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# Ambulatory Heart Rate Variability in Schizophrenia or Depression

## Impact of Anticholinergic Burden and Other Factors

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### Abstract:

**Background:** Heart rate variability (HRV) has been found reduced in patients with schizophrenia and depression. However, there is a lack of knowledge on how demographic, lifestyle, and pharmacological factors contribute to the reduction in HRV in these patients.

**Methods:** We recruited 37 patients with schizophrenia, 43 patients with unipolar depression, and 64 healthy controls. A combined chest-worn HRV and accelerometer device was used in an ambulatory measurement. Age, sex, anticholinergic burden of medication, nicotine use, body mass index, and ongoing physical activity were assessed in multiple regression models regarding their influence on HRV, measured as the standard deviation of all the RR intervals (SDNN).

**Results:** In the fully adjusted model, schizophrenia ( $\beta = -0.23$ ,  $P = 0.019$ ), depression ( $\beta = -0.18$ ,  $P = 0.028$ ), age ( $\beta = -0.34$ ,  $P < 0.000$ ), ongoing physical activity ( $\beta = -0.23$ ,  $P = 0.001$ ), and anticholinergic burden ( $\beta = -0.19$ ,  $P = 0.025$ ) influenced SDNN negatively. Sex, nicotine use, and BMI had negligible effects on SDNN.

**Conclusions:** We show for the first time that a quantified score of anticholinergic burden of medication has a negative relationship to HRV in patients with schizophrenia or depression, but that the diagnoses themselves still exhibit an effect on HRV.

**Key Words:** schizophrenia, depression, anticholinergics, antipsychotics, antidepressants

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Heart rate variability (HRV) has, with some exceptions, repeatedly been found to be reduced in patients with schizophrenia and depression respectively.<sup>1–4</sup> Heart rate variability is the variation in the time between two adjacent heart beats, and it reflects the functioning of the autonomic nervous system.<sup>5</sup> Low HRV is regarded as an indicator of an unresponsive system, whereas high HRV is thought to reflect a more adaptive system, and both reduced and elevated HRV have been associated with various heart diseases.<sup>6</sup> There are many ways to operationalize HRV, and they are all based on the RR interval, also called the interbeat interval (IBI). The RR interval is the elapsed time between two R-spikes, and it is measured in milliseconds. The standard deviation of all the RR intervals is called SDNN. SDNN is recommended as a standard HRV metric, especially in ambulatory settings where it might

be difficult to isolate vagal activity.<sup>7,8</sup> In more controlled settings, other HRV metrics, such as the root-mean-square of successive RR interval differences (RMSSD) and the frequency domain measure, high-frequency (HF) band HRV, can be used, and both are conceptualized as representing vagal activity.<sup>5,6</sup> The HRV within the low-frequency (LF) band has been regarded as a mixture of both parasympathetic and sympathetic function. The LF/HF ratio is often termed the “sympathovagal balance” or “vagal tone.” This model, however, has been criticized for being overly simplified.<sup>8,9</sup>

There are several factors that influence HRV and potentially contribute to the observed lower levels in schizophrenia and depression. Both body mass index (BMI) and nicotine use have a modest negative influence on HRV.<sup>6,10</sup> The effect of alcohol on HRV seems to be dose dependent: the more alcohol, the lower the vagal measures of HRV are. However, this has mainly been studied in heavy drinkers and patients with alcohol use disorders, and the effect on HRV in social drinkers is much less pronounced and thus only essential to account for in studies where the subjects have excessive alcohol consumption.<sup>11,12</sup> A course of at least 4 weeks of aerobic exercise has been found to increase HRV.<sup>13</sup> Also, a higher level of fitness seems to be associated with higher HRV,<sup>14,15</sup> although some have found no such association.<sup>16</sup> It is important to distinguish between a subject's general fitness level and the actual performed physical activity while recording HRV in an ambulatory setting. In such a setting, there are indications that everyday physical activities are not associated with alterations in HRV,<sup>17,18</sup> but nonetheless, it has been recommended to account for ongoing physical activity.<sup>8,19</sup> Regarding sex, women have been suggested to exhibit higher parasympathetic tone, although this has not been replicated in some studies.<sup>20,21</sup> The effect of age on HRV has been thoroughly investigated: HRV declines with age.<sup>22</sup>

Anticholinergic drugs are known to significantly reduce HRV,<sup>2</sup> and many of the drugs commonly used in schizophrenia and depression have substantial anticholinergic effects. Nevertheless, many former HRV studies have not accounted for the individual anticholinergic burden of the patients, even though there are validated instruments available for this purpose.<sup>23,24</sup> To summarize, there are many possible factors influencing HRV in patients with schizophrenia and depression. Their contribution to individual differences in HRV has not yet been disentangled satisfactorily.

The aims of this study were to evaluate if there is a difference in HRV (measured as SDNN) between patients with schizophrenia, patients with depression, and healthy controls when adjusting for factors known to influence HRV, and to estimate the relative importance of these factors. Of specific interest for these patient groups is the influence of anticholinergic burden.

## METHODS

### Participants

Inclusion criteria were being 18 to 59 years old and having a diagnosis of either schizophrenia spectrum disorder or unipolar

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depression according to the *International Statistical Classification of Diseases and Related Health Problems (ICD-10)*. This was confirmed through a Mini-International Neuropsychiatric Interview.<sup>25</sup> Exclusion criteria were changes in medication in the last month, alcohol or illicit drug abuse, and insufficient Swedish command. Thirty-seven patients with a diagnosis of schizophrenia and 43 with a diagnosis of unipolar depression were included in the study. Patients were recruited from the outpatient clinic at Uppsala University Hospital, Sweden. Sixty-four healthy controls were recruited by word of mouth and advertisement at the hospital and the university and interviewed with the Mini-International Neuropsychiatric Interview to assure that they had no ongoing psychiatric disorders. All participants provided written informed consent. The study was approved by the Research Ethical Review Board in Uppsala (Dnr: 2014/286, 2015/018, 2015/362, and 2017/073) and conducted in accordance with the Helsinki declaration.

## Clinical Assessment

Demographic and clinical characteristics (eg, medication status) were obtained by questionnaires and medical records. Body mass index was calculated ( $\text{kg}/\text{m}^2$ ) by weighing and measuring all subjects. Psychiatric symptoms were assessed by experienced and trained clinicians using a semistructured clinical interview with the 24-item, 7-point Brief Psychiatric Rating Scale (BPRS).<sup>26,27</sup> The patients were also rated with the Clinical Global Impression–Severity, which is a 7-point Likert scale, ranging from 1 (normal) to 7 (among the most extremely ill patients).<sup>28</sup>

## Heart Rate Variability

Heart rate was monitored using the two-lead heart rate recorder Firstbeat Bodyguard 2 (Firstbeat Technologies Ltd, Jyväskylä, Finland) attached across the chest for 24 hours with continuous sampling of RR intervals. Sampling rate was 1000 Hz with a resolution of 1 millisecond. The device was attached in the morning by a research nurse, and participants were instructed not to pay any attention to the device or change their normal everyday activities. Visual inspection of the entire 24-hour data revealed many artifacts, but there was a time window between 9:00 AM and 1:00 PM during which all participants had at least 1 hour of relatively good data quality. This time window was also chosen in order not to have data from disparate parts of the day. A full 1-hour interval of data was extracted from this time window. The starting time for this 1-hour interval was randomly selected between subjects. Within this hour, the main outcome SDNN and the following HRV metrics were calculated: RMSSD, HF, LF, and LF/HF ratio. First, the data were visually inspected, and if deemed necessary, an artifact correction was made using the software's inbuilt algorithm. The artifact correction algorithm compares the length of each IBI to an average of the surrounding IBIs and then classifies IBIs that differ from a selected threshold as potential artifacts. The software Kubios HRV Standard (version 3.0.2) was used.

## Anticholinergic Burden

To quantify anticholinergic burden we used the Anticholinergic Drug Scale (ADS).<sup>29</sup> This scale divides drugs in 4 different categories where level 0 drugs have no known anticholinergic effects, level 1 drugs have potentially anticholinergic effects (based on receptor binding studies), level 2 implicates drugs that sometimes exhibit anticholinergic adverse events (most often at high doses), and level 3 drugs have marked anticholinergic effects. All the patient's drugs are scored separately and then summed to achieve the final score. This score is referred to as the anticholinergic burden of each participant in our study. We used a slightly modified version of the original scale. Medications prescribed as needed were not included in the total score. Because the

dose-adjusted score was reported not to add any additional explanatory value when the ADS was developed, we chose not to adjust for dose. Some drugs that are not listed in the original scale were added and rated in accordance with our clinical experience and to fit the scores of other similar substances in the original scale (eg, benzodiazepines that were not included in the original scale were rated as 1 because other benzodiazepines in the original scale were rated as 1). These were the following (with our score in parenthesis): agomelatine (0), alimemazine (3), aripiprazole (0), atomoxetine (0), desogestrel (0), dexamphetamine (0), flupentixol (0), levomepromazine (2), melatonin (0), nitrazepam (1), paliperidone (0), paracetamol (0), paroxetine (0), pregabalin (0), propiomazine (2), vortioxetine (0), and zuclopenthixol (0). Finally, quetiapine was rated as 2 (instead of 0 in the original scale) because of its moderate anticholinergic activity, which may not have been evident when the original scale was developed.<sup>30–32</sup>

## Ongoing Physical Activity During HRV Recording

Accelerometer data were monitored over 24 hours using the accelerometer in the same Firstbeat Bodyguard 2 that was attached across the chest. Data were sampled at 12.5 Hz. Sample size was set to 8 bits. Maximum values in all three directions (anteroposterior, mediolateral, and vertical) were reached at a force of 4G. Accelerometer data were extracted during the same hour interval as the HRV data for each subject. Raw acceleration data were plotted and visually inspected for missing or spurious data. Participants were excluded if any data were missing during the selected period or deemed artefactual. This resulted in that 8 participants were excluded (3 patients with schizophrenia, 2 patients with depression, and 3 healthy controls) because one axis was stuck on full acceleration (4G) during the selected period. The raw acceleration data were converted to a vector magnitude, and an algorithm derived from ActiGraph accelerometers was used to calculate activity counts using scripts in Matlab R2017b kindly provided by the authors.<sup>33</sup> The mean activity counts per minute were used as a measure of ongoing physical activity.

## Statistics

To assess differences between the groups, one-way analysis of variance (ANOVA) was used for continuous variables and  $\chi^2$  for dichotomous variables. After having theorized the possible interactions between diagnosis, HRV, and covariates, we chose six covariates to control for age, sex, ongoing physical activity, nicotine use, BMI, and anticholinergic burden. These covariates were introduced successively in multiple regression models to follow their respective contribution of the effect on SDNN. We first performed a crude analysis with all variables separately inserted in a linear regression, with SDNN as the dependent variable. Second, we created a multiple regression model where we included the variables diagnosis (coded as dummy variables defining the presence of absence of schizophrenia or depression), age, sex, and ongoing physical activity (model 1). Third, we created a model that added nicotine use and BMI (model 2). Finally, we added anticholinergic burden of medication (model 3). In all regression analyses, we computed both *P* values and Bayes factors (using the JASP software package, JASP Team 2019, version 0.11.1), with default prior settings. The Bayes factor reported is “BF\_inclusion,” which indicates the probability of the data under a model that includes the covariate compared with the same model without the covariate. A Bayes factor below 1 indicates evidence against an effect of that covariate, whereas a Bayes factor above 1 indicates evidence in favor of an effect of the current covariate. To handle the potential contribution of heart period on HRV, we performed the same regression analyses with an adjusted value of SDNN, according to

earlier recommendations.<sup>6</sup> The adjusted SDNN was calculated as the coefficient of variation of SDNN (cvSDNN) with the formula  $cvSDNN = 100 * (SDNN/IBI)$ . A Pearson correlation analysis was performed to investigate the correlations between SDNN and cvSDNN, assessing the extent to which the correction affected HRV. Pearson correlations were also used to assess relationship between artifact correction and all HRV metrics to rule out that artifact correction would influence the results. To assess consistency between different HRV metrics, we performed the regression analyses with the frequency domain measure HF (log transformed to achieve normal distribution) as the dependent variable. In all models, linearity assumptions were confirmed through visual inspection. Absence of influential outliers and multicollinearity were confirmed with Cook's distance and the variance inflation factor, respectively. The distribution of the residuals was inspected visually with PP plots, and

the independency of the residual's values was tested with the Durbin-Watson statistic. The variance of the residuals revealed that there was no severe heteroscedasticity in the data.

## RESULTS

### Background Variables

There was a significant difference in age between the groups. There were also significant differences in sex, BMI, and anticholinergic burden, but not in nicotine use and ongoing physical activity. No significant differences were observed regarding alcohol or drug use. As expected, there were significant differences between the groups regarding clinical data such as symptom severity and medication. See Table 1 for all demographics.

**TABLE 1.** Demographics

	Schizophrenia (n = 37)	Depression (n = 43)	Controls (n = 64)	P*
Age, mean (SD), y	40 (10)	30 (9)	31 (10)	<0.000
Sex (males), n (%)	27 (73%)	22 (51%)	27 (42%)	0.011
BMI, mean (SD), kg/m <sup>2</sup>	30 (8)	26 (6)	24 (5)	<0.000
Supported housing, n (%)	13 (35%)	7 (16%)	0 (0%) <sup>†</sup>	<0.000
Graduated from high school, n (%)	34 (92%)	36 (84%)	62 (97%)	0.053
Working/studying at least half-time, n (%)	13 (35%)	26 (60%)	61 (95%)	<0.000
Sheltered work program, n (%)	15 (40%)	1 (2%) <sup>†</sup>	1 (2%) <sup>‡</sup>	<0.000
Nicotine use, n (%)	15 (40%)	15 (35%)	14 (22%)	0.111
Coffee, day of assessment (cups), mean (SD)	1.8 (1.4) <sup>†</sup>	1.4 (1.3) <sup>†</sup>	1.4 (1.3)	0.209
AUDIT total score, mean (SD)	3.5 (5.4)	4.4 (3.4)	5.3 (3.0)	0.071
DUDIT total score, mean (SD)	1.0 (2.0)	1.0 (1.8)	0.3 (1.7)	0.109
CGI-S, mean (SD)	4.0 (1.0)	4.9 (0.8)	n.a.	<0.000
BPRS total score, mean (SD)	44 (12)	49 (7)	27 (3)	<0.000
BPRS positive symptoms subscale <sup>§</sup> , mean (SD)	7 (4)	3 (1.5)	3 (0)	<0.000
BPRS negative symptoms subscale <sup>§</sup> , mean (SD)	8 (3)	9 (3)	3 (1)	<0.000
MADRS-S total score, mean (SD)	14 (6)	30 (8)	3 (3)	<0.000
ADS score our version, mean (SD)	3.0 (3.0)	1.1 (1.5)	0.0 (0.0)	<0.000
ADS score original version, mean (SD)	2.7 (2.5)	1.7 (2.0)	0.0 (0.1)	<0.000
ADS score above 0, n (%)	29 (78%)	20 (47%)	0 (0%)	<0.000
Clozapine prescription, n (%)	16 (43%)	0 (0%)	0 (0%)	<0.000
TCA prescription, n (%)	2 (5%)	6 (14%)	0 (0%)	0.008
ESRS total score, mean (SD)	2.1 (2.6)	0.6 (1.3)	0 (0.1)	<0.000
Positive chronotropic drug use <sup>  </sup> , n (%)	1 (3%)	11 (26%)	2 (3%)	<0.000
Negative chronotropic drug use <sup>  </sup> , n (%)	5 (14%)	6 (14%)	0 (0%)	0.009
Antidiabetics <sup>¶</sup> , n (%)	4 (11%)	1 (3%)	0 (0%)	0.015
Antihypertensives <sup>¶</sup> , n (%)	2 (5%)	0 (0%)	1 (2%)	0.223
Ongoing physical activity, mean (SD), cpm	265 (447) <sup>#</sup>	232 (389) <sup>‡</sup>	267 (474) <sup>#</sup>	0.919

\*One-way ANOVA for continuous variables and  $\chi^2$  for dichotomic variables.

<sup>†</sup>One missing.

<sup>‡</sup>Two missing.

<sup>§</sup>Positive symptoms subscale comprises items suspiciousness, hallucinations, and unusual thought content. Negative symptoms subscale comprises items blunted affect, emotional withdrawal, and motor retardation.

<sup>||</sup>Positive chronotropic drugs included dexamphetamine, levothyroxine and methylphenidate. Negative chronotropic drugs included  $\beta$ -blockers, guanfacine, and thiamazole. Anticholinergics were not included as neither positive nor negative chronotropic drugs (eg, clozapine).

<sup>¶</sup>Antidiabetics included metformin, empagliflozin, sitagliptin, liraglutide, glipizide, and insulin. Antihypertensives included angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists ( $\beta$ -blockers were only coded as negative chronotropic drugs).

<sup>#</sup>Three missing.

AUDIT indicates Alcohol Use Disorders Identification Test; CGI-S, Clinical Global Impression–Severity; cpm, counts per minute; DUDIT, Drug Use Disorders Identification Test; ESRS, Extrapyramidal Symptom Rating Scale; MADRS-S, Montgomery Asberg Depression Rating Scale self-rating; TCA, tricyclic antidepressant agent.

### Heart Rate Variability Metrics

There was a significant difference in IBI, HR, SDNN, and all other HRV metrics except LF/HF ratio between the groups. There was no significant difference in the percentage of beats removed during artifact correction between the groups. Moreover, there was no correlation between artifact correction and any of the HRV metrics (data not shown). See Table 2 for all HRV metrics. The main regression results are presented in Table 3. In the crude analysis, both patients with schizophrenia and depression had lower SDNN compared with controls. Other covariates related to SDNN were age, ongoing physical activity, BMI, and anticholinergic burden. After controlling for age, sex, and ongoing physical activity in model 1, both patient groups still had lower SDNN than controls. The findings of lower SDNN in patients with schizophrenia and depression compared with controls were consistent in all models. Controlling for nicotine use and BMI did not change the results substantially (model 2). Adding anticholinergic burden to the model lowered the effect of both diagnoses on SDNN, indicating that the effect was partially mediated by anticholinergic burden (model 3). In this fully adjusted model, patients with schizophrenia or depression still had statistically significant lower SDNN than the controls (9.7 milliseconds in schizophrenia and 7.1 milliseconds in depression). Age, ongoing physical activity, and anticholinergic burden also had a negative significant relationship with SDNN. There were similar results when running the same regression models using cvSDNN as the dependent variable (data not shown). When using the frequency domain logHF as the dependent variable, the effect of both diagnoses on HRV was no longer significant, but age, ongoing physical activity, and anticholinergic burden still exerted a statistically significant effect on HRV (Table 4).

### Correlations

To follow up on the finding of anticholinergic burden being important for HRV, we performed correlations between anticholinergic burden and SDNN in each group separately. We found a significant correlation in patients with schizophrenia ( $r = -0.36$ ,  $P = 0.031$ ) and a borderline significant correlation in patients with depression ( $r = -0.26$ ,  $P = 0.091$ ) (Table 5). There was a significant

TABLE 2. HRV Metrics

	Schizophrenia (n = 37)	Depression (n = 43)	Controls (n = 64)	P*
IBI, ms	678 (105)	723 (126)	776 (142)	0.001
HR, bpm	91 (13)	86 (15)	80 (16)	0.004
SDNN, ms	26 (18)	38 (17)	47 (18)	<0.000
cvSDNN	3.7 (2.2)	5.1 (1.8)	5.9 (1.7)	<0.000
RMSSD, ms	21 (16)	28 (17)	39 (19)	<0.000
logLF	2.3 (0.8)	2.9 (0.4)	3.0 (0.4)	<0.000
logHF	1.9 (0.8)	2.3 (0.5)	2.6 (0.6)	<0.000
LF/HF	3.8 (2.8)	4.0 (2.3)	3.1 (1.9)	0.165
Artifacts corrected (% of beats removed)	3.3 (7.3)	1.1 (1.6)	1.6 (2.6)	0.054

All values presented as “mean (standard deviation)”.

\*One-way ANOVA.

bpm indicates beats per minute; cv, coefficient of variance; HR, heart rate.

TABLE 3. Regression Results (Dependent Variable SDNN)

	Crude*			Model 1†			Model 2†			Model 3†							
	B	β	P	B	β	P	B	β	P	B	β	P	B	β	P	BF	
Diagnosis (ref: healthy)																	
Schizophrenia	-20.72	-0.50	<0.000	-14.2	-0.34	<0.000	-14.4	-0.34	<0.000	-14.4	-0.34	<0.000	-9.74	-0.23	0.019	8.4	
Depression	-9.20	-0.25	0.008	-9.33	-0.24	0.003	-9.29	-0.23	0.004	-9.29	-0.23	0.004	-7.14	-0.18	0.028	8.2	
Age	-0.84	-0.46	<0.000	-0.62	-0.35	<0.000	-0.62	-0.35	0.000	-0.62	-0.35	0.000	-0.59	-0.34	<0.000	>1000	
Women (ref: men)	3.60	0.09	0.264	-2.30	-0.06	0.392	-2.55	-0.07	0.355	-2.55	-0.07	0.355	-2.39	-0.07	0.380	0.8	
Ongoing physical activity	-0.01	-0.26	0.002	-0.01	-0.25	0.001	-0.01	-0.25	0.001	-0.01	-0.25	0.001	-0.01	-0.23	0.001	58.5	
Nicotine use (ref: no use)	-6.38	-0.15	0.067	-0.01	-0.25	0.001	-1.65	-0.04	0.577	-1.65	-0.04	0.577	-1.68	-0.04	0.565	0.8	
BMI	-0.75	-0.26	0.002	-0.26	-0.02	15.1	0.06	0.02	0.795	0.06	0.02	0.795	0.07	0.03	0.733	0.7	
Anticholinergic burden	-3.83	-0.42	<0.000	-3.83	-0.42	<0.000	-3.83	-0.42	<0.000	-3.83	-0.42	<0.000	-1.79	-0.19	0.025	4.7	

\*All analyses are bivariate.

†Multivariate analysis of all variables below and n = 136 in all analyses including ongoing physical activity due to 8 participants without acceleration data (see “Ongoing physical activity during HRV recording” section).

BF indicates Bayes factor.

**TABLE 4.** Regression Results (Dependent Variable logHF)

	Crude*				Model 1†				Model 2†				Model 3†			
	B	β	P	BF	B	β	P	BF	B	β	P	BF	B	β	P	BF
Diagnosis (ref: healthy)																
Schizophrenia	-0.76	-0.51	<0.000	>1000	-0.51	-0.34	0.000	>1000	-0.51	-0.34	0.000	>1000	-0.24	-0.16	0.085	3.0
Depression	-0.30	-0.29	0.002	15.0	-0.31	-0.22	0.004	63.7	-0.31	-0.22	0.006	33.1	-0.19	-0.13	0.089	2.4
Age	-0.03	-0.47	<0.000	>1000	-0.02	-0.33	0.000	>1000	-0.02	-0.33	0.000	>1000	-0.02	-0.30	<0.000	>1000
Women (ref: men)	0.27	0.21	0.013	3.1	0.10	0.07	0.316	1.9	0.09	0.07	0.348	1.1	0.10	0.08	0.277	1.1
Ongoing physical activity	<0.00	-0.24	0.005	5.9	<0.00	-0.22	0.002	76.6	<0.00	-0.22	0.002	43.1	<0.00	-0.20	0.004	16.8
Nicotine use (ref: no use)	-0.21	-0.15	0.082	0.7					-0.02	-0.01	0.888	0.7	-0.02	-0.01	0.871	0.6
BMI	-0.03	-0.29	<0.000	64.9					<0.00	-0.01	0.895	0.8	<0.00	<0.00	0.992	0.7
Anticholinergic burden	-0.16	-0.49	<0.000	>1000									-0.10	-0.31	<0.000	114.3

\*All analyses are bivariate.

†Multivariate analysis of all variables below and n = 136 in all analyses including ongoing physical activity due to 8 participants without acceleration data (see "Ongoing physical activity during HRV recording" section).

BF indicates Bayes factor; logHF, logarithmic high frequency.

correlation between our version of the ADS score and the original version ( $r = 0.803$ ,  $P = 0.000$ ). The correlation between SDNN and cvSDNN was high ( $r = 0.930$ ,  $P = 0.000$ ).

## DISCUSSION

To the best of our knowledge, this is the first study showing that a quantified score of anticholinergic burden exhibits a contribution to the reduced HRV in patients with schizophrenia and depression. Nevertheless, even after adjusting for potential confounders, schizophrenia and depression still explained an additional part of the variance in HRV. Our results indicate that there is a reduction in HRV intrinsic to the respective condition, which is in line with former studies.<sup>19,34</sup>

The effect of age on HRV was the most pronounced throughout all analyses. This confirms previous findings and iterates the importance of taking age into account in HRV studies.<sup>22,35</sup>

It has been known for a long time that drugs with a pronounced anticholinergic profile lower HRV.<sup>36</sup> Some recent studies have also successfully differentiated the effects of different anticholinergic profiles.<sup>30,37,38</sup> However, there are still claims that antipsychotics as a group does not lower HRV, which is hard to state without assessing the respective anticholinergic action of each drug.<sup>39</sup> We believe that it is of great importance not to regard antipsychotics as a homogeneous group of drugs, but rather assess their actual receptor profiles depending on the focus of the study.

It is unlikely that the result of anticholinergic burden being important for HRV is only reflecting actual group differences in anticholinergic burden and SDNN. There was a significant correlation between anticholinergic burden and SDNN not only in the

whole sample but also within the schizophrenia group. In the depression group, there was a correlation in the same direction as in the whole sample, although this finding was only borderline significant. This might be due to the depression group not having enough anticholinergic burden to produce a detectable effect in HRV and the use of medication with anticholinergic effects was quite low in this group. There might be a dose-dependent effect of anticholinergic burden where HRV is affected only if the vagal activity is inhibited to a certain extent. Inspecting the scatter plot (Fig. 1) lends support to that; if this is the case, such a threshold would be around an ADS score of 4. A recent study focusing on cognitive impairment in patients with schizophrenia used an ADS score of 3 or more as a cutoff to define a high ADS group.<sup>40</sup>

It is interesting that when analyzing a more vagal measure (logHF), anticholinergic burden seems to be an even stronger predictor of HRV than when using SDNN. This is in line with the theory, given that anticholinergic drugs affect vagal activity. However, some recommend not to estimate vagal activity during ambulatory recordings.<sup>8</sup>

We found that ongoing physical activity had a significant relationship to HRV. This might be mediated by the increasing heart rate that accompanies a higher intensity of physical activity. Our results differ somewhat from earlier findings. In a study of 45 healthy controls, there were no correlations between ongoing physical activity (measured as metabolic equivalents with an accelerometer) and any time or frequency domain measure of HRV.<sup>17</sup> Another study of 49 participants used self-reported measures of ongoing physical activity and found no correlation with RMSSD.<sup>18</sup> Although it is hard to compare our results with these earlier findings, it is an interesting novel finding that will need to be followed up in more controlled settings.

## Limitations

Although we assessed many covariates in this study, there is always potential unmeasured residual confounding.

The groups are not ideally matched for age or sex. This reflects the difficulties in recruiting patients with different diagnoses to the same study (schizophrenia being more common among men and depression among women). In order not to lose valuable patient data, we instead chose to include age and sex as variables in the regression model.

We did not assess psychiatric comorbidity in this study. Yet, we believe that we capture the majority of this potential effect of

**TABLE 5.** Correlations Between SDNN and Anticholinergic Burden

	Anticholinergic Burden	
	Pearson <i>r</i>	<i>P</i>
Whole sample (n = 144)	-0.42	<0.000
Schizophrenia (n = 37)	-0.36	0.031
Depression (n = 43)	-0.26	0.091
Controls (n = 64)	n.a.	n.a.

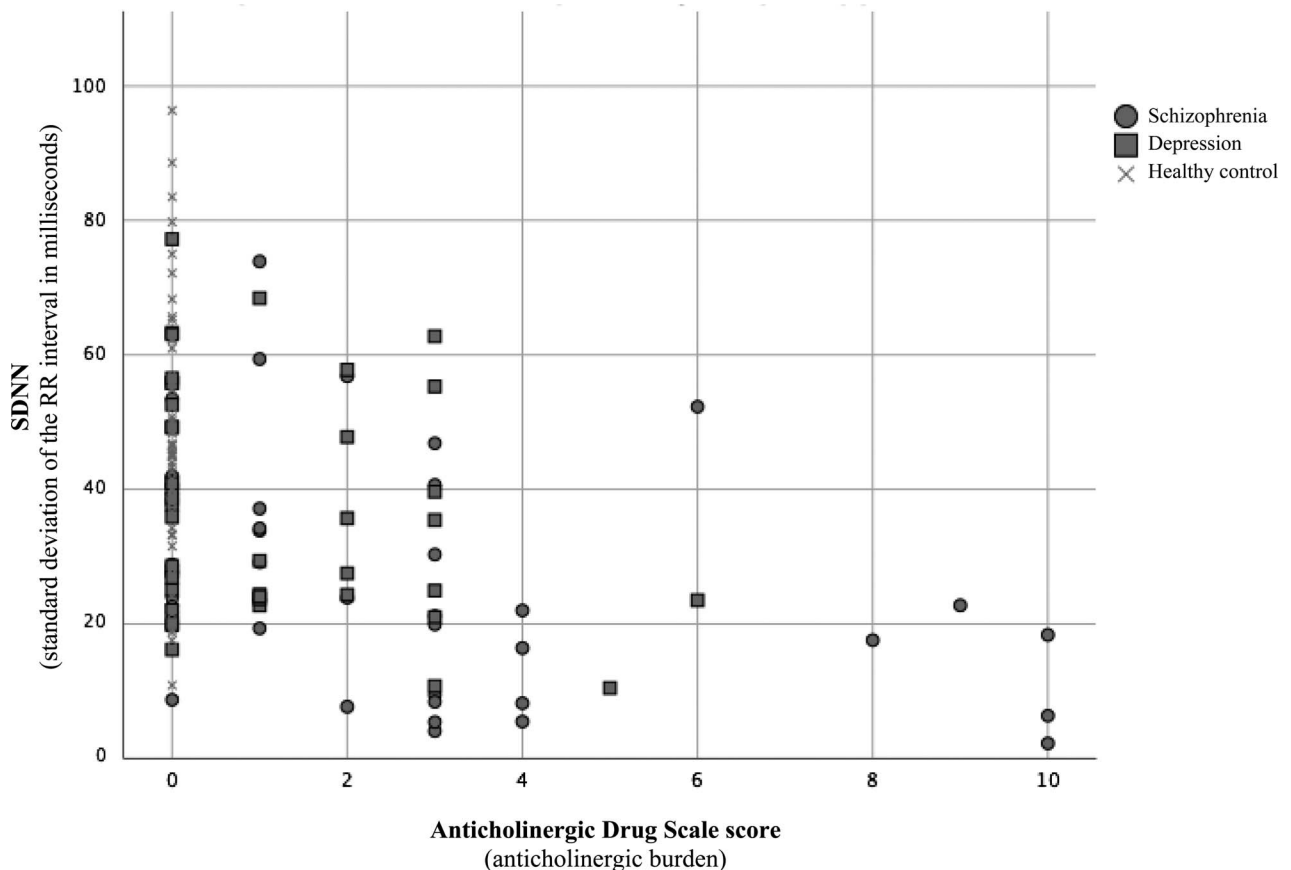


FIGURE 1. Scatterplot of SDNN and anticholinergic burden.

such comorbidity by including the anticholinergic effect of all of the patients' prescribed drugs.

The optimal way of calculating HRV metrics is by a raw electrocardiogram (ECG) signal.<sup>35</sup> The device we used does not provide an ECG, but there are many other groups that reliably have used various devices for assessing HRV, including the device we used in this study.<sup>34,41</sup> The main issue with not using an ECG is that the software cannot distinguish between ectopic and ordinary heartbeats to the same extent. However, this would occur in all groups. The artifact correction between the groups in our study was only borderline nonsignificant, being slightly higher in the schizophrenia group. This could be a potential problem because stronger artifact correction in general reduces HRV. Nonetheless, there was no correlation between the amount of artifact correction and any HRV measure, assuring us that different levels of artifact correction did not influence the results.

We chose to use HRV data from a 1-hour interval, during which the participants performed everyday activities. Most HRV studies collect data in laboratory settings. Our choice might therefore reduce comparability between studies. However, we wanted to assess HRV in an ambulatory setting and also take account the physical activity performed.

We have assessed the anticholinergic burden of the patients from their prescribed medication. Because compliance is not always 100%, a more precise, yet demanding method would have been to assess the serum activity of anticholinergic compounds. However, the ADS was originally validated by examining its relation to serum anticholinergic activity. An even more precise method would have been to assess the actual receptor binding of each patient

or at least to consider the potency of the different compounds.<sup>24</sup> It would also be of interest to know at which level of serum anticholinergic activity the maximum occupancy is achieved. No anticholinergic rating scale will possibly be able to perfectly reflect the actual occupancy of the muscarinic receptors, but it is nevertheless of interest to implement existing scales in research and clinical practice. More knowledge on the anticholinergic properties of different compounds<sup>42</sup> will probably aid in developing newer versions of the ADS, and such attempts have already been made.<sup>43</sup>

Inspection of the accelerometer data revealed that many of the participants were not performing much physical activity during the HRV recording. This has probably reduced the amount of variance in the sample. However, it is important to remember that we only wanted to account for the potential influence of ongoing movement during the actual recording, not assess the subjects' overall fitness level or performed physical activity over time. This would nonetheless have been of interest and could potentially have diminished the group differences observed in our study. It is recommended that future studies also account for general fitness level in some way. Eight participants did not have acceleration data. Excluding ongoing physical activity during HRV recording as a covariate from the regression analyses did not change the coefficients or significance of any of the other covariates (data not shown).

## CONCLUSIONS

A contributor to the observed reduction in HRV in patients with schizophrenia or depression is the anticholinergic burden of

medication. However, there is an intrinsic effect of these diagnoses on HRV even after controlling for important confounders.

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