emotional states will also be examined.

Part II focuses on the role of the autonomic nervous system in psychological and physical health. It examines how autonomic regulation interacts with psychological well-being, health behaviours, and clinical health factors in the context of supportive and eHealth behavioural interventions. **Chapter 4** investigates the role of the autonomic nervous system in psychological well-being by analysing the associations between autonomic regulation, emotional states, and cardiac symptoms in daily life. This chapter also explores the extent to which myocardial ischemia is related to autonomic nervous system activity during daily life activities. **Chapter 5** investigates the effects of an eHealth behavioural intervention on lifestyle and examines its association with autonomic function. **Chapter 6** expands on this topic by exploring the relationship between individual components of the American Heart Association's Life's Essential 8, comprising both health behaviours

and clinical health factors, and autonomic regulation. These associations are assessed in patients with coronary artery disease during an eHealth behavioural intervention as a follow-up on cardiac rehabilitation.

Chapter 7 concludes this dissertation with a synthesis of the findings from the preceding chapters and provides recommendations for the development of future interventions aimed at improving psychological and physical health in patients with cardiovascular disease. The general discussion also highlights the potential new applications of integrated eHealth interventions and outlines directions for future research.

REFERENCE LIST

1. Chong, B., et al., Global burden of cardiovascular diseases: projections from 2025 to 2050. Eur J Prev Cardiol, 2024.
2. Mensah, G.A., et al., Decline in Cardiovascular Mortality: Possible Causes and Implications. Circ Res, 2017. 120(2): p. 366-380.
3. Luengo-Fernandez, R., et al., Economic burden of cardiovascular diseases in the European Union: a population-based cost study. Eur Heart J, 2023. 44(45): p. 4752-4767.
4. Tsao, C.W., et al., Heart Disease and Stroke Statistics—2022 Update: A Report From the American Heart Association. Circulation, 2022. 145(8): p. e153-e639.
5. Bekendam, M.T., Facing the Heart: On the role of acute emotions and psychological factors in patients with ischemic heart disease, in Medical and Clinical Psychology. 2022, Tilburg University: Tilburg.
6. Roth, G.A., et al., Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol, 2017. 70(1): p. 1-25.
7. Crea, F., R.A. Montone, and R. Rinaldi, Pathophysiology of Coronary Microvascular Dysfunction. Circulation Journal, 2022. 86(9): p. 1319-1328.
8. Godo, S., et al., Coronary Microvascular Spasm: Clinical Presentation and Diagnosis. Eur Cardiol, 2023. 18: p. e07.
9. Libby, P. and P. Theroux, Pathophysiology of Coronary Artery Disease. Circulation, 2005. 111(25): p. 3481-3488.
10. Sanchis-Gomar, F., et al., Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med, 2016. 4(13): p. 256.
11. Pencina, M.J., et al., Quantifying Importance of Major Risk Factors for Coronary Heart Disease. Circulation, 2019. 139(13): p. 1603-1611.
12. Lloyd-Jones, D.M., et al., Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association. Circulation, 2022. 146(5): p. e18-e43.
13. López-Bueno, R., et al., Global prevalence of cardiovascular risk factors based on the Life's Essential 8 score: an overview of systematic reviews and meta-analysis. Cardiovascular Research, 2023. 120(1): p. 13-33.
14. Hallman, T., et al., Stress, burnout and coping: differences between women with coronary heart disease and healthy matched women. J Health Psychol, 2003. 8(4): p. 433-45.
15. Karami, N., et al., Global prevalence of depression, anxiety, and stress in cardiac patients: A systematic review and meta-analysis. J Affect Disord, 2023. 324: p. 175-189.
16. Oxlad, M., et al., Psychological Risk Factors for Increased Post-Operative Length of Hospital Stay Following Coronary Artery Bypass Graft Surgery. Journal of Behavioral Medicine, 2006. 29(2): p. 179-190.
17. Culić, V., D. Eterović, and D. Mirić, Meta-analysis of possible external triggers of acute myocardial infarction. Int J Cardiol, 2005. 99(1): p. 1-8.

18. Edmondson, D., et al., Emotional triggers in myocardial infarction: do they matter? European Heart Journal, 2012. 34(4): p. 300-306.

19. Smeijers, L., et al., Anxiety and anger immediately prior to myocardial infarction and long-term mortality: Characteristics of high-risk patients. J Psychosom Res, 2017. 93: p. 19-27.

20. Ghadri, J.R., et al., Happy heart syndrome: role of positive emotional stress in takotsubo syndrome. European Heart Journal, 2016. 37(37): p. 2823-2829.

21. Boehm, J.K., Positive psychological well-being and cardiovascular disease: Exploring mechanistic and developmental pathways. Soc Personal Psychol Compass, 2021. 15(6): p. e12599.

22. Kupper, N., et al., The longitudinal association of optimism with quality of life after percutaneous coronary intervention for coronary heart disease; The THORESCI study. General Hospital Psychiatry, 2025. 94: p. 1-9.

23. Habibovic, M., et al., Positive Psychological Constructs and Lifestyle Behaviours in a Community-Based Sample. Psychology and Behavioral Sciences, 2022. 11(6): p. 185-192.

24. Bekendam, M.T., et al., Facial Expressions of Emotions During Pharmacological and Exercise Stress Testing: the Role of Myocardial Ischemia and Cardiac Symptoms. Int J Behav Med, 2021. 28(6): p. 692-704.

25. Gutiérrez, E., et al., Endothelial dysfunction over the course of coronary artery disease. Eur Heart J, 2013. 34(41): p. 3175-81.

26. Shao, C., et al., Coronary Artery Disease: From Mechanism to Clinical Practice, in Coronary Artery Disease: Therapeutics and Drug Discovery, M. Wang, Editor. 2020, Springer Singapore: Singapore. p. 1-36.

27. Libby, P., P.M. Ridker, and A. Maseri, Inflammation and Atherosclerosis. Circulation, 2002. 105(9): p. 1135-1143.

28. Gordan, R., J.K. Gwathmey, and L.H. Xie, Autonomic and endocrine control of cardiovascular function. World J Cardiol, 2015. 7(4): p. 204-14.

29. Goldstein, D.S., et al., Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. Exp Physiol, 2011. 96(12): p. 1255-61.

30. Bigger, J.T., et al., Autonomic nervous system activity during myocardial ischemia in man estimated by power spectral analysis of heart period variability. The American Journal of Cardiology, 1990. 66(4): p. 497-498.

31. Krantz, D.S., et al., Mental stress as a trigger of myocardial ischemia and infarction. Cardiol Clin, 1996. 14(2): p. 271-87.

32. Dekker, J.M., et al., Low Heart Rate Variability in a 2-Minute Rhythm Strip Predicts Risk of Coronary Heart Disease and Mortality From Several Causes. Circulation, 2000. 102(11): p. 1239-1244.

33. Gerritsen, J., et al., Impaired Autonomic Function Is Associated With Increased Mortality, Especially in Subjects With Diabetes, Hypertension, or a History of Cardiovascular Disease: The Hoorn Study. Diabetes Care, 2001. 24(10): p. 1793-1798.

34. Montano, N., et al., Heart rate variability explored in the frequency domain: a tool to investigate the link between heart and behavior. Neurosci Biobehav Rev, 2009. 33(2): p. 71-80.

35. Umetani, K., et al., Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. J Am Coll Cardiol, 1998. 31(3): p. 593-601.

36. Mangla, A., et al., Cardiac Imaging in the Diagnosis of Coronary Artery Disease. Current Problems in Cardiology, 2017. 42(10): p. 316-366.

37. Cantoni, V., et al., Long-term prognostic value of stress myocardial perfusion imaging and coronary computed tomography angiography: A meta-analysis. J Nucl Cardiol, 2016. 23(2): p. 185-97.

38. Levine, G.N., et al., 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. Circulation, 2011. 124(23): p. e574-e651.

39. Eijsvogels, T.M.H., et al., Association of Cardiac Rehabilitation With All-Cause Mortality Among Patients With Cardiovascular Disease in the Netherlands. JAMA Netw Open, 2020. 3(7): p. e2011686.

40. Heimer, M., et al., eHealth for maintenance cardiovascular rehabilitation: a systematic review and meta-analysis. Eur J Prev Cardiol, 2023. 30(15): p. 1634-1651.

41. Kroesen, S.H., et al., A remote booster program to attenuate sedentary behaviour in patients with coronary artery disease: a randomized controlled trial. European Journal of Preventive Cardiology, 2025.

42. Bekendam, M.T., et al., Facial Expressions of Emotions During Pharmacological and Exercise Stress Testing: the Role of Myocardial Ischemia and Cardiac Symptoms. International Journal of Behavioral Medicine, 2021. 28(6): p. 692-704.

43. Bui, K.T., et al., Scanxiety: a scoping review about scan-associated anxiety. BMJ Open, 2021. 11(5): p. e043215.

44. Van Schalkwijk, D.L., et al., ShareHeart: A patient journey map of patients with ischemia and non-obstructive coronary artery disease based on qualitative research. J Clin Nurs, 2023. 32(13-14): p. 3434-3444.

45. Gerteis, M., et al., Through the patient's eyes: understanding and promoting patient-centered care. First edition ed. Jossey-Bass health series. 1993, San Francisco: Jossey-Bass.

46. Stewart, M., et al., The impact of patient-centered care on outcomes. J Fam Pract, 2000. 49(9): p. 796-804.

47. Grupe, D.W. and J.B. Nitschke, Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. Nat Rev Neurosci, 2013. 14(7): p. 488-501.

48. Chindhy, S., et al., Current challenges in cardiac rehabilitation: strategies to overcome social factors and attendance barriers. Expert Rev Cardiovasc Ther, 2020. 18(11): p. 777-789.

Part I

Patient Experiences and Emotional Responses to Cardiac Diagnostic Procedures

Chapter 2

Psychological well-being and the effects of supportive coaching during SPECT myocardial perfusion imaging in patients with suspected ischemic heart disease

Roovers, T., Vermeltfoort, I.A.C., Widdershoven, J.W., Kop, W.J.

The contents of this chapter have been published in the Journal of Psychosomatic Research (2025)

ABSTRACT

Background: Diagnostic procedures for ischemic heart disease are common, but the consequences for the patient's psychological well-being are not well understood. The current study investigates changes in negative affect as a measure of psychological well-being during myocardial perfusion imaging (MPI-SPECT) and whether supportive coaching during diagnostic testing improves well-being, reduces symptom burden, and increases patient satisfaction.

Methods: Patients undergoing MPI-SPECT were randomly assigned to a supportive coaching intervention group or a care-as-usual control group. Negative affect was assessed at nine time-points throughout the 2-day diagnostic MPI visits. Anginal and adenosine-related symptoms were evaluated during cardiac stress testing (CST) and patient satisfaction at completion of MPI-SPECT. Data were analysed using regression analysis, t-tests, and linear mixed models.

Results: A total of 149 patients were randomised (mean age=68.5 [SD=9.6] years, 41.6% women; 74 intervention and 75 control condition). Negative affect changed significantly throughout the MPI procedure ($F(8, 244.098)=8.689$, $p<.001$), with the highest level occurring during the peak phase of CST. Negative affect was associated with higher concurrent anginal ($\beta=0.285$, $p=.001$) and adenosine-related symptoms ($\beta=0.252$, $p=.004$) during CST. No significant benefits of supportive coaching were found for well-being or symptoms, inducibility of ischemia, or patient satisfaction (all p-values > .200).

Conclusion: Negative affect during MPI-SPECT is associated with cardiac symptoms during CST. No benefits were found for the short-term supportive coaching intervention during the MPI-SPECT procedure. Patient well-being might be improved by providing support during the entire diagnostic phase for ischemic heart disease rather than just during the MPI-SPECT procedure.

INTRODUCTION

Cardiovascular diseases (CVDs) are the number one cause of morbidity and mortality worldwide [1, 2]. Among cardiovascular diseases, ischemic heart disease (IHD) is the leading cause of mortality [3], with 244.1 million people affected by it in 2020 globally [2]. The high incidence, symptom burden, and risk of acute coronary syndromes (ACS) highlight the importance of adequate and timely diagnostic testing for the detection of IHD. However, the consequences of the diagnostic process for IHD on the patient's well-being are insufficiently understood [4].

Myocardial perfusion imaging single-photon emission computed tomography (MPI-SPECT) is one of the most prominent and widely used non-invasive functional cardiovascular tests for the detection of IHD [5-7]. However, MPI-SPECT can be stressful to patients because of its components, including radioactive tracer injection, side effects related to the pharmacological stress test, claustrophobia in response to lying in the scanner, and hospital visits in general [8]. Providing patients with support during MPI-SPECT imaging could, therefore, lower the perceived stress of the diagnostic procedure and consequently reduce negative affect states during MPI-SPECT.

Patient-centred care has long been suggested as a way to assist patients during and after diagnosis. This approach has been shown to improve health outcomes, patient satisfaction, and quality of life [9-11]. A coach or 'patient navigator' could provide this support by guiding patients through the diagnostic process, helping them overcome concerns and barriers, and thereby facilitating the successful completion of the diagnostic procedure [12]. Such support might also meet patients' needs for social and emotional support during the diagnostic process [13], and decrease unnecessary costs by reducing no-shows, which waste scanning and laboratory staff time and shorten waiting lists. It is not known, however, if and how supportive coaching contributes to improved psychological and physical well-being in the setting of MPI-SPECT for the diagnosis of ischemic heart disease.

Based on this background, the current study investigates: (1) the pattern of changes in psychological and physical well-being throughout MPI-SPECT for evaluation of ischemic heart disease; and (2) the effects of supportive coaching on psychological well-being (i.e., reducing negative affect states), as well as cardiac symptoms, inducibility of ischemia, and patient satisfaction with the MPI-SPECT procedure. It is hypothesised that supportive coaching will attenuate negative affect and reduce cardiac symptoms and ischemia during MPI-SPECT. We will also explore if patients with high levels of distress prior

to MPI-SPECT will disproportionally benefit from supportive coaching. This knowledge could aid in predicting which patients will experience symptoms during stress testing and who could benefit from additional support.

METHODS

Patients

The study sample consisted of patients who underwent pharmacological or exercise rest/stress MPI-SPECT between November 2022 and February 2024. This randomised controlled trial is referred to as the OPTIMIZE study and is registered with ClinicalTrials.gov (protocol NCT:05896982).

Inclusion criteria were: referred for MPI-SPECT diagnostic testing with adenosine or exercise, 18 years of age or older, and sufficient knowledge of the Dutch language to answer questionnaires and understand the study procedures. Patients were excluded from participating if they had a life-threatening disease with a < 1-year survival expectancy (e.g., metastatic cancer) or if they did not provide informed consent.

The final study sample consisted of 149 patients (see Figure 1 for a flowchart of patient enrolment). During the enrolment period, a total of 1704 MPI SPECT procedures were performed at Institute Verbeeten, and 246 patients were approached for participation. The patients were approached consecutively based on the availability of research staff who could explain the study, obtain informed consent, and conduct the research-related assessments (see below for details). Of the 246 patients who were approached for participation in the OPTIMIZE study, 154 (63%) agreed to participate. Reasons for non-participation were: patients expecting that participation would be too burdensome in addition to undergoing MPI-SPECT (n = 27), participation in another study (n = 10), language barrier (n = 5), health condition (n = 3), privacy concerns (n = 4), and 43 patients did not give a reason for non-participation. Of the 154 consenting patients, five (3.2%) patients did not complete the study till the end of day 2 and were, therefore, regarded as dropouts, resulting in a total of 149 patients available for analysis.

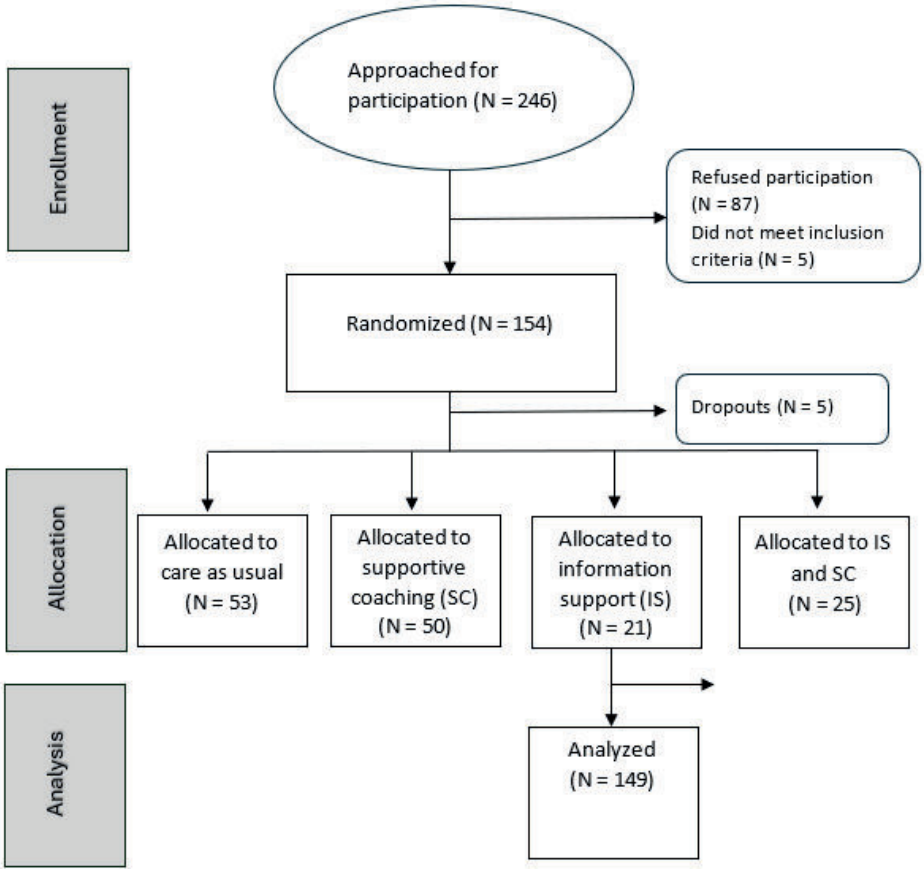


Figure 1. Flowchart of participant eligibility for this study.

Ethical aspects

The OPTIMIZE study was approved by the Medical Ethics Committee Brabant (METC-Brabant NL81600.028.22 / P2234), and the project was conducted in accordance with the Helsinki Declaration. All participants signed the informed consent form before data collection.

Procedure

Patients were informed about the project by the scheduling office. Information about the study was provided verbally and in writing, and patients were given 2 to 5 days to consider their participation. Patients were then approached by a member of the research team on the day of the first MPI-SPECT testing

to receive further information about the study, ask questions, and sign the informed consent form if they agreed to participate.

Patients were subsequently randomised into one of two groups (1:1 ratio): supportive coaching + care-as-usual or care-as-usual only, using a random number generator after enrolment but before the first baseline measures. This was necessary to directly provide supportive coaching at this time.

Because of the nature of the intervention, it was impossible to blind the research team member who provided supportive coaching from the patient's group allocation. However, laboratory technicians and nuclear physicians who performed the MPI-SPECT and assessed SPECT images were blind to the patient's group allocation. Patients were also not explicitly informed about which condition they were allocated to, but could have perceived which group they were in; the level of perceived support was evaluated for both groups at the end of the MPI-SPECT (see below for details). The data were coded such that questionnaire-based outcomes were also evaluated blinded to group allocation status.

A subset of patients (N = 46) also received additional information about the diagnostic procedure through a video before both study days. It was originally planned to also randomise patients to get access to this information video prior to their first MPI-SPECT visit, but this was not feasible because of practical reasons related to patient privacy and providing the video prior to written informed consent.

The primary outcome measure of this study is the patient-reported psychological well-being as measured by the patient's affect state during diagnostic MPI-SPECT. In addition, secondary outcome measures were the severity of physical symptoms and inducibility of myocardial ischemia. This study also evaluated patient satisfaction with the entire diagnostic procedure as related to having received support, and we explored the potential additional beneficial effects of an information video. Self-report assessments were obtained using an online survey tool to distribute questionnaires (Qualtrics, Provo, UT, USA).

To assess intervention fidelity, participants in both groups were asked to rate the perceived support from the research team member on a scale of 0 to 10 after each of the two study days to assess whether the level of perceived degree of coaching was higher in the intervention group than in the control group. In addition, the members of the research team also rated the extent

to which supportive coaching was provided on a scale of 0 to 3, with 0 being 'none' and 3 being 'a lot'.

Intervention and care-as-usual

The coaching included providing patients with additional information and support based on the patient's needs (see Supplemental Materials S1 for a complete description of the intervention). The development and implementation of the intervention were based on the RE-AIM framework [14] (details are presented in Supplementary Table ST1). In brief, the supportive coaching intervention was based on prior qualitative analysis of patients who underwent MPI-SPECT [15] and focused on reassurance, providing information, and reducing feelings of insecurity, worry, or anxiety. The supportive coaching primarily took place before and during the diagnostic procedure components (i.e., before tracer injection, during cardiac stress testing and recovery, and before and after MPI-SPECT imaging); the coach was also present during all procedures throughout the two testing days to support the patient.

Care-as-usual involved standard diagnostic procedures, with clinical staff providing answers to the patient's questions and briefly explaining the diagnostic procedures. Both the control group and the supportive coaching group received care-as-usual and were repeatedly asked about affect states and symptoms (see Supplementary Material S2 for more details).

Cardiac rest and stress testing protocol

The cardiac stress testing protocol consisted of two days; one day to obtain rest MPI-SPECT and the second day for stress MPI-SPECT. On the resting day, patients were injected with Technetium-99m-tetrofosmin (dosage: 370 MBq) as the radioactive tracer, followed by a 45-minute waiting period, after which MPI-SPECT scans were obtained. The second day, consisted of a cardiac stress test, which could either be performed pharmacologically using intravenous adenosine injection (140 mcg/kg/minute for 5 min) or through physical exertion (i.e. bicycling using the modified Bruce protocol)(more information on the cardiac stress test protocols, image acquisition, and analysis can be found in the Supplemental Materials: S3).

Assessment of the inducibility of myocardial ischemia

The inducibility of myocardial ischemia was assessed using single-photon emission computed tomography (SPECT) and by comparing the perfusion images on the rest day with the perfusion images of the cardiac stress testing

day. The inducibility of ischemia was determined by analysis of the 17-segment perfusion images [16, 17]. The interpretation of myocardial perfusion images was based on visual analysis as recommended by the American Society of Nuclear Cardiology (ASNC) [18] (See Supplementary Material S3 for more details).

Psychological well-being based on affect states during MPI-SPECT

The Profile of Mood States-Short Form (POMS) short form was used to evaluate the patients' self-reported affect states during diagnostic testing [19]. The POMS-SF was modified to capture the short-term changes in affect states relevant to the activities involved in the two-day MPI-SPECT procedure. Specifically, the following states were asked by a member of the research team: stressed, anxious, insecure, relaxed, worried, irritated, excited, and tired, and were rated on a scale from 0 to 10.

The POMS was administered at the following time points: Day 1: (1) after informed consent before tracer injection, (2) just before MPI-SPECT, (3) 2 – 5 minutes after resting MPI-SPECT imaging; and Day 2: (4) upon arrival, (5) just before CST, (6) during peak stress of CST, (7) 2 minutes post-CST, (8) just before MPI-SPECT, and (9) 2 – 5 minutes after stress MPI-SPECT imaging. The POMS scores were coded such that higher scores indicate higher levels of negative affect, with a score ranging from 0 to 10.

Cardiac and adenosine-related symptoms

Patients were asked whether they experienced anginal symptoms or other complaints during CST. If symptoms were present, patients were asked to rate the severity on a scale from 0 to 10. Symptoms included chest pain, shortness of breath, or palpitations, characterised as anginal symptoms, and dry throat, headache, stomach ache, jaw pain, leg pain, dizziness, nausea, fatigue, or hot flashes, characterised as adenosine-related symptoms.

Patient Satisfaction

Patient satisfaction was assessed using the Patient Satisfaction Questionnaire (PSQ-18) [20] (Dutch validation [21]) at home after the second day of the diagnostic procedure. To obtain an overall index of patient satisfaction, a general satisfaction score was calculated by averaging the scores of the 18 items (score range 1 to 5). The internal consistency of the 18 items was high in the present study (Cronbach's $\alpha = .82$). Data were analysed for the general satisfaction score and the PSQ-18 sub-scales.

Psychological background factors

To explore whether psychological well-being during MPI-SPECT was adversely affected by the patient's level of general psychological distress prior to diagnostic testing and to evaluate whether supportive coaching would be particularly effective in patients with high levels of distress, assessments of anxiety and depressive symptoms, as well as patients' perceived levels of social support during the two weeks before diagnostic testing, were evaluated. These measures were obtained on the first day of the diagnostic procedure but after randomisation using Generalized Anxiety Disorder Scale (GAD-7) (Cronbach's α = .88) [22] (Dutch validation [23]), the Patient Health Questionnaire (PHQ-9) (Cronbach's α = .86) [24] (Dutch validation [25]), and The Multidimensional Scale of Perceived Social Support (MSPSS) (Cronbach's α = .95) [26] (Dutch validation [27]).

Demographic measures and clinical data

Demographic measures, including age, sex, and educational level, were retrieved through self-report. Clinical data were retrieved from the electronic health records at the Elisabeth TweeSteden Hospital in Tilburg and included cardiac history (i.e., previous myocardial infarction, percutaneous coronary intervention (PCI), or bypass surgery) and cardiovascular risk factors (see Table 1 for patient characteristics).

Statistical analyses

Data are presented as mean and standard deviation (SD) for continuous variables and frequencies and percentages for categorical variables. Psychological well-being during MPI-SPECT was assessed by the affect scores at each of the nine timepoints by averaging the values of the POMS items such that higher scores reflect higher levels of negative affect (i.e., lower psychological well-being). In addition to each of the negative affect scores at each time point, an overall negative affect state score for the full diagnostic process was also calculated (potential score range 0-10; a minimum of six out of nine time points with available data was set for the calculation of the overall affect state score).

Group differences in demographic and clinical patient characteristics, symptoms, patient satisfaction, and perceived supportive coaching, including subgroup analyses for patients with high levels of psychological distress at baseline on the first day of diagnostic testing, were evaluated using

independent t-tests (continuous variables) and chi-square tests (categorical variables).

To evaluate differences in affect states between both groups and to assess changes over time, linear mixed models were used to address the interdependence of repeated measures as well as optimise the handling of missing data. The main parameters of interest in this analysis were the main effect of group, time, and the interaction between group and time. To examine the moderating effects of baseline negative affect on the coaching intervention, a separate analysis was conducted, including interaction terms between time, group, and whether patients had above or below-average baseline negative affect. Results are presented as regression weights (B) and 95% confidence intervals (CI). In additional analysis, adjustments were made for potential confounders, including the type of stress test and whether patients had viewed informational videos. For exploratory purposes, the two groups (supportive coaching vs. no coaching) were also compared on the affect state score at each of the 9 time points using t-tests. The effect of the informational videos on negative affect was evaluated as an exploratory analysis using the same analytic approach as the main model described above.

The association between affect state and psychological background factors, specifically anxiety, depression, and social support, was assessed using stepwise regression models. Separate models were performed for each psychological factor to prevent multicollinearity. The overall affect state score across the full diagnostic process was the dependent measure, and the psychological background factor and group (control or supportive coaching) were entered as predictor variables in the first step of the model. The interaction between the psychological background factor and the group was entered in the second step. Beta coefficients were used to evaluate the associations between negative affect and the background factors. The R^2 difference between steps was used to evaluate whether including the interaction term significantly improved the model's explanatory power for each psychological outcome.

Data were analysed using the Statistical Package for the Social Sciences (SPSS) software package (Version 27.0). Results are presented with 95% confidence intervals, and a p-value of < 0.05 was considered to indicate statistical significance.

RESULTS

Patient characteristics

Table 1 displays the demographic and clinical patient characteristics. The sample consisted of 149 patients with a mean age of 68.5 ± 9.6 years, and 41.6% were women. The control and supportive coaching groups were comparable concerning demographic and clinical variables, except for hypertension (X^2 = 4.083, p =.043, 47.3% vs. 31.1% for the control and supportive coaching group respectively) and a history of PCI (X^2 = 6.020, p = .014, 12.2% vs. 28.4% for the control and supportive coaching group respectively) (Table 1).

Table 1. Demographics and patient characteristics

	No Coaching (N = 74)	Coaching (N = 75)
Demographics		
Age (years)	68.7 ± 9.5	68.2 ± 9.8
Sex (female)	30 (40.5%)	32 (42.7%)
Ethnicity (European descent)	41 (55.4%)	41 (54.7%)
Living alone	15 (20.3%)	18 (24%)
College education or higher	13 (17.6%)	16 (21.3%)
Smoking (current)	9 (13.0%)	5 (7.6%)
BMI (kg/m^2)	27.0 ± 4.2	28.8 ± 5.2
Hypertension	35 (47.3%)	23 (31.1%)
Myocardial infarction	4 (5.4%)	10 (13.5%)
PCI	9 (12.2%)	21 (28.4%)
Coronary bypass surgery	6 (8.1%)	6 (8.0%)
Test type (Adenosine)	55 (73%)	54 (73.3%)

Changes in negative affect during MPI-SPECT and the effect of supportive coaching

Figure 2 displays negative affect at the nine time points throughout the diagnostic visits on day 1 (resting MPI-SPECT) and day 2 (CST MPI-SPECT) for the control and supportive coaching groups. The level of negative affect changed significantly across the nine points during the two days of MPI-SPECT (F(8, 244.098) = 8.689, p <.001). As shown in Figure 2, an increase in negative affect was observed during the peak of the stress test (time point 6).

The supportive coaching group showed overall higher levels of negative affect compared to the control group across the nine timepoints (Δ = .255 [95% CI .070; .439], p = .007). There was no interaction between time and group (F(8, 244.098) = 1.337, p = .225) (Supplementary Table ST2). Although a significant difference in negative affect was observed between groups in the full model, the effect size was small. Specifically, the groups differed only during the peak CST (timepoint 6; Cohen's d = 0.493, p = .006) but not at any of the other time points (Cohen's d < 0.350, p-values > .200; see also Figure 2). Further exploratory analysis comparing patients with high versus low baseline negative affect at baseline revealed that the observed difference between the supportive coaching versus the control group was only present in patients with high baseline negative affect at baseline (F(1, 1031,562) = 11.030, p <.001) (Supplementary Figure SF1). Additionally, an interaction effect was observed between baseline negative affect groups (high vs. low) and time (F(8, 225,037) = 375.331, p <.001). Adjusting for the type of stress test protocol (adenosine vs. exercise) or viewing the informational video did not change the pattern or statistical significance of the results.

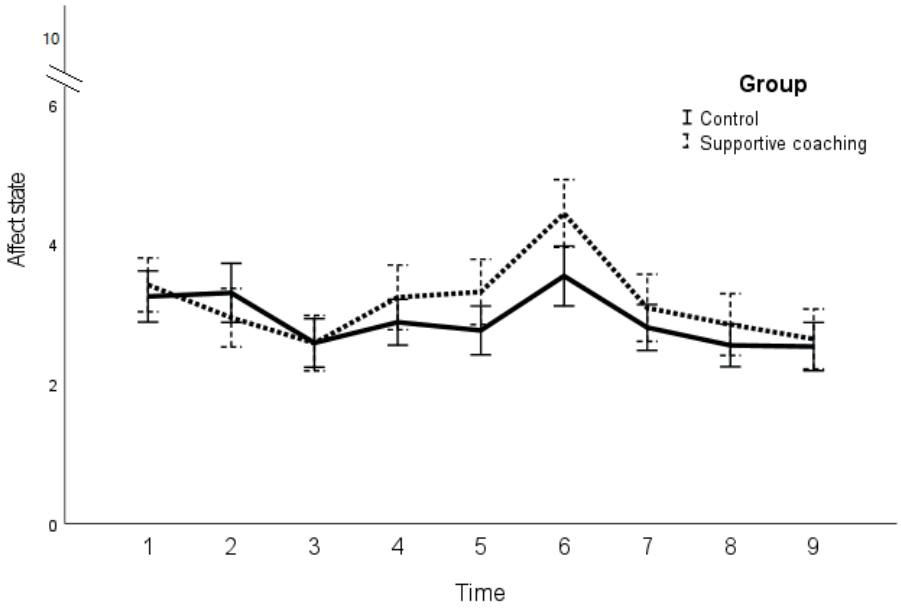


Figure 2. Changes in affect states across the diagnostic MPI-SPECT visit for patients who received coaching and patients who did not. The affect state score represents the average of all affective states, with higher scores reflecting higher negative affect. The vertical dotted line represents the separation of days 1 and 2. Error bars represent the standard error of the mean.

The effects of supportive coaching on physical symptoms and inducibility of myocardial ischemia

As shown in Table 2, there were no differences between the control and supportive coaching groups in the severity of anginal symptoms (Cohen's d = −0.116, p = .511) or adenosine-related symptoms (Cohen's d = −0.173, p = .327). No significant differences were found in anginal or adenosine-related symptoms in patients who were stressed using the adenosine protocol compared to patients who performed bicycle exercise (Supplementary Table ST3).

Table 2 also shows that the prevalence of inducible ischemia did not differ between patients in the supportive coaching group compared to the control group. There were also no differences between patients with versus without ischemia in terms of symptoms or negative affect just before and during CST (Supplementary Table ST4).

Table 2. Symptoms and ischemic response for the control and supportive coaching groups.

	No coaching	Coaching	p-value	Cohen's d
Anginal symptoms	1.0 ± 1.6	1.1 ± 1.4	.511	−0.116
Adenosine-related symptoms	0.6 ± 0.7	0.7 ± 0.8	.327	−0.173
Ischemia (Yes)	18 (24.3%)	21 (28%)	.476	–[a]

[a] A Chi-square test was performed for this measure, and therefore, Cohen's d was not calculated.

A significant association was found between the level of negative affect during cardiac stress testing and the severity of anginal and adenosine-related symptoms during CST (β = 0.252, p = .004, and β = 0.285, p = .001, respectively: Supplementary Table ST5). These associations reflected concordant assessments, and the level of negative affect just before cardiac stress testing did not predict subsequent anginal symptoms (β = 0.148, p = .111) or adenosine-related symptoms (β = 0.176, p = .059).

Patient satisfaction

Patient satisfaction scores were generally high, ranging from 3.6 to 4.1 (on a scale of 1 to 5) on the seven subscales of the PSQ-18. The supportive coaching group did not report significantly higher overall patient satisfaction compared to the control group (Cohen's d = 0.239, p = .211). None of the PSQ-18 subscales were statistically different between the two groups (Cohen's d < 0.348, p > 0.65) (Supplementary Table ST6).

Subgroup analysis of patients with high levels of psychological distress prior to MPI-SPECT

We examined whether the patient's level of distress and perceived social support in the weeks before MPI-SPECT played a role in the effectiveness of the supportive coaching intervention on negative affect during the diagnostic procedure using a stepwise regression analysis. The addition of the interaction term did not significantly improve any of the three models (ΔR^2 $_{\text{anxiety * group interaction}}$ = .013, p = .132; ΔR^2 $_{\text{depression * group interaction}}$ = .009, p = .251; and ΔR^2 $_{\text{social support * group interaction}}$ < .001, p = .964; see Table 3 for total R^2) and therefore main effects from step 1 of the models will be reported below.

As shown in Table 3 (top part; model step 1), the level of anxiety and depressive symptoms in the two weeks before diagnostic testing was significantly associated with negative affect during MPI-SPECT (β = 0.667, p < .001 and β = 0.558, p < .001, respectively). Table 3 also shows that social support prior to MPI-SPECT was not associated with negative affect during MPI-SPECT (β = -0.139, p = .176). These results suggest that anxiety and depression levels, but not social support in the weeks before the diagnostic procedure, can predict the level of negative affect during MPI-SPECT, but that these psychological background factors do not play a role in the effectiveness of a supportive coaching intervention.

Table 3. Separate stepwise linear regression models for anxiety, depression, and social support in association with negative affect throughout the diagnostic procedure.

		Anxiety				Depression				Social support			
		β	t	p-value	R^2	β	t	p-value	R^2	β	t	p-value	R^2
Step 1					.445				.347				.021
	Main effect	0.667	8.712	<.001		0.588	7.090	<.001		−0.139	−1.363	.176	
	Group	0.009	.119	.905		0.036	.432	.667		0.036	.349	.728	
Step 2					.457				.356				.021
	Main effect	0.306	1.230	.222		0.309	1.214	.228		−0.125	−.392	.696	
	Group	−0.110	−1.008	.316		−0.071	−.574	.567		0.058	.115	.908	
	Interaction effect	0.401	1.520	.132		0.313	1.156	.251		−0.026	−.046	.964	

Exploratory analyses

The supportive coaching group did, as intended, receive significantly more coaching compared to the control group on both days based on the investigator's observation (Cohen's d > 2.5, p < .001 for both days). These coach ratings were not significantly correlated to the patient's negative affect or satisfaction score at the end of the study (Table 4).

Both the control and coaching groups reported similar support during the first (Cohen's d = 0.186, p = .350) and the second day (Cohen's d = 0.194, p = .378) (Table 4). These data suggest that the level of perceived support was not significantly higher in the supportive coaching group compared to the control group that did not receive supportive coaching. When focusing the analyses on patients with high levels of psychological distress (i.e., high anxiety (N=18) or depression (N=19)) prior to MPI-SPECT, the level of perceived support was also not higher in the supportive coaching group than the control group (all p >.680). Social support was excluded from this analysis due to the limited number of patients with low social support (N=5). The level of perceived support was not associated with negative affect during MPI-SPECT, symptoms, or patient satisfaction.

The informational videos did not result in significantly lower levels of negative affect during MPI-SPECT (Δ = .048 [95% CI -.156; .243], p = .644) and there was no interaction effect between having watched the information video and time (reflecting the repeated measures of negative affect during MPI-SPECT; F(8, 239,097) = .293, p = .968) (see Supplementary Table ST7 for details).

Table 4. Association between perceived coaching and negative affect during MPI-SPECT and patient satisfaction.

	No coaching	Coaching	p-value	Cohen's d	r Patient satisfaction	r negative affect
Investigator-rated coaching rest day	1.3 ± 0.6	3.0 ± 0.7	< .001*	2.540	.045	.067
Investigator-rated coaching stress day	1.6 ± 0.7	3.3 ± 0.8	< .001*	2.505	.090	.143
Perceived coaching rest day	7.5 ± 1.5	7.8 ± 1.4	.350	0.186	.045	-.032
Perceived coaching stress day	7.9 ± 1.8	8.2 ± 1.6	.378	.0194	.090	-.190

The rating scale for the investigator ranged from 1 to 4, and for the patient from 0 to 10.

DISCUSSION

This study documents the pattern of changes in psychological and physical well-being throughout MPI-SPECT diagnostic testing and evaluates whether supportive coaching has beneficial effects on well-being during the diagnostic process. Unique to this study is the assessment of psychological well-being at nine time points throughout the MPI-SPECT procedure. The highest level of negative affect, as an index of reduced psychological well-being, was observed during peak cardiac stress testing by adenosine or bicycle exercise. Negative affect was also associated with more anginal and adenosine-related symptoms at this time point during MPI-SPECT. Patients were randomised to receive supportive coaching during the two-day diagnostic process. Supportive coaching did not improve psychological well-being (the primary outcome measure), and no benefits were found for the secondary outcomes either (symptoms during MPI-SPECT, ischemia, and post-diagnostic patient satisfaction). Elevated levels of anxiety and depressive symptoms before the procedure were associated with lower patient well-being during the MPI-SPECT procedure. These findings indicate that psychological and physical well-being are primarily relevant at peak levels of cardiac stress testing and that short-term supportive coaching is not sufficient to improve well-being during MPI-SPECT.

The current findings regarding patterns of changes in mental well-being revealed that the highest levels of negative affect are experienced during peak cardiac stress (either following adenosine administration or bicycle exercise). These findings show that peak levels of cardiac demand during CST, and not isotope injection or the imaging procedure itself, are perceived as the most stressful component of the MPI-SPECT procedure. A previous study in the same clinical setting reported consistent findings and showed that patients expressed more negative emotions during CST compared to baseline [28]. It is worth noting that, in the current study, the level of negative affect during CST was 4 out of 10, highlighting that even the most stressful component of the diagnostic procedure does not induce high levels of negative affect. These moderate levels of negative affect were associated with higher severity of anginal and adenosine-related symptoms during CST. This association could reflect the bidirectional relationship between psychological distress and cardiac symptoms [29-32]. Furthermore, anxiety and depression levels in the weeks before the diagnostic testing procedure were also associated with negative affect during MPI-SPECT, which is consistent with prior studies [4]. These results highlight the role of individual differences and the

interconnectedness between negative affect and symptoms during diagnostic testing for inducibility of myocardial ischemia. Knowledge of these patient characteristics before testing could help clinicians predict which patients are more prone to experience negative affect or other indices of reduced psychological or physical well-being.

Recent systematic reviews report improvements in quality of life and patient satisfaction in response to supportive coaching when provided from a perspective of 'patient navigation' in patients with heart failure or cancer [11, 33, 34]. The present investigation did not find similar improvements in psychological well-being or patient satisfaction in patients with suspected IHD. A study focusing specifically on distress in response to a patient navigator in a hospital setting in cancer patients reported similar findings [35]. The current intervention mainly included emotional support and patient education, which may have been insufficient to produce a substantial reduction in negative affect. As described in previous studies, coaching using a patient navigation approach is broader than just supportive coaching [11]. It is possible that focusing on longer diagnostic or treatment trajectories, instead of just one diagnostic procedure, might be more beneficial. Additionally, the timing and context of the supportive interventions are important in the setting of myocardial perfusion imaging, which is designed to provoke and detect ischemia under conditions of stress. These diagnostic stress conditions involve either exercise or pharmacological challenges. In addition, there is a growing research literature on the effects of acute mental stress on the inducibility of ischemia. Recent studies indicate that mental stress-induced ischemia is an independent predictor of adverse long-term clinical outcomes [36]. However, mental stress-induced ischemia is currently not part of routine clinical diagnostic evaluation. Interventions aimed at reducing stress during testing carry a potential risk of masking stress-induced ischemia. Although the impact of such interventions may not be sufficient to interfere with diagnostic accuracy, it highlights the need for thoughtful integration of psychosocial support in the overall diagnostic and treatment process.

A trend towards an opposite effect was observed in the current study, such that supportive coaching was associated with higher levels (instead of lower levels) of negative affect during MPI-SPECT, particularly during peak levels of cardiac demand and in patients with higher baseline levels of negative affect. This finding could reflect a phenomenon known as the nocebo effect [37]. It is possible that descriptions of upcoming procedures or potential side effects can unintentionally induce distress and provoke or worsen symptoms [38, 39], which might explain the higher levels of negative affect

in the supportive coaching group. Supportive coaching might also reduce the likelihood of patients reporting undesirable symptoms, such as negative affect. Even though no coaching was given in the control group, patients could still have experienced the attention to their well-being as social support. This notion is consistent with the finding that patients' perceived coaching ratings were similar in the control and supportive coaching groups. These explanations might also apply to the lack of effect of the intervention on the secondary outcomes (i.e., anginal and adenosine-related symptoms, ischemia, and patient satisfaction). In addition, patient satisfaction scores were high, and negative affect was generally low in both groups, suggesting a ceiling effect that may have limited further improvements. These findings raise the question of whether delivering an intervention to patients who potentially do not need it can increase negative affect rather than reduce it and whether such interventions should be provided based on patient characteristics, such as history of anxiety, negative affect, or prior negative experiences with the procedure. In the current study, we explored this by examining the impact of the coaching intervention based on baseline levels of negative affect. The results showed that patients with higher baseline negative affect experienced worse affect-related outcomes from the intervention, while this was not observed in patients with low baseline negative affect. This suggests that the intervention may exacerbate negative feelings in distressed patients but does not induce negative affect in other patients.

The current study has several strengths and limitations. Limitations include that the extent of supportive coaching was tailored to the patient's needs and consequently differed between patients. The level of perceived support was not correlated with the patient's psychological well-being or satisfaction with the MPI-SPECT procedure. These findings indicate that the level of coaching used in this study (consisting of emotional support and education) was not sufficient to produce meaningful improvements in psychological and physical well-being. Furthermore, it should be noted that the supportive coaching group more often had a clinical history of prior PCI and myocardial infarction compared to the control group, which may have influenced the outcomes. The coaching group may therefore have included patients with a more severe cardiac history, potentially increasing their vulnerability to stress during the diagnostic procedure and thereby masking potential benefits of the intervention. However, this is not likely to be a substantial challenge to the interpretation of the findings because there was no significant association between a history of PCI or MI and the level of distress at baseline. Finally, the randomisation of patients to the video-based informational support

was not possible because of practical limitations regarding patient privacy related to sending links via the patient's e-mail before consent. Therefore, the effectiveness of the informational videos was examined as part of an exploratory analysis, which revealed no significant beneficial effect on psychological well-being. The strengths of the present study lie in the repeated measures of psychological well-being throughout the diagnostic procedure, the assessment of symptoms during the cardiac stress test, and the multi-method approach of assessing psychological measures, symptoms, ischemia, and patient satisfaction in one comprehensive study.

Future studies are needed to investigate a more elaborate form of supportive coaching or patient navigation beyond the MPI-SPECT procedure and throughout the full trajectory of IHD diagnosis. Starting at the first clinic visit, throughout all diagnostic procedures and treatments, and potentially even during clinical follow-up. This type of support is relatively common in cancer care [40] but almost non-existent in cardiology, and advances in this area could be beneficial to both patients and healthcare providers. Additionally, future research is needed to identify which patients are most likely to benefit from such an intervention.

ACKNOWLEDGMENTS

The authors would like to thank all contributing patients for their participation in the OPTIMIZE study. We also thank nuclear physicians Dr. van Dijk, Dr. Pauw, and Dr. Pijpers, as well as the entire staff of the Nuclear Medicine department at the Institute Verbeeten, for their work and support during this study.

REFERENCE LIST

1. Mozaffarian, D., et al., Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation, 2016. 133(4): p. e38-360.
2. Tsao, C.W., et al., Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. Circulation, 2022. 145(8): p. e153-e639.
3. Roth, G.A., et al., Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol, 2017. 70(1): p. 1-25.
4. Bekendam, M.T., et al., Anxiety and hemodynamic reactivity during cardiac stress testing: The role of gender and age in myocardial ischemia. J Nucl Cardiol, 2021. 28(6): p. 2581-2592.
5. Nudi, F., et al., A novel clinically relevant segmentation method and corresponding maximal ischemia score to risk-stratify patients undergoing myocardial perfusion scintigraphy. J Nucl Cardiol, 2014. 21(4): p. 807-18.
6. Nudi, F., et al., Prognostic impact of location and extent of vessel-related ischemia at myocardial perfusion scintigraphy in patients with or at risk for coronary artery disease. J Nucl Cardiol, 2016. 23(2): p. 274-84.
7. Cantoni, V., et al., Long-term prognostic value of stress myocardial perfusion imaging and coronary computed tomography angiography: A meta-analysis. J Nucl Cardiol, 2016. 23(2): p. 185-97.
8. Bui, K.T., et al., Scanxiety: a scoping review about scan-associated anxiety. BMJ Open, 2021. 11(5): p. e043215.
9. Stewart, M., et al., The impact of patient-centered care on outcomes. J Fam Pract, 2000. 49(9): p. 796-804.
10. Gerteis, M., et al., Through the patient's eyes: understanding and promoting patient-centered care. First edition ed. Jossey-Bass health series. 1993, San Francisco: Jossey-Bass.
11. Chan, R.J., et al., Patient navigation across the cancer care continuum: An overview of systematic reviews and emerging literature. CA Cancer J Clin, 2023. 73(6): p. 565-589.
12. Gilbert, J.E., et al., Nurses as patient navigators in cancer diagnosis: review, consultation and model design. European Journal of Cancer Care, 2011. 20(2): p. 228-236.
13. Van Schalkwijk, D.L., et al., ShareHeart: A patient journey map of patients with ischemia and non-obstructive coronary artery disease based on qualitative research. J Clin Nurs, 2023. 32(13-14): p. 3434-3444.
14. Glasgow, R.E., T.M. Vogt, and S.M. Boles, Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health, 1999. 89(9): p. 1322-7.
15. Bekendam, M., et al., Psychological factors of suspect coronary microvascular dysfunction in patients undergoing SPECT imaging. Journal of Nuclear Cardiology, 2020. 29: p. 1-11.

16. Berman, D.S., et al., Prognostic validation of a 17-segment score derived from a 20-segment score for myocardial perfusion SPECT interpretation. J Nucl Cardiol, 2004. 11(4): p. 414-23.

17. Germano, G. and D. Berman, Clinical gated cardiac SPECT. 2007. 1-367.

18. Dorbala, S., et al., Single Photon Emission Computed Tomography (SPECT) Myocardial Perfusion Imaging Guidelines: Instrumentation, Acquisition, Processing, and Interpretation. J Nucl Cardiol, 2018. 25(5): p. 1784-1846.

19. McNair, D.M., Lorr, M., and Droppleman, L.F. Manual profile of mood states. 1971.

20. Marshall, G.N., Hays, R.D., and Rand, C. The Patient Satisfaction Questionnaire short-form (PSQ-18). P (Rand Corporation); P-7865. 1994, Santa Monica, Calif.: RAND.

21. Vrijhoef, H.J.M., et al., Quality of integrated chronic care measured by patient survey: identification, selection and application of most appropriate instruments. Health Expectations, 2009. 12(4): p. 417-429.

22. Spitzer, R.L., et al., A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med, 2006. 166(10): p. 1092-7.

23. Donker, T., et al., Quick and easy self-rating of Generalized Anxiety Disorder: validity of the Dutch web-based GAD-7, GAD-2 and GAD-SI. Psychiatry Res, 2011. 188(1): p. 58-64.

24. Kroenke, K., Spitzer, R.L., and Williams, J.B. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med, 2001. 16(9): p. 606-13.

25. Zuithoff, N.P.A., et al., The Patient Health Questionnaire-9 for detection of major depressive disorder in primary care: consequences of current thresholds in a crosssectional study. BMC Family Practice, 2010. 11(1): p. 98.

26. Zimet, G.D., et al., The Multidimensional Scale of Perceived Social Support. Journal of Personality Assessment, 1988. 52(1): p. 30-41.

27. Pedersen, S.S., et al., Poor perceived social support in implantable cardioverter defibrillator (ICD) patients and their partners: cross-validation of the multidimensional scale of perceived social support. Psychosomatics, 2009. 50(5): p. 461-7.

28. Bekendam, M.T., et al., Facial Expressions of Emotions During Pharmacological and Exercise Stress Testing: the Role of Myocardial Ischemia and Cardiac Symptoms. Int J Behav Med, 2021. 28(6): p. 692-704.

29. Bekkouche, N.S., et al., Psychological and physiological predictors of angina during exercise-induced ischemia in patients with coronary artery disease. Psychosom Med, 2013. 75(4): p. 413-21.

30. Arnold, S.V., et al., Psychosocial modulators of angina response to myocardial ischemia. Circulation, 2009. 120(2): p. 126-33.

31. Pimple, P., et al., Angina and mental stress-induced myocardial ischemia. J Psychosom Res, 2015. 78(5): p. 433-437.

32. Glusman, M., et al., Pain sensitivity in silent myocardial ischemia. Pain, 1996. 64(3): p. 477-483.

33. Checa, C., et al., Effectiveness and Cost-Effectiveness of Case Management in Advanced Heart Failure Patients Attended in Primary Care: A Systematic Review and Meta-Analysis. International Journal of Environmental Research and Public Health, 2022. 19(21): p. 13823.

34. Yin, Y.-n., et al., Can case management improve cancer patients quality of life?: A systematic review following PRISMA. Medicine, 2020. 99(40): p. e22448.

35. Berezowska, A., Passchier, E., and Bleiker, E. Professional patient navigation in a hospital setting: a randomized controlled trial. Supportive Care in Cancer, 2021. 29(4): p. 2111-2123.

36. Vaccarino, V., et al., Association of Mental Stress-Induced Myocardial Ischemia With Cardiovascular Events in Patients With Coronary Heart Disease. Jama, 2021. 326(18): p. 1818-1828.

37. Wartolowska, K., The nocebo effect as a source of bias in the assessment of treatment effects. F1000Res, 2019. 8: p. 5.

38. Blasini, M., et al., Nocebo and pain: An overview of the psychoneurobiological mechanisms. Pain Rep, 2017. 2(2).

39. Varelmann, D., et al., Nocebo-induced hyperalgesia during local anesthetic injection. Anesth Analg, 2010. 110(3): p. 868-70.

40. Chen, M., et al., Patient Navigation in Cancer Treatment: A Systematic Review. Current Oncology Reports, 2024. 26(5): p. 504-537.

41. Heller, E.N., et al., Extracardiac activity complicates quantitative cardiac SPECT imaging using a simultaneous transmission-emission approach. Journal of nuclear medicine: official publication, Society of Nuclear Medicine, 1997. 38(12): p. 1882-1890.

42. Hachamovitch, R., Clinical Value of Combined Perfusion and Function Imaging in the Diagnosis, Prognosis, and Management of Patients with Suspected or Known Coronary Artery Disease, in Clinical Gated Cardiac SPECT. 2006. p. 189-215.

SUPPLEMENTARY MATERIAL

Additional methodological details

S1. Intervention

Patients allocated to the supportive coaching group received additional support from a coach (a member of the research team). The supportive coaching primarily took place in between the diagnostic procedure components (i.e., before and after tracer injection, imaging, and cardiac stress testing), but the coach was present during all procedures throughout the two testing days to support the patient.

The intervention was designed to be delivered by existing clinic staff without extensive training or education in psychology or mental health. The rationale for this approach was to maximise the implementation potential of the supportive coaching intervention in a wide range of cardiac diagnostic settings in which most of the staff interacting with patients are biomedically trained rather than having a mental health professional background.

Coaches, including the first author and master's students in medical psychology, received an intervention manual containing a script and modules related to procedure components. These modules covered topics such as general anxiety, uncertainty, fear of needles, information on the radioactive tracer, claustrophobia, cardiac stress testing, potential side effects of adenosine, and what to expect after the procedure. because of differences in the needs for coaching between patients, it was not possible to completely script the intervention. The script was primarily used for training purposes, and the modules were selected that were appropriate for each patient. In addition to the specific modules, the coach would answer questions, listen, and respond to worries, aspects of the procedure that were perceived as irritating, or any other topic related to the diagnostic procedure that the patient felt like sharing. The degree of support was, therefore, tailored to the patient's needs.

S2. Development and implementation of the intervention

The intervention was designed and evaluated using the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework, which was developed to assess and improve the adoption and sustainable implementation of evidence-based interventions in healthcare settings (A detailed application of the RE-AIM framework is provided in Supplementary Table ST1).

The control group did not receive any additional supportive coaching from the research team during the investigation. However, usual care at the clinic included standard support provided by the clinic staff during the diagnostic procedures. Additionally, the research team interacted with control group patients to explain the study information and administer the Profile of Mood States at multiple timepoints during the two-day diagnostic testing phase. These interactions were kept as minimal as possible, and in cases where patients had questions or expressed concerns, they were referred to the clinic staff to avoid providing unintended support by the coach.

Supplementary Table ST1. The RE-AIM framework assessment of the OPTIMIZE study.

RE-AIM Domain	Operationalisation in OPTIMIZE study	Metrics and results
Reach	1. Target population 2. Exclusion criteria 3. Study recruitment and participation	1. All patients with suspected ischemic heart disease undergoing MPI SPECT procedure with adenosine or exercise stress testing. 2. Life-threatening disease with <1-year survival expectancy. 3. a. Total eligible patients during study period: 1704 b. Patients approached: 246 (14%) c. Consented to participate: 154 (63%)
Effectiveness	1. Primary outcome 2. Secondary outcomes 3. Measure of robustness across subgroups 4. Short-term attrition	1. Change in negative affect throughout the MPI SPECT procedure using Profile of Mood State Short Form. 2. Patient satisfaction (PSQ-18), cardiac symptoms, and inducibility of myocardial ischemia. 3. Was the intervention more effective for patients with high anxiety (PHQ-9) and depression (GAD-7) or for patients on the exercise protocol compared to the adenosine protocol? 4. 3.2% dropout rate.
Adoption	1. Providers 2. Setting 3. Adoption metrics	1. Interventionists were research team members (Medical Psychology PhD and master students). The intervention was designed to be delivered by clinic staff without extensive additional training. 2. Medical clinic to which patients are referred by the hospital. 3. Willingness of the clinic staff to implement the coaching intervention in routine practice and the feasibility of the time investment in addition to current work.
Implementation	1. Delivery of intervention 2. Adaptations to intervention 3. Cost of intervention 4. Use of qualitative methods	1. The degree of support was rated higher in the supportive coaching group by the interventionist but not by patients. 2. The intervention started using the scripted manual, but due to differences in the need for support, the script was not used, and only the separate modules were selected when appropriate for each patient. 3. 45 to 60 minutes. 4. The degree of support rated by interventionists or patients did not differ between interventionists.
Maintenance	Not available	Not available

S3. Cardiac stress test, image acquisition, and analysis

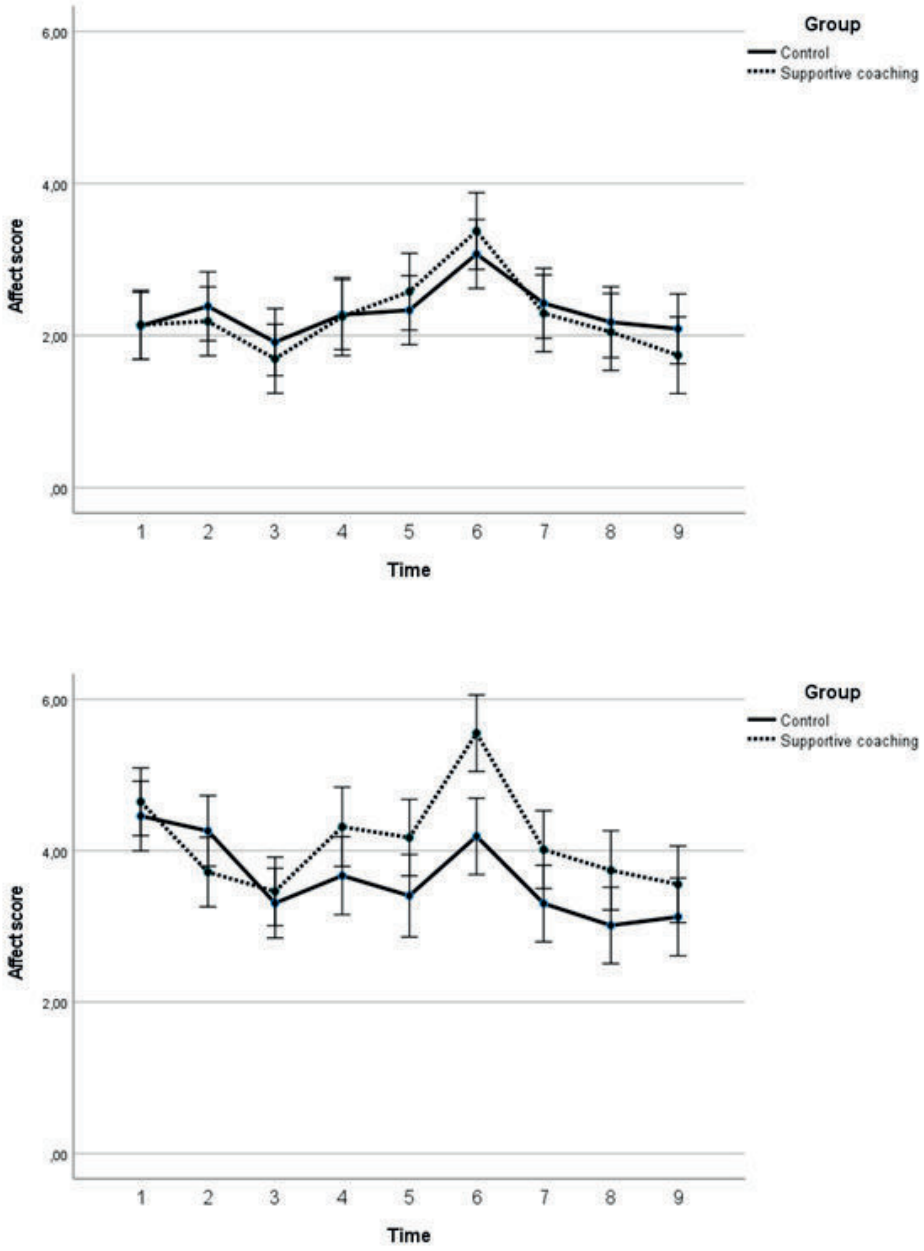
For the adenosine protocol, the radioactive tracer was injected two minutes after adenosine administration [41]. During the exercise protocol, the tracer was injected at 85% of the patient's maximum heart rate (0.85*(220 – patient age) after which the patient had to continue cycling for one minute. The MPI-SPECT scan was performed 45 minutes after the tracer injection.

Image acquisition was conducted using a hybrid dual-headed gated IQ SPECT/CT system (Symbia T, Siemens Medical Solutions AG) with multifocal collimators (SmartzoomTM) of 128 x 128 matrix size and zoom factor of 1. Images were reconstructed using an iterative reconstruction. Attenuation correction was performed using a patient-dedicated low-dose CT-derived mu map. A 15% symmetric window was centred at 140 keV, using three-lead electric cardiographic monitoring. Acquired images were first inspected by qualified staff before interpretation by nuclear physicians. Quantitative perfusion single-photon emission computed tomography software was used to visualise and quantify the data. Summed difference scores (SDS) were calculated between the rest and stress images from the 17-segment perfusion images [42].

The myocardial perfusion images were assessed and interpreted by semiquantitative (SDS) as well as visual analysis, as recommended by the American Society of Nuclear Cardiology [42]. The presence or absence of myocardial ischemia was based on this assessment.

Supplementary Table ST2. The association of average affect state during the diagnostic procedure with supportive coaching and the effect of time.

Predictor	Category	B (95%)	p-value
Group	Control	Reference	
	Supportive coaching	0.255 [.070 to .439)	.007
Timepoints	1	0.657 [-.017 to 11.330]	.065
	2	0.865 [.158 to 1.572]	.004
	3	1.404 [.733 to 2.076]	<.001
	4	0.930 [.242 to 1.618]	<.001
	5	0.949 [.249 to 1.649]	<.001
	6	Reference	
	7	1.042 [.347 to 1.738]	<.001
	8	1.289 [.617 to 1.961]	<.001
	9	1.401 [.719 to 2.084]	<.001



Supplementary Figure SF1. Changes in affect states across the diagnostic MPI-SPECT visit for patients who received coaching and the control group. The top figure shows the trajectory for patients with below-average negative affect at baseline, and the bottom figure for patients with above-average negative affect at baseline. The affect state score represents the average of all affective states, with higher scores reflecting higher negative affect. Error bars represent the standard error of the mean.

Supplementary Table ST3. Symptoms and ischemic response for the patients examined using the adenosine and modified Bruce exercise protocol.

	Adenosine	Exercise	p-value	Cohen's d
Anginal symptoms	1.2 ± 1.7	0.7 ± 1.0	.086	0.403
Adenosine symptoms	0.7 ± 0.8	0.4 ± 0.6	.052	0.403
Ischemia (Yes)	36 (33%)	3 (7.5%)	< .001*	-

Supplementary Table ST4. Differences in anginal and adenosine symptoms, as well as affective state before and during CST between patients with or without ischemia.

	No ischemia	Ischemia	p-value	Cohen's d
Anginal symptoms	0.6 ± 0.8	0.7 ± 0.7	.544	−0.119
Adenosine-related symptoms	1.0 ± 1.6	1.2 ± 1.5	.517	−0.126
Affect state before CST (T5)	3.0 ± 1.6	3.0 ± 1.6	.916	−0.021
Affect state during CST (T6)	3.9 ± 1.8	4.1 ± 2.0	.656	−0.088

Supplementary Table ST5. Linear regression model with the average affect state at cardiac stress testing as the dependent variable and adenosine and anginal symptoms as predictor variables.

	Before CST (T5)					During CST (T6)				
	B	SE B	Beta	t	p-value	B	SE B	Beta	t	p-value
Anginal symptoms	0.176	0.197	0.376	1.905	.059	0.603	0.204	0.252	2.956	.004
Adenosine-related symptoms	0.148	0.097	0.156	1.604	.111	0.371	0.111	0.285	3.333	.001

Supplementary Table ST6. The association of coaching with subsequent patient satisfaction after diagnostic testing.

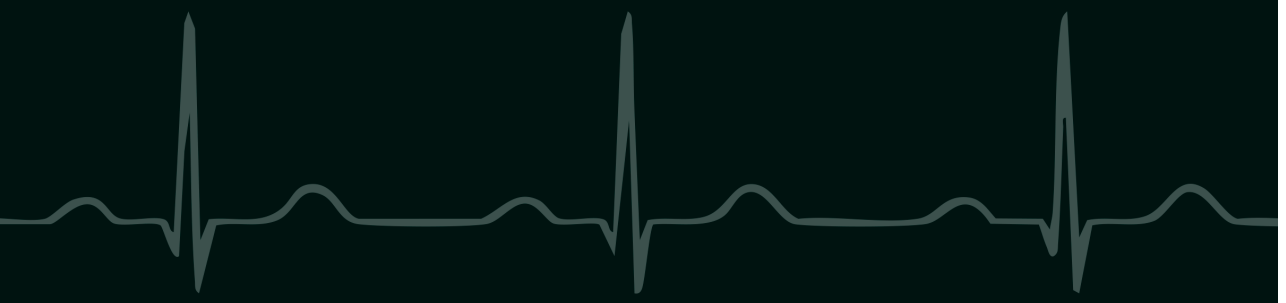
Patient Satisfaction	No Coaching	Coaching	p-value	Cohen's d
PSQ-18 Total	69.5 ± 6.3	71.0 ± 6.6	.211	−0.239
PSQ-18 GS	4.1 ± 0.5	4.1 ± 0.5	.414	−0.154
PSQ-18 TQ	3.9 ± 0.5	4.0 ± 0.4	.185	−0.252
PSQ-18 IM	4.1 ± 0.5	4.2 ± 0.5	.066	−0.349
PSQ-18 CO	4.1 ± 0.5	4.1 ± 0.6	.768	−0.056
PSQ-18 FA	3.7 ± 0.7	3.6 ± 0.9	.421	0.152
PSQ-18 TD	4.0 ± 0.5	4.1 ± 0.5	.152	−0.270
PSQ-18 AC	3.6 ± 0.5	3.7 ± 0.4	.265	−0.212

GS = General satisfaction, TQ = Technical quality, IM = Interpersonal manner, CO = Communication, FA = Financial aspects, TD = Time with the doctor, AC = Accessibility.

Supplementary Table ST7. The association of the average affect state during the diagnostic procedure with the informational video.

Predictor	Category	B (95%)	p-value
Group	No Video	Reference	
	Video	0.048 [-.156 to .243]	.644

Chapter 3



Emotional responses to cardiac stress testing using digital analysis of facial expressions in patients with suspected ischemic heart disease

Roovers, T., Vermeltfoort, I.A.C., Widdershoven, J.W., Kop, W.J.

Submitted for publication

ABSTRACT

Background: Cardiac stress testing with myocardial perfusion imaging single-photon emission computed tomography (MPI-SPECT) is widely used for the detection of ischemic heart disease, but can evoke negative emotional responses. Most research in this area is restricted to self-report measures of emotions. The current study investigates changes in facial emotional expression during MPI-SPECT.

Methods: Video recordings were made during cardiac stress testing and digitally analysed for facial emotional expressions. The effects of myocardial ischemia and symptoms during stress testing on facially expressed emotions were examined. We also investigated whether the type of cardiac stress testing protocol (exercise vs. pharmacological) and receiving supportive coaching during diagnostic testing influenced facial emotion expression.

Results: A total of 108 patients were included (mean age=68.2 [SD=9.7] years, 42 women, 51 receiving supportive coaching). Facial expression of negative emotions increased significantly during stress testing (η^2 = 0.040, p = .004), specifically in the first stage of cardiac stress testing (Δ =.037 [95% CI .013; .062], p < .001). Symptoms during testing were associated with negative facial emotion expression, whereas no associations between the inducibility of ischemia and negative emotion expression were observed. Patients undergoing the exercise-based protocol had less negative emotions compared to those receiving the pharmacological protocol (Δ = .080 [95% CI .020; .139], p = .009). Supportive coaching did not reduce negative emotions.

Conclusion: Cardiac stress testing with MPI-SPECT can negatively affect facial emotion expression. Exercise-based stress protocols might result in less negative emotional responses than pharmacological protocols. Short-term supportive coaching was insufficient to mitigate potential negative emotional responses in this specific diagnostic context.

INTRODUCTION

Patients with ischemic heart disease (IHD) often live with chronic disabilities, impaired physical and emotional well-being, and poor quality of life [1]. In addition to the chronic emotional challenges caused by IHD, diagnostic and follow-up tests can themselves be significant sources of distress [2]. One of the most used non-invasive diagnostic tests for IHD involves cardiac stress testing combined with myocardial perfusion imaging single-photon emission computed tomography (MPI-SPECT) [3-5]. Evidence indicates that cardiac MPI-SPECT testing can evoke acute emotional responses [6]. The anticipation of the stress test, coupled with the potential onset of symptoms such as chest pain or dyspnoea, can evoke heightened negative emotions, including anxiety and anger [7], which are common in patients with IHD [8, 9]. In addition, it has been established that such negative emotions can induce myocardial ischemia during laboratory testing as well as in daily life settings [10-12]. These emotional responses could contribute to physiological and hemodynamic changes related to increased myocardial oxygen demand [13, 14], which might influence the results of cardiac stress testing. It is therefore important to determine factors that influence the emotional responses of patients during cardiac stress testing to optimise patient care and diagnostic accuracy.

Most studies on emotional responses to cardiac diagnostic testing thus far have relied on self-report data. However, this approach might not fully capture the dynamic changes in emotions during a medical procedure that can be highly stressful to some patients [15]. It is therefore important to use different methods that do not solely rely on self-reports of emotional responses. One approach involves analysing facial expressions of emotions captured through video recordings. Digital tools based on the Facial Action Coding System, which recognise patterns in the face and classify emotions, have been successfully employed in clinical and research settings [16, 17].

Given the potential interplay between emotional responses, physiological changes, and outcomes in IHD, integrating patient-centred care strategies could help improve the diagnostic procedure and patient experiences. It has been shown that patients value patient-centred care in the form of social and emotional support [18], which also improves health outcomes and quality of life [19-21]. Providing such support is especially relevant during potentially distressing diagnostic procedures, such as cardiac stress testing, in which negative emotions can impact patient experiences and the successful completion of the test. Adding a supportive coaching component to the investigation of emotional responses to cardiac stress testing also creates

the opportunity to experimentally reduce the level of challenges related to the diagnostic procedure, which aids in understanding individual differences in emotional responses to cardiac stress testing. However, as shown in Chapter 2 (see also [22]), we did not find benefits of supportive coaching during cardiac stress testing with MPI-SPECT when using self-report measures, but the effects of supportive coaching on non-verbal facial emotion expression are not known.

The current study investigates the changes in facial emotion expressions during cardiac stress testing using digital analysis of video-recorded facial expressions. It was hypothesized that cardiac stress testing would result in an increase in negative emotions. We also investigated whether the presence of inducible ischemia and anginal symptoms was related to negative emotions during cardiac stress testing, and whether the type of cardiac stress testing protocol (pharmacological vs. exercise) had consequences for the emotional response. Finally, this study investigated whether supportive coaching would result in attenuation of the negative emotional response to cardiac stress testing with MPI-SPECT when analysing facial expressions in addition to self-report measures. Unique to this study is the systematic assessment of patients' non-verbal emotional expressions during cardiac stress testing, which could further optimise diagnostic testing for IHD and improve patient care.

METHODS

Patients

The study sample consisted of patients referred for cardiac stress testing with MPI-SPECT for IHD-related diagnosis. Consecutive patients were enrolled at the Institute Verbeeten, Tilburg, The Netherlands, between November 2022 and February 2024. The study is referred to as the OPTIMIZE trial and is registered with ClinicalTrials.gov (protocol NCT:05896982).

Inclusion criteria were as follows: referral for MPI-SPECT procedure with either the adenosine or exercise protocol, adequate knowledge of the Dutch language to fill out questionnaires and understand the study procedures, and 18 years of age or older. Exclusion criteria were: a life-threatening condition with an expected survival of less than one year, and refusal to provide informed consent.

Figure 1 provides a flowchart of patient inclusion for the present study. A total of 246 patients were approached for participation in the OPTIMIZE study, of whom 149 (61%) agreed to participate. Outcomes of the self-report data of these 149 patients have been reported in Chapter 1, and the present study focuses on patients with valid facial emotion expression data. Of these 149 patients, 108 (72%) were included in the present analyses. The reasons for not being included in the current analyses were related to missing or invalid FaceReader recordings (e.g., because the patient did not look in the camera, poor video recording quality, or scheduling problems (see Figure 1)). Of the 108 participants, 51 received supportive coaching plus video recordings during MPI-SPECT, and 57 received care-as-usual plus video recordings during MPI-SPECT.

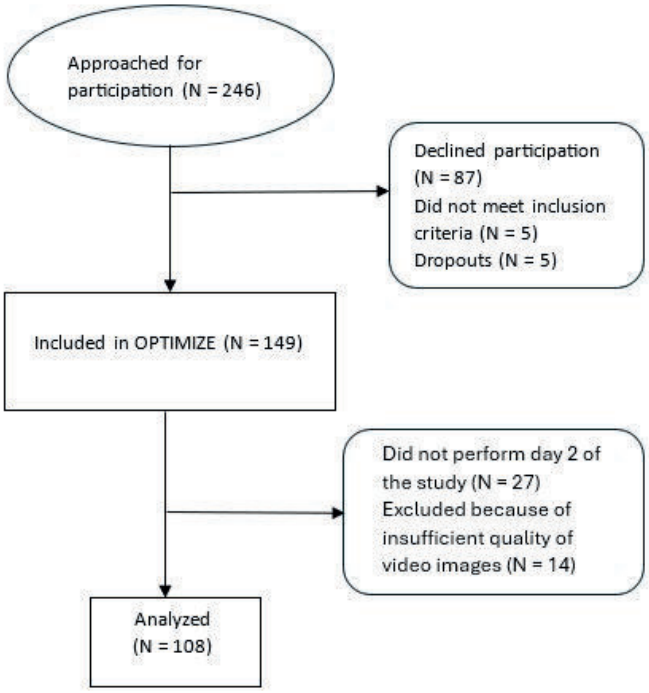


Figure 1. Flowchart of participant inclusion.

Ethical aspects

The OPTIMIZE study was approved by the local Medical Ethics Committee (METC-Brabant NL81600.028.22 / P2234) and conducted in accordance with the Helsinki Declaration. Video recordings of the facial expressions were saved

in a coded manner, and the research staff members involved in the analyses of the videos were not involved in the clinical care of the participating patients. All participants gave written informed consent before participating in the study.

Procedure

Patients were informed about the study verbally and in writing and given two to five days to consider participation. On the first day of the MPI-SPECT diagnostic procedure, a member of the research team approached patients to provide further information and answer questions. If patients agreed to participate, they were asked to sign the informed consent form, after which the study procedures were started.

Patients were subsequently randomised into one of two groups (1:1 ratio): supportive coaching + care-as-usual or care-as-usual only. A random number generator was used to allocate the number of target participants in one of the two groups. Supportive coaching was started on the first day of MPI-SPECT testing (i.e., imaging at rest) to ensure that the coaching covered the full duration of the diagnostic procedure. It was not possible to blind the research team member who provided the supportive coaching from the patient's group allocation because of the nature of the intervention. However, laboratory technicians and nuclear physicians who performed the MPI-SPECT and assessed SPECT images were blind to the patient's group allocation. Patients were also not explicitly informed about which condition they were allocated to, but could have perceived which group they were in. The data were coded such that questionnaire-based outcomes were also evaluated blinded to group allocation status. Patients in the supportive coaching group were accompanied by a coach throughout the diagnostic procedure, who explained the different steps of the procedure, was available for questions, and was there for general support (see Chapter 2 and [22] for more details).

Cardiac Stress Testing Protocol

The assessment of myocardial ischemia using myocardial perfusion imaging consisted of a two-day procedure: a resting day and a cardiac stress testing day. The current investigation focuses on the facial emotion expression during the day of cardiac stress testing.

Cardiac stress testing was performed pharmacologically or through physical exertion. Patients undergoing pharmacological testing received intravenous adenosine (140 mcg/kg/minute) over 5 minutes. Patients were then injected

with the radioactive tracer (Technetium-99m-tetrofosmin (dosage: 370 MBq)) two minutes after the start of adenosine administration. Once adenosine administration was completed, patients were instructed to remain seated until all adenosine-related effects were gone. The physical exertion stress test was performed using the modified Bruce protocol. The radioactive tracer was injected at 85% of the patient's maximum heart rate (0.85*(220 – patient age), after which the patient had to continue cycling at maximum effort for one minute. The physical exertion test ended with a cool-down with minimal resistance.

Supportive coaching and care-as-usual

In order to also have experimental control in this investigation, we not only monitored emotions during MPI-SPECT but also randomised patients to either supportive coaching or no coaching. This addition to the assessments of facial emotion expression and self-reported emotions during the diagnostic testing procedure enables the assessment of emotional states in two different diagnostic scenarios (i.e., supportive coaching or care-as-usual).

Patients allocated to the supportive coaching group received additional support from a coach (a member of the research team). The intervention was developed based on prior qualitative interviews with patients undergoing MPI-SPECT [23], and the support components were designed such that they could be provided by people without formal training in psychology or mental health care (see Chapter 2 for details). The coach was present during the entire cardiac stress testing procedure to provide information such as the safety of the adenosine and radioactive tracer injections or to explain possible side effects. Furthermore, the coach would answer questions and provide a supportive response to the patient's worries if present. The coaching was therefore tailored to the patient's needs.

Measures

Facial expressions during cardiac stress testing

Facial expressions of emotions were recorded using a tripod-mounted video camera aimed at the participant's face. At the start of cardiac stress testing (either pharmacologically or through physical exertion), participants were asked to look into the camera with a neutral expression for 5 seconds, which was used for calibration purposes. Throughout the testing procedure, participants were instructed to keep their faces directed towards the camera. The stress protocol was divided into four distinct phases: "Baseline", "Start of

cardiac stress testing", "Peak cardiac stress testing", and "Recovery", which were separated by the start of the stress test, the injection of the radioactive tracer, and the end of the stress test, respectively.

Facial expression analysis

The analysis of the video recordings during the cardiac stress test took place in the GO-Lab ("Gedragsfysiologisch Onderzoekslaboratorium": "Behavioral-Physiological Research Laboratory") at Tilburg University using the software package FaceReader 9.0. The software locates the participant's face in the recording and creates a 3D Active Appearance Model. FaceReader recognises patterns in the face using deep artificial network analysis. This method results in a mean score of the intensity of facial expressions of emotions on a scale from 0 to 1 (0 – 100%) in each phase for the universal emotional states, including happiness, sadness, anger, and fear. In addition, an overall valence index was calculated, ranging from negative to positive affect (potential score range -1 to 1). The valence index was used as the primary facial emotion expression index, and additional analyses were reported for the separate emotions: happiness, sadness, anger, and anxiety.

The mean number of analysed frames per phase of the cardiac testing protocol was: Baseline, 1940 ± 1520; Start cardiac stress testing, 2433 ± 1912; Peak cardiac stress testing, 2027 ± 873; Recovery, 2210 ± 1407 frames.

Before analysis, each of the video recordings was calibrated over 2 of the 5 seconds of neutral expression to correct for person-specific features that may result in a bias toward a specific facial emotion expression. After calibration, frame-by-frame analysis was performed for all video recordings. The values presented reflect the percentage of time that patients expressed a specific emotion during each of the phases of cardiac stress testing.

Self-reported emotional responses to cardiac stress testing

The Profile of Mood States (POMS) short form was used to evaluate self-reported emotional states. A member of the research team performed the assessment just before, during (coinciding with the radioactive tracer injection), and after cardiac stress testing (2 – 5 minutes after completion). The POMS-SF was modified to investigate short-term changes in emotional states relevant to the cardiac stress testing with MPI-SPECT procedure and included the following states: stressed, anxious, insecure, relaxed, worried, irritated, excited, and tired, rated on a scale from 0 ("not at all") to 10 ("extremely"). The average of these items was used as the primary index

of self-reported emotional state (after reverse-coding of the positive items: relaxed and excited). This average score had a potential range from 0 to 10, with higher scores indicating more self-reported negative emotions.

Inducibility of ischemia

The inducibility of myocardial ischemia was assessed using single-photon emission computed tomography and comparing the perfusion images on the rest day with the perfusion images of the cardiac stress testing day. Quantitative Perfusion MPI-SPECT software (QPS, Cedars-Sinai Medical Center) was used, and the inducibility of ischemia was determined by analysis of the 17-segment perfusion images [24, 25]. The interpretation of myocardial perfusion images was assessed by visual analysis as recommended by the American Society of Nuclear Cardiology (ASNC) [26].

Cardiac and adenosine-related symptoms

Patients were asked whether they experienced any anginal or other symptoms during cardiac stress testing and to rate the severity of the symptoms on a scale from 0 to 10. These symptoms included chest pain, shortness of breath, dizziness, nausea, tiredness, hot flashes, jaw pain, palpitations, and other less common symptoms such as sore legs, dry throat, headache, or stomach ache. The following symptoms were included when referring to anginal symptoms: chest pain, shortness of breath, and/or jaw pain.

Sociodemographic and clinical variables

Information about sociodemographic factors (age, sex, living with a partner or not, educational level) and lifestyle-related cardiovascular risk factors (current smoking status and BMI) was obtained using questionnaires. The level of education was analysed as college education or higher versus lower education. Body mass index (BMI was calculated as kg/m^2).

Clinical information was extracted from the patient's medical records. The following variables were assessed: diagnosis of hypertension and hypercholesterolemia. Cardiac history of IHD was recorded, including a history of myocardial infarction, percutaneous coronary intervention, and coronary artery bypass surgery.

Statistical analysis

Data are presented as mean and standard deviation (SD) for continuous variables and frequencies and percentages for categorical variables. Differences in demographic and clinical patient characteristics between groups were examined using independent t-tests (continuous variables) and χ^2 tests (categorical variables).

To evaluate differences in facial expressions of emotions (i.e., valence (primary outcome), and the specific emotions happiness, sadness, anger, and anxiety) between groups and assess changes over time, general linear model (GLM) repeated measures analyses were used. The main effects of time, group, and the interaction between group and time were evaluated as the main parameters of interest. Results are presented as partial eta-squared (η^2) to evaluate the effect size. To examine differences between groups and time points, regression weights (B) along with 95% confidence intervals (CI) are reported. For exploratory purposes, the type of stress test (pharmacological vs. physical exertion) as related to facial expression of emotions was also assessed using the same analytical approach. Assumptions for general linear models were tested prior to analyses, including normality of the data distribution and homogeneity of variance.

To assess changes over time in the self-reported emotional state index, repeated measures GLM was used. The associations between the self-reported emotional state index and facially expressed emotions were assessed using unadjusted bivariate analysis. Pearson correlations were performed between the self-reported emotional state index and the facial expression valence index, and the four expressed emotions. Independent t-tests were used to evaluate the difference in expressed emotions between patients grouped by the presence or absence of inducibility of myocardial ischemia, symptoms in general, or anginal symptoms specifically. Finally, to explore the combined effect of all symptoms and myocardial ischemia on facial expressions of emotions, one-way ANOVAs were performed to compare four groups: asymptomatic without ischemia, symptomatic with ischemia, asymptomatic without ischemia, and symptomatic with ischemia. This analysis was conducted for the peak cardiac stress testing phase and at baseline.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS: version 28). Results are presented with 95% confidence intervals, and a p-value of $< .05$ was considered to indicate statistical significance.

RESULTS

Patient characteristics

Table 1 displays the demographic and clinical characteristics. The mean age of the sample was 68.2 (SD = 10.0) years, and 42 (38.5%) were women. Of the 108 patients, 51 were randomised to receive supportive coaching, and 57 received care-as-usual. A total of 83 (76.9%) patients were examined using pharmacologically induced stress, and 25 (23.1%) using physical exertion.

Table 1. Demographic and clinical patient characteristics.

Demographic measures	N = 108
Age (years)	68.2 ± 9.7
Sex (female)	42 (38.5%)
Living alone	25 (22.9%)
Education (college or higher)	23 (21.1%)
Cardiovascular risk factors BMI (kg/m^2)	 27.8 ± 5.0
Current smoking status	11 (10.2%)
Hypertension	45 (41.3%)
Hypercholesterolemia	33 (30.3%)
Cardiovascular history	
Myocardial infarction	12 (11.0%)
Percutaneous coronary intervention	26 (23.9%)
Coronary artery bypass surgery	10 (9.2%)
MPI-SPECT diagnostic procedure	
Cardiac stress testing type (Adenosine)	84 (77.1%)
Inducibility of myocardial ischemia Symptoms during stress testing History of prior MPI-SPECT	32 (29.4%) 80 (73.4%) 29 (26.6%)

Changes in facial expression of emotions during cardiac stress testing

Figure 2 shows that cardiac stress testing produced a significant increase in facial expressions of negative emotions (i.e., lower valence values). Specifically, the overall valence of the facial expression decreased significantly from baseline to the start of the cardiac stress testing (Δ = −0.037 [95% CI −0.062; −0.013], $p < .001$) (see also Supplementary Table ST1). The overall general linear model also showed a significant change over the four time

points (F(3, 107) = 4.444, p = .004, η^2 = 0.040). Investigation of the separate timepoints indicated that the change from baseline to the start of cardiac stress testing was the only change that was statistically significant (Figure 2).

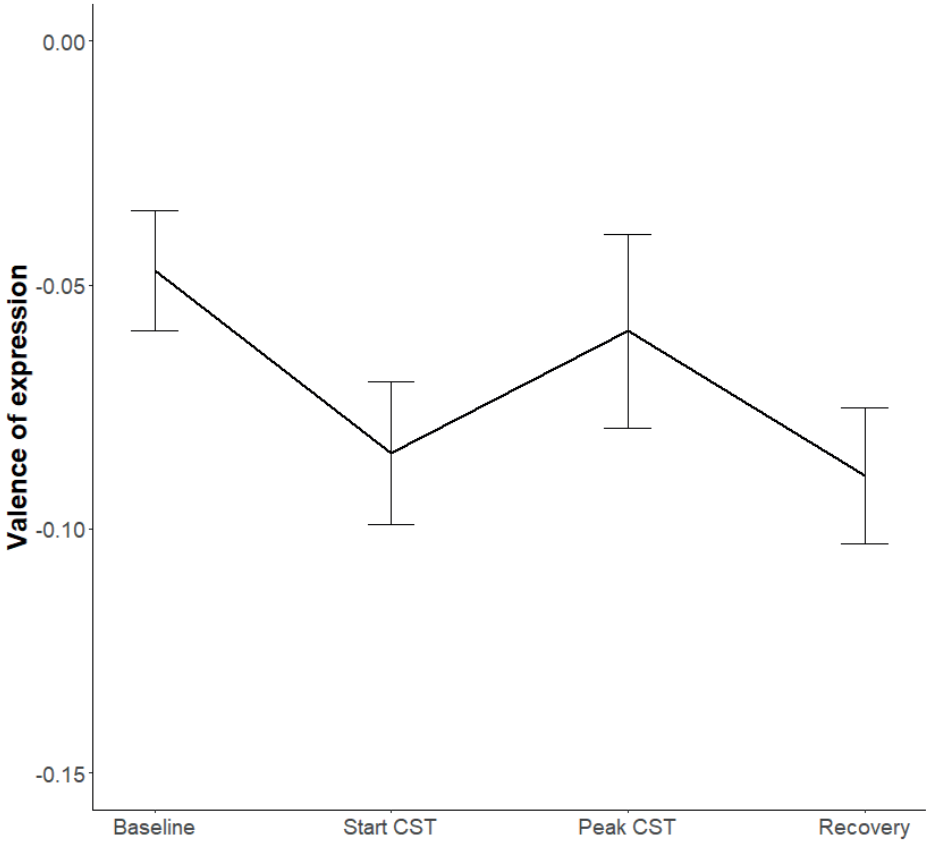


Figure 2. The valence of emotion expression throughout the four phases of the cardiac stress test. Higher valence scores indicate a higher level of positive emotions, and a decrease over time indicates more negative facially expressed emotions. CST = Cardiac stress testing. * = p < 0.05 for comparison of subsequent time points.

Table 2 shows the results for the separate facially expressed emotions (happiness, sadness, anger, and anxiety). The overall levels of facially expressed happiness and sadness were relatively high compared to the levels of anger and anxiety. Specifically, after an increase from baseline to peak cardiac stress testing, the expression of happiness decreased significantly during the recovery phase (Δ = −.032 [95% −0.056; −0.008], p = .003) to below the levels observed at baseline. Anxiety expressions increased from baseline to the start of the cardiac stress test (Δ = 0.004 [95% CI 0.001; 0.008], p = .010)

and also from peak cardiac stress to the recovery phase (Δ = 0.007 [95% CI .001; .012], p = .015). Levels of sadness and anger did not significantly change during the testing procedure. The overall GLM, combining the four facial emotions as the dependent measure over the four time points, revealed a significant effect over time ($F(12, 960) = 4.568$, $p < .001$, $\eta^2 = .054$).

Table 2. The mean values with standard errors for each of the four emotions during the four phases of the cardiac stress testing.

	Baseline	Start CST	Peak CST	Recovery
Happiness	0.052 (0.006)	0.047 (0.008)	0.074 (0.012)	0.042 (0.006)**
Sadness	0.054 (0.007)	0.069 (0.009)	0.065 (0.010)	0.062 (0.009)
Anger	0.012 (0.002)	0.014 (0.003)	0.014 (0.002)	0.018 (0.003)
Anxiety	0.006 (0.001)	0.010 (0.002)*	0.009 (0.002)	0.016 (0.003)*

* < .05, ** p < .01, *** p < .001 for differences between the subsequent time points. CST = cardiac stress testing

The association of facially expressed emotion with self-reported emotion during cardiac stress testing

We also investigated the correspondence between facially expressed emotions and self-reported emotions during cardiac stress testing. The self-report index was performed at three time points, before, at the peak, and after completion of cardiac stress testing. Self-reported negative affect increased from the baseline assessment before cardiac stress testing to peak cardiac stress (Δ = 0.944 [95% CI 0.645; 1.244], p < .001), and other time-point comparisons of self-reported negative affect were statistically not significant.

No significant correlations were found between the facially expressed emotional valence and self-reported negative emotions (Table 3; see Supplementary Table ST1 for analyses of each of the four emotions separately). These data indicate that the two methods of assessment capture different aspects of the emotional response to cardiac stress testing.

Table 3. Pearson correlations between the mean facially expressed valence during the four phases of cardiac stress testing (CST) with self-reported emotional state index before, during, at the peak, and after cardiac stress testing.

		Self-reported emotional state index	
Facial expression valence	**Before CST**	**Peak CST**	**After CST**
Baseline	0.076	0.180	0.074
Start CST	0.041	0.096	0.097
Peak CST	−0.176	−0.121	−0.038
Recovery	−0.042	0.0002	0.092

Higher valence scores indicate more positive emotions, hence, negative correlations were expected.

Inducibility of myocardial ischemia and symptoms as related to facially expressed emotion during cardiac stress testing

There were no differences between patients with versus without inducible myocardial ischemia during cardiac stress testing with regard to the level of facially expressed emotions (all $p > .30$).

With regard to symptoms, the valence of the expressed emotions was significantly less positive for patients who developed symptoms (anginal or adenosine-related) during cardiac stress testing at peak cardiac stress testing (−0.087 ± 0.180 vs 0.0156 ± 0.256; $t(106, 38.585) = -2.332$, $p = .022$, Cohen's $d = .506$). When examining the emotions separately (i.e., happiness, sadness, anger, and anxiety), patients with symptoms expressed less facial happiness at peak cardiac stress testing compared to asymptomatic patients (0.135 ± 0.191 vs 0.526 ± 0.08; $t(106) = -3.164$, $p = .002$, Cohen's $d = .687$). However, when analysing the presence or absence of anginal symptoms separately, no significant differences were found for valence or any of the separate emotions (all $p > .220$).

The analysis comparing facial expressions across the four groups, categorised by the presence or absence of ischemia and/or symptoms (anginal and adenosine-related), revealed significant differences in negative emotions (valence $F(3, 104) = 3.922$, $p = .011$) during peak cardiac stress testing. Post-hoc analysis revealed that patients with ischemia but without symptoms showed less negative emotions than patients with symptoms and ischemia ($p = .010$) or without ischemia ($p = .021$). These findings should be interpreted with caution, given the small number of patients in the asymptomatic ischemia group.

Facial expressions observed at baseline were not associated with inducibility of myocardial ischemia or symptoms during stress testing (all p > .375).

Responses to exercise protocol type: Exercise versus pharmacological stress testing

The level of facially expressed negative emotions was less in patients who performed the physical exercise protocol compared to patients who received the pharmacological stress protocol (Δ emotional valence = .080 [95% CI .020; .139], p = .009). This finding was supported by a significant interaction between test protocol type and time (F(3, 318) = 6.179, p < .001). This relatively positive response to the exercise protocol was primarily attributable to higher expressed happiness (F(3, 318) = 12.864, p < .001) in patients performing exercise compared to those receiving pharmacological stress testing (see Supplemental Figure SF1 for details).

Facially expressed emotions in response to supportive coaching

To extend the present investigation on emotional responses to cardiac stress testing with MPI-SPECT beyond an observational design, patients were randomised to either supportive coaching or a no-coaching condition during the diagnostic testing procedures (for details see [22]). Patients receiving supportive coaching did not differ from patients receiving care-as-usual on clinical or demographic variables, except for the history of PCI (supportive coaching 33.3% vs. care-as-usual 15.8%; χ^2 = 4.532, p = .033) (Supplemental Table ST2).

The overall valence of the expressed emotions was lower in patients who received supportive coaching than in those receiving usual care during cardiac stress testing (Δ = 0.054 [95% CI 0.003; 0.105], p = .040), but no significant interaction between time and group was observed (p > .075) (Supplementary Table ST3).

Consistent with these findings is that patients in the supportive coaching group also reported higher self-reported negative emotions during peak cardiac stress testing compared to care-as-usual (3.45 ± 1.77 vs 4.23 ± 1.80; t(106, 104.266) = 2.000, p = .048, d = .386) (for more details, see Chapter 2 and [22])

DISCUSSION

The present investigation evaluated the pattern of changes in emotional states during cardiac stress testing with myocardial perfusion imaging. The study used an innovative approach by utilising facial expressions of emotions as a measure of a patient's emotional state that does not rely on self-reported data. Cardiac stress testing resulted in an increase in expressed negative emotions, particularly at the start of the stress test. These facially expressed emotions were not significantly correlated with patients' self-reported emotional states and might provide information that cannot be obtained via questionnaires or interviews. Patients with symptoms during cardiac stress testing expressed a higher level of negative emotions. In addition, patients on the physical exertion stress protocol exhibited fewer negative emotions than those on the pharmacological testing protocol. Supportive coaching did not result in an attenuation of facially expressed negative emotions during cardiac stress testing. These findings highlight the impact of cardiac stress testing on patients' emotional states and also suggest that short-term supportive coaching is not sufficient to mitigate potential negative emotional responses in this specific diagnostic context.

The current findings regarding changes in emotional responses during cardiac stress testing reveal that the most pronounced negative emotional responses occur at the beginning of the stress test, rather than during the peak of the test as might be expected. The increase in negative facial expressions during the start of cardiac stress testing could be caused by the anticipation of upcoming side effects, physical discomfort, or adverse outcomes. We also observed a statistically significant increase in anxiety and a decrease in happiness from peak stress to recovery, and a corresponding (but not statistically significant) decrease in overall emotional valence. This increase in negative emotions during the recovery phase is less intuitive, as one might expect the patients to feel relieved knowing the most demanding part of the stress test is over. However, following the stress test, patients were still required to undergo the scanning procedure, which may have left them feeling anxious about the test results and the meaning of symptoms that could have occurred during the stress testing.

Patients who received the physical exertion protocol expressed a higher intensity of emotions, primarily positive (i.e., happiness) but to some extent also negative emotions (i.e., anxiety). In recent years, particularly since the COVID-19 pandemic, there has been a shift away from physical exertion protocols as these were avoided to reduce the spread of viral particles exhaled

during exertion. However, the current findings suggest that the physical exertion protocol may be more beneficial for patients compared to the pharmacological stress protocol in terms of less negative emotional responses. In addition, frequent encouragement from the staff to reach the target heart rate during bicycling could have contributed to an improved overall emotional state, as reflected by the relatively higher valence scores of patients performing exercise. Furthermore, self-reported emotional states were assessed by the research staff at the time of maximal exertion. This timing, coinciding with physical exhaustion, often elicited a heightened emotional response, which could either be positive or negative. These responses are reflected by the peaks observed in the expressed specific emotions during the peak phase of the testing procedure. If both negative and positive emotions are elevated, then these will balance out in the overall valence score; hence, this study used the overall valence score as the primary outcome measure of facially expressed emotional states during cardiac stress testing with MPI-SPECT. The overall increase in negative facial expressions is consistent with a previous study in the same clinical setting, which found increases in sadness, anxiety, anger, and a reduction in happiness throughout cardiac stress testing compared to baseline [27]. Although the overall expression of negative emotions was relatively low, the findings highlight the psychological burden associated with cardiac stress testing.

Supportive coaching did not improve the facially expressed emotional state during cardiac stress testing, which is consistent with the findings based on self-report that are presented in Chapter 2 and the related article [22]. Although the facial expression of emotions and self-reported emotional states were not intercorrelated in the current study, neither of these domains of measurement was positively affected by supportive coaching. These findings are in contrast to several studies that report positive effects of supportive coaching on quality of life in cardiac and cancer care [21, 28, 29]. The discrepancy might be caused by the difference in the duration of the intervention that was investigated. The current study evaluated a brief, short-term coaching intervention focused on addressing acute emotional responses, whereas previous research has predominantly focused on long-term intervention programs designed to influence long-term emotional well-being. It is also possible that the standard patient care of routine cardiac stress testing in the clinical setting of this study is already of high quality and that there is a ceiling effect that obscures the potential effectiveness of short-term supportive coaching.

Patients with symptoms, but not specifically angina-related symptoms, expressed significantly less happiness compared to patients who remained asymptomatic during cardiac stress testing. The previously documented additive consequences of inducible ischemia and symptoms on facial expressions of emotions during cardiac stress testing [7] were not replicated in the present study. Overall, the findings highlight the importance of addressing not only the physical but also the emotional aspects of care, which may influence health outcomes and the inducibility of myocardial ischemia [27, 30-32].

The current study has several strengths and limitations. Limitations include that the timing of the self-reported emotional states assessment during peak exertion might have affected the facial expression assessments. In addition, the levels of anger and anxiety were very low, and the overall valence index of facial expression of negative emotions might therefore have underestimated the role of these specific negative emotions. The level of supportive coaching was tailored to the patient's needs during the procedure, which might have introduced variability in the intervention intensity. The key strength of the study lies in the measurement of emotional states using facial expression analysis that is not dependent on patient self-report, combined with self-reported emotional states and symptom assessments. Patients were also randomised to supportive coaching or care-as-usual without coaching during cardiac stress testing. This approach allows for a better understanding of emotional responses during cardiac stress testing and highlights potential discrepancies between non-verbal facially expressed emotions and self-reported emotions.

In conclusion, the current investigation shows that analyses of facial emotion expression can identify increases in negative emotions in response to cardiac stress testing. Patients with symptoms during cardiac stress testing had more facially expressed negative emotions than patients who remained asymptomatic, but facial expressions at baseline did not predict symptoms during cardiac stress testing. In addition, patients undergoing a physical exertion protocol displayed less negative emotional states compared to those on the pharmacological protocol. Supportive coaching did not attenuate the negative impact of cardiac stress testing on a patient's emotional state. Together, these results highlight the use of a holistic patient care approach addressing both emotional states, physical symptoms, and their inter-relationships during cardiac stress testing. The choice of exercise versus pharmacological stress testing protocols needs to be based not only on the patient's physical characteristics, but also on the expected symptomatic and

emotional responses to these protocols. Short-term supportive coaching was not sufficient to improve patients' emotional well-being during cardiac stress testing, and future studies are therefore warranted to develop interventions that can reduce negative emotions throughout the full diagnostic trajectory for ischemic heart disease, including procedures that occur before and after the cardiac stress testing phase.

ACKNOWLEDGMENT

The authors would like to thank all contributing patients for their participation in the OPTIMIZE study. We also thank nuclear physicians Dr. van Dijk, Dr. Pauw, Dr. Pijpers, and the entire staff of the Nuclear Medicine department of the Institute Verbeeten for their work and support during this study.

REFERENCE LIST

1. Moran, A.E., et al., Temporal Trends in Ischemic Heart Disease Mortality in 21 World Regions, 1980 to 2010. Circulation, 2014. 129(14): p. 1483-1492.
2. Bui, K.T., et al., Scanxiety: a scoping review about scan-associated anxiety. BMJ Open, 2021. 11(5): p. e043215.
3. Nudi, F., et al., A novel clinically relevant segmentation method and corresponding maximal ischemia score to risk-stratify patients undergoing myocardial perfusion scintigraphy. J Nucl Cardiol, 2014. 21(4): p. 807-18.
4. Nudi, F., et al., Prognostic impact of location and extent of vessel-related ischemia at myocardial perfusion scintigraphy in patients with or at risk for coronary artery disease. J Nucl Cardiol, 2016. 23(2): p. 274-84.
5. Cantoni, V., et al., Long-term prognostic value of stress myocardial perfusion imaging and coronary computed tomography angiography: A meta-analysis. J Nucl Cardiol, 2016. 23(2): p. 185-97.
6. Bekendam, M.T., et al., Facial Expressions of Emotions During Pharmacological and Exercise Stress Testing: the Role of Myocardial Ischemia and Cardiac Symptoms. International Journal of Behavioral Medicine, 2021. 28(6): p. 692-704.
7. Bekendam, M.T., et al., Anxiety and hemodynamic reactivity during cardiac stress testing: The role of gender and age in myocardial ischemia. J Nucl Cardiol, 2021. 28(6): p. 2581-2592.
8. Dimsdale, J.E., Psychological Stress and Cardiovascular Disease. Journal of the American College of Cardiology, 2008. 51(13): p. 1237-1246.
9. Rosengren, A., 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): p. 953-62.
10. Strike, P.C., and Steptoe, A. Systematic review of mental stress-induced myocardial ischaemia. European Heart Journal, 2003. 24(8): p. 690-703.
11. Vaccarino, V., et al., Mental Stress–Induced-Myocardial Ischemia in Young Patients With Recent Myocardial Infarction. Circulation, 2018. 137(8): p. 794-805.
12. Wei, J., et al., Meta-Analysis of Mental Stress Induced Myocardial Ischemia and Subsequent Cardiac Events in Patients With Coronary Artery Disease. American Journal of Cardiology, 2014. 114(2): p. 187-192.
13. Verkuil, B., Brosschot, J.F., and Thayer, J.F. Cardiac reactivity to and recovery from acute stress: Temporal associations with implicit anxiety. International Journal of Psychophysiology, 2014. 92(2): p. 85-91.
14. Rutledge, T., et al., Anxiety associations with cardiac symptoms, angiographic disease severity, and healthcare utilization: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation. Int J Cardiol, 2013. 168(3): p. 2335-40.
15. Rosenberg, E.L., and Ekman, P. Emotion: Methods of study, in Encyclopedia of Psychology, Vol. 3. 2000, American Psychological Association: Washington, DC, US. p. 171-175.
16. Ekman, P. and W.V. Friesen, Facial action coding system: manual. 1978, Palo Alto, Calif.: Consulting Psychologists Press.

17. Sayette, M.A., et al., A psychometric evaluation of the facial action coding system for assessing spontaneous expression. Journal of Nonverbal Behavior, 2001. 25(3): p. 167-185.

18. Van Schalkwijk, D.L., et al., ShareHeart: A patient journey map of patients with ischemia and non-obstructive coronary artery disease based on qualitative research. J Clin Nurs, 2023. 32(13-14): p. 3434-3444.

19. Stewart, M., et al., The impact of patient-centered care on outcomes. J Fam Pract, 2000. 49(9): p. 796-804.

20. Gerteis, M., et al., Through the patient's eyes: understanding and promoting patient-centered care. First edition ed. Jossey-Bass health series. 1993, San Francisco: Jossey-Bass.

21. Chan, R.J., et al., Patient navigation across the cancer care continuum: An overview of systematic reviews and emerging literature. CA Cancer J Clin, 2023. 73(6): p. 565-589.

22. Roovers, T., et al., Psychological well-being and the effects of supportive coaching during SPECT myocardial perfusion imaging in patients with suspected ischemic heart disease. Journal of Psychosomatic Research, 2025. 197: p. 112355.

23. Bekendam, M.T., Psychological factors in patients with ischemic heart disease and cardiac complaints: A qualitative investigation of perceptions and experiences, in Facing the heart, on the role of acute emotions and psychological factors in patients with ischemic heart disease. 2022, Tilburg University: Tilburg, The Netherlands.

24. Berman, D.S., et al., Prognostic validation of a 17-segment score derived from a 20-segment score for myocardial perfusion SPECT interpretation. J Nucl Cardiol, 2004. 11(4): p. 414-23.

25. Germano, G., and Berman, D. Clinical gated cardiac SPECT. 2007. 1-367.

26. Dorbala, S., et al., Single Photon Emission Computed Tomography (SPECT) Myocardial Perfusion Imaging Guidelines: Instrumentation, Acquisition, Processing, and Interpretation. J Nucl Cardiol, 2018. 25(5): p. 1784-1846.

27. Boehm, J., and Kubzansky, L. The Heart's Content: The Association Between Positive Psychological Well-Being and Cardiovascular Health. Psychological bulletin, 2012. 138: p. 655-91.

28. Yin, Y.-n., et al., Can case management improve cancer patients quality of life?: A systematic review following PRISMA. Medicine, 2020. 99(40): p. e22448.

29. Checa, C., et al., Effectiveness and Cost-Effectiveness of Case Management in Advanced Heart Failure Patients Attended in Primary Care: A Systematic Review and Meta-Analysis. International Journal of Environmental Research and Public Health, 2022. 19(21): p. 13823.

30. Gabbay, F.H., et al., Triggers of myocardial ischemia during daily life in patients with coronary artery disease: Physical and mental activities, anger and smoking. Journal of the American College of Cardiology, 1996. 27(3): p. 585-592.

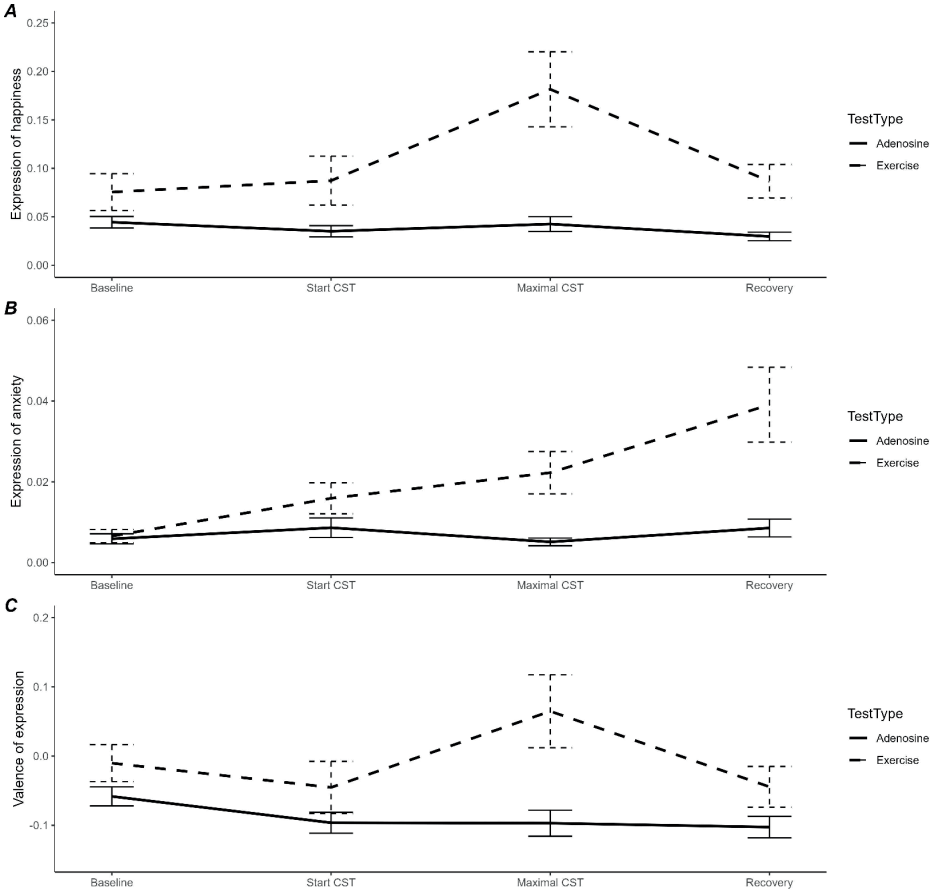
31. Stébenne, P., et al., Positive and Negative Affect Is Related to Experiencing Chest Pain During Exercise-Induced Myocardial Ischemia. Biopsychosocial Science and Medicine, 2017. 79(4).

32. Pressman, S.D., Jenkins, B.N., and Moskowitz, J.T. Positive Affect and Health: What Do We Know and Where Next Should We Go? Annual Review of Psychology, 2019. 70(Volume 70, 2019): p. 627-650.

SUPPLEMENTARY MATERIAL

Supplementary Table ST1. Pearson correlations between the mean facially expressed four emotions during peak cardiac stress testing with self-reported emotional state index before, at the peak, and after cardiac stress testing.

			Self-reported negative emotions	
Facial expression of emotions during CST		**Before CST**	**Peak CST**	**After CST**
Happiness	Baseline	0.123	0.198*	0.091
	Start CST	0.090	0.125	0.081
	Peak CST	−0.201*	−0.130	−0.089
	Recovery	0.017	−0.028	−0.011
Sadness	Baseline	0.127	0.048	0.162
	Start CST	0.176	0.123	0.121
	Peak CST	0.148	0.077	0.127
	Recovery	0.134	0.069	0.070
Anger	Baseline	0.041	0.003	0.029
	Start CST	−0.054	−0.089	−0.033
	Peak CST	0.099	0.128	0.117
	Recovery	0.149	0.129	0.125
Anxiety	Baseline	−0.090	−0.120	0.002
	Start CST	−0.077	−0.052	0.021
	Peak CST	−0.112	−0.067	−0.070
	Recovery	−.0100	−0.088	−.0019



Supplementary Figure SF1. Expressions of (A) happiness, (B) anxiety, and (C) valence throughout the four phases of the cardiac stress test for patients on the adenosine (pharmacological) and exercise protocol.

Supplementary Table ST2. Demographic and patient characteristics of patients in the supportive coaching and no-coaching groups.

	No Coaching (N = 57)	Coaching (N = 51)
Demographics		
Age (years)	68.8 ± 9.6	67.6 ± 10.5
Sex (female)	21 (36.8%)	20 (39.2%)
Living alone	14 (24.6%)	11 (21.6%)
College education or higher	9 (15.8%)	14 (27.5%)
BMI (kg/m^2)	26.8 ± 4.3	28.6 ± 5.4
Myocardial ischemia	16 (28.1%)	16 (31.4%)
Hypertension	27 (47.4%)	17 (33.3%)
Hypercholesterolemia	20 (35.1%)	13 (25.5%)
Myocardial infarction	4 (7.0%)	8 (15.7%)
PCI	9 (15.8%)	17 (33.3%)
CABG	5 (8.8%)	5 (9.8%)
Diagnostic testing		
Test type (Adenosine)	43 (75.4%)	40 (78.4%)
SPECT before	15 (26.3%)	14 (27.5%)

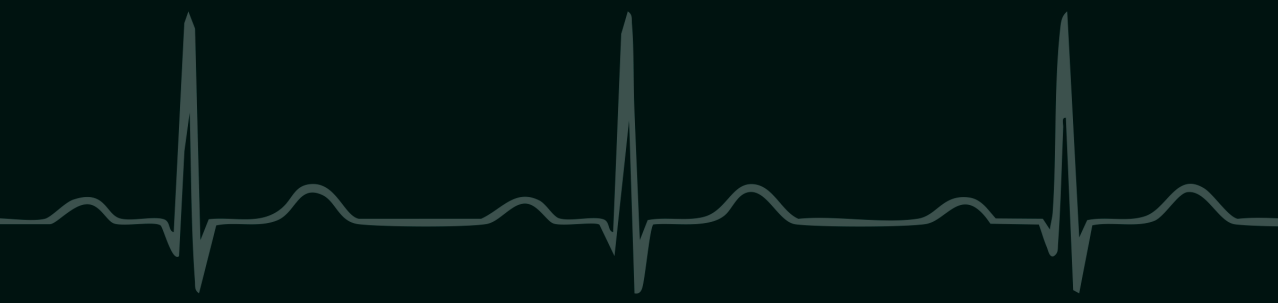
Supplementary Table ST3. The main effects of time, intervention groups, and the interaction for the five expressed emotions during CST.

		SS	df	Mean Square	F	p-value
Happiness	Time	0.065	3	0.022	5.515	<.001
	Group	0.025	1	0.025	1.336	.250
	Group x time	0.015	3	0.005	1.341	.261
Sadness	Time	0.013	3	0.004	1.205	.308
	Group	0.006	1	0.006	0.259	.612
	Group x time	0.008	3	0.003	0.697	.555
Anger	Time	0.002	3	0.001	1.930	.125
	Group	0.003	1	0.003	2.156	.145
	Group x time	0.002	3	0.001	2.207	.087
Anxiety	Time	0.005	3	0.002	8.534	<.001
	Group	0.000082	1	0.000082	0.068	.795
	Group x time	0.00009	3	0.00003	0.147	.932
Valence	Time	0.131	3	0.044	4.444	.004
	Group	0.310	1	0.310	4.343	.040
	Group x time	0.067	3	0.022	2.298	.077

Part II

Autonomic Regulation in Behavioural and Psychological Contexts of Cardiovascular Disease

Chapter 4



Heart rate variability and its association with psychological well-being in patients with suspected ischemic heart disease

Roovers, T., Vermeltfoort, I.A.C., Widdershoven, J.W., Kop, W.J.

Submitted for publication

ABSTRACT

Background: Heart rate variability (HRV) indices reflect autonomic regulation and have been linked to cardiovascular disease risk. Both long-term and short-term emotional distress have also been associated with adverse cardiovascular outcomes. However, the relationship between acute emotional states and autonomic regulation in patients with ischemic heart disease remains unclear. This study examines the association between in-the-moment emotional states and short-term heart rate variability indices and cardiac symptoms during daily life activities.

Methods: Patients referred for diagnostic myocardial perfusion imaging underwent ECG monitoring for assessment of HRV indices (repeated short-term 10-minute epochs and 24-hour). Ecological momentary assessments (EMA) of emotional states and cardiac symptoms were obtained using electronic diaries. Associations between emotional states and short-term HRV indices and cardiac symptoms during daily life were analysed using General Estimation Equation models. The role of inducible ischemia was also investigated.

Results: A total of 175 EMA assessments were obtained in 26 patients (mean age = 66.5 ± 9.3 years, 26.9% women). Negative emotional states were significantly associated with HRV indices (lower low-frequency power and SDNN values) and higher heart rate. Lower HRV indices were also associated with cardiac symptoms (angina pectoris and dyspnoea). The severity of reversible perfusion defects was negatively correlated with 24-hour low-frequency HRV, but not with negative emotions or cardiac symptoms during daily life.

Conclusions: Momentary negative emotions are related to potentially adverse changes in autonomic regulation, contributing to physiological strain and cardiac symptoms. These results highlight the value of capturing in-the-moment emotional states for understanding autonomic dysregulation and cardiovascular risk.

INTRODUCTION

Intense emotional states can trigger acute coronary syndromes (ACS) such as myocardial infarction and sudden cardiac death [1]. Recent meta-analyses have reported strong associations of acute experiences of anger, anxiety, sadness, grief, and stress with myocardial infarction incidence [2, 3]. There is also evidence that ACS survivors whose event was triggered by acute emotions experience a higher psychological burden [4] and an increased risk of mortality after the myocardial infarction [5]. Given that ischemic heart disease affected approximately 244.1 million people globally in 2020 [6], and since these patients are at increased risk of acute cardiac events, it is crucial to understand the biobehavioural processes involved in cardiac health.

Myocardial ischemia and infarction are preceded by vagal withdrawal, a shift in autonomic nervous system balance from parasympathetic to sympathetic dominance [7–9]. This shift may contribute to ACS by increasing myocardial oxygen demand [10], reducing coronary blood supply through vasoconstriction [11], and increasing the risk of ventricular arrhythmias [12], especially in susceptible patients with vulnerable atherosclerotic plaques. Low baseline levels of parasympathetic activity are predictive of adverse cardiovascular outcomes, including myocardial infarction and sudden cardiac death [11]. Autonomic dysregulation, particularly an imbalance with increased sympathetic activity, is thought to promote cardiac instability, making individuals more susceptible to ischemic events [9, 13]. Autonomic imbalance is not only an acute trigger but also a long-term risk factor associated with increased all-cause and cardiovascular mortality [14, 15].

Acute emotional states can result in cardiovascular physiological dysregulation and myocardial ischemia and ACS via autonomic nervous system pathways. Mental-stress-induced myocardial ischemia is associated with parasympathetic withdrawal and increased sympathetic activity [7], a pattern that has also been observed in episodes of negative emotions such as sadness, anger, and anxiety [16, 17]. Beyond the immediate physiological impact, repeated exposure to emotional distress may lead to chronic autonomic dysregulation, which increases the long-term risk of future cardiovascular events [18].

Measures of heart rate variability are commonly used to assess autonomic nervous system regulation, particularly changes in parasympathetic activity [19]. The variability in inter-beat intervals reflects the degree of parasympathetic activation. Well-established measures of HRV include frequency domain metrics such as low-frequency (0.04 – 0.15 Hz) and high-

frequency (0.15 – 0.40 Hz) power, and time domain metrics, such as the standard deviation of normal-to-normal inter-beat intervals (SDNN), and the root mean square of successive differences (RMSSD) [20]. High-frequency power and RMSSD are highly correlated and primarily reflect parasympathetic activity [21]. In contrast, both sympathetic and parasympathetic influences contribute to low-frequency power and SDNN [22].

The present study investigates the relationship between acute emotional states and HRV indices in patients with suspected ischemic heart disease. It is hypothesised that acute negative emotional states are associated with impaired short-term autonomic regulation. In addition, the role of inducibility of myocardial ischemia, emotional states, and HRV as related to cardiac symptoms during daily life activities will be assessed. To ensure the patient's status with regard to inducibility of ischemia, all tests were conducted in the week prior to diagnostic exercise or pharmacological cardiac stress testing with myocardial perfusion imaging. Unique to this study is the use of digital diary entries via patients' smartphones with ecological momentary assessment (EMA) methodology to monitor acute emotional state, daily activities, and cardiac symptoms.

METHODS

Patients

The study sample consisted of patients who underwent diagnostic testing for the presence of inducible myocardial ischemia at Institute Verbeeten, Tilburg, the Netherlands, between November 2022 and February 2024. The present analyses are part of a larger project on psychological well-being in patients undergoing diagnostic testing for myocardial ischemia, referred to as the OPTIMIZE study (registered with ClinicalTrials.gov; protocol NCT:05896982); see Chapter 2 and [23] for details.

Inclusion criteria for the overall project were: referred for diagnostic cardiac stress testing with myocardial perfusion imaging (MPI), 18 years of age or older, and sufficient knowledge of the Dutch language to answer questionnaires and understand the study procedures. Patients were excluded from participating if they had a life-threatening disease with a < 1-year survival expectancy (e.g., metastatic cancer) or if they did not provide informed consent. For the present sub-project, patients were also excluded if they did not have a mobile phone to answer the ambulatory assessments

of emotional states, had active pacemaker pacing during the 24-hour Holter ECG, or had any other cardiac arrhythmias that interfered with HRV analyses.

As shown in Figure 1, a total of 246 patients were approached for participation in the OPTIMIZE study, and 149 (61%) agreed to participate. The current investigation includes 26 patients (18% of the total sample) who agreed to take part in the additional 24-hour ECG, symptom, and emotional state recordings. Supplementary Table ST1 provides data comparing the 26 patients who took part in this sub-study with the 123 patients who did not participate and shows no significant differences in demographic and clinical variables between the groups.

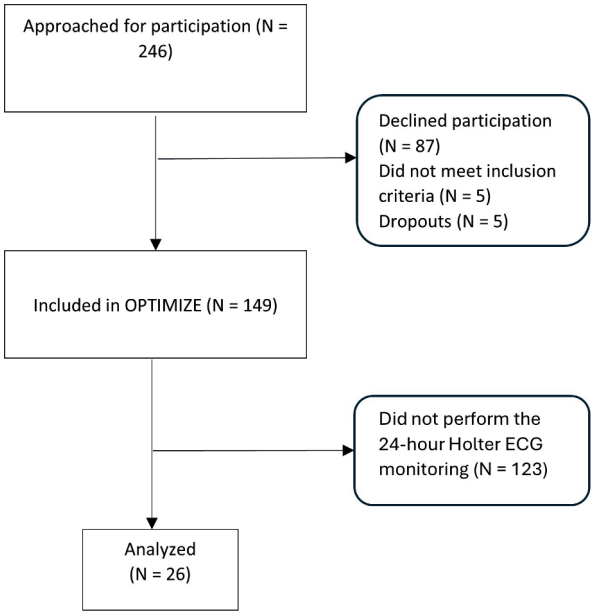


Figure 1. Flowchart of participant inclusion.

Ethical aspects

The study was conducted in accordance with the Helsinki Declaration and was approved by the local Medical Ethics Committee (METC-Brabant NL81600.028.22 / P2234). All participants gave written informed consent before taking part in the study.

Procedure

Patients were informed about the project by the scheduling office of the Institute Verbeeten 2 to 5 days before MPI diagnostic testing. A research team member approached patients on the day of the first diagnostic testing for informed consent. The overall study also included detailed monitoring of psychological well-being and symptoms during the diagnostic MPI testing procedure, and half of the patients were randomised to receive supportive coaching. These assessments during the MPI diagnostic procedure are not the focus of the present study, and the current analyses focus on the ambulatory assessment of emotional states and HRV during the 24-hour monitoring period that occurred between the first and the second day of diagnostic MPI testing.

The myocardial perfusion imaging procedure took place over two days, with several days in between. At the start of the first diagnostic day, patients were informed about the option to participate in 24-hour monitoring of ECG, cardiac symptoms, and emotional states, a voluntary additional component of the study. Patients could choose whether or not to take part, and their decision had no impact on the diagnostic procedures.

For patients who opted in, ambulatory ECG monitoring was performed during daily life for 24 hours between the two testing days. Patients were asked to keep a digital diary with ecological momentary assessments (EMA) on their smartphone, recording their current 'acute' emotional state, daily activities, and anginal complaints (see below for details). These EMA assessments were then cross-tabulated with the 24-hour ambulatory ECG recordings to determine the associations between emotional states and ECG-derived HRV indices during the same time period.

Ambulatory electrocardiography

A 3-lead ambulatory ECG monitor (GE Health SEER light Global Holter Recorder, Boston, Massachusetts, USA; ISO EN13485:2016) was applied to each participant at the end of the first diagnostic day. A modified trunk-based 7-electrode (Leads 2, 3, and aVF) configuration was used to capture inter-beat-intervals for HRV analysis, cardiac arrhythmias, and/or myocardial ischemia (defined as down-sloping ST-segment depression > 1 minute) following guidelines for optimal electrode placement. The sampling rate of the ECG recordings was 200 Hz.

Participants were instructed to continue their usual daily activities, except for any activities involving water, as the ECG recorder is not waterproof. After the

monitoring period, participants were instructed to remove the ECG electrodes and bring the recorder to the next diagnostic visit day.

The ECG recordings were pre-processed and analysed using the MARS Ambulatory ECG Analysis System in the physiological data processing laboratory ("Gedragsfysiologisch Onderzoekslaboratorium" (GO-Lab)) at Tilburg University, the Netherlands. The QRS complexes were identified automatically, manually verified, and adjusted if necessary. Artifacts associated with premature ventricular complexes and other erratic cardiac rhythms were automatically flagged and manually reviewed. The ECG analyses were supervised by a cardiologist who reviewed the ECGs for cardiac arrhythmias and the onset, duration, and magnitude of ST-segment depression.

Heart rate variability analysis

Heart rate variability measures were assessed over 10-minute time intervals (i.e., 5 minutes preceding and succeeding each EMA assessment for emotional states and cardiac symptoms) and included low-frequency and high-frequency band power, as well as time-domain HRV indices (SDNN and RMSSD), and heart rate. Semi-automatic software (MARS Holter Analysis System Version 6, GE Medical Systems) was used for HRV calculations. All beats corresponding to arrhythmic events, including those immediately preceding and succeeding them, were excluded to ensure that only beats with a normal sinus rhythm were included in the calculation of HRV.

Frequency domain data were obtained using spectral analysis by Fast Fourier Transform to separate R-R intervals and were analysed for low (0.04 to 0.15 Hz) and high (0.15 to 0.40 Hz) frequency bands. The power of each frequency band was logarithmically transformed to avoid the undue influence of extreme values in parametric statistical analyses and expressed in ln (ms^2). Long-term 24-hour time and frequency domain heart rate variability metrics were also obtained.

Ecological Momentary Assessment of emotional states and cardiac symptoms

Throughout the 24-hour monitoring period, participants were asked to complete ecological momentary assessments (EMAs) using a mobile app (Avicenna Data, Avicenna Research, 2025). A total of up to 12 EMA prompts were given, randomly triggered within two-hour intervals, starting one hour after Holter hook-up time and expiring after 90 minutes. Participants were

instructed to keep their smartphones with them at all times and remain alert for EMA notifications, except during sleep.

The assessments included questions regarding the participant's current emotional states, including tension, frustration, sadness, happiness, stress, health-related worry, and fatigue. Participants were also asked to rate the severity of their anginal symptoms and dyspnoea. All questions were rated on a Likert scale from 1 ('not at all') to 5 ('very much'), with participants instructed to base their responses on the preceding 10 minutes. The emotional state was calculated by averaging the scores of tension, frustration, sadness, happiness, stress, health-related worry, and fatigue. Happiness was reverse-coded such that higher scores in all emotions represent a more negative emotional state (potential score range 1-5).

Detection of myocardial ischemia during diagnostic MPI testing

The MPI images were assessed and interpreted by semiquantitative analysis (Summed Stress Score (SSS) and Summed Difference Score (SDS)) and also using visual analysis, as recommended by the American Society of Nuclear Cardiology [24]. The presence or absence of myocardial ischemia, as well as the severity of the perfusion defect, were used for the present analyses (see Chapter 2 for more details).

Demographic measures and clinical data

Demographic measures, including age, sex, and educational level, were retrieved through self-report. Clinical data were obtained from the electronic health records and included cardiac history (i.e., previous myocardial infarction, percutaneous coronary intervention, or bypass surgery) and cardiovascular risk factors (see Table 1 for patient characteristics).

Psychological measures were used to explore the construct validity of the EMA assessments for emotional states during daily life. Levels of anxiety, depressive symptoms, and levels of perceived stress were evaluated using standard questionnaires. The 7-item Generalized Anxiety Disorder Scale (GAD-7) was used to assess levels of general anxiety in the two weeks before participating in the study (Cronbach's α = .88) [25] (Dutch validation [26]. Depressive symptoms were assessed using the Patient Health Questionnaire (PHQ-9) (Cronbach's α = .86) [27] (Dutch validation [28]. The level of perceived stress was assessed using the Perceived Stress Scale (PSS-4) (Cronbach's α = .89) [29] (Dutch validation [30]).

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables and as frequencies (%) for categorical variables. Emotional states were captured during waking hours during the 24-hour recording period. Violin plots are used to display the distribution of the emotional states.

To investigate the association between emotional states with HRV indices, t-tests were used to compare short-term HRV measures between patients with below-average versus above-average negative emotional states aggregated over the 24-hour observation period. Multivariate analyses were conducted using Generalized Estimating Equations (GEE) to account for the repeated assessments within participants. Results of the GEE are presented as regression weights (B) with 95% confidence intervals (CI). Separate GEE models were performed for all short-term HRV indices using restricted maximum likelihood estimation (REML), with average emotional state as a fixed effect, and accounting for repeated measures by modelling time as a repeated factor with an autoregressive covariance structure (AR1) for within-subject correlations. Adjusted models included age, beta-blocker use, presence of ischemia, or time of day as covariates. Additional GEE analyses were used to examine associations between ischemia (presence and severity based on SDS) and HRV. Multivariate GEE models were also used to evaluate the combined association of inducibility of ischemia, emotional states, and HRV indices with cardiac symptoms (anginal complaints or shortness of breath). Sensitivity analyses stratifying for beta-blocker use and sex were also conducted.

Data were analysed using the Statistical Package for the Social Sciences (SPSS, version 28). P-values < 0.05 or 95% confidence intervals (CI) were used to indicate statistical significance.

RESULTS

Patient characteristics

Table 1 displays the demographic and clinical patient characteristics (mean age = 66.5 ± 9.3 years, 7 / 26 (26.9%) women). Inducibility of ischemia during diagnostic MPI testing was found in 7 (26.9%) of the patients.

Table 1. Demographics and clinical patient characteristics

Demographics	N=26
Age (years)	66.5 ± 9.3
Sex (female)	7 (26.9%)
Living alone	4 (15.4%)
College education or higher	6 (23.1%)
Cardiovascular risk factors	
Smoking (current)	3 (11.5%)
BMI (kg/m^2)	28.9 ± 3.7
Hypertension	8 (30.8%)
Cardiac history and medications	
Myocardial infarction	3 (11.5%)
PCI	5 (19.2%)
CABG	3 (11.5%)
Beta-blocker	13 (50%)
ACE Inhibitor	7 (26.9%)
ARBs	3 (11.5%)
MPI-SPECT results	
SRS SSS SDS	1.0 ± 2.5 2.0 ± 4.0 1.0 ± 2.4
Positive for ischemia	7 (26.9%)

ACE inhibitor = Angiotensin converting enzyme inhibitor, ARBs = Angiotensin receptor blockers, BMI = Body mass index, PCI = Percutaneous coronary intervention, SDS = Summed Difference Score, SSS = Summed Stress Score, SRS = Summed Rest Score

Heart rate variability during ambulatory monitoring

The HRV measures and heart rate data are presented in Table 2. A total of 175 10-minute ECG recordings were used to analyse associations with concurrent emotional states and cardiac symptom assessments using EMA diary inputs, with an average of 7.6 ± 1.9 time points per patient. Time of day was significantly correlated with heart rate ($r = -.296$, $p < .001$), but not with any of the HRV indices.

As shown in Table 2, the HRV data averaged over the 175 10-minute epochs corresponded closely to the 24-hour HRV measures. The average 24-hour heart rate was lower than the average 10-minute HRV data because the 24-hour HR measures include assessments obtained during sleep, whereas the

10-minute epochs were only obtained during daytime (to cross-tabulate these values with the EMA assessments).

Table 2. Average 24-hour heart rate variability measures and heart rate.

Heart rate variability	10-minute [1]	24-hour
Frequency domain		
Low frequency (ln(ms^2))	5.7 ± 1.0	5.8 ± 0.8
High frequency (ln(ms^2))	5.0 ± 1.0	5.0 ± 0.8
Time domain		
SDNN (ms)	58.6 ± 26.2	119.9 ± 40.2
RMSSD (ms)	33.4 ± 18.4	35.2 ± 13.0
Heart rate (bpm)	77.1 ± 12.7	73.8 ± 9.6

SDNN = Standard Deviation of Normal to Normal (R-R) intervals, RMSSD = Root Mean Square Successive Difference, [1] = averaged over 175 10-min ECG recordings in 26 patients

Emotional states during ambulatory monitoring

The average emotional state score for all EMA diary inputs was 1.7 ± 0.5 (possible score range 1-5). Figure 2 shows violin plots for each emotion across all patients and measurements. Overall, patients reported low scores on negative emotions with low variability and moderate levels of happiness. The average time of the first EMA response of the day, which corresponds to the wake-up time, was 8:31 AM (range 4:01-10:12 AM).

To determine construct validity of the EMA assessments of negative emotions, the associations with standard questionnaires that assess psychological constructs relevant to negative affect (anxiety, depressive symptoms, and perceived stress) were evaluated. The mean emotional response across all diary inputs for each patient was significantly correlated with anxiety ($r = .618$, $p < .001$), depressive symptoms ($r = .703$, $p < .001$), and perceived stress ($r = .515$, $p = .007$).

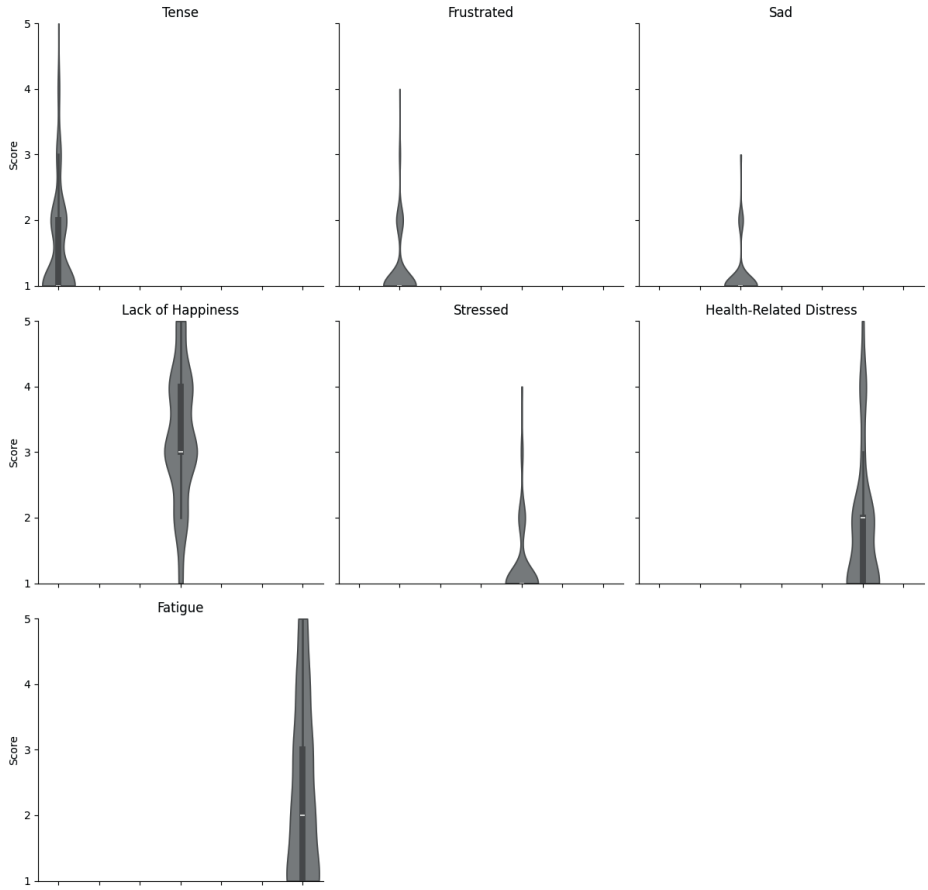


Figure 2. Violin plots showing the distribution of individual emotions from the ecological momentary assessment. Happiness was reverse-coded so that higher scores represent less happiness. The vertical axes represent the emotion rating on a 5-point scale, and the horizontal axis displays the occurrence of the different emotional states.

Associations between emotional states and heart rate variability during daily life

Patients with above-average negative emotional states during daily life exhibited lower low-frequency (Cohen's d = 0.458, p = 0.006), reduced SDNN (Cohen's d = 0.358, p = .030), and an elevated heart rate (Cohen's d = -.425, p = .010) compared to those with below-average levels of negative emotions.

Results from the GEE models, which take the repeated assessments within participants into account, also revealed significant associations between

emotional states and low-frequency power (B = −0.437 [95% CI −0.791; −0.083], p =.015), SDNN (B = −11.338 [95% CI −17.652; −5.025], p <.001) and heart rate (B = 6.074 [95% CI 0.652; 11.496], p =.028). Analyses adjusting for age, beta-blocker use, presence of ischemia, and time of day (each covariate evaluated in a separate model) yielded the same pattern of results as the main unadjusted models.

Myocardial ischemia as related to emotional states and heart rate variability during daily life

Inducibility of myocardial ischemia was detected in seven patients based on the MPI analyses, and the mean SDS score was 1.0 ± 2.4. In contrast, ST-segment depression indicative of myocardial ischemia was not present during the 24-hour ECG monitoring period.

No associations were found between the inducibility of ischemia or the magnitude of perfusion defects based on SDS values and emotional states during daily life (B = −0.001 [95% CI −0.075; 0.074], p =.989, and B = −0.005 [95% CI −0.019; 0.008], p =.409, respectively).

To examine associations between myocardial ischemia and HRV, both within-subjects and between-subjects analyses were conducted. Within-subjects analyses on the repeated 10-minute HRV intervals did not show significant associations between SDS and short-term HRV indices (all p >.100), whereas higher SDS values were associated with a lower heart rate during daily life (B = −1.439 [95% CI −2.274; −0.604], p <.001). Between-subjects analyses revealed that the severity of perfusion defects (SDS) was negatively correlated with 24-hour low-frequency power (r = −.419, p =.033) but not with heart rate or other HRV indices.

The combined association of ischemia, ambulatory emotional states, and heart rate variability with cardiac symptoms

Patients reported angina and dyspnoea with a mean score of 1.4 ± 0.7 for both symptoms (possible score range 1–5). Time of day was not associated with any of the symptoms (p = .415 and p = .510, respectively).

Negative emotional states were significantly associated with anginal complaints (B = 0.167 [95% CI 0.067; 0.268], p <.001) and shortness of breath (B = 0.136 [95% CI 0.071; 0.202], p <.001). These associations remained significant when adjusting for the presence of inducible ischemia based on MPI.

Results from the GEE models showed a significant inverse association between low-frequency HRV and anginal symptoms (B = −0.287 [95% CI −0.541; −0.034]; p =.026) and SDNN (B = −8.823 [95% CI −13.531; −4.116], p <.001), and a positive association of heart rate with anginal complaints (B = 5.930 [95% CI 1.895; 9.966], p =.004). Shortness of breath was negatively associated with SDNN only (B = −6.830 [95% CI −11.918; −1.741], p =.009).

When emotional states, HRV indices, and inducibility of ischemia were included in one model to predict anginal complaints, both negative emotional states (B = 0.449 [95% CI 0.093; 0.805], p = .013) and heart rate (B = 0.015 [95% CI 0.007; 0.022], p <.001) were significantly associated with anginal complaints. Emotional states (B = 0.445 [95% CI 0.258; 0.652], p <.001) along with SDNN (B = −0.005 [95% CI −0.008; −0.002], p <.001) were also significantly associated with dyspnoea in the model that also included ischemia based on MPI.

Sensitivity and exploratory analyses

Sensitivity analyses stratified by beta-blocker use revealed that the association between negative emotional states and low-frequency power remained significant in patients not using beta-blockers (B = −0.606 [95% CI −1.037; −0.174], p =.006), but not in those on beta-blockers (B = −0.167 [95% CI −.566; 0.231], p =.410). In patients not using beta-blockers, inducible ischemia was significantly associated with low-frequency HRV (B = 0.783 [95% CI 0.051; 1.516], p =.036), high-frequency HRV (B = 1.254 [95% CI 0.703; 1.804], p <.001), SDNN (B = 19.384 [95% CI 1.564; 37.205], p =.033), and RMSSD (B = 10.646 [95% CI 0.682; 20.611], p =.036). These associations were absent in patients on beta-blockers.

Among women, emotional states were significantly associated with low-frequency (B = −0.592 [95% CI −0.855; −0.328], p <.001) and SDNN (B = −13.602 [95% CI −19.370; −7.833], p <.001). These associations were not observed in men (all p >.200). For women only, significant associations were observed between SDS and both low-frequency power (B = −0.501 [95% CI −0.748; −0.254], p <.001) and SDNN (B = −11.993 [95% CI −16.392; −7.593], p <.001).

This study included fatigue as one of the components of ambulatory negative emotional states because fatigue is one of the key expressions of psychological distress [31]. When analysing fatigue separately, it was found that this feeling was rated higher than most other symptoms (see Figure 2 (average score of 2.4 ± 1.3)). When omitting fatigue from the emotional state score, the GEE revealed significant findings for the association between negative emotions (not including fatigue) and heart rate (B = 6.422, [95% CI 1.073; 11.772], p =

.019), but not for the HRV indices. Fatigue by itself was significantly associated with low-frequency power (B = -0.185 [95% CI -0.342; -0.028]; p =.021) and SDNN (B= -5.958 [95% CI -8.867; -3.048], p <.001), but not with heart rate.

DISCUSSION

The present study shows that negative emotional states during daily life are associated with lower heart rate variability indices in patients with suspected ischemic heart disease. This investigation is innovative because digitally time-stamped EMAs were used to assess emotional states and cardiac symptoms that were aligned with continuous ECG recordings. The EMA methodology enables the investigation of the short-term autonomic responses to real-time emotional states. Negative emotional states and some of the HRV indices were also associated with cardiac symptoms such as angina pectoris and dyspnoea during daily life, which was independent of the inducibility of ischemia observed during the MPI diagnostic testing. These findings suggest that momentary negative emotional responses may acutely disrupt autonomic regulation, thereby contributing to physiological strain and cardiac symptoms. The results highlight the value of capturing "in-the-moment" emotional states for understanding autonomic function and cardiovascular risk.

The current study demonstrates a relationship between acute negative emotions and autonomic regulation. Specifically, heightened negative emotional responses were associated with reductions in low-frequency power, as well as SDNN. Low-frequency power is commonly understood to primarily reflect baroreflex-mediated modulation of cardiac autonomic outflow [32]. Therefore, lower low-frequency power may reflect impaired baroreflex control and decreased sensitivity to changes in blood pressure and volume [33]. Reductions in SDNN may reflect a broad impairment in autonomic flexibility [19]. These findings suggest that acute negative emotions can diminish autonomic regulatory capacity. This pattern is consistent with the neurovisceral integration model, which posits that a shared set of neural structures is involved in both autonomic and emotional regulation [34]. In the current context, lower HRV may reflect reduced adaptability of these neural structures, resulting in less efficient emotional and physiological regulation. Elevated negative emotional states, especially when not effectively regulated, can potentially increase strain on the cardiovascular system through dysregulated autonomic activity. Specifically, a shift towards sympathetic activity increases heart rate, blood stroke volume, and peripheral resistance,

and is predictive of CAD and other cardiovascular disease outcomes [11, 35]. The present study did not find associations between negative emotional states and HRV indices of reduced parasympathetic activity, such as high-frequency HRV or RMSSD, which is not consistent with prior studies [36, 37]. Importantly, the experienced negative emotions reported in this study were generally mild to moderate, highlighting that even moderate emotional distress can have a significant impact on autonomic modulation.

Heart rate variability was not strongly associated with the presence of myocardial ischemia as documented during diagnostic MPI testing. The only HRV index associated with ischemia was low-frequency power, which was inversely associated with more perfusion defects (i.e., higher summed difference scores). This finding might reflect reduced baroreceptor sensitivity and autonomic modulation as risk factors for myocardial ischemia [32]. A previous study found that lower HRV was associated with a 2-fold increased likelihood of myocardial ischemia, even after adjusting for CAD risk factors and exercise stress test results [38]. Although the study focused on patients with low to intermediate CAD risk, it highlights the potential clinical utility of HRV in enhancing the pretest probability of myocardial ischemia [9, 39]. Future research is warranted to clarify for which patients and in which contexts HRV may provide additional diagnostic value.

Cardiac symptoms, including angina pectoris and dyspnoea, were associated with negative emotional states and also with some of the HRV indices. These findings suggest a potential pathway in which negative emotional states contribute to diminished autonomic function, which may lead to physiological strain on the cardiovascular system, triggering symptoms such as angina and dyspnoea. It is possible that a bidirectional relationship exists, in which heightened emotional responses increase the likelihood of experiencing cardiac symptoms [40], and the occurrence of such symptoms may, in turn, elicit negative emotional responses. More research is warranted to disentangle the time-trajectories of these bidirectional associations.

The current study has several strengths and limitations. A primary limitation is the relatively small sample size. However, this limitation is partially mitigated by the use of the 175 repeated measures through ecological momentary assessments. Additionally, the use of a bipolar three-lead placement may have limited the detection of ST-segment depression during daily life, which, combined with the low incidence of myocardial ischemia in the sample, could have reduced the ability to evaluate associations between HRV and ischemia. Furthermore, because of the observational design, causal

relationships between emotional responses, HRV, and cardiac symptoms cannot be determined. Despite these limitations, the study has several strengths. The use of real-time and simultaneous assessments of emotional responses, HRV, and cardiac symptoms provides a detailed view of natural fluctuations in emotional and physiological states. This methodology enhances ecological validity and enables the study of psychophysiological processes in daily life, which is highly relevant to patients with cardiovascular disease. Another strength of this investigation is that assessments were obtained in the week prior to MPI diagnostic testing, ensuring a current assessment of the inducibility of myocardial ischemia in the present sample.

In conclusion, the present study demonstrates that higher levels of negative emotions during daily life are associated with reduced HRV indices that reflect diminished autonomic regulatory capacity. In addition, negative emotional states and some of the HRV measures were associated with more severe cardiac symptoms during daily life. Together, these findings point to a complex interplay between emotional states and autonomic regulation, which is relevant to cardiac symptoms and potentially also the risk of long-term cardiovascular events.

ACKNOWLEDGMENT

The authors would like to thank all contributing patients for their participation in the OPTIMIZE study. We also thank nuclear physicians Dr. van Dijk, Dr. Pauw, Dr. Pijpers, and the entire staff of the Nuclear Medicine department of the Institute Verbeeten for their work and support during this study.

REFERENCE LIST

1. Edmondson, D., et al., Emotional triggers in myocardial infarction: do they matter? European Heart Journal, 2012. 34(4): p. 300-306.
2. Culić, V., Eterović, D., and Mirić, D. Meta-analysis of possible external triggers of acute myocardial infarction. Int J Cardiol, 2005. 99(1): p. 1-8.
3. Nawrot, T.S., et al., Public health importance of triggers of myocardial infarction: a comparative risk assessment. Lancet, 2011. 377(9767): p. 732-40.
4. Bhattacharyya, M.R., et al., The long-term effects of acute triggers of acute coronary syndromes on adaptation and quality of life. Int J Cardiol, 2010. 138(3): p. 246-52.
5. Smeijers, L., et al., Anxiety and anger immediately prior to myocardial infarction and long-term mortality: Characteristics of high-risk patients. J Psychosom Res, 2017. 93: p. 19-27.
6. Tsao, C.W., et al., Heart Disease and Stroke Statistics—2022 Update: A Report From the American Heart Association. Circulation, 2022. 145(8): p. e153-e639.
7. Kop, W.J., et al., Changes in heart rate and heart rate variability before ambulatory ischemic events(1). J Am Coll Cardiol, 2001. 38(3): p. 742-9.
8. Pozzati, A., et al., Transient sympathovagal imbalance triggers "ischemic" sudden death in patients undergoing electrocardiographic Holter monitoring. J Am Coll Cardiol, 1996. 27(4): p. 847-52.
9. Shah, A.S., et al., Alterations in heart rate variability are associated with abnormal myocardial perfusion. International Journal of Cardiology, 2020. 305: p. 99-105.
10. Bigger, J.T., et al., Autonomic nervous system activity during myocardial ischemia in man estimated by power spectral analysis of heart period variability. The American Journal of Cardiology, 1990. 66(4): p. 497-498.
11. Borchard, U., The Role of the Sympathetic Nervous System in Cardiovascular Disease. J Clin Basic Cardiol, 2001. 4.
12. Krantz, D.S., et al., Mental stress as a trigger of myocardial ischemia and infarction. Cardiol Clin, 1996. 14(2): p. 271-87.
13. Dütsch, M., et al., Cardiovascular autonomic function in poststroke patients. Neurology, 2007. 69(24): p. 2249-2255.
14. Dekker, J.M., et al., Low Heart Rate Variability in a 2-Minute Rhythm Strip Predicts Risk of Coronary Heart Disease and Mortality From Several Causes. Circulation, 2000. 102(11): p. 1239-1244.
15. Gerritsen, J., et al., Impaired Autonomic Function Is Associated With Increased Mortality, Especially in Subjects With Diabetes, Hypertension, or a History of Cardiovascular Disease: The Hoorn Study. Diabetes Care, 2001. 24(10): p. 1793-1798.
16. McCraty, R., et al., The effects of emotions on short-term power spectrum analysis of heart rate variability. Am J Cardiol, 1995. 76(14): p. 1089-93.

17. Kreibig, S.D., Autonomic nervous system activity in emotion: a review. Biol Psychol, 2010. 84(3): p. 394-421.

18. Lucini, D., et al., Impact of chronic psychosocial stress on autonomic cardiovascular regulation in otherwise healthy subjects. Hypertension, 2005. 46(5): p. 1201-6.

19. Shaffer, F., and Ginsberg, J.P. An Overview of Heart Rate Variability Metrics and Norms. Frontiers in Public Health, 2017. 5.

20. Montano, N., et al., Heart rate variability explored in the frequency domain: a tool to investigate the link between heart and behavior. Neurosci Biobehav Rev, 2009. 33(2): p. 71-80.

21. Kleiger, R.E., Stein, P.K., and Bigger, J.T. Jr. Heart rate variability: measurement and clinical utility. Ann Noninvasive Electrocardiol, 2005. 10(1): p. 88-101.

22. Umetani, K., et al., Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. J Am Coll Cardiol, 1998. 31(3): p. 593-601.

23. Roovers, T., et al., Psychological well-being and the effects of supportive coaching during SPECT myocardial perfusion imaging in patients with suspected ischemic heart disease. Journal of Psychosomatic Research, 2025. 197: p. 112355.

24. Hachamovitch, R., Clinical Value of Combined Perfusion and Function Imaging in the Diagnosis, Prognosis, and Management of Patients with Suspected or Known Coronary Artery Disease, in Clinical Gated Cardiac SPECT. 2006. p. 189-215.

25. Spitzer, R.L., et al., A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med, 2006. 166(10): p. 1092-7.

26. Donker, T., et al., Quick and easy self-rating of Generalized Anxiety Disorder: validity of the Dutch web-based GAD-7, GAD-2 and GAD-SI. Psychiatry Res, 2011. 188(1): p. 58-64.

27. Kroenke, K., Spitzer, R.L., and Williams, J.B. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med, 2001. 16(9): p. 606-13.

28. Zuithoff, N.P.A., et al., The Patient Health Questionnaire-9 for detection of major depressive disorder in primary care: consequences of current thresholds in a crosssectional study. BMC Family Practice, 2010. 11(1): p. 98.

29. Lee, E.H., Review of the Psychometric Evidence of the Perceived Stress Scale. Asian Nursing Research, 2012. 6(4): p. 121-127.

30. van Eck, M., et al., The effects of perceived stress, traits, mood states, and stressful daily events on salivary cortisol. Psychosom Med, 1996. 58(5): p. 447-58.

31. Fan, J., et al., Effects of mindfulness and fatigue on emotional processing: an event-related potentials study. Front Behav Neurosci, 2023. 17: p. 1175067.

32. Goldstein, D.S., et al., Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. Exp Physiol, 2011. 96(12): p. 1255-61.

33. Salah, H.M., et al., Baroreflex Function in Cardiovascular Disease. Journal of Cardiac Failure, 2025. 31(1): p. 117-126.

34. Thayer, J.F., et al., Heart Rate Variability, Prefrontal Neural Function, and Cognitive Performance: The Neurovisceral Integration Perspective on Self-regulation, Adaptation, and Health. Annals of Behavioral Medicine, 2009. 37(2): p. 141–153.

35. Fang, S.C., Wu, Y.L., and Tsai, P.S. Heart Rate Variability and Risk of All-Cause Death and Cardiovascular Events in Patients With Cardiovascular Disease: A Meta-Analysis of Cohort Studies. Biological Research For Nursing, 2020. 22(1): p. 45–56.

36. Kim, H.G., et al., Stress and Heart Rate Variability: A Meta-Analysis and Review of the Literature. Psychiatry Investig, 2018. 15(3): p. 235–245.

37. Martens, E.J., et al., Depression and anxiety as predictors of heart rate variability after myocardial infarction. Psychol Med, 2008. 38(3): p. 375–83.

38. Goldenberg, I., et al., Heart Rate Variability for Risk Assessment of Myocardial Ischemia in Patients Without Known Coronary Artery Disease: The HRV-DETECT (Heart Rate Variability for the Detection of Myocardial Ischemia) Study. J Am Heart Assoc, 2019. 8(24): p. e014540.

39. Lucini, D., and Pagani, M. Heart rate variability, autonomic regulation and myocardial ischemia. International Journal of Cardiology, 2020. 312: p. 22–23.

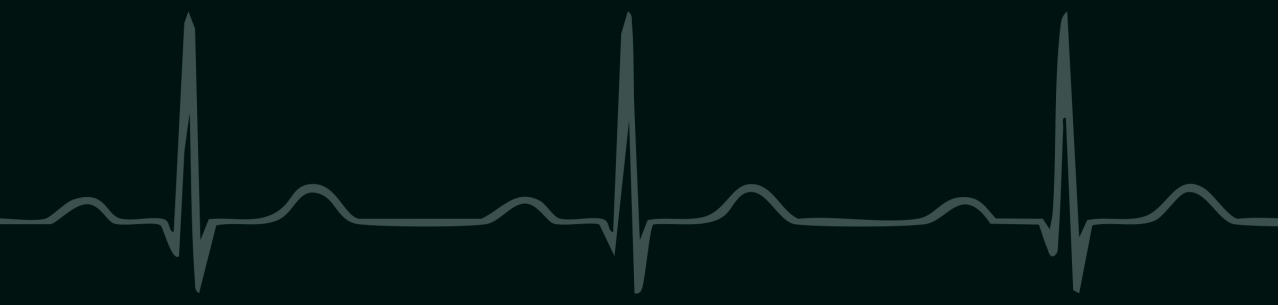
40. Zhang, X., and Xu, H. Prediction of Angina Pectoris Events in Middle-Aged and Elderly People Using RR Interval Time Series in the Resting State: A Cohort Study Based on SHHS. International Journal of Computational Intelligence Systems, 2023. 16(1): p. 10.

SUPPLEMENTARY MATERIAL

Supplementary Table ST1. Baseline demographics and patient characteristics comparing the patients in the present investigation with the overall study sample.

Demographics	ECG N=26	No ECG N= 123	p-value
Age (years)	66.5 ± 9.3	66.9 ± 9.3	.246
Sex (female)	7 (26.9%)	55 (44.7%)	.094
Living alone	4 (15.4%)	29 (23.6%)	.547
College education or higher	6 (23.1%)	23 (18.7%)	.104
Smoking (current)	3 (11.5%)	11 (8.9%)	.881
BMI (kg/m^2)	28.9 ± 3.6	27.7 ± 5.1	.341
Hypertension	8 (30.8%)	50 (40.7%)	.333
Myocardial infarction	1 (3.9%)	13 (10.6%)	.281
Beta-blocker	13 (50%)	56 (45.5%)	.704
ACE Inhibitor	7 (26.9%)	26 (21.1%)	.533
ARBs	3 (11.5%)	25 (20.3%)	.290
PCI	5 (19.2%)	25 (20.3%)	.885
CABG	3 (11.5%)	9 (7.3%)	.480
Atrial fibrillation	3 (11.5%)	16 (13.0%)	.827

Chapter 5



Changes in heart rate variability during an eHealth behaviour change intervention program in patients with cardiovascular disease

Roovers, T., Habibovic, M., Lodder, P., Widdershoven, J.W., Kop, W.J.

The contents of this chapter are published in the International Journal of Cardiology Heart & Vasculature (2024)

ABSTRACT

***Background*:** Cardiovascular disease (CVD) risk is associated with health behaviours such as physical inactivity, dietary habits, and smoking. The autonomic nervous system plays a key role in this association. The present longitudinal study examines whether ECG-based indices of autonomic nervous system activity change during an eHealth-based behaviour intervention program and assesses whether improvements in health behaviours are associated with increases in parasympathetic autonomic nervous system activity.

***Methods*:** Data from the DoCHANGE-2 eHealth-based behaviour intervention study in patients with CVD were analysed for participants with valid ECG recordings (N=58, mean age=58.9 [SD=12.7] years, 21% women). Heart rate variability (indexed as RMSSD) was calculated from home-recorded (40-second) ECGs over 5-day periods at baseline, 3, and 6 months. Health behaviours, clinical, and psychosocial information were obtained from questionnaires and medical records. Data were analysed using linear mixed models and general linear models.

***Results*:** Over the 6-month period, RMSSD decreased significantly, with the lowest values at six months (B=-19.336 [95%CI -36.291; 2.381], p=.026). Health behaviours improved significantly during the active (0-3 months) intervention period (B=13.360 [95%CI 6.931 19.789], p<.001). Higher BMI (B=-.369 [-.739; .000]; p=.05) and older age (B=-.404 [95% CI -.597; - .211]; p<.001) were associated with lower RMSSD across the three timepoints. No consistent associations were found between changes in health behaviours and changes in RMSSD.

***Conclusion*:** This study shows that changes in HRV during an eHealth-based behavioural intervention were not associated with the observed improvements in health behaviours. These findings require replication in larger, well-controlled investigations.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality worldwide, accounting for 20.5 million deaths in 2021. Coronary artery disease (CAD) is the most common clinical manifestation of cardiovascular disease. Behavioural factors such as low physical activity levels, poor dietary habits, and a continued high prevalence of smoking play an important role in CAD incidence and prognosis [1]. Studies show that improving health behaviours can prevent up to 70% of heart diseases, CVD events, and significantly reduce health and economic burden [2]. It has been suggested that health behaviours directly affect CAD pathophysiology by adverse effects on atherosclerotic disease processes [3]. In addition, health behaviours also indirectly affect clinical CAD-related outcomes (e.g., myocardial infarction, stroke, and CVD-related mortality) through adverse effects on the autonomic nervous system (ANS) [4]. Evidence suggests a relationship between cardiac unhealthy behaviours and autonomic dysregulation in patients with CAD [5]. However, there is a knowledge gap in how health behaviour changes are related to autonomic nervous system activity among patients with CAD and other manifestations of cardiovascular disease [6].

Previous studies show that an increased activation of the sympathetic branch and decreased activation of the parasympathetic branch of the autonomic nervous system are associated with adverse cardiovascular prognosis [7]. Parasympathetic nervous system activity plays a role in the regulation of heart rate, stroke volume, and peripheral resistance, and low levels of parasympathetic activity are predictive of CAD and other cardiovascular disease outcomes [8]. The autonomic nervous system is bi-directionally associated with cardiac unhealthy behaviours [5]. Evidence shows that behavioural factors such as insufficient physical activity, poor dietary habits, obesity, tobacco usage, alcohol overconsumption, and drug use are associated with decreased parasympathetic activity resulting in autonomic imbalance, as indicated by reduced HRV values [4, 5, 9, 10]. Behavioural interventions can also alter autonomic dysregulation. For example, increasing physical activity levels, losing weight, and smoking cessation lead to higher parasympathetic activity, resulting in reduced blood pressure, heart rate, and peripheral resistance [11-13]. Autonomic dysregulation might therefore be a common pathway linking modifiable risk factors to cardiovascular disease progression [5]. However, these associations have not been studied in the setting of clinical behavioural interventions in patients with cardiovascular disease.

The link between autonomic regulation and health behaviours can be explained by common neurobehavioural mechanistic factors. Both processes are regulated by components of the central autonomic network (CAN), a system of brain structures that is critical for goal-directed behaviour, adaptability, and health [14]. The CAN regulates the cardiac system through the innervation of sympathetic and parasympathetic neurons, and the output from the CAN is therefore directly related to HRV indices [15]. The CAN is also thought to play a role in health behaviour through executive functioning, which is the process of effortful and strategically directed behaviour in pursuit of future goals. Specifically, healthy behaviours often come with short-term costs and longer-term benefits, and a larger capacity for executive functioning could therefore improve the chance of initiation and maintenance of healthy behaviours [16]. A recent meta-analysis also found a direct association between HRV indices and executive functioning [17]. Together, these studies form a plausible mechanistic explanation for the association between autonomic regulation and health behaviours.

Autonomic nervous system activity, particularly changes in the activity of the parasympathetic branch, can be measured using heart rate variability (HRV) indices [18]. The extent of changes in inter-beat intervals reflects activation of the parasympathetic nervous system. Validated measures of HRV-based indices of autonomic nervous system activity include the high-frequency range (0.15 to 0.40 Hz), the standard deviation of successive inter-beat intervals (SDNN), and the root mean square of successive differences (RMSSD) [19-21].

The present study examines whether HRV indices of autonomic nervous system activity change over time during an eHealth-based behaviour intervention. Furthermore, the association of changes in HRV throughout the intervention with changes in health behaviours will be assessed. It is hypothesised that HRV values will increase throughout the health behaviour intervention program. Additionally, it is expected that the magnitude of improvements in health behaviours will be positively associated with the magnitude of increases in HRV indices of parasympathetic activity. Unique to this study is that HRV indices are obtained in the patient's home environment using multiple repeated measures during and following the active behavioural intervention phase.

METHODS

Data for this study were collected as part of the multicentre randomised controlled trial Cardiac Health Advanced New Generation Ecosystem 2 (Do CHANGE 2). The Do CHANGE 2 trial aimed to evaluate a multi-component digital behavioural intervention for lifestyle change in patients with cardiovascular disease and is described in more detail elsewhere [22]. The current investigation is a secondary analysis of the Do CHANGE 2 trial. The effect of the intervention on physiological data, including patients' ECG, was registered as a secondary 'other' outcome, however, heart rate variability was not mentioned specifically in the trial pre-registration.

Patients

Patients were recruited between June 2017 and December 2017 in the Netherlands (Elisabeth-TweeSteden Hospital), Spain (Badalona Serveis Assistencials), and Taiwan (Buddhist Tzu Chin Dalin General Hospital). Data from Spain and the Netherlands were used for the current study because of the lack of ECG measures in the Taiwan sample. The study sample consisted of patients diagnosed with hypertension (systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 at two different measurements 1-2 minutes apart and after 3-5 minutes in a sitting position), coronary artery disease (CAD) (having experienced angina pectoris, a myocardial infarction, percutaneous coronary intervention and/or coronary artery bypass surgery), or symptomatic heart failure (HF) (New York Heart Association Class I-IV).

In addition to having CVD, inclusion criteria were: aged 18 to 75 years, and 2 or more of the following risk factors: positive family history of cardiovascular disease, cholesterol levels indicating dyslipidaemia, current smoking status, diabetes mellitus, sedentary lifestyle, and/or psychosocial risk factors (i.e., depression or anxiety levels above clinical cut-off values). Patients were excluded from participating if they did not have access to the Internet or a compatible smartphone, did not have sufficient knowledge of the local language (i.e. Spanish or Dutch), suffered from life-threatening co-morbidities, had a life expectancy of less than one year, were on the waiting list for heart transplantation, if major cognitive impairments interfering with completing questionnaires were present, or had a history of psychiatric disorder other than mood or anxiety disorders.

An initial pool of 557 potential participants was approached to take part in the Do CHANGE 2 study. After checking eligibility criteria and ruling out patients who declined to participate, the study sample consisted of 150

participants. Electrocardiograms (ECGs) were only obtained in the patients who participated in the active intervention group (N = 74). Based on the examination of the ECGs (see below for details), valid ECGs were available for 58 of the 74 participants (78.4%)(see Supplementary Figure SF1 for a flow-chart of participant eligibility for the present analysis).

Ethical aspects

The Do Change study is registered with ClinicalTrials.gov under protocol NCT:03178305, was approved by the Medical Ethics Committee (METC-Brabant NL61660.028.17/P1726), and is in line with the Helsinki Declaration. All participants signed the informed consent form prior to data collection.

Procedure

Patients who met the inclusion criteria were invited to participate by their treating cardiologist or cardiac nurse. They were provided information (verbally and in writing) regarding the study and given 10 days to consider their participation. Participants were contacted by telephone, and if interested in participation, a hospital visit was scheduled to sign the informed consent form and complete the first set of questionnaires (baseline assessments).

Subsequently, participants were randomised to either the control or intervention group. The present study only focuses on participants of the active intervention group because repeated ECGs were not obtained in the care-as-usual control group. Participants assigned to the intervention group received information on the intervention program, including the accompanying devices [22].

The active intervention phase took place during the first three months (first follow-up) and included the following monitoring devices: CarePortal, Moves app, Beddit, Fitbit, blood pressure monitor, COOKiT, and Vire (the Do CHANGE app). In addition, patients received the Do Something Different behavioural program developed to change behavioural habits and flexibility, and subsequently change habits associated with an unhealthy lifestyle and psychological distress. The behavioural program helps patients to step out of their comfort zone by sending behavioural prompts (Do's) such as "Explore more today instead of going the same old way, take a different route. Look around, spot ten things you wouldn't see on your usual journey." Such prompts can help break old, unhealthy habits and increase flexibility in patients, which facilitates behaviour change. Patients received a total of 32 Do's during the active intervention phase. In addition, patients received 16 "ToDo's" based on

their current functioning (e.g., if the Fitbit showed that the patient was not exercising enough, participants received a "Do" based on that information). Depending on the patient's preference, Do's were sent through the CarePortal, the Do CHANGE app, or via short message services [22, 23].

After completion of this initial phase, patients in the active treatment condition were instructed to continue using the monitoring devices for an additional three-month period (second follow-up), but no additional intervention cues were provided during that period. Hence, data were collected at baseline, 3-month, and 6-month follow-up.

Electrocardiogram and heart rate variability analysis

Participants randomised to the intervention group received the CarePortal, a clinically certified portable device (ISO EN13485:2016), which was used to assess daily physical symptoms and an electrocardiogram. The CarePortal, a handheld device, includes an electrocardiogram recorder with a standard lead I ECG with a sampling rate of 500 Hz. Using the CarePortal, participants were asked to take an ECG of ± 40 seconds every day for 6 months (210 days). Participants were asked to sit comfortably at the same time each day while holding the CarePortal in both hands while the measure was assessed. From these data, a total of 15 ECGs per participant were selected for analysis, five successive recordings at each of the three time points (i.e., baseline, three months, and six months). At baseline, the first five recordings were selected. Recordings for the follow-up time points were selected by taking recordings three and six months after the date of the first recording at baseline.

The ECGs were pre-processed and analysed using BIOPAC Acqknowledge (Version 5) [24]. The QRS complexes were identified automatically, checked manually, and removed if necessary. To avoid artifacts related to premature ventricular complexes or other manifestations of erratic cardiac rhythm, it was made sure that the ECG recordings were in normal sinus rhythm. If an HRV measure could not be obtained because of a noisy signal, premature ventricular complexes, or arrhythmias, the recording was replaced with that of the next day. A measure was excluded if a valid ECG recording was not obtained within two weeks of the first date of the time point. The ECG analyses were supervised by a cardiologist, and only ECGs in sinus rhythm of at least 30 seconds were included. The root mean square of successive differences (RMSSD, expressed in ms) was calculated (time domain analysis) over the complete 30 to 40-second ECG signal using the BIOPAC Acqknowledge HRV function [24]. Several studies have validated the use of these (ultra)

short-term ECG recordings for HRV time-domain measures [25-27]. These investigations demonstrate that short-duration ECG segments of 30-40 seconds are a reliable and accurate alternative to 5-minute recordings. Higher values of RMSSD reflect higher activation of the parasympathetic component of the autonomic nervous system [28]. Heart rate measures (in beats per minute: bpm) were based on the inter-beat interval of the complete 40-second recording.

Health behaviours

Health behaviours were evaluated using the Health Promoting Lifestyle Profile (HPLP) questionnaire, which was completed at baseline, three, and six months. The HPLP has a total of 52 items [29] with a Likert scale, ranging from 1 (never) to 4 (routinely). The composite score of the HPLP questionnaire ranged from 52 to 208, with a higher score indicating better health behaviours. The HPLP has six subscales, capturing various domains of health. These subscales include physical activity (eight items, range 8 - 32), nutrition (nine items, range 9 - 36), stress management (eight items, range 8 - 32), health responsibility (nine items, range 9 - 36), spiritual growth (nine items, range 9 - 36), and interpersonal relationships (nine items, range 9 – 36). The estimated reliability of the HPLP was excellent in the present study (McDonald's Omega = .92). Because some of the HPLP subscales reflect domains of mental well-being rather than health behaviours per se, exploratory analyses were also conducted for each of the HPLP subscales separately. Smoking behaviour was retrieved through self-report.

Demographic and clinical data

Demographic data, including age, sex, marital status, and level of education, were retrieved through self-report. Clinical data were retrieved from the electronic health records, including primary diagnosis, Charlson Comorbidity Index, diagnosed with Diabetes Mellitus, body mass index (BMI in kg/m^2), and blood pressure (mmHg) (measured during the most recent outpatient visit).

Statistical analysis

Data are presented as mean and standard deviation (SD) (continuous variables) or frequencies and percentages (categorical variables). Measures of RMSSD, heart rate, health behaviours (HPLP), BMI, and smoking status were assessed at each timepoint, and change scores were evaluated by computing the difference between the mean values at baseline and after three months as well as between three and six months. For exploratory purposes, the subscales of

the HPLP, including physical activity, nutrition, stress management, spiritual growth, health responsibility, and interpersonal relationships, were also analysed separately from the HPLP total score.

To evaluate whether RMSSD and heart rate levels changed over time (hypothesis 1), linear mixed models were used (comparing baseline with 3-months and 6-months). Linear mixed models were used to account for nesting of the five repeated assessments at each of the three time points within participants (using covariance pattern analysis). The Bayesian Information Criterion (BIC) was used for model evaluation. Results are presented as regression weights (B) with 95% confidence intervals (CI). In addition, general linear modelling was used to test for change over time in the HPLP score, BMI, and smoking status, as well as the HPLP subscales as these only consisted of one measure per timepoint in contrast to the 5 nested timepoints of the RMSSD measures. The main parameter of interest in these analyses was the main effect of Timepoint. Mauchly's test was used to assess the assumption of sphericity, and if not met, Greenhouse-Geisser corrections were applied. Post hoc analysis with Bonferroni correction was performed to adjust for multiple testing while assessing differences between time points. For data presentation purposes, the mean values of the five within-timepoint measurements are also displayed for RMSSD and heart rate.

The associations between changes in health behaviour-related measures and changes in RMSSD and heart rate (hypothesis 2) were investigated using unadjusted bivariate analysis and multivariate models. Pearson correlations were used to examine the association between, on the one hand, the mean values of RMSSD at baseline and change scores at three and six months, and on the other hand, the HPLP composite and subscale scores, smoking status, and BMI, and their change scores. After the bivariate correlation analyses, multivariate analyses were conducted using linear mixed models. The base model included timepoint, measurement, health behaviours (HPLP), and the interaction between timepoint and HPLP as fixed effects. The adjusted model included smoking, BMI, age, and sex on top of the base model. An unstructured covariance matrix was used in both models to minimise assumptions related to the residual variance-covariance matrix. A sensitivity analysis was conducted using the base model to evaluate whether the effects differed when stratifying by whether or not patients used beta-adrenergic blocking agents.

All analyses described above for RMSSD were also performed for heart rate as a secondary outcome measure. Data were analysed using the Statistical Package for the Social Sciences (SPSS) software package (Version 27.0) [30].

RESULTS

The mean age of the sample was 58.9 (SD = 12.7) years, and 21% were women. The most prevalent primary diagnoses were hypertension (41.4%) and coronary artery disease (37.9%), and to a lesser extent, heart failure (20.7%). Of the 58 patients, 28 were enrolled in Spain and 30 in the Netherlands. Baseline characteristics are presented in Table 1. Some missing data were encountered in the sample, primarily at the six-month follow-up (six out of 58 (10.3%) patients had missing data for all five ECG recordings at the six-month follow-up).

Table 1. Participant characteristics at baseline.

Variable	Mean (SD) or N(%)
Demographic characteristics	
Age (years)	58.9 (12.7)
Sex (female)	12 (20.7%)
Partner (yes)	49 (84.5%)
Education (years)	14.0 (5.5)
Main diagnosis	
Hypertension	24 (41.4%)
Coronary artery disease	22 (37.9%)
Heart failure	12 (20.7%)
Clinical characteristics	
Charlson Comorbidity Index	1.17 (0.97)
Diabetes Mellitus	16 (27.6%)
Systolic blood pressure (mmHg)	140.1 (23.9)
Diastolic blood pressure (mmHg)	81.2 (14.0)
Risk factors and Medication	
Smoking status (current)	9 (15.5%)
BMI (kg/m^2)	29.64 (4.9)
Beta blockers prescription	32 (55.2%)

Changes in RMSSD and heart rate during the intervention program

Figure 1 shows the average RMSSD and heart rate levels for each measurement at baseline, three, and six months (data for each of the separate 15 time points are shown in Figure 1A). A significant decrease in RMSSD was observed throughout the six-month study period in the linear mixed model analysis ($F(2, 46.47) = 6.95$, $p = .002$) (see Table 2). The RMSSD values were significantly lower at six months compared to baseline ($\Delta = -19.34$ [95% CI -36.29; 2.38]; $p = .026$). Figure 1B shows that the most substantial decrease occurred between the three and six-month timepoint. A statistically significant difference was not observed between baseline and three months, right after cessation of the intervention (Table 2). The differences between the five subsequent measures within each timepoint were not significant (all p-values >.30). No statistically significant changes in heart rate were found (baseline, 3-month, and 6-month HR were: 69.0 (SD = 10.9), 68.8 (SD = 11.2), and 70.2 (SD = 10.2) respectively: $F(2, 50.87) = 2.99$, $p = .059$) (see Supplementary Table ST1).

Table 2. The association of health behaviours with RMSSD using linear mixed-effect modelling.

Predictor	Category	'Base' model [a] BIC = 7103		'Adjusted' model [b] BIC = 6893	
		B [95% CI]	p-value	B [95% CI]	p-value
Timepoints	Baseline	*Reference*			
	3 months	7.09 [-8.08 to 22.26]	.353	7.04 [-8.75 to 22.84]	.375
	6 months	-20.67 [-37.18 to – 4.16]	.015	-19.34 [-36.29 to -2.38]	.026
Measurement	5	*Reference*			
	4	-1.301 [-3.656 to 1.055]	.273	-1.715 [-4.122 to .691]	.159
	3	-2.059 [-4.811 to .693]	.139	-2.115 [-5.029 to .799]	.150
	2	-1.814 [-4.549 to .921]	.188	-2.247 [-5.088 to .595]	.118
	1	-2.426 [-5.177 to .326]	.083	-2.509 [-5.414 to .396]	.089
HPLP		-.05 [-.16 to .05]	.311	-.08 [-.19 to .02]	.113
HPLP x Timepoints	Baseline	*Reference*			
	3 months	-.06 [-.17 to .06]	.331	-.05 [-.17 to .07]	.400
	6 months	.11 [-.01 to .23]	.061	.11 [-.01 to .23]	.074
Age				-.40 [-.60 to -.21]	<.001
Sex				-2.92 [-8.90 to 3.06]	.330
BMI				-.37 [-.74 to .00]	.050
Smoking				1.07 [-3.44 to 5.57]	.639

Data are presented for the 'base' model without covariates and the 'adjusted' model including age, sex, BMI, and smoking as covariates. Results are presented as estimates with 95% confidence intervals and p-values. Sex was coded as 1 = male and 2 = female. [a]The 'base' model for RMSSD included timepoint, measurement, health behaviour (HPLP), and the interaction between timepoint and HPLP as fixed effects. [b]The adjusted model included time-invariant predictors age, sex, and time-varying predictors BMI and smoking.

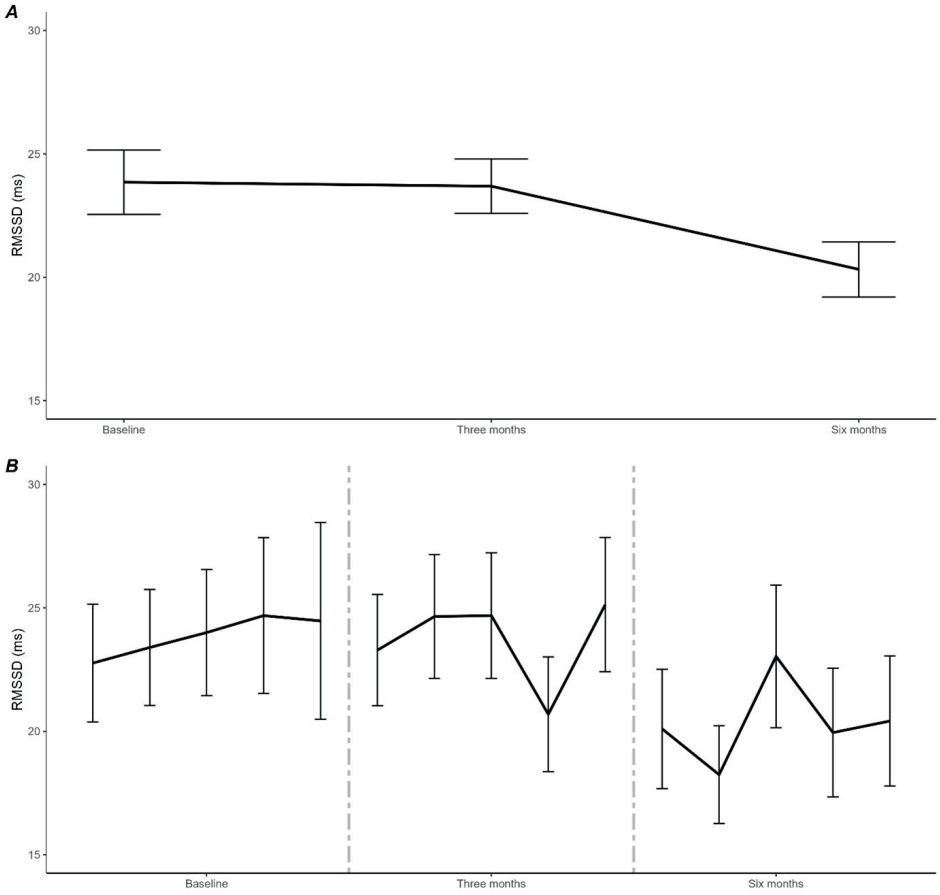


Figure 1. Changes in RMSSD during the behavioural intervention program. (A) RMSSD values for each of the measurements at each time point (in ms); (B) Average RMSSD over 5 days at each time point. Error bars indicate the standard error of the mean.

Association between changes in health behaviour and changes in RMSSD and heart rate

As shown in Figure 2, the HPLP total score improved significantly during the intervention period (Δ = 13.36 [95% CI 6.93; 19.79], p < .001), and a non-significant further improvement occurred from three to six months follow-up (Δ = 2.84 [95% CI -3.36; 9.04], p = .783; overall change over time: F(2, 94 = 8.55, p < .001). Changes in health behaviours (HPLP subscales and total score, BMI, and smoking status) are presented in Supplementary Table ST2. There were significant improvements in all HPLP subscales except physical activity, and no significant changes in BMI and smoking status were found (see Supplementary Tables ST3 and ST4). Post hoc analysis revealed that

these improvements occurred during the active intervention period (baseline to three months), and not during the three to six months follow-up period.

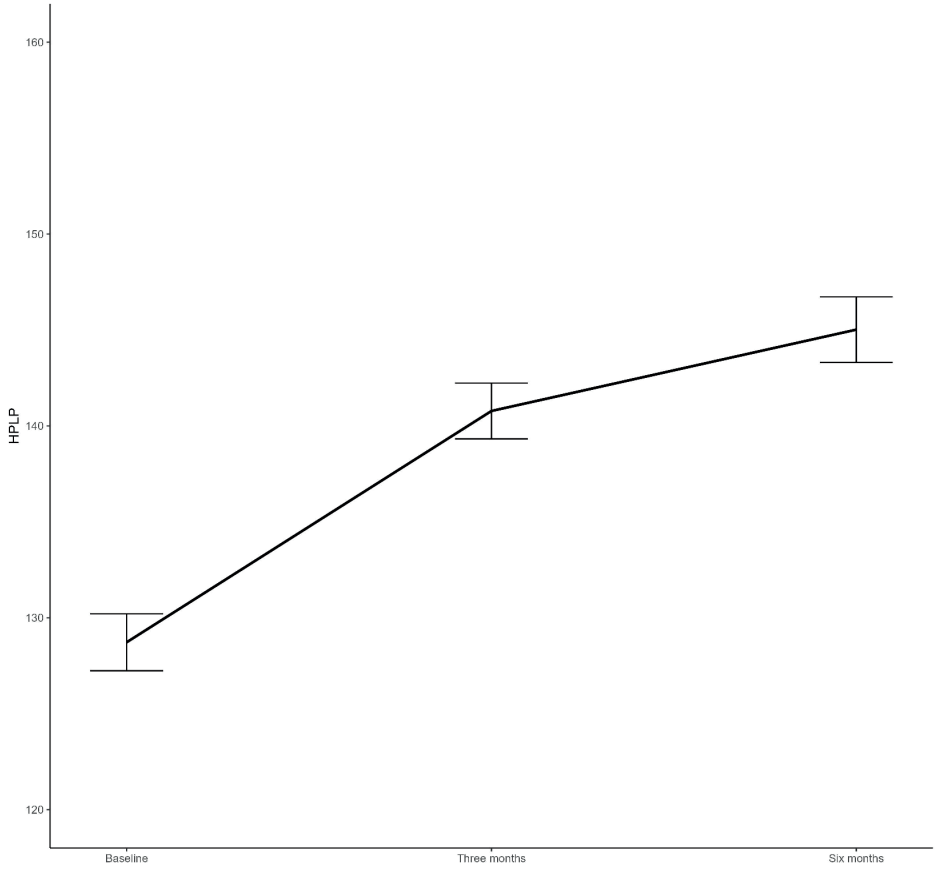


Figure 2. Changes in HPLP total score during the behavioural intervention program. Error bars indicate the standard error of the mean.

The associations between baseline health behaviour-related measures and changes in health behaviour measures (HPLP, BMI, and smoking) with changes in RMSSD and heart rate were first investigated using unadjusted bivariate Pearson correlations. Overall, the correlations were small and in most instances non-significant (see Supplementary Table ST5). The change in RMSSD from three to six months was positively correlated with the baseline HPLP score ($r = .315$, $p = .023$) and specifically with the dietary habit subscale ($r = .280$, $p = .044$). These findings indicate that participants who showed higher HPLP and diet subscale scores showed a less pronounced decrease in

RMSSD during follow-up. A similar positive correlation was observed between smoking at baseline and RMSSD change (baseline – 3 months) (r = .285, p = .03). Participants who did not smoke at baseline appeared to show an increase in RMSSD during the intervention period. The other correlations were not significant (Supplementary Table ST5). The same set of correlation analyses was performed for heart rate and revealed significant correlations between a change in heart rate from baseline to three months and HPLP total score, as well as with changes in HPLP subscale scores over time (see Supplementary Table ST6).

The linear mixed models also indicated that RMSSD was not associated with the HPLP total score (see Table 2 for details). Table 2 also shows that RMSSD was significantly and negatively associated with BMI (B = -.37 [95% CI -.74; .000 ms]; p = .050) and age (B = -.40 [95% CI -.60; -.21 ms]; p < .001). These results suggest that both higher BMI and higher age were associated with lower RMSSD, although the effect sizes were small. No associations of participant sex with changes in RMSSD were found (B = -2.92 [95% CI -8.90; 3.06 ms]; p = .330). No evidence was found for an association of smoking with RMSSD (B = 1.07 [95% CI -3.44; 5.57 ms]; p = .639), even though it is known to be more strongly related to autonomic nervous system activity [31, 32]. Exploratory analysis for the subscales of the HPLP did not reveal any significant associations with RMSSD (see Supplementary Table ST7). Stratifying patients with and without beta blockers revealed other outcomes compared to the main analysis. The parallel model for heart rate revealed a significant association between BMI and heart rate (B = .28 [95% CI .01; .56]; p = .041) and age (B = -.25 [95% CI -4.41; -.08 bpm]; p < .001) (see Supplementary Table ST1), suggesting an overall higher heart rate in patients with a higher BMI as well as a lower heart rate in older patients.

DISCUSSION

This is the first study to assess changes in autonomic regulation throughout a behaviour change program in people with CVD. The active phase of the health behaviour intervention occurred during the first three months of the study, after which participants were followed up for another three months. Results indicate a significant change in autonomic nervous system activity, as indexed by RMSSD. Minimal changes occurred during the active intervention phase (baseline to three months), and a subsequent reduction in RMSSD was observed during the follow-up period after cessation of the active phase of

the intervention (i.e., three to six months). This decrease in RMSSD was less pronounced for patients who, at baseline, engaged in health behaviours that are associated with reduced cardiovascular risk (i.e., higher HPLP scores). However, the improvements in health behaviours during the intervention were not associated with parallel changes in autonomic nervous system activity.

Several studies have established positive effects of individual health behaviours, including physical activity [33], diet [34], and stress management [35] on autonomic function in cardiac samples. However, multiple other studies did not confirm these results [11, 36, 37], and consensus on the effects of these behavioural interventions on autonomic nervous system activity has not been reached. A review of the effects of biobehavioural, medication, or exercise treatments in CAD patients concluded that health behaviour change interventions can improve HRV by a moderate magnitude [6]. However, such associations were not observed in the current study. A possible explanation for this discrepancy could be that the current intervention did not specifically focus on improving physical activity levels. In addition, after the third month, the behaviour change prompts were terminated, and participants only used monitoring devices without behaviour change support. This might have affected their motivation to pursue healthy behaviours in the long term, although this was not reflected by a decrease in HPLP scores, as these scores continued to improve slightly during follow-up. The findings from the study by Broers et al., showing a decrease in step count and activity level after termination of the active phase of the intervention in the DO CHANGE sample, may underline this speculation [38]. Furthermore, pharmacotherapy is known to impact autonomic regulation. In general, medication used for secondary prevention of cardiac events, such as beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and calcium channel blockers, improves autonomic regulation [6, 39, 40]. However, other types of medication often used in cardiovascular disease patients, such as antidepressants [41], have been shown to reduce measures of autonomic regulation in patients with major depression [42] as well as in a healthy sample [43]. Pharmacotherapy was not withdrawn during the study period, and even though no differences were observed for either patients with or without beta-adrenergic blocking agents, other medications could have attenuated the associations between health behaviours and measures of autonomic nervous system activity.

The relationship between autonomic function and health behaviours is likely subject to influence from various psychological and social factors, which are established as contributors to behavioural and physiological risk factors associated with cardiovascular disease. These factors, among others, include

depression, anxiety, optimism, and psychological flexibility [44, 45]. Within the context of HRV, exploring the role of psychological measures associated with the physiological stress response is potentially relevant. For example, there might be a direct connection between an organism's flexibility and autonomic regulation [15, 46–50]. It is therefore plausible to assume a role for flexibility in health behaviour and in its relationship with autonomic regulation and cardiovascular disease. Future studies are needed to delve into the potential role of psychological factors in health behaviour change and autonomic function.

Limitations

The current study has several strengths and limitations. Limitations include the use of self-report measures to assess health behaviours. Furthermore, even though adequate instructions were given, conditions during ECG measurements could not be controlled completely. Measures of HRV are known to be subject to several factors, including time of day, posture, and climatic conditions, among others [51, 52], which could have affected the study results. Furthermore, even though a medical-certified device was used for ECG measurements, it only encompassed a 1-lead ECG. Previous research has demonstrated variations in HRV parameters in different ECG lead configurations [53]. Expert guidelines also recommend 5-minute ECG recordings for HRV analysis [18, 19]. The use of 40-second recordings in the current study could therefore be viewed as a limitation. However, (ultra)short-term recordings have been shown to be a reliable and accurate alternative to 5-minute time-domain measures [25-27]. It is also possible that additional HRV indices (e.g., hf-HRV or DFA) could have revealed stronger associations with health behaviour change. Future studies are needed to explore if other indices of HRV (e.g., frequency domain-based) and/or longer durations of HRV recordings are useful in identifying associations between changes in health behaviours and changes in HRV-based indices of parasympathetic nervous system activity. Furthermore, RMSSD values could partially reflect erratic (disorganised) sinus rhythm, particularly in participants older than 65 years [54, 55]. Detailed analysis of the Poincaré plots of the SD and SD-squared could elucidate this issue, but it is unlikely that this would yield different results, as all ECGs were carefully screened and only selected if they were in normal sinus rhythm. In addition, it is important to acknowledge that the current study is a secondary analysis of the Do CHANGE study on a small and heterogeneous sample, and therefore lacks a dedicated control condition. Results can therefore not be attributed to the intervention, and the absence

of an association between HRV and health behaviours in the current study should not be viewed as evidence of the absence of this relationship in other clinical settings. Finally, the Health Promoting Lifestyle Profile questionnaire does not encompass all relevant health behaviours and also includes several subscales that are not directly relevant to the present research question. This limitation was handled by also evaluating the relevant subscales of the HPLP (e.g., dietary habits and physical activity). A key strength of the present study lies in the comprehensive dataset, featuring multiple measures of RMSSD (15 per patient over a 6-month time period) and the evaluation of health behaviours before a health behaviour intervention, immediately following completion of the active intervention phase, and at six-month follow-up.

Future directions

Future studies should consider the development of a composite score that encompasses all health behaviours (i.e., physical activity, smoking, sleep, nutrition) related to cardiovascular disease and also includes other risk factors (i.e., BMI, cholesterol, blood sugar, blood pressure). Such a comprehensive measure, which has been advocated by the AHA [44], would take into account the known influences individual behaviours have on each other [56] as well as the connection to other risk factors. Such an approach could potentially give more nuanced insights into the relationship between autonomic function and the combined and individual effects of health behaviours [57, 58]. In addition, future studies could benefit from a non-intervention control group and incorporating analyses of more frequent ECG measurements to assess changes in HRV over extended time periods to disentangle early from late-onset changes. One reason for the inconsistencies in prior studies might be the difficulty of measuring health behaviours and the wide variety of measures used. Health behaviours are complex, consisting of individual actions, and are influenced by many different factors [59]. This makes reliably assessing behaviour difficult, especially through self-report, which is often the case [60]. These pitfalls related to health behaviour measuring may explain the inconsistencies between prior studies as well as the lack of findings in the current study.

In conclusion, the current study reports changes in autonomic regulation within the context of a behavioural change intervention. Measures of parasympathetic autonomic nervous system activity did not change during the active intervention period but showed a reduction during the follow-up period. Improvements in health behaviours were not associated with parasympathetic nervous system activity as was anticipated. Delving deeper

into the connection between health behaviours and autonomic regulation in patients with cardiovascular disease could yield valuable insights into the efficacy of behavioural change interventions and the interplay between health behaviours and autonomic regulation in the progression of coronary artery disease.

REFERENCE LIST

1. Sanchis-Gomar, F., et al., Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med, 2016. 4(13): p. 256.
2. Tsao, C.W., et al., Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. Circulation, 2022. 145(8): p. e153-e639.
3. Lechner, K., et al., Lifestyle factors and high-risk atherosclerosis: Pathways and mechanisms beyond traditional risk factors. Eur J Prev Cardiol, 2020. 27(4): p. 394-406.
4. Reginato, E., et al., Dietary and Lifestyle Patterns are Associated with Heart Rate Variability. J Clin Med, 2020. 9(4).
5. Thayer, J.F., Yamamoto, S.S., and Brosschot, J.F. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. International Journal of Cardiology, 2010. 141(2): p. 122-131.
6. Nolan, R.P., et al., Effects of drug, biobehavioral and exercise therapies on heart rate variability in coronary artery disease: a systematic review. Eur J Cardiovasc Prev Rehabil, 2008. 15(4): p. 386-96.
7. McCorry, L.K., Physiology of the autonomic nervous system. Am J Pharm Educ, 2007. 71(4): p. 78.
8. Borchard, U., The Role of the Sympathetic Nervous System in Cardiovascular Disease. J Clin Basic Cardiol, 2001. 4.
9. Kupari, M., et al., Short-term heart rate variability and factors modifying the risk of coronary artery disease in a population sample. Am J Cardiol, 1993. 72(12): p. 897-903.
10. Rossy, L.A., and Thayer, J.F. Fitness and gender-related differences in heart period variability. Psychosom Med, 1998. 60(6): p. 773-81.
11. Iellamo, F., et al., Effects of a residential exercise training on baroreflex sensitivity and heart rate variability in patients with coronary artery disease: A randomized, controlled study. Circulation, 2000. 102(21): p. 2588-92.
12. Ståhle, A., Nordlander, R., and Bergfeldt, L. Aerobic group training improves exercise capacity and heart rate variability in elderly patients with a recent coronary event. A randomized controlled study. Eur Heart J, 1999. 20(22): p. 1638-46.
13. Minami, J., Ishimitsu, T., and Matsuoka, H. Effects of smoking cessation on blood pressure and heart rate variability in habitual smokers. Hypertension, 1999. 33(1 Pt 2): p. 586-90.

14. Benarroch, E.E., The Central Autonomic Network: Functional Organization, Dysfunction, and Perspective. Mayo Clinic Proceedings, 1993. 68(10): p. 988-1001.

15. Thayer, J.F., et al., Heart Rate Variability, Prefrontal Neural Function, and Cognitive Performance: The Neurovisceral Integration Perspective on Self-regulation, Adaptation, and Health. Annals of Behavioral Medicine, 2009. 37(2): p. 141-153.

16. Allan, J.L., McMinn, D., and Daly, M. A Bidirectional Relationship between Executive Function and Health Behavior: Evidence, Implications, and Future Directions. Front Neurosci, 2016. 10: p. 386.

17. Magnon, V., et al., Does heart rate variability predict better executive functioning? A systematic review and meta-analysis. Cortex, 2022. 155: p. 218-236.

18. Shaffer, F. and Ginsberg, J.P. An Overview of Heart Rate Variability Metrics and Norms. Frontiers in Public Health, 2017. 5.

19. Task Force of the European Society of Cardiology and The North American Society of Pacing Electrophysiology, Heart Rate Variability. Circulation, 1996. 93(5): p. 1043-1065.

20. Leyro, T.M., Buckman, J.F., and Bates, M.E. Theoretical implications and clinical support for heart rate variability biofeedback for substance use disorders. Current Opinion in Psychology, 2019. 30: p. 92-97.

21. Montano, N., et al., Heart rate variability explored in the frequency domain: a tool to investigate the link between heart and behavior. Neurosci Biobehav Rev, 2009. 33(2): p. 71-80.

22. Habibović, M., et al., Enhancing Lifestyle Change in Cardiac Patients Through the Do CHANGE System (''Do Cardiac Health: Advanced New Generation Ecosystem''): Randomized Controlled Trial Protocol. JMIR Res Protoc, 2018. 7(2): p. e40.

23. Pine, K., and Fletcher, B. Time to shift brain channels to bring about effective changes in health behaviour. Perspectives in Public Health, 2014. 134(1): p. 16-17.

24. Acqknowledge 5. Biopac Systems, Inc.

25. Salahuddin, L., et al., Ultra short term analysis of heart rate variability for monitoring mental stress in mobile settings. Annu Int Conf IEEE Eng Med Biol Soc, 2007. 2007: p. 4656-9.

26. Hamilton, R.M., McKechnie, P.S., and Macfarlane, P.W. Can cardiac vagal tone be estimated from the 10-second ECG? Int J Cardiol, 2004. 95(1): p. 109-15.

27. Dekker, J.M., et al., Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men. The Zutphen Study. Am J Epidemiol, 1997. 145(10): p. 899-908.

28. Pham, T., et al., Heart Rate Variability in Psychology: A Review of HRV Indices and an Analysis Tutorial. Sensors (Basel), 2021. 21(12).

29. Walker, S.N., Sechrist, K., and Pender, N. Health Promotion Model - Instruments to Measure Health Promoting Lifestyle: Health Promoting Lifestyle Profile (HPLP II) Adult Version. 1995 18-8-2023]; Available from: http://deepblue.lib.umich.edu/handle/2027.42/85249.

30. IBM SPSS Statistics for Windows. 2020, IBM Corp: Armonk, NY.

31. Girard, D., et al., Smoking cessation and heart rate variability: Is it possible to fully recover? European Respiratory Journal, 2014. 44(Suppl 58): p. P319.

32. Bodin, F., et al., The Association of Cigarette Smoking With High-Frequency Heart Rate Variability: An Ecological Momentary Assessment Study. Psychosom Med, 2017. 79(9): p. 1045-1050.

33. Oliveira, N.L., et al., Heart rate variability in myocardial infarction patients: Effects of exercise training. Revista Portuguesa de Cardiologia, 2013. 32(9): p. 687-700.

34. Kopp, W., Chronically increased activity of the sympathetic nervous system: Our diet-related "evolutionary" inheritance. JNHA - The Journal of Nutrition, Health and Aging, 2009. 13(1): p. 27-29.

35. Blumenthal, J.A., 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(13): p. 1626-1634.

36. Duru, F., et al., Effect of exercise training on heart rate variability in patients with new-onset left ventricular dysfunction after myocardial infarction. Am Heart J, 2000. 140(1): p. 157-61.

37. Kim, H.G., et al., Stress and Heart Rate Variability: A Meta-Analysis and Review of the Literature. Psychiatry Investig, 2018. 15(3): p. 235-245.

38. Broers, E.R., et al., Usefulness of a Lifestyle Intervention in Patients With Cardiovascular Disease. Am J Cardiol, 2020. 125(3): p. 370-375.

39. Niemelä, M.J., Airaksinen, K.E.J., and Huikuri, H.V. Effect of Beta-blockade on heart rate variability in patients with coronary artery disease. Journal of the American College of Cardiology, 1994. 23(6): p. 1370-1377.

40. Lampert, R., et al., Effects of propranolol on recovery of heart rate variability following acute myocardial infarction and relation to outcome in the Beta-Blocker Heart Attack Trial. Am J Cardiol, 2003. 91(2): p. 137-42.

41. Carney, R.M., and Freedland, K.E. Depression and coronary heart disease. Nature Reviews Cardiology, 2017. 14(3): p. 145-155.

42. van Zyl, L.T., Hasegawa, T., and Nagata, K. Effects of antidepressant treatment on heart rate variability in major depression: A quantitative review. BioPsychoSocial Medicine, 2008. 2(1): p. 12.

43. Aarts, N., et al., Antidepressants and heart-rate variability in older adults: a population-based study. Psychological Medicine, 2016. 46(6): p. 1239-1247.

44. Lloyd-Jones, D.M., et al., Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association. Circulation, 2022. 146(5): p. e18-e43.

45. Levine, G.N., et al., Psychological Health, Well-Being, and the Mind-Heart-Body Connection: A Scientific Statement From the American Heart Association. Circulation, 2021. 143(10): p. e763-e783.

46. Brown, V.J., and Tait, D.S. Behavioral Flexibility: Attentional Shifting, Rule Switching, and Response Reversal, in Encyclopedia of Psychopharmacology, I.P. Stolerman and L.H. Price, Editors. 2010, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 1-7.

47. Fletcher, B., et al., FIT – Do Something Different. Swiss Journal of Psychology, 2011. 70(1): p. 25-34.

48. Grol, M., and De Raedt, R. The link between resting heart rate variability and affective flexibility. Cognitive, Affective, & Behavioral Neuroscience, 2020. 20(4): p. 746-756.

49. Ruiz-Padial, E., et al., The rhythm of the heart in the blink of an eye: Emotion-modulated startle magnitude covaries with heart rate variability. Psychophysiology, 2003. 40(2): p. 306-313.

50. Thayer, J.F., and Lane, R.D. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord, 2000. 61(3): p. 201-16.

51. Wang, H., et al., Effects of trunk posture on cardiovascular and autonomic nervous systems: A pilot study. Front Physiol, 2022. 13: p. 1009806.

52. Tiwari, R., et al., Analysis of Heart Rate Variability and Implication of Different Factors on Heart Rate Variability. Curr Cardiol Rev, 2021. 17(5): p. e160721189770.

53. Jeyhani, V., et al., Effect of Different ECG Leads on Estimated R-R Intervals and Heart Rate Variability Parameters. Annu Int Conf IEEE Eng Med Biol Soc, 2019. 2019: p. 3786-3790.

54. Arakaki, X., et al., The connection between heart rate variability (HRV), neurological health, and cognition: A literature review. Frontiers in Neuroscience, 2023. 17.

55. Hayano, J., et al., Impact of Heart Rate Fragmentation on the Assessment of Heart Rate Variability. Applied Sciences, 2020. 10(9): p. 3314.

56. Cockerham, W.C., Health lifestyle theory and the convergence of agency and structure. J Health Soc Behav, 2005. 46(1): p. 51-67.

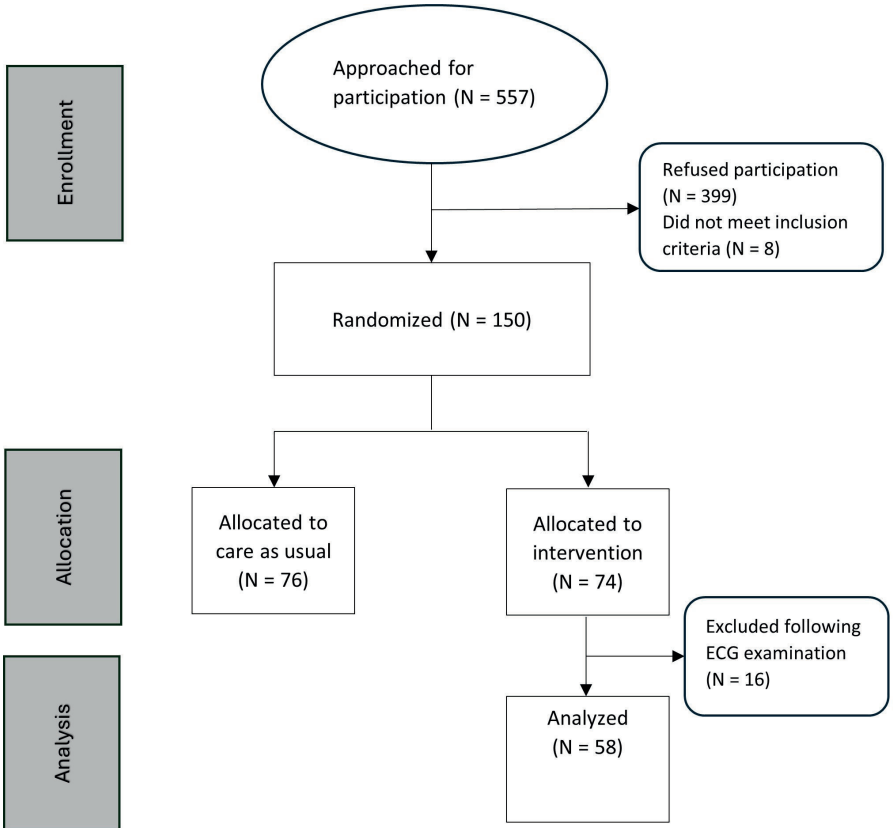
57. Speer, K.E., et al., Heart rate variability for determining autonomic nervous system effects of lifestyle behaviors in early life: A systematic review. Physiol Behav, 2020. 217: p. 112806.

58. Grosicki, G.J., et al., Self-recorded heart rate variability profiles are associated with health and lifestyle markers in young adults. Clin Auton Res, 2022. 32(6): p. 507-518.

59. Short, S.E., and Mollborn, S. Social Determinants and Health Behaviors: Conceptual Frames and Empirical Advances. Curr Opin Psychol, 2015. 5: p. 78-84.

60. Mokdad, A.H., and Remington, P.L. Measuring health behaviors in populations. Prev Chronic Dis, 2010. 7(4): p. A75.

SUPPLEMENTARY MATERIAL



Supplementary Figure SF1. Flowchart of participant eligibility for the present analysis.

Supplementary table ST1. The association of health behaviours with heart rate using linear mixed-effect modelling.

Predictor	Value of Category	'Base' model [a] BIC = 5320		'Adjusted' model [b] BIC = 5135	
		B [95% CI]	p-value	B [95% CI]	p-value
Timepoints	Baseline	*Reference*			
	Three months	-10.04 [-21.16 to 1.09]	.076	-3.81 [-12.25 to 4.63]	.369
	Six months	-7.82 [-19.56 to 3.92]	.187	9.92 [-1.72 to 21.56]	.093
Measurement	5	*Reference*			
	4	-.238 [-1.530 to 1.055]	.714	-.201 [-1.517 to 1.115]	.761
	3	-1.626 [-2.828 to -.425]	.009	-1.759 [-3.010 to -.509]	.007
	2	-.602 [-2.025 to .821]	.399	-.451 [-1.931 to 1.749]	.544
	1	.132 [-1.504 to 1.769]	.872	.074 [-1.601 to 1.749]	.930
HPLP		-.02 [-.09 to 0.56]	.624	.03 [-.03 to .09]	.085
HPLP x Timepoints	Baseline	*Reference*			
	Three months	.06 [-.02 to .14]	.117	.03 [-.03 to .09]	.089
	Six months	0.42 [-.4 to .12]	.311	-.06 [-.14 to .02]	.024
Age				-.25 [-.41 to -.08]	<.001
Sex				3.26 [-1.87 to 8.39]	.208
BMI				.28 [.01 to .56]	.041
Smoking				-1.98 [-5.27 to 1.31]	.236

Data are presented for the 'base' model without covariates and the 'adjusted' model including age, sex, BMI, and smoking as covariates. Results are presented as estimates with 95% confidence intervals and p-values.
[a] The 'base' model for heart rate included timepoint, measurement, health behaviour (HPLP), and the interaction between timepoint and HPLP as fixed effects. [b] The adjusted model included time-invariant predictors age, sex, and time-varying predictors BMI and smoking.

Supplementary table ST2. Mean values of the HPLP total score, subscales, BMI, and smoking status at baseline, three months, and six months.

	Baseline	Three months	Six months
HPLP Total score	129.21 ± 23.63	140.81 ± 23.79	145.44 ± 24.74
HPLP physical activity	2.00 ± 0.71	2.32 ± 0.71	2.38 ± 0.70
HPLP dietary habits	2.71 ± 0.50	2.88 ± 0.45	2.94 ± 0.48
HPLP stress management	2.49 ± 0.55	2.70 ± 0.60	2.75 ± 0.65
HPLP spiritual growth	2.67 ± 0.65	2.91 ± 0.67	3.04 ± 0.69
HPLP Health responsibility	2.20 ± 0.55	2.45 ± 0.56	2.56 ± 0.55
HPLP interpersonal relationships	2.79 ± 0.57	2.93 ± 0.53	3.06 ± 0.56
BMI	29.64 ± 4.91	29.77 ± 5.15	29.77 ± 5.09
Smoking status (Yes)	15.5%	12.1%	15.5%

Supplementary table ST3. General linear model results showing the main effects of timepoint for the HPLP total score, BMI, and smoking.

	SS	df	Mean Square	F	p-value
HPLP	3099.20	2	1549.60	8.55	<.001
BMI	27.99	2	13.99	2.85	.063
Smoking	.08	2	.04	.74	.480

SS: Type III Sum of Squares, df: degrees of freedom.

Supplementary table ST4. General linear model results showing the main effects of timepoint for the HPLP subscales: Physical activity, Dietary habits, Stress management, Health Responsibility, Spiritual growth, and Interpersonal relationships.

	SS	df	Mean Square	F	p-value
HPLP Physical activity	.16	2	.08	.36	.669
HPLP Dietary habits	.84	2	.42	4.53	.013
HPLP Stress management	1.03	2	.52	4.22	.017
HPLP Health responsibility	1.06	2	.53	4.45	.014
HPLP Spiritual growth	2.12	2	1.06	7.11	.001
HPLP Interpersonal relationships	1.19	2	.59	4.91	.009

SS: Type III Sum of Squares, df: degrees of freedom.

Supplementary table ST5. Pearson correlations between RMSSD at baseline, and its change score between baseline – three months, and three and six months with HPLP scores, BMI, and smoking at their change scores.

Health behaviours	RMSSD Baseline	RMSSD change Baseline – Three months	RMSSD change Three months – Six months
Baseline			
HPLP T0	-.206	.093	.315 *
HPLP PA T0	.050	.015	.161
HPLP Diet T0	-.252	-.004	.280 *
HPLP Stress T0	-.254	.129	.147
BMI T0	-.183	.070	-.129
Smoking T0	-.156	.285 *	-.163
Change Baseline – Three months			
HPLP BL – 3m	.073	-.102	-.154
HPLP PA BL – 3m	.173	-.208	-.072
HPLP Diet BL – 3m	.092	-.004	-.027
HPLP Stress BL – 3m	.043	-.115	-.111
BMI BL – 3m	.270	-.121	-.207
Smoking BL – 3m	.138	-.071	.072
Change Three – Six months			
HPLP 3m – 6m	-.094	.050	.082
HPLP PA 3m – 6m	-.212	.108	.185
HPLP Diet 3m – 6m	-.035	.025	.021
HPLP Stress 3m – 6m	-.128	.086	-.018
BMI 3m – 6m	.133	-.117	-.004
Smoking 3m – 6m	.057	-.166	.043

* p < .05, ** p < .01, HPLP: Health Promoting Lifestyle Profile, PA: Physical activity.

Supplementary table ST6. Pearson correlations between Heart rate at baseline, and its change score between baseline – three months, and three and six months with HPLP scores, BMI, and smoking at their change scores.

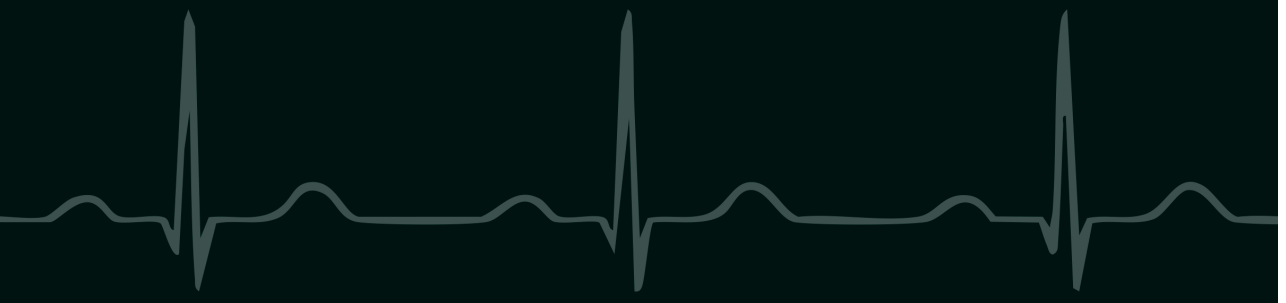
Health behaviours	HR Baseline	HR change Baseline – Three months	HR change Three months – Six months
Baseline			
HPLP T0	.074	-.137	-.151
HPLP PA T0	-.119	-.063	-.059
HPLP Diet T0	.072	-.093	-.046
HPLP Stress T0	.178	-214	-.157
BMI T0	.022	-.003	-.112
Smoking status T0	-.230	.065	.093
Change Baseline – Three months			
HPLP BL – 3m	-.073	.297 *	-.016
HPLP PA BL – 3m	.031	.374 **	-.092
HPLP Diet BL – 3m	-.148	.232	-.036
HPLP Stress BL – 3m	-.189	.302 *	.049
BMI BL – 3m	-.159	-.001	.317 *
Smoking status BL – 3m	-.160	.040	.049
Change Three months – Six months			
HPLP 3m – 6m	.113	-.304 *	.182
HPLP PA 3m – 6m	.110	-.406 **	.075
HPLP Diet 3m – 6m	.152	-.367 **	-.029
HPLP Stress 3m – 6m	.050	-.183	.194
BMI 3m – 6m	.010	.245	-.079
Smoking status 3m – 6m	-.023	.081	-.122

* p < .05, ** p < .01, HPLP: Health Promoting Lifestyle Profile, PA: Physical activity.

Supplementary table ST7. Exploratory mixed model parameter estimates for the relation between the six HPLP subscales and the outcome RMSSD, while controlling for age, sex, BMI, and smoking.

Predictor	Category	B [95% CI]	p-value
HPLP physical activity (PA)		.96 [-.28 to 4.73]	.612
HPLP PA x Timepoints	Baseline	*Reference*	
	Three months	-.87 [-4.99 to 3.26]	.675
	Six months	1.781 [-2.63 to 6.19]	.420
HPLP Health responsibility (HealthR)		-4.491 [-9.01 to .02]	.051
HPLP HealthR x Timepoints	Baseline	*Reference*	
	Three months	-.94 [-5.94 to 4.06]	.706
	Six months	7.78 [2.37 to 13.20]	.006
HPLP Dietary habits		-3.65 [-8.77 to 1.47]	.157
HPLP Diet x Timepoints	Baseline	*Reference*	
	Three months	-.06 [-6.31 to 6.19]	.985
	Six months	8.24 [2.01 to 14.46]	.011
HPLP Spiritual growth (SpirGrowth)		-3.44 [-7.19 to .30]	.070
HPLP SpirGrowth x Timepoints	Baseline	*Reference*	
	Three months	-1.34 [-5.56 to 2.88]	.527
	Six months	3.43 [-1.02 to 7.89]	.127
HPLP Stress management (StressMan)		-4.38 [-8.97 to .21]	.061
HPLP StressMan	Baseline	*Reference*	
	Three months	-3.18 [-7.84 to 1.47]	.175
	Six months	2.24 [-3.03 to 7.50]	.396
HPLP Interpersonal Relationships (InterRela)		-2.90 [-7.21 to 1.41]	.181
HPLP InterRela x Timepoints	Baseline	*Reference*	
	Three months	-2.99 [-8.15 to 2.17]	.250
	Six months	2.26 [-3.13 to 7.65]	.404

Chapter 6



The effects of an integrated health behaviour intervention on autonomic regulation: A secondary analysis of the TIMELY trial on the associations with changes in cardiovascular risk factors

Roovers, T., Douma, E.R., Habibovic, M., Hammer, A., Schmitz, B., Widdershoven, J.W., Kop, W.J.

In preparation for publication submission

ABSTRACT

Background: Improvements in overall cardiovascular health and changes in health behaviours and factors have been associated with changes in autonomic regulation. However, the link between health behaviours and clinical health factors (i.e., the components of the American Heart Association's Life's Essential 8) with heart rate variability indices is insufficiently understood. This study assesses this association during an eHealth behaviour change intervention in patients with coronary artery disease (CAD).

Methods: Patients with stable CAD and referred to cardiac rehabilitation received a 6-month eHealth intervention period with weekly 24-hour ECG recordings for the assessment of HRV indices. Health behaviours and clinical health factors of the Life's Essential 8 index were evaluated using validated questionnaires and analyses from blood samples. Associations between cardiovascular health, individual components of Life's Essential 8, and HRV indices were analysed using Linear Mixed Models. The role of adherence to the intervention, psychological factors, and beta-blocker use was also assessed.

Results: A total of 551 ECG recordings were obtained from 52 patients (mean age = 62.6 ± 9.1 years, 26.9% women) over a period of 6 months. The overall cardiovascular health score (AHA Life's Essential 8 index) improved throughout the intervention (Cohen's d = 0.274, p = .100), but no significant improvements were observed in the individual components of the index. Heart rate variability indices changed significantly and were associated with increases in overall cardiovascular health, and specifically, physical activity and diet.

Conclusions: Cardiovascular health, health behaviours, but not clinical factors, were related to autonomic regulation. These findings support the potential of HRV as a marker for improvements in autonomic regulation and cardiovascular health within behavioural interventions in patients with cardiovascular disease.

INTRODUCTION

Cardiovascular diseases remain the leading cause of mortality globally, responsible for approximately 20.5 million deaths each year. Coronary artery disease is the most prevalent clinical manifestation of cardiovascular disease and may culminate in acute events such as myocardial infarction. Projections indicate an increase of 90% in cardiovascular disease prevalence, accompanied by a 73.4% rise in mortality, and a 54.7% increase in disability adjusted life years in 2050 [1]. Health behaviours and clinical risk factors play a crucial role in the onset and progression of coronary artery disease. The American Heart Association has identified eight components essential for maintaining cardiovascular health, referred to as Life's Essential 8 [2]. These include four health behaviours (physical activity, healthy diet, smoking cessation, and sufficient sleep) and four clinical risk factors (blood pressure, cholesterol levels, blood glucose, and body mass index (BMI)). Cardiovascular disease and the Life's Essential 8 can be considered from the biopsychosocial framework of health and disease. Psychological factors, such as stress, anxiety, and depression, as well as social factors (e.g., poverty), can shape individuals' capacity to adopt and sustain healthy behaviours, thereby contributing to cardiovascular health outcomes [2]. A recent umbrella review of 79 studies in 104 countries (N = 2,555,639) reported global prevalence estimates for the components of Life's Essential 8 and concluded that recommendations are often not met [3]. Particularly common are adverse health behaviours, including insufficient physical activity (26.3%), a lack of a healthy diet (34.1%), nicotine exposure (15.4%), and poor sleep quality (38.5%). Optimal cardiovascular health behaviours are associated with a 50% lower risk for coronary events, even in individuals with high genetic risk [4]. Targeted interventions can support improvements in cardiovascular health, however, adherence remains challenging, limiting the long-term maintenance of healthy behaviours [5, 6]. Further research is warranted to understand how these interventions drive behavioural change and improve cardiovascular health. Interventions could be improved by a better understanding of the biobehavioural mechanisms linking Life's Essential 8 to adverse health outcomes.

The components of Life's Essential 8 are known to influence cardiovascular outcomes through several physiological mechanisms, including inflammation, endothelial function, atherosclerosis, cardiac stress and remodelling, and haemostatic factors [7, 8]. An additional, less extensively studied but potentially common pathway is the role of autonomic nervous system

regulation. Specifically, the activity of the parasympathetic branch of the autonomic nervous system plays a crucial role in the modulation of heart rate, cardiac stroke volume, and peripheral resistance [9]. Engagement in the four core health behaviours (physical activity, healthy diet, non-smoking, and adequate sleep) has been associated with higher levels of parasympathetic activity, suggesting a possible physiological link between lifestyle and cardiovascular health [10-12]. In addition to health behaviours, the clinical health factors included in Life's Essential 8 have also been linked with autonomic nervous system regulation. Elevated BMI, blood pressure, blood glucose, and cholesterol levels have all been associated with reduced heart rate variability, indicating impaired autonomic function [13-16]. Improvements in physical activity levels, weight, and smoking cessation as a result of behavioural interventions have also been shown to enhance parasympathetic activity [17-19]. This increase in vagal tone may, in turn, contribute to improvements in blood pressure, and potentially in lower blood glucose levels and low-risk lipid profiles. Therefore, autonomic regulation could represent a key physiological mechanism through which behavioural changes influence cardiovascular health outcomes. The biopsychosocial factors related to health behaviours may also be linked to autonomic regulation. Repeated exposure to emotional distress (e.g., stress, anxiety, and depression) can lead to autonomic dysregulation, further increasing the negative effects on clinical factors and overall cardiovascular risk [20, 21].

Measures of heart rate variability are commonly used to assess autonomic nervous system regulation, particularly changes in parasympathetic activity [22]. Variability in inter-beat intervals reflects the degree of parasympathetic activation. Well-established measures of HRV for evaluating autonomic function include frequency domain metrics such as high-frequency (0.15 – 0.40 Hz) and low-frequency (0.04 – 0.15 Hz) power, and time domain metrics, such as the standard deviation of normal-to-normal inter-beat intervals (SDNN), and the root mean square of successive differences (RMSSD) [23]. High-frequency power and RMSSD are highly correlated and primarily reflect parasympathetic activity [24]. In contrast, both sympathetic and parasympathetic influences contribute to low-frequency HRV and SDNN [25].

The current study examines the extent to which the health behaviours and clinical risk factors outlined in the Life's Essential 8 are associated with autonomic nervous system activity, as reflected by heart rate variability indices, in patients with coronary artery disease enrolled in an eHealth intervention trial. It is hypothesised that the intervention results in improvements in overall cardiovascular health, as measured by the Life's

Essential 8 and its components, and these improvements are associated with improved autonomic regulation. The study also explores the role of intervention adherence in this relationship. In addition, associations between psychological well-being, Life's Essential 8, and heart rate variability will be examined to gain a deeper understanding of autonomic function within a broader biopsychosocial framework.

METHODS

Data for this study were collected as part of an international, multicentre, randomised controlled trial: TIMELY. The TIMELY trial evaluated the effectiveness of a personalised eHealth platform and health behaviour change app on reducing cardiac risk in patients with coronary artery disease (CAD). The TIMELY trial is registered at http://www.clinicaltrials.gov/ (NCT05955625). The protocol has been described in [26], and the primary outcomes have been reported elsewhere [27]. The present investigation is a sub-study of the overall TIMELY project, and the analyses focus on the association between lifestyle factors and HRV-based measures of autonomic nervous system activity in the active intervention group.

Patients

Patients with CAD were recruited in the Netherlands (Elisabeth-TweeSteden Hospital), Spain (Hospital Universitario de Santiago de Compostela), and Germany (Clinic Königsfeld at the University of Witten). Inclusion criteria were: age 18 years and older, documented stable CAD and referred for cardiac rehabilitation (CR), having access and ability to operate a smartphone, and proficiency in the native language of the country (i.e., Dutch, Spanish, or German). Patients were excluded from participating if they were unable to fully understand the provided study information and the consequences of participating in the study, had difficulty using the app or devices, were diagnosed with malignant tumour or any other medical condition associated with a life expectancy of less than one year, had unstable cardiovascular, cerebrovascular or other unstable medical condition, or had a pacemaker.

A total of 809 potential participants were approached for participation in the TIMELY study. After checking eligibility criteria and ruling out patients who declined to participate, 358 participants were randomised to either the intervention group or the control group. The intervention group received online behaviour change support through the TIMELY app for six months.

Assessments were conducted at baseline, 3, 6, and 12-month follow-up. Electrocardiograms (ECGs) were only obtained in the participants who were randomised to the intervention group (N = 180). A total of 52 participants (28.9%) actively used the ambulatory ECG monitors during the intervention period and were included in the present analysis (Figure 1). The current investigation used data collected between baseline and six-month follow-up because ECGs were only obtained during the active intervention period.

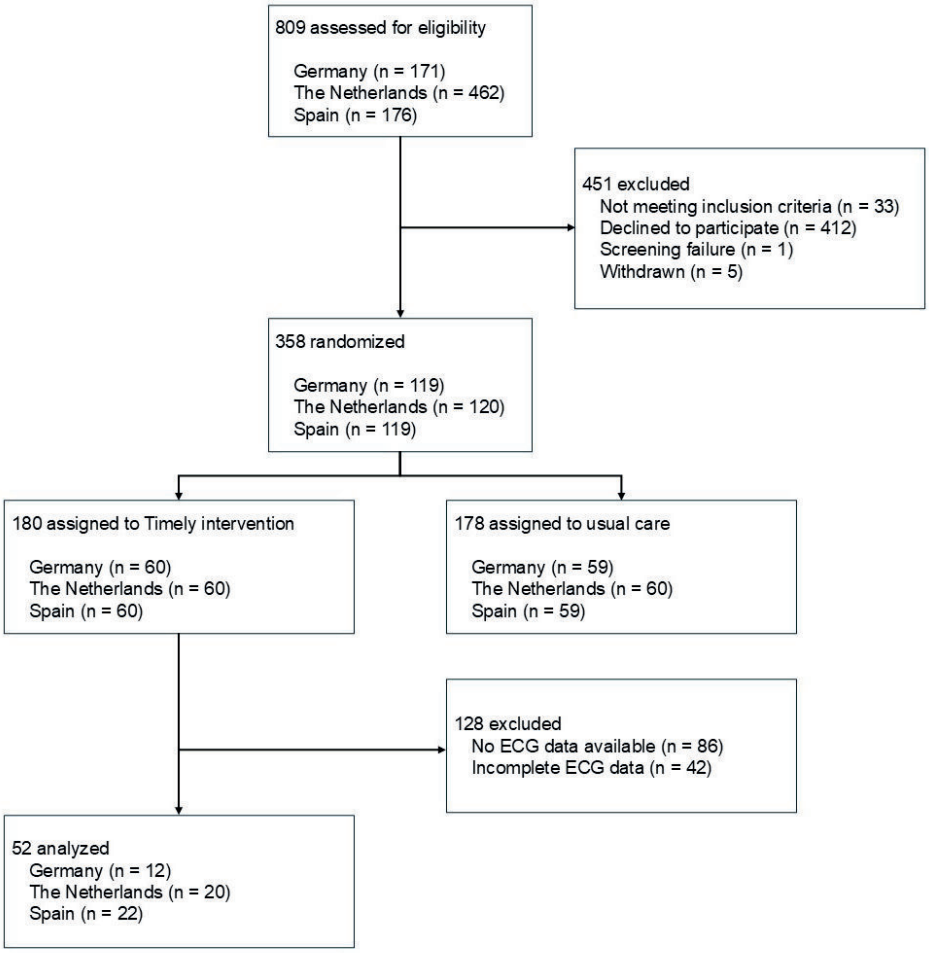


Figure 1. Flowchart of participant inclusion and analysis.

Ethical aspects

The TIMELY trial has been approved by the Medical Ethics Committee Brabant, Tilburg, the Netherlands (protocol #NL82723.028.22 / P2251). Local approvals from the participating centres have also been obtained (Spain: CEIm-G nr: 2023/119; Germany: Z-125/2023). Data collection was initiated after receiving signed informed consent from the participants. Participants had the option to opt out before, during, or after data collection. In this case, their data were not used for the present analyses.

Procedure

Eligible patients were invited to participate by a member of the research team, and study information was provided verbally and in writing. Potential participants were approached approximately two weeks before completing cardiac rehabilitation or after a routine outpatient clinic visit and were given two days or more to consider taking part in the study before being contacted for follow-up through phone calls, e-mail, or during a clinic visit by one of the case managers. Patients who consented to participate in the study completed the baseline assessments and were subsequently randomised (1:1) to either the intervention group or the care-as-usual group by the case managers using a computer-generated randomisation sequence, which was site-specific and remained concealed until the time of randomisation. Baseline assessments included completion of questionnaires, a six-minute walk test, body composition assessment, and a blood draw. Then, patients received the TIMELY intervention or care-as-usual for 6 months. At six months, participants returned to the hospital for follow-up assessments, which included the same measures as obtained at the baseline visit. The ECG data used for HRV analyses of the present study were obtained in the active intervention group only.

Given the nature of the study, blinding of the case managers and/or participants during the TIMELY health behaviour intervention trial was not possible. However, the outcome measures were analysed by research team members who were blinded to the participants' group assignments. The ECGs were analysed for HRV using criteria described below without readers' knowledge of the patient's clinical and lifestyle-related data.

Intervention

The TIMELY intervention was co-designed with input from patients and healthcare professionals, including cardiologists, cardiovascular nurses, and therapists, to ensure that its technical components, a digital dashboard, mobile app, and wearable monitoring devices, met the needs of both users and providers [28]. Patients randomised to the intervention group received a set of monitoring devices, including an activity tracker (Vivosmart 4; Garmin, Garching, Germany), an upper arm blood pressure (BP) monitor (Tel-O-Graph BT; IEM, Stolberg, Germany), and a three-channel Holter monitor (netECG; livetec, Lörrach, Germany). The monitoring devices were connected to the mobile app through a digital dashboard. The goal of the intervention was to provide personalised information and advice regarding health behaviour change through seven core functionalities: (1) messaging function for nudging and information, (2) ecological momentary assessment diary of symptoms, perceived stress, sleep quality, affective states, social behaviour, motivation, and goal setting, (3) lifestyle and health information; (4) chatbot interaction guided by specific counselling techniques and methods; (5) weekly exercise prescription; (6) documentation and visualisation of physical activity and vital signs; and (7) documentation and visualisation of blood pressure.

Demographic and clinical patient data, such as the ECG and exercise capacity results from the preceding clinic visits or rehabilitation sessions, were entered into a risk profile database accessible to healthcare providers and case managers via the TIMELY platform. Based on this information, machine learning algorithms generated an optimal personalised exercise schedule accessible to the participants through the TIMELY app. These exercise plans were dynamically updated each week to reflect the participants' actual activity levels and progress. For additional information on the TIMELY intervention and trial, see the protocol paper [26].

Adherence to the intervention was assessed using an adherence index, which combines the number of active weeks (i.e., weeks with synchronised activity data) and the average daily step count. The index was calculated using the formula: 0.5 x (active weeks / 24) + 0.5 x (daily steps / 10.000). The index can exceed 1 if participants surpass the target for daily steps. See the primary outcome paper for more details [27].

Electrocardiogram and heart rate variability analysis

Patients randomised to the intervention group were instructed to obtain a 24-hour electrocardiogram (ECG) once a week using a three-channel monitor

(netECG; livetec, Lörrach, Germany) for 24 hours. All ECG recordings from all three sites were stored on a data-secure server, and preprocessing and initial analyses were performed at the Technical University of Dresden.

The signals from the three leads (I, II, III) were processed separately. First, the signals were band-pass filtered between 0.3 and 150 Hz (3rd order Butterworth) and, depending on the origin of the data, notch-filtered at 50 or 60 Hz to remove grid noise. Zero-padding was used for filtering to avoid boundary effects. Subsequently, noisy parts were detected and ignored for QRS detection [29] with subsequent QRS correction, based on amplitude heights and signs as well as peak-to-peak and peak-to-signal edge distances [30]. The RR intervals for HRV analysis were extracted from consecutive QRS complexes. Before calculating HRV indices, noisy heartbeats [31] and abnormal RR intervals were rejected [32]. The remaining RR intervals were used to calculate HRV indices described by Vollmer (2015) [33], complemented by heart rate (HR) metrics, including mean, median, minimum, and maximum. Spectral analysis by Fast Fourier Transform to separate R-R intervals was used to determine low (0.04 to 0.15 Hz) and high (0.15 to 0.40 Hz) frequency bands. The power of each frequency band was logarithmically transformed to avoid the undue influence of extreme values in parametric statistical analyses and expressed in ln (ms^2).

Heart rate variability indices were calculated in consecutive 5-minute windows and averaged across each recording to derive long-term HRV indices. Recordings with fewer than twelve 5-minute windows were excluded from analyses. High correlations ($r > .8$) were observed among the three ECG signals, and lead I was selected for analysis based on signal quality and strong agreement with the other leads.

Life's Essential 8

The cardiovascular health behaviours and clinical health factors from the Life's Essential 8 (LE8) [2] were assessed at baseline and 6-month follow-up. These included four health behaviours: physical activity, diet, smoking, and sleep, and four clinical health factors: blood pressure, BMI, non-HDL cholesterol, and blood glucose. The updated definitions and scoring criteria from the LE8 were used to the extent possible. For each component of cardiovascular health, a score ranging from 0 to 100 was computed in accordance with AHA guidelines [2] (see Supplementary Table ST1 for more details). These component scores were then averaged for patients with at least 5 scores to produce an overall cardiovascular health (CVH) score. In the

analyses, both the overall cardiovascular health score and the raw values for the individual components were included.

Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) [34]. Weekly minutes of moderate and vigorous activity were used to compute the CVH score for physical activity, ranging from 0 to 100.

To assess diet, the diet subscale from the Health Promoting Lifestyle Profile questionnaire [35] was used, which consisted of nine items rated on a Likert scale from 1 ("never") to 4 ("routinely"), yielding a total score ranging from 9 to 36. This raw score was rescaled to a 0–100 CVH score.

Smoking was evaluated using the Fageström questionnaire [36], incorporating both the current smoking status and years since quitting for former smokers, and converted to a 0–100 CVH score.

Sleep quality was based on the Patient Health Questionnaire (PHQ-9) [37] item asking about the frequency of "trouble falling or staying asleep, or sleeping too much", rated on a 4-point Likert scale from 0 ("not at all") to 3 ("nearly every day"). Scores of 0,1,2, and 3 correspond to CVH scores of 100, 66, 33, and 0, respectively.

Body mass index (BMI) was assessed at the baseline and 6-month follow-up measurements. Diastolic and systolic blood pressure were retrieved from electronic health records from the hospital visit closest to each timepoint. Non-HDL cholesterol levels and blood glucose were obtained from blood samples collected during the study visits and analysed at the Medical University of Graz, Austria (see Supplementary Material S1). Each of these four health factors was also scored from 0 to 100, following the AHA guidelines.

Psychological measures

To explore autonomic function within a broader biopsychosocial framework, psychological health factors were assessed at baseline and 6-month follow-up, including anxiety, depressive symptoms, and perceived stress, using online questionnaires.

The 7-item Generalised Anxiety Disorder Scale (GAD-7) was used to assess levels of general anxiety during the past two weeks. Responses were rated on a 4-point Likert scale from 0 ("not at all") to 3 ("nearly every day") [38]. Depressive symptoms were assessed using the Patient Health Questionnaire (PHQ-9), a 9-item questionnaire that captures the severity of depressive symptoms over the previous two weeks using a 4-point Likert scale ranging

from 0 ("not at all") to 3 ("nearly every day") [37]. The item related to sleep was not included because it was used for the LE8 score. Stress levels were assessed using the 10-item Perceived Stress Scale (PSS-10), which measures stress over the past month using a 5-point Likert scale ranging from 0 ("never") to 4 ("very often") [39].

Demographic and clinical data

Demographic data, including age, sex, ethnicity, working status, and income, were retrieved through self-report. Clinical data retrieved from the electronic health records, including primary diagnosis, diagnosed with Diabetes Mellitus, hypertension, chronic kidney disease, previous treatments, including coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI), and beta-blocker use.

Statistical analysis

Data are presented as mean and standard deviation (SD) for continuous variables and as frequency and percentages for categorical variables. Electrocardiogram recordings with valid date stamps were selected for analysis. For each recording, the number of days between the ECG recording date and the baseline questionnaire was calculated. Based on this time difference, recordings were grouped into five periods: baseline (first 2 weeks), from 2 weeks to 2 months, halfway through the intervention (3rd month), months 4 and 5, and month 6. Heart rate variability indices were averaged across recordings within each time period, resulting in one HRV value per feature per period per participant.

Paired sample t-tests were used to assess changes in LE8 components and psychological background factors between baseline and six-month follow-up. Pearson correlations were conducted to assess correlations between LE8 components and age, sex, and beta-blocker use.

To assess overall trends in HRV and heart rate over time, linear mixed models were conducted with time period as a fixed effect and a random intercept for each participant to account for repeated measures.

Associations between changes in LE8 components and HRV indices were first explored using unadjusted bivariate analysis. Pearson correlations were conducted to explore the association between average HRV features in the first two weeks and the LE8 baseline scores, as well as between average HRV indices across the whole study period and LE8 component change scores.

Following the bivariate correlation analyses, linear mixed models were conducted to account for the repeated assessments. These models included the change score for each LE8 component, time period, their interaction, adherence index, and the interaction between adherence and LE8 as fixed effects. A random intercept and random slope for time were included to account for individual differences in baseline HRV and trajectories. A repeated covariance structure with an identity matrix was specified to model the correlation of observations across time within individuals. The models were estimated using restricted maximum likelihood (REML), and the significance of fixed effects was assessed using the Satherwaite approximation [15].

The role of psychological factors was explored by conducting Pearson correlations between anxiety, depressive symptoms, and perceived stress with the LE8 components. Additionally, Pearson correlations were performed between the psychological factors and HRV indices at baseline and their corresponding change scores.

Data were analysed using the Statistical Package for the Social Sciences (SPSS; Version 28), and p-values < 0.05 were considered to indicate statistical significance.

RESULTS

Patient characteristics

Table 1 displays the demographic and clinical patient characteristics. The sample consisted of 52 patients, with a mean age of 62.6 ± 9.1 years, and 14 patients (26.9%) were women. Patients were from Spain (N=22), the Netherlands (N=20), and Germany (N=10).

The initial ECG dataset consisted of 551 ECG recordings, with an average of 221 ± 99 5-minute windows per recording. These data correspond to an average of 18:25 ± 8:15 hours of clean ECG signal per recording in the 52 participants with ECG data. Patients in the current analysis demonstrated high adherence to the intervention, with an average adherence index of 0.995 (range 0.57 to 1.59). The adherence index reflects a combination of active weeks (i.e., weeks with synchronised activity data) and average daily steps; values above 1 indicate that a participant was more physically active than requested by the instruction.

Table 1. Demographics and patient characteristics

Demographics	N=52
Age (years)	62.6 ± 9.1
Sex (female)	14 (26.9%)
Hypertension	21 (40.4%)
Myocardial infarction	14 (26.9%)
Chronic kidney disease	27 (51.9%)
Diabetes Mellitus	10 (19.2%)
PCI	36 (69.2%)
CABG	12 (23.1%)
Beta-blocker	39 (75%)
Adherence Index	1.0 ± 0.2

PCI = Percutaneous Coronary Intervention, CABG = Coronary artery bypass grafting.

Life's Essential 8 cardiovascular risk factors

Table 2 shows the average values for the LE8 components at baseline and after six months. Overall, the intervention group of the study showed a moderate cardiovascular health status, according to AHA recommendations [2], with a trend towards a slight improvement over the intervention period (Cohen's d = 0.274, p = .100).

When examining the 8 components separately, none of the factors showed significant improvement over time. An unexpected significant increase in blood glucose was found from baseline to six months (p =.011, Cohen's d = .372), but this increase was offset by the improvements in other LE-8 domains.

The components of LE8 were intercorrelated at baseline. Higher physical activity was significantly correlated with lower BMI (r = -.285, p =.040), lower systolic blood pressure (r = -.267, p =.029), and higher non-HDL cholesterol (r = .305, p =.028). Additionally, a healthier diet was significantly associated with lower non-HDL cholesterol (r = -.358, p =.012) and lower HbA1c (r = -.283, p =.048). As expected, systolic blood pressure was also strongly correlated with diastolic blood pressure (r = .522, p <.001).

Table 2. Average raw values at baseline and six months for the Life's Essential 8 components, as well as the overall cardiovascular health score.

Life's Essential raw score	Baseline	6-months	p-value	Cohen's d
Cardiovascular Health Score [a]	72.71 ± 10.93	75.04 ± 11.04	.100	0.274
Health behaviours				
Physical activity (min/week)	541.92 ± 551.40	711.28 ± 1088.67	.335	0.156
Diet (HPLP)	24.82 ± 4.38	25.42 ± 3.81	.271	0.181
Smoking (yes)	1 (2.6%)	1 (2.6%)	.999	na
Sleep (PHQ)	1.0 ± 1.7	0.9 ± 1.1	.753	.056
Clinical health factors				
BMI (kg/m^2)	29.73 ± 4.68	29.78 ± 5.19	.892	0.020
Diastolic BP (mmHg)	74.40 ± 9.69	75.18 ± 9.94	.592	0.076
Systolic BP (mmHg)	122.02 ± 15.74	122.18 ± 14.90	.944	0.010
Non-HDL cholesterol (mg/dl)	88.24 ± 31.16	95.25 ± 42.15	.086	.245
HbA1c (%)	5.96 ± 0.62	6.10 ± 0.62	.011	.372

[a] Higher LE8 scores indicate better cardiovascular health.

Changes in heart rate variability during the intervention

The average HRV indices and heart rate aggregated across the full 6-month study period are shown in Table 3. Recordings were grouped in five periods and averaged within each period (see Methods for more details). Period 1 comprised 30 patient-timepoints, and there were 49 patient-timepoints in period 2, 43 in period 3, 36 in period 4, and 17 in period 5.

Table 3. Average 24-hour heart rate variability measures and heart rate.

Heart rate variability	24-hour
Frequency domain	
High frequency (ln(ms^2))	4.5 ± 1.1
Low frequency (ln(ms^2))	4.8 ± 1.1
Time domain	
SDNN (ms)	50.7 ± 18.8
RMSSD (ms)	29.4 ± 20.6
Heart rate (bpm)	70.7 ± 12.0

SDNN = Standard Deviation of Normal to Normal (R-R) intervals, RMSSD = Root Mean Square Successive Difference

Figure 2 shows the average HRV indices and heart rate across the 6-month study period based on the period averages. Overall, HRV values remained relatively stable over time with some slight fluctuations. Linear mixed models revealed a significant change over time for low-frequency (Δ = -0.065 ln(ms^2) [95% CI -0.122; -0.008], p =.026), RMSSD (Δ = 1.602 ms [95% CI 0.373; 2.831], p =.011), and SDNN (Δ = 1.798 ms [95% CI 0.647; 2.949], p =.002).

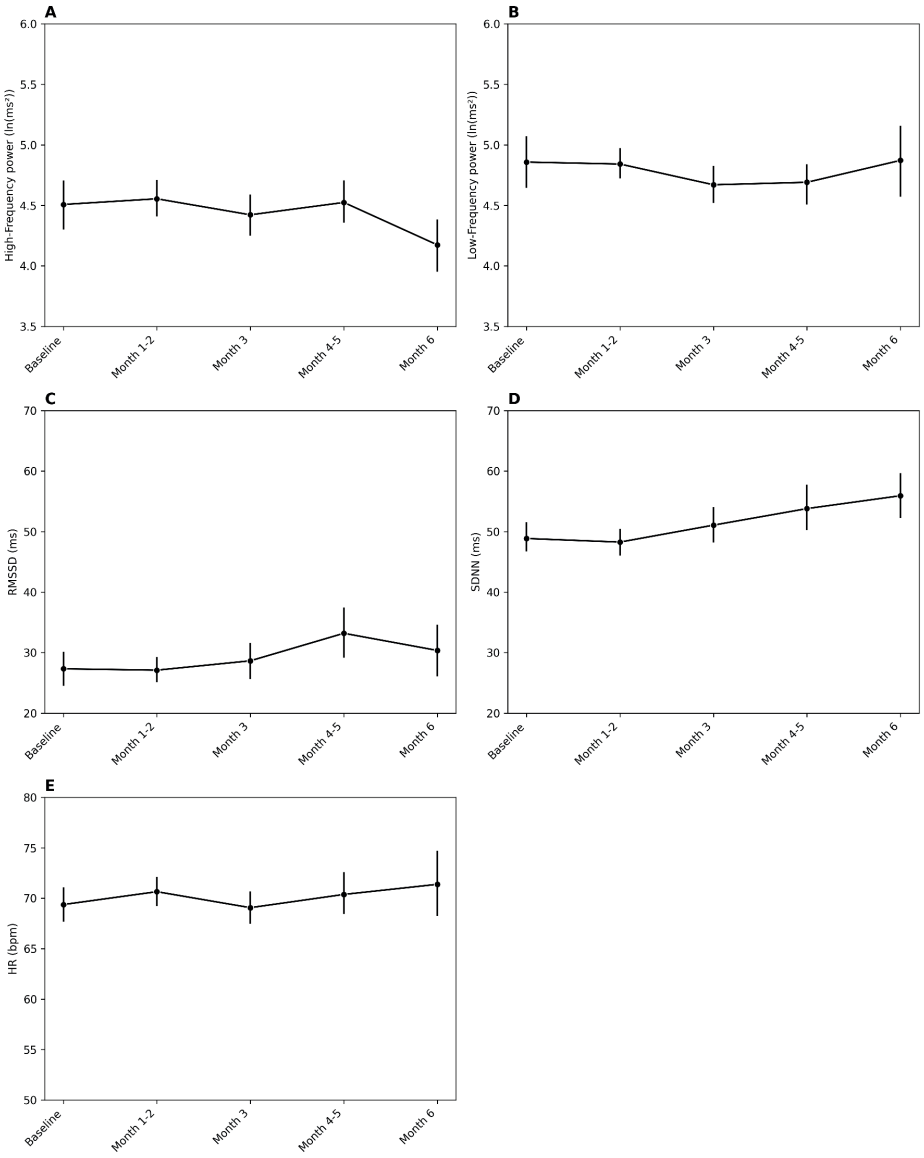


Figure 2. Changes in HRV indices and heart rate over the 6 months of the TIMELY intervention. (A) High frequency power; (B) Low frequency power; (C) Root mean square of successive differences (RMSSD); (D) Standard Deviation of Normal to Normal (R-R) intervals (SDNN); (E) Heart rate.

Associations between Life's Essential 8 components and heart rate variability at baseline

The associations between baseline LE8 components and heart rate variability indices within 14 days of the baseline assessment were first examined using bivariate Pearson correlations (Table 4). The overall cardiovascular health score or health behaviours at baseline were not correlated with HRV indices or heart rate. Regarding clinical factors, a higher BMI was associated with a higher heart rate (r = .459, p =.011). Higher diastolic blood pressure was also associated with a higher heart rate (r = .535, p =.002) as well as higher low-frequency power (r = .402, p =.028). Furthermore, HbA1c was positively correlated with high-frequency power (r = .381, p =.038). Age was associated with lower low-frequency power (r =-.569, p =.001) and lower heart rate (r =-665, p <.001).

Table 4. Pearson correlations between baseline Life's Essential components, patient characteristics, and average HRV indices.

Life's Essential	HF Power	LF Power	SDNN	RMSSD	Heart Rate
CVH Score	-.030	-.110	.229	.148	-.281
Physical activity	.009	-.039	.078	.182	.108
Diet	.200	.328	.330	.290	.130
Smoking	-.107	.357	-.082	-.130	.326
Sleep	-.167	.178	.014	-.064	.323
BMI	-.026	.328	-.030	-.166	.459*
Diastolic BP	-.127	.402*	-.199	-.291	.535**
Systolic BP	-.072	-.062	.083	-.055	-.043
Non-HDL Cholesterol	-.273	.035	.039	-.207	.110
HbA1c	.381*	-.201	-.168	.098	-.283
Co-variates					
Age	.257	-.569**	.012	.206	-.665***
Sex	-.094	.021	.254	.247	-.267
Beta-blockers	-.190	.051	-.245	-.260	.015

BMI = Body Mass Index, BP = Blood pressure, CVH = Cardiovascular health. *p < .05, ** p <.01

Associations between changes in Life's Essential 8 components and changes in heart rate variability during the TIMELY eHealth intervention

No significant correlations between the change score from baseline to the six-month follow-up and mean HRV indices across the six months were

observed (see Supplementary Table ST2). However, these correlations do not take adherence to the intervention into account.

The associations between the change in LE8 CVH score and its components from baseline to 6-month follow-up and HRV indices were also investigated using linear mixed models while taking the repeated recordings within patients into account and adjusting for adherence (Supplementary Table ST3). The overall LE8 cardiovascular health score was positively associated with high-frequency power (B = 0.211 [95% CI 0.097; 0.324], p <.001), RMSSD (B = 3.750 [95% CI 2.066; 5.433], p <.001), and SDNN (B = 2.163 [95% CI 0.462; 3.865], p =.013). Significant negative interaction effects with adherence were also observed for high-frequency power (B = −0.217 [95% CI −0.330; −0.103], p <.001), RMSSD (B = −4.439 [95% CI −6.136; −2.743], p<.001), and SDNN (−3.023 [95% CI −4.759; −1.288], p <.001). This pattern of results suggests that the positive associations between the LE8 CVH score and HRV were strongest among patients with lower adherence.

When examining the different components of the LE8 CVH score, it was found that the extent of increase in physical activity level was significantly associated with an increase in higher high-frequency power. (B = 0.002 [95% CI 0.001; 0.004], p =.010). An interaction effect between physical activity change and the adherence index was also observed (B = −0.002 [95% CI −0.004; −0.001], p =.003), suggesting that the association between physical activity and high-frequency power was weaker among more adherent patients. The same pattern was observed for diet change, which was positively associated with high-frequency power (B = 0.583 [95% CI 0.174; 0.993], p =.006) and showed a significant negative interaction with adherence (B = −0.587 [95% CI −0.984; −0.190], p =.004). In addition, diet change was related to higher RMSSD (B = 12.363 [95% CI 6.145; 18.582], p <.001), and this association was moderated by adherence (B = −12.189 [95% CI −18.210; −6.167], p <.001).

Associations between psychological factors, Life's Essential 8, and heart rate variability

There were no significant changes in the psychological factors from baseline to six months (Table 5). No significant correlations were found between changes in psychological factors and Life's Essential 8 scores. Furthermore, psychological factors were not significantly associated with HRV indices or heart rate, either at baseline or between change scores.

Table 5. Changes in psychological factors from baseline to six months.

Psychological factor	Baseline	Six months	p-value
Anxiety (GAD-7)	3.1 ± 3.6	3.4 ± 4.4	.577
Depressive symptoms (PHQ-9)	3.9 ± 4.7	4.1 ± 5.5	.622
Perceived Stress (PSS)	22.2 ± 6.7	21.9 ± 7.7	.715

Sensitivity analysis

Sensitivity analyses examined the associations between LE8 components and HRV indices, stratified by beta-blocker use, but the results were generally inconsistent (Supplementary Table ST4; for brevity, only significant results are presented). Some associations were observed only in participants without beta-blockers, and the direction of effects varied across components and HRV indices. Interactions with adherence were occasionally significant, but patterns were not uniform. Overall, these findings should be interpreted with caution due to the small sample size and the exploratory nature of the analysis.

DISCUSSION

This study examined the association between the American Heart Association's Life's Essential 8 components, an integrated measure of cardiovascular health, and autonomic nervous system functioning, as reflected by heart rate variability indices. The association was examined in a multicentre context across three countries, as part of an eHealth behaviour change program in patients with coronary artery disease. The findings reveal that while overall cardiovascular health showed modest improvements during the intervention, patients with higher CVH scores also exhibited better autonomic regulation. Contrary to our initial hypothesis, clinical risk factors and psychological health measures were not associated with HRV. These results highlight the complex interplay between behavioural and physiological factors, emphasising the importance of integrating behavioural and biopsychosocial perspectives in cardiovascular health research.

Results from the current investigation point towards a relationship between health behaviours from the LE8 and autonomic regulation. The overall cardiovascular health score was related to improvements in high-frequency power and RMSSD. Additionally, increases in physical activity were linked to higher high-frequency power, although the effect size for this association was small. Diet change was also associated with higher high-frequency power as

well as RMSSD values. These findings are consistent with previous studies, with systematic reviews reporting positive effects of physical activity and a healthy diet on HRV [40, 41]. Higher high-frequency power and RMSSD values are commonly understood to reflect a shift towards parasympathetic activity and improved autonomic regulation [24]. These findings suggest that behaviour change may result in downstream effects in the autonomic nervous system, which may reduce strain on the cardiovascular system and consequently reduce cardiovascular risk. It was observed that these relationships were moderated by adherence to the intervention. Stronger associations between changes in physical activity, diet, and cardiovascular health were observed among patients with lower adherence. Paradoxically, higher adherence may have limited further improvements. Engaged and more adherent patients are more likely to be proactive and confident in managing their health [42] and may therefore represent a relatively healthier subgroup within the cardiac population. This could lead to a ceiling effect, in which their health status leaves little room for further improvement. It is important to emphasise that even patients with lower adherence in the current sample still demonstrated good engagement with the intervention.

It was further hypothesised that improvements in clinical health factors (i.e., BMI, blood pressure, lipid profiles, and blood glucose levels) would be associated with improvements in autonomic regulation. Previous research has established a relationship between BMI [15], hypertension [16], hypercholesterolemia [13], and hyperglycaemia [14], and HRV. However, no such significant associations were observed in the present study. This finding may be explained by the patients' disease stage and pharmacological treatment. Most patients were still under active cardiological care, and medication was not withdrawn throughout the study. Sensitivity analyses for beta-blocker use were performed to explore this issue, but no consistent findings were observed. Clinical health factors were likely strongly regulated by these treatments. The physiological effect of behaviour change or improved autonomic regulation may not have been sufficiently strong to produce measurable changes beyond the impact of medication.

Despite participation in the intervention, no significant improvements were observed over time in the LE8 health behaviours and clinical health factors, and blood glucose levels even showed an increase. Nevertheless, a trend towards improvement was observed in the overall LE8 cardiovascular health score. The absence of improvements in the individual components may also be explained by the ceiling effect, which is potentially attributable to the high adherence and relatively good health of the sample. In addition,

most participants completed cardiac rehabilitation, which may have laid a foundation for positive health behaviours. Research has shown that patients often struggle to maintain the healthy lifestyle acquired during rehabilitation once they return to daily life [43, 44]. In this context, the maintenance of relatively stable health and lifestyle factors can be interpreted as a favourable outcome. However, interpretation remains speculative as the current analysis did not include a control group because this group did not obtain ECG recordings as part of this study. Finally, the disease stage and ongoing cardiological care may influence the capacity for significant health improvements, especially in the clinical health factors, and should therefore be considered.

This study also investigated the relationship between psychological factors and measures of autonomic regulation to place it in a broader psychosocial framework. It was found that high-frequency power was significantly and negatively correlated with increases in perceived stress over the study period. This highlights the intricate relationship between autonomic regulation and psychological health, which may play an important role in a patient's ability to change and maintain a healthy lifestyle.

This investigation has several strengths and limitations. A limitation is the reliance on self-report measures for health behaviours, which are prone to recall and social desirability bias. Additionally, Life's Essential components were assessed only at baseline and at six-month follow-up. To be able to link these to HRV indices, ECG data had to be grouped into five time periods. Although methodologically necessary, it may have limited the ability to detect subtle changes in autonomic regulation over time. The absence of a dedicated control group, due to the lack of ECG data in the control group, also limits the ability to make causal inferences. Furthermore, patients continued to use their medication throughout the study, which may have influenced changes in clinical health factors and potentially affected the effects of behaviour change or autonomic regulation. The dataset had some missing data, but this limitation was mitigated by the use of linear mixed models. In addition, previous research has demonstrated that cardiovascular health can still be accurately estimated when data for one or more LE8 components are missing [45]. Despite these limitations, the study also has notable strengths. It is a multicentre trial conducted across three countries, incorporating ECG recordings over six months alongside the assessments of both behavioural and clinical components of the LE8. This design enhances generalisability and enables the exploration of the relationship between cardiovascular health and autonomic nervous system functioning.

In conclusion, the current investigation demonstrates that improvements in overall cardiovascular health, and specifically in physical activity and diet, show small but significant associations with high-frequency power and RMSSD, reflecting improved autonomic regulation (i.e., an increase in parasympathetic activation). In contrast, no such associations were observed for clinical health factors within LE8. In addition, higher perceived stress was related to lower HRV. These findings support the potential of HRV as a meaningful marker of improvements in autonomic regulation and cardiovascular health within behavioural interventions in patients with coronary artery disease. However, individual variability, such as baseline fitness and medication use, may influence its relationship and should be assessed in future research. Future work should also explore the implementation of continuous HRV monitoring and real-time feedback within interventions. This could not only enhance our understanding of the relationship between HRV, health behaviours, and clinical outcomes, but also assess the potential of HRV as a biofeedback tool to support self-regulation in behaviour change.

REFERENCE LIST

1. Chong, B., et al., Global burden of cardiovascular diseases: projections from 2025 to 2050. Eur J Prev Cardiol, 2024.
2. Lloyd-Jones, D.M., et al., Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association. Circulation, 2022. 146(5): p. e18-e43.
3. López-Bueno, R., et al., Global prevalence of cardiovascular risk factors based on the Life's Essential 8 score: an overview of systematic reviews and meta-analysis. Cardiovascular Research, 2023. 120(1): p. 13-33.
4. Khera, A.V., et al., Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. N Engl J Med, 2016. 375(24): p. 2349-2358.
5. Chindhy, S., et al., Current challenges in cardiac rehabilitation: strategies to overcome social factors and attendance barriers. Expert Rev Cardiovasc Ther, 2020. 18(11): p. 777-789.
6. Douma, E.R., et al., Effectiveness of behavior change techniques in eHealth-based cardiac rehabilitation in patients with coronary artery disease: A systematic review: Effective behavior change techniques in eHealth CR. Am J Prev Cardiol, 2024. 20: p. 100892.
7. Xanthakis, V., et al., Ideal cardiovascular health: associations with biomarkers and subclinical disease and impact on incidence of cardiovascular disease in the Framingham Offspring Study. Circulation, 2014. 130(19): p. 1676-83.
8. Gaye, B., et al., Ideal Cardiovascular Health and Incident Cardiovascular Disease: Heterogeneity Across Event Subtypes and Mediating Effect of Blood Biomarkers: The PRIME Study. Journal of the American Heart Association, 2017. 6(10): p. e006389.
9. Borchard, U., The Role of the Sympathetic Nervous System in Cardiovascular Disease. J Clin Basic Cardiol, 2001. 4.
10. Reginato, E., et al., Dietary and Lifestyle Patterns are Associated with Heart Rate Variability. J Clin Med, 2020. 9(4).
11. Thayer, J.F., Yamamoto, S.S., and Brosschot, J.F. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. International Journal of Cardiology, 2010. 141(2): p. 122-131.
12. Strüven, A., et al., Obesity, Nutrition and Heart Rate Variability. Int J Mol Sci, 2021. 22(8).
13. Christensen, J.H., et al., Heart rate variability and plasma lipids in men with and without ischaemic heart disease. Atherosclerosis, 1999. 145(1): p. 181-6.
14. Singh, J.P., et al., Association of hyperglycemia with reduced heart rate variability (The Framingham Heart Study). The American Journal of Cardiology, 2000. 86(3): p. 309-312.
15. Karason, K., et al., Heart rate variability in obesity and the effect of weight loss. The American Journal of Cardiology, 1999. 83(8): p. 1242-1247.
16. Schroeder, E.B., et al., Hypertension, Blood Pressure, and Heart Rate Variability. Hypertension, 2003. 42(6): p. 1106-1111.

17. Iellamo, F., et al., Effects of a residential exercise training on baroreflex sensitivity and heart rate variability in patients with coronary artery disease: A randomized, controlled study. Circulation, 2000. 102(21): p. 2588-92.

18. Ståhle, A., Nordlander, R., and Bergfeldt, L. Aerobic group training improves exercise capacity and heart rate variability in elderly patients with a recent coronary event. A randomized controlled study. Eur Heart J, 1999. 20(22): p. 1638-46.

19. Minami, J., Ishimitsu, T., and Matsuoka, H. Effects of smoking cessation on blood pressure and heart rate variability in habitual smokers. Hypertension, 1999. 33(1 Pt 2): p. 586-90.

20. Kreibig, S.D., Autonomic nervous system activity in emotion: a review. Biol Psychol, 2010. 84(3): p. 394-421.

21. Lucini, D., et al., Impact of chronic psychosocial stress on autonomic cardiovascular regulation in otherwise healthy subjects. Hypertension, 2005. 46(5): p. 1201-6.

22. Shaffer, F., and Ginsberg, J.P. An Overview of Heart Rate Variability Metrics and Norms. Frontiers in Public Health, 2017. 5.

23. Montano, N., et al., Heart rate variability explored in the frequency domain: a tool to investigate the link between heart and behavior. Neurosci Biobehav Rev, 2009. 33(2): p. 71-80.

24. Kleiger, R.E., Stein, P.K., and Bigger, J.T. Jr. Heart rate variability: measurement and clinical utility. Ann Noninvasive Electrocardiol, 2005. 10(1): p. 88-101.

25. Umetani, K., et al., Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. J Am Coll Cardiol, 1998. 31(3): p. 593-601.

26. Habibovic, M., et al., A patient-centered risk prediction, prevention and intervention platform to support the continuum of care in coronary artery disease using eHealth and artificial intelligence: The TIMELY Randomized controlled trial protocol (Preprint). JMIR Research Protocols, 2024.

27. Schmidt, E.B., et al., Effects of an AI-supported eHealth intervention on cardiac risk factors: Primary outcomes of the TIMELY trial. In preparation.

28. Douma, E.R., et al., Patient-reported preferences in eHealth-based cardiac rehabilitation: A qualitative investigation of behavior change techniques, barriers and facilitators. Internet Interv, 2024. 35: p. 100728.

29. Johnson, A., et al., R-Peak Estimation using Multimodal Lead Switching. Vol. 41. 2014. 281-284.

30. Hammer, A., et al., Automatic Classification of Full- and Reduced-Lead Electrocardiograms Using Morphological Feature Extraction. in 2021 Computing in Cardiology (CinC). 2021.

31. Schmidt, M., et al., Two-Dimensional Warping for One-Dimensional Signals—Conceptual Framework and Application to ECG Processing. IEEE Transactions on Signal Processing, 2014. 62(21): p. 5577-5588.

32. Wichterle, D., et al., Prevalent Low-Frequency Oscillation of Heart Rate. Circulation, 2004. 110(10): p. 1183-1190.

33. Vollmer, M. A robust, simple and reliable measure of heart rate variability using relative RR intervals. in 2015 Computing in Cardiology Conference (CinC). 2015.

34. Cleland, C., et al., Validity of the International Physical Activity Questionnaire (IPAQ) for assessing moderate-to-vigorous physical activity and sedentary behaviour of older adults in the United Kingdom. BMC Medical Research Methodology, 2018. 18(1): p. 176.

35. Walker, S., Sechrist, K., and Pender, N. Health Promotion Model - Instruments to Measure Health Promoting Lifestyle: Health-Promoting Lifestyle Profile [HPLP II] (Adult Version). 2011.

36. Pomerleau, C.S., et al., Reliability of the Fagerstrom Tolerance Questionnaire and the Fagerstrom Test for Nicotine Dependence. Addict Behav, 1994. 19(1): p. 33-9.

37. Kroenke, K., Spitzer, R.L., and Williams, J.B. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med, 2001. 16(9): p. 606-13.

38. Spitzer, R.L., et al., A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med, 2006. 166(10): p. 1092-7.

39. Lee, E.H. Review of the Psychometric Evidence of the Perceived Stress Scale. Asian Nursing Research, 2012. 6(4): p. 121-127.

40. Young, H.A., and Benton, D. Heart-rate variability: a biomarker to study the influence of nutrition on physiological and psychological health? Behavioural Pharmacology, 2018. 29(2 and 3).

41. El-Malahi, O., et al., Beneficial impacts of physical activity on heart rate variability: A systematic review and meta-analysis. PLoS One, 2024. 19(4): p. e0299793.

42. Barello, S., et al., 'Engage me in taking care of my heart': a grounded theory study on patient–cardiologist relationship in the hospital management of heart failure. BMJ Open, 2015. 5(3): p. e005582.

43. Janssen, V., et al., 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(4): p. 620-40.

44. Kotseva, K., et al., Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. European Journal of Preventive Cardiology, 2020. 26(8): p. 824-835.

45. Zheng, Y., et al., Estimation of Life's Essential 8 Score with Incomplete Data of Individual Metrics. medRxiv, 2023.

SUPPLEMENTARY MATERIAL

S1: Biological Assays

Blood samples were collected at each of the study sites at three time points: baseline, six months, and 12 months. At each collection, up to 45 mL of blood was drawn from an easily accessible vein in the arm. The blood was collected into EDTA-vacutainer tubes and serum-vacutainer tubes.

From the EDTA-vacutainer tubes, whole blood and plasma were processed according to the study protocol and divided into four aliquots of 1.5 ml each. Serum obtained from the serum-vacutainers was similarly divided into 4 aliquots. An additional EDTA-vacutainer was used to perform assays for HbA1c levels, which were analysed at the local hospital laboratories. All aliquots of whole blood, plasma, and serum were stored at -80 °C at the Hospital until shipment on dry ice to the core laboratory at Graz University Medical Center.

For long-term storage, the remaining blood samples were stored using the participant's study ID in an access-restricted area at the local research sites for a maximum period of fifteen years after study completion. This was done for follow-up determination of further blood parameters relevant to the development of risk factors for cardiovascular diseases. The reason for retaining blood samples in addition to those that were sent to the core laboratory is that scientific research is constantly evolving, and thus, currently unknown blood-based biological risk factors may be discovered, which may be relevant and meaningful for this study. There was no testing for genetic parameters (targeted examinations of individual genes or gene segments; examinations of the complete genome) based on the samples collected in this project. Any residual material will be destroyed after 15 years.

As part of the informed consent process, patients were informed about the blood collection procedures, potential discomfort (e.g., additional venipuncture), and potential risks, such as hematoma or light-headedness.

Supplementary Table ST1. Metrics and quantification for cardiovascular health scores for each Life's Essential component based on AHA guidelines and the adjusted quantification methods used in the current study.

Life's Essential 8 Components	AHA guidelines		Quantification in the current study	
Physical activity	Metric: Minutes of moderate- (or greater) intensity activity per week Scoring:		Metric: Minutes of moderate- (or greater) intensity activity per week from IPAQ questionnaire Scoring:	
	Points	Minutes	Points	Minutes
	100	≥150	100	≥150
	90	120–149	90	120–149
	80	90–119	80	90–119
	60	60–89	60	60–89
	40	30–59	40	30–59
	20	1–29	20	1–29
	0	0	0	0
Diet			Metric: HPLP diet subscale	
	Points	MEPA score (points)	Points	MEPA score (points)
	100	15–16	100	≥29
	80	12–14	80	24–28
	50	8–11	50	19–23
	25	4–7	25	14–18
	0	0–3	0	9–13
Smoking			Metric: Fagestrom questionnaire	
	Points	Status	Points	Status
	100	Never smoker	100	Never smoker
	75	Former smoker, quit ≥5 y	75	Former smoker, quit ≥5 y
	50	Former smoker, quit 1–<5 y	50	Former smoker, quit
	25	Former smoker, quit <1 y, or currently using inhaled NDS	25	Former smoker, quit <1 y, or currently using inhaled NDS
	0	Current smoker	0	Current smoker

<table>
<tr><th>Life's Essential 8 Components</th><th>AHA guidelines</th><th>Quantification in the current study</th></tr>
<tr><td>Sleep</td><td>Metric: Average hours of sleep per night
Scoring:<table><tr><th>Points</th><th>Level</th></tr><tr><td>100</td><td>7–<9</td></tr><tr><td>90</td><td>9–<10</td></tr><tr><td>70</td><td>6–<7 or ≥10</td></tr><tr><td>40</td><td>4–<5</td></tr><tr><td>20</td><td>5–<6</td></tr><tr><td>0</td><td>0–3
<4</td></tr></table></td><td>Metric: PHQ-9 Sleep question: Trouble falling or staying asleep or sleeping too much.<table><tr><td>100</td><td>0 = not at all</td></tr><tr><td>66</td><td>1 = several days</td></tr><tr><td>33</td><td>2 = more than half of the days</td></tr><tr><td>0</td><td>3 = nearly every day</td></tr></table></td></tr>
<tr><td>BMI</td><td>Metric: BMI (kg/m²)
Scoring:<table><tr><th>Points</th><th>Level</th></tr><tr><td>100</td><td><25</td></tr><tr><td>70</td><td>25.0–29.9</td></tr><tr><td>30</td><td>30.0–34.9</td></tr><tr><td>15</td><td>35.0–39.9</td></tr><tr><td>0</td><td>≥40.0</td></tr></table></td><td>Metric: BMI (kg/m²)
Scoring:<table><tr><th>Points</th><th>Level</th></tr><tr><td>100</td><td><25</td></tr><tr><td>70</td><td>25.0–29.9</td></tr><tr><td>30</td><td>30.0–34.9</td></tr><tr><td>15</td><td>35.0–39.9</td></tr><tr><td>0</td><td>≥40.0</td></tr></table></td></tr>
<tr><td>Blood lipids</td><td>Metric: Non–HDL cholesterol (mg/dL) Scoring:<table><tr><th>Points</th><th>Level</th></tr><tr><td>100</td><td><130</td></tr><tr><td>60</td><td>130–159</td></tr><tr><td>40</td><td>160–189</td></tr><tr><td>20</td><td>190–219</td></tr><tr><td>0</td><td>≥220</td></tr></table>If drug-treated level, subtract 20 points</td><td>Metric: Non–HDL cholesterol (mg/dL) Scoring:<table><tr><th>Points</th><th>Level</th></tr><tr><td>100</td><td><130</td></tr><tr><td>60</td><td>130–159</td></tr><tr><td>40</td><td>160–189</td></tr><tr><td>20</td><td>190–219</td></tr><tr><td>0</td><td>≥220</td></tr></table>If drug-treated level, subtract 20 points</td></tr>
</table>

Life's Essential 8 Components	AHA guidelines		Quantification in the current study	
Blood glucose	Metric: FBG (mg/dL) or HbA1c (%) Scoring:		Metric: HbA1c (%) Scoring:	
	Points	Level	Points	Level
	100	No history of diabetes and FBG <100 (or HbA1c <5.7)	100	No history of diabetes and FBG <100 (or HbA1c <5.7)
	60	No diabetes and FBG 100–125 (or HbA1c 5.7–6.4) (prediabetes)	60	No diabetes and FBG 100–125 (or HbA1c 5.7–6.4) (prediabetes)
	40	Diabetes with HbA1c <7.0	40	Diabetes with HbA1c <7.0
	30	Diabetes with HbA1c 7.0–7.9	30	Diabetes with HbA1c 7.0–7.9
	20	Diabetes with HbA1c 8.0–8.9	20	Diabetes with HbA1c 8.0–8.9
	10	Diabetes with Hb A1c 9.0–9.9	10	Diabetes with Hb A1c 9.0–9.9
	0	Diabetes with HbA1c ≥10.0	0	Diabetes with HbA1c ≥10.0
Blood pressure	Metric: Systolic and diastolic BPs (mmHg) Scoring:		Metric: Systolic and diastolic BPs (mmHg) Scoring:	
	Points	Level	Points	Level
	100	<120/<80 (optimal)	100	<120/<80 (optimal)
	75	120–129/<80 (elevated)	75	120–129/<80 (elevated)
	50	130–139 or 80–89 (stage 1 hypertension)	50	130–139 or 80–89 (stage 1 hypertension)
	25	140–159 or 90–99	25	140–159 or 90–99
	0	≥160 or ≥100	0	≥160 or ≥100
	Subtract 20 points if treated level		Subtract 20 points if treated level	

Supplementary Table ST2. Pearson correlations between change scores of Life's Essential components and mean HRV indices.

LE8 Change score	HF Power	LF Power	SDNN	RMSSD	Heart Rate
CVH Score	.207	−.083	−.092	.121	.072
Physical activity	−.292	.265	−.032	−.160	.081
Diet	.193	−.310	.040	.225	−.199
Smoking [a]	Na	Na	Na	Na	Na
Sleep	−.086	.123	.228	.110	.104
BMI	.135	−.097	.064	.099	−.146
Diastolic BP	.054	−.214	−.058	.023	−.093
Systolic BP	.168	−.141	.078	.099	−.191
Non-HDL Cholesterol	−.079	.138	.020	−.042	.251
HbA1c	−.125	.182	.033	.016	.251

[a] Because there was no change in smoking status during the intervention, this correlation could not be calculated.

Supplementary Table ST3. Results from the linear mixed models on the associations between HRV indices and Life's Essential 8 components.

LE8 Component	Effect	HF (B)	LF (B)	RMSSD (B)	SDNN (B)	HR (B)
CVH score	Main Effect	0.211 ***		3.750 ***	2.163 *	
	Time					
	Adherence					
	CVH * Time					
	CVH*Adherence	-0.217 ***		-4.439 ***	-3.023 ***	
Physical activity	Main effect	0.002 *				
	Time					
	Adherence					
	PA * Time					
	PA * Adherence	-0.002 **				
Diet	Main effect	0.583 **		12.363 ***		
	Time					
	Adherence					
	Diet * Time					
	Diet * Adherence	-0.587 **		-12.189 ***		
Smoking	Main Effect	NA	NA	NA	NA	NA
	Time					
	Adherence					
	Smoking * Time	NA	NA	NA	NA	NA
	Smoking * Adherence	NA	NA	NA	NA	NA
Sleep	Main Effect					
	Time					
	Adherence					
	Sleep * Time		-1.433 *			
	Sleep * Adherence					
BMI	Main effect					
	Time					
	Adherence					

LE8 Component	Effect	HF (B)	LF (B)	RMSSD (B)	SDNN (B)	HR (B)
	BMI * Time					
	BMI*Adherence					-9.750 *
DBP	Main effect					
	Time					
	Adherence					
	DBP * Time					
	DBP*Adherence					
SBP	Main Effect					
	Time					
	Adherence					
	SBP * Time					
	SBP*Adherence					
HbA1c	Main Effect					
	Time					
	Adherence					
	HbA1c * Time					
	HbA1c*Adherence					
Cholesterol	Main Effect					
	Time					
	Adherence		-1.060 *			
	Cholesterol * Time					
	Cholesterol*Adherence					

Results are presented as estimated coefficients and corresponding p-values. Smoking was coded as 0 = no change in smoking status, 1 = change in smoking status. PA = Physical activity (change in moderate and vigorous active minutes per week); Diet (Change in Health-Promoting Lifestyle Profile (HPLP) total score); BMI = Change in Body mass index, DBP = Change in Diastolic blood pressure, SBP = Change in Systolic blood pressure, Cholesterol = Change in Non-HDL cholesterol. *< .05, ** < .01 *** < .001, empty = not significant.

Supplementary Table ST4. Significant associations from the sensitivity analysis stratified by beta-blocker use in the main model.

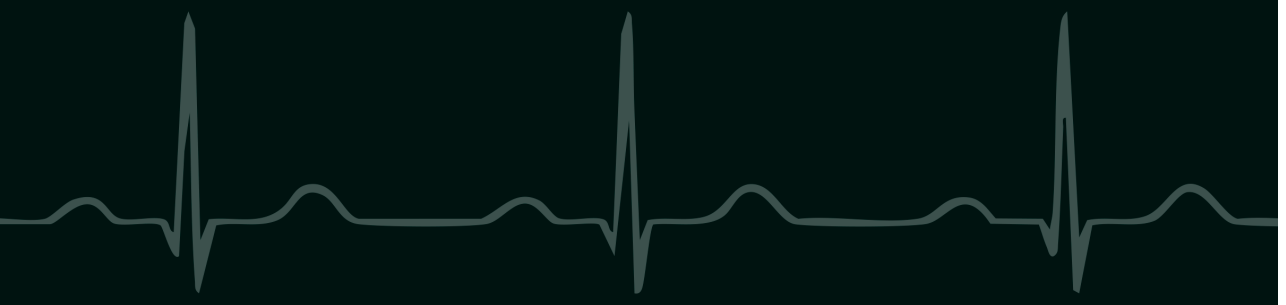
HRV Indices	LE Component	Beta-blocker (B; p)	No Beta-blocker (B; p)
HF	Diet		1.570; .014
HF	HPLP*Adherence		−1.626, .013
HF	HbA1c		2.341; .028
HF	HbA1c		−12.451; .010
HF	DBP		.275; .024
HF	DBP*Adherence		−.282; .014
LF	PA		−.007; <.001
LF	PA*Adherence		6.065; .004
LF	Cholesterol		−.253; .022
LF	Cholesterol*Adherence		.264; .014
LF	CVH		5.747; <.001
LF	CVH*Adherence		−56.324; <.001
RMSSD	DBP		3.373; .016
RMSSD	DBP*Adherence		−3.643; .006
RMSSD	CVH	3.184; .005	
SDNN	CVH	3.583; .004	
SDNN	CVH*Adherence	−4.318; <.001	

Results are presented as estimated coefficients and corresponding p-values. HF = High frequency, LF = Low frequency, Diet = Change in Health-Promoting Lifestyle Profile (HPLP) total score; DBP = Change in Diastolic blood pressure, SBP = Change in Systolic blood pressure, PA = Physical activity (change in moderate and vigorous active minutes per week), BMI = Change in Body mass index, Cholesterol = Change in Non-HDL cholesterol, CVH = Cardiovascular Health score. An empty field is not significant.

Part III

Discussion

Chapter 7



General Discussion

Cardiovascular disease (CVD) remains a leading global health challenge [1] with a major impact on patients' quality of life and survival [2, 3]. In the Netherlands, approximately 40.000 patients died from CVD in 2021 [4]. The clinical manifestations of CVD vary substantially, from unrecognised high blood pressure to sudden cardiac death. A major contributor is coronary artery disease, which occurs when narrowed coronary arteries reduce oxygen supply to the heart muscle and, consequently, cause myocardial ischemia. Myocardial ischemia can cause anginal symptoms such as chest pain, and when persistent and severe, result in permanent damage to the heart muscle (i.e., myocardial infarction). This dissertation addresses three important aspects of coronary artery disease: psychological well-being, cardiac healthy behaviours, and dysregulation of the autonomic nervous system. The common aim is to identify biobehavioural processes that will help develop patient-centred interventions to understand and improve the mental and physical well-being of patients with ischemic heart disease.

The first part of this dissertation addresses a series of studies on mental well-being, primarily assessed in the OPTIMIZE study [5]. The OPTIMIZE study was conducted at the Nuclear Medicine department of the Institute Verbeeten, Tilburg, the Netherlands, and explored the psychological impact of diagnostic testing for myocardial ischemia. Unique to this study is the evaluation of a supportive coaching intervention combined with assessments of emotional states using novel measures of digitally analysed facial expressions (*Chapters 2 and 3)*. Part two of this dissertation explores the underlying biological mechanisms of psychological and physical functioning in patients with coronary artery disease, with a focus on the autonomic nervous system. *Chapter 4* describes the role of the autonomic nervous system in daily life in patients undergoing diagnostic testing for ischemic heart disease. The role of the autonomic nervous system was also investigated in the context of two multi-centre randomised controlled trials: DoCHANGE [6] and TIMELY [7]. In these studies, the effects of behaviour change interventions on cardiac healthy behaviours were investigated in patients with CVD, and these effects were linked to changes in autonomic nervous system activity (*Chapters 5 and 6*). This General Discussion provides an overview of the main findings, followed by a discussion of methodological issues, study limitations and strengths, a theoretical framework, and implications for implementation and future research.

OVERVIEW AND DISCUSSION OF THE MAIN FINDINGS

Part I Patient Experiences and Emotional Reactions to Cardiac Diagnostic Procedures

Patients with coronary artery disease face multiple challenges. In addition to the discomfort caused by physical symptoms, the diagnostic process can also pose a significant psychological burden. The possibility of a severe diagnosis and anticipation of treatment may evoke uncertainty and concern about one's health, which may result in psychological distress and anxiety [8]. The OPTIMIZE study was conducted as a follow-up to the 'Heart Inside Out' study, which highlighted the psychological burden of diagnostic procedures for the detection of myocardial ischemia [9]. Consistent with this earlier work, increases in negative affect, indicating reduced psychological well-being, were observed throughout the diagnostic procedure, particularly during cardiac stress testing (*Chapter 2*). When emotional states during cardiac stress testing were examined using facial expression analyses, an increase in expressed negative emotions was also observed (*Chapter 3*). Interestingly, facially expressed emotions were not correlated with self-reported emotional states, suggesting that these methods capture different aspects of patients' experiences.

Cardiac stress testing as part of the diagnostic procedure can be performed either through physical exertion or pharmacologically induced stress. The present findings suggest that the bicycling protocol may elicit a less aversive emotional response compared to pharmacological stress testing (*Chapter 3*). There has been a shift towards more frequent use of pharmacological stress testing instead of exercise testing over the past decade, even among patients who are capable of performing the exercise protocol. This trend may partially be a long-term consequence of the COVID-19 pandemic, during which exercise testing was limited. From the perspective of patient well-being, the current results indicate that the bicycling protocol, when clinically safe and feasible, may be preferable to most patients.

The effect of the interventions on psychological well-being

Based on the earlier work by Bekendam et al. [10], the next step was the development of a supportive and informational intervention to support patients throughout the diagnostic procedure and improve psychological well-being. Patient-centred support across the diagnostic and treatment process has been shown to improve health outcomes and quality of life [11, 12]. While such care is relatively common in cancer care [13], it remains uncommon

in cardiology, despite CVD being the leading cause of hospitalisation [14]. The present supportive coaching primarily focused on emotional support and patient education to help patients overcome concerns and barriers and facilitate a successful completion of the diagnostic procedure. However, supportive coaching did not improve psychological well-being, as measured by either self-reported emotional states or facially expressed emotions or patient satisfaction with the overall diagnostic procedure, and may have even increased short-term negative affect (*Chapters 2 and 3*).

In addition to supportive coaching, an informational support intervention was implemented through two informational videos that explained the diagnostic procedure. This video-based intervention was developed specifically for this study, together with Institute Verbeeten, and focused on providing essential information in a clear and accessible format to reduce uncertainty [15]. The informational videos did not reduce negative affect or increase patient satisfaction (*Chapter 2*). Even though the videos did not improve psychological well-being beyond information on paper, they may still offer a more accessible format for communicating critical information to patients and their family members or other informal caregivers.

Inducibility of myocardial ischemia and symptoms during diagnostic testing

No associations between psychological factors and the inducibility of ischemia were found. There were also no differences between patients in the supportive coaching compared to the control group in the inducibility of myocardial ischemia during diagnostic stress testing.

Symptoms, whether anginal symptoms, discomfort from exertion, or effects of pharmacological stress testing, are an important source of distress and negative affect. Results presented in *Chapter 2* indicate that self-reported negative affect was significantly associated with the severity of anginal or adenosine-related symptoms during diagnostic testing. However, the supportive coaching intervention did not significantly influence the occurrence or severity of symptoms during the diagnostic procedure.

Part II Autonomic Regulation in Behavioural and Psychological Contexts of Cardiovascular Disease

Autonomic nervous system in psychological well-being, myocardial ischemia, and symptoms

To understand the underlying mechanisms linking psychological well-being, myocardial ischemia, and symptoms, autonomic regulation was assessed during daily life in patients with suspected ischemic heart disease using heart rate variability analyses. Higher levels of negative emotions were associated with reduced autonomic regulation. Negative emotional states were also associated with anginal symptoms (*Chapter 4*). Together, these findings indicate a potential pathway whereby negative emotional states contribute to diminished autonomic function, which may lead to physiological strain on the cardiovascular system, triggering symptoms such as angina. A bidirectional relationship is also plausible, in which heightened emotional responses increase the likelihood of experiencing cardiac symptoms [16], while the occurrence of such symptoms may, in turn, elicit negative emotional responses.

Health behaviour interventions

The DoCHANGE [6] and TIMELY [7] studies were conducted to support patients with CVD in improving their cardiac healthy behaviours and reducing the risk of CVD progression. These interventions included several eHealth components and enabled accessible alternatives to traditional long-term cardiac care and rehabilitation [17]. Interventions using eHealth can also facilitate follow-up strategies to maintain lifestyle changes adopted in cardiac rehabilitation or other programs that target CVD reduction [18, 19]. By offering continuous support, such interventions can bridge the gap between structured rehabilitation and long-term adherence to cardiac healthy behaviours [20]. To understand the effects of the interventions on lifestyle changes, these outcomes will be described first, followed by the main focus of this dissertation: the association between improvements in health behaviours and changes in autonomic regulation in the direction of more parasympathetic and less sympathetic nervous system activity.

The DoCHANGE study focused on a specific set of cardiac healthy behaviours, including physical activity, diet, smoking, and stress management, and also obtained assessments of autonomic regulation indices. The TIMELY trial

extended the scope by also incorporating other cardiac healthy behaviours, such as sleep, and the clinical health factors recommended by the American Heart Association (AHA) in Life's Essential 8, known to be BMI, blood pressure, blood glucose, and blood lipids [21], as well as a comprehensive set of HRV indices to capture autonomic regulation.

Health behaviour change

The DoCHANGE intervention targeted lifestyle improvements through enhancing behavioural flexibility. Results indicated significant improvement in overall cardiac healthy behaviours throughout the 3-month active intervention period, with a further non-significant improvement during follow-up. Improvements in individual cardiac healthy behaviours were only observed for dietary habits and stress management (*Chapter 5*) [22]. In the TIMELY trial, which integrated patient-tailored recommendations for exercise and feedback on goals, a trend towards improved overall cardiovascular health was observed. However, no significant improvements in individual cardiac healthy behaviours or factors were observed during the intervention period (*Chapter 6*) [23].

Changes in heart rate variability during health behaviour interventions

In the DoCHANGE trial, changes in autonomic nervous system activity were assessed using RMSSD as the heart rate variability index of autonomic regulation. RMSSD is a frequently used and validated index of parasympathetic nervous system activity [24]. No significant changes in RMSSD were observed during the active intervention period. Furthermore, during the follow-up phase, RMSSD decreased, indicating a shift away from parasympathetic activity toward sympathetic activity after the intervention was terminated (*Chapter 5*).

In the TIMELY trial, a broad range of heart rate variability indices was assessed, including high-frequency, low-frequency, SDNN, RMSSD, and heart rate. Overall, these indices remained relatively stable over time. Although statistically significant changes were detected for low-frequency power, RMSSD, and SDNN, the effect sizes were small, and the pattern of results was inconsistent, limiting their clinical relevance (*Chapter 6*).

Autonomic regulation, cardiac healthy behaviours, and cardiovascular health

It was hypothesised that changes in cardiac healthy behaviours and improvements in cardiovascular health would result in subsequent changes in heart rate variability indices. However, data from the DoCHANGE trial revealed no association between overall or individual cardiac healthy behaviours with RMSSD. Higher BMI, a clinical health factor also included in the AHA's Life's Essential 8, was associated with lower RMSSD and a higher heart rate (*Chapter 5*).

The investigation of the TIMELY data, in addition to individual cardiac healthy behaviours and clinical health factors (i.e., BMI, blood pressure, lipids, and blood glucose), focused on the overall cardiovascular health score proposed by the American Heart Association [21]. Results indicated that overall cardiovascular health was positively associated with improved autonomic regulation, as reflected by higher RMSSD and high-frequency power. Individual cardiac healthy behaviours, including physical activity and diet, were also linked to improved autonomic regulation, suggesting a downstream effect of a healthier lifestyle on the autonomic nervous system, which may reduce strain on the cardiovascular system and reduce cardiovascular risk.

It was further hypothesised that a healthier lifestyle would also result in improved clinical factors, which would fit in the pathway of reduced strain on the cardiovascular system. Cardiac healthy behaviours were indeed correlated with clinical health factors such as BMI, blood pressure, non-HDL cholesterol, and blood glucose. However, these clinical health factors were not correlated with HRV-based measures of autonomic nervous system activity (*Chapter 6*).

METHODOLOGICAL CONSIDERATIONS

Methodological issues in health behaviour assessment

In order to design and evaluate effective interventions and understand the relationships between biological mechanisms and cardiac healthy behaviours, clear definitions of cardiac healthy behaviours and accurate measurements are a prerequisite. Even though recommendations for cardiac healthy behaviours have been widely agreed upon, these uniform thresholds do not fully capture nuances and individual differences. For example, physical activity recommendations tend to focus on high levels of activity, even though the greatest health benefit occurs in inactive patients who start becoming slightly

active [25]. With respect to diet, the situation is even more complex, as the effects of diet components and composition are still debated [26].

The complexity of cardiac healthy behaviours, their interrelationship, and link to other factors such as psychology make assessing them accurately extremely difficult. Especially because most research still relies on self-report measures of behaviour, which, although practical, have questionable validity [27]. The use of objective measures, such as fitness trackers for physical activity and sleep, may serve as a solution. Assessing diet, however, remains more challenging. While food diaries provide a more accurate alternative to dietary questionnaires, they are burdensome and often suffer from low compliance [28, 29]. Recent advancements in artificial intelligence (AI) image-assisted diary assessment methods show potential, but they still face challenges in estimating portion size and identifying individual ingredients, and require substantial technological expertise [30]. Furthermore, even with objective and accurate measures, relating cardiac healthy behaviours to health outcomes is complex. Outcomes such as blood pressure, blood glucose, and cholesterol are regulated by multiple biological processes [31], under the influence of factors beyond health behaviours, and their effects are therefore hard to isolate, especially in clinical trials.

Given these difficulties in accurately assessing health behaviours and linking them to outcomes, this dissertation approaches the problem by first examining system-level effects and then integrating them with outcomes. *Chapters 4* and *5* connect psychological factors and cardiac healthy behaviours to autonomic nervous system activity rather than distant health outcomes. Building upon this, *Chapter 6* incorporates an overall cardiovascular health score, combining both cardiac healthy behaviours and clinical outcomes, to investigate their relationship with autonomic regulation. This combined index might be of particular relevance to integrated interventions that focus on multiple cardiac healthy behaviours.

Methodological issues in the interpretation of heart rate variability

Even though heart rate variability has been studied for over 50 years [32], the interpretation of some of its indices remains under discussion. Heart rate variability primarily reflects the dynamic and intricate relationship between the sympathetic and parasympathetic nervous systems, the regulatory mechanisms of heart rate through respiratory sinus arrhythmia, and baroreceptor reflex control of blood pressure [33]. This dissertation uses

the most widely applied indices of HRV, which include SDNN, RMSSD, low-frequency, and high-frequency power.

The SDNN is regarded as the gold standard for cardiac risk prediction, capturing inputs from both branches of the autonomic nervous system, and higher values reflect better overall autonomic balance and overall health [24]. RMSSD is considered the primary time-domain index of parasympathetic activity, reflecting vagally mediated changes. The interpretation of low-frequency power remains more controversial. Although there has been speculation that it reflects sympathetic activity, especially in ambulatory recordings, this is based on limited evidence [34]. Instead, low-frequency power is generally considered to reflect baroreceptor reflex activity, which is primarily vagally mediated. Reductions in low-frequency power were therefore interpreted as impaired baroreflex control and reduced sensitivity to changes in blood pressure and volume [35]. High-frequency HRV is widely accepted as an index of parasympathetic or vagal activity and corresponds to heart rate variations in response to the respiratory cycle.

It is important to note that contextual factors such as ECG recording length, sampling frequency, respiration rate, and patient characteristics can significantly influence both time- and frequency domain measurements [36, 37]. Although alternative interpretations based on new research continue to emerge, the interpretations adopted in this dissertation optimally reflect the current consensus on the assessment and interpretation of HRV indices [37, 38].

LIMITATIONS AND STRENGTHS OF THE RESEARCH PRESENTED IN THIS DISSERTATION

The research in this dissertation contains several limitations, but also important merits and strengths that are relevant to the interpretation of the findings presented in Chapters 2 through 6. A general limitation that pertains to all studies, and has been discussed in part above, is the use of self-report measures for emotional states and cardiac healthy behaviours, which are prone to recall and social desirability bias [39]. Not all information can be captured objectively, for example, experienced symptoms are inherently subjective and rely on self-report. The same applies to emotional states and other psychosocial factors to some extent. Although validated questionnaires were used, these may not provide a complete picture, but their use was necessary with regard to efficiency. To partly mitigate this

limitation, measures of emotion that do not depend on self-report were also used, specifically facial emotion expression that was quantified using digital analyses of video recordings, alongside self-report measures in the OPTIMIZE study. With respect to cardiac healthy behaviours in the DoCHANGE study, assessment was limited to a single validated questionnaire covering multiple behaviours, which may not adequately capture their complex nature. To overcome this, cardiac healthy behaviours and cardiovascular health were assessed in the TIMELY study using the AHA's Life's Essentials 8 framework, which allowed for separate evaluation of each component. Still, objective measures of physical activity and sleep through activity trackers would represent a valuable improvement over questionnaires and should be incorporated in future research. Developments in AI-assisted food image analysis are promising for dietary assessment [40]. However, these systems still face substantial challenges and are currently mainly applied in nutritional studies [28]. To advance their use in intervention studies, collaboration between behavioural science, including medical psychology and nutrition research, will be essential. Such interdisciplinary research can improve the accuracy and feasibility of dietary assessments in real-world settings and in combination with other cardiac healthy behaviour measures. In addition, integrating these systems into AI-assisted eHealth platforms could allow for real-time dietary feedback and personalised recommendations, potentially further improving the effectiveness of lifestyle interventions.

Other limitations are study-specific. In the OPTIMIZE study, participant randomisation presented challenges. Group allocation was revealed to the investigator before the participant's consent in order to provide immediate coaching within clinical scheduling constraints. Although unavoidable, this may have introduced bias in enrolment. In addition, randomisation to the informational support group was not feasible due to concerns related to patient privacy. Informational videos were therefore sent to a subset of patients without randomisation, and upon consent, it was assessed which patients actually watched the video. Engagement with the video was limited, and as a result, the effects of the videos were only assessed in exploratory analysis. Furthermore, numerous laboratory staff members and four nuclear physicians were involved in the diagnostic procedure. The degree of support in the intervention and care-as-usual groups from the staff may therefore have varied depending on the team. Such variability is inherent to research in clinical practice, but it nonetheless represents a limitation. Furthermore, the low number of patients participating in the optional 24-hour ECG recording

limited the statistical power of this investigation, and the findings should therefore be interpreted with caution.

Another limitation is related to the DoCHANGE and TIMELY studies. The collection of ECG recordings was limited to the active intervention group, and therefore, comparisons with a control group were not possible. Furthermore, specific to the TIMELY trial, the behaviour change program and TIMELY platform were fine-tuned during the trial. This may have introduced differences in intervention effectiveness between patients enrolled early versus later in the study. Conducting research on a complex intervention poses challenges, and findings should be interpreted in the context of the developmental phase of the intervention. Nonetheless, this process has provided valuable insights into user experiences and practical challenges in the development of such platforms.

The primary strength of this dissertation lies in the inclusion of three randomised controlled trials with a total of 657 participants with CVD (of whom 259 were included in the analyses), conducted across multiple countries. This enhances the generalisability of the findings to populations with diverse backgrounds. Several interventions were examined, targeting improvements in psychological and physical functioning in daily practice and everyday life, which support translation and implementation into clinical practice. Ultimately, this dissertation adopts a comprehensive, multidisciplinary approach to CVD and health. It incorporates insights from psychology, cardiology, nuclear medicine, and neuroscientific theory, and applies a biopsychological framework to improve understanding of physical and psychological risk factors in autonomic regulation. This knowledge will aid in improving support for patients with ischemic heart disease.

MECHANISMS EXPLAINING THE INTERACTION BETWEEN PSYCHOLOGICAL FACTORS, ADVERSE HEALTH BEHAVIOURS, AUTONOMIC DYSREGULATION, AND CARDIOVASCULAR DISEASE

Biopsychological framework

In this dissertation, autonomic regulation was shown to be linked to emotional states (*Chapter 4*) and cardiac healthy behaviours (*Chapter 6*). These findings align with a biopsychological framework (Figure 1), which connects emotional states, autonomic regulation, and cardiac healthy behaviours.

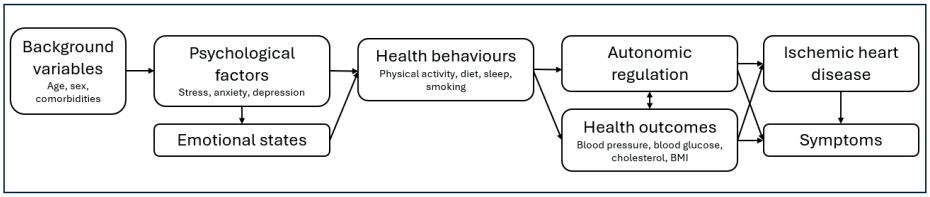


Figure 1. Biopsychological framework linking emotional states and health behaviours to autonomic regulation and cardiovascular health.

It is plausible to hypothesise a biopsychological model in which negative emotional states, in combination with adverse health behaviours, contribute to sustained autonomic imbalance and increased cardiac workload, thereby elevating the risk of myocardial ischemia and cardiac symptoms. Information on psychological factors, health behaviours, and autonomic markers may therefore have the potential to improve risk prediction and pre-test probability models for coronary artery disease. Supporting this idea, studies have shown that the addition of heart rate variability to traditional coronary artery disease risk factors significantly improves pre-test estimates for myocardial ischemia [41], and similar promising results have been reported for the inclusion of psychological factors in risk prediction models [42]. However, evidence remains limited, and the practical implications for implementations in health care systems have not been explored. In the current age of AI and machine learning and increasing pressure on healthcare systems, it is tempting to rely on algorithmic automation. Nonetheless, it remains essential to take the patient-centred perspective into account, as patient experiences provide valuable information that cannot be obtained via other ways of assessment [43]. The addition of psychological factors, health behaviours, and autonomic function offers a promising step toward holistic and personalised approaches to cardiovascular risk prediction and patient care that is grounded in the biopsychological model of health and disease.

Autonomic and central nervous system processes as related to cardiovascular disease risk

The foundation of the biopsychological model is the integration of fundamental biological processes with psychological and social factors that are important to health and disease. The brain plays a key role in the pathophysiology of CVD, not only in terms of disease processes, but also in the experience and expression of symptoms. For example, the brain and the autonomic nervous system regulate physiological processes and guide behaviour to maintain

continuous homeostasis in the body. The brain processes sensory information from the body's internal and external environment, while the two branches of the autonomic nervous system act on this information by stimulating or inhibiting physiological processes to maintain a balanced internal state [44]. The regulation of cardiac function offers a key example of this process. Sensory signals from the heart and blood vessels, including information from baroreceptors, chemoreceptors, and mechanoreceptors, are transmitted to the brain through vagal and spinal afferents. This information is integrated in the brain, primarily in the central autonomic network, which sends signals back to the heart through sympathetic and parasympathetic pathways. Together, these two branches innervate the sinoatrial node to regulate heart rate, contractility, and conduction velocity, and are thereby directly related to heart rate variability [45].

The neurovisceral integration model provides theoretical support for understanding how emotional states and cardiac healthy behaviours are involved in this system. This model posits that the same set of neural structures responsible for the regulation of autonomic processes (i.e., the central autonomic network (CAN)) is also involved in affective regulation and is critical for goal-directed behaviour [46]. Emotional states are processed in the limbic and cortical regions of the CAN and translated to autonomic signals appropriate for the valence of the emotion [47]. Negative or threatening emotions increase sympathetic activation with corresponding stimulating cardiac effects, whereas positive or safe emotions increase vagal activity and promote a calm state, measurable through HRV.

Cardiac healthy behaviours can be understood from the biopsychological perspective, with an important contribution of the autonomic and central nervous systems. Decisions on cardiac healthy behaviours and other goal-directed behaviours rely on various complex brain processes (e.g., prefrontal regions of the CAN), which align behaviour with long-term goals. These regions guide behaviour while also modulating the autonomic nervous system outflow [48]. For example, prefrontal activity may increase vagal tone, resulting in higher HRV, while simultaneously supporting health-promoting behavioural choices such as engaging in physical activity or refraining from an unhealthy diet [49, 50].

Future research is needed to evaluate whether central nervous system networks, such as the CAN, are potential targets to understand brain-behaviour relationships in patients with coronary artery disease or other cardiovascular disorders. Such networks could be used to understand the links between

psychological factors, cardiac healthy behaviours, and autonomic regulation. These links could be at the level of integrating affective and motivational states and their modulation of autonomic output to the heart and other organs to maintain homeostasis [51]. This perspective is consistent with the present findings that momentary emotional states were associated with HRV (*Chapter 4*). Similarly, cardiac healthy behaviours (e.g., physical activity and diet) were linked to HRV indices (*Chapter 6*), reflecting the potential of central nervous system involvement in decision making, motivation, regulation of impulse control, and long-term goal regulation [51]. Taken together, the investigations in this dissertation highlight the inter-relationships between psychological, behavioural, and biological processes and raise the question of the extent to which the brain plays an important role in these factors involved in coronary artery disease.

IMPLICATIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Implementation of interventions on psychological well-being

The OPTIMIZE intervention, developed to improve psychological well-being during MPI-SPECT, was designed to be provided by staff without specialised education in psychology or a related discipline and flexible enough to adjust to individual patient needs. However, even though prior research indicated high levels of distress throughout the diagnostic procedure [9] and therefore potential for improvement [13], the current intervention was unable to improve psychological well-being and may even increase negative affect in some patients (*Chapter 2*). These findings suggest that supportive interventions may not be universally beneficial and raise the hypothesis that such interventions should be delivered more selectively.

This issue is especially relevant in the current healthcare landscape, characterised by a shortage of staff and a large diversity in patient characteristics [52], which calls for personalised care and necessitates innovative and straightforward interventions to continue enhancing care with limited resources. To be able to provide such care and for it to be effective, patients at higher risk of distress and who may benefit from support have to be identified before starting the intervention. In our study, baseline anxiety and depressive symptoms were predictive of negative affect during diagnostic testing with MPI-SPECT (*Chapter 2*), highlighting their possible value as indicators for additional support. A brief online psychological evaluation consisting of such psychological factors upon first admission,

which automatically flags patients at higher risk, could already be sufficient. Such an evaluation might provide essential information for first selection, which can be used throughout the full diagnostic and treatment process without increasing staff burden [53].

However, screening alone is unlikely to provide a complete picture, as receiving unwanted support may inadvertently increase distress through mechanisms such as the nocebo effect [54, 55]. Although providing information about upcoming procedures or potential side effects can help reduce uncertainty, it may also unintentionally induce stress and exacerbate symptoms in some patients [56]. A similar increase in negative affect in response to supportive coaching was observed in the OPTIMIZE study (*Chapter 2*). Patient perspectives should therefore be taken into account. Shared decision-making is essential in health care [57], and interventions may be most effective when guided by both clinical factors and patient preferences, while remaining sensitive to the risk of counterproductive effects if these elements are not aligned.

Personalised care may also extend to the diagnostic procedure itself. For example, cardiac stress testing performed through physical exertion was shown to elicit less negative emotional responses compared to pharmacological stress testing. Allowing patients to voice their preferences could enhance their experience, although the final decision must remain with the physician to ensure safety and feasibility.

Together, the findings of the OPTIMIZE study (*Chapters 2 and 3*) raise the question of the extent to which supportive interventions can be beneficial to patients, and whether preferences and perceived needs are key factors for future implementation. Future research is needed to test this hypothesis and to determine which patients are most likely to benefit and how to identify these patients to maximise benefit and minimise the risk of unintended harm.

Timing and duration of intervention

In addition to personalisation concerning which patients may benefit from additional support, the timing and extent of supportive interventions may be equally important. The OPTIMIZE trial focused on the diagnostic procedure for the detection of myocardial ischemia, which represents only one phase in a longer diagnostic trajectory (See General Introduction for more information). For many patients, distress may arise earlier, at the time of referral or when awaiting test results, and may continue into treatment and follow-up, sometimes developing into depression [8]. In oncology, support and patient navigation systems that extend across diagnosis, treatment, and

follow-up have shown promising results with improvements in quality of life, patient satisfaction, and health outcomes [58, 59]. These interventions work by offering continuous access to social and informational support, reducing uncertainty, and providing a consistent point of contact. In comparison, the current brief 2-day supportive intervention might have been insufficient to address the broader psychological burden associated with CVD progression. A patient navigation system may therefore also be relevant in cardiology. Social and informational support that extends beyond MPI-SPECT, for example, by a personal coach available in moments of worry or uncertainty throughout the diagnostic and treatment process, could potentially improve psychological well-being, support adherence, reduce no-shows and cancellations or rescheduling of clinic visits related to incorrect preparation, and even improve health outcomes. Whether such an approach can be effective and efficiently implemented in current cardiology practice warrants future research. In addition, such interventions could be combined with long-term interventions, such as in the DoCHANGE and TIMELY trials, as described in this dissertation.

Diagnostic accuracy

Beyond their effects on psychological well-being, the timing and context of supportive interventions may have implications for diagnostic accuracy. Myocardial perfusion imaging is designed to provoke and detect ischemia under conditions of physical or pharmacological stress. In addition, myocardial ischemia can be induced by mental stress, which is associated with a greater risk of cardiovascular death or nonfatal myocardial infarction compared to conventionally induced ischemia [60]. Even though mental stress-induced ischemia is not part of the routine clinical diagnostic evaluation, interventions aimed at reducing distress during diagnostic testing carry the risk of masking such mental stress-induced ischemia. Although supportive interventions are unlikely to influence ischemia at this magnitude, it remains important to consider potential effects on diagnostic accuracy and to prioritise successful and accurate test completion and interpretability over short-term reductions in distress.

Clinical utility of heart rate variability to assess autonomic nervous system activity in patients with coronary artery disease

Heart rate variability has been widely used as an index for autonomic nervous system activity. In the current investigations, associations were observed between HRV and cardiovascular health, and cardiac healthy behaviours

(*Chapter 6*). These findings align with extensive literature showing that reduced HRV is linked to an increased risk of CVD events [61] and poorer physical functioning and recovery [62]. In cardiovascular populations, reductions in HRV below a certain range may indicate increased risk of mortality. Prior studies have shown that reduced parasympathetic nervous system activity precedes episodes of myocardial ischemia [63], and ischemia might also adversely affect autonomic nervous system regulation [64]. However, in the present dissertation, no evidence was found for an association between HRV and ischemia (*Chapter 4*). Furthermore, coronary revascularisation has been shown to restore autonomic balance [65], and HRV following the operation may be indicative of long-term mortality [66]. Heart rate variability may therefore serve as a risk factor for adverse clinical outcomes in patients with CAD and an indicator for additional support.

Beyond risk prediction, HRV also holds promise as a marker of progress in health tracking and behaviour change interventions. In this dissertation, support was found for an association of improvements in cardiovascular health and cardiac healthy behaviours with HRV indices of higher levels of parasympathetic nervous system activity (*Chapter 6*). Increases in HRV have also been reported in response to exercise programs [67]. These findings suggest that HRV could serve as an indicator of improvements in functional capacity and cardiovascular health, similar to heart rate and blood pressure, but providing a more integrative picture of overall health. This opens up opportunities for the use of HRV as a biofeedback tool for tailoring physical activity interventions to patients' fitness levels, especially in combination with AI and machine learning in telemedicine [68]. Such an approach that combines biofeedback tools and AI systems may facilitate the development of highly personalised interventions, while ensuring scalability and avoiding additional strain on hospital staff.

The utility of HRV in these situations depends highly on reliable and accurate measurements. Electrocardiography remains the gold standard for HRV measurement, but its reliance on medical personnel limits its usability in daily life. Consumer devices such as watches, straps, and rings using photoplethysmography have increased accessibility and show promising accuracy [62]. However, the absence of standardised algorithms and inconsistency across devices raises concerns about the reliability of such data, which complicates clinical interpretation and limits utility [64]. Future research should prioritise the development of standardised HRV measurement protocols and explore how these can be integrated into healthcare systems,

for cardiovascular risk prediction and for monitoring functional capacity in eHealth interventions.

Integrating psychological and autonomic markers in the management of coronary artery disease

Negative emotional states may not only be relevant from a patient care perspective but also play an important role in disease onset and progression. Findings from the OPTIMIZE study suggest an association between negative emotional states and reduced autonomic regulation (*Chapter 4*). These findings are in line with the literature and suggest that negative emotions contribute to physiological arousal, particularly in the autonomic nervous system [69]. A shift towards sympathetic dominance may result in increased cardiac demand through elevated heart rate, stroke volume, and peripheral resistance [70]. In addition, impaired baroreflex sensitivity can reduce adequate responses to changes in blood pressure and volume, further limiting adaptive cardiovascular regulation [35, 71]. Autonomic dysregulation was, in turn, related to cardiac symptoms, and although limited evidence was found for a direct relationship between autonomic regulation and inducibility and severity of myocardial ischemia (*Chapter 4*), this association has been observed in previous studies [72, 73]. The absence of a clear link in the OPTIMIZE study is therefore likely explained by patient characteristics, such as the low severity of psychological distress and relatively infrequent incidence of myocardial ischemia, rather than evidence contradicting the biobehavioural mechanisms linking psychological factors to ischemic heart disease progression.

The health intervention patient paradox

The limited improvements in cardiac healthy behaviours and cardiovascular health observed in the current investigations (*Chapters 5 and 6)* may be related to the study population and a phenomenon we describe as the "health intervention patient paradox." This paradox refers to the discrepancy between patients who are most likely to engage with the health interventions and those who may need them the most.

Patients who are proactive in managing their health and who are digitally literate are more likely to participate in health interventions. Their baseline levels of motivation are typically higher, and consequently, their overall physical functioning is relatively good [74]. Even though they may still benefit from these programs, it limits the potential for large improvements because of a ceiling effect in cardiac healthy behaviours or cardiovascular outcomes, which was also observed in the current studies. In contrast, patients who

experience the greatest difficulty with maintaining optimal cardiac healthy behaviours are less likely to engage with or adhere to eHealth interventions. These are exactly the patients who require additional support and may benefit the most from interventions. Barriers related to socioeconomic status, age, digital literacy, and health literacy [20, 75] may reduce participation and also limit the generalisability of findings [76].

This paradox may explain why intervention effects across studies are inconsistent despite strong theoretical foundations. More importantly, it raises significant implications for the development and evaluation of eHealth behaviour change programs. If interventions primarily attract patients in relatively good health, this may inadvertently widen rather than narrow health disparities [77]. These considerations extend beyond eHealth programs and may also apply to other behavioural or psychological interventions. To address this challenge, researchers need to prioritise the inclusion of less-engaged patients in both study recruitment and the co-design of interventions, and evaluate the differential effects across subgroups. Such strategies are crucial for creating and implementing effective interventions that reach patients most in need and contribute to reducing health inequalities.

GENERAL CONCLUSION

This dissertation contributes to a better understanding of the effectiveness of supportive and cardiac health behaviour change interventions with respect to psychological functioning and autonomic regulation. Psychological distress during MPI-SPECT was found to occur primarily during cardiac stress testing, and overall levels of distress were low to moderate. Brief supportive coaching was not sufficient to improve psychological well-being. Furthermore, evidence indicated that negative emotional states and anginal symptoms in daily life are related to reduced autonomic regulation in patients with suspected ischemic heart disease. These findings highlight the downstream straining effect of negative emotions on the autonomic nervous system and clinical outcomes. Concerning the link between autonomic regulation and cardiac health behaviour change in eHealth interventions, inconsistent findings were observed. While no association between heart rate variability and cardiac health behaviour change was observed in the DoCHANGE study, such a relationship emerged in the TIMELY study. These mixed findings highlight the complexity of both autonomic regulation and behavioural adaptation as well as their link, and may depend on study design, measurement tools,

and intervention characteristics. Taken together, this dissertation advanced both practical and mechanistic insights that can support the development of interventions and guide future research on psychological and physical support to improve well-being in patients with coronary artery disease.

REFERENCE LIST

1. Tsao, C.W., et al., Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. Circulation, 2022. 145(8): p. e153-e639.
2. Lui, J.N.M., et al., Impact of New Cardiovascular Events on Quality of Life and Hospital Costs in People With Cardiovascular Disease in the United Kingdom and United States. Journal of the American Heart Association, 2023. 12(19): p. e030766.
3. Lewis, E.F., et al., Impact of cardiovascular events on change in quality of life and utilities in patients after myocardial infarction: a VALIANT study (valsartan in acute myocardial infarction). JACC Heart Fail, 2014. 2(2): p. 159-65.
4. World Heart Obervatory. 2021; Available from: https://world-heart-federation.org/world-heart-observatory/countries/netherlands/.
5. Roovers, T., et al., Psychological well-being and the effects of supportive coaching during SPECT myocardial perfusion imaging in patients with suspected ischemic heart disease, in Journal of Psychosomatic Research. 2025.
6. Habibović, M., et al., Enhancing Lifestyle Change in Cardiac Patients Through the Do CHANGE System (''Do Cardiac Health: Advanced New Generation Ecosystem''): Randomized Controlled Trial Protocol. JMIR Res Protoc, 2018. 7(2): p. e40.
7. Habibovic, M., et al., Patient-Centered Risk Prediction, Prevention, and Intervention Platform (TIMELY) to Support the Continuum of Care in Coronary Artery Disease Using eHealth and Artificial Intelligence: Protocol for a Randomized Controlled Trial. JMIR Res Protoc, 2025. 14: p. e66283.
8. Borkowski, P., and Borkowska, N. Understanding Mental Health Challenges in Cardiovascular Care. Cureus, 2024. 16(2): p. e54402.
9. Bekendam, M.T., Psychological factors in patients with ischemic heart disease and cardiac complaints: A qualitative investigation of perceptions and experiences, in Facing the heart, on the role of acute emotions and psychological factors in patients with ischemic heart disease. 2022, Tilburg University: Tilburg, The Netherlands.
10. Bekendam, M.T. Facing the Heart: On the role of acute emotions and psychological factors in patients with ischemic heart disease, in Medical and Clinical Psychology. 2022, Tilburg University: Tilburg.
11. Stewart, M., et al., The impact of patient-centered care on outcomes. J Fam Pract, 2000. 49(9): p. 796-804.
12. Gerteis, M., et al., Through the patient's eyes: understanding and promoting patient-centered care. First edition ed. Jossey-Bass health series. 1993, San Francisco: Jossey-Bass.
13. Gilbert, J.E., et al., Nurses as patient navigators in cancer diagnosis: review, consultation and model design. European Journal of Cancer Care, 2011. 20(2): p. 228-236.
14. Townsend, N., et al., Cardiovascular disease in Europe: epidemiological update 2016. European Heart Journal, 2016. 37 42: p. 3232-3245.

15. Grupe, D.W., and Nitschke, J.B. Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. Nat Rev Neurosci, 2013. 14(7): p. 488-501.

16. Zhang, X., and Xu, H. Prediction of Angina Pectoris Events in Middle-Aged and Elderly People Using RR Interval Time Series in the Resting State: A Cohort Study Based on SHHS. International Journal of Computational Intelligence Systems, 2023. 16(1): p. 10.

17. Thomas, R.J., et al., Home-Based Cardiac Rehabilitation: A Scientific Statement From the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology. Circulation, 2019. 140(1): p. e69-e89.

18. Redfern, J., et al., A digital health intervention for cardiovascular disease management in primary care (CONNECT) randomized controlled trial. npj Digital Medicine, 2020. 3(1): p. 117.

19. Su, J.J., Yu, D.S.F., and Paguio, J.T. Effect of eHealth cardiac rehabilitation on health outcomes of coronary heart disease patients: A systematic review and meta-analysis. J Adv Nurs, 2020. 76(3): p. 754-772.

20. Douma, E.R., et al., Patient-reported preferences in eHealth-based cardiac rehabilitation: A qualitative investigation of behavior change techniques, barriers and facilitators. Internet Interv, 2024. 35: p. 100728.

21. Lloyd-Jones, D.M., et al., Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association. Circulation, 2022. 146(5): p. e18-e43.

22. Roovers, T., et al., Changes in heart rate variability during an eHealth behavior change intervention program in patients with cardiovascular disease. IJC Heart & Vasculature, 2024. 55: p. 101563.

23. Roovers, T., et al., The effects of the TIMELY intervention on autonomic regulation and the association with Life's Essential factors. 2025, Tilburg University, Tilburg, The Netherlands.

24. Electrophysiology, T.F.o.t.E.S.o.C.t.N.A.S.o.P., Heart Rate Variability. Circulation, 1996. 93(5): p. 1043-1065.

25. Rhodes, R.E., et al., Physical activity: Health impact, prevalence, correlates and interventions. Psychology & Health, 2017. 32(8): p. 942-975.

26. de Ridder, D., et al., Healthy diet: Health impact, prevalence, correlates, and interventions. Psychol Health, 2017. 32(8): p. 907-941.

27. Conner, M., and Norman, P. Health behaviour: Current issues and challenges. Psychology & Health, 2017. 32(8): p. 895-906.

28. Tanweer, A., et al., Improving dietary data collection tools for better nutritional assessment – A systematic review. Computer Methods and Programs in Biomedicine Update, 2022. 2: p. 100067.

29. Park, Y., et al., Comparison of self-reported dietary intakes from the Automated Self-Administered 24-h recall, 4-d food records, and food-frequency questionnaires against recovery biomarkers1. The American Journal of Clinical Nutrition, 2018. 107(1): p. 80-93.

30. Chotwanvirat, P., et al., Advancements in Using AI for Dietary Assessment Based on Food Images: Scoping Review. J Med Internet Res, 2024. 26: p. e51432.

31. Ramsey, S.A., Gold, E.S., and Aderem, A. A systems biology approach to understanding atherosclerosis. EMBO Mol Med, 2010. 2(3): p. 79–89.

32. Billman, G.E., Heart rate variability – a historical perspective. Front Physiol, 2011. 2: p. 86.

33. Schwartz, M.S., and Andrasik, F. Biofeedback: A practitioner's guide. 2017: Guilford Publications.

34. Shaffer, F., McCraty, R., and Zerr, C.L. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. Front Psychol, 2014. 5: p. 1040.

35. Salah, H.M., et al., Baroreflex Function in Cardiovascular Disease. Journal of Cardiac Failure, 2025. 31(1): p. 117–126.

36. Laborde, S., Mosley, E., and Thayer, J.F. Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research – Recommendations for Experiment Planning, Data Analysis, and Data Reporting. Front Psychol, 2017. 8: p. 213.

37. Shaffer, F., and Ginsberg, J.P. An Overview of Heart Rate Variability Metrics and Norms. Frontiers in Public Health, 2017. 5.

38. Quigley, K.S., et al., Publication guidelines for human heart rate and heart rate variability studies in psychophysiology–Part 1: Physiological underpinnings and foundations of measurement. Psychophysiology, 2024. 61(9): p. e14604.

39. Althubaiti, A., Information bias in health research: definition, pitfalls, and adjustment methods. J Multidiscip Healthc, 2016. 9: p. 211–7.

40. Lo, F.P.W., et al., Dietary Assessment With Multimodal ChatGPT: A Systematic Analysis. IEEE Journal of Biomedical and Health Informatics, 2024. 28(12): p. 7577–7587.

41. Goldenberg, I., et al., Heart Rate Variability for Risk Assessment of Myocardial Ischemia in Patients Without Known Coronary Artery Disease: The HRV-DETECT (Heart Rate Variability for the Detection of Myocardial Ischemia) Study. J Am Heart Assoc, 2019. 8(24): p. e014540.

42. Dorraki, M., et al., Cardiovascular disease risk prediction via machine learning using mental health data. European Heart Journal, 2022. 43(Supplement_2).

43. Shah, N.R., and Hulten, E.A. Listening is still the first 'test' in diagnosing patients with chest pain. J Nucl Cardiol, 2024. 31: p. 101772.

44. Buijs, R.M., Chapter 1 – The autonomic nervous system: a balancing act, in Handbook of Clinical Neurology, Buijs, R.M., and Swaab, D.F. Editors. 2013, Elsevier. p. 1–11.

45. Saul, J., Beat-To-Beat Variations of Heart Rate Reflect Modulation of Cardiac Autonomic Outflow. Physiology, 1990. 5(1): p. 32–37.

46. Thayer, J.F., et al., Heart Rate Variability, Prefrontal Neural Function, and Cognitive Performance: The Neurovisceral Integration Perspective on Self-regulation, Adaptation, and Health. Annals of Behavioral Medicine, 2009. 37(2): p. 141–153.

47. ten Donkelaar, H.J., et al., The Limbic System, in Clinical Neuroanatomy: Brain Circuitry and Its Disorders. 2020, Springer International Publishing: Cham. p. 745-830.

48. Thayer, J.F., and Ruiz-Padial, E. Neurovisceral integration, emotions and health: An update. International Congress Series, 2006. 1287: p. 122-127.

49. Plessow, F., Kiesel, A., and Kirschbaum, C. The stressed prefrontal cortex and goal-directed behaviour: acute psychosocial stress impairs the flexible implementation of task goals. Experimental Brain Research, 2012. 216(3): p. 397-408.

50. Hasselmo, M.E. A Model of Prefrontal Cortical Mechanisms for Goal-directed Behavior. Journal of Cognitive Neuroscience, 2005. 17(7): p. 1115-1129.

51. Thayer, J., and Koenig, J. The Neurobiology of Self-regulation: A Neurovisceral Integration Perspective. 2023.

52. OECD and E. Commission, Health at a Glance: Europe 2024. 2024.

53. Kupper, N., et al., The importance, consequences and treatment of psychosocial risk factors in heart disease: less conversation, more action! Neth Heart J, 2024. 32(1): p. 6-13.

54. Wartolowska, K., The nocebo effect as a source of bias in the assessment of treatment effects. F1000Res, 2019. 8: p. 5.

55. Blasini, M., et al., Nocebo and pain: An overview of the psychoneurobiological mechanisms. Pain Rep, 2017. 2(2).

56. Varelmann, D., et al., Nocebo-induced hyperalgesia during local anesthetic injection. Anesth Analg, 2010. 110(3): p. 868-70.

57. Shay, L.A., and Lafata, J.E. Where Is the Evidence? A Systematic Review of Shared Decision Making and Patient Outcomes. Medical Decision Making, 2015. 35(1): p. 114-131.

58. Yin, Y.N., et al., Can case management improve cancer patients quality of life? A systematic review following PRISMA. Medicine, 2020. 99(40): p. e22448.

59. Berezowska, A., Passchier, E., and Bleiker, E. Professional patient navigation in a hospital setting: a randomized controlled trial. Supportive Care in Cancer, 2021. 29(4): p. 2111-2123.

60. Vaccarino, V., et al., Association of Mental Stress-Induced Myocardial Ischemia With Cardiovascular Events in Patients With Coronary Heart Disease. Jama, 2021. 326(18): p. 1818-1828.

61. Fang, S.C., Wu, Y.L., and Tsai, P.S. Heart Rate Variability and Risk of All-Cause Death and Cardiovascular Events in Patients With Cardiovascular Disease: A Meta-Analysis of Cohort Studies. Biological Research For Nursing, 2020. 22(1): p. 45-56.

62. Turcu, A.-M., et al., The Impact of Heart Rate Variability Monitoring on Preventing Severe Cardiovascular Events. Diagnostics, 2023. 13(14): p. 2382.

63. Kop, W.J., et al., Changes in heart rate and heart rate variability before ambulatory ischemic events. J Am Coll Cardiol, 2001. 38(3): p. 742-9.

64. Khan, M.S., et al., Heart rate variability in patients with cardiovascular diseases. Progress in Cardiovascular Diseases, 2025.

65. Abdelnabi, M., et al., Effects of coronary revascularization by elective percutaneous coronary intervention on cardiac autonomic modulation assessed by heart rate variability: a single-center prospective cohort study. American Journal of Cardiovascular Disease, 2021. 11(1): p. 164.

66. Mehrabanian, M.J., et al., The value of heart rate variability in predicting long-term poorer outcome in patients undergoing coronary artery bypasses grafting and referring intensive care unit: a prospective cohort study. 2023.

67. Iellamo, F., et al., Effects of a residential exercise training on baroreflex sensitivity and heart rate variability in patients with coronary artery disease: A randomized, controlled study. Circulation, 2000. 102(21): p. 2588-92.

68. Casanova-Lizón, A., et al., Impact of heart rate variability-based exercise prescription: self-guided by technology and trainer-guided exercise in sedentary adults. Frontiers in Sports and Active Living, 2025. 7.

69. Kreibig, S.D. Autonomic nervous system activity in emotion: a review. Biol Psychol, 2010. 84(3): p. 394-421.

70. Borchard, U. The Role of the Sympathetic Nervous System in Cardiovascular Disease. J Clin Basic Cardiol, 2001. 4.

71. Goldstein, D.S., et al., Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. Exp Physiol, 2011. 96(12): p. 1255-61.

72. Lucini, D., and Pagani, M. Heart rate variability, autonomic regulation and myocardial ischemia. International Journal of Cardiology, 2020. 312: p. 22-23.

73. Shah, A.S., et al., Alterations in heart rate variability are associated with abnormal myocardial perfusion. International Journal of Cardiology, 2020. 305: p. 99-105.

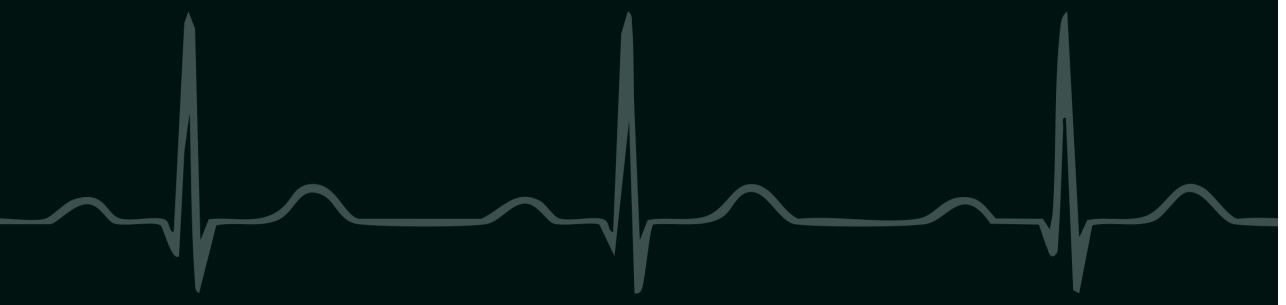
74. Barello, S., et al., 'Engage me in taking care of my heart': a grounded theory study on patient–cardiologist relationship in the hospital management of heart failure. BMJ Open, 2015. 5(3): p. e005582.

75. Reiners, F., et al., Sociodemographic Factors Influencing the Use of eHealth in People with Chronic Diseases. International Journal of Environmental Research and Public Health, 2019. 16(4): p. 645.

76. Toscos, T., et al., Selection biases in technology-based intervention research: patients' technology use relates to both demographic and health-related inequities. J Am Med Inform Assoc, 2019. 26(8-9): p. 835-839.

77. Veinot, T.C., Mitchell, H., and Ancker, J.S. Good intentions are not enough: how informatics interventions can worsen inequality. Journal of the American Medical Informatics Association, 2018. 25(8): p. 1080-1088.

Appendix



SUMMARY

Cardiovascular diseases have a profound impact on patients' lives, affecting both psychological and physical functioning. Mental health is influenced not only by cardiac symptoms and worries over the disease itself, but also by the diagnostic procedures patients undergo. While the current healthcare primarily focuses on the clinical outcomes of these procedures, which are undoubtedly important, more attention should be given to the psychological burden associated with diagnostics and treatments. In terms of treatment, prevention and lifestyle improvements should be prioritized. eHealth interventions offer a promising, cost-effective alternative or complement to traditional cardiac rehabilitation. Lifestyle-related health behaviours and psychological factors are interrelated and both are associated with the autonomic nervous system, which is closely linked to cardiac function. A better understanding of how psychological factors and health behaviours are related to autonomic nervous system regulation and cardiovascular health, and how interventions targeting these domains work from a biobehavioural perspective, will help to improve both quality of life and clinical outcomes in patients with cardiovascular disease.

RESEARCH AIMS

This dissertation explores key aspects of coronary artery disease to enhance our understanding of biobehavioural processes and to evaluate interventions aimed at improving mental well-being and lifestyle behaviours in patients with coronary artery disease. The first part of the dissertation examines the effects of a supportive intervention on mental well-being during the diagnostic process of coronary artery disease. The second part addresses the role of the autonomic nervous system in psychological and physical functioning.

MAIN FINDINGS

Part I Patient Experiences and Emotional Reactions to Cardiac Diagnostic Procedures

In **Chapter 2**, negative affect, as a measure of mental well-being, was assessed in patients undergoing myocardial perfusion imaging (MPI-SPECT), and the effects of a supportive coaching intervention were evaluated. Overall,

negative affect changed significantly throughout the diagnostic procedure, with patients experiencing the greatest distress during the cardiac stress testing phase. The supportive coaching intervention, however, did not produce significant benefits compared with the control group in terms of negative affect, symptoms, inducibility of ischemia, or patient satisfaction. Notably, higher levels of negative affect were associated with increased anginal and adenosine-related symptoms during cardiac stress testing. The current, relatively brief, supportive intervention was therefore insufficient to produce meaningful psychological or clinical results. This study highlights the need to evaluate interventions implemented over a longer period, from first admission through treatment, to better understand their potential impact and limitations.

Assessment of mental well-being is most commonly based on self-report. **Chapter 3** builds upon the findings in Chapter 2 by introducing an objective approach to assess well-being through analyses of facial emotion expression. This study specifically focused on the most stressful component of MPI-SPECT identified in the previous chapter: the cardiac stress test. The findings showed that analyses of facial emotion expression can capture changes in negative emotions during cardiac stress testing. However, consistent with the previous chapter, short-term supportive coaching did not reduce negative emotional responses during cardiac stress testing. Interestingly, differences emerged between stress test protocols. Patients undergoing the exercise-based protocol exhibited fewer negative emotions than those receiving the pharmacological protocol. Furthermore, the presence of symptoms during testing was associated with negative emotions. Together, these findings highlight the importance of a holistic patient care approach that addresses emotional states, physical symptoms, and their inter-relationships during cardiac stress testing. The selection between exercise and pharmacological stress testing protocols should therefore consider not only the patient's physical characteristics but also their expected symptomatic and emotional responses.

Part II Autonomic Regulation in Behavioural and Psychological Contexts of Cardiovascular Disease

In **Chapter 4**, the relationship between psychological functioning and autonomic nervous system activity was examined through analyses of heart rate variability (HRV) indices and ecological momentary assessments over a 24-hour period. Acute negative emotional states, representing psychological functioning, were significantly associated with HRV. Specifically, heightened

emotional responses were related to lower low-frequency power and SDNN, and to higher heart rate, indicating impaired baroreflex control and overall reduced autonomic regulatory capacity. In addition, cardiac symptoms were associated with both acute negative emotional states and reduced autonomic regulation. These findings suggest a potential pathway in which negative emotional states contribute to diminished autonomic function, potentially leading to physiological strain on the cardiovascular system and triggering symptoms such as angina and dyspnoea. Finally, some evidence emerged for a relationship between the severity of perfusion defects and autonomic regulation, possibly reflecting reduced baroreflex sensitivity and autonomic regulatory capacity as risk factors for myocardial ischemia. However, results were inconsistent and should therefore be interpreted with caution. Overall, this chapter indicates that momentary negative emotions are linked to adverse changes in autonomic regulation, which may in turn contribute to physiological strain and symptoms. The findings highlight the importance of capturing in-the-moment emotional states for understanding autonomic dysregulation and cardiovascular risk.

The role of autonomic nervous system activity in cardiovascular risk was also assessed in relation to cardiac healthy behaviours. **Chapter 5** examined changes in HRV indices throughout a behaviour change program and their association with changes in health behaviours. Changes in RMSSD were observed throughout the 6-month study period, primarily showing reductions during the follow-up phase but not during the active intervention. This reduction in autonomic regulatory capacity was less pronounced among patients who, at baseline, already engaged in cardiac healthy behaviours. Furthermore, improvements in behaviours such as dietary habits and stress management were observed throughout the active intervention phase. However, these behavioural improvements were not associated with parallel changes in autonomic nervous system activity. Overall, this chapter emphasizes the complex relationship between behavioural change and autonomic function, and underscores the need for further research to clarify how sustained lifestyle improvements translate to autonomic functioning.

Chapter 6 extended this work by examining the role of overall cardiovascular health, particularly cardiac healthy behaviours and clinical health factors, in autonomic regulation during an eHealth behaviour change program. Modest improvements in cardiovascular health were observed throughout the intervention, driven mainly by physical activity and healthier dietary habits, whereas clinical health factors showed no significant improvements over time. Improvements in cardiovascular health, physical activity, and

diet showed small but significant associations with HRV indices, indicating enhanced autonomic regulation. In contrast, no such associations were found for clinical health factors. These findings support the value of HRV as a meaningful marker of changes in autonomic regulation and cardiovascular health within behavioural interventions for patients with coronary artery disease.

Conclusion

This dissertation enhances understanding of the interplay between psychological and health behaviour interventions, psychological functioning and autonomic regulation in patients with cardiovascular disease. Brief supportive coaching did not improve psychological well-being during cardiac diagnostic testing and there is a need for other approaches that cover the full duration of the diagnostic and treatment components of cardiovascular disease. Evidence was found that the type of cardiac stress testing contributes to the levels of psychological well-being, with relative benefits of bicycle exercise testing over pharmacological stress testing. Moreover, objective measures of emotional states through facial expression analysis may provide insights into psychological well-being that self-report measures cannot capture. Negative emotions and cardiac symptoms were associated with reduced autonomic regulation, suggesting that emotional strain may adversely affect cardiovascular function. Findings on the relationship between autonomic regulation and behaviour change were inconsistent, highlighting the complexity of these processes. Overall, the work provides both practical and mechanistic insights to guide future interventions aimed at improving psychological and physical well-being in patients with coronary artery disease.

NEDERLANDSE SAMENVATTING (DUTCH SUMMARY)

Hart- en vaatziekten hebben een grote impact op het leven van patiënten, zowel psychologisch als lichamelijk. Hun mentale gezondheid wordt niet alleen beïnvloed door zorgen over de ziekte zelf, maar ook door de diagnostische procedures die zij moeten ondergaan. De huidige gezondheidszorg richt zich vooral op de klinische uitkomsten van deze procedures. Ondanks dat deze uitkomsten van groot belang zijn, verdient de psychologische belasting van het diagnostisch proces meer aandacht. Daarnaast moet er worden ingezet op preventie, onder andere via leefstijlverbetering. eHealth interventies vormen hierbij een veelbelovend kosteneffectief alternatief of een waardevolle aanvulling op traditionele cardiorevalidatie. Vanuit een mechanistisch perspectief worden zowel psychologisch functioneren als gezondheidsgedrag gereguleerd door het autonoom zenuwstelsel, dat nauw verbonden is met het cardiovasculaire systeem. Een beter begrip van hoe psychologische factoren en gezondheidsgedrag de cardiovasculaire gezondheid beïnvloeden, inclusief de onderliggende biologische mechanismen en de effecten van interventies, kan leiden tot richtlijnen die kunnen bijdragen aan het verbeteren van zowel de kwaliteit van leven als klinische uitkomsten.

ONDERZOEKSDOELEN

Dit proefschrift onderzoekt aspecten van coronaire hartziekte met als doel biologische en gedragsmatige processen beter te begrijpen en interventies te evalueren die gericht zijn op het verbeteren van mentaal welbevinden en leefstijlgedrag. Het eerste deel van het proefschrift onderzoekt de effecten van een ondersteunende interventie op het mentale welbevinden tijdens het diagnostisch proces. Het tweede deel onderzoekt de rol van het autonoom zenuwstelsel in het psychologisch en lichamelijk functioneren.

BELANGRIJKSTE BEVINDINGEN

Deel I Patiëntervaringen en emotionele reacties tijdens diagnostische procedure

In **Hoofdstuk 2** is negatieve affectiviteit onderzocht als maat voor mentaal welbevinden bij patiënten die een myocardperfusiescan (MPI-SPECT) ondergingen. De effecten van een ondersteunende coaching interventie bij deze ingreep werden ook bekeken. Negatieve affectiviteit veranderde

significant gedurende het diagnostisch proces waarbij patiënten de hoogste stressniveaus rapporteerden tijdens de inspanningstest. Desondanks leidde de ondersteunende coaching interventie niet tot verbeteringen in negatieve affectiviteit, symptomen, ischemie of patiënttevredenheid ten opzichte van de controlegroep. Opvallend was dat hogere negatieve affectiviteit samenhing met meer hartklachten en adenosine-gerelateerde symptomen tijdens de inspanningstest. De relatief korte ondersteunende interventie bleek onvoldoende om betekenisvolle psychologische of klinische effecten te bewerkstelligen, wat de noodzaak onderstreept om interventies te evalueren die over een langere periode zijn toegepast, van eerste opname tot en met behandeling, met de verwachting dat potentiële effecten en beperkingen beter zichtbaar worden.

Mentaal welzijn wordt voornamelijk geëvalueerd door zelfrapportage. In **Hoofdstuk 3** is voortgebouwd op hoofdstuk 2 door een objectieve maat te gebruiken voor psychologisch welzijn, namelijk door middel van gezichtsuitdrukkingen. Dit is onderzocht gedurende het meest stressvolle onderdeel van de MPI-SPECT, zoals geïdentificeerd in het voorgaande hoofdstuk: de inspanningstest. De analyse van gezichtsuitdrukkingen laat veranderingen zien in negatieve emoties tijdens de inspanningstest. In lijn met de bevindingen uit het vorige hoofdstuk was de kortdurende ondersteunende coaching onvoldoende om de negatieve emotionele reacties te verminderen. Interessant genoeg werden er wel verschillen gevonden voor de afzonderlijke inspanningstestprotocollen. Patiënten die een fietstest uitvoerden, vertoonden minder negatieve emoties dan patiënten bij wie inspanning werd nagebootst door middel van medicijnen. Daarnaast hing het optreden van symptomen tijdens de test samen met negatieve emoties. Deze bevindingen benadrukken het belang van een holistische benadering van patiëntenzorg, waarin aandacht is voor het psychologisch welzijn, lichamelijke symptomen en hun onderlinge samenhang tijdens inspanningstesten en diagnostische procedures in het algemeen. De keuze tussen het fiets- of farmacologisch inspanningsprotocol moet daarnaast niet alleen worden gebaseerd op fysieke kenmerken van de patiënt, maar ook op de verwachte symptomatische en emotionele reacties.

Deel II Autonome regulatie in gedragsmatige en psychologische contexten van hart- en vaatziekten

In **Hoofdstuk 4** is de relatie tussen psychologisch functioneren en activiteit van het autonoom zenuwstelsel onderzocht door middel van analyses van hartslagvariabiliteit (HRV) en dagboekmetingen (Ecological Momentary Assessment) over een periode van 24 uur. Acute negatieve emoties waren

significant geassocieerd met HRV. Sterkere emotionele reacties hingen samen met lagere low-frequency power en SDNN, en met een hogere hartslag, wat wijst op een verminderde baroreflex controle en algemene autonome regulatiecapaciteit. Daarnaast waren hartklachten geassocieerd met zowel acute negatieve emoties als slechtere autonome regulatie. Deze resultaten suggereren een mechanisme waarbij negatieve emoties bijdragen aan een verstoring van de autonome balans, wat kan leiden tot hogere fysiologische belasting van het cardiovasculaire systeem en vervolgens tot symptomen zoals angina pectoris en dyspneu. Ten slotte werd bewijs gevonden voor een relatie tussen de mate van perfusiedefecten en autonome regulatie, wat mogelijk kan wijzen op verminderde baroreflex controle en autonome functie (risicofactoren voor ischemie). Deze bevindingen waren echter inconsistent en moeten daarom voorzichtig worden geïnterpreteerd. Dit onderzoek levert bewijs dat acute negatieve emoties samenhangen met ongunstige veranderingen in autonome regulatie. Deze disregulatie kan vervolgens bijdragen aan verhoogde fysiologische belasting en het optreden van symptomen. De resultaten onderstrepen het belang van het onderzoeken en monitoren van acute emoties om autonome disregulatie en cardiovasculair risico beter te kunnen begrijpen.

De rol van het autonoom zenuwstelsel in cardiovasculair risico werd daarnaast onderzocht in relatie tot gezondheidsgedrag. **Hoofdstuk 5** richt zicht op veranderingen in HRV tijdens een gedragsveranderingsprogramma, evenals op de samenhang tussen veranderingen in HRV en gezondheidsgedrag. Tijdens de zes maanden van het onderzoek werden veranderingen in RMSSD waargenomen. Er trad een afname op in de follow-up fase maar niet tijdens de actieve interventieperiode. De afname in autonome regulatiecapaciteit was minder uitgesproken bij patiënten die bij aanvang van het onderzoek al gezond gedrag vertoonden. Daarnaast vonden er verbeteringen plaats in gezondheidsgedrag, zoals dieetgewoonte en stressmanagement, tijdens de actieve interventiefase. Deze gedragsverbeteringen hingen echter niet samen met parallelle veranderingen in de activiteit van het autonome zenuwstelsel. Deze resultaten benadrukken daarmee de complexe relatie tussen gezondheidsgedrag en autonome functie, en onderstrepen de noodzaak van verder onderzoek naar hoe duurzame leefstijlverbeteringen zich vertalen in veranderingen in autonome regulatie.

Hoofdstuk 6 borduurt verder op hoofdstuk 5 door de relatie tussen cardiovasculaire gezondheid, waaronder gezondheidsgedrag en klinische gezondheidsfactoren, en autonome regulatie te onderzoeken tijdens een eHealth-gedragsveranderingsprogramma. Tijdens de interventie werden kleine verbeteringen waargenomen in algemene cardiovasculaire gezondheid,

lichamelijke activiteit en eetgewoonten. Er traden echter geen verbeteringen op in klinische gezondheidsfactoren, zoals bijvoorbeeld bloeddruk. De positieve verandering in cardiovasculaire gezondheid, lichamelijke activiteit en dieet vertoonden kleine maar significante associaties met HRV, wat wijst op gunstige verandering in autonome regulatie. Voor de klinische gezondheidsfactoren werd geen relatie met HRV gevonden. Dit onderzoek ondersteunt de waarde van HRV als een waardevolle indicator voor veranderingen in autonome regulatie en cardiovasculaire gezondheid bij gedragsinterventies voor patiënten met coronaire hartziekte.

Conclusie

Dit proefschrift draagt bij aan de kennis over hoe ondersteunende coaching en gedragsverandering interventies psychologisch functioneren en autonome regulatie beïnvloeden. Kortdurende ondersteunende coaching tijdens diagnostische procedures verbeteren het mentaal welbevinden niet. Het type inspanningstest heeft wel invloed op de mate van psychologische belasting. Daarnaast kunnen objectieve metingen van emoties, door middel van gezichtsuitdrukkingen, inzichten geven die niet via zelfrapportage kunnen worden verkregen. Negatieve emoties en hartklachten zijn geassocieerd met verminderde autonome regulatie, wat suggereert dat acute negatieve emoties een ongunstig effect hebben op het cardiovasculair systeem. De bevindingen met betrekking tot de relatie tussen autonome regulatie en gedragsveranderingen waren inconsistent, wat de complexiteit van deze processen benadrukt. Samengevat biedt het onderzoek in dit proefschrift zowel praktische als mechanische inzichten die van waarde kunnen zijn voor toekomstige interventies gericht op het verbeteren van het psychologisch en lichamelijk welzijn van patiënten met coronaire hartziekte.

LIST OF PUBLICATIONS

Roovers, T., Vermeltfoort, I.A.C., Widdershoven, J.W., & Kop, W.J. (2025). Psychological well-being and the effects of supportive coaching during SPECT myocardial perfusion imaging in patients with suspected ischemic heart disease. Journal of Psychosomatic Research. 197: p. 112355.

Roovers, T., Vermeltfoort, I.A.C., Widdershoven, J.W., & Kop, W.J. Emotional responses to cardiac stress testing using digital analysis of facial expressions in patients with suspected ischemic heart disease. *Under review.*

Roovers, T., Vermeltfoort, I.A.C., Widdershoven, J.W., & Kop, W.J. Heart rate variability and its association with psychological well-being in patients with suspected ischemic heart disease. *Under review.*

Roovers, T., Habibovic, M., Lodder, P., Widdershoven, J.W., & Kop, W.J. (2024). Changes in heart rate variability during an eHealth behavior change intervention program in patients with cardiovascular disease. IJC Heart & Vasculature. 55: p. 101563.

Roovers, T., Douma, E.R., Habibovic, M., Hammer, A., Schmitz, B., Widdershoven, J.W., & Kop, W.J. The effects of an integrated health behaviour intervention on autonomic regulation: A secondary analysis of the TIMELY trial on the associations with changes in cardiovascular risk factors. *In preparation for publication submission.*

Douma, E.R., **Roovers, T.,** Habibovic, M., Bruijn, G.J., Bosch, J.A., Schmitz, B., & Kop, W.J. (2024). Effectiveness of behavior change techniques in eHealth-based cardiac rehabilitation in patients with coronary artery disease: A systematic review: Effective behavior change techniques in eHealth CR. *American Journal of Preventive Cardiology, 20,* 100892.

Habibovic, M., Douma, E.R., Schäfer, H., Sestayo-Fernandez, M., **Roovers, T.,** Sun, X., Schmidt, H., Kotewitsch, M., Widdershoven, J.W., Cantarero-Prieto, D., Mooren, F., Pena-Gil, C., González Juanatey, J.R., Schmidt, M., Malberg, H., Tsakanikas, V., Fotiadis, D., Gatsios, D., Bosch, J.A., Kop, W.J., & Schmitz, B. (2025). Patient-Centered Risk Prediction, Prevention, and Intervention Platform (TIMELY) to Support the Continuum of Care in Coronary Artery Disease Using eHealth and Artificial Intelligence: Protocol for a Randomized Controlled Trial. *Journal of Medical Internet Research Protocols, 14(1),* e66283.

Douma, E.R., **Roovers, T.,** Kop, W.J., Widdershoven, J.W., Bosch, J.A., Schäfer, H., Schmitz, B., & Habibovic, M. Experiences of patients with an eHealth-

based cardiac rehabilitation intervention: A qualitative investigation in patients with coronary artery disease. *Under review.*

ACKNOWLEDGEMENTS (DANKWOORD)

De afgelopen vier jaar waren bijzonder en leerzaam. Al het werk dat in deze periode is verzet, en de kennis die daaruit is voortgekomen, zouden niet mogelijk zijn geweest zonder de steun, samenwerking en inspiratie van de vele mensen om mij heen. Collega's, vrienden en familie: jullie hebben mij geholpen om mijn promotietraject interessant en betekenisvol te maken, zowel binnen als buiten het werk. Ik ben dankbaar voor de kansen, die ik kreeg om mijzelf te ontwikkelen in verschillende werkvelden, en voor de professionele en vriendschappelijke relaties, die daaruit zijn ontstaan.

Ik wil alle deelnemers bedanken die hebben deelgenomen aan het OPTIMIZE-onderzoek bij Instituut Verbeeten en het TIMELY-onderzoek bij het Elisabeth-TweeSteden ziekenhuis. Zonder jullie bereidheid om mee te doen waren deze onderzoeken niet mogelijk geweest. Ik kijk met plezier en waardering terug op de vele open en leerzame gesprekken die ik met velen van jullie heb mogen voeren.

Daarnaast ben ik dankbaar voor de fijne begeleiding van mijn promotieteam. Jullie verschillende achtergronden vulden elkaar goed aan wat het onderzoek en mijn eigen ontwikkeling ten goede kwam. Ik waardeer het dat jullie altijd bereid waren om mee te denken, feedback te geven en mij uit te dagen om verder te kijken.

Prof. dr. **Kop**, beste **Wijo**, de afgelopen vier jaar heb ik met plezier intensief met je samengewerkt aan verschillende projecten. Je gaf me de vrijheid om mijzelf te ontwikkelen, maar gaf ook sturing wanneer ik dat nodig had. Ik heb veel geleerd van je kritische blik op onze papers, op dit proefschrift en op het onderzoek in het algemeen, maar ook over het inzetten van sociale vaardigheden die nodig zijn. Ik vond het mooi om te zien hoe je ervoor zorgde dat overleggen zowel luchtig maar ook productief bleven. Meer dan eens had je slimme en handige tips om iets voor elkaar te krijgen, wat anders niet was gelukt. Ook wil ik je bedanken dat je mij hebt betrokken bij NeurolabNL, wat me waardevolle inzichten gaf buiten mijn onderzoek, en voor je inzet om mij als 'sprokkel-AIO' dezelfde kansen te bieden.

Dr. **Vermeltfoort,** beste **Ilse**, ik ben blij dat ik de eerste jaren van mijn promotietraject onder jouw hoede bij Instituut Verbeeten heb mogen werken. Ik heb niet alleen veel geleerd van je vriendelijke begeleiding van patiënten tijdens de stress-testen, maar ook over nucleaire geneeskunde tijdens de momenten waarop je de tijd nam om samen MPI-SPECT scans te beoordelen. Ik waardeer je enthousiaste en geïnteresseerde houding ten opzichte van

het onderzoek. Daarnaast kijk ik met plezier terug op de vele lunches die we samen met de andere nucleaire geneeskundigen hadden. Deze waren niet alleen gezellig, maar boden mij ook een waardevolle inkijk in jullie vakgebied. Jouw inzicht in hoe onderzoek écht relevant kan zijn voor de praktijk heeft de papers en dit proefschrift sterk verbeterd. Daarnaast heb je me erop gewezen hoe belangrijk het is om stil te staan bij wat er uiteindelijk met opgedane kennis gebeurt.

Prof. dr. **Widdershoven**, beste **Jos**, ik begrijp goed waarom veel van je patiënten zo lovend over je zijn. Het was bijzonder om te zien hoe betrokken je bent en hoe je met patiënten in gesprek gaat. De momenten waarop je, tussen je werkzaamheden in het ziekenhuis door, tijd nam om me in vogelvlucht het cardiovasculaire systeem uit te leggen, hielpen mij om me snel thuis te voelen in deze materie. Tijdens het analyseren van de resultaten van de 24-uurs Holters in het lab verbaasde ik me over hoe snel je deze kon beoordelen. En het vertrouwen dat je daarbij in mij uitsprak, dat ik dat ook kan, heeft me echt geholpen. Daarnaast veel dank voor de momenten waarop je samen met Emma en mij patiënten belde voor de werving.

Dr. **Habibovic,** beste **Mirela**, het was waardevol om jou als copromotor te hebben. Binnen een team met voornamelijk medische expertise bracht jij belangrijk en aanvullend psychologisch perspectief. Je kritische blik en scherpe vragen hebben me meerdere keren aan het denken gezet, en je moedigde me altijd aan om bewuste keuzes te maken in de analyses en hoe ze gebruikt moesten worden in onze papers. Bedankt voor de mogelijkheid om aan de slag te gaan met de data-analyse van het DoCHANGE project, waaruit een mooi paper is voortgekomen. Onze wekelijkse paper meetings waren daarnaast altijd inspirerend en prettig. De laagdrempeligheid en het leren van elkaars onderzoek maakten het leerzaam.

Ik wil graag de leden van de commissie, prof. dr. Marije **van der Lee**, prof. dr. Lukas **Dekker**, dr. Pieter **Raijmakers** en em. prof. dr. Ad **Vingerhoets**, hartelijk bedanken voor de beoordeling van dit proefschrift en het opponeren tijdens mijn verdediging.

Alle co-auteurs die mee hebben gewerkt aan het onderzoek in dit proefschrift wil ik bedanken voor de fijne samenwerking en hun bijdragen.

Dank ook aan alle medewerkers van Instituut Verbeeten voor hun bereidheid om mee te werken aan het OPTIMIZE-onderzoek. Ik wil de nucleaire geneeskundigen, **Arjan, Mischa en Rik** bedanken voor hun begeleiding, het extra scoren van de ischemie-formulieren en de gezellige lunches waarin ik

bij jullie kon aansluiten. Dank aan alle laboranten, **Ashley, Bart, Debbie, Eline, Eveline, Franka, Gemma, Ilse, Mahamed, Mariska, Monique, Nicole, Seyma, Silvia** en **Vera** voor de hulp bij alle praktische zaken rondom het onderzoek, en voor jullie geduld wanneer ik weer mijn vragen moest stellen aan de patiënt tijdens het hartonderzoek, en dat jullie me hebben betrokken bij de afdeling. Ook het **secretariaat nucleaire geneeskunde**, **Claudia, Fabiënne, Monique en Thea,** wil ik bedanken voor hun hulp bij alle praktische vragen die ik had en voor hun inzet om alle patiënten in te lichten over het onderzoek. Ik kon altijd terecht bij jullie wanneer ik vragen had of zomaar voor een gezellig praatje. **Jef** wil ik bedanken voor het realiseren van twee mooie video's voor het onderzoek en de afdeling **Communicatie** voor hun hulp bij de ontwikkeling en implementatie hiervan.

Ook de medewerkers van het Elisabeth-TweeSteden ziekenhuis wil ik bedanken; zonder jullie was het uitvoeren van het TIMELY-onderzoek niet mogelijk geweest. Dank aan alle fysiotherapeuten voor de ruimte die jullie boden om deelnemers te werven en in het bijzonder **Peter Dekkers** en **Joost in 't Veld**, voor al jullie hulp en waardevolle inzichten vanuit jullie expertise die ervoor hebben gezorgd dat de werving en het onderzoek soepeler verliepen. Verder bedank ik het **secretariaat cardiologie**, **Annabel en Anouk,** voor alle hulp bij de organisatie van het onderzoek. Ook wil ik alle verpleegkundigen en overig personeel bedanken die hebben geholpen bij het uitvoeren van de fietstesten en voor de kans om mee te kijken bij Holter-analyses en een pacemakerplaatsing. Het **KCHL**, **Ellen, Mandy en Stefanie** wil ik bedanken voor de hulp bij het opslaan en analyseren van de bloedsamples.

Thanks to all members of the **TIMELY consortium** for the collaboration on this exciting and ambitious project. Dr. **Schmitz, Boris**, thank you for your guidance on the practical aspects and for your critical perspective, which have definitely improved the project as a whole. Prof. dr. **Scharnagl, Hubert,** thank you for your guidance in the analysis and shipment of the blood samples. I would also like to thank **Alexander** for his help with the ECG analysis. This research would not have been possible without your expertise.

Special thanks to the TIMELY casemanager team: **Hendrik, Manuela, Marta, and Emma.** We have overcome many barriers throughout the project, which was only possible because of incredible teamwork. We would not have been able to pull this project off without your help. I really enjoyed working with you and had a great time during the TIMELY meetings in Tilburg, Ioannina, and Santiago de Compostela.

Ik wil ook alle studenten bedanken die hebben bijgedragen aan de onderzoeken van dit proefschrift. **Barbara, Cleo, Evi** en **Merel,** ik heb met plezier met jullie samengewerkt in het OPTIMIZE-onderzoek. **Britt, Imke** en **Roos,** bedankt voor jullie bijdragen aan het TIMELY-onderzoek. Zonder jullie inzet was het niet mogelijk geweest om zoveel deelnemers te includeren.

De leden van **NeurolabNL**, **Eliana, Maaike, Melanie, Michiel, Peter, Richard, Roger, Wessel** en **Wijo** wil ik bedanken voor de fijne samenwerking. Ik heb veel geleerd van jullie over de 'andere kant' van onderzoek en het werken op beleidsmatig niveau. Met veel plezier heb ik samen met jullie bijgedragen aan de verdere ontwikkeling van de NeurolabNL-route. Ook wil ik de leden van de Taskforce bedanken voor hun betrokkenheid en inzet. In addition, I would like to thank the members of **Young NeurolabNL**: **Amy, Carmen, Chris, Danique, Desiderio, Ewa, Florian, Julia, Kubra, Sandra,** and **Sanne.** I enjoyed organizing events together with all of you and I am grateful for your efforts in connecting young researchers within the NeurolabNL field. A special thanks to **Desiderio** for initiating the Tilburg University NeurolabNL community, it was inspiring to see how passionate and committed you are in bringing researchers together. Also thanks to **Harm** and **Wouter** for their contribution to the NeurolabNL community in Tilburg.

Graag wil ik ook alle (ex-) collega's van MKP bedanken voor de collegialiteit en de fijne werksfeer in de afgelopen vier jaar. Bedankt voor de gezellige afdelingsuitjes en feestjes; ze maakten de werkweek altijd net een beetje leuker. En wat hadden we een leuke en hechte AIO-groep! Daarom wil ik graag alle mede AIO's en junior onderzoekers bedanken: **Abbie, Anouk, Babette, Bo, Carmen, Charlotte, Daniëlle, Dinah, Ellen, Eveline de G., Eveline G., Hilde, Isabel, Jamie, Janniek, Lianne, Lisa, Lotte, Manon, Marijn, Marlot, Noor, Paul, Rosie, Sandra, Silke, Sophie, Tom, Trang, Vivian** en **Wiebke**. Ik kijk met plezier terug op de AIO-uitjes, op de gezellige (en productieve) schrijfweken in de Beekse Bergen en op alle borrels en feestjes waarvan we samen hebben mogen genieten. Ondanks dat Marijn en ik niet altijd bij de 'oude garde' hoorden, voelde dat voor ons wel zo, en deze groep heeft ervoor gezorgd dat ik met veel plezier terugkijk op mijn AIO-tijd. Ik hoop dat we elkaar blijven zien op reünies of daarbuiten. **Lisa**, wat heb ik veel kunnen lachen met jou. Op alle borrels en uitjes was het altijd feest met jou. Soms werd het ook iets te gezellig, zoals op het kerstfeest in 013, toen je niet naar huis wilde en jij je 'aan de bewaker vastklampte' en daardoor bijna je laatste trein miste. Omdat we tegelijkertijd in de laatste fase zaten, was het ook fijn om met elkaar te sparren tijdens de mini-schrijfweken. **Lotte**, wat was het gezellig met jou. Wanneer ik iets wilde vragen aan Emma, bleef ik uiteindelijk altijd

langer hangen op jullie kamer om bij te praten. Dankzij jou let ik voortaan ook beter op verkeersdrempels (sorry!). **Manon**, ik heb je oprechte interesse gewaardeerd. Toen je eenmaal volledig bij ons op de afdeling werkte, was je altijd in voor een korte wandeling, waarin we fijn konden praten over werk maar ook over alles daarbuiten. En natuurlijk zal ik de heerlijke babyccino's van jou en **Lotte** tijdens de schrijfweken nooit vergeten! **Paul,** dank voor je bereidheid om mee te denken met analyses en voor je waardevolle inbreng als coauteur. Dankzij jouw hulp kon ik met vertrouwen verder werken aan mijn papers. Ik blijf het bewonderingswaardig vinden hoe helder en begrijpelijk jij statistische vraagstukken kunt uitleggen. **Dinah,** wat was het leuk dat Marijn en ik bij jou op de kamer kwamen. Jouw enthousiaste begroeting elke ochtend werkte aanstekelijk en zorgde ervoor dat ik gelijk zin kreeg in de dag, vooral wanneer het 'dreamteam' van T524 compleet was. Het was fijn om met je te kunnen sparren over onze projecten en je had vaak waardevolle en praktische tips vanuit je eigen ervaring. Ik kijk met plezier terug op alle feestjes, en in het bijzonder op het dansen in de sneeuw met de straatmuzikant na het kerstfeest in 013.

Gaëtan, Heidi, Ivan, Nina, Stefanie en **Paula,** dank jullie wel voor alle gezellige momenten op kantoor en tijdens de cardiomeetings. **Gaëten**, jouw deur stond altijd open voor een praatje; iets waar ik graag en regelmatig gebruik van maakte. Je was daarnaast ook altijd van de partij bij de vele borrels en feestjes waar je voor veel gezelligheid zorgde. **Nina,** ik waardeer het dat je altijd bereid was om mee te denken over analyses in het lab en je kennis hierover met me te delen. Ook jouw hulp bij het werken met de vriezers op de afdeling heeft me erg geholpen. **Stefanie,** met vragen over het lab of voor ander advies kon ik altijd bij je terecht. Ik kijk bovendien met plezier terug op het APS-congres in Puerto Rico.

Emma, de samenwerking met jou heeft het werk de afgelopen jaren niet alleen makkelijker, maar vooral een stuk leuker gemaakt, zelfs wanneer we in het TIMELY-project op de proef werden gesteld. De vele dagen die we in het ziekenhuis doorbrachten, in het EPD of bij de patiënten, waren een stuk leuker doordat we dit samen deden. Het was fijn dat we taken van elkaar konden overnemen wanneer de piekdrukte toesloeg, bijvoorbeeld wanneer er een paper ingediend moest worden. Zonder jou was het niet mogelijk geweest om mijn projecten goed te combineren. Ik heb veel met je gelachen, soms met kiespijn over de struggles van het project, maar we vonden altijd wel weer een oplossing. De vele app-gesprekken hierover met al je stickers waren een welkome onderbreking (en soms uitstelgedrag). Met veel plezier kijk ik terug op onze trips naar Puerto Rico en Santiago de Compostella.

Marijn, wat was het leuk dat we bijna tegelijk zijn begonnen en meteen samen op een kantoor kwamen. Vanaf het eerste moment hadden we een fijne klik, en die is in de loop van de jaren alleen maar sterker geworden. We konden altijd goed sparren over onze projecten, maar ik heb minstens zoveel gehad aan onze lunchwandelingen en andere momenten waarin we ook spraken over de écht belangrijke dingen in het leven (zoals voetbal). Je stond altijd klaar om te helpen, bijvoorbeeld om dozen vol droogijs en bloedsamples te sjouwen. Ik herinner me nog goed dat je zelfs als proefpersoon wilde optreden toen ik moest oefenen met het opplakken van de Holter-ECG elektroden. Met plezier kijk ik terug op ons congresbezoek in Brighton, inclusief de korte spontane tussenstop in Londen. Daarnaast vond ik het bijzonder dat ik bij jullie bruiloft mocht zijn, en ik vond het mooi om jullie zo te zien stralen. Als de enige twee mannelijke AIO's vormden we een onafscheidelijk duo, iets wat ik zeker zal gaan missen, maar waar ik met plezier aan terugdenk als een van de hoogtepunten van mijn AIO-tijd.

Dank aan **Wiel** voor het redigeren van dit proefschrift en het scherp oog voor detail.

Lieve vrienden, **Bas, Bor, Jip, Louk, Maik, Mark, Rowin, Sjors** en **Stein**, bedankt voor jullie vriendschap en voor de gezelligheid die voor ontspanning zorgde tijdens de afgelopen vier jaar. Ik kan stuk voor stuk ontzettend met jullie lachen en ik weet ook dat jullie altijd voor me klaarstaan. Het betekent veel voor me om zo'n hechte vriendengroep te hebben, en ondanks dat er periodes zijn waarin we elkaar minder zien, voelt het altijd weer als vanouds wanneer we samen zijn.

Lieve **Mart, Nicole** en **Finn,** dank voor de fijne familieband die we hebben. Het voelt altijd vertrouwd en goed om samen met jullie te zijn. **Mart**, ik ben ontzettend blij met jou als grote broer. Wanneer we elkaar kwallen of samen lachen, lijkt er niets veranderd vergeleken met vroeger. Tegelijkertijd kan ik ook fijn met je praten en waardeer ik hoe betrokken en meelevend je bent. Ik bewonder de manier waarop je leeft en de dingen doet die je leuk vindt zonder je al te veel aan te trekken van wat anderen daarvan vinden. Tijdens het afronden van dit proefschrift was het fijn om af en toe naar Voorhout te komen, het zorgde voor een leuke afwisseling en gaf me de kans om Finn wat vaker te zien. **Finn,** ik ben nog steeds ontzettend trots dat je naar mij vernoemd bent. Dat ik uitgerekend op jouw verjaardag dit proefschrift verdedig moet je me vergeven, al zorgt het ook weer voor extra verbondenheid. Het is bijzonder om je te zien opgroeien en te ervaren hoe snel je nieuwe dingen leert, altijd met vrolijkheid en plezier. **Nicole,** het is

mooi om te zien van wie Finn zijn vrolijkheid heeft. Door jouw uitbundigheid is het altijd gezellig. Ik waardeer enorm hoe vanzelfsprekend en fijn het is wanneer we met z'n allen samen zijn.

Lieve **Femke**, er is niemand bij wie ik zo mezelf kan zijn als bij jou. Je bent lief en zorgzaam en we kunnen samen ontzettend lachen. Dank je wel voor je steun, je geduld en vertrouwen in mij. Je wist te relativeren wanneer ik dat nodig had, en ik vond het erg bijzonder om samen aan het ontwerp van dit proefschrift te werken. Het voelt alsof we al zoveel avonturen samen hebben beleefd en ik kijk uit naar alles dat nog gaat komen.

Lieve **Pap** en **Mam**, ik ben dankbaar dat ik jullie als ouders heb. Ik bewonder jullie betrokkenheid bij het mooier maken van onze wereld, of dat nu is door actie te voeren, door op te komen voor wat echt belangrijk is, of simpelweg door er voor een ander te zijn. Jullie staan altijd voor me klaar en jullie oprechte interesse en betrokkenheid waardeer ik enorm. Ik vond het fijn om tijdens mijn AIO-tijd met jullie te kunnen sparren, of dit nou over mijn werk ging of over alles daaromheen. Onze gesprekken tijdens wandelingen, of gewoon bij jullie aan de keukentafel, gaven me rust, perspectief en vaak ook nieuwe energie. **Mam,** jouw positieve instelling bewonder ik enorm, niets is ooit te veel gevraagd. De manier waarop je met iedereen verbinding weet te maken door oprechte aandacht blijft voor mij een groot voorbeeld. **Pap,** jouw gedrevenheid en doorzettingsvermogen wanneer je ergens echt voor gaat is voor mij inspirerend. Je zoekt alles tot in de puntjes uit en laat zien wat het betekent om met overtuiging ergens voor te staan.

ABOUT THE AUTHOR

Tom Roovers was born on September 6, 1995, in Oosterhout, the Netherlands. After completing secondary education at Cambreur College in Dongen, he earned a bachelor's degree in Applied Biology from HAS University of Applied Sciences in 's-Hertogenbosch in 2018. During his studies, he completed internships at the Donders Institute for Brain, Cognition and Behaviour in Nijmegen, where he investigated the "Neural and behavioural interplay of intrinsic and extrinsic motivation", and at the University of Lisbon in Portugal, where he examined "Epiphytic lichen size as a promising ecological indicator for climate change". Following his Bachelor's degree, he completed both the Pre-Master's and Research Master's in Medical Biology with a specialization in Neurobiology at Radboud University in Nijmegen, graduating with an average grade of 8.1. During his Master's, he returned to the Donders Institute for a second internship, this time studying "Fear memory replay in the human hippocampal-amygdala circuit using fMRI", and subsequently interned at De Lerende Mens assessing "The effectiveness of dyslexia treatment in primary school children". From 2022 to 2025, he conducted his PhD research at the Department of Medical and Clinical Psychology at Tilburg University and at the Institute Verbeeten, under the supervision of Prof. Dr. Willem Johan Kop, Dr. Ilse Vermeltfoort, Dr. Mirela Habibovic, and Prof. Dr. Jos Widdershoven. Currently, he works as a program manager at the Task Force for Applied Research SIA at NWO.