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Temporal stability and drivers of change in cardiac autonomic nervous system activity

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ABSTRACT

Objectives: This study determined temporal stability of ambulatory measured cardiac autonomic activity for different time periods and investigated potential drivers of changes in this activity.
Methods: Data was drawn from baseline (n = 2379), 2-year (n = 2245), and 6-year (n = 1876) follow-up from the Netherlands Study of Depression and Anxiety. Cardiac autonomic activity was measured with heart rate (HR), respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP). Autonomic temporal stability was determined across 2, 4, and 6 year intervals. We subsequently examined the association between sociodemographics, lifestyle, mental health, cardiometabolic health, and the use of antidepressant and cardiac medication with change in cardiac autonomic activity.
Results: Over 2 years, stability was good for HR (ICC = 0.703), excellent for RSA (ICC = 0.792) and moderate for PEP (ICC = 0.576). Stability decreased for a 4- (HR ICC = 0.688, RSA ICC = 0.652 and PEP ICC = 0.387) and 6-year interval (HR ICC = 0.633, RSA ICC = 0.654 and PEP ICC = 0.355). The most important determinants for increase in HR were (increase in) smoking, increase in body mass index (BMI) and (starting) the use of antidepressants. Beta-blocking/antiarrhythmic drug use led to a decrease in HR. Decrease in RSA was associated with age, smoking and (starting) antidepressant use. Decrease in PEP was associated with age and (increase in) BMI.
Conclusions: Cardiac autonomic measures were rather stable over 2 years, but stability decreased with increasing time span. Determinants contributing to cardiac autonomic deterioration were older age, (increase in) smoking and BMI, and (starting) the use of antidepressants. (Starting) the use of cardiac medication improved autonomic function.

1. Introduction

The autonomic nervous system (ANS) plays a key role in cardiovascular regulation, and is a major determinant of resting heart rate (HR) and blood pressure (BP), two independent risk factors for coronary artery disease (MacMahon et al., 1990; Palatini & Julius, 2004). Indicators of cardiac sympathetic and parasympathetic activity can be non-invasively and unobtrusively measured by electrocardiography (ECG) and impedance cardiography (ICG) (De Geus et al., 1995; De Geus & Van Doornen, 1996). In order to draw conclusions from longitudinal studies on indices of cardiac autonomic activity, these indices are assumed to remain rather stable within individuals. Since there are many factors in a person's life that may influence autonomic measures, it is impossible to achieve 100% agreement within a person over time. Therefore, it is useful to determine the temporal stability of cardiac autonomic activity when interpreting the results of longitudinal studies. In addition, it is necessary to investigate which factors contribute to cardiac autonomic change, so that these factors are accounted for in longitudinal studies.

Temporal stability has been investigated for HR, stroke volume, cardiac output, pre-ejection period (PEP), total peripheral resistance, systolic BP, and heart rate variability (HRV) (Bertsch et al., 2012; Barnes et al., 2004; Sloan et al., 1995; Vrijkotte et al., 2004; Goedhart et al., 2007, 2008; Colloca et al., 2006; Mukherjee et al., 2012; Burleson et al., 2003). These studies generally yielded moderate to high stability. However, found correlation coefficients showed variations among

Abbreviations: ANS, autonomic nervous system; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; ECG, electrocardiogram; HR, heart rate; HRV, heart rate variability; IAT, implicit association task; IBI, interbeat interval; ICG, impedance cardiography; METmin, multiple of resting metabolic rate times minutes of physical activity per week; NESDA, Netherlands Study of Depression and Anxiety; PEP, pre-ejection period; RSA, respiratory sinus arrhythmia; SNRI, selective serotonin and noradrenalin reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; VU-AMS, Vrije Universiteit Ambulatory Monitoring System

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studies, likely caused by differences in methodology. For instance, studies differ in time span (ranging from a couple of days to a couple of years), sample size (ranging from tens of participants to over a hundred participants) and sample population (population versus clinical samples). While it would be intuitively appealing for temporal stability to decrease with increasing time span, this was not inferred from the literature. To our knowledge, Goedhart and colleagues conducted the longest study in this research field across 3.3 years and still found moderate to high stability for both cardiac sympathetic and parasympathetic activity (Goedhart et al., 2007, 2008). Regarding sample population, it has been suggested that HRV, for instance, has significantly worse stability in clinical populations than in healthy controls, as shown for populations with chronic heart failure (Ponikowski et al., 1996) and cardiac transplant recipients (Lord et al., 2001).

ANS dysregulation has been associated with unfavorable health outcomes, such as the metabolic syndrome (Hu et al., 2016a; Koskinen et al., 2009) and cardiometabolic health (Curtis & O'Keefe, 2002; Grassi et al., 2015; Carnethon et al., 2006). This can partly reflect a causal role of ANS activity in the onset of these diseases, but it is possible that in parallel changes in cardiac ANS activity over time might themselves be affected by these health issues, for instance through the effects of cardiac medication (MacFadyen, 1997; Harada et al., 2003). Many more factors have been suggested to influence the ANS. Sociodemographics such as age (Pfeifer et al., 1983), sex (Dart, 2002) and social economic status (Sloan et al., 2005) have been linked to autonomic activity. In addition, several lifestyle factors have been associated with ANS activity (Hu et al., 2017), including physical activity (Rennie et al., 2003), alcohol use (Ohira et al., 2009), smoking behavior (Middlekauff et al., 2014), and unhealthy dietary patterns as indexed by e.g. body mass index (BMI) (Molfino et al., 2009). Patients with psychiatric disorders, such as depression and anxiety, have been suggested to have altered ANS (re)activity, with causal effects possible in both directions (Phillips et al., 2011; Hu et al., 2016b). Importantly, there is increasing evidence that the use of antidepressants might negatively impact autonomic balance (Kemp et al., 2010; Licht et al., 2010, 2012). For many of these factors, studies mostly investigated cross-sectional relationships with ANS and occasionally short-term longitudinal relationships. Longitudinal studies over the course of years are scarce.

The current study aims to establish the temporal stability of ambulatory measured cardiac autonomic activity during several laboratory conditions over a 2-, 4- and 6-year time period in a large cohort of the Netherlands Study of Depression and Anxiety (NESDA). We used the following indicators of cardiac ANS activity: HR (controlled by both sympathetic and parasympathetic activity) (De Geus & Van Doornen, 1996), respiratory sinus arrhythmia (RSA: an indicator of parasympathetic activity) (De Geus et al., 1995) and PEP (indicative of sympathetic activity) (De Geus & Van Doornen, 1996). We investigated whether sociodemographics or (changes in) lifestyle, mental health, cardiometabolic health, and the use of antidepressant or cardiac medication were significant drivers of changes in cardiac autonomic activity over time.

2. Methods

2.1. Subjects

Data was obtained from NESDA, an ongoing longitudinal cohort study to examine the long-term course of depression and anxiety. Participants were recruited from community, primary care and mental health care in The Netherlands. The NESDA sample includes 2981 participants aged 18–65 years with a current diagnosis of depression and/or anxiety disorder, a prior history of these disorders, and healthy controls. A four-hour baseline measurement was conducted between September 2004 and February 2007, and follow-up assessments took place after two, four and six years. A detailed description of the rationale, objectives and methods of the NESDA study can be found elsewhere (Penninx et al., 2008). The study protocol was approved by the Ethical Review Board of each participating center, and all participants provided written informed consent. The study was performed conform the declaration of Helsinki.

Data for the present study were drawn from baseline (n = 2981), 2-year (n = 2596) and 6-year (n = 2256) follow-up assessments (cardiac autonomic activity was not measured during 4-year follow-up). Subjects were included when they had measurement of either HR, RSA or PEP during at least two assessments, so that temporal stability could be determined. This resulted in a total of 2379 subjects at baseline, 2245 subjects at 2-year follow-up and 1876 subjects at 6-year follow-up. Missing physiological data was due to telephone or at-home interviews without ANS recording, equipment failure during assessment or poor electrocardiogram quality.

2.2. Procedures

The clinic visits consisted of biological assessment including a supine blood pressure measurement, a psychiatric interview, a general interview and a computer task. The psychiatric interview included questions about various indicators of anxious and depressive symptoms, as well as suicide ideation, mood disorder symptoms and experience of adverse life events. The general interview contained questions about somatic health, smoking behavior, use of medication, daily functioning and health care utilization. The computer task was an implicit association task (IAT) (Greenwald et al., 1998).

2.3. Determinants of change in autonomic activity

Determinants of autonomic instability were measured at all three waves and described in detail below.

2.3.1. Sociodemographics

The following sociodemographic factors were investigated: age (years), sex (1 = male, 2 = female), and education (years) as a proxy for social economic status.

2.3.2. Lifestyle factors

Physical activity was measured by the short IPAQ (Booth et al., 2003), a 7-item instrument assessing the amount of habitual vigorous activity, moderate and walking activities over the last 7 days. A continuous score is calculated in Metabolic Equivalent Total (MET)-minutes per week: MET level * minutes of activity * events per week. Alcohol use was assessed by the Alcohol Use Disorder Identification Test questionnaire (Babor et al., 1992) from which the number of alcoholic drinks per week was derived. A drink was defined as follows: 1) a single small (8 oz) glass of beer, 2) a single shot/measure of liquor/spirits, 3) a single glass of wine. Smoking was indicated by the current number of cigarettes/day. Body mass index (BMI) was measured in kg/m^2.

2.3.3. Mental health

Participants were considered to have a current psychopathology when they had a 6-month diagnosis of major depressive disorder and/or anxiety disorder (panic disorder, social phobia and/or generalized anxiety disorder) according to the DSM-IV-based Composite International Diagnostic Interview, version 2.1.

2.3.4. Antidepressant use

Participants were requested to bring their medication containers to the assessments so that medication use could be determined. We investigated the use of tricyclic antidepressants (TCAs: ATC code N06AA), selective serotonin reuptake inhibitors (SSRIs: ATC code N06AB), and selective serotonin and noradrenalin reuptake inhibitors (SNRIs: ATC code N06AX). Previous research on NESDA data has indicated that TCAs and SNRIs have a different effect on ANS activity than SSRIs, with detrimental effects of TCAs and SNRIs on HR, RSA and PEP, while SSRIs

had less pronounced detrimental effects on RSA and even a beneficial effect on HR and PEP (Licht et al., 2010, 2012). Therefore, we decided to divide antidepressant use into 1) TCA and/or SNRI use, and 2) SSRI use.

2.3.5. Cardiometabolic health

Cardiometabolic health consisted of self-reported presence of cardiovascular disease (CVD: coronary disease, cardiac arrhythmia, angina pectoris, heart failure, and/or myocardial infarction), hypertension and diabetes which received medical attention.

2.3.6. Cardiac medication use

We investigated the use of beta-blocking/antiarrhythmic drugs (C01B, C07), and use of other cardiac medication (C08CA, C01D, C02AC01, C02CA01, C02CA04, C04, C09).

2.4. Physiological measurements

During the assessments physiological data was recorded with the 'Vrije Universiteit Ambulatory Monitoring System' (VU-AMS), an unobtrusive lightweight portable device. The VU-AMS contains a six-electrode configuration that measures electrocardiograms (ECG) and changes in thorax impedance (ICG) (De Geus & Van Doornen, 1996). An event marker was used to divide the assessment into different conditions. Movement registration through vertical accelerometry was used to remove periods where the subjects were not stationary.

HR was directly derived from the interbeat interval (IBI) time series from the ICG signal (De Geus & Van Doornen, 1996). RSA combined ECG with the respiration signal obtained from ICG, and was obtained by subtracting the shortest IBI during HR acceleration at inhalation from the longest IBI during HR deceleration at exhalation for all breaths (De Geus et al., 1995). Since it has been suggested that repeatability of HRV is affected by differences in HR (Gąsior et al., 2016), we decided to add a variable of RSA divided by average interbeat interval (IBI) to investigate whether this would impact our results. PEP was ensemble averaged across one-minute periods time-locked to the R-waves in the ECG. PEP was extracted from the interval between the Q-onset in the ECG, indicating onset of left ventricular electrical activity, and the upstroke (B-point) of the ICG signal, indicating the beginning of left ventricular ejection (De Geus & Van Doornen, 1996).

Automated and visual data cleaning assured that suspicious IBIs and breathing cycles were corrected or discarded when displaying irregularities. Crucial landmarks in the ICG were detected by an automated scoring algorithm, which were visually inspected and manually corrected.

For baseline, 2- and 6-year assessment an average score of HR, RSA, RSA/IBI, and PEP was made by combining the conditions that were present at all waves: a supine rest condition with blood pressure measurement (± 11 min) and three sitting conditions: a psychiatric interview (± 41 min), a general interview (± 33 min) and a computer task (± 13 min). Since postural changes are the main source of change in preload (Houtveen et al., 2005), the supine condition was excluded in the average score of PEP. We will refer to these combined conditions as 'total assessment'.

2.5. Statistical analyses

Cardiac autonomic temporal stability was determined by Two Way Random intraclass correlation coefficients (ICC), which indicates the absolute agreement between autonomic variables measured at one time point with those measured at another time point within subjects (McGraw & Wong, 1996). We compared ICC confidence intervals between the different sitting conditions with the total assessment to determine whether certain 'demarcated' conditions would have better temporal stability than an overall average. In addition, we compared ICC confidence intervals of temporal stability over 2 years (baseline and 2-year follow-up), 4 years (2- and 6-year follow-up) and 6 years (baseline and 6-year follow-up). RSA values were highly skewed and therefore ln-transformed for analyses.

Multiple linear regression analyses were used to examine whether sociodemographics or (changes in) lifestyle, mental health, cardiometabolic health, and the use of antidepressant or cardiac medication were significantly associated with absolute change in cardiac autonomic activity over each of the three time intervals (baseline to 2-year, 2- to 6-year, and baseline to 6-year). For all lifestyle factors, continuous absolute change scores were included beside their basal value. For mental health, cardiometabolic health and medication use, categories were made based on patterns of change. Since we investigated two waves per analysis, the change scores and patterns were solely based on the values of the two waves within an analysis, disregarding a third wave (i.e. when analyzing 6-year ANS change, chronic psychopathology is defined as having a diagnosis at baseline and at 6-year follow-up, regardless of the diagnosis at 4-year follow-up). For mental health, the groups were divided as follows: 1) a control group with no 6-month diagnosis at the start and end of the interval, 2) a chronic psychopathology group with a present 6-month diagnosis at the start and end of the interval, 3) a new onset psychopathology group with no 6-month diagnosis at the start of the interval but a 6-month diagnosis at the end of the interval, and 4) a

Table 1
Sample characteristics.

Characteristics	Baseline n = 2379[a]	2-y follow-up n = 2245[b]	6-y follow-up n = 1876[c]
Social demographics			
Age, years	42.0 ± 13.1	44.2 ± 13.2	48.1 ± 13.1
Female sex (%)	65.9	66.2	65.4
Education, years	12.3 ± 3.3	12.5 ± 3.3	12.9 ± 3.3
Lifestyle			
Physical activity, median 1000 METmin/week (IQR)	2.8 (1.4–5.1)	3.1 (1.6–5.5)	2.9 (1.5–5.4)
Alcohol use, median drinks/week (IQR)	3.7 (0.2–8.7)	3.7 (0.2–8.7)	3.7 (0.2–8.2)
Smoking, median no. cigarettes/day (IQR)	0.0 (0.0–7.0)	0.0 (0.0–5.0)	0.0 (0.0–0.3)
Body mass index, kg/m^2	25.5 ± 4.9	25.8 ± 4.8	26.1 ± 5.0
Mental health			
Psychopathology (%)	53.9	37.3	27.8
Use of TCAs (%)	2.6	2.9	3.1
Use of SNRIs (%)	4.0	4.1	3.8
Use of SSRIs (%)	17.2	14.1	11.9
Cardiometabolic health			
CVD (%)	4.2	5.6	6.6
Diabetes (%)	3.7	5.0	5.4
Hypertension (%)	13.9	17.2	21.8
Use of beta-blocking/antiarrhythmic drugs (%)	8.3	9.4	10.7
Use of other cardiac medication (%)	7.4	9.2	11.5
Cardiac autonomic measures			
HR, beats/min	72.0 ± 9.7	72.7 ± 9.7	71.6 ± 9.4
RSA, ms	43.8 ± 24.9	41.7 ± 22.5	45.0 ± 25.8
PEP, ms	119.9 ± 17.9	119.4 ± 17.3	111.6 ± 21.7
Respiration rate, breaths/min	17.1 ± 1.2	17.3 ± 1.3	16.3 ± 1.4

Note: Values represent mean ± SD unless otherwise indicated. METhours = multiple of resting metabolic rate times hours of physical activity per week. IQR = interquartile range. CVD = cardiovascular disease. HR = heart rate. RSA = respiratory sinus arrhythmia. PEP = pre-ejection period.

[a] Values were missing for physical activity (143), alcohol use (24), smoking (12), BMI (1) and PEP (21).

[b] Values were missing for physical activity (221), alcohol use (49), smoking (10), BMI (4), CVD (5), diabetes (5), hypertension (4), use of beta-blocking/antiarrhythmic drugs (5), use of other cardiac medication (5), HR (6), RSA (4), PEP (14) and respiration rate (4).

[c] Values were missing for physical activity (125), alcohol use (59), smoking (2), BMI (3), diabetes (1), hypertension (1), use of beta-blocking/antiarrhythmic drugs (1), use of other cardiac medication (1), RSA (1), PEP (23) and respiration rate (1).

Table 2
Intraclass correlation coefficients of autonomic nervous system activity over different time periods.

Condition	ICC (95% confidence interval)					
	N	0–2 years	N	2–6 years	N	0–6 years
HR						
Total assessment	2169	0.703 (0.680–0.724)	1667	0.688 (0.661–0.713)	1805	0.633 (0.605–0.660)
General interview	2062	0.688 (0.664–0.710)	1499	0.662 (0.633–0.690)	1646	0.612 (0.581–0.641)
Psychiatric interview	2111	0.681 (0.643–0.715)	1609	0.670 (0.642–0.696)	1765	0.613 (0.583–0.643)
Computer task	1997	0.661 (0.635–0.685)	1424	0.629 (0.533–0.702)	1550	0.572 (0.459–0.657)
RSA						
Total assessment	2170	0.792 (0.774–0.809)	1666	0.652 (0.619–0.682)	1804	0.654 (0.627–0.680)
General interview	2096	0.767 (0.749–0.784)	1520	0.614 (0.549–0.668)	1641	0.628 (0.585–0.667)
Psychiatric interview	2142	0.751 (0.718–0.778)	1629	0.602 (0.522–0.666)	1762	0.608 (0.573–0.640)
Computer task	2000	0.734 (0.713–0.754)	1427	0.572 (0.536–0.606)	1546	0.572 (0.537–0.604)
RSA/IBI						
Total assessment	2166	0.831 (0.816–0.845)	1663	0.682 (0.653–0.710)	1804	0.684 (0.659–0.708)
General interview	2055	0.812 (0.797–0.827)	1492	0.656 (0.580–0.715)	1641	0.657 (0.610–0.698)
Psychiatric interview	2107	0.794 (0.771–0.815)	1605	0.640 (0.558–0.704)	1762	0.638 (0.599–0.673)
Computer task	1988	0.774 (0.756–0.756)	1419	0.591 (0.556–0.624)	1546	0.594 (0.559–0.626)
PEP						
Total assessment	2142	0.576 (0.547–0.603)	1643	0.387 (0.286–0.472)	1772	0.355 (0.262–0.436)
General interview	2080	0.563 (0.533–0.592)	1519	0.375 (0.256–0.473)	1631	0.337 (0.232–0.426)
Psychiatric interview	2127	0.565 (0.535–0.593)	1623	0.377 (0.278–0.461)	1752	0.343 (0.235–0.436)
Computer task	1989	0.545 (0.513–0.575)	1426	0.385 (0.311–0.451)	1541	0.346 (0.283–0.405)

Note: HR = heart rate. RSA = respiratory sinus arrhythmia. IBI = interbeat interval. PEP = pre-ejection period. ICC = intraclass correlation coefficients.
RSA was ln-transformed for analyses.

remitted psychopathology group with a 6-month diagnosis at the start of the interval but no 6-month diagnosis at the end of the interval. Cardiometabolic health patterns were categorized as: 1) a control group with no diagnosis at the start and end of the interval, 2) a chronic group with diagnosis already present at the start of the interval, and 3) a new onset group with no diagnosis at the start of the interval but a present diagnosis at the end of the interval. Medication use patterns were defined as: 1) a control group with no current medication use at the start and end of the interval, 2) a chronic group using medication at the start and end of the interval, 3) a starting group who did not use medication at the start of the interval but who did use medication at the end of the interval, and 4) a stopping group who used medication at the start of the interval but who did not use medication at the end of the interval. The analyses were adjusted for basal ANS values at the start of the interval. Since it has been linked to RSA (Hirsch & Bishop, 1981), change in respiration rate was included as a covariate when analyzing change in RSA.

Data was analyzed using SPSS, version 22.0. Correction for multiple testing was based on Matrix Spectral Decomposition suggested by Nyholt (2004), which estimated and corrected for the number of independent predictor variables. Accordingly, the criterion for statistical significance was set at $p < 0.0016$. In addition, we looked at the consistency of the results across the different time intervals and considered a finding to be more reliable when it was found significant across multiple intervals.

3. Results

At baseline our sample ($n = 2379$) had a mean age of 42.0 years (SD = 13.1) and 65.9% were female (Table 1). Over time, there was a slight increase in BMI and a decrease in number of people with psychopathology, as well as a decrease in the use of SSRIs. The number of people with cardiometabolic diseases increased over time (incidence of cardiovascular diseases at 2-year follow-up: 0.3% coronary disease, 0.8% cardiac arrhythmia, 0.4% angina pectoris, and 0.4% heart failure; incidence at 6-year follow-up: 0.4% coronary disease, 0.8% cardiac arrhythmia, 0.6% angina pectoris, and 0.5% heart failure). The use of cardiac medication also increased over time.

Table 2 shows the ICC of cardiac autonomic variables for several conditions over different time periods. When comparing the ICC confidence intervals of the separate conditions and the total assessment, we concluded that these intervals showed great overlap. In addition, the ICC were very similar for RSA and RSA/IBI. We therefore decided to report the results only for HR, RSA and PEP of the total assessment, and to use these variables for further analyses. For the total assessment, 2-year temporal stability was good for HR (ICC = 0.703), excellent for RSA (ICC = 0.792) and moderate for PEP (ICC = 0.576). In addition, for almost all cardiac autonomic variables temporal stability decreased with increasing time span (for HR: 0.688, and 0.633; for RSA: 0.652, and 0.654; and for PEP: 0.387, and 0.355 for a 4-, and 6-year interval respectively). When comparing confidence intervals, decrease in temporal stability was significant for HR over 6 years compared to 2 and 4 years. For RSA and PEP, a significantly lower temporal stability was seen over 4 years compared to 2 years.

Table 3 shows the association between our determinants and change in HR over the different time periods. No significant associations were seen for sociodemographic variables. Considering lifestyle, an increase in BMI was associated with an increase in HR over all three time periods ($\beta = 0.131$, $\beta = 0.127$ and $\beta = 0.145$ for a 2-, 4- and 6-year interval respectively). Basal number of cigarettes/day was significantly associated with an increase in HR over two time periods ($\beta = 0.092$ and $\beta = 0.108$ for a 4- and 6-year interval respectively), as was increase in number of cigarettes/day ($\beta = 0.089$ and $\beta = 0.112$ for a 2- and 6-year interval respectively). Regarding mental health, the most consistent associations were seen for use of TCA/SNRI: chronic use was associated with increase in HR over two time periods ($\beta = 0.078$ and $\beta = 0.106$ for a 2- and 6-year interval respectively), started using with an increase in HR over all three time periods ($\beta = 0.137$, $\beta = 0.112$ and $\beta = 0.099$ for a 2-, 4- and 6-year interval respectively), and stopped using with a decrease in HR over two time periods ($\beta = -0.127$ and $\beta = -0.091$ for a 4- and 6-year interval respectively). A significant association was also seen for the group that stopped using SSRIs with an increase in HR over 2 years ($\beta = 0.093$), while associations were marginally significant over the other time periods. When investigating cardiometabolic health, consistent associations were found for use of beta-blocking/antiarrhythmic drugs, with chronic use being significantly

Table 3
Determinants of change in HR over time.

Determinants	ΔHR, beats/min					
	0–2 years n = 1820		2–6 years n = 1411		0–6 years n = 1571	
	β	p	β	p	β	p
Sociodemographics						
Age, years	− 0.025	0.27	− 0.008	0.76	− 0.023	0.35
Female sex	0.060	0.005	0.022	0.37	0.037	0.10
Education, years	− 0.044	0.041	− 0.018	0.48	− 0.004	0.87
Lifestyle						
Physical activity, METmin/week	− 0.026	0.25	− 0.017	0.53	− 0.012	0.63
ΔPhysical activity, METmin/week	− 0.034	0.14	− 0.040	0.14	− 0.055	0.027
Alcohol use, drinks/week	0.047	0.055	− 0.041	0.17	0.007	0.81
ΔAlcohol use, drinks/week	0.002	0.95	− 0.025	0.37	0.035	0.18
Smoking, cigarettes/day	0.060	0.011	**0.092**	**0.001**	**0.108**	**< 0.001**
ΔSmoking, cigarettes/day	**0.089**	**< 0.001**	0.072	0.006	**0.112**	**< 0.001**
Body mass index, kg/m^2	0.056	0.014	− 0.009	0.72	0.012	0.60
ΔBody mass index, kg/m^2	**0.131**	**< 0.001**	**0.127**	**< 0.001**	**0.145**	**< 0.001**
Mental health						
No psychopathology	Reference group					
Chronic psychopathology	**− 0.081**	**0.001**	− 0.004	0.87	− 0.039	0.11
New onset psychopathology	− 0.056	0.008	− 0.004	0.87	0.006	0.77
Remitted psychopathology	− 0.048	0.038	0.003	0.91	− 0.013	0.59
Not using TCA/SNRI	Reference group					
Chronic use	**0.078**	**< 0.001**	0.028	0.25	**0.106**	**< 0.001**
Started using	**0.137**	**< 0.001**	**0.112**	**< 0.001**	**0.099**	**< 0.001**
Stopped using	− 0.044	0.035	**− 0.127**	**< 0.001**	**− 0.091**	**< 0.001**
Not using SSRI	Reference group					
Chronic use	− 0.004	0.84	0.008	0.72	0.013	0.55
Started using	− 0.053	0.011	− 0.059	0.013	− 0.055	0.011
Stopped using	**0.093**	**< 0.001**	0.075	0.002	0.063	0.005
Cardiometabolic health						
No CVD	Reference group					
Chronic CVD	0.058	0.014	− 0.039	0.16	− 0.025	0.30
New onset CVD	0.010	0.63	− 0.029	0.27	− 0.015	0.51
No diabetes	Reference group					
Chronic diabetes	0.042	0.049	0.009	0.72	0.024	0.29
New onset diabetes	0.025	0.23	0.034	0.15	0.051	0.020
No hypertension	Reference group					
Chronic hypertension	0.041	0.19	0.049	0.19	0.013	0.70
New onset hypertension	0.016	0.47	− 0.014	0.60	0.047	0.067
Not using beta-blocking/antiarrhythmic drugs	Reference group					
Chronic use	**− 0.102**	**0.001**	− 0.058	0.061	− 0.032	0.25
Started using	**− 0.174**	**< 0.001**	**− 0.200**	**< 0.001**	**− 0.178**	**< 0.001**
Stopped using	**0.097**	**< 0.001**	0.032	0.20	0.066	0.004
Not using other cardiac medication	Reference group					
Chronic use	− 0.006	0.81	0.010	0.74	− 0.007	0.81
Started using	1.2E-4	> 0.99	0.032	0.25	0.036	0.16
Stopped using	0.039	0.062	0.003	0.90	0.003	0.90

Note: HR = Heart rate. Metmin = multiple of resting metabolic rate times minutes of physical activity per week. CVD = cardiovascular disease.
Multiple linear regression analyses were adjusted for basal HR.
Boldface indicates statistical significance ($p < 0.0016$).

associated with a decrease in HR over 2 years (β = − 0.102), started using with a decrease in HR over all three time periods (β = − 0.174, β = − 0.200 and β = − 0.178 for a 2-, 4- and 6-year interval respectively), and stopped using significantly with an increase in HR over 2 years (β = 0.097) and marginally significantly over 6 years.

Table 4 shows which determinants were associated with change in RSA over the different time periods. Of the sociodemographic variables, older age was significantly associated with a decrease in RSA over two time periods (β = − 0.227 and β = − 0.090 for a 2- and 6-year interval respectively). Regarding lifestyle, higher basal number of cigarettes/day was significantly associated with a decrease in RSA over 4 years (β = − 0.092) and 6 years (β = − 0.110). Of the mental health factors, similar to findings for HR, use of TCA/SNRI had the greatest impact on change in RSA over time: chronic use was significantly associated with a decrease in RSA over 2 years (β = − 0.096) and marginally significantly over 6 years, started using with a decrease in RSA over all three time periods (β = − 0.137, β = − 0.101 and β = − 0.102 for a 2-, 4- and 6-year interval respectively), and stopped using marginally significantly over 2 and 4 years. In addition, persons that started using SSRI showed a decrease in RSA over 2 years (β = − 0.076) and 6 years (β = − 0.077). Considering cardiometabolic health, only chronic use of beta-blocking/antiarrhythmic drugs was significantly associated with a decrease in RSA over 2 years (β = − 0.102), and marginally significantly over 6 years.

Table 5 shows the determinants associated with change in PEP over the different time periods. Of the sociodemographic variables, older age was significantly associated with a decrease in PEP over 2 time periods (β = − 0.174 and β = − 0.144 for a 4- and 6-year interval respectively). Female sex was significantly associated with an increase in PEP over 6 years (β = 0.079) and marginally significantly over 4 years. Considering lifestyle, higher basal BMI was associated with a decrease in PEP over 4 years (β = − 0.125) and 6 years (β = − 0.118), and

Table 4
Determinants of change in RSA over time.

Determinants	ΔRSA, ms					
	0–2 years n = 1820		2–6 years n = 1409		0–6 years n = 1570	
	β	p	β	p	β	p
Sociodemographics						
Age, years	**− 0.227**	**< 0.001**	− 0.098	0.002	**− 0.090**	**0.001**
Female sex	0.049	0.015	− 0.069	0.007	− 0.067	0.003
Education, years	**0.067**	**0.001**	− 0.043	0.10	− 0.026	0.26
Lifestyle						
Physical activity, METmin/week	− 0.022	0.30	− 0.044	0.12	− 0.032	0.21
ΔPhysical activity, METmin/week	− 0.013	0.56	0.001	0.98	0.033	0.18
Alcohol use, drinks/week	− 0.026	0.25	0.070	0.023	0.010	0.73
ΔAlcohol use, drinks/week	− 1.5E-4	0.99	0.081	0.006	0.010	0.70
Smoking, cigarettes/day	0.004	0.84	**− 0.092**	**0.001**	**− 0.110**	**< 0.001**
ΔSmoking, cigarettes/day	− 0.031	0.14	− 0.033	0.22	− 0.060	0.016
Body mass index, kg/m^2	− 0.054	0.011	− 0.028	0.29	− 0.055	0.020
ΔBody mass index, kg/m^2	− 0.061	0.002	− 0.019	0.45	− 0.035	0.13
Mental health						
No psychopathology	Reference group					
Chronic psychopathology	0.030	0.19	− 0.007	0.80	0.049	0.050
New onset psychopathology	0.032	0.11	0.018	0.49	0.034	0.13
Remitted psychopathology	0.027	0.21	− 0.017	0.50	0.025	0.30
Not using TCA/SNRI	Reference group					
Chronic use	**− 0.096**	**< 0.001**	− 0.040	0.11	− 0.049	0.027
Started using	**− 0.137**	**< 0.001**	**− 0.101**	**< 0.001**	**− 0.102**	**< 0.001**
Stopped using	0.059	0.002	0.066	0.008	0.012	0.58
Not using SSRI	Reference group					
Chronic use	− 0.034	0.081	− 0.062	0.012	− 0.049	0.027
Started using	**− 0.076**	**< 0.001**	− 0.049	0.045	**− 0.077**	**< 0.001**
Stopped using	0.008	0.69	0.069	0.006	0.047	0.037
Cardiometabolic health						
No CVD	Reference group					
Chronic CVD	− 0.010	0.66	0.020	0.48	0.032	0.19
New onset CVD	− 0.012	0.55	0.015	0.59	0.024	0.30
No diabetes	Reference group					
Chronic diabetes	− 0.022	0.27	0.032	0.21	0.022	0.33
New onset diabetes	− 0.021	0.28	− 0.025	0.31	− 0.024	0.28
No hypertension	Reference group					
Chronic hypertension	− 0.029	0.31	0.037	0.33	0.006	0.86
New onset hypertension	− 0.040	0.053	− 0.026	0.35	− 0.003	0.89
Not using beta-blocking/antiarrhythmic drugs	Reference group					
Chronic use	0.017	0.49	**− 0.102**	**0.001**	− 0.069	0.012
Started using	0.030	0.14	− 0.009	0.75	− 0.015	0.54
Stopped using	− 0.021	0.29	− 0.033	0.20	0.024	0.28
Not using other cardiac medication	Reference group					
Chronic use	0.030	0.23	− 0.009	0.78	0.005	0.86
Started using	0.019	0.35	0.011	0.71	− 0.043	0.095
Stopped using	− 0.019	0.33	− 0.008	0.75	− 0.006	0.79

Note: RSA = respiratory sinus arrhythmia. Metmin = multiple of resting metabolic rate times minutes of physical activity per week. CVD = cardiovascular disease.
Multiple linear regression analyses were adjusted for basal RSA and change in respiration rate.
Boldface indicates statistical significance ($p < 0.0016$).

increase in BMI with a decrease in PEP over all three time periods (β = − 0.109, β = − 0.110 and β = − 0.141 for a 2-, 4-, and 6-year interval respectively). Of the mental health factors, a significant association was found between people that started using SSRI and an increase in PEP over 2 years (β = 0.081). This association was marginally significant over 6 years. Finally, regarding cardiometabolic health, chronic use of beta-blocking/antiarrhythmic drugs was marginally significantly associated with an increase in PEP over all three time periods.

Fig. 1 illustrates the associations between change patterns of antidepressant use and beta-blocking/antiarrhythmic drug use with change in ANS variables over a 6-year interval.

4. Discussion

The present study investigated temporal stability for cardiac autonomic activity measured during comparable laboratory conditions over a 2-, 4-, and 6-year time period. Over 2 years, temporal stability was good for HR, excellent for RSA and moderate for PEP. As expected, cardiac autonomic temporal stability decreased with increasing time span. Since temporal stability of autonomic measures is imperfect, we investigated which determinants were the most important drivers of change in cardiac autonomic activity over time. The most important determinants for an increase in HR were (increase in) smoking behavior, increase in BMI and (starting) the use of antidepressant drugs. In contrast, (starting) the use of beta-blocking/antiarrhythmic drugs was associated with a decrease in HR. Decrease in RSA was strongly associated with age, smoking and (starting) antidepressant use. As for decrease in PEP, the most consistent associations were found with older age and (increase in) BMI.

When comparing the different time periods, we found that temporal stability especially decreased for PEP over a 4- and 6-year interval

Table 5
Determinants of change in PEP over time.

Determinants	ΔPEP, ms					
	0–2 years n = 1799		2–6 years n = 1390		0–6 years n = 1542	
	β	p	β	p	β	p
Sociodemographics						
Age, years	0.011	0.61	**− 0.174**	**< 0.001**	**− 0.144**	**< 0.001**
Female sex	− 0.012	0.56	0.066	0.010	**0.079**	**0.001**
Education, years	0.027	0.20	− 0.019	0.48	− 0.004	0.87
Lifestyle						
Physical activity, METmin/week	0.021	0.35	− 0.014	0.63	0.017	0.51
ΔPhysical activity, METmin/week	0.021	0.35	0.013	0.64	0.009	0.72
Alcohol use, drinks/week	− 0.020	0.38	0.015	0.63	0.008	0.77
ΔAlcohol use, drinks/week	0.021	0.35	0.044	0.13	− 0.010	0.71
Smoking, cigarettes/day	− 0.001	0.96	− 0.029	0.31	− 0.042	0.12
ΔSmoking, cigarettes/day	− 0.019	0.39	0.024	0.37	− 0.018	0.49
Body mass index, kg/m^2	− 0.065	0.004	**− 0.125**	**< 0.001**	**− 0.118**	**< 0.001**
ΔBody mass index, kg/m^2	**− 0.109**	**< 0.001**	**− 0.110**	**< 0.001**	**− 0.141**	**< 0.001**
Mental health						
No psychopathology	Reference group					
Chronic psychopathology	− 0.003	0.90	0.022	0.42	0.027	0.31
New onset psychopathology	0.036	0.082	0.007	0.78	0.003	0.91
Remitted psychopathology	0.021	0.34	0.050	0.053	0.024	0.34
Not using TCA/SNRI	Reference group					
Chronic use	**− 0.109**	**< 0.001**	0.005	0.86	0.002	0.93
Started using	**0.094**	**< 0.001**	0.012	0.63	− 0.003	0.89
Stopped using	0.062	0.002	0.078	0.002	0.032	0.15
Not using SSRI	Reference group					
Chronic use	0.039	0.054	0.016	0.51	− 0.005	0.83
Started using	**0.081**	**< 0.001**	− 4.1E-4	0.99	0.062	0.007
Stopped using	**− 0.157**	**< 0.001**	− 0.028	0.26	0.004	0.88
Cardiometabolic health						
No CVD	Reference group					
Chronic CVD	− 0.007	0.77	0.006	0.83	0.018	0.48
New onset CVD	− 0.024	0.24	0.036	0.19	0.021	0.39
No diabetes	Reference group					
Chronic diabetes	0.005	0.81	0.012	0.64	− 0.030	0.20
New onset diabetes	− 0.021	0.30	0.026	0.29	0.059	0.011
No hypertension	Reference group					
Chronic hypertension	− 0.016	0.59	0.015	0.70	− 0.011	0.75
New onset hypertension	− 0.010	0.63	0.040	0.14	0.015	0.58
Not using beta-blocking/antiarrhythmic drugs	Reference group					
Chronic use	0.073	0.005	0.098	0.002	0.091	0.002
Started using	0.034	0.10	0.041	0.15	0.061	0.020
Stopped using	− 0.024	0.24	0.020	0.44	0.017	0.46
Not using other cardiac medication	Reference group					
Chronic use	− 0.021	0.41	− 0.010	0.75	0.030	0.31
Started using	− 0.030	0.16	− 0.026	0.38	− 0.066	0.014
Stopped using	− 0.015	0.46	− 2.6E-4	0.99	− 0.006	0.81

Note: PEP = pre-ejection period. Metmin = multiple of resting metabolic rate times minutes of physical activity per week. CVD = cardiovascular disease.
Multiple linear regression analyses were adjusted for basal PEP.
Boldface indicates statistical significance ($p < 0.0016$).

compared to a 2-year interval. Visual inspection of the ICG was used to determine the B-point (beginning of left ventricular ejection) for PEP. However, the scoring of this B-point is difficult since many subject present with a less than ideal ICG wave form, introducing ambiguity in the scoring (Van Lien & Schutte, 2013). This ambiguity adds to measurement error in the PEP, particularly if different raters are used for visual scoring. Here, the 6-year follow-up scoring of PEP from the ECG/ICG traces was done by a different rater than at baseline and 2-year follow-up. These factors most likely contributed to the lower temporal stability for PEP compared to the other autonomic variables. In general, our found cardiac autonomic stability over 2 years was similar to studies investigating these measures from weeks to a year (Bertsch et al., 2012; Barnes et al., 2004; Sloan et al., 1995; Colloca et al., 2006; Burleson et al., 2003). Despite this rather high stability, we could still determine factors contributing to 2-year autonomic instability, which were more or less consistent to those found for the longer intervals.

Regarding sociodemographic determinants of autonomic instability over time, previous studies have established an association with older age and decline in autonomic function (Pfeifer et al., 1983; O'Brien et al., 1986). Our results imply that older age is also significantly associated with a greater decrease in RSA and PEP over time. Although ANS functioning has been associated with SES (Sloan et al., 2005), we did not find evidence for an association between years of education (a proxy for SES) and change in ANS activity over time. Similarly, although we found a trend of a greater decrease in PEP for men than for women, we did not find convincing evidence that gender influenced changes in autonomic activity over time.

Considering lifestyle determinants, our results indicated that (change in) smoking and BMI had the most robust associations with change in ANS values. These findings comply with the bulk of literature suggesting that smoking (Middlekauff et al., 2014) and obesity (Troisi et al., 1991) have a detrimental effect on cardiac autonomic activity.

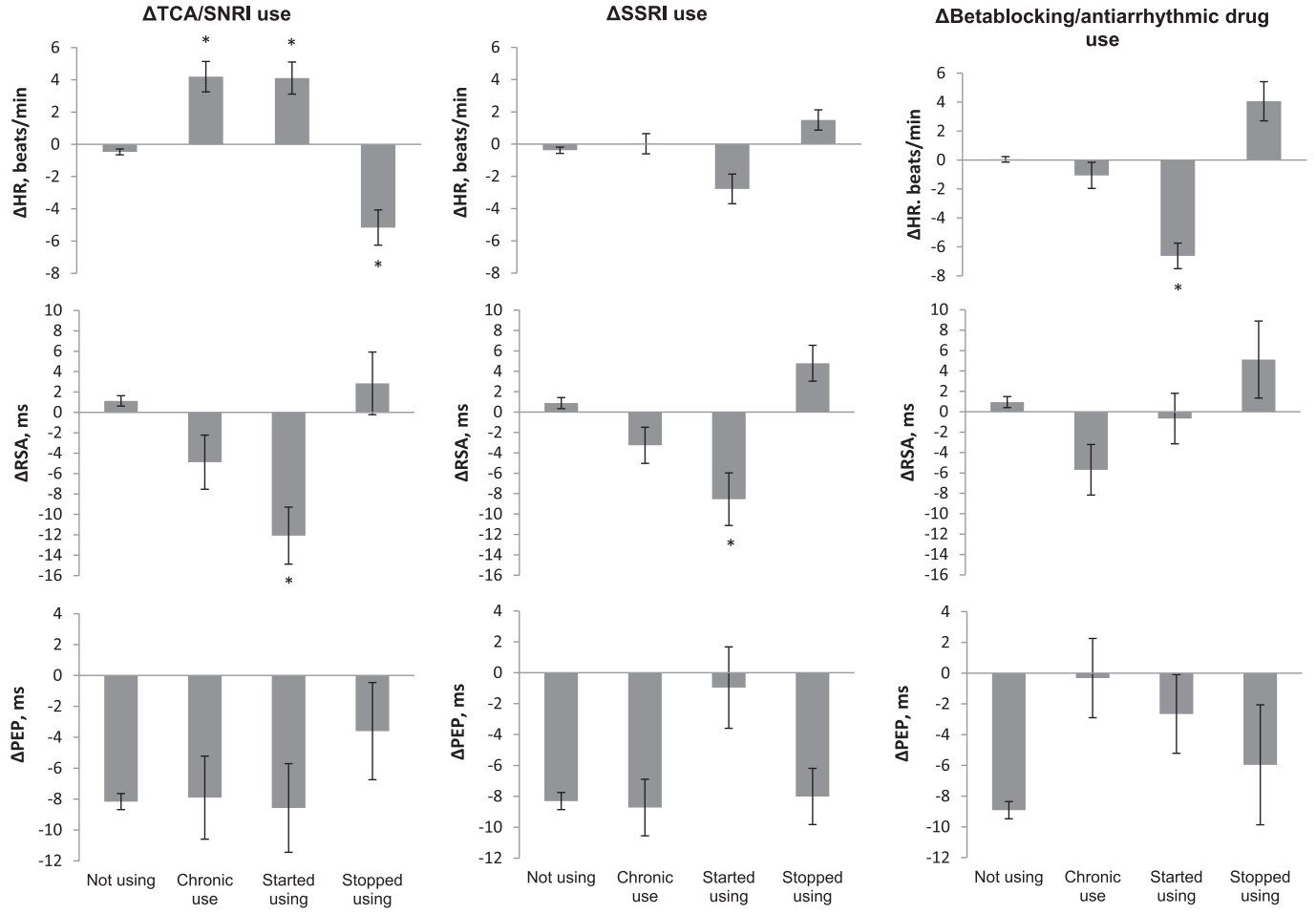

Fig. 1. The association between changes in antidepressant and beta-blocking/antiarrhythmic drug use with changes in HR (n = 1571), RSA (n = 1570) and PEP (n = 1542) over six years. P-values were based on ANCOVA analyses comparing the different change-patterns to the chosen reference group (not using medication at either baseline or 6-year follow-up). *$p < 0.0016$.

Our results add to the increasing evidence that it is not psychopathology, but rather use of antidepressants that drive autonomic dysregulations (Kemp et al., 2010; Licht et al., 2010, 2012). Moreover, they were in line with findings of NESDA research conducted by Licht et al. (Licht et al., 2010), who found that use of all antidepressants were associated with a 2-year decrease in cardiac vagal control. Our longer follow-up also confirmed that specifically TCAs and SNRIs increased HR and decreased cardiac vagal activity, while SSRIs reduced cardiac parasympathetic activity but had a beneficial effect on cardiac sympathetic activity and HR over time.

We did not find the expected associations between (change in) cardiometabolic health and change in cardiac ANS measures, despite that the association between autonomic dysregulation with cardiometabolic dysregulation has been well established in the literature (Curtis & O'Keefe, 2002; Grassi et al., 2015; Carnethon et al., 2006). It is possible that autonomic dysregulations occur long before full-blown cardiometabolic diseases emerge (Dekker et al., 2000), explaining why disease onset was not associated with change in ANS activity. Use of beta-blocking/antiarrhythmic drugs was found to significantly decrease HR (and sympathetic activity), in conformity with their mechanism of action on cardiac function on cardiac function (Bristow, 1993; Singh & Hauswirth, 1974). Surprisingly, this was paired to a less favorable effect on cardiac parasympathetic activity as reflected in lowered RSA. However, this effect was only (inconsistently) found for chronic use of medication.

This study has some limitations. For instance, lifestyle factors and cardiometabolic disease status were based on self-report, which is prone to inaccuracy and bias. However, cotinine levels at baseline showed good correlations with self-reported number of smoked cigarettes/day, enhancing our confidence in the reliability and validity of the used lifestyle measures. In addition, previous research has shown that self-reported CVD and general practitioners information are in good agreement (Kriegsman et al., 1996). Another limitation concerns our relatively young and healthy sample. Over the course of 6 years only a small percentage of our participants had or developed CVD or diabetes, perhaps contributing to our null-findings for cardiometabolic health. Finally, the potential for rater-bias in PEP scoring warrants caution for interpreting these findings.

These limitations are balanced by several strengths. To our knowledge, this is the largest and the longest follow-up study investigating ANS temporal stability, and the first to compare different time periods within one study. Furthermore, this study investigated many plausible determinants of autonomic instability in one model, so that each determinant was adjusted for effects of the other determinants. In addition, determinants were measured during all three time points, allowing us to critically look at the consistencies of associations over different time periods.

In summary, cardiac autonomic measures were rather stable over 2 years, but stability decreased with increasing time span. Determinants contributing to cardiac autonomic instability were older age, (increase in) smoking and BMI, and (starting) the use of antidepressants and cardiac medication. These determinants should be taken into account when researching ANS activity in longitudinal designs.

Declarations of interest

Conflict of interest: none declared.

Author contribution statement

M.X. Hu formulated the research question, performed statistical analyses, wrote the manuscript and incorporated feedback from all co-authors. F. Lamers provided feedback in all drafts of the manuscript and critically interpreted the results. B.W.J.H. Penninx and E.J.C. de Geus reviewed and provided feedback for the research question, provided feedback in all drafts of the manuscript, and critically interpreted the results.

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