The Heart of the Matter: Discovery of new genetic loci for heart rate variability and its relationship with blood pressure and mortality

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DOI:
10.33612/diss.193633004

Chapter 3

Determinants of heart rate variability in the general population: The Lifelines Cohort Study

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Heart Rhythm 2018; 15(10):1552-1558

Abstract

Background: Heart rate variability (HRV) is an important marker of heart health, with low values reflecting reduced vagal control ofthe heart rhythm.

Objective: The purpose of this study was to investigate the extent to which a broad range of demographic (age, sex), lifestyle (physical activity, smoking, alcohol use), and psychosocial factors (stress, social well-being, neuroticism) explain individual differences in HRV in the general population.

Methods: Using baseline data of 10-second electrocardiograms from the Lifelines Cohort Study (n =149,205; 58.7% female; mean age ± SD: 44.6 ± 13.2 years), we calculated the root mean square of successive differences (RMSSD) between adjacent inter- beat intervals as an index of cardiac parasympathetic nervous system activity. We also calculated RMSSD adjusted for its dependency on heart rate (cRMSSD). The association of demographic, lifestyle, and psychosocial factors with RMSSD was assessed using hierarchical linear regression models adjusting for potential con- founding effects of medication use, disease, and body mass index.

Results: HRV strongly declined with age and was consistently higher in women. These demographic factors together explained 17.4% of the variance in RMSSD and 21.9% in cRMSSD. Physical activity, alcohol use, and smoking showed some significant associations with RMSSD, but stress, social well-being, and neuroticism did not. Adding lifestyle and psychosocial factors to the model additionally explained <0.50% of the variance.

Conclusion: Age and sex were the most important determinants in this very large general population cohort, explaining almost one-fifth of the individual differences in HRV. The additional contribution of lifestyle and psychosocial factors was negligible.

Keywords: Demographics; Determinants; Heart rate variability; Lifelines; Lifestyle; Psychosocial factors

Introduction

Heart rate variability (HRV) is the variation over time of the interval between consecutive heart beats[1]. HRV has been used as an important marker of heart health[2], with low values reflecting reduced vagal control of the heart rhythm. Even in the general population, reduced HRV is found to be a significant predictor of cardiac-related deaths[3] and mortality from all causes[4]. However, a comprehensive inventory and quantification of the relative influence of factors determining HRV in a large study representative of the general population has not been reported in the literature.

HRV is strongly negatively associated with age[5] and thus may be considered a marker of (un)healthy aging. Several studies have reported sex differences in HRV, with women reported to have a higher HRV compared to men[6]. However, other studies reported nonsignificant sex differences[7]. Not only is there inconsistency in the literature, but sex-related differences also have been reported to decrease after the age of 50 years[5]. In contrast, for both men and women, a healthy lifestyle has been associated with a higher HRV[8], and several studies showed that smoking cigarettes[8,9] and reduced physical activity[8,10] were associated with a lower HRV.

The negative effect of psychosocial stress on cardiovascular health may be attributed to dysregulation of stress–response systems such as the cardiac autonomic nervous system (ANS)[11]. In 1 study, adverse life events during the lifespan were found to be a negative predictor of HRV[12]. However, the effect size was too small to show clinical relevance, and the effect was no longer significant after controlling for lifestyle factors. The authors also did not include social well-being in their analyses, which might potentially protect against the detrimental effect of stressful life events on HRV[13]. Furthermore, the personality trait neuroticism is linked to increased stress vulnerability and has been found to be associated with reduced HRV[14].

In general, it can be stated that most previous studies suffered from important limitations. They were restricted to specific age groups, limited to small sample sizes, lacked a proper adjustment for the well-known influence of heart rate on HRV, or failed to control for relevant potential confounders such as medication use and diseases.

The population-based Lifelines Cohort Study, with its large sample size of 167,548 participants, broad age range, and in-depth phenotypic characterization, is ideally

suited to address previous limitations, offering the opportunity to accurately quantify and comprehensively describe the association of demographic (age and sex), lifestyle (physical activity, alcohol use, smoking), and psychosocial factors (stressful life events, social well-being, neuroticism) with HRV[15]. Hence, the aim of this study was to estimate to what extent demographic, lifestyle and psychosocial factors explain individual differences in HRV in the general population[16].

Methods

Study design and population

In this cross-sectional study, we used baseline data from theLifelines Cohort Study. The design and cohort profile of the Lifelines has been described previously[15]. In short, Lifelines is a large representative population-based cohort study in the northern part of The Netherlands, aiming to investigate risk factors for multifactorial diseases.

Between 2006 and 2013, baseline data were collected for 167,548 participants (152,662 adults and 14,886 children) age 6 months to 93 years. All participants had visited one of the Lifelines research sites, where a physical examination including anthropometric and electrocardiogram (ECG) measurements was conducted by trained medical personnel, using a standardized protocol. All adults (18 years) filled out an extensive questionnaire, including items on demographic characteristics, lifestyle, psychosocial factors, health status, and medication use. All participants signed an informed consent form before they received an invitation for the physical examination. The Lifelines Cohort Study is conducted according to the Principles of the Declaration of Helsinki and in accordance with the research code of University Medical Center Groningen and was approved by its medical ethical committee.

Measurement of HRV

To calculate HRV, ECG signals were extracted from the Lifelines ECG database. The 10-second single 12-lead resting ECGs were recorded using CardioPerfect software (Welch Allyn DT100 recorder, Welch Allyn, Skaneateles Falls, NY)[17]. Dedicated software was developed to calculate HRV semi-automatically using the ECG data. ECG recordings were excluded from HRV calculation if (1) the number of beats was < 5; (2) the ratio between maximal and minimal interbeat intervals (IBI) exceeded 1.4, indicating a missing trigger or extrasystolic beat; (3) there was extremely low variability (SD of IBI <1.2ms); and (4) <60% of the recording time was included

in the average. In addition, if the interpretation, made by the software and/or cardiologist, contained specific keywords (atriumflutter, atriumfib, pacemaker, and systole), the recording was inspected to determine whether the ECG could be used. The first 2 refer to atrium fibrillation and result in an approximately random variability pattern. A pacemaker can cause very low variability. The last keyword refers to extrasystolic beats or arrhythmias. They can occur by premature triggering of the atrium (supraventricular), or the beat can start by a trigger in the ventricle (details of HRV calculation are given in the Supplementary Methods, Supplementary Table S1, and Supplementary Figure S1). All ECG recordings with arrhythmia, pacemaker, and triggering failure were excluded (Figure 1). For the current study, we used the root mean square of successive differences (RMSSD) between adjacent IBI, which captures short-term components of HRV that mainly reflect parasympathetic nervous system activity on the heart[18]. RMSSD is one of the most widely used indices of HRV[18] and has good reliability for short-duration measurements[19]. In a previous study from our laboratory, we demonstrated that single 10-second ECG recordings capture the true HRV well and yield a valid RMSSD measurement[19]. As the relationship between mean heart rate and HRV has been well established[20], RMSSD was corrected for its dependency on heart rate (ie, IBI of consecutive R peaks) as proposed by van Roon et al[21] using the variation coefficient of IBI expressed as corrected RMSSD (cRMSSD):

$$cRMSSD = 100\frac{RMSSD}{IBI}$$

Measurement of determinant factors and potential confounders

Lifestyle factors

Our study included the following lifestyle factors: physical activity level (categorized into insufficient, low, moderate, and vigorous); smoking status (categorized as nonsmoker, ex-smoker, and current smoker); and alcohol use (classified as nondrinker, light drinker, moderate drinker, and heavy drinker). The measurement details of these variables are available in the Supplementary Methods.

Psychosocial factors

The following psychosocial factors were included: social well-being, stressful life events and chronic stress measured by the List of Threatening Experiences (LTE) and the Long-term Difficulties Inventory (LDI), respectively, and neuroticism (details are available in the Supplementary Methods).

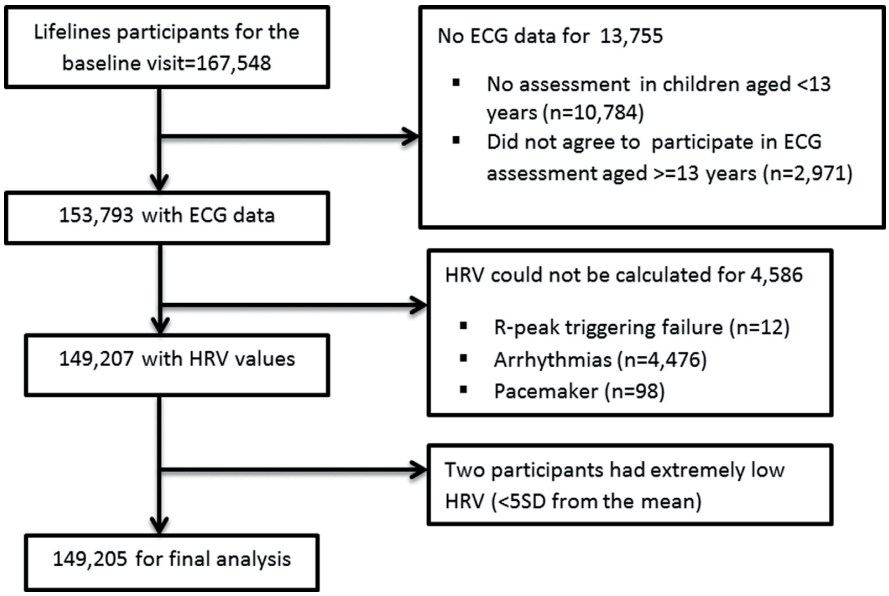

Figure 1: *Flow chart of participants. ECG=Electrocardiogram; HRV=Heart rate variability.*

Medication use, body mass index, and history of disease

Medication: Medications that are known to affect the ANS (antidepressants, beta-blockers, and vagal modulating agents) were classified according to the Anatomical Therapeutic Chemical classification system[22].

Body mass index: Body mass index (BMI) was calculated as weight/height squared (kg/m^2).

History of disease: A detailed description of the ascertainment of cardiovascular disease (CVD) and type 2 diabetes (T2D) in the Lifelines cohort has been reported previously[23,24]. Details on medication use and history of disease are given in the Supplementary Methods.

Statistical analysis

For this study, we included all 153,793 participants with ECG records during the baseline visit, of whom 149,205 participants with HRV data were eligible for statistical analysis (Figure 1).

The outcome variables RMSSD and cRMSSD were transformed by natural logarithm (ln) to achieve an approximately normal distribution. Participant's characteristics, stratified by sex, were described as frequency (percentage) for categorical variables and mean for continuous variables. We used *t* test and analysis of variance to compare means for different groups and the Pearson correlation to determine the relationship between continuous variables. Because most of the variables, such as lifestyle and psychosocial factors, were available only for the adults (age 18 years), children between 12 and 18 years old (n=1,631) were included only in the descriptive analysis.

For the final analysis, hierarchical linear regression models were used to assess whether demographic, lifestyle and psychosocial factors independently contributed to the outcomes natural log transformed RMSSD and cRMSSD. Covariates were entered into the model sequentially based on the group of variables in different blocks. Sex and age were included in the first step as a base model (model 1). Centered age^2 was also included in the base model to account for a curvilinear relationship with age. Confounders (medication use, disease and BMI) were added to the base model in the second step (model 2). To test how much additional variance were explained by lifestyle and psychosocial factors, we separately added them to the second model (model 3 and model 4, respectively). The final model (model 5), which included all variables, was also compared with the base model (model 1). Separate models were performed for neuroticism in the subsample in which data were available. Adjusted R^2 and ΔR^2 were calculated to estimate the total variance explained by blocks of determinant factors. Before conducting the multivariate analysis, multicollinearity for all variables was checked and indicated that multicollinearity did not affect our results. Given our large sample size, we used a stringent significance level of $p<0.01$.

Results

From the total of 149,205 participants, more than half (58.7%) were female. The mean (±SD) age was 44.6±13.2 years. We found that the proportion of men with T2D and hypertension was higher than in women; they also had a higher BMI ($P \leq .001$). Men drank larger amounts of alcohol and were more often smokers. Women more often used anti-depressants (6.7% vs 3.2%), beta-blockers (5.8% vs 5.4%) and had higher scores on stress and lower scores on social well-being ($P \leq .001$) (Supplementary Table S2).

Men and women differed markedly in HRV, with mean lnRMSSD was significantly higher in women ($p < .001$))(Figure 2). Overall, the mean lnRMSSD was higher at younger age, and comparison by age categories showed that the most marked decrease (7.5%) occurred between ages 30-40y and 40-50y (Figure 2A). Similar differences were also observed after correction of RMSSD for its dependency on mean IBI (Figure 2B). In general, lnRMSSD decreased sharply with age categories until age 60 and then remained stable until the last decade (80+); no sex differences were observed in mean lnRMSSD for the age categories <20 years ($P > .15$), 70-80 years ($P > .25$) and 80+ ($P > .57$), whereas for mean lncRMSSD only the 80+ age group did not differ.

Mean values of lnRMSSD and lncRMSSD in relationship to participant's characteristics are given in Supplementary Table S3. Having a history of chronic disease (T2D, hypertension, and CVD) was significantly related to lower RMSSD. Furthermore, compared to never smokers, both ex-smokers and current smokers had a significantly lower lnRMSSD. Similarly, participants who drank ≥2 drinks per day had a lower lnRMSSD compared to nondrinkers. However, light drinkers (≤ 1 drink per day) had a higher lnRMSSD.

Participants who exercised (low, moderate or high) had significantly higher lnRMSSD ($p \leq .001$) compared to insufficient physical activity level. Results were highly comparable for lncRMSSD. The correlations of lnRMSSD and lncRMSSD with age, BMI and psychosocial factors are given in Supplementary Table S4. lnRMSSD showed a negative correlation with age (r=-0.42), which became even stronger when RMSSD was corrected for mean IBI (r=-0.46).

Multiple linear regression analysis identified which blocks of factors were significantly associated with HRV. In the first model, age and sex alone explained 17.37% of the individual differences in lnRMSSD. The inclusion of potential confounding effects of medication use and disease status (model2) increased the amount of explained variance by 1.67%. Adding lifestyle and psychosocial factors to the baseline model explained only an additional 0.36% of the variance at most (models 3, 4, and 5) (Table 1). Correcting RMSSD for its dependency on heart rate resulted in findings that explained almost 5% more variance. That is, the inclusion of demographic factors and potential confounders explained nearly one-fourth of the variance in lncRMSSD (R^2 =22.87%). Similarly, the addition of both lifestyle and psychosocial factors to the model hardly improved the explained variance of lncRMSSD (models 3, 4 and 5) (Table 1).Neuroticism did not additionally explain individual differences in either lnRMSSD or lncRMSSD (Supplementary Table S5).

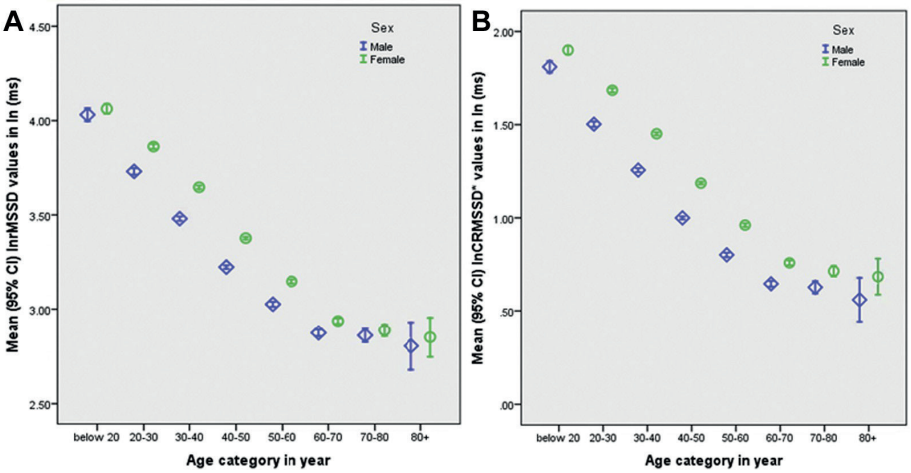

Figure 2: *Mean (95% CI) of (A) lnRMSSD and (B) lncRMSSD values across age categories stratified by sex (diamond=male; circle=female). RMSSD is corrected for mean inter beat interval (IBI) to obtain cRMSSD:* $_{cRMSSD} = 100\frac{RMSSD}{IBI}$. *The total number of participants [N (% women)] in each age category was as follows: < 20 years: 4227 (61.2); 20-30 years: 18106 (61.9); 30-40 years: 30478 (58.4); 40-50 years: 50775 (58.7); 50-60 years: 25018 (58.6); 60-70 years: 15759 (55.9); 70-80 years: 4353 (54.4); 80+ years: 491(55.0). CI=confidence interval; cRMSSD = root mean square of successive differences adjusted for its dependency on heart rate; RMSSD= root mean square of successive differences.*

Table 2 lists effect sizes of determinants of (log-transformed) RMSSD and cRMSSD after taking into accountthe effect of other variables in the full model (model 5). Age was negatively associated with RMSSD (β = –0.022; 95% confidence interval [CI] –0.022 to –0.021). Women had a higher RMSSD (β = 0.132; 95% CI 0.124–0.140).

All antidepressants (tricyclic antidepressants, selective serotonin and norepinephrine reuptake inhibitors) included in our analysis were associated with lower RMSSD. Participants with a diagnosis of T2D and hypertension showed significantly lower RMSSD (β = –0.157; 95% CI –0.179 to –0.134; and β = –0.114; 95% CI –0.122 to –0.105, respectively). In contrast, CVD did not show a significant association (β = –0.017; 95% CI –0.034 to 0.001); only after standardization of RMSSD for IBI was a significant negative relationship revealed. Compared to never smokers, ex-smokers showed a higher RMSSD (β = 0.029; 95% CI 0.021–0.038), but current smokers had a significantly lower RMSSD (β = –0.079; 95% CI –0.089 to –0.069). Only those with low and moderate levels of physical activity showed significantly higher RMSSD than those with insufficient activity levels. Light and moderate alcohol use were also associated with a higher RMSSD. None of the

psychosocial factors included showed a significant association with RMSSD (Table 2). Likewise, neuroticism score was not a significant determinant of individual differences in RMSSD (Supplementary Table S6). Although association patterns were very similar, effect sizes for most determinants attenuated after adjustment for mean IBI, with the exception of CVD as mentioned previously and the sex difference, which became more prominent (Table 2 and Figure 2).

***Table 1**: Variance of lnRMSSD and lncRMSSD explained by determinant factors*

		lnRMSSD			lncRMSSD*		
Model	**Determinant factors**	**R^2 (%)**	**ΔR^2 (%)**	***P* value**	**R^2 (%)**	**ΔR^2 (%)**	***P* value**
1	Base model (sex 1 age 1 age^{2†})	17.37	—		21.88	—	
2	Model 1 + confounders	19.04	1.67	.001	22.87	1.00	.001
3	Model 2 + lifestyle factors	19.39	0.36	.001	22.97	0.10	.001
4	Model 2 + psychosocial factors‡	19.06	0.02	.001	22.88	0.008	.006
5	Model 2 + lifestyle factors + psychosocial factors‡	19.40	0.36	.010	22.97	0.10	.079

Confounders: body mass index, antidepressant medication, autonomic nervous system medication, type 2 diabetes, hypertension, and cardiovascular diseases. Lifestyle factors: smoking, alcohol use, and physical activity. Psychosocial factors: List of Threatening Events (LTE), Long-term Difficulties Inventory (LDI), and social-well-being. cRMSSD = root mean square of successive differences adjusted for its dependency on heart rate; RMSSD = root mean square of successive differences.

*RMSSD corrected for mean inter beat interval (IBI) using the formula: $_{cRMSSD} = 100\frac{RMSSD}{IBI}$

†Age is centered to the mean.

‡Models 4 & 5 are compared to model 2.

***Table 2**: Regression coefficients of predictors associated with lnRMSSD and lncRMSSD based on the full model*

	lnRMSSD		lncRMSSD*	
Determinant factors	**β (95% CI)†**	***P* value**	**β (95% CI)†**	***P* value**
Demographics				
Age (years)	-0.022 (-0.022, -0.021)	$<1 \times 10^{-20}$	-0.022 (-0.023, -0.022)	$<1 \times 10^{-20}$
Sex	0.132 (0.124, 0.140)	$<1 \times 10^{-20}$	0.174 (0.166, 0.181)	$<1 \times 10^{-20}$
Disease and medication				
Type 2 diabetes	-0.157 (-0.179, -0.134)	$<1 \times 10^{-20}$	-0.107 (-0.127, -0.087)	$<1 \times 10^{-20}$
CVD	-0.017 (-0.034, -0.0001)	.047	-0.031 (-0.045, -0.015)	$<1 \times 10^{-5}$
Hypertension	-0.114 (-0.122, -0.105)	$<1 \times 10^{-20}$	-0.072 (-0.079, -0.069)	$<1 \times 10^{-20}$
BMI (Kg/m^2)	-0.005 (-0.006, -0.005)	$<1 \times 10^{-20}$	-0.002 (-0.003, -0.001)	$<1 \times 10^{-5}$
Anti-depressant use				
TCAs	-0.379 (-0.416, -0.342)	$<1 \times 10^{-20}$	-0.278 (-0.311, -0.245)	$<1 \times 10^{-20}$
SSRIs	-0.160 (-0.181, -0.139)	$<1 \times 10^{-20}$	-0.170 (-0.189, -0.152)	$<1 \times 10^{-20}$
SNRIs	-0.292 (-0.326, -0.257)	$<1 \times 10^{-20}$	-0.240 (-0.270, -0.209)	$<1 \times 10^{-20}$
Autonomic nervous system medication use				
Beta-blockers	0.172 (0.154, 0.190)	$<1 \times 10^{-20}$	0.072 (0.056, 0.088)	$<1 \times 10^{-20}$
Atropine	0.187 (-0.378, 0.752)	.516	0.052 (-0.452, 0.556)	.839
Acetylcholinesterase inhibitors	-0.366 (-0.716, -0.015)	.041	-0.370 (-0.682, -0.058)	.02
Lifestyle				
Physical activity§				
Low	0.024 (0.016, 0.032)	$<1 \times 10^{-5}$	0.009 (0.002, 0.016)	.014
Moderate	0.026 (0.011, 0.042)	.001	0.019 (0.005, 0.033)	.006
Vigorous	0.008 (-0.009, 0.025)	.365	0.008 (-0.009, 0.025)	.311
Alcohol use				
Light	0.030 (0.020, 0.039)	$<1 \times 10^{-5}$	0.012 (0.003, 0.020)	.006
Moderate	0.035 (0.023, 0.047)	$<1 \times 10^{-5}$	0.010 (-0.001, 0.020)	.072
Heavy	0.021 (0.005, 0.037)	.012	0.007 (-0.007, 0.022)	.317
Smoking				
Ex-smoker	0.029 (0.021, 0.038)	$<1 \times 10^{-10}$	0.021(0.014, 0.029)	$<1 \times 10^{-5}$
Current smoker	-0.079 (-0.089, -0.069)	$<1 \times 10^{-20}$	-0.033(-0.042, -0.024)	$<1 \times 10^{-10}$
Psychosocial				
LTE score	-0.003 (-0.006, -0.0001)	.043	-0.002 (-0.005, 0.001)	.160
LDI score	-0.002 (-0.003, 0.0001)	.070	-0.001 (-0.003, 0.001)	.109
Social well-being score	-2.1×10^{-5} (-0.001, 0.001)	.969	3.1×10^{-4} (-0.001, 0.001)	.662

BMI = body mass index; CVD = Cardiovascular disease; cRMSSD = root mean square of successive differences adjusted for its dependency on heart rate; CVD = cardiovascular disease; LDI = Long-term Difficulties Inventory; LTE = List of Threatening Events; SNRI = serotonergic and noradrenergic

antidepressant; SNRI = serotonin and norepinephrine reuptake inhibitors; RMSSD = root mean square of successive differences; TCA = tricyclic antidepressant.
*RMSSD corrected for mean inter beat interval (IBI) using the formula: $cRMSSD = 100\frac{RMSSD}{IBI}$
†Effects are expressed as compared with reference categories (Male sex, no medication use, no prevalent disease, insufficient physical activity, no alcohol use, and never-smoker)

Discussion

In the present study, we investigated the contribution of a wide range of determinants of RMSSD in a large sample from the general population. Demographic factors (age and sex) were the major determinants, together accounting for 17.4% of the variance. Correcting the effect of mean IBI on HRV led to an increase in explained variance (21.9%). The additional contribution of lifestyle and psychosocial factors was very small (0.36%).

Consistent with previous studies, higher age was associated with a lower RMSSD[25,26]. This negative relationship of age with HRV supports previous findings, which indicate that longevity is associated with proper maintenance of cardiac ANS function[27]. Furthermore, we found remarkable sex differences in RMSSD. In line with some previous findings, women had higher RMSSD, and this effect was magnified further after correcting RMSSD for mean IBI[6,25,26]. The higher parasympathetic activity in women as indexed by a higher RMSSD has been suggested to partly explain the lower proportion of prevalent CVD in women. In agreement with this, earlier studies reported that greater vagal activity is considered to be cardioprotective[2].

We further analyzed the role of lifestyle factors in explaining the individual difference in HRV in the general population. We observed a negative association between current smoking status and RMSSD, although ex-smokers were found to have higher RMSSD compared to never smokers. This unexpected observation may be due to participants quitting smoking as part of a medical intervention, which probably leads them to be engaged in other healthy activities. In accordance with our study, a previous study also showed lower RMSSD values among current smokers[9]. Only light and moderate alcohol drinking was found to be positively associated with RMSSD. This finding was expected, as several previous studies reported that light to moderate alcohol consumption is associated with cardioprotective benefits[28]. Although the effect is small, we could confirm previous findings that physically active participants had a higher HRV[10]. However, contrary to the findings of Rennie et al[29], we could not confirm the benefit of vigorous activity.

Lastly, we analyzed the influence of various psychosocial factors on RMSSD. We hypothesized that adverse life events during the lifespan and chronic stressors negatively affect RMSSD, but our findings did not confirm this. Another study also reported no differences in HRV in individuals with a history of adverse life events[30]. In contrast, other investigators have shown self-reported adverse life events to be a significant negative predictor of HRV[12]. Also, the present study did not show a significant relationship between social well-being and RMSSD; similarly, social support was not associated with RMSSD[31]. However, there was a difference in assessment of social support, as the latter used the Perceived Social Support Scale and participants were >45 years. In contrast to our result, Horsten et al[32] showed low social support was associated with low HRV in a population of healthy women. Moreover, in accordance with a previous study, neuroticism score was not a significant determinant of individual differences in RMSSD[31]. However, in another study, neuroticism was negatively associated with HRV in a homogeneous group of young adult women[14].

Study limitations

There are several possible limitations to consider in this study. First, because most of the variables, such as lifestyle and psychosocial factors, were available only for the adult participants, our regression models were restricted to adults; therefore, the findings cannot be generalized to children and adolescents. Second, the associations of psychosocial factors with RMSSD might have been underestimated compared to other studies because we first took confounding factors such as medical history and medication use into account. Third, data on neuroticism were only collected in a subsample of 43,815 subjects. However, this substantial sample size still affords solid conclusions, and we believe that the lack of association between RMSSD and neuroticism is an important finding. Fourth, the effect of ethnicity could not be estimated in our models because the vast majority (98%) of Lifelines participants were of Caucasian ancestry[33]. As such, our results cannot be generalized to other ethnic groups. Finally, the cross-sectional nature of this study does not allow conclusions on possible causal relationships between associated determinants and RMSSD.

Conclusion

Age and sex were the most important determinants, explaining almost one-fifth of the individual differences in HRV. This finding implies age and sex always need to be taken into account when assessing HRV. The findings also revealed that the contribution of lifestyle and psychosocial factors in explaining differences in HRV between individuals from the general population is small. Further research should

consider unmeasured variables such as genetic factors to improve the estimation of individual differences in HRV.

Acknowledgments

The authors would like to acknowledge the services of the Lifelines Cohort Study, the contributing research centers delivering data to Lifelines, and all the study participants.

Appendix

Supplementary data

Supplementary data associated with this article can be foundin the online version at https://doi.org/10.1016/j.hrthm.2018.05.006.

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