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Differential Associations of Specific Selective Serotonin Reuptake Inhibitors with Resting-State Heart Rate and Heart Rate Variability: Implications for Health and Wellbeing

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Abstract:

Objective: Debate has focused on the effects of the selective serotonin reuptake inhibitor (SSRI) antidepressants on heart rate (HR) and heart rate variability (HRV), both of which are predictors of adverse cardiovascular events. Here we examine the associations between specific SSRI antidepressants and resting state HR (and HRV) after accounting for a host of potential confounding factors.

Methods: Participants included 10,466 not taking antidepressants, 46 participants taking escitalopram, 86 taking citalopram, 66 taking fluoxetine, 103 taking paroxetine, and 139 taking sertraline. HR and HRV (RMSSD, HF) were extracted from 10-minute resting-state electrocardiograms. Analyses including propensity score weighting and matching were conducted using R-statistics to control for potentially confounding variables.

Results: Major findings indicated that users of all SSRI medications – except fluoxetine – displayed lower HRV relative to non-users. Users of paroxetine also displayed significantly lower HRV relative to users of citalopram (Cohen's d = 0.42), fluoxetine (Cohen's d = 0.54) and sertraline (Cohen's d = 0.35), but not escitalopram. While associations were also observed for HR these were less robust than those for HRV.

Conclusions: While paroxetine is associated with decreases in HRV relative to non-users, as well as users of other SSRI medications, fluoxetine was the only medication not to display significant alterations in HR or HRV. These conclusions are limited by the cross-sectional design and non-randomized nature of medication prescriptions. Findings highlight the importance of focusing on specific medications, rather than more heterogeneous groupings according to antidepressant action, and may have implications for health and wellbeing over the longer term.

Abbreviations: analysis of covariance (ANCOVA); analysis of variance (ANOVA); Anatomical Therapeutic Chemical Classification code (ATC); body mass index (BMI); Brazilian longitudinal study of adult health (ELSA-Brasil); Clinical Interview Schedule-Revised (CIS-R); coronary heart disease (CHD); electrocardiogram (ECG); heart rate (HR); heart rate variability (HRV); high frequency power (HF-HRV); Minnesota code (MC); propensity score matching (PSM); propensity score weighting (PSW); root mean square of successive squared

differences (RMSSD); serotonin and noradrenaline reuptake inhibitors (SNRIs); selective serotonin reuptake inhibitor (SSRI); tricyclic antidepressants (TCA's)

Introduction

Antidepressant medications are a first-line treatment option for moderate to severe mood and anxiety disorders, yet some studies suggest that long-term use may be associated with an increased risk for cardiovascular disease [1-3]. We recently reported that use of tricyclic antidepressants (TCA's) is associated with a two-fold higher prevalence in coronary heart disease (CHD), relative to non-use in a cross-sectional analysis on the Brazilian longitudinal study of adult health (ELSA-Brasil) [4]. Although no associations were observed for the SSRI class, antidepressant use in Brazil is lower than in high-income countries. With the exception of sertraline and fluoxetine, SSRIs are not freely dispensed in public health pharmacies, as are tricyclics [5]. While TCA's are generally not recommended for depressed patients who have CHD [6], the effects of the selective serotonin reuptake inhibitor (SSRI) class of antidepressants remain unclear. In the present study, we examined the associations of specific medications in the SSRI class with resting state heart rate (HR) and heart rate variability (HRV), two psychophysiological indicators of health and wellbeing shown to predict future mortality [7]. The heart is under tonic inhibitory control by the parasympathetic (vagal) nervous system when at rest [8], and both HR and HRV under resting conditions may reflect vagally mediated cardiac activity. It is noted however, that HRV is a more specific measure of vagal activity [9, 10], while HR may also include sympathetic input.

While the SSRIs are considered to be the safest class of antidepressant medications for use in cardiac patients [e.g. 11], they have also been reported to reduce HRV in depressed patients, compared to those not receiving an antidepressant, and to normal controls [12]. A variety of mechanisms have been proposed to contribute to the development of cardiovascular disease in users of antidepressants including SSRIs. These include increased HR, orthostatic hypotension, slowing of ventricular cardiac conduction, and antiarrhythmic activity [13]. Another strong candidate for increased risk of cardiovascular disease is impairment in vagal

function [7]. Vagal function plays an important regulatory role over a variety of allostatic systems [14] and investigation of the associations between SSRIs, HR and HRV have important implications for the physical wellbeing of patients who use these medications over the long-term.

Use of antidepressants is associated with impairment in vagally mediated cardiac activity [15] [see also 16], associations that are most pronounced for the tricyclic antidepressants, followed by the serotonin and noradrenaline reuptake inhibitors (SNRIs) and the SSRIs. We recently observed that the SSRIs are associated with a small decrease in heart rate *and* HRV [15]. Consistent effects had been reported in a prior study [16], with decreases in HR interpreted as a decrease in sympathetic activity and decreases in HRV reflecting parallel decreases in cardiac vagal effects. SSRIs may interfere with the activation of fast Na+ channels consistent with class I anti-arrhythmic agents, and calcium current, which reflects a negative inotropic effect reducing contractility [17, 18]. The HRV reductions associated with SSRI use have also been shown to be at least partly reversible, suggesting a possible causal effect [16]. Although adverse effects of SSRIs have been reported [15, 16], these findings contradict other reports of increases [19] and no impact [20] on HRV. We have suggested previously [21] that one of the factors underpinning these contradictory findings may be the practice of grouping together heterogeneous medications within the SSRI class, leading to variable findings that depend on what SSRI medications are combined in a particular study. For instance, paroxetine displays six times more antimuscarinic (anticholinergic) potency than sertraline [22], highlighting the heterogeneity of these medications. This limitation of prior studies highlights the importance of comparing specific medications within the SSRI class. Other explanations for the reported contradictory findings are that studies have often not controlled for various confounding factors, which may impact on measures of vagal function. When studies *have* controlled for these factors, statistical analyses such as ANCOVA have often been employed,

which may lead to a phenomenon known as the "reversal paradox" – such that the relationship between two variables is reversed, diminished or enhanced when attempting to statistically control for a third variable – when studies do not randomly allocate participants to group [see 21 for discussion]. This makes it difficult to draw conclusions from prior studies that have employed this statistical approach.

For the first time, we compare multiple medications within the SSRI class, to determine and compare the impact of specific SSRI antidepressants on HR and HRV. Some of the limitations in prior studies were addressed using robust analytical techniques for controlling potential confounding factors. This approach has several advantages over traditional regression-based approaches, including improved control of confounding by not conflating propensity score methods with the modelling approach, and application of flexible machine learning methods to capture complex and nonlinear relationships between participant grouping and potential confounding variables without over-fitting the data [23].

Methods

Participants

ELSA-Brasil is a cohort of 15,105 civil servants aged 35-74 years enrolled between August 2008 and December 2010 at 6 different sites in Brazil (Belo Horizonte, Porto Alegre, Rio de Janeiro, Salvador, Sao Paulo and Vitoria). The study design and sampling procedures of ELSA-Brasil have been reported previously [24, 25]. Briefly, eligible participants included males and females aged between 35 and 74 years who were active or retired employees of the six institutions. Exclusion criteria included severe cognitive or communication impairment, intention to quit working at the institution, and, if retired, residence outside the corresponding metropolitan area. Women with current or recent pregnancy were rescheduled so that the first interview could take place 4 months after delivery of their child

[24]. The ethics committees of the participating universities approved the research protocol. All participants provided written informed consent after a complete description of the study.

Here we report on a total of 10,906 participants after dropping participants on antidepressants other than an SSRI (n=382 including 113 on SNRIs, 174 on TCA's, and 96 on other antidepressants), participants on whom no HRV exam was available (n=1813, including 504 participants with ectopic beats), participants on whom ECGs were not available for scoring major Q wave abnormalities (n=1740), and participants missing data on other variables used in analysis (n=563). Included participants comprised non-users of antidepressant medications (controls, n=10,466), those taking escitalopram (n=46), citalopram (n=86), fluoxetine (n=66), paroxetine (n=103) and sertraline (n=139). Participants on fluvoxamine were not included in the present study due to small numbers of participants taking this medication (n=3).

Procedures

Participants were asked to abstain from caffeine, alcohol and physical activity for at least 12 hours before assessments. Participants were asked to bring all of the prescription and over-the-counter pill bottles to an interview for review by the interviewer. Individuals taking one selective serotonin reuptake inhibitor (SSRI) medication continuously over the past two weeks were classified as users, and grouped according to the specific antidepressant they were taking. Selective serotonin reuptake inhibitors were defined using the Anatomical Therapeutic Chemical (ATC) Classification code: N06AB. A continuous, 10-minute, resting-state ECG was also obtained from participants while in the supine position from which HR and HRV were extracted using standardised methods. [See also: 26, 27]. The electrocardiograms (ECGs) were always collected in the morning (8:00 to 12:00h) in a temperature-controlled room (21-24°C) and were sampled at 250 Hz with a digital electrocardiograph (Micromed,

Brazil) consistent with Task Force recommendations. ECGs were processed blindly at a Central ECG Reading Center, where they were visually inspected for technical errors and inadequate quality, and then stored for subsequent analysis in a Pyramis ECG management system (version 6.2.b, Cardiac Science Corporation, Bothel, WA, USA). ECGs were codified electronically using the Minnesota code manual of electrocardiographic findings by validated software, with manual over-reading by trained cardiologists to ensure quality control. Major Q wave abnormalities were determined from a 12-lead ECG as defined by the Minnesota code (MC) scheme (MC 1-1-X through to 1-2-X). Dedicated software (Micromed Wincardio 4.4a, Brazil) automatically generated the R-R interval series from the selected ECG lead with the highest R-wave amplitude (usually D2). Data were then processed to obtain measures of HR and HRV including the root mean square of successive squared differences (RMSSD) and high frequency power (HF-HRV). RMSSD and HF-HRV both reflect vagal parasympathetic activity and are usually highly correlated. HF-HRV (0.15–0.40 Hz) was estimated and expressed in absolute units. Both RMSSD and HF-HRV were then log-transformed as a normalisation strategy.

Covariates

Covariates included sociodemographic factors (age; sex; level of education; race), cardiovascular risk factors (smoking; body mass index; hypertension; diabetes; and dyslipidemia), established heart disease and associated medications, physical inactivity and psychiatric morbidity. Level of education was entered as two dummy coded variables (less than high school: yes versus no; completed high school: yes versus no), while race was entered as a categorical variable indicating whether participants were non-White (yes versus no). Smoking status was indicated if participants were current smokers (current versus past/never) and body mass index (BMI) was determined as follows: weight in kilograms divided by height in meters squared. Hypertension was defined as a systolic blood pressure

≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or use of antihypertensive medications. Diabetes was defined as self-reported or fasting blood glucose level ≥126 mg/dL, a 2-hour oral glucose tolerance test glucose level ≥200 mg/dL, or a glycated hemoglobin level ≥6.5%. Dyslipidemia was defined as an LDL cholesterol level ≥130 mg/dL or use of lipid-lowering medication. Blood samples were collected after a 12-hour overnight fast and medication use was determined on the basis of pill bottle review. Established heart disease was determined through a prior history of a physician-diagnosed myocardial infarction, a prior percutaneous coronary intervention including balloon angioplasty with or without stent placement, a prior surgical revascularization consisting of either arterial or venous grafts. Complementing this self-report information, major Q wave abnormalities (yes versus no) on the 12-lead ECG were also entered into analyses as a covariate. Physical activity was measured using the International Physical Activity Questionnaire [28] and categorized according to low activity versus moderate or high activity, as determined using scoring guidelines. Psychiatric morbidity was determined by trained interviewers using the Portuguese version [29] of the Clinical Interview Schedule-Revised (CIS-R) [30]. The CIS-R version was applied and severity scores were obtained ranging from zero to 57.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics Version 21 and the R-statistical environment (version 3.0.1). Participant characteristics were examined using one-way analyses of variance (ANOVA) for contrasts involving continuous dependent measures, and χ^2 statistics for categorical variables (Table 1). Tukey's HSD is reported for ANOVAs, correcting for multiple comparisons, while standardised residuals (z-scores) were used to help interpret χ^2 statistics. Our main analyses involved comparison of SSRI antidepressant users and non-users on HR, RMSSD and HF-HRV, before and after application of propensity score techniques including propensity score weighting (PSW) [23] and propensity score matching (PSM) [31]

to adjust findings for the above covariates. These techniques involve calculating a single propensity score on the basis of entered covariates for each participant that relates to the probability that the participant belongs to the same distribution (i.e. antidepressant grouping). Two propensity analytic methods were employed: PSW and PSM. While PSW involves entering the propensity score into regression models, PSM involves selecting comparison participants (non-users of antidepressants) to match other groups on propensity scores. PSW was carried out using the 'twang' and 'survey' packages, while PSM was conducted using the 'MatchIt' package in the R statistical environment. Details on how to implement these procedures have been described previously [23, 31]. PSM was conducted as a sensitivity analysis, allowing the *effective sample size* of medication groupings to be increased and potential Type 1 error associated with discrepant sample sizes (i.e. between users and non-users of antidepressants) in PSW to be avoided. Effective sample sizes reflect the adverse impact of increased variance on precision and power [23], providing an estimate of the number of comparable participants in each group after introducing propensity score weights or dropping cases when matching. Additional PSW analyses were conducted after dropping control participants from analysis. This analysis allowed the effective sample size of medication groupings to be increased, achieving a higher-powered, head-to-head comparison between SSRI medications. Cohen's d effect size statistics were calculated for each pair-wise comparison with values of 0.2, 0.5, and 0.8 interpreted as small, medium, and large effects, respectively according Cohen's guidelines [32, 33]. Effect sizes were calculated using an online calculator (available here at The Campbell Collaboration: http://goo.gl/zeLyuH) [based on: 34].

Results

Participant Characteristics

Descriptive statistics for participants are reported in Table 1. Participants differed on age, sex, education, ethnicity, LDL cholesterol, and psychiatric morbidity, highlighting the importance of propensity score techniques to better control for the associations between these variables and HR, and HRV. It is possible for instance, that the differences in confounding variables may account for differences between groups on HR and HRV. The unadjusted results for HR and HRV are also reported in Table 1. Findings indicate that HR is reduced in users of citalopram, and that HRV is reduced in all users of SSRIs with the exception of those on fluoxetine. In the following sections, we report results after adjusting for potentially confounding variables on the basis of propensity scores. It is relevant to note here that the findings for fluoxetine did not change after controlling for confounding variables.

Impact of SSRIs on Heart Rate and HRV: Propensity Score Analyses

The differential impact of SSRIs was determined following PSW and PSM. Effective sample sizes after PSW were as follows: controls, n=10,451; escitalopram, n=28; citalopram=28; fluoxetine=48; paroxetine=62; sertraline=61. PSW analyses revealed significant alterations in RMSSD ($F(5,10900)=10.66$, $p<0.001$) and HF-HRV ($F(5,10900)=8.06$, $p<0.001$), while alterations were observed for HR at trend levels ($F(5,10900)=1.91$, $p=0.089$). Effective sample sizes after PSM were as follows: escitalopram, n=46; citalopram=86; fluoxetine=66; paroxetine=103; sertraline=139. Descriptive data, statistical tests and Cohen's *d*' effect size measures are summarised in Table 2. The major finding was that alterations in HR and HRV were observed for all users of SSRIs except for fluoxetine (light grey shaded cells). In addition, users of paroxetine displayed robust reductions in both measures of HRV (RMSSD, HF-HRV) in both PSW and PSM, relative to non-users, findings associated with small to moderate effect size (dark grey shaded cells in Table 2).

Specificity Analyses

Additional PSW analysis was conducted to compare each SSRI medication after dropping controls from the analyses. This allowed for the effective sample size of medication groupings to be increased and for a higher-powered, head-to-head comparison between SSRI medications to be conducted. After application of PSW, effective sample sizes were as follows: escitalopram, n=36; citalopram=73; fluoxetine=57; paroxetine=84; sertraline=122. Analyses revealed significant differences on HR ($F(4,435)=2.52$, $p=0.041$) and RMSSD ($F(4,435)=2.99$, $p=0.019$), but not HF-HRV ($F(4,435)=1.48$, $p=0.21$). Post hoc tests indicated that users of paroxetine ($M_{HR}=67.48$, SE=1.12) and sertraline ($M_{HR}=66.89$, SE=0.83) displayed significantly higher HR than users of citalopram ($M_{HR}=63.83$, SE=0.82) ($p=0.009$, Cohen's d= 0.43; $p=0.009$, Cohen's d= 0.36). Users of paroxetine ($M_{RMSSD}=2.88$, SE=0.05) also displayed significantly lower RMSSD than users of citalopram ($M_{RMSSD}=3.08$, SE=0.06; $p=0.019$, Cohen's d= 0.42), fluoxetine ($M_{RMSSD}=3.14$, SE=0.07; $p=0.003$, Cohen's d = 0.54) and sertraline ($M_{RMSSD}=3.06$, SE=0.05; $p=0.011$, Cohen's d= 0.35).

Discussion

This study examined and compared the impact of specific antidepressants within the SSRI class on resting-state HR and HRV. This is an important issue as chronic alterations of HR and HRV by SSRI antidepressants may lead to morbidity from a host of conditions and diseases, and mortality [7, 35]. Major findings from this study suggest that: 1) all users of SSRIs – except fluoxetine – display alterations in HR or HRV relative to non-users; findings for HRV appeared to be more robust and consistent for HRV, than those for HR, 2) users of citalopram display a mild bradycardia, characterised by reductions in HR by up to 4 beats per minute, findings associated with a small to moderate effect size, 3) only users of paroxetine display robust reductions in both measures of HRV, findings again associated with a small to moderate effect size, and 3) users of paroxetine also display small to moderate reductions on HRV relative to users of citalopram, fluoxetine and sertraline, but not escitalopram.

These associations may be produced through a variety of mechanisms including serotonergic receptors in brainstem regions involved in cardiovagal control, including the nucleus tractus solitarius at which cardiorespiratory afferent fibres terminate, and the cardiac vagal preganglionic neurones and rostral ventrolateral medulla (the location of sympathetic premotor neurones) [36, 37]. While different receptors appear to have variable effects, 5-HT_{1A} and 5-HT_7 contribute to mild bradycardia, a finding that was observed here for users of citalopram, who displayed a reduction in resting state HR by approximately ~4 beats per minute. SSRIs may also inhibit cardiac and vascular Ca^{2+}, Na^+ and K^+ channels further contributing to mild bradycardia [17, 18]. In addition, the effect of paroxetine may also be associated with anticholinergic effects [22], including inhibition of vagal efferent activity through blockade of muscarinic acetylcholine receptors at the sinoatrial node.

Large cohort studies and meta-analyses on the impact of SSRI medications have reported contradictory findings including increases [19], decreases [15, 16] and no alterations [20] in HRV, leading to much discussion in the literature [21, 38, 39]. These reports highlight the need for comparisons between different antidepressant medications from the SSRI class, an important contribution of the present study. Our findings extend our recent study on the impact of *antidepressant class* [15] to *specific antidepressants* within the SSRI class, demonstrating that paroxetine displays the most robust reductions in HRV after controlling for a number of confounding factors relative to controls, as well as users of other SSRI medications. These findings provide important new evidence for individual medications within the SSRI class, and highlight the need for further study in this area including investigation of the long-term effects of specific antidepressants within the SSRI class – and paroxetine in particular – on physical health and illness. To our knowledge, this is the first comparison of multiple medications within the SSRI class on measures of HR and HRV.

Paroxetine displayed the most pronounced reductions in HRV, relative to both controls as well as users of other medications, with the exception of escitalopram. Interestingly, a prior study on 28 inpatients with a DSM-IV diagnosed depressive episode also reported HRV reductions when paroxetine was prescribed at 40mg per day over a 35 day period [40]. The authors of this study [40] suggested that the higher dosage of paroxetine may impact on HRV in a similar way to tricyclic antidepressants. At higher concentrations (40 mg / day and higher), paroxetine is known to act as a dual serotonin/noradrenaline reuptake inhibitor [41, 42] and is characterised by appreciable antimuscarinic (anticholinergic) potency [41]. It is interesting to note that our earlier study [15] reported that tricyclic antidepressants and SNRIs were associated with moderate to large increases in HR and decreases in HRV. By contrast, paroxetine in the present study is associated with small to moderate reductions in HRV. These effect sizes are presumably smaller than those we observed for tricyclic and SNRI medications, as some participants on paroxetine may have been prescribed dosages less than 40mg/day. It is also notable that while SNRIs and tricyclic antidepressants may also lead to tachycardia in addition to reductions in HRV, users of paroxetine in the present study only exhibited decreases in HRV, not increases in HR (relative to non-users).

In contrast to paroxetine, fluoxetine was the only antidepressant that was not associated with significant alterations in cardiac activity. Fluoxetine is generally considered a safe medication for patients with cardiovascular disease. An early study [43] on depressed elderly patients with pre-existing cardiovascular disease reported that fluoxetine decreased HR by 6% (n=27), while nortriptiline, a tricyclic antidepressant, was associated with a 9% increase (n=52). This study highlighted the contrasting effects of fluoxetine versus nortriptiline on HR, with the authors concluding that increases in HR may reflect an increase in cardiac work, which over time may have clinically adverse effects. The only medication associated with robust

406 decreases in HR in the present study was citalopram (PSW Cohen's *d*: 0.35; PSM Cohen's *d*:
407 0.49).
408
409 Although fluoxetine has been a popular pharmacological treatment for mood and anxiety
410 disorders, recent systematic reviews indicate that other medications (e.g. sertraline,
411 escitalopram) may be more efficacious [44]. In fact, sertraline is the most commonly studied
412 SSRI medication in depressed patients with cardiovascular disease and is considered to be the
413 first line drug of choice in this patient population [45]. In the present study, sertraline
414 displayed some alterations of cardiac activity relative to non-users, however PSW findings
415 were not confirmed using PSM. We have recently reported [46] that chronic treatment with
416 sertraline (50-mg/d) does not impact on HRV over a period of 6-weeks in an independent
417 cohort of patients with major depressive disorder.
418
419 Escitalopram also displayed alterations of cardiac activity, including moderate reductions in
420 RMSSD in both PSW and PSM. Escitalopram was also the only SSRI medication that did not
421 significantly differ from paroxetine in a direct comparison across multiple antidepressants
422 highlighting the potentially adverse chronic effects of this medication on HRV. Recall that
423 these findings were observed in users taking this medication continuously over the past two
424 weeks. In contrast to these results, we have previously reported that a *single dose* of
425 escitalopram (20mg), relative to placebo, is associated with *increases in HF-HRV*, findings
426 associated with a moderate to large effect size [47]. It is possible therefore that acute versus
427 chronic administration of escitalopram leads to different effects on HRV. Others have noted
428 that chronic administration of SSRIs may lead to significant inhibition of various
429 cardiovascular ion channels leading to certain pro- or arrhythmic effects [17, 18].
430

It is important to acknowledge here a variety of limitations associated with our study including a lack of additional information on participant's use of antidepressants including dose and length of use. It is possible for instance that the findings observed here are less than what might be observed for participants on higher dosage (e.g. paroxetine at dosages higher than 40mg / day) and extended use (e.g. years). While sensitivity analyses confirmed findings for paroxetine (robust reductions in HRV) and fluoxetine (no significant associations for HR or HRV), it is possible that factors including dosage and length of use may have contributed to the findings that could not be confirmed using sensitivity analyses especially HRV reductions for other medications including escitalopram, citalopram and sertraline. It is important however, to place these limitations in the context of various strengths of our study, including a comparison of multiple medications from the SSRI class on HR and HRV for the first time and use of propensity score techniques to better control for potentially confounding factors.

In summary, users of all SSRI medications – with the exception of fluoxetine – display alterations in cardiac activity, relative to non-users. Critically, users of paroxetine even display reductions in HRV relative to users of other SSRI medications, with the exception of escitalopram. These findings may have important clinical implications. First, HRV in particular reflects the functioning of the vagus nerve [48] and its impairment may lead to impaired regulation over various allostatic systems [14, 49], which may have adverse impacts on physical health in those patients who use these medications over the long-term. Second, patients with mood and anxiety disorders already display alterations in HR and HRV [15, 46, 50, 51] and further reductions may have further consequences for patient health. Third, clinicians should be particularly mindful of physical health in patients treated with paroxetine, and also, possibly escitalopram, which are associated with the greatest impacts on HRV. Future research on the long-term effects of SSRI antidepressants, and the possibility that simple changes in health behaviours may ameliorate these associations, is needed.

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Table 1: Participant characteristics (unadjusted) including means (M) and standard errors (SE) for co

participants (n) and percentage of participants relative to sample size of sub-group (%).

	Controls (n=10,466)	**Escitalopram (n=46)**	**Citalopram (n=86)**	**Fluoxetine (n=66)**	**Paroxetine (n=103)**	
Age, M (SE)	52.10 (0.09)	54.48 (1.37)	55.95 (1.02)*	53.86 (1.18)	53.63 (0.92)	
Females, n (%)	5,515 (52.7)	32 (69.6)	67 (77.9)*	55 (83.3)*	78 (75.7)*	
Education, n (%)						
Less than High School	1386 (13.2)	0*	3 (3.5)*	8 (12.1)	5 (4.9)*	
High School	3620 (34.6)	4 (8.7) *	31 (36.0)	25 (37.9)	26 (25.2)	
Ethnicity, n (%)						
Non-White	5,154 (49.2)	15 (32.6)	28 (32.6) *	22 (33.3)	37 (35.9)	
Current Smokers, n (%)	1,330 (12.7)	6 (13.0)	9 (10.5)	12 (18.2)	16 (15.5)	
Body Mass Index, M (SE)	27.03 (0.05)	27.27 (0.78)	26.60 (0.51)	27.31 (0.55)	25.98 (0.42)	
Hypertension, n (%)	3,773 (36.1)	16 (34.8)	32 (37.2)	21 (31.8)	34 (33.0)	
Diabetes, n (%)	2,063 (19.7)	7 (15.2)	13 (15.1)	9 (13.6)	12 (11.7)	
Dyslipidemia, n (%)	5,985 (57.2)	33 (71.7)	60 (69.8)	44 (66.7)	73 (70.9)	
Hard CHD, n (%)	474 (4.5)	2 (4.3)	1 (1.2)	1 (1.5)	9 (8.7)	
Major Q-Waves, n (%)	263 (2.5)	1 (2.2)	1 (1.2)	0	2 (1.9)	

Physical Inactivity, n (%)	8,037 (76.8)	40 (87.0)	61 (70.9)	52 (78.8)	80 (77.7)	
CIS-R Total Score[2], M (SE)	7.87 (0.08)	9.15 (1.08)	12.26 (1.03)*	10.12 (1.10)	11.29 (1.04)*	
Heart Rate, M (SE)	66.78 (0.09)	65.55 (1.19)	63.72 (0.80)*	65.64 (0.94)	66.53 (0.95)	
RMSSD, M (SE)	3.23 (0.01)	2.98 (0.08)*	3.08 (0.06)	3.17 (0.07)	2.94 (0.05)*	
HF-HRV, M (SE)	5.36 (0.01)	4.83 (0.18)*	4.97 (0.12)*	5.19 (0.13)	4.84 (0.11)*	

[1] CIS-R Total Score: Severity of psychiatric morbidity determined using Clinical Interview Schedule-Re
*Refers to one-way ANOVA in which each group is compared to controls (Tukey's HSD, $p<0.05$) or
from $\chi 2$ statistics lying outside ± 1.96 reflecting a significance value of $p < 0.05$ using Fisher's exac
necessary

Table 2. Effects of multiple selective serotonin reuptake inhibitors (SSRIs) on heart rate and heart rate variability usin weighting (PSW) and propensity score matching (PSM).

	Propensity Score Weighting (using 'twang' and 'survey' packages)																			
	Non-users (n=10,451)		**Escitalopram (n=28)**				**Citalopram (n=28)**				**Fluoxetine (n=48)**				**Paroxetine (n=62)**			
	M	**SE**	**M**	**SE**	**Cohen's *d***	**PSW *p***	**M**	**SE**	**Cohen's *d***	**PSW *p***	**M**	**SE**	**Cohen's *d***	**PSW *p*[3]**	**M**	**SE**	**Cohen's *d***	**PS**
HR	66.81	0.09	66.50	1.77	-0.03	0.005	63.55	1.58	-0.35	<0.001	64.75	0.93	-0.22	0.68	67.25	1.16	0.05	<0.
RMSSD	3.23	0.01	2.98	0.09	-0.24	0.001	2.98	0.08	-0.24	0.001	3.20	0.07	-0.03	0.60	2.89	0.06	-0.33	<0.
HF-HRV	5.36	0.01	4.91	0.17	-0.44	0.009	4.78	0.17	-0.57	0.001	5.28	0.15	-0.08	0.60	4.78	0.18	-0.57	<0.
	Propensity Score Matching (using MatchIt package)[1]																	
	Non-users (matched)[2]		**Escitalopram (n=46)**				**Citalopram (n=86)**				**Fluoxetine (n=66)**				**Paroxetine (n=103)**			
	M	**SE**	**M**	**SE**	**Cohen's *d***	**PSM *p***	**M**	**SE**	**Cohen's *d***	**PSM *p***	**M**	**SE**	**Cohen's *d***	**PSM *p*[3]**	**M**	**SE**	**Cohen's *d***	**PSI**
HR	67.75	0.99	65.55	1.19	-0.07	0.74	63.72	0.80	-0.49	0.002	65.64	0.94	-0.30	0.09	66.53	0.95	-0.03	0.8
RMSSD	3.15	0.05	2.98	0.08	-0.46	0.038	3.08	0.06	-0.14	0.42	3.17	0.07	0.11	0.55	2.94	0.05	-0.50	<0.
HF-HRV	5.16	0.12	4.82	0.18	-0.34	0.11	4.97	0.12	-0.17	0.28	5.19	0.14	0.04	0.82	4.84	0.11	-0.34	0.0

lotes: [1] PSM was conducted to confirm findings from PSW to enhance effective sample size and combat potential for Type 1 error resulting from unequal sample ntidepressant to display robust reductions in both measures of HRV (RMSSD, HF-HRV) in both PSW and PSM, relative to non-users, findings associated with s ells). Fluoxetine did not show any alterations in heart rate or HRV relative to non-users on either analysis (light grey coloured cells). [2] Values for non-users from ipartite matching was used, and control participants were matched to each antidepressant group, values differ for each comparison. For brevity the values for nor roupings are not shown here. Note however, that the Cohen's d effect size measure for each comparison was calculated using the values from controls that were

ntidepressant being compared. [3] Light grey shaded cells reflect correspond to p-values for fluoxetine, the only antidepressant not associated with alterations in H
ndings for users of paroxetine in which robust reductions in both measures of HRV (RMSSD, HF-HRV) on both PSW and PSM were observed, relative to non-u
ffect size.