Preventive Medicine 94 (2017) 12–19

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

# Influences of lifestyle factors on cardiac autonomic nervous system activity over time

Mandy Xian Hu, MD [a,*], Femke Lamers, PhD [a], Eco J.C. de Geus, PhD [b], Brenda W.J.H. Penninx, PhD [a]

[a] Department of Psychiatry and EMGO Institute for Health and Care Research, VU University Medical Centre, Amsterdam, The Netherlands
[b] Department of Biological Psychology and EMGO Institute for Health and Care Research, VU University, Amsterdam, The Netherlands

ARTICLE INFO

*Article history:*
Received 21 June 2016
Received in revised form 8 September 2016
Accepted 6 November 2016
Available online 9 November 2016

*Keywords:*
Autonomic nervous system
Lifestyle
Physical activity
Alcohol use
Smoking

ABSTRACT

Physical activity, alcohol use and smoking might affect cardiovascular disease through modifying autonomic nervous system (ANS) activity. We investigated: 1) whether there are consistent relationships between lifestyle factors and cardiac ANS activity over time, and 2) whether 2-year changes in lifestyle factors relate to 2-year changes in cardiac activity. Baseline (n = 2618) and 2-year follow-up (n = 2010) data of the Netherlands Study of Depression and Anxiety was combined. Baseline data was collected in the Netherlands from 2004–2007. Lifestyle factors were habitual physical activity, frequency of sport activities, alcohol use, and smoking. Indicators of cardiac activity were heart rate (HR), respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP) (100 min of registration). The results showed that high physical activity (−1.8 beats/min compared to low activity), high frequency of sport activities ('couple of times/week': −2.5 beats/min compared to 'almost never') and mild/moderate alcohol use (−1.2 beats/min compared to non-drinking) were related to low HR. Heavy smoking was related to high HR (>30 cigarettes/day: +5.1 beats/min compared to non-smoking). High frequency of sport activities was associated with high RSA ('couple of times/week': +1.7 ms compared to 'almost never') and moderate smoking with longer PEP (11–20 cigarettes/day: +2.8 ms compared to non-smoking). Associations were consistent across waves. Furthermore, 2-year change in frequency of sport activities and number of smoked cigarettes/day was accompanied by 2-year change in HR (β = −0.076 and β = 0.101, respectively) and RSA (β = 0.046 and β = −0.040, respectively). Our findings support consistent effects of lifestyle on HR and parasympathetic activity in the expected direction. Cardiac autonomic dysregulation may be partly mediating the relationship between lifestyle and subsequent cardiovascular health.



## 1. Introduction

Autonomic nervous system (ANS) dysfunction has been found to be prognostic for unfavorable health outcomes, such as the metabolic syndrome (MetS) (Vrijkotte et al., 2015; Koskinen et al., 2009; Brunner et al., 2002; Hu et al., 2016a) and cardiovascular disease (CVD) (Curtis and O'Keefe, 2002; Kop et al., 2010). Several lifestyle factors that are known risk factors for MetS and CVD have been hypothesized to affect these adverse health outcomes through modifying ANS activity. For instance, physical activity is suggested to be beneficial for cardiac ANS activity (Rosenwinkel et al., 2001; Joyner and Green, 2009; Carter et al., 2003; Mueller, 2007; Wichi et al., 2009; Goldsmith et al., 2000). Indeed, exercise was found to be associated with a favorable shift from sympathetic to parasympathetic cardiac activity (Ueno and Moritani, 2003; Grassi and Seravalle, 1994; Melo et al., 2005; Soares-Miranda et al., 2012; Rennie et al., 2003; Van Lien et al., 2011; Amano et al., 2001; Iwane et al., 2000; Killavuori et al., 1995; La Rovere et al., 1992). In contrast, alcohol use has been associated with unfavorable effects on cardiac ANS activity, illustrated by studies showing increased sympathetic and/or decreased parasympathetic activity with increased alcohol intake (Boschloo et al., 2011; Ohira et al., 2009; Ryan and Howes, 2002; Reed et al., 1999.; Vaschillo et al., 2008; Sagawa et al., 2011; Spaak et al., 2010). Similarly, data suggests that smoking has a detrimental effect on cardiac ANS activity (Middlekauff et al., 2014; Haass and Kubler, 1997; Dinas et al., 2013). This effect has been found after chronic (Hering et al., 2010; Lucini et al., 1996; Poulsen et al., 1998; Hayano et al., 1990) and acute (Hayano et al., 1990; Niedermaier et al., 1993; Sjoberg and Saint, 2011; Narkiewicz et al., 1998; Pope et al., 2001) exposure to tobacco smoke.

Studies on alcohol use and smoking have either investigated acute effects of these substances or effects of habitual drinking or smoking at one time point and studies on physical activity have often looked at effects of short-term exercise interventions on cardiac ANS activity. To our knowledge, only one study investigated the association between habitual physical activity and parasympathetic activity over a longer time period (Soares-Miranda et al., 2012), and found that physical

* Corresponding author at: AJ Ernststraat 1187, 1081 HL Amsterdam, The Netherlands.
*E-mail address:* m.hu@ggzingeest.nl (M.X. Hu).

http://dx.doi.org/10.1016/j.ypmed.2016.11.003
0091-7435/

activity predicted positive changes in heart rate variability (HRV), an often-used measure of cardiac parasympathetic activity. Otherwise, not much is known about the longitudinal relationships between habitual lifestyle factors and both sympathetic and parasympathetic activity, leaving important questions unanswered, such as how changes in lifestyle affect cardiac ANS activity. Finally, the relationship between habitual lifestyle factors and cardiac ANS activity may not be linear and it is important to understand at which threshold a certain behavior is likely to be detrimental or beneficial. Some studies have found decreased HR and increased HRV with increased amounts of regular exercise behavior (Rennie et al., 2003; Okazaki, 2005). In contrast, one study found that the effect of taking up regular exercise leveled off at a moderate dose, such that more prolonged and intense exercise training did not lead to more improvements in cardiac ANS activity (Iwasaki et al., 2003). Regarding alcohol use, one study demonstrated that increasing doses of habitual drinking were associated with increasing sympathetic activity (Ohira et al., 2009), while another study found that only heavy drinkers had significantly elevated sympathetic activity (Boschloo et al., 2011). As for smoking, one study implied that heavy smoking, but not moderate smoking, caused reduction in parasympathetic activity (Hayano et al., 1990). Most of these studies have used small, diverse samples and different methodology, which may have caused the discrepancies in results.

The aim of the current study was to investigate: 1) whether there are consistent relationships between physical activity, alcohol use and smoking with – both sympathetic and parasympathetic – cardiac activity over a 2-year follow-up, and 2) whether changes in these lifestyle factors are related to changes in cardiac ANS activity over 2 years. Indicators of cardiac ANS activity were heart rate (HR), controlled by both branches of the ANS (De Geus and Van Doornen, 1996), respiratory sinus arrhythmia (RSA) as an index of parasympathetic control (Neijts et al., 2014; De Geus et al., 1995), and pre-ejection period (PEP) as an index of sympathetic activity (De Geus and Van Doornen, 1996; Lien et al., 2015). Our large sample size allowed for the inclusion of many important confounding factors.

## 2. Methods

### 2.1. Subjects

Participants belonged to the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort including 2981 respondents aged 18–65 years consisting of persons with depressive/anxiety disorders and healthy controls. Respondents were recruited from the community, primary care and mental health care in the Netherlands. A four-hour baseline measurement, including demographic, psychiatric and physical assessments, was conducted between September 2004 and February 2007, and follow-up assessments took place after two, four and six years. Questions about lifestyle factors were incorporated in a self-report questionnaire filled out by the participants before every assessment. A detailed description of the rationale, objectives and methods of the NESDA study can be found elsewhere (Penninx et al., 2008). The research protocol was approved by the Ethical Review Board of each participating center, and written informed consent was provided by all participants.

Data for the present study were drawn from the baseline ($n = 2981$) and 2-year follow-up ($n = 2596$) assessment. Of the total baseline sample, 225 individuals were excluded because of missing questionnaire data on lifestyle factors, and an additional 138 individuals because of missing physiological data due to equipment failure or poor electrocardiogram quality. At 2-year follow-up 331 individuals were excluded because of missing data on lifestyle factors, and 255 individuals because of missing physiological data. Consequently, the analyses were conducted with 2618 participants at baseline and 2010 participants at 2-year follow-up.

### 2.2. Lifestyle factors

We investigated four self-reported lifestyle factors: physical activity, sport activities, alcohol use and smoking.

*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. The continuous score is calculated in Metabolic Equivalent Total (MET)-minutes per week: MET level * minutes of activity * events per week (Booth et al., 2003). The categorical score indicates three levels of physical activity: low, moderate and high. Detailed information about the methodological development of the IPAQ can be found at the IPAQ website www.ipaq.ski.se.

*Sport activities* were determined by the question: 'How often do you engage in sport activities, such as swimming, cycling, playing soccer or other sports?' Participants were required to choose from the categories: 1) almost never, 2) a couple of times/year, 3) every month, 4) a couple of times/month, 5) every week, or 6) a couple of times/week.

*Alcohol use* was assessed by the Alcohol Use Disorder Identification Test questionnaire (Babor et al., 1992) from which we derived the number of alcoholic drinks per week. 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. For the categorical score, this number was divided into three categories: non-drinker (<1 drink/week), mild/moderate drinker (men: 1–21 drinks/week, women: 1–14 drinks/week), and heavy drinker (men: >21 drinks/week, women: >14 drinks/week).

*Smoking* was indicated by the current number of cigarettes/day. For the categorical score, this number was divided into the following categories: 0 cigarettes, 1–10 cigarettes, 11–20 cigarettes, 21–30 cigarettes, and >30 cigarettes per day (Heatherton et al., 1989).

### 2.3. Physiological measurements

Cardiac ANS measures were recorded with the 'Vrije Universiteit Ambulatory Monitoring System' (VU-AMS). The VU-AMS records electrocardiograms (ECG) and changes in thorax impedance (ICG) from a six-electrode configuration (De Geus and Van Doornen, 1996). During the recording, an event marker was used to indicate the start and end of the different assessment conditions. Movement registration through vertical accelerometry indicated periods where the subjects were not stationary. These non-stationary periods were removed from the analyses, resulting in four conditions: a supine rest condition with blood pressure measurement, a psychiatric interview, a general interview and an Implicit Association (computer) Task. The recording of these four conditions lasted approximately 100 min and data from these conditions were averaged to create a single value of HR and RSA per individual. Since postural changes are the main source of change in preload (Houtveen et al., 2005), the supine condition was excluded when averaging PEP.

HR, controlled by both branches of the ANS, was derived from the interbeat interval (IBI) time series from the ICG signal (Neijts et al., 2014). The HRV measure of RSA was used as an index of cardiac parasympathetic activity, combined the 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 (Neijts et al., 2014; De Geus et al., 1995). PEP, an index of sympathetic activity, was ensemble averaged across one-minute periods time-locked to the R-waves in the ECG. PEP was defined as 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 and Van Doornen, 1996; Lien et al., 2015). Automated scoring of HR, RSA and PEP was checked by visual inspection and, where necessary, corrected or discarded.

### 2.4. Covariates

Analyses were adjusted for sociodemographic characteristics, including age, sex and years of education. In addition, adjustments were made for health indicators, including body mass index (BMI), number of chronic diseases for which people were under treatment (cardiovascular disease, epilepsy, diabetes, osteoarthritis, stroke, cancer, chronic lung disease, thyroid disease, liver disease, intestinal disorders and ulcer), current depression and/or anxiety disorder (according to the DSM-IV based Composite International Diagnostic Interview), and former smoking (for analyses of smoking). We also adjusted for use of heart medication (ATC codes C01, C02, C03, C04, C05, C07 and C08), and 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). Since it has been linked to RSA (Hirsch and Bishop, 1981), respiration rate was included as a covariate when analyzing RSA.

### 2.5. Statistical analyses

RSA values were highly skewed and therefore ln-transformed for analyses. We used generalized estimated equations (GEE) analyses with an exchangeable correlation structure to examine the consistency of the association between the lifestyle factors and HR/RSA/PEP over time. GEE allowed us to conduct a combined cross-sectional analyses on the relationship between lifestyle factors and HR/RSA/PEP for both baseline and follow-up. We first entered the predictors as continuous variables, and then as categorical variables to illustrate the dose-response effects and possible critical thresholds in non-linear relationships. To test for U-curve type effects we added quadratic effects of physical activity, alcohol use and smoking to the GEE (since sport activities was a categorical variable we did not add a quadratic term for this variable). For these analyses we mean-centered the predictors to avoid multicollinearity of the linear and quadratic variables. To investigate whether the effects of lifestyle factors on cardiac ANS activity differed between the two assessments, the above analyses were repeated with the inclusion of an interaction term between lifestyle factors and time. Analyses were adjusted for sociodemographic and health characteristics. Covariates age, sex, years of education and former smoking were held at baseline, other covariates could vary over time.

Change-variables of lifestyle factors, cardiac ANS activity and covariates were calculated by subtraction of the variables at baseline from the variables at 2-year follow-up. We then conducted multiple linear regression analyses to examine whether 2-year changes in lifestyle factors were associated with 2-year changes in cardiac ANS activity. These analyses were adjusted for the corresponding lifestyle and ANS values at baseline, as well as for baseline age, sex, education and former smoking. Additional adjustments were made for 2-year change-scores of BMI, number of chronic diseases, use of heart medication, current psychopathology, antidepressant use, and respiration rate. We then investigated with analyses of covariance whether certain patterns of behavioral changes (Table 4) were accompanied by different changes in autonomic activity over time.

Since it has been suggested that parasympathetic activity is underestimated in people with low HR (Van Lien et al., 2011), we performed sensitivity analyses for which we excluded people with HR < 55 (Neijts et al., 2014). We also performed sensitivity analyses for which we excluded cardiac ANS activity during the psychiatric interview, since this condition has been shown to evoke differential stress reactivity in people with psychopathology compared to controls (Hu et al., 2016b).

Data was analyzed using SPSS, version 20.0. The criterion for statistical significance was $p < 0.05$.

## 3. Results

At baseline, our sample (n = 2618) had a mean age of 41.6 years (SD = 13.0) and 66.2% were female (Table 1).

Consistent associations existed between several lifestyle factors and Cardiac ANS activity across waves (Table 2). Physical activity and sport activities were associated with lower HR (B = −0.141; p = 0.001 and B = −0.461; p < 0.001, respectively). Sport activities was also associated with higher RSA (ln(B) = 0.010; p = 0.001). Smoking was associated with higher HR (B = 0.075; p < 0.001) and, unexpectedly, with longer PEP (B = 0.098; p = 0.013). The addition of an interaction term between lifestyle factors and time showed that the associations were generally consistent across the waves, except for the association between smoking * time and PEP (B = −0.106; p = 0.015).

Fig. 1 illustrates the associations between categories of lifestyle factors and cardiac ANS activity over time, showing that the association between physical activity and HR was mainly driven by high physical activity (−1.8 beats/min; p < 0.001 compared to low physical activity). The association between sport activities and HR was mainly driven by

**Table 1**
Sample characteristics.

| Variables | Participants, % | |
|---|---|---|
| | Baseline n = 2618 | 2-year follow-up n = 2010 |
| Demographics | | |
| Age, mean (SD), years | 41.6 (13.0) | 44.1 (13.2) |
| Female sex | 66.2 | 66.5 |
| Education, mean (SD) years | 12.2 (3.2) | 12.6 (3.3) |
| Health factors | | |
| Body mass index, mean (SD), kg/m$^2$ | 25.5 (4.9) | 25.7 (4.9) |
| Number of chronic diseases, median (IQR) | 0.0 (0.0–1.0) | 0.0 (0.0–1.0) |
| Use of heart medication | 12.5 | 15.0 |
| Current depression and/or anxiety | 56.8 | 37.6 |
| Antidepressant use | | |
| TCA | 2.6 | 2.9 |
| SSRI | 16.8 | 14.2 |
| SNRI | 4.0 | 3.7 |
| Lifestyle factors | | |
| Physical activity, median (IQR), 1000 METmin/week | 2.8 (1.4–5.0) | 3.1 (1.6–5.5) |
| Low physical activity | 23.1 | 19.6 |
| Moderate physical activity | 42.2 | 40.5 |
| High physical activity | 34.6 | 39.9 |
| Sport activities | | |
| Almost never | 26.2 | 24.6 |
| Couple of times a year | 12.3 | 12.3 |
| Every month | 6.1 | 5.6 |
| Couple of times a month | 8.1 | 9.0 |
| Every week | 22.7 | 23.5 |
| Couple of times a week | 24.7 | 25.1 |
| Alcohol use, median (IQR), drinks/week | 3.7 (0.2–8.7) | 3.7 (0.2–8.7) |
| Non-drinker | 32.3 | 31.7 |
| Mild/moderate drinker | 51.5 | 52.7 |
| Heavy drinker | 16.2 | 15.6 |
| Smoking, median (IQR), no. Cigarettes/day | 0.0 (0.0–8.0) | 0.0 (0.0–5.0) |
| Current smoker | 37.9 | 30.2 |
| Autonomic variables | | |
| HR, mean (SD), beats/min | 72.0 (9.6) | 72.6 (9.5) |
| RSA, mean (SD), ms | 44.6 (26.0) | 41.8 (22.3) |
| PEP, mean (SD), ms | 120.1 (17.7) | 119.7 (17.2) |
| Respiration rate, breaths/min | 17.1 (1.2) | 17.3 (1.2) |

*Note*: Metmin = multiple of resting metabolic rate times minutes of physical activity per week. IQR = interquartile range. HR = heart rate. RSA = respiratory sinus arrhythmia. PEP = pre-ejection period.
Baseline data was collected in the Netherlands from 2004 to 2007.

**Table 2**
Association between lifestyle factors with ANS values over two time points (baseline: n = 2618; 2-year follow-up: n = 2010).

| | HR (beats/min) | | RSA (ms) | | PEP (ms) | |
|---|---|---|---|---|---|---|
| | B | P | B | P | B | P |
| Linear effects | | | | | | |
| Physical activity | **−0.141** | **0.001** | 0.001 | 0.71 | 0.078 | 0.32 |
| Sport activities | **−0.461** | **<0.001** | **0.010** | **0.001** | −0.021 | 0.87 |
| Alcohol use | 0.021 | 0.29 | −0.001 | 0.39 | −0.002 | 0.94 |
| Smoking | **0.075** | **<0.001** | 0.001 | 0.44 | **0.098** | **0.013** |
| Linear and quadratic effects | | | | | | |
| Mean-centered physical activity | **−0.201** | **<0.001** | 0.002 | 0.32 | 0.109 | 0.30 |
| Mean-centered physical activity$^2$ | 0.012 | 0.14 | −3.4E-4 | 0.45 | −0.007 | 0.65 |
| Mean-centered alcohol use | **−0.067** | **0.008** | 0.002 | 0.11 | .041 | 0.36 |
| Mean-centered alcohol use$^2$ | **0.003** | **0.001** | **−9.0E-5** | **0.024** | −0.002 | 0.17 |
| Mean-centered smoking | 0.018 | 0.57 | 0.002 | 0.19 | **0.235** | **<0.001** |
| Mean-centered smoking$^2$ | **0.003** | **0.018** | −6.0E-5 | 0.30 | **−0.007** | **0.006** |
| Time interaction effects | | | | | | |
| Physical activity * time | 0.001 | 0.98 | −0.003 | 0.31 | 0.033 | 0.78 |
| Sport activities * time | 0.022 | 0.81 | −0.005 | 0.29 | 0.244 | 0.19 |
| Alcohol use * time | 0.041 | 0.061 | −1.03E-5 | 0.99 | −0.008 | 0.83 |
| Smoking * time | 0.037 | 0.11 | −0.001 | 0.16 | **−0.106** | **0.015** |

*Note*: HR = heart rate. RSA = respiratory sinus arrhythmia. PEP = pre-ejection period. RSA was ln-transformed for analyses.
For quadratic analyses the predictors were mean-centered to avoid multicollinearity of the linear and quadratic variables.
Physical activity was measured in 1000 metmin/week, alcohol use was measured in number of glasses per week and smoking in number of cigarettes per day.
GEE analyses were adjusted for age, sex, education, BMI, number of chronic diseases, use of heart medication, current psychopathology, antidepressant use and time. RSA was additionally adjusted for respiration rate and smoking for former smoking.
Boldface indicates statistical significance ($p < 0.05$).
Baseline data was collected in the Netherlands from 2004 to 2007.

engaging 'every week' or 'a couple of times/week' in sport activities (−1.4 beats/min; $p < 0.001$ and −2.5 beats/min; $p < 0.001$ compared to 'almost never', respectively). These two categories also drove the association between sport activities and RSA (+1.5 ms; $p = 0.013$, and +1.7 ms; $p = 0.007$ compared to 'almost never', respectively). Analyses of quadratic relationships (Table 2) indicated that there was a non-linear association between number of drinks and HR and RSA. When analyzing categories of alcohol use, it seemed like these relationships were U-shaped with mild/moderate drinking being significantly associated with lower HR (−1.2 beats/min; $p < 0.001$) and non-significantly with higher RSA than non-drinking. Analyses of quadratic relationships (Table 2) also indicated that there was a non-linear association between smoking and HR and PEP. Fig. 1 suggests that the association between HR and smoking was J-shaped with minimal effects of light smoking but substantial effects of heavy smoking on HR (21–30 cigarettes/day: +1.6 beats/min; $p = 0.024$; >30 cigarettes/day: +5.1 beats/min; $p < 0.001$ compared to non-smoking). In addition, the association between smoking and PEP seemed U-shaped with the moderately smoking group (11–20 cigarettes/day) showing longer PEP (+2.8 ms; $p = 0.002$ compared to non-smoking).

Table 3 shows that a 2-year increase in sport activities was associated with a 2-year decrease in HR ($\beta = -0.076$; $p = 0.001$) and a 2-year increase in RSA ($\beta = 0.046$; $p = 0.026$). In addition, a 2-year increase in number of smoked cigarettes/day was associated with a 2-year increase in HR ($\beta = 0.101$; $p < 0.001$) and a 2-year decrease in RSA ($\beta = -0.040$; $p = 0.040$).

We investigated the lifestyle variables further by distinguishing categories of consistency and change in behavior (Table 4). We performed analyses of covariance to see whether certain patterns of change in lifestyle were accompanied by differences in changes in HR, RSA and PEP over time (Fig. 2). Regarding physical activity, results indicated that the persistently active group (−1.0 beats/min; $p = 0.017$) and the newly active (−1.4 beats/min; $p = 0.001$) group increased less in HR over time than the persistently inactive group. For sport activities, results showed that persistent activity was accompanied with smaller increase in HR over time compared to persistent inactivity (−0.8 beats/min; $p = 0.022$). For alcohol use, an overall effect was found for HR ($p = 0.044$), but post-hoc tests did not show that any of the groups significantly differed from the non-drinking group. For smoking, persistently heavy smoking (+3.2 beats/min; $p < 0.001$) and starting heavy smoking (+5.2 beats/min; $p < 0.001$) were associated with a larger increase in HR over time compared to non-smoking. In addition, starting heavy smoking was related to a larger decrease of RSA compared to non-smoking (−5.1 ms; $p = 0.027$).

Sensitivity analyses excluding people with HR < 55 did not alter any of the lifestyle associations with (change in) RSA. Similarly, excluding the psychiatric interview from our averaged values of cardiac ANS activity did not change our results.

## 4. Discussion

The current study showed that high physical activity, high frequency of sport activities and mild/moderate alcohol use were related to low HR, and heavy smoking was related to high HR. In addition, high frequency of sport activities was associated with high RSA and moderate smoking with longer PEP. These effects were consistent over a 2-year period. Longitudinal analyses showed that 2-year increase in the frequency of sport activities had beneficial effects on HR and RSA over time. In addition, 2-year increase in number of smoked cigarettes/day had a negative impact on HR and RSA over time.

Our findings indicate a more robust effect of frequency of sport activities on cardiac ANS activity than of general habitual physical activity (which was only associated with HR), possibly due to lower error in recall of these salient activities and therefore better reliability of the former measure (Rzewnicki et al., 2003). Another possibility is that frequency of sport activities captures a more vigorous form of being active than physical activity, since the former comprises purely sports while the latter also reflects more moderate forms of exercise. Since it is likely that the ANS is mainly influenced by the more vigorous form of activity, this might explain the more robust effect of frequency of sport activities. The results on sport activities are in line with previous research finding associations between exercise and improved parasympathetic activity (Ueno and Moritani, 2003; Melo et al., 2005; Amano et al., 2001; La Rovere et al., 1992), and comparable to studies that found increasing improvement of HR and HRV with increasing exercise (Rennie et al., 2003; Okazaki, 2005). In contrast to some studies (Grassi and Seravalle, 1994; Amano et al., 2001; La Rovere et al., 1992), we did not find evidence for a relationship between physical activity or sport activities with sympathetic activity. However, most of those studies sampled people with obesity, hypertension or cardiovascular disease. Since these conditions are related to compromised cardiac ANS activity (Curtis and O'Keefe, 2002; Kop et al., 2010; Thorp and Schlaich, 2015; Grassi et al., 2015), there may have been more obvious effects of exercise on sympathetic activity than in our study with relatively young and physically healthy respondents. Longitudinally, Soares-Miranda and colleagues (Soares-Miranda et al., 2012) found a relationship between *baseline* moderate to vigorous physical activity and 3-year increase in HRV. The current study adds to these findings by investigating how *change* in physical activity affects change in cardiac ANS activity, and found evidence that increase in frequency of sport activities had a beneficial effect on HR and RSA over time.

Interestingly, our results on alcohol use did not corroborate the suggestion that there is a linear relationship between alcohol use and cardiac ANS activity (Ohira et al., 2009). Our results rather imply that there is a U-shape relationship, with mild/moderate drinking being more favorable for HR than either non-drinking or heavy drinking, comparable to the results of Boschloo and colleagues on baseline NESDA data

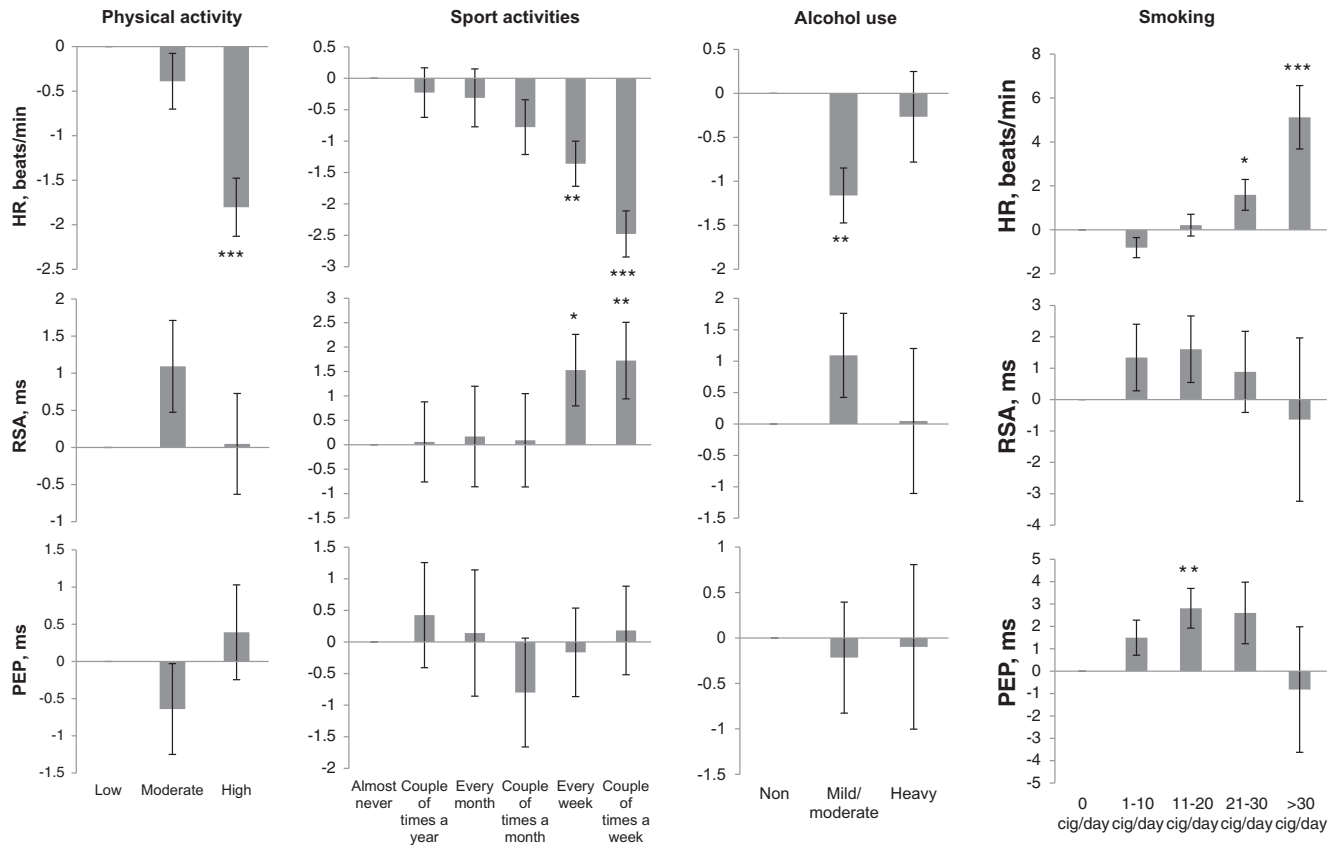


**Fig. 1.** Differences in HR, RSA and PEP over two time points for different lifestyle categories. RSA was ln-transformed for analyses and back-transformed to display the differences between the categories. p-values are based on GEE analyses comparing the different categories to the chosen reference categories (low physical activity, almost never engaging in sport activities, non-drinking, and non-smoking respectively). *p < 0.05 **p < 0.01 ***p < 0.001. Baseline data was collected in the Netherlands from 2004–2007.

(Boschloo et al., 2011). A U-shaped relationship has been found between alcohol use and other health outcomes (Gronbaek et al., 1995; Koppes et al., 2005), and likely reflects the association between non-drinking and formerly heavy drinking, diseases and medication use (sick quitter hypothesis) (Wannamethee and Shaper, 1988).

This U-shaped relationship also seems applicable for smoking and sympathetic activity, since we found a positive relationship between moderate smoking and PEP. The mechanisms underlying this counter-intuitive finding are unclear, since smoking has been suggested to lead to sympathetic activation and attenuated baroreflex suppression of sympathetic activation (Middlekauff et al., 2014). A possible explanation is compensatory down-regulation of cardiac beta-adrenergic receptors by moderate smoking which would compensate for increased cardiac sympathetic activity. At heavier levels of smoking this down-regulation may either level off or fail to compensate for the stronger smoking-induced increase in cardiac sympathetic activity (Laustiola et al., 1988). Another possibility is that baroreflex sensitivity is only impaired by heavy smoking, but is still intact in moderate smokers, providing the necessary negative feedback to suppress activation of the sympathetic nervous system (Shinozaki et al., 2008). In contrast to many studies reporting smoking to be associated with lower parasympathetic activity (Lucini et al., 1996; Hayano et al., 1990; Barutcu et al., 2005; Eryonucu et al., 2000; Alyan and Kacmaz, 2008; Mølgaard et al., 1991), our results did not show this association across waves. One could argue that our non-smoker group consists of a considerable group of former smokers who might already have compromised ANS activity at baseline. However, former smoking was added as a covariate to our analyses and additional analyses separating the former smokers from our non-smoking group, did not significantly change our results. It therefore remains to be elucidated why our study did not robustly replicate the previously established relationship between smoking and lower parasympathetic activity. The effect of smoking on HR, however, followed expectation and was worst for heavy smoking. In addition, increase in number of smoked cigarettes/day was accompanied by detoriation of HR and RSA over time, and subjects who started to smoke heavily showed worse deterioration than non-smokers, persistent light or heavy smokers and people who stopped smoking. These findings comply with the major impact of smoking on cardiovascular disease (Lloyd-Jones et al., 2006).

**Table 3**
Association between change in lifestyle factors with change in ANS activity over time.

| | | Δ HR, beats/min | | Δ RSA, ms | | Δ PEP, ms | |
|---|---|---|---|---|---|---|---|
| | N | β | P | β | P | β | P |
| Δ physical activity | 1824 | −0.043 | 0.065 | **−0.011** | 0.91 | 0.027 | 0.22 |
| Δ sport activities | 2071 | **−0.076** | **0.001** | **0.046** | **0.026** | 0.004 | 0.85 |
| Δ alcohol use | 2075 | 0.033 | 0.14 | 0.005 | 0.80 | 0.016 | 0.43 |
| Δ smoking | 2118 | **0.101** | **<0.001** | **−0.040** | **0.040** | −0.033 | 0.099 |

*Note*: HR = heart rate. RSA = respiratory sinus arrhythmia. PEP = pre-ejection period.
Change-variables of lifestyle factors and ANS activity were calculated by subtraction of the continuous variables at baseline from the continuous variables at 2-year follow-up.
Multiple linear regression analyses were adjusted for the corresponding lifestyle and ANS values at baseline, as well as for baseline age, sex, education and former smoking (for analyses of smoking). In addition, adjustments were made for 2-year change-scores of BMI, number of chronic diseases, use of heart medication, current psychopathology, antidepressant use and respiration rate (for analyses of RSA).
Boldface indicates statistical significance (p < 0.05).
Baseline data was collected in the Netherlands from 2004 to 2007.

### 4.1. Limitations

When interpreting these findings, some limitations have to be taken into account. For instance, questions might be raised about the

**Table 4**
Patterns of change in lifestyle factors over time.

| Physical activity patterns | N | Baseline | 2-year follow-up | ΔHR, beats/min | ΔRSA, ms | ΔPEP, ms |
|---|---|---|---|---|---|---|
| Persistently inactive | 834 | Low/moderate | Low/moderate | 1.215 ± 0.228 | −2.606 ± 0.443 | −0.794 ± 0.468 |
| Persistently active | 392 | High | High | 0.236 ± 0.336 | −2.036 ± 0.651 | 0.025 ± 0.688 |
| Newly active | 345 | Low/moderate | High | −0.160 ± 0.353 | −1.178 ± 0.687 | 0.020 ± 0.727 |
| Newly inactive | 253 | High | Low/moderate | 1.222 ± 0.412 | −1.796 ± 0.803 | −0.025 ± 0.850 |
| | | | | **p = 0.003** | p = 0.35 | p = 0.66 |

| Sport activities patterns | N | Baseline | 2-year follow-up | ΔHR, beats/min | ΔRSA, ms | ΔPEP, ms |
|---|---|---|---|---|---|---|
| Persistently inactive | 791 | Engaging less than every week in sport activities | Engaging less than every week in sport activities | 1.087 ± 0.239 | −2.476 ± 0.462 | -−.788 ± 0.485 |
| Persistently active | 736 | Engaging at least every week in sport activities | Engaging at least every week in sport activities | 0.290 ± 0.248 | −1.193 ± 0.479 | −0.610 ± 0.503 |
| Newly active | 267 | Engaging less than every week in sport activities | Engaging at least every week in sport activities | 0.351 ± 0.407 | −2.079 ± 0.790 | 0.940 ± 0.830 |
| Newly inactive | 277 | Engaging at least every week in sport activities | Engaging less than every week in sport activities | 1.173 ± 0.399 | −3.368 ± 0.773 | 0.229 ± 0.813 |
| | | | | p = 0.062 | p = 0.076 | p = 0.26 |

| Alcohol use patterns | N | Baseline | 2-year follow-up | ΔHR, beats/min | ΔRSA, ms | ΔPEP, ms |
|---|---|---|---|---|---|---|
| Persistently non-drinking | 537 | Non-drinking | Non-drinking | 0.905 ± 0.296 | −2.216 ± 0.573 | −0.477 ± 0.594 |
| Persistently mild/moderate drinking | 864 | Mild/moderate drinking | Mild/moderate drinking | 0.375 ± 0.229 | −1.605 ± 0.442 | 0.165 ± 0.459 |
| Persistently heavy drinking | 226 | Heavy drinking | Heavy drinking | 1.809 ± 0.453 | −2.384 ± 0.877 | 0.037 ± 0.912 |
| Starting heavy drinking | 86 | Non- or mild/moderate drinking | Heavy drinking | 0.033 ± 0.718 | −2.772 ± 1.389 | −0.108 ± 1.443 |
| Stopping heavy drinking | 117 | Heavy drinking | Non- or mild/moderate drinking | 0.317 ± 0.616 | −2.738 ± 1.192 | -1.646 ± 1.240 |
| | | | | **p = 0.044** | p = 0.77 | p = 0.69 |

| Smoking patterns | N | Baseline | 2-year follow-up | ΔHR, beats/min | ΔRSA, ms | ΔPEP, ms |
|---|---|---|---|---|---|---|
| Persistently non-smoking | 1982 | Non-smoking | Non-smoking | 0.549 ± 0.187 | −2.278 ± 0.367 | −0.613 ± 0.387 |
| Persistently light smoking | 60 | Smoking 1–20 cigarettes/day | Smoking 1–20 cigarettes/day | 0.764 ± 0.335 | −1.727 ± 0.657 | 0.543 ± 0.693 |
| Persistently heavy smoking | 33 | Smoking > 20 cigarettes/day | Smoking > 20 cigarettes/day | 3.744 ± 0.866 | −5.063 ± 1.694 | −2.093 ± 1.416 |
| Starting heavy smoking | 43 | Smoking < 20 cigarettes/day | Smoking > 20 cigarettes/day | 5.752 ± 1.152 | −7.351 ± 2.252 | −4.879 ± 2.375 |
| Stopping heavy smoking | 43 | Smoking > 20 cigarettes/day | Smoking < 20 cigarettes/day | 2.141 ± 1.012 | −3.087 ± 1.979 | 2.697 ± 2.088 |
| | | | | **p < 0.001** | p = 0.067 | p = 0.063 |

Cut-off points for patterns of change were based on significant associations between lifestyle categories and ANS activity (Fig. 1).
Change-variables of ANS activity were calculated by subtraction of the continuous variables at baseline from the continuous variables at 2-year follow-up, and represent estimated marginal means and standard errors after correction for baseline ANS and lifestyle values respectively, baseline age, sex, education, former smoking (for analyses of smoking) and change in BMI, number of chronic diseases, use of heart medication, current psychopathology, antidepressant use and respiration rate (for analyses of RSA).
Boldface indicates statistical significance ($p < 0.05$).
Baseline data was collected in the Netherlands from 2004 to 2007.

generalizability of this study, since the majority of the NESDA sample consists of people with a (history of) depressive and/or anxiety disorder. However, our results remained robust after adjustments for psychopathology status and previous research has indicated that psychopathology was not associated with ANS activity (Licht et al., 2009; Licht et al., 2008). We are therefore confident that our results apply to the general population. In addition, the effects found for lifestyle on cardiac ANS activity were rather modest and whether these are clinically relevant remains to be determined. However, we stress that our aim was to examine a potential biological mechanism in the association between lifestyle and cardiovascular disease, as opposed to providing a clinically useful marker of ANS dysregulation at the level of individuals. Also, in general, we found little evidence that PEP was affected by lifestyle factors. The reason for this remains unclear, since several other studies have shown sympathetic activity to be associated with physical activity (Grassi and Seravalle, 1994; Amano et al., 2001), alcohol use (Boschloo et al., 2011; Ohira et al., 2009) and smoking (Hering et al., 2010; Lucini et al., 1996). Our sample consisted of relatively healthy behaving individuals. Perhaps a more unhealthy lifestyle would have larger effects on sympathetic activity. Finally, our results are based on self-reported lifestyle factors and not on e.g. accelerometer data. Self-reports of lifestyle is more prone to inaccuracy and bias than such objective measurements. However, we did have data on cotinine levels at baseline and these levels showed strong correlations with self-reported number of smoked cigarettes/day, confirming the reliability and validity of our used measures.

## 5. Conclusion

Our findings support consistent effects of habitual exercise behavior, smoking and alcohol use on HR and cardiac parasympathetic activity in the expected directions. Cross-sectionally and longitudinally, high frequency of sport activities and heavy smoking had the most robust effects. Our finding support the hypothesis that altered regulation of cardiac autonomic activity is one of the mechanisms mediating the relationship between lifestyle and subsequent cardiovascular disease.

## Source of funding

The infrastructure for the NESDA study (www.nesda.nl) has been funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (Zon-Mw, grant number 10-000-1002) and participating universities (VU University Medical Center, Leiden University Medical Center, University Medical Center Groningen).

FL has received funding from the European Union Seventh Framework Programme (FP7/2007–2013) under grant agreement n°

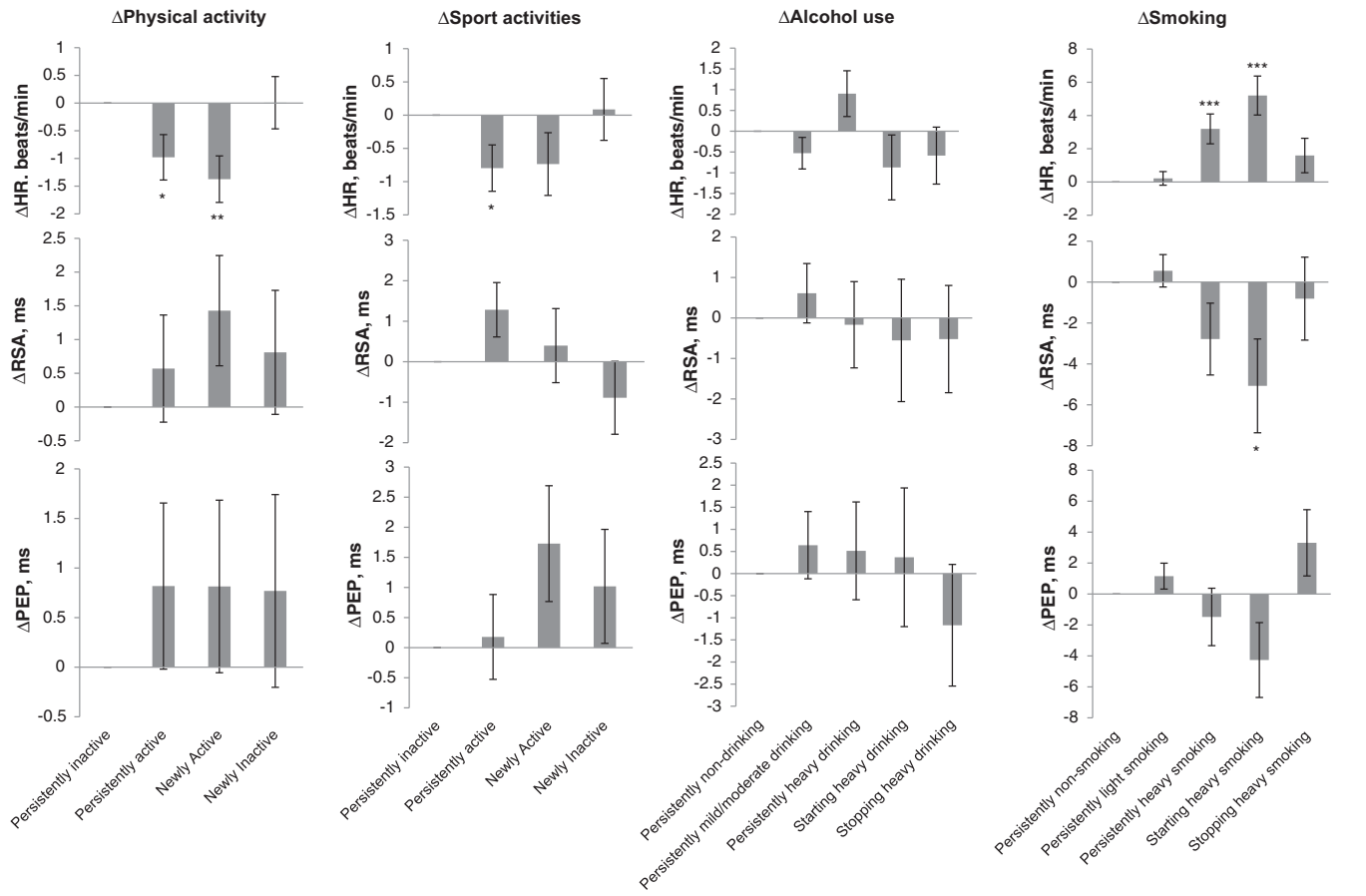


**Fig. 2.** The association between patterns of changes in physical activity, sport activities, alcohol use and smoking with changes in HR, RSA and PEP over time. p-values are based on ANCOVA analyses comparing the different change-patterns to the chosen reference group (persistently inactive, persistently non-drinking and persistently non-smoking respectively). *p < 0.05 **p < 0.01 ***p < 0.001. Baseline data was collected in the Netherlands from 2004 to 2007.

PCIG12-GA-2012-334065. BP has received – unrelated - grant funding from Jansen.

## Conflicts of interest

None declared.

## Acknowledgments

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.

No financial disclosures were reported by the authors of this paper.

## References

Alyan, O., Kacmaz, F., 2008. Effects of cigarette smoking on heart rate variability and plasma N-terminal pro-B-type natriuretic peptide in healthy subjects: is there the relationship between. Ann. (Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1542-474X.2008.00213.x/full. Accessed August 17, 2016).

Amano, M., Kanda, T., Ue, H., Moritani, T., 2001. Exercise training and autonomic nervous system activity in obese individuals. Med. Sci. Sports Exerc. 33 (8):1287–1291. http://dx.doi.org/10.1097/00005768-200108000-00007.

Babor, T.F., De La Fuente, J.R., Saunders, J., Grant, M., 1992. The alcohol use identification test: guidelines for use in primary health care. World Heal Organ Geneva, Switzerland.

Barutcu, I., Esen, A., Kaya, D., 2005. Cigarette smoking and heart rate variability: dynamic influence of parasympathetic and sympathetic maneuvers. Ann. (Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1542-474X.2005.00636.x/full. Accessed August 17, 2016).

Booth, M.L., Ainsworth, B.E., Pratt, M., et al., 2003. International physical activity questionnaire: 12-country reliability and validity. Med. Sci. Sports Exerc. 195 (9131/03), 1381–3508.

Boschloo, L., Vogelzangs, N., Licht, C.M.M., et al., 2011. Heavy alcohol use, rather than alcohol dependence, is associated with dysregulation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. Drug Alcohol Depend. 116 (1–3): 170–176. http://dx.doi.org/10.1016/j.drugalcdep.2010.12.006.

Brunner, E.J., Hemingway, H., Walker, B.R., et al., 2002. Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome nested case-control study. Circulation 106 (21), 2659–2665.

Carter, J.B., Banister, E.W., Blaber, A.P., 2003. Effect of endurance exercise on autonomic control of heart rate. Sports Med. 33 (1):33–46. http://dx.doi.org/10.2165/00007256-200333010-00003.

Curtis, B.M., O'Keefe, J.H., 2002. Autonomic Tone as a Cardiovascular Risk Factor: The Dangers of Chronic Fight or Flight. Mayo Clinic Proceedings vol. 77. Elsevier, pp. 45–54.

De Geus, E.J.C., Van Doornen, L.J.P., 1996. Ambulatory Assessment of Parasympathetic/Sympathetic Balance by Impedance Cardiography. Ambulatory Assessment: Computer-Assisted Psychological and Psychophysiological Methods in Monitoring and Field Studies, pp. 141–163.

De Geus, E.J.C., Willemsen, G.H.M., Klaver, C.H.A.M., van Doornen, L.J.P., 1995. Ambulatory measurement of respiratory sinus arrhythmia and respiration rate. Biol. Psychol. 41 (3), 205–227.

Dinas, P.C., Koutedakis, Y., Flouris, A.D., 2013. Effects of active and passive tobacco cigarette smoking on heart rate variability. Int. J. Cardiol. 163 (2):109–115. http://dx.doi.org/10.1016/j.ijcard.2011.10.140.

Eryonucu, B., Bilge, M., Güler, N., Uzun, K., Gencer, M., 2000. Effects of cigarette smoking on the circadian rhythm of heart rate variability. Acta Cardiol. (Available at: http://europepmc.org/abstract/med/11103830. Accessed August 17, 2016).

Goldsmith, R.L., Bloomfield, D.M., Rosenwinkel, E.T., 2000. Exercise and autonomic function. Coron. Artery Dis. 11 (2), 129–135.

Grassi, G., Seravalle, G., 1994. Calhoun D a, Mancia G. Physical training and baroreceptor control of sympathetic nerve activity in humans. Hypertension 23:294–301. http://dx.doi.org/10.1161/01.HYP.23.3.294.

Grassi, G., Mark, A., Esler, M., 2015. The sympathetic nervous system alterations in human hypertension. Circ. Res. 116 (6), 976–990.
Gronbaek, M., Deis, A., Sorensen, T.I.A., Becker, U., Schnohr, P., Jensen, G., 1995. Mortality associated with moderate intakes of wine, beer, or spirits. BMJ 310 (6988): 1165–1169. http://dx.doi.org/10.1136/bmj.310.6988.1165.
Haass, M., Kubler, W., 1997. Nicotine and sympathetic neurotransmission. Cardiovasc. Drugs Ther. 10 (6):657–665. http://dx.doi.org/10.1007/BF00053022.
Hayano, J., Yamada, M., Sakakibara, Y., 1990. Al. E. Short- and long-term effects of cigarette smoking on heart rate variability. Am. J. Cardiol. 65, 84–88.
Heatherton, T.F., Kozlowski, L.T., Frecker, R.C., Rickert, W., Robinson, J., 1989. Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. Addiction 84 (7):791–800. http://dx.doi.org/10.1111/j.1360-0443.1989.tb03059.x.
Hering, D., Kucharska, W., Kara, T., Somers, V.K., Narkiewicz, K., 2010. Smoking is associated with chronic sympathetic activation in hypertension. Blood Press. 19 (3): 152–155. http://dx.doi.org/10.3109/08037051.2010.484150.
Hirsch, J.A., Bishop, B., 1981. Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate. Am. J. Physiol. Circ. Physiol. 241 (4), H620–H629.
Houtveen, J.H., Groot, P.F.C., De Geus, E.J.C., 2005. Effects of variation in posture and respiration on RSA and pre-ejection period. Psychophysiology 42 (6):713–719. http://dx.doi.org/10.1111/j.1469-8986.2005.00363.x.
Hu, M.X., Lamers, F., Hiles, S.A., Penninx, B.W.J.H., de Geus, E.J.C., 2016a. Basal autonomic activity, stress reactivity, and increases in metabolic syndrome components over time. Psychoneuroendocrinology 71, 119–126.
Hu, M.X., Lamers, F., de Geus, E.J.C., Penninx, B.W.J.H., 2016b. Differential autonomic nervous system reactivity in depression and anxiety during stress depending on type of stressor. Psychosom. Med. 78 (5), 562–572.
Iwane, M., Arita, M., Tomimoto, S., et al., 2000. Walking 10,000 steps/day or more reduces blood pressure and sympathetic nerve activity in mild essential hypertension. Hypertens. Res. 23:573–580. http://dx.doi.org/10.1291/hypres.23.573.
Iwasaki, K., Zhang, R., Zuckerman, J.H., Levine, B.D., 2003. Dose-response relationship of the cardiovascular adaptation to endurance training in healthy adults: how much training for what benefit? J. Appl. Physiol. 95 (4):1575–1583. http://dx.doi.org/10.1152/japplphysiol.00482.2003.
Joyner, M.J., Green, D.J., 2009. Exercise protects the cardiovascular system: effects beyond traditional risk factors. J. Physiol. 587 (Pt 23):5551–5558. http://dx.doi.org/10.1113/jphysiol.2009.179432.
Killavuori, K., Toivonen, L., Naveri, H., Leinonen, H., 1995. Reversal of autonomic derangements by physical training in chronic heart failure assessed by heart rate variability. Eur. Heart J. 16 (4):490–495 (Available at: http://eurheartj.oxfordjournals.org/content/16/4/490. Accessed December 17, 2015).
Kop, W.J., Stein, P.K., Tracy, R.P., Barzilay, J.I., Schulz, R., Gottdiener, J.S., 2010. Autonomic nervous system dysfunction and inflammation contribute to the increased cardiovascular mortality risk associated with depression. Psychosom. Med. 72 (7), 626.
Koppes, L.L.J., Dekker, J.M., Hendriks, H.F.J., Bouter, L.M., Heine, R.J., 2005. Moderate alcohol consumption lowers the risk of type 2 diabetes: a meta-analysis of prospective observational studies. Diabetes Care 28 (3):719–725. http://dx.doi.org/10.2337/diacare.28.3.719.
Koskinen, T., Kähönen, M., Jula, A., et al., 2009. Metabolic syndrome and short-term heart rate variability in young adults. Diabet. Med. 26 (4), 354–361.
La Rovere, M., Mortara, A., Sandrone, G., Lombardi, F., 1992. Autonomic nervous system adaptations to short-term exercise training. CHEST J. 101, 299S–303S.
Laustiola, K.E., Lassila, R., Kaprio, J., Koskenvuo, M., 1988. Decreased beta-adrenergic receptor density and catecholamine response in male cigarette smokers. A study of monozygotic twin pairs discordant for smoking. Circulation 78 (5):1234–1240. http://dx.doi.org/10.1161/01.CIR.78.5.1234.
Licht, C.M.M., de Geus, E.J.C., Zitman, F.G., Hoogendijk, W.J.G., van Dyck, R., Penninx, B.W.J.H., 2008. Association between major depressive disorder and heart rate variability in the Netherlands study of depression and anxiety (NESDA). Arch. Gen. Psychiatry 65 (12), 1358–1367.
Licht, C.M.M., de Geus, E.J.C., van Dyck, R., Penninx, B.W.J.H., 2009. Association between anxiety disorders and heart rate variability in the Netherlands study of depression and anxiety (NESDA). Psychosom. Med. 71 (5), 508–518.
Lien, R., Neijts, M., Willemsen, G., de Geus, E.J.C., 2015. Ambulatory measurement of the ECG T-wave amplitude. Psychophysiology 52 (2), 225–237.
Lloyd-Jones, D.M., Leip, E.P., Larson, M.G., et al., 2006. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation 113 (6):791–798. http://dx.doi.org/10.1161/CIRCULATIONAHA.105.548206.
Lucini, D., Bertocchi, F., Malliani, A., Pagani, M., 1996. A controlled study of the autonomic changes produced by habitual cigarette smoking in healthy subjects. Cardiovasc. Res. 31 (4):633–639. http://dx.doi.org/10.1016/0008-6363(96)00013-2.
Melo, R.C., Santos, M.D.B., Silva, E., et al., 2005. Effects of age and physical activity on the autonomic control of heart rate in healthy men. Braz. J. Med. Biol. Res. 38 (9), 1331–1338 (doi:/S0100-879X2005000900007).
Middlekauff, H.R., Park, J., Moheimani, R.S., 2014. Adverse effects of cigarette and noncigarette smoke exposure on the autonomic nervous system: mechanisms and implications for cardiovascular risk. J. Am. Coll. Cardiol. 64 (16):1740–1750. http://dx.doi.org/10.1016/j.jacc.2014.06.1201.
Mølgaard, H., Sørensen, K., Bjerregaard, P., 1991. Circadian variation and influence of risk factors on heart rate variability in healthy subjects. Am. J. (Available at: http://www.sciencedirect.com/science/article/pii/0002914991906533. Accessed August 17, 2016).
Mueller, P.J., 2007. Exercise training and sympathetic nervous system activity: evidence for physical activity dependent neural plasticity. Clin. Exp. Pharmacol. Physiol. 34 (4):377–384. http://dx.doi.org/10.1111/j.1440-1681.2007.04590.x.
Narkiewicz, K., van de Borne, P.J.H., Hausberg, M., et al., 1998. Cigarette smoking increases sympathetic outflow in humans. Circulation 98 (6):528–534. http://dx.doi.org/10.1161/01.CIR.98.6.528.
Neijts, M., Van Lien, R., Kupper, N., Boomsma, D., Willemsen, G., Geus, E.J.C., 2014. Heritability of cardiac vagal control in 24-h heart rate variability recordings: influence of ceiling effects at low heart rates. Psychophysiology 51 (10), 1023–1036.
Niedermaier, O.N., Smith, M.L., Beightol, L.A., Zukowska-Grojec, Z., Goldstein, D.S., Eckberg, D.L., 1993. Influence of cigarette smoking on human autonomic function. Circulation 88 (2):562–571. http://dx.doi.org/10.1161/01.CIR.88.2.562.
Ohira, T., Tanigawa, T., Tabata, M., et al., 2009. Effects of habitual alcohol intake on ambulatory blood pressure, heart rate, and its variability among japanese men. Hypertension 53 (1):13–19. http://dx.doi.org/10.1161/HYPERTENSIONAHA.108.114835.
Okazaki, K., 2005. Dose-response relationship of endurance training for autonomic circulatory control in healthy seniors. J. Appl. Physiol. 99 (3):1041–1049. http://dx.doi.org/10.1152/japplphysiol.00085.2005.
Penninx, B.W.J.H., Beekman, A.T.F., Smit, J.H., et al., 2008. The Netherlands study of depression and anxiety (NESDA): rationale, objectives and methods. Int. J. Methods Psychiatr. Res. 17 (3), 121–140.
Pope 3rd, C.A., Eatough, D.J., Gold, D.R., et al., 2001. Acute exposure to environmental tobacco smoke and heart rate variability. Environ. Health Perspect. 109 (7), 711–716.
Poulsen, P., Ebbehoj, E., Hansen, K., Mogensen, C., 1998. Effects of smoking on 24-h ambulatory blood pressure and autonomic function in normoalbuminuric insulin-dependent diabetes mellitus patients. Am. J. Hypertens. 11 (9):1093–1099. http://dx.doi.org/10.1016/S0895-7061(98)00115-0.
Reed, S.F., Porges, S.W., Newlin, D.B., 1999. Effect of alcohol on vagal regulation of cardiovascular function: contributions of the polyvagal theory to the psychophysiology of alcohol. Exp. Clin. Psychopharm 7 (4), 484–492.
Rennie, K.L., Hemingway, H., Kumari, M., Brunner, E., Malik, M., Marmot, M., 2003. Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. Am. J. Epidemiol. 158 (2):135–143. http://dx.doi.org/10.1093/aje/kwg120.
Rosenwinkel, E.T., Bloomfield, D.M., Allison Arwady, M., Goldsmith, R.L., 2001. Exercise and autonomic function in health and cardiovascular disease. Cardiol. Clin. 19 (3): 369–387. http://dx.doi.org/10.1016/S0733-8651(05)70223-X.
Ryan, J.M., Howes, L.G., 2002. Relations between alcohol consumption, heart rate, and heart rate variability in men. Heart 88 (6), 641–642.
Rzewnicki, R., Vanden Auweele, Y., De Bourdeaudhuij, I., 2003. Addressing overreporting on the international physical activity questionnaire (IPAQ) telephone survey with a population sample. Public Health Nutr. 6 (3):299–305. http://dx.doi.org/10.1079/PHN2002427.
Sagawa Y, Kondo H, Matsubuchi N, et al. Alcohol has a dose-related effect on parasympathetic nerve activity during sleep. Alcohol. Clin. Exp. Res. 2011;35(11):2093–100. doi: 10.1111/j.1530-0277.2011.01558.x.
Shinozaki, N., Yuasa, T., Takata, S., 2008. Cigarette smoking augments sympathetic nerve activity in patients with coronary heart disease. Int. Heart J. 49 (3):261–272. http://dx.doi.org/10.1536/ihj.49.261.
Sjoberg, N., Saint, D.A., 2011. A single 4 mg dose of nicotine decreases heart rate variability in healthy nonsmokers: implications for smoking cessation programs. Nicotine Tob. Res. 13 (5):369–372. http://dx.doi.org/10.1093/ntr/ntr004.
Soares-Miranda, L., Sandercock, G., Vale, S., et al., 2012. Metabolic syndrome, physical activity and cardiac autonomic function. Diabetes Metab. Res. Rev. 28 (4), 363–369.
Spaak, J., Tomlinson, G., McGowan, C.L., et al., 2010. Dose-related effects of red wine and alcohol on heart rate variability. Am. J. Physiol. Heart Circ. Physiol. 298 (6): H2226–H2231. http://dx.doi.org/10.1152/ajpheart.00700.2009.
Thorp, A.A., Schlaich, M.P., 2015. Relevance of sympathetic nervous system activation in obesity and metabolic syndrome. J. Diabetes Res.
Ueno, L.M., Moritani, T., 2003. Effects of long-term exercise training on cardiac autonomic nervous activities and baroreflex sensitivity. Eur. J. Appl. Physiol. 89 (2):109–114. http://dx.doi.org/10.1007/s00421-002-0777-z.
Van Lien, R., Goedhart, A., Kupper, N., Boomsma, D., Willemsen, G., de Geus, E.J.C., 2011. Underestimation of cardiac vagal control in regular exercisers by 24-hour heart rate variability recordings. Int. J. Psychophysiol. 81 (3):169–176. http://dx.doi.org/10.1016/j.ijpsycho.2011.06.007.
Vaschillo, E.G., Bates, M.E., Vaschillo, B., et al., 2008. Heart rate variability response to alcohol, placebo, and emotional picture cue challenges: effects of 0.1-Hz stimulation. Psychophysiology 45 (5):847–858. http://dx.doi.org/10.1111/j.1469-8986.2008.00673.x.
Vrijkotte, T.G.M., van den Born, B.-J.H., Hoekstra, C.M.C.A., et al., 2015. Cardiac autonomic nervous system activation and metabolic profile in young children: the ABCD study. PLoS One 10 (9), e0138302. http://dx.doi.org/10.1371/journal.pone.0138302.
Wannamethee, G., Shaper, A.G., 1988. Men who do not drink: a report from the British regional heart study. Int. J. Epidemiol. 17 (2):307–316. http://dx.doi.org/10.1093/ije/17.2.307.
Wichi, R.B., De Angelis, K., Jones, L., Irigoyen, M.C., 2009. A brief review of chronic exercise intervention to prevent autonomic nervous system changes during the aging process. Clinics (Sao Paulo) 64 (3):253–258. http://dx.doi.org/10.1590/S1807-59322009000300017.