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

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ABSTRACT

Background: Cardiovascular disease (CVD) risk is associated with health behaviors 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 behavior intervention program and assesses whether improvements in health behaviors are associated with increases in parasympathetic autonomic nervous system activity.

Methods: Data from the DoCHANGE-2 (https://clinicaltrials.gov/study/NCT03178305) eHealth-based behavior intervention study in patients with CVD were analyzed 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 s) ECGs over 5-day periods at baseline, 3, and 6 months. Health behaviors, clinical, and psychosocial information was obtained from questionnaires and medical records. Data were analyzed 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 = 0.026). Health behaviors improved significantly during the active (0–3 months) intervention period (B = 13.360 [95 %CI 6.931 19.789], p < 0.001). Higher BMI (B = −0.369 [−0.739; 0.000]; p = 0.05) and older age (B = −0.404 [95 % CI −0.597; − 0.211]; p < 0.001) were associated with lower RMSSD across the three timepoints. No consistent associations were found between changes in health behaviors and changes in RMSSD.

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

1. 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 [1]. Behavioral 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 [2]. Studies show that improving health behaviors can prevent up to 70 % of heart diseases, CVD events, and significantly reduce health and economic burden [3]. It has been suggested that health behaviors directly affect CAD pathophysiology by adverse effects on atherosclerotic disease processes [4]. In addition, health behaviors 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) [5]. Evidence suggests a relationship between cardiac unhealthy behaviors and autonomic dysregulation in patients with CAD [6]. However, there is a knowledge gap in how health behavior changes are related to autonomic nervous system activity among patients with CAD and other manifestations of cardiovascular disease [7].

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

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cardiovascular prognosis [8]. 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 [9]. The autonomic nervous system is bi-directionally associated with cardiac unhealthy behaviors [6]. Evidence shows that behavioral 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 [5,6,10,11]. Behavioral 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 [12–14]. Autonomic dysregulation might therefore be a common pathway linking modifiable risk factors to cardiovascular disease progression [6]. However, these associations have not been studied in the setting of clinical behavioral interventions in patients with cardiovascular disease.

The link between autonomic regulation and health behaviors can be explained by common neurobehavioral 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 behavior, adaptability, and health [15]. 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 [16]. The CAN is also thought to play a role in health behavior through executive functioning, which is the process of effortfully and strategically directed behavior in pursuit of future goals. Specifically, healthy behaviors 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 behaviors [17]. A recent meta-analysis also found a direct association between HRV indices and executive functioning [18]. Together these studies form a plausible mechanistic explanation for the association between autonomic regulation and health behaviors.

Autonomic nervous system activity, particularly changes in the activity of the parasympathetic branch, can be measured using heart rate variability (HRV) indices [19]. 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) [20–22].

The present study examines whether HRV indices of autonomic nervous system activity change over time during an eHealth-based behavior intervention. Furthermore, the association of changes in HRV throughout the intervention with changes in health behaviors will be assessed. It is hypothesized that HRV values will increase throughout the health behavior intervention program. Additionally, it is expected that the magnitude of improvements in health behaviors 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 behavioral intervention phase.

2. Methods

Data for this study were collected as part of the multicenter randomized controlled trial Cardiac Health Advanced New Generation Ecosystem 2 (Do CHANGE 2). The Do CHANGE 2 trial aimed to evaluate a multi-component digital behavioral intervention for lifestyle change in patients with cardiovascular disease and is described in more detail elsewhere [23]. 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.

2.1. 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 min apart and after 3–5 min 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 dyslipidemia, 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 74 (78.4 %) of the participants (see Supplementary Figure SF1 for a flow-chart of participant eligibility for the present analysis).

2.2. 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.

2.3. 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 to sign the informed consent form and complete the first set of questionnaires was scheduled (baseline assessments).

Subsequently, participants were randomized 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 [23].

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 behavioral program developed to change behavioral habits and flexibility, and subsequently change habits associated with an unhealthy lifestyle and psychological distress. The behavioral program helps patients to step out of their comfort zone by sending behavioral 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 behavior 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 [23,24].

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.

2.4. Electrocardiogram and heart rate variability analysis

Participants randomized 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 s 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 preprocessed and analyzed using BIOPAC Acqknowledge (Version 5) [25]. 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 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 s 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 [25]. Several studies have validated the use of these (ultra) short-term ECG recordings for HRV time-domain measures [26–28]. These investigations demonstrate that short-duration ECG segments of 30–40 s 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 [29]. Heart rate measures (in beats per minute: bpm) were based on the interbeat interval of the complete 40-second recording.

2.5. Health behaviors

Health behaviors 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 [30] 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 behaviors. 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 = 0.92). Because some of the HPLP subscales reflect domains of mental wellbeing rather than health behaviors per se, exploratory analysis will also be conducted for each of the HPLP subscales separately. Smoking behavior was retrieved through self-report.

2.6. 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).

2.7. 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 behaviors (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 analyzed 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 modeling 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 behavior-related measures with changes in RMSSD and heart rate (hypothesis 2) were investigated using unadjusted bi-variate 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 bi-variate correlation analyses, multivariate analyses were conducted using linear mixed models. The base model included timepoint, measurement, health behaviors (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 minimize 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 analyzed using the Statistical Package for the Social Sciences (SPSS) software package (Version 27.0) [31].

3. 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).

3.1. Changes in RMSSD and heart rate during the intervention program

Fig. 1 shows the average RMSSD levels for each measurement at baseline, three, and six months (data for each of the separate 15 time points are shown in Fig. 1A). A significant decrease in RMSSD was observed throughout the six month study period in the linear mixed model analysis ($F(2, 46.47) = 6.95$, $p = 0.002$) (see Table 2). The RMSSD values were significantly lower at six months compared to baseline ($\Delta = -19.34$ [95 % CI −36.29; 2.38]; $p = 0.026$). Fig. 1B shows that the most substantial decrease occured 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 > 0.30). 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: $F(2, 50.87) = 2.99$, $p = 0.059$) (see Supplementary Table ST1).

3.2. Association between changes in health behavior with changes in RMSSD and heart rate

As shown in Fig. 2, the HPLP total score improved significantly during the intervention period ($\Delta = 13.36$ [95 % CI 6.93; 19.79], $p < 0.001$), and a non-significant further improvement occurred from three to six months follow-up ($\Delta = 2.84$ [95 % CI −3.36; 9.04], $p = 0.783$; overall change over time: $F(2, 94 = 8.55, p < 0.001)$. Changes in health behaviors (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.

The associations between baseline health behavior-related measures and changes in health behavior 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 ($r = 0.315$, $p = 0.023$) and specifically with the dietary habit subscale ($r = 0.280$, $p = 0.044$). 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) ($r = 0.285$, $p = 0.03$). 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 model 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 ($B = -0.37$ [95 % CI −0.74;.000 ms]; $p = 0.050$) and age ($B = -0.40$ [95 % CI −0.60; −.21 ms]; $p < 0.001$). 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]; $p = 0.330$). No evidence was found for an association of smoking with RMSSD ($B = 1.07$ [95 % CI −3.44; 5.57 ms]; $p = 0.639$), even though it is known to be more strongly related to autonomic nervous system activity[32,33]. Exploratory analysis for the subscales of the HPLP did not reveal any significant associations with RMSSD (see Supplementary Table ST6 and ST7). Stratifying by patients with and without beta blockers did not reveal other outcomes compared to the main analysis. The parallel model for heart rate revealed a significant association between BMI with heart rate ($B = 0.28$ [95 % CI 0.01; 0.56]; $p = 0.041$) and age ($B = -0.25$ [95 % CI −4.41; −.08 bpm]; $p < 0.001$) (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.

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 %)

4. Discussion

This is the first study to assess changes in autonomic regulation throughout a behavior change program in people with CVD. The active phase of the health behavior 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 behaviors that are associated with reduced cardiovascular risk (i.e., higher HPLP scores). However, the improvements in health behaviors during the intervention were not associated with parallel changes in autonomic nervous system activity.

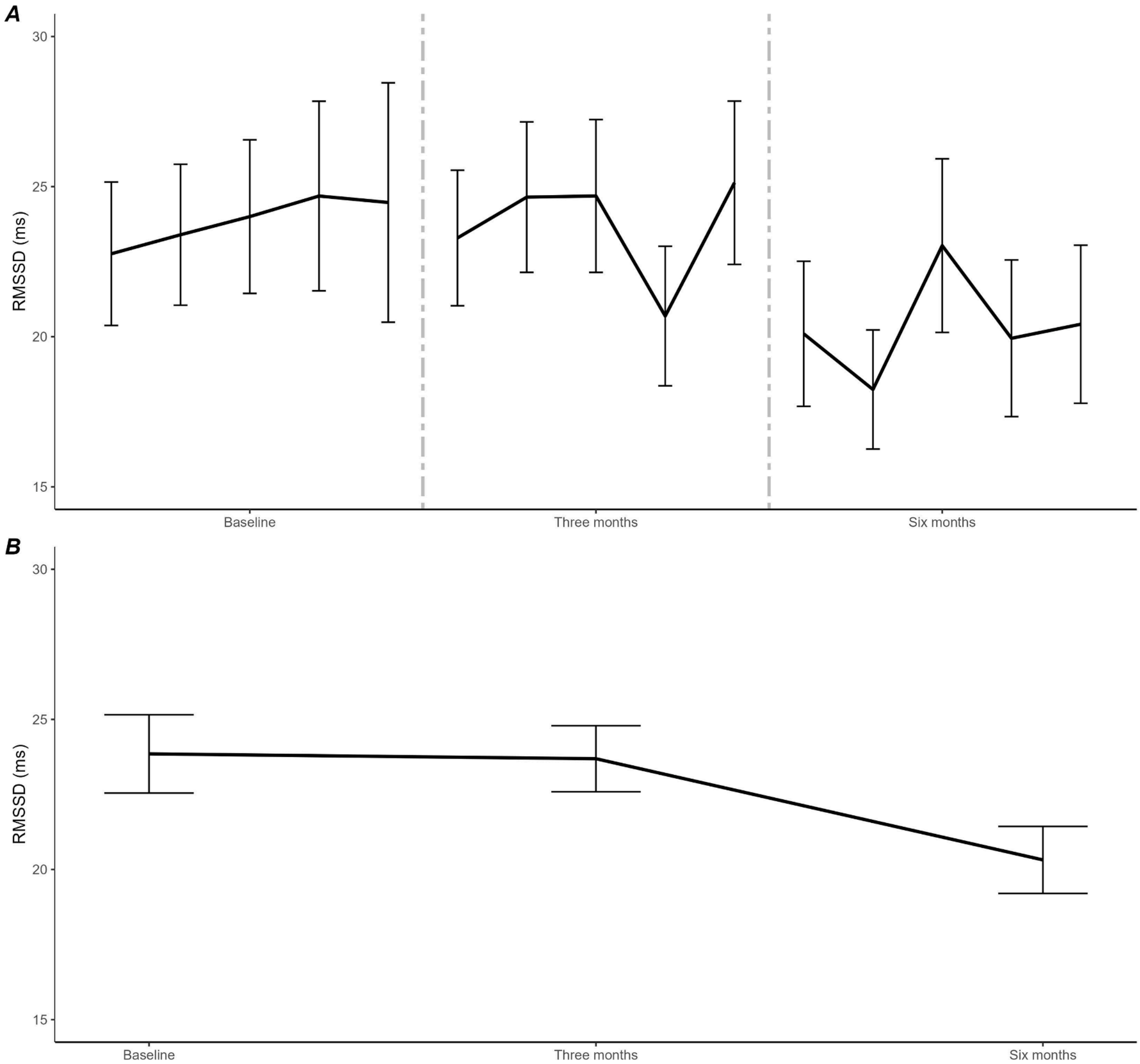

Fig. 1. Changes in RMSSD during the behavioral intervention program. (A) RMSSD values for each of the measurements at each time point (in ms); (B) Average RMSSD over 5 days at each time point. Error bars indicate the standard error of the mean.

Several studies have established positive effects of individual health behaviors including physical activity [34], diet [35], and stress management [36] on autonomic function in cardiac samples. However, multiple other studies did not confirm these results [12,34,37,38] and consensus on the effects of these behavioral interventions on autonomic nervous system activity has not been reached. A review of the effects of biobehavioral, medication, or exercise treatments in CAD patients concluded that health behavior change interventions can improve HRV by a moderate magnitude [7]. 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 behavior change prompts were terminated and participants only used monitoring devices without behavior change support. This might have affected their motivation to pursue healthy behaviors 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 [39]. 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 improve autonomic regulation [7,40,41]. However, other types of medication often used in cardiovascular disease patients such as antidepressants [42] have been shown to reduce measures of autonomic regulation in patients with major depression [43] as well as in a healthy sample [44]. 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 behaviors with measures of autonomic nervous system activity.

The relationship between autonomic function and health behaviors is likely subject to influence from various psychological and social factors, which are established as contributors to behavioral and physiological risk factors associated with cardiovascular disease. These factors, among others, include depression, anxiety, optimism, and psychological flexibility [45,46]. 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 with autonomic regulation [16,47–51]. It is therefore plausible to assume a role for flexibility in health behavior 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 behavior change and autonomic function.

Table 2
The association of health behaviors with RMSSD using linear mixed effect modeling.

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]	0.353	7.04 [−8.75 to 22.84]	0.375
	6 months	−20.67 [−37.18 to −4.16]	0.015	−19.34 [−36.29 to −2.38]	0.026
Measurement	5	*Reference*			
	4	−1.301 [−3.656 to 1.055]	0.273	−1.715 [−4.122 to 0.691]	0.159
	3	−2.059 [−4.811 to 0.693]	0.139	−2.115 [−5.029 to 0.799]	0.150
	2	−1.814 [−4.549 to 0.921]	0.188	−2.247 [−5.088 to 0.595]	0.118
	1	−2.426 [−5.177 to 0.326]	0.083	−2.509 [−5.414 to 0.396]	0.089
HPLP		−0.05 [-0.16 to 0.05]	0.311	−0.08 [−0.19 to 0.02]	0.113
HPLP x Timepoints	Baseline	*Reference*			
	3 months	−0.06 [−0.17 to 0.06]	0.331	−0.05 [−0.17 to 0.07]	0.400
	6 months	0.11 [−0.01 to 0.23]	0.061	0.11 [−0.01 to 0.23]	0.074
Age				−0.40 [−0.60 to −0.21]	<0.001
Sex				−2.92 [−8.90 to 3.06]	0.330
BMI				−0.37 [−0.74 to 0.00]	0.050
Smoking				1.07 [−3.44 to 5.57]	0.639

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 behavior (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.

4.1. Limitations

The current study has several strengths and limitations. Limitations include the use of self-report measures to assess health behaviors. 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 [52,53] 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 [54]. Expert guidelines also recommend 5-minute ECG recordings for HRV analysis [19,20]. 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 [26–28]. It is also possible that additional HRV indices (e.g., hf-HRV or DFA) could have revealed stronger associations with health behavior 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 behaviors with changes in HRV-based indices of parasympathetic nervous system activity. Furthermore, RMSSD values could partially reflect erratic (disorganized) sinus rhythm, particularly in participants older than 65 years [55,56]. Detailed analysis of the Poincare 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 behavior in the current study should not be viewed as evidence of absence of this relationship in other clinical settings. Finally, the Health Promoting Lifestyle Profile questionnaire does not encompass all relevant health behaviors 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 behaviors before a health behavior intervention, immediately following completion of the active intervention phase, and at six months follow-up.

4.2. Future directions

Future studies should consider the development of a composite score that encompasses all health behaviors (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 [45], would take into account the known influences individual behaviors have on each other [57] 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 behaviors [58,59]. 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 behaviors and the wide variety of measures used. Health behaviors are complex, consisting of individual actions, and are influenced by many different factors [60]. This makes reliably assessing behavior difficult, especially through self-report, which is often the case [61]. These pitfalls related to health behavior measuring may explain the inconsistencies between prior studies as well as the lack of findings in the current study.

5. Conclusion

In conclusion, the current study reports changes in autonomic regulation within the context of a behavioral 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 behaviors were not associated with parasympathetic nervous system activity as was anticipated. Delving deeper into this connection between health behaviors and autonomic regulation in patients with cardiovascular disease could yield valuable insights into the efficacy of behavioral change interventions and the interplay between health behaviors and autonomic regulation in the progression of coronary artery disease.

These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

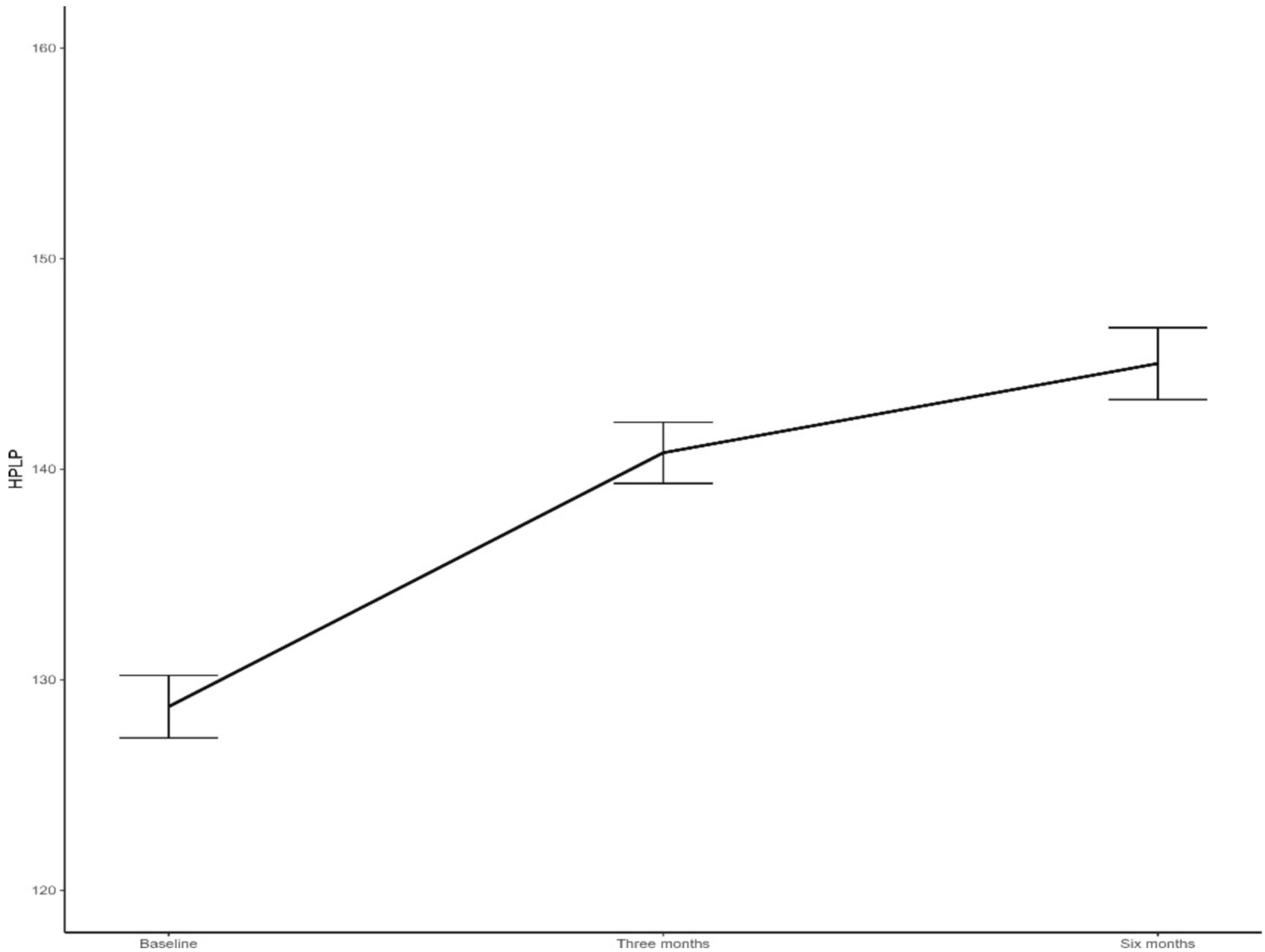

Fig. 2. Changes in HPLP total score during the behavioral intervention program. Error bars indicate the standard error of the mean.

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CRediT authorship contribution statement

T. Roovers: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **M. Habibovic:** Writing – review & editing, Funding acquisition, Conceptualization. **P. Lodder:** Writing – review & editing, Methodology, Formal analysis. **J. Widdershoven:** Writing – review & editing. **W.J. Kop:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101563.

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