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Effects of depression, anxiety, comorbidity and antidepressants on resting-state heart rate and its variability: An ELSA-Brasil cohort baseline study

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Disclosures

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Objective: Increases in resting-state heart rate and decreases in its variability are associated with substantial morbidity and mortality, yet contradictory findings have been reported for the effects of the mood and anxiety disorders, and antidepressants. Here we apply a relatively novel method – propensity score weighting – to control for a host of potential confounds in a large cohort from Brazil. **Method:** A total of 15,105 participants were recruited in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) between 2008 and 2010. Mood and anxiety disorders were determined using the Portuguese version of the Clinical Interview Schedule-Revised. Heart rate and its variability were extracted from 10-minute resting-state electrocardiogram recordings. **Results:** Use of antidepressant medications was associated with increases in heart rate and decreases in its variability. Effects were most pronounced for the tricyclics (Cohen's d's 0.72 – 0.81), followed by serotonin and noradrenaline reuptake inhibitors (serotonin and noradrenaline reuptake inhibitors; Cohen's d's 0.42 – 0.95) and other antidepressants (Cohen's d's 0.37 – 0.40), relative to those not on any antidepressants. Only participants with generalised anxiety disorder (GAD) showed robust, though small, increases in heart rate and decreases in its variability after propensity score weighting. **Conclusions:** Findings may, in part, underpin epidemiological findings of increased risk for cardiovascular morbidity and mortality. It is important to note that many factors adversely impacting on cardiac activity were controlled in this study, highlighting the importance of cardiovascular risk reduction strategies. Future studies are needed to examine whether, how and when such effects contribute to morbidity and mortality.

noradrenaline reuptake inhibitors; SNRIs; selective serotonin reuptake inhibitors; SSRIs

Introduction

Heart rate and its variability are determined by a variety of physiological factors, the most prominent of which is the autonomic system. In the resting state, the heart is under tonic inhibitory control by the parasympathetic (vagal) nervous system (1). The parasympathetic and sympathetic nervous systems are typically conceptualised as two opposing components, however, recent thinking indicates that vagal activity may be withdrawn without a corresponding increase in sympathetic nervous system activity (2). This metabolically conservative response during challenge may mirror autonomic dysregulation in psychiatric illness during the resting state. It is in this regard that we refer to resting state heart rate and its variability as surrogate markers of vagally-mediated, cardiac activity. It is important to acknowledge however, that measures of heart rate variability and the high frequency component in particular are more pure indicators of vagal activity (3) than heart rate, which may include sympathetic input. The present paper examines the impact of depression, anxiety, comorbidity and antidepressants on resting-state heart rate and its variability, measures we now denote as vagal activity, for brevity.

Vagal activity plays an important role in mental and physical wellbeing (see 4 for review). Increases in vagal activity are associated with positive emotions, social connectedness and longevity. By contrast, decreases in vagal activity are associated with depression, anxiety, cardiovascular disease and mortality, findings that may be attributable to the downstream effects of a poorly functioning cholinergic anti-inflammatory reflex. Other mechanisms including chronically elevated activity in the sympathetic nervous system are also involved in the pathway from emotion to morbidity. However, we suggest that vagal activity may provide a unique, structural link from day-to-day emotion experience to morbidity and mortality from a host of

conditions. In this regard, within-subject, phasic changes in vagal activity reflect a normal response to environmental challenge, while between-subject, resting state, tonic differences in vagal activity predict future mortality. In this regard, an early, seminal study on the effects of decreased heart rate variability in participants following acute myocardial infarction – as measured by the standard deviation of all normal RR intervals in 24-hour continuous electrocardiogram recordings from Holter monitors – (5) reported a five-fold increased relative risk of mortality.

We and others have demonstrated that vagal activity is reduced in the mood and anxiety disorders (see 4 for review). In one of the first studies on this topic more than two decades ago (6), depressed patients with coronary artery disease were found to have increased heart rate, relative to non-depressed patients with coronary artery disease, independent of age, smoking and beta blocker medication. Depressed patients also displayed reduced heart rate variability, albeit at trend levels. This study was also based on data extracted from 24-hour ambulatory electrocardiogram recordings. Reliable and valid measures of heart rate and its variability may also be obtained from shorter recordings under standardised and controlled conditions (7). Using short-term electrocardiogram recordings in another early study (8), we reported that patients with generalised anxiety disorder display lower high frequency heart rate variability. High frequency heart rate variability, in particular, is mediated solely by changing levels of vagal activity (3). We concluded that generalised anxiety disorder and its cardinal feature (worry) are associated with reduced vagal activity. More recently, we demonstrated that patients with comorbid major depressive disorder (hereby denoted as depression) and generalised anxiety disorder (see 4 for review; 9) display the most robust reductions in resting-state vagal activity. Our explanation for these findings is that chronic worry and hypervigilance to threat may

underpin chronic withdrawal of vagal activity that may subsequently lead to increased morbidity and mortality.

Recent debate has focused on whether mental disorders such as depression and anxiety are associated with reductions in vagal activity (see 4 for review) or whether these findings are driven by antidepressant medications (10; 11). However, studies have seldom used appropriate measures to adequately control for the effects of these variables on vagal activity. Inappropriate control of confounding factors may lead to a phenomenon known as the 'reversal paradox', in which "the association between two variables may be reversed, diminished or enhanced when another variable is statistically controlled" (12). Here we control for confounding factors through propensity score weighting using a generalised boosted modelling technique (13).

This relatively novel method has several advantages over traditional regression-based techniques including 1) application of flexible machine learning algorithms yielding well-calibrated estimates, 2) capture of complex and nonlinear relationships between groups and covariates without overfitting, 3) reduced bias by estimating the propensity score without reference to the outcome variable, and 4) the opportunity to analyse observational data to mimic the advantages of a randomised controlled trial design. This methodological approach provides an alternative to multiple regression that is more interpretable and less prone to violation of model assumptions (14). We apply this technique on a large sample of participants recruited for the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) (15).

ELSA-Brasil is the first large multi-centre cohort study of adult health conducted in Brazil. It is an ongoing cohort study designed to investigate the relationship between cardiovascular diseases and diabetes, their social determinants and risk factors. In this regard, vagal activity is an important consideration (see 4 for a review), and cross-sectional analysis of the ELSA-Brasil cohort at baseline will provide an important foundation for future longitudinal analyses on this cohort. Consistent with our prior studies on relatively smaller samples (9; 16; 17), we hypothesised that individuals diagnosed with the mood and anxiety disorders would display reductions in vagal activity, while use of antidepressants would be associated with further reductions, a finding that would be most apparent in users of tricyclic medications.

Method

Participants

A total of 15,105 civil servants aged 35 to 74 were recruited for the first wave of ELSA-Brasil (15) between August 2008 and December 2010 at 6 different sites in Brazil. Exclusion criteria comprised current or recent pregnancy (within 4 months of first interview), intention to quit working at the institution in the near future, severe cognitive or communication impairment, and if retired, residence outside of a study centre's metropolitan area. The study design and sampling procedures of ELSA-Brasil have been reported previously (15).[1]

Procedures

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[1] See also vol.47, supl.2 of Rev. Saúde Pública (available at: http://goo.gl/ai2i1z). This supplement is dedicated to methodological aspects of the ELSA-Brasil study and includes articles in English.

Data were collected from participants in two phases: the first, lasting approximately 1 hour, included collection of informed consent and an initial interview at the participant's job site, while the second, lasting approximately 6 hours, was conducted in a study clinic and involved additional interviews, clinical exams and collection of blood and urine samples. Participants were asked to abstain from caffeine, alcohol and physical activity 12 hours prior to electrocardiogram assessment. A comprehensive set of examinations and measurements including electrocardiogram assessment were carried out. These procedures are described in more detail below (see also 15).

Psychiatric Evaluation

Mental disorders were determined by trained interviewers using the Portuguese version (18) of the Clinical Interview Schedule-Revised (CIS-R) (19). This is a structured interview used for diagnosis of current, common, non-psychotic psychiatric conditions in the community. The following categories were determined according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems: depression (F32.xx), agoraphobia (F40.0), social phobia (F40.1), specific phobia (F40.2), generalised anxiety disorder (F41.1), panic disorder (F41.0) and social anxiety disorder (F42). These diagnostic groupings were then reduced to five categories: depression, generalised anxiety disorder, all phobias, panic disorder, and a comorbid group comprised of participants with depression and any anxiety disorder.

Electrocardiogram Assessment

Ten-minute, resting-state electrocardiogram was recorded from participants during spontaneous breathing without task demands, in the supine position. The electrocardiogram was always collected in the morning (8:00 to 12:00h) in a temperature-controlled room (21-24°C) and was sampled at 250 Hz with a digital electrocardiograph (Micromed, Brazil), consistent with international standards for the collection of heart rate variability (7). Wincardio (4.4a) software generated the R-R interval series from a selected lead (D2), associated with higher R-wave amplitude. We have described the artefact detection and spectral analytic techniques previously (20). Briefly, the R–R series was automatically pre-processed to remove ectopic beats and artefact, and linear interpolation was employed to replace any removed beats. Power spectral analysis was carried out by autoregressive modelling, estimated by the Yule Walker method, using the recursive algorithm of Levinson-Durbin. Measures of heart rate and its variability including the root mean square of successive squared differences, and high frequency were then extracted. The high frequency (0.15–0.40 Hz) component was estimated and expressed in absolute units. Measures of heart rate variability were then log-transformed as a normalisation strategy.

Covariates

A host of covariates considered to impact on vagal activity were used in propensity-score matching. Sociodemographic information included age and sex. Behavioural and lifestyle characteristics included smoking status (past or current versus never), physical activity (measured with the International Physical Activity Questionnaire and categorised according to low activity versus moderate or high activity as determined using scoring guidelines: http://www.ipaq.ki.se/scoring.pdf) and body mass index (weight in kilograms divided by height in meters squared). Health information included hypertension, diabetes mellitus, dyslipidemia, myocardial infarction and

coronary revascularisation. Hypertension was defined as systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥ 90mm Hg, or use of antihypertensive medications. Diabetes was defined as self-reported or fasting blood glucose ≥ 126mg/dL or 2-hour oral glucose tolerance test ≥ 200mg/dL or glycated haemoglobin ≥ 6.5%. Dyslipidemia was defined as LDL-cholesterol ≥ 130mg/dL or use of lipid lowering medication. Blood samples were collected following a 12-hour overnight fast. Medication use for hypertension, diabetes, and lipid reduction, as well as antidepressants were identified on the basis of pill bottle review. Analysis on the mood and anxiety disorders also included CIS-R total score to control for disorder severity.

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics Version 21 and the R-statistical environment (version 3.0.1). Regressions weighted by propensity scores were carried out using the 'twang' and 'survey' packages in the R statistical environment. Both R and the two packages are freely available, and details on how to implement procedures have been described previously (13). Two main analyses were conducted. The first, involved comparison of controls, depression, phobias, panic disorder, generalised anxiety disorder and participants with comorbid depression and any anxiety disorder on measures of vagal activity (heart rate, root mean square of successive differences and high frequency). The second, compared users of selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, tricyclic and other antidepressants on these same measures. Effective sample sizes (reported as 'n') were obtained after propensity score weighting; these reflect numbers of participants with similar features on covariates in

each of the groups. Effective sample sizes capture the adverse impact of increased variance on precision and power (13). Sensitivity analyses were conducted using propensity score *matching*. While *weighting* involves covariance-adjusted, regression-based modelling in which propensity scores are used as a covariate, *matching* involves selecting control participants to match comparison groups on propensity scores. Here, propensity score *matching* was carried using the 'MatchIt' package in the R-statistical environment using one-to-one, exact matching, which paired each participant of the comparison group with a participant from the control group based on the propensity score. IBM SPSS Statistics software was then used to conduct between-group t-tests on matched samples.

Results

Participant Characteristics

Participant characteristics before and after propensity score weighting are presented in supplementary tables. Supplementary Table 1 displays characteristics for the mood and anxiety disorder groupings. Supplementary Table 2 displays characteristics for each of the antidepressant groupings.

Impact of Disorder on Vagal Activity

After propensity-score weighting, effective sample sizes were as follows: controls, n=10,346; depression, n=98; phobias, n=121; panic disorder, n=43; generalised anxiety disorder, n=1,183; and comorbid, n=311. Average heart rate was slightly increased in participants with generalised anxiety disorder relative to controls, a finding at trend levels, associated with a small effect size [M=67.30 versus 66.79, p=0.086, *d*=0.053]. No other groups differed from controls. Sensitivity analysis using

propensity-score matching revealed similar, trend-level findings for generalised anxiety disorder (n=1249) relative to controls (n=1236) [M=67.23 versus 67.90, p=0.065, *d*=0.074]. Analysis on heart rate variability revealed significant effects for both measures after propensity-score weighting; root mean square of successive differences was decreased in generalised anxiety disorder relative to controls [M=3.17 versus 3.21, p=0.015, *d*=0.075] as was high frequency [M=5.23 versus 5.32, p=0.033, *d*=0.066]. Again, no other groups differed from controls. Again, sensitivity analysis using propensity-score matching revealed similar findings for generalised anxiety disorder relative to controls [root mean square of successive differences: M=3.18 versus 3.25, p=0.004, *d*=0.116; high frequency: M=5.29 versus 5.42, p=0.005, *d*=0.113].

Impact of Antidepressants on Vagal Activity

After propensity-score weighting, effective sample sizes were as follows: participants not on antidepressants, n=14,069; selective serotonin reuptake inhibitors, n=356; serotonin and noradrenaline reuptake inhibitors, n=52; tricyclic antidepressants, n=84; and other antidepressants, n=75. Tricyclic antidepressants (M=73.94, p<0.001, *d*=0.721), other antidepressants (M=71.00, p=0.001, *d*=0.380) and serotonin and noradrenaline reuptake inhibitors (M=70.55, p=0.003, *d*=0.420) were associated with an increase in heart rate relative to those not on antidepressants (M=66.87), while selective serotonin reuptake inhibitors were associated with a small decrease (M=65.40, p=0.003, *d*=0.161). In addition, all antidepressants were associated with a decrease in heart rate variability [root mean square of successive differences, tricyclic antidepressants: M=2.71, p<0.001, *d*=0.810, serotonin and noradrenaline reuptake inhibitors: M=2.79, p<0.001, *d*=0.952, Other: M=2.95, p<0.001, *d*=0.402;

selective serotonin reuptake inhibitors: M=3.08, p<0.001, *d*=0.280; high frequency, tricyclic antidepressants: M=4.26, p<0.001, *d*=0.730, serotonin and noradrenaline reuptake inhibitors: M=4.48, p<0.001, *d*=0.789, Other: M=4.82, p=0.001, *d*=0.367, selective serotonin reuptake inhibitors: M=5.05, p<0.001, *d*=0.254] relative to those not on antidepressants [root mean square of successive differences: M=3.23; high frequency: M=5.36]. These findings were all replicated in sensitivity analysis using propensity-score matching (results not shown).

Discussion

The most striking effects from our study relate to the use of antidepressant medications; tricyclic, serotonin and noradrenaline reuptake inhibitors and other antidepressants were associated with moderate to large adverse effects. With respect to the impact of mood and anxiety disorders – an issue that has attracted the most debate – findings demonstrate that only generalised anxiety disorder is associated with a reduction in vagal activity after controlling for a host of clinical covariates including biomarkers of metabolic and cardiovascular risk. The effects of generalised anxiety disorder on vagal activity were statistically significant and robust, although effect sizes were small. This is an important finding as other researchers have recently argued that it is the antidepressant medication, rather than the disorder per se, that adversely impacts on vagal activity (10; 11). While it is notable that participants with comorbid depression and anxiety disorders did not display reductions in vagal activity, it is important to remind readers that many of the factors that adversely affect vagal activity were controlled in this study.

The mood and anxiety disorders raise metabolic and cardiovascular risk (21), emphasising the need for comprehensive cardiovascular risk reduction strategies in all patients with these disorders to minimise subsequent morbidity and mortality. In the present study, we show that only generalised anxiety disorder without comorbidity is associated with reductions in vagal activity. These findings highlight the independent, adverse effects of generalised anxiety disorder without comorbidity on vagal activity. It is important to note here however, that generalised anxiety disorder and depression are linked to each other sequentially such that each disorder increases the likelihood of developing the other disorder over time (22). Longitudinal follow-up of our participants will provide important data to further examine the relationship between depression and generalised anxiety disorder over time, and their effects on vagal activity. In line with our prior studies on generalised anxiety disorder (8; 9), we suggest that the cardinal features of this disorder, including chronic worry and hypervigilance to threat independently contribute to long-term reductions in vagal activity and subsequent increases in morbidity and mortality.

Our study is now placed in the context of prior studies, which have reported contradictory findings leading to significant debate and discussion. In 2007, Rottenberg (23) reported findings from a meta-analysis indicating that depression adversely impacted on vagal activity, a finding associated with a small-to-medium effect size. He also suggested that low heart rate variability may be a consequence of comorbid anxiety, rather than depression *per se*. In 2008 and 2009, Licht and colleagues reported that although heart rate variability is reduced in patients with depression (24) and those with anxiety disorders (25), these reductions are driven by antidepressant medications. These findings contrasted with smaller studies that had reported adverse effects of the mood and anxiety disorders leading to the publication

of our meta-analysis in 2010 (16). We reported that heart rate variability was reduced in depressed, unmedicated patients relative to controls, a finding associated with a large effect size when focusing on non-linear measures of heart rate variability. Recent years have witnessed increasing calls for independent replication of published findings in science (26; 27). Consistent with this goal, we have examined the impacts of the mental disorders and antidepressants on vagal activity using a variety of approaches. In addition to meta-analysis, we have replicated reductions in the mood and anxiety disorders in multiple independent cohorts of patients (9; 17; 28). In the largest independent cohort to date, we now report that after controlling for multiple confounding variables, generalised anxiety disorder displays robust, albeit small, reductions in vagal activity. It is possible that the lack of findings for MDD relate to disorder heterogeneity. For example, specific patient characteristics (e.g. melancholia) may be associated with more robust effects on vagal activity.

We suggest here that the effects we observed for the tricyclics and serotonin and noradrenaline reuptake inhibitors in particular, may underpin previously reported increases in risk for cardiovascular morbidity and mortality (29; 30). There is strong evidence for a continuous increase in risk for cardiovascular and all-cause mortality in men and women with a resting heart rate above 60 beats/minute, regardless of whether individuals have a history of cardiovascular disease (31). In the present study we show that tricyclic antidepressants are associated with an average resting heart rate of ~74 beats per minute (BPM), while serotonin and noradrenaline reuptake inhibitors and other antidepressants are associated with an average resting heart rate of approximately ~71 BPM, relative to non-users of antidepressants (~67 BPM). In light of the increasing concerns over the impact of antidepressant medications (10; 29; 30), we recently investigated the moderating effects of physical

activity on the impact of the selective serotonin reuptake inhibitors, escitalopram, on cardiac stress responses (32). We found that participants who engaged in exercise at least 3 times per week display a more resilient vagal response to stress, relative to irregular exercisers, a finding associated with a moderate effect size. We also observed that acute escitalopram had a similar impact on irregular exercisers during stress. The moderating effects of regular exercise in long-term users of antidepressant medications needs to be examined in future research. In the present study, the selective serotonin reuptake inhibitors were associated with a decrease in heart rate *as well as* its variability. It is particularly interesting that these findings have been reported previously for this class of medication (10); findings that were interpreted as both a decrease in sympathetic activity and parallel decreases in net cardiac vagal effects.

While our study has important strengths – particularly the application of propensity score weighting on a large, independent cohort of participants – a number of limitations should also be noted. Firstly, the reliability of short-term measurements of heart rate variability has been questioned (33). However, we have demonstrated that the protocol on which the present study is based shows good reproducibility (see 34). Secondly, we acknowledge that respiration rate may influence estimates of heart rate and its variability. While we did not collect data on respiration rate in our participants, the question of whether or not respiration rate should be controlled remains a divisive issue in the field of psychophysiology. Researchers have even cautioned against experimentally controlling for respiration as this may confound the visceral-medullary feedback system and shift respiratory parameters (2). Also, the root mean square of successive differences, unlike frequency-based measures, may actually be more robust to changes in breathing patterns (35). In the present study,

key findings were obtained across both measures of heart rate variability highlighting the robustness of findings. Finally, it should be noted that although we controlled for a variety of important covariates, there are likely other factors that we did not measure or include in our models that may have impacted on findings. Thus, there remains the potential for residual confounding factors in our study.

In summary, the present study provides much needed evidence for the impact of the mood and anxiety disorders, and antidepressants on resting-state vagal activity, after controlling for a large number of confounding factors. Future studies employing a randomized-controlled design will provide further, important evidence for the impact of specific antidepressants on vagal activity. Further research is also needed to determine whether certain clinical characteristics and their amelioration moderate observed findings. It is possible for instance, that specific subtypes of depression (e.g. melancholia) or symptoms of a depressive episode or the anxiety disorders (e.g. somatic symptoms) have more robust effects on vagal activity. There is also a need for future research to determine how and when reduced vagal activity leads to morbidity and mortality from a host of conditions.

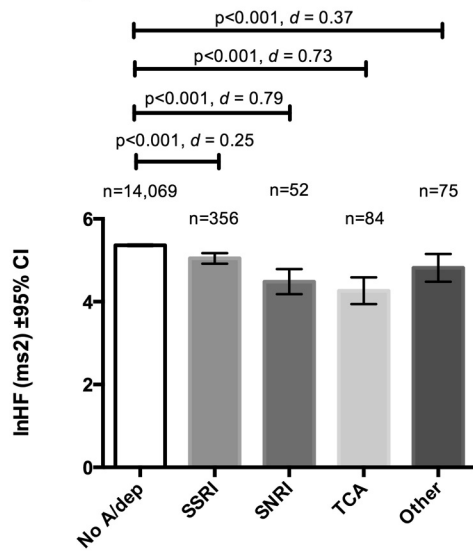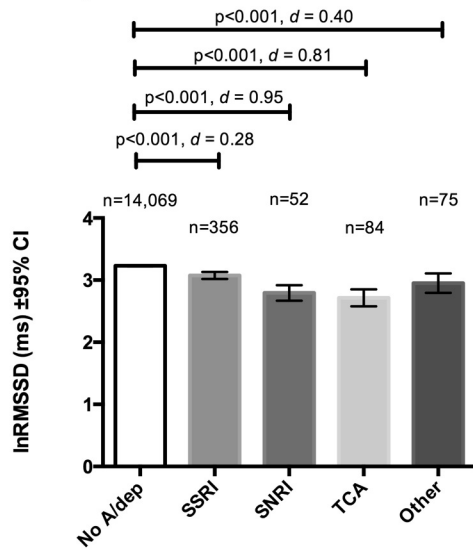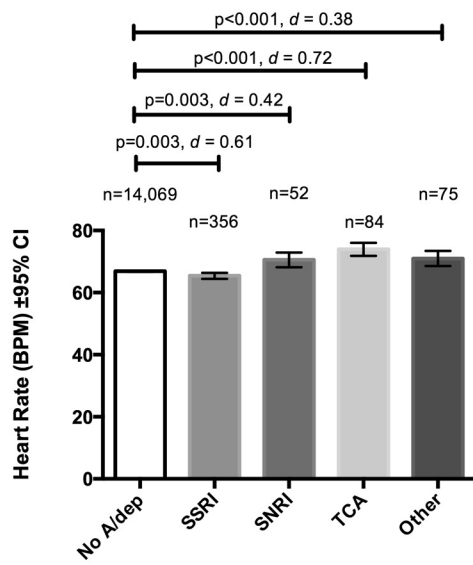Fig 1: Key findings associated with the impact of antidepressants on heart rate and its variability (including root mean square of successive squared differences and high frequency after log-transformation) following propensity score weighting. Group means and 95% confidence intervals corresponding to the propensity score weighted regression are displayed. These were extracted using the 'svyby' function.

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p<0.001, *d* = 0.38
p<0.001, *d* = 0.72
p=0.003, *d* = 0.42
p=0.003, *d* = 0.61

n=14,069   n=52   n=75
n=356   n=84

Heart Rate (BPM) ±95% CI

No A/dep   SSRI   SNRI   TCA   Other

p<0.001, *d* = 0.40
p<0.001, *d* = 0.81
p<0.001, *d* = 0.95
p<0.001, *d* = 0.28

n=14,069   n=52   n=75
n=356   n=84

lnRMSSD (ms) ±95% CI

No A/dep   SSRI   SNRI   TCA   Other

p<0.001, *d* = 0.37
p<0.001, *d* = 0.73
p<0.001, *d* = 0.79
p<0.001, *d* = 0.25

n=14,069   n=52   n=75
n=356   n=84

lnHF (ms2) ±95% CI

No A/dep   SSRI   SNRI   TCA   Other