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

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A B S T R A C T

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 ‘almostnever’) 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.

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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., 2010). Similarly, data suggests that smoking has a detrimental effect on cardiac ANS activity (Melo et al., 2005; Soares-Miranda et al., 2012; Rennie et al., 2002; Hu et al., 2016a) and cardiovascular disease (CVD) (Curtis et al., 2012; Rennie et al., 2003; Van Lien et al., 2011; Amano et al., 2001; Grassi and Seravalle, 1994; Melo et al., 2005; Soares-Miranda et al., 2012; 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). 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; Niedermayer 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...
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.

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 accelerometer 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>
<thead>
<tr>
<th>Table 1 Sample characteristics.</th>
<th>Participants, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td>Baseline n = 2618</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>41.6 (13.0)</td>
</tr>
<tr>
<td>Female sex</td>
<td>66.2</td>
</tr>
<tr>
<td>Education, mean (SD) years</td>
<td>12.2 (3.2)</td>
</tr>
<tr>
<td>Health factors</td>
<td></td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>25.5 (4.9)</td>
</tr>
<tr>
<td>Number of chronic diseases, median (IQR)</td>
<td>0.0 (0.0–1.0)</td>
</tr>
<tr>
<td>Use of heart medication</td>
<td>12.5</td>
</tr>
<tr>
<td>Current depression and/or anxiety</td>
<td>56.8</td>
</tr>
<tr>
<td>Antidepressant use</td>
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<tr>
<td>TCA</td>
<td>2.6</td>
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<tr>
<td>SSRI</td>
<td>16.8</td>
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<tr>
<td>SNRI</td>
<td>4.0</td>
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<tr>
<td>Lifestyle factors</td>
<td></td>
</tr>
<tr>
<td>Physical activity, median (IQR), 1000 MET/min/week</td>
<td>2.8</td>
</tr>
<tr>
<td>Low physical activity</td>
<td>23.1</td>
</tr>
<tr>
<td>Moderate physical activity</td>
<td>42.2</td>
</tr>
<tr>
<td>High physical activity</td>
<td>34.6</td>
</tr>
<tr>
<td>Sport activities</td>
<td></td>
</tr>
<tr>
<td>Almost never</td>
<td>26.2</td>
</tr>
<tr>
<td>Couple of times a year</td>
<td>12.3</td>
</tr>
<tr>
<td>Every month</td>
<td>6.1</td>
</tr>
<tr>
<td>Couple of times a month</td>
<td>8.1</td>
</tr>
<tr>
<td>Every week</td>
<td>22.7</td>
</tr>
<tr>
<td>Couple of times a week</td>
<td>24.7</td>
</tr>
<tr>
<td>Alcohol use, median (IQR), drinks/week</td>
<td>3.7</td>
</tr>
<tr>
<td>Non-drinker</td>
<td>32.3</td>
</tr>
<tr>
<td>Mild/moderate drinker</td>
<td>51.5</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>16.2</td>
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<tr>
<td>Smoking, median (IQR), no. Cigarettes/day</td>
<td>0.0</td>
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<tr>
<td>Current smoker</td>
<td>37.9</td>
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<tr>
<td>Autonomic variables</td>
<td></td>
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<tr>
<td>HR, mean (SD), beats/min</td>
<td>72.0 (9.6)</td>
</tr>
<tr>
<td>RSA, mean (SD), ms</td>
<td>44.6 (26.0)</td>
</tr>
<tr>
<td>PEP, mean (SD), ms</td>
<td>120.1</td>
</tr>
<tr>
<td>Respiration rate, breaths/min</td>
<td>17.1 (1.2)</td>
</tr>
</tbody>
</table>

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.
The number of smoked cigarettes/day was associated with a 2-year increase in RSA ($p = 0.002$ compared to non-smoking). In addition, the association between sport activities and RSA (+1.5 ms; $p = 0.013$) was associated with higher RSA than non-drinking. Analyses of quadratic relationships (Table 2) indicated that there was a non-linear association between sport activities and RSA (+1.5 ms; $p = 0.013$, and $b = 0.101$; $p = 0.001$) 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.
A U-shaped relationship has been found between 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 baroreceptor sensitivity (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 deterioration 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).

4.1. Limitations

When interpreting these findings, some limitations have to be taken into account. For instance, questions might be raised about the
Baseline data was collected in the Netherlands from 2004 to 2007. 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 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 (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.

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Conflicts of interest
None declared.

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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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References


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.


