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Replicated ECG-based Autonomic Profiles for Depression

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Abstract

Electrocardiography-derived autonomic profiles have been proposed as accessible markers of depression and suicide risk, but whether such a profile keeps its meaning outside the population in which it was derived has not been tested. We attempted a constrained reproduction of a published four-profile model in an independent, differently ascertained cohort: 35,980 hospital patients from MIMIC-IV-ECG, using 10-second routine clinical ECGs and ICD-10 diagnoses. Assigning patients to the published centroids without re-fitting, the heart-rate-variability magnitude axis reproduced: membership of a low-HRV profile was associated with depression (age- and sex-adjusted OR 1.19, 95% CI 1.13–1.26), anxiety (1.22, 1.15–1.29) and antidepressant prescription (1.32, 1.26–1.38), and the profile ranking held. The axis separating the two low-HRV profiles did not reproduce, consistent with an attenuation we quantified in advance from the spectral reconstruction the record length forced on us. Standardizing patients on the original cohort's statistics collapsed 75.1% of them into a single profile, showing that a centroid-based profile carries its meaning only together with the population frame in which it was computed. In a nonlinear extension over 123,932 patients, Higuchi fractal dimension of the raw 12-lead waveform was lower in depression (d = -0.39), anxiety (-0.42) and suicidality (-0.70), consistent with a transdiagnostic loss of physiological complexity rather than a depression-specific marker. In the same cohort, depression prevalence ranged from 26.2% to 51.3% depending only on which diagnostic codes were admitted. Autonomic profiles are reproducible in routine care data, but they are not portable without their coordinate system.

Introduction

Malzberg wrote about cardiovascular diseases as a major cause of death among depression patients in 1937; his patients had almost eight times higher cardiovascular mortality than the general population[1]. The link between depression and increased cardiovascular risk is thus long established. Underneath that connection is most likely aberrated functioning of the Autonomous Nervous System (ANS). Two neuroanatomical and functional connections are implicated: the Allostatic-interoceptive Network (AIN) and the Cortico-Autonomic Network (CAN). Nicolini et al.[2] described CAN's role in the context of orthostatic challenge to examine mild cognitive impairment (as a prodromal phase) in dementia patients, and allostatic load[3] is established as a central concept in the field, too. Including the impact those networks have via direct cardiovascular risk factors, this approach can lead to transition to more holistic view of autonomic regulation in depression research. Regarding CAN, it is a complex network of cortical

and subcortical regions (insula, hippocampus and prefrontal cortex) that have projections to the preganglionic neurons of ANS; it has been widely identified as a neuroanatomic substrate of a brain-heart axis[2]. Allostatic-interoceptive network-AIN is a different complex network that partly overlap with CAN, and consists of Insula, anterior cingulate cortex (ACC), hippocampus and parahoppocampal giri, amygdala and talamus[3]. It is, in essence, ensemble of cerebral regions crucial to integrate the signals from the afferent networks from the body with cognitive and emotional responses. That link of cognitive and emotional responses to autonomic regulation is crucial for understanding why cardiovascular diseases are connected to mood disorders, as aberrated ANS influence can be better understood in context of depression and its hidden cardiovascular risks.

Our engineering angle is to use electrophysiological signal analytics to approach neurocognitive phenomena as a highly complex dynamical system, utilizing fractal and nonlinear measures from statistical physics, belonging to the field of Physiological Complexity[4–9]. Decomplexification is the term that links the stereotypy of disease clinicians recognize (and use for diagnostics for a long time) with measurable instruments from the physiological complexity toolkit[10]. It denotes pathologically low levels of complexity in electrophysiological signals, characteristic of the disordered state[5]. In that context we previously used fractal and nonlinear analysis to characterize various signals (EEG, ECG, EMG) to detect measurable small changes that could improve clinical outcomes if detected early[11–14]. ECG is a particularly attractive source because of the ANS connection described above and because it can be measured outside clinics with medical-grade portable devices in case of translation of those findings. The analysis of heart rate variability (HRV) is the principal tool to assess autonomic function.

Many research groups used HRV in the context of depression and anxiety. Kemp et al.[15–17], among others, used the mix of standard frequency and time-based measures together with some of the nonlinear ones to interpret aberrant ANS function in both MDD and GAD. A review of nonlinear HRV measures in depression, focused on effect sizes, is provided in Čukić et al.[18]. The role of fractal and nonlinear analysis here rests on a fundamental point: Fourier-based measures assume stationarity and linearity (additivity), properties that are not characteristics of electrophysiological signals[19,20]. Furthermore, human physiology operates by complex systems dynamics rules, and could be misinterpreted if put in a mechanistic (reductionistic) framework[10]. All electrophysiological signals are 3N: Nonstationary, Nonlinear and Noisy[19]. They are also irregular under healthy dynamics[6] and nonadditive — rules from mechanical systems do not apply to physiology. Hence interpreting electrophysiological signals with reductionistic methods and excessive filtering leads to misinterpretation. Klonowski showed that applying Fourier analysis to EEG discards the component of interest in the second step[19]; Kalauzi showed that HFD uses FFT amplitudes as weight functions[20], hence FFT is redundant.

After an initial period of popularity of Computational Psychiatry, where we combined fractal and nonlinear measures with various statistical learning models[11,21–24], we also learned that one must use several measures as features — never relying on one alone — as each extracts different information from the signal[25]. Eventually, even large feature sets combined with sophisticated learning models led to saturation, as theoretical limitations — the curse of dimensionality, blind spots, nuisance variables — jeopardize practical clinical use[26].

The idea of one causal neuropsychiatric factor (unfortunately named p factor) is not new, but it ended with acknowledging defeat: there are simply too many factors for mental illness than we previously hoped to isolate. A large genetic study[27] showed that almost all disorders (except for PTSD) are related; depression and anxiety are strongly correlated[28]. After ECNP published its Precision Psychiatry Roadmap[29], a consensus emerged that current therapeutic approaches have very low effectivity and that the future should be focused on physiology-based biomarkers rather than ever-increasing complexity of diagnostic manuals.

That changed when Weber et al.[30] published their work on ECG-based cluster biomarkers for depression — called autonomic profiles. Besides demonstrating that distinct autonomic profiles exist, they also extracted four clusters of biomarkers, among which two with low Heart Rate Variability-HRV were associated with different risks, and highly correlated with clinical presentation. The first (High Relative Sympathetic cluster-HRS) was characterized by high relative sympathetic tonus and lower breathing rate, indicated higher resilience with less likely depressive symptoms and suicidal thoughts whereas another cluster (Low Relative Sympathetic cluster-LRS) with dominant relative parasympathetic activity and high breathing rate, aligned with greater depression and suicide attempt prevalence, potentially representing a high-risk cluster (Weber et al., 2025). It makes sense that the aberrated ANS can be quantified and personalized by a list (cluster) of HRV measures plus breathing rate and epidemiological data (as a Profile), and formulating profiles are highly correlated with depression and suicide risk.

Here, we present our replication of that important study with our extension and commentary important for further translation.

Methods

Study design and reproduction strategy

This study is a constrained reproduction of Weber et al.[30] in an independent, differently ascertained cohort, followed by a nonlinear extension. Weber and colleagues identified four autonomic nervous system profiles (clusters of specific markers) from HRV measures in 15,768 UK Biobank participants using K-means clustering on ten HRV features; two low-HRV clusters showed divergent associations with depression and suicidality. Age, sex and BMI were not clustering inputs but post-hoc covariates.

Three constraints could not be removed: the cohort is a hospital population rather than a community volunteer sample, the outcome is derived from diagnostic codes rather than from the CIDI-SF, and our recordings are 10 s while Weber's averaged 24.23 ± 19.34 s. Where the original procedure could be followed exactly, we followed it; what this section reports are the points at which our procedure necessarily diverged (Figure 1).

Figure 1 here, please

Figure 1. Replication pipeline. Solid boxes denote steps applied to MIMIC-IV-ECG; the dashed box on the right shows fixed inputs from Weber et al.[30]. Predictor correlations (Weber Fig. 1) enter spectral proxy estimation; cluster centroids (Weber Table 2) enter fixed-centroid assignment. No Weber parameters were re-fitted.1

Cohort

We used MIMIC-IV-ECG[31] linked to the MIMIC-IV Clinical Database[32]. The nonlinear extension retains the full cohort (290,189 records from 123,960 subjects; 123,932 with complete age and sex). The replication cohort is the quality-controlled subset with all ten clustering features available (N = 35,980 subjects, 63,794 records; Figure 2).

Figure 2 here, please

Figure 2. Cohort flow. Left: nonlinear extension retains all 290,189 records (123,932 subjects with complete age and sex). Right: cluster replication cascade from Lead II extraction (72,468 records) through null-feature removal (65,164), BPM quality control (63,794), subject-level aggregation (35,980) and cohort linkage (35,706).

HRV feature extraction

Four decisions were mandated by silence (missing information or unfulfilled request for clarification by the Authors) in the original report or by differences MIMIC could not bridge.

> **Lead selection.** Weber does not state which lead was analyzed. We fixed Lead II and treated records without it as extraction failures.
>
> **Software.** Weber used HeartPy[33]; we used it too so that R-peak detection would not itself become a source of divergence. No filter was applied to the waveform; artefact correction was performed on the RR series using HeartPy's quotient filter.
>
> **Quality control.** Weber excluded recordings whose HeartPy heart rate differed by ≥20% from the GE Cardiosoft device reading. MIMIC carries no device reference, so we substituted NeuroKit2[34] as an independent software estimate and applied the same threshold.
>
> **Missing data.** Weber imputed missing values by mean substitution. We excluded records missing any core feature, accepting a smaller cohort in exchange for leaving the multivariate distribution intact.

Thirteen features were extracted per record. SDNN, SD1 and SD2 were dropped because Weber excluded them after correlation-based feature selection, leaving the ten clustering variables: BPM, RMSSD, pNN20, pNN50, MAD, LF, HF, LFnu, TP and BR. Before applying the published cluster structure, we compared the MIMIC correlation matrix against Weber's (Figure 3). No pair strongly correlated in Weber became unrelated in MIMIC, and we treated this as a compatibility check only.

Figure 3 here, please

Figure 3. Pearson correlation structure of 9 shared time-domain HRV variables. (a) Values reported in Weber et al.[30], Fig. 1 (UK Biobank, N = 15,768). (b) MIMIC-IV-ECG (this study, N = 35,980 subjects; record-level features averaged within subject).2

Spectral proxy reconstruction and cluster assignment

LF and LFnu were undefined in 100% of records; HF and TP in 27.2%. We reconstructed the four indices as linear proxies from the six directly measured predictors, using coefficients derived from Weber's published correlation matrix ($\beta_{std} = R_{xx}^{-1} r_{xy}$; full derivation in Supplementary Methods). $R^2 = 0.34$ (LF), 0.46 (HF), 0.30 (LFnu), 0.47 (TP). Physical bounds were imposed after

prediction; 45.9% of LF values were clipped to zero, so this variable is substantially left-censored. The published LFnu cluster ordering (HRS > HP > MP > LRS) is preserved but its spread is compressed by roughly half, predicting weaker separation on the autonomic-balance axis.

Subjects were assigned to Weber's four published clusters without re-fitting: the cluster means from Weber's Table 2 served as fixed centroids, and each subject was assigned to the nearest by Euclidean distance. Standardization used MIMIC-derived statistics for subjects and Weber's pooled statistics for centroids. Under Weber-referenced standardization, 75.1% of subjects collapsed into LRS, confirming that the coordinate system is not transferable across populations without adjustment.

Nonlinear extension: Higuchi fractal dimension (HFD)

Fractal dimension (FD) of a signal is a measure of its self-similarity and complexity in the time domain. General rule is that the higher self-similarity and complexity- the higher FD. The fractal dimension of ECG was calculated using Higuchi's algorithm[35] demonstrated to be the most appropriate for electrophysiological data[36,37]. This method works directly in the time domain, gives a reasonable estimate of the fractal dimension even in the case of short signal segments and is computationally fast (since it does not attempt to reconstruct the strange attractor). Although in the original Higuchi paper the maximal scale was recommended as $k_{max} = 8$, as a consequence of another later specific analysis on k_{max} values in physiology[38] we decided to use 16 instead. In our prior work in depression detection, HFD calculated from EEG showed different trend, namely it was higher than in healthy controls (HC) due to increased cortical excitability characteristic for MDD; that was explained in ref. 11. But due to additional complex interplay via heart-brain axis, it is confirmed that in depression, HFD calculated from ECG shows lower values than in HC[39]. That is in line with the concept of Decomplexification, where with ageing and disease, intrinsic dynamic of control mechanism changes, destroying many healthy regulatory processes, that can result in pathologically low physiological complexity (here measured by HFD)[4,5].

The algorithm used here was a custom implementation of original Higuchi's algorithm[35] written in MATLAB and found on physionet website toolkit, was first adapted in Java programming language, and later implemented in GO, to increase calculation speed for on-cloud calculation. Per-lead HFD was computed on the raw, unfiltered waveform of each 10-second record; HFD was computed independently for each of the 12 standard ECG leads and averaged, removing any lead-selection dependency. HFD is scale-invariant and assumes no stationarity, supporting its use at this record length.

Outcome measures and statistical analysis

Mental-health outcomes were defined at subject level from ICD-10 codes, coded 1 if the code appeared in any admission: depression F32/F33; anxiety F40–F48; suicidality T14.91 and Z91.5 (attempt and self-harm only; ideation excluded). Antidepressant and lithium exposure were derived from prescription records. A sensitivity analysis adding ICD-9 codes is reported in the Discussion.

For the cluster replication, record-level features were averaged per subject before assignment (N = 35,980); associations between cluster membership and outcomes were estimated by logistic regression with age and sex as covariates (complete cases N = 35,706), reporting odds ratios with 95% CIs. For the nonlinear extension (N = 123,932), 12-lead mean HFD was compared between outcome groups using Cohen's d[40]; discrimination was assessed as AUC with bootstrap CIs.

Code and data availability

MIMIC-IV-ECG and MIMIC-IV Clinical Database are available from PhysioNet[41] under a credentialed data use agreement. All analysis code: https://github.com/yulimjchoi/fair-mind-ecg-depression-works.

Results

Cohort characteristics

Table 1 reports the composition of the four assigned profiles (N = 35,706 linked to the clinical cohort). The profiles differ on age — LRS (62.1 years) and HP (61.4) are older than HRS (57.7) and MP (56.8), a spread of roughly five years — while sex composition (38.4–42.2% male) and BMI (28.7–29.0) are close to flat. Age therefore carries the main confounding weight and is central to the adjusted models below.

Table 1 here, please

Table 1. Cohort characteristics by assigned autonomic profile. Outcomes defined from ICD-10 codes; antidepressant and lithium from prescription records. N = 35,706 subjects linked to the clinical cohort. BMI was available for 23,919 (67.0%) of these; BMI means are computed on available data.

Cluster assignment

Under self-referenced fixed-centroid assignment, the four clusters comprised MP 6,615 (18.4%), HRS 14,228 (39.5%), LRS 10,985 (30.5%), and HP 4,152 (11.5%) of 35,980 subjects. This distribution is broadly consistent with Weber (MP 23.7%, HRS 32.7%, LRS 33.9%, HP 9.8%), with the main difference being a shift from LRS toward HRS — consistent with higher baseline heart rates in the hospital population. Assignment confidence was adequate: the ambiguity gap (distance to second-nearest centroid relative to nearest) fell below 0.05 for 4.95% of subjects and below 0.10 for 9.53%.

Figure 4 here, please

Figure 4. PCA projection of MIMIC subjects assigned to Weber's four clusters under self-referenced standardization. Points subsampled to 6,000 per cluster for display.

Cluster profiles

Figure 5 compares the ten-feature profiles across both cohorts. The HRV-magnitude features (RMSSD, pNN20, pNN50, MAD) reproduce the Weber ordering across all four profiles — HP highest, HRS and LRS lowest, MP intermediate — with cluster spread in MIMIC equal to or larger than Weber's (spread ratio 1.06–2.02). The reconstructed spectral features show the predicted compression: LFnu spread across clusters is 17.5 units in MIMIC against 38.5 in Weber

(ratio 0.45), consistent with the $R^2 = 0.30$ attenuation quantified in Methods. Breathing rate, derived from the 0.15–0.4 Hz band of the same tachogram rather than measured directly, separates LRS from HRS in both cohorts (0.32 vs 0.23 in MIMIC; 0.23 vs 0.15 in Weber). Within the two low-HRV clusters, heart rate is nearly identical (LRS 83.9 vs HRS 82.4 bpm), so the LRS–HRS distinction rests almost entirely on the reconstructed balance axis and breathing rate.

Figure 5 here, please

Figure 5. Cluster profiles across ten HRV features, min–max scaled within each cohort. (a) Weber et al.[30] measured centroids. (b) MIMIC-IV-ECG assigned-cluster means; shaded region marks reconstructed spectral proxies. Raw ranges shown beneath each feature.

Association with depression and suicidality

Depression prevalence was highest in LRS (27.8%) and lowest in HP (22.1%), with the ranking LRS > HRS > MP > HP. In age- and sex-adjusted models, low-HRV membership (LRS + HRS) was associated with depression (OR 1.19, 95% CI 1.13–1.26), anxiety (1.22, 1.15–1.29), and antidepressant prescription (1.32, 1.26–1.38). HP was protective across all five outcomes (depression OR 0.79, 0.73–0.85; anxiety 0.73, 0.66–0.80; antidepressant 0.73, 0.68–0.78; lithium 0.48, 0.31–0.74).

Two findings diverged from Weber. The LRS–HRS separation within low HRV was modest (depression OR 1.08, 1.02–1.14; anxiety 1.08, 1.02–1.16; antidepressant 1.09, 1.04–1.15), and HP was protective rather than mildly maladaptive. For suicidality, the crude low-HRV association pointed protective (OR 0.84, 0.72–0.98), but age adjustment reversed the direction (1.14, 0.97–1.34) without reaching significance — consistent with suicidality concentrating in younger patients who are also more likely to fall in the high-HRV profiles. Figure 6 shows all thirty contrasts; Table 2 tabulates them.

Figure 6 here, please

Figure 6. Cluster–outcome associations. Odds ratios with 95% confidence intervals for three cluster contrasts and five outcomes, crude (grey circles) and adjusted for age and sex (black squares). Asterisks mark adjusted intervals excluding 1. N = 35,706.

Table 2 here, please

Table 2. Odds ratios by cluster contrast and outcome, crude and age/sex-adjusted. N = 35,706. Asterisk: 95% CI excludes 1.

Nonlinear extension

HFD was lower in depression (1.287 vs 1.330; d = −0.39) and markedly lower in suicidality (1.249 vs 1.327; d = −0.70), with the direction consistent across all 12 leads (Figure 7). No lead showed a reversal. The reduction was not specific to depression: anxiety-only subjects showed a comparable decrease (d = −0.42), depression-only −0.37, and subjects meeting both definitions −0.43. Each SD increase in HFD was associated with 33% lower odds of depression (OR 0.67, 0.66–0.69) and 43% lower odds of suicidality (0.57, 0.53–0.61). Added to age and sex, HFD raised discrimination for depression from AUC 0.555 to 0.634; for suicidality the demographic

model was already strong (0.783) and HFD added little (0.814), so the suicidality result is reported as an effect size rather than as discrimination.

Figure 7 here Please

Figure 7. Per-lead Cohen's d for depression, suicidality, and anxiety across all 12 standard ECG leads. All leads show consistent effects with no reversal, validating multi-lead averaging as the primary measure.

Discussion

Reproduction and divergence

There are several important findings from our research presented in this section.

The HRV-magnitude axis reproduced: low-HRV membership was associated with depression (OR 1.19, 95% CI 1.13–1.26), anxiety (1.22, 1.15–1.29) and antidepressant prescription (1.32, 1.26–1.38), and HP was protective (depression OR 0.79, 0.73–0.85). The cluster ranking LRS > HRS > MP > HP held. This replicates Weber's core finding in a hospital population, with a different outcome instrument and a different standardization frame, which is the strongest evidence that the magnitude effect is not an artefact of any single design choice.

Two features of the original report did not reproduce. The LRS–HRS separation within low HRV was modest (depression OR 1.08, 1.02–1.14; anxiety 1.08, 1.02–1.16), and High Parasympathetic cluster (HP) was protective rather than mildly maladaptive. We offer a measurement explanation for the first and a coordinate-system explanation for the second, and note that the two are not independent.

The axis that distinguishes LRS from HRS is autonomic balance, which in our feature space is carried almost entirely by the reconstructed spectral variables (R^2 0.30–0.47). The attenuation was quantified before the result was known: applying the reconstruction to Weber's own centroids compresses the LFnu spread from 38.5 to 19.2 units, almost exactly the halving that the explained variance predicts; the observed spread across MIMIC assigned clusters was 17.5 (Figure 5). The observed pattern—magnitude strong, balance weak—is therefore what attenuation of this size would produce even if the balance effect were entirely real. We cannot separate a genuinely weaker balance effect from an attenuated measurement of a real one, and do not claim to; long-record data are required to resolve it.

The HP reversal has a different origin. Under self-referenced standardization, HP denotes high parasympathetic tone within a hospital population—not the same physiological group as HP among community volunteers. Relatively preserved vagal function in an older, hospitalized cohort plausibly indexes lower illness burden, which would make HP protective here regardless of what it means in a volunteer sample. The Weber-scaler contrast is the strongest evidence for reading profiles this way: standardizing MIMIC subjects on Weber's pooled statistics collapses 75.1% of them into LRS and leaves HRS with 2.0%, because the hospital population sits so far below the volunteer sample on the magnitude axis that nearly everyone falls closest to the lowest-*HRV centroid*. Self-referencing restores the four-cluster structure (Figure 4) by placing each

subject relative to their own cohort. The divergence is a shift, not an inversion: in Weber's data the protective pole is HRS, lowest on essentially every depression and suicidality item; in ours it is HP. The protective profile moved from a sympathetic-dominant low-HRV pattern in an unmedicated community sample to a high-HRV parasympathetic pattern in a medicated hospital sample.

The generalizable claim, and in our view the most transferable conclusion in the paper, is that an *autonomic profile is not portable without its coordinate system*. A profile defined by K-means on one population's feature distribution acquires its meaning from that distribution; applied to a population with a different distribution, the same label denotes a different physiological group. This is not a limitation of Weber's method but a property of any centroid-based profile, and it means that the measurement and standardization context has to travel with the profile if the label is to mean the same thing across cohorts.

One further observation belongs here. Covariate adjustment is a precondition for interpreting autonomic profiles, and the suicidality contrast shows it within a single dataset: the low-HRV association points protective when crude (OR 0.84, 0.72–0.98) and reverses direction once age is controlled (1.14, 0.97–1.34). LRS is the oldest cluster, and documented suicidality falls with age — negative confounding that an unadjusted comparison would have misread as protection. The adjusted estimate does not reach significance, and we read the cluster-based suicidality contrast as inconclusive; the fractal measure examined below separates the same outcome more sharply, though as an effect size rather than as an improvement in discrimination.

Outcome definitions and confounders

Two features of the outcome data affect how the associations should be read. The first concerns diagnostic code composition. MIMIC-IV spans the ICD-9 to ICD-10 transition, and the choice of which codes constitute "depression" is not neutral. With ICD-10 F32/F33 alone, prevalence in the replication cohort is 26.2%. Adding the ICD-9 major depressive disorder codes (296.2x, 296.3x) raises it to 29.2%. Adding ICD-9 311 — "depressive disorder, not elsewhere classified", a residual category — raises it to 51.3%: that single code doubles the depression-positive population. The cluster ranking LRS > HRS > MP > HP holds under all three definitions, and the low-HRV depression OR is stable (1.19–1.27), so the association itself is robust to the choice. What is not robust is the population being described: half of routinely coded depression sits in a category no questionnaire instrument would produce. The question of which codes belong in an outcome definition — and how that choice should be documented so that a profile computed on one cohort can be meaningfully compared with another — is one we return to in the companion work on semantic infrastructure. Our suicidality outcome is attempt and self-harm only — ideation codes were deliberately excluded — so it measures a different construct from Weber's questionnaire-based ideation items.

The second concerns medication. Antidepressants reduce HRV pharmacologically, so the low-HRV-depression association mixes indication with drug effect; some part of it may travel through treatment rather than the depressive state. Weber excluded every participant on psychopharmacological medication with potential HRV effects; we retain them, and 44% of our cohort carry an antidepressant prescription. Medication-driven HRV reduction can relocate

treated patients across cluster boundaries in our data in a way excluded by design from theirs, and is a plausible contributor to both divergences above. Two observations argue against a purely medication-driven reading. Lithium showed essentially null associations apart from the protective HP contrast, behaving as a negative control consistent with its bipolar indication, for which a distinct pattern of HRV alteration has been described[42]. And the HFD reduction is smaller, not larger, among medicated depressed subjects (d -0.31 vs -0.39 overall), which is the opposite of what a drug effect on cardiac complexity would produce.

The complexity extension

Human physiology is exemplary complex systems dynamics. It can be described by statistical physics approach, leading to better understanding of how and why certain pathologies develop. The first theoretical studies of the healthy heartbeat discovered that physiological systems combine organization (order) and variability (disorder), rather than being simply orderly. This healthy state exhibits hierarchical, long-range organization, which is enabled by scale-invariance or self-similarity[5]. This 'organized variability' is the characteristic signature of a natural, healthy physiological process in which a fractal system exhibits a type of 'roughness' or irregularity that remains statistically similar across a wide range of scales[10]. This underlying scale-invariant mechanism allows for a wide range of interindividual variability and aligns with contemporary models of biological self-regulation, such as the Active Inference model (predictive coding)[43–45]. Healthy complexity is usually interpreted as an organism's natural ability to adapt to continuous internal and external changes. With healthy ageing, usual levels of physiological complexity slightly present that the overall dynamic is 'slowing down', making the system less adaptable, as shown in ref. 46. Contrary to that natural ageing trend, disease often causes an abrupt breakdown of this fractal organization, meaning the physiological system becomes severely disrupted. Goldberger calls that 'central paradox': many illnesses, despite being labeled 'disorders', exhibit strikingly predictable (periodic) behavior[5]. This 'stereotypy of disease', where the pathological pattern is rigid and regular (very predictable), is a key concept for clinicians and is the very opposite of healthy variability[4,6]. This pathological loss of complexity is termed 'decomplexification'[5]. In other words, the measurable loss of physiological complexity, which leads to more predictable, rigid and periodic behavior, is the mathematical counterpart to clinical stereotypy.
In our research HFD is lower in depression (1.287 vs 1.330, d -0.39) and markedly lower in suicidality (1.249 vs 1.327, d -0.70), with the same direction in all twelve leads. The direction agrees with earlier nonlinear ECG work in depression and suicide risk[47–50], although those studies used RR-interval measures on longer recordings. Because it is computed on the raw waveform rather than on the RR-interval series, it draws on a different property of the same ten-second record — signal complexity rather than beat-to-beat variability. This closes a loop with our own criticism of the replication: averaging across all twelve leads removes the lead-selection problem entirely. The replication could not avoid that problem—Weber does not document which lead was used, so we had to fix one—whereas the extension is not exposed to it at all.

Two estimator properties support use at this record length. HFD is scale-invariant, and it assumes no stationarity—which matters given the position taken in the Introduction that electrophysiological signals are nonstationary by nature. Discrimination is on the scale of an

auxiliary signal, not a diagnostic. For depression, HFD raises AUC from 0.555 for age and sex alone to 0.634. For suicidality, HFD alone (0.706) does not reach the demographic model (0.783) and adds about 0.03 when combined, so the suicidality finding rests on its effect size, not on discrimination. That the demographic model already performs this well is itself a consequence of the outcome definition: attempt and self-harm, unlike ideation, concentrate sharply in younger patients. We therefore read HFD as a population-level stratification signal rather than as an individual screening test.

Methodological observations on the original study

Weber released their analysis code, and we do not claim their methods are undocumented in general. What the paper and the released code do not provide is which ECG lead was used for HRV extraction, the per-variable missingness underlying the imputation step, and the ECG processing pipeline itself. Those three are what a full end-to-end reproduction would need, and correspondence with the authors did not supply them. The lead question is the sharpest: every downstream feature depends on it, and we found the same omission in several other ECG-based mental health studies, which suggests a field-level reporting gap rather than an isolated one.

Two design choices merit comment as notes for future iterations rather than criticisms of work we regard as an important advancement in this field. First, features uncorrelated with the outcomes were discarded before clustering. The feature space in which the clusters were derived was therefore chosen using the outcomes those clusters were later tested against, so the reported cluster-symptom associations are not fully independent of the selection step and some upward bias is expected. This does not undermine the finding—the associations are modest, the procedure is stated plainly, and our reproduction inherits their feature set without performing any selection of its own—but the published effect sizes should be read as upper bounds.

Second, missing values were imputed by mean substitution[51,52]. K-means places each centroid at the mean of its assigned points, so imputed values sitting exactly at the sample mean form an artificial dense region at the center of the feature space and pull centroids toward it. Since per-variable missingness is not reported, a reader cannot bound how much of the published geometry this accounts for. Our own reproduction, obtained without imputation in a different cohort, recovers the magnitude axis, which is some independent reassurance that the core structure is not an imputation artefact.

That reassurance runs in one direction only, and the converse question also stands. What might be very large influence on overall results was the missing data imputation, before K-means performance; what is known to distort the original distribution among the data. The question that can be additionally asked is how that further affects the extracted individual clusters and their validity; the differences that our partial replication demonstrated could be a simple consequence of that missing values imputation with averaged values.

Limitations and future directions

The defining constraint of our research is the record length. A 10 s ECG cannot support frequency-domain HRV estimation at all—LF and LFnu were undefined in every record we

processed—and the time-domain indices it does yield rest on roughly a dozen intervals, far short of the five-minute standard[53]. The resulting floor effect is visible in the features themselves: pNN50 is exactly zero in 68.9% of records and pNN20 in 40.9%, so two of the ten clustering variables carry little information at this length. Weber computed HRV on recordings of at least 20 s (mean 24.23 ± 19.34), using a 10 s strip only as the device-derived control marker; excluding sub-20 s records was the single largest step in their exclusion cascade. Our records are shorter than the ones they discarded as unfit. Ultra-short surrogates for short-term HRV have been evaluated repeatedly and found acceptable only for a subset of time-domain indices[54–56]. We would rather frame this as the defining condition of the study than as a caveat appended to it: such records are what routine care produces, at a scale no research protocol will match, and the question of what survives the record length is worth answering on its own terms. Our answer is that the magnitude axis and the fractal measure survive, and the balance axis does not.

Source-data limitations follow from the cohort. It is hospital-based, so absolute prevalences are far above population values and the comparison group is itself unwell; diagnoses are lifetime with no temporal alignment to the ECG, permitting associational language only; ICU status, cardiovascular comorbidity and medication are uncontrolled; outcomes come from billing codes rather than a structured instrument; and BMI is missing for 33.5% of subjects. A further 8.7% of the replication cohort had no diagnostic record of any kind and were therefore coded negative on every outcome, which biases the odds ratios toward the null. For the fractal measure, the effect size also varied with admission route — from $d = -0.63$ in emergency presentations to $+0.10$ in planned observation admissions — so confounding by acuity cannot be excluded. On comparing magnitudes with the original, the odds scale is the right one: code-based ascertainment in a hospital population gives depression prevalences well above those of the CIDI-SF in a volunteer cohort (26.2% against Weber's 20.4–23.1%), so percentage-point spreads between cohorts with such different baseline risks are not interpretable. Effect sizes in our data—OR 1.1–1.3 for the profile contrasts, d 0.4–0.7 for HFD—are consistent with an auxiliary, population-level stratification signal rather than an individual diagnostic.

Two directions follow. Long-record cohorts are needed where the reconstructed spectral indices can be checked against measured ones and where entropy- and DFA-based measures become viable. Beyond that, what travels between studies is not a prevalence but a structure, and what makes a structure travel is an explicit record of the population frame, the standardization and the measurement constraints under which it was computed. Systematic specification of feature definitions, computation parameters and cohort-level coordinate systems—the infrastructure needed to make autonomic profiles portable across sites—is the subject of a companion paper on semantic infrastructure for autonomic biomarker data.

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Ethics

MIMIC-IV and MIMIC-IV-ECG are de-identified and are distributed by PhysioNet under a credentialed data use agreement; their collection was approved by the institutional review board of the Beth Israel Deaconess Medical Center with a waiver of informed consent. Access was obtained through credentialed PhysioNet accounts held by the authors, and no further ethical approval was required for this secondary analysis. [authors: confirm wording against the current PhysioNet DUA]

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Author Contributions

I.C.: Conceptualisation, Methodology, Data curation, Formal analysis, Software, Writing — original draft and revision, Project administration, Funding acquisition. Y.C.: Software, Data curation, Formal analysis, Validation. M.Č.R.: Conceptualization, Methodology, HFD calculation, Writing — original draft and revision, Supervision.

Competing interests

The authors declare no competing interests.

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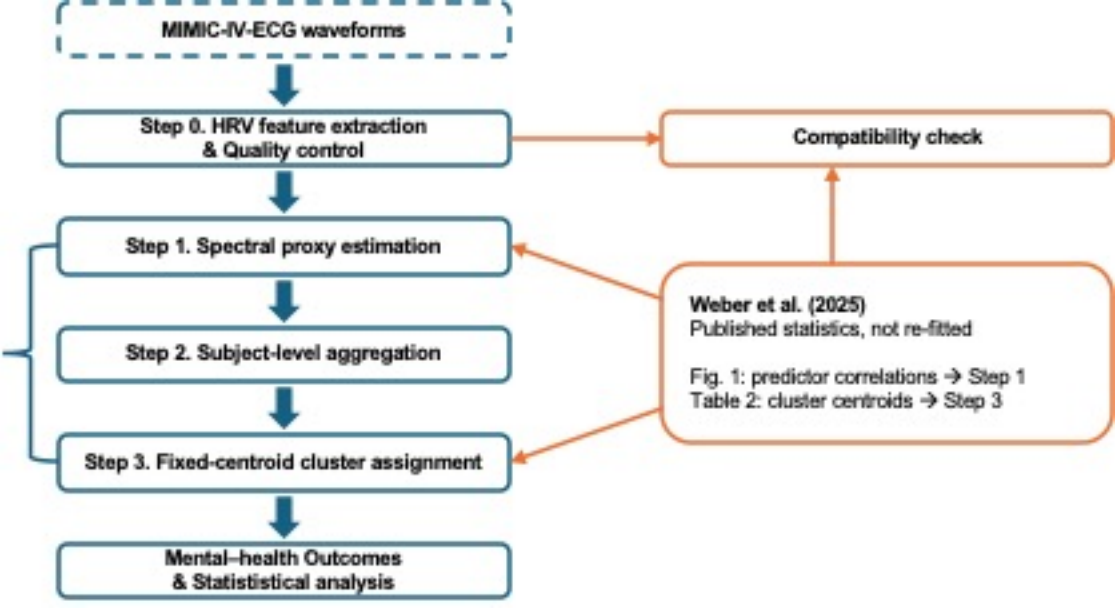
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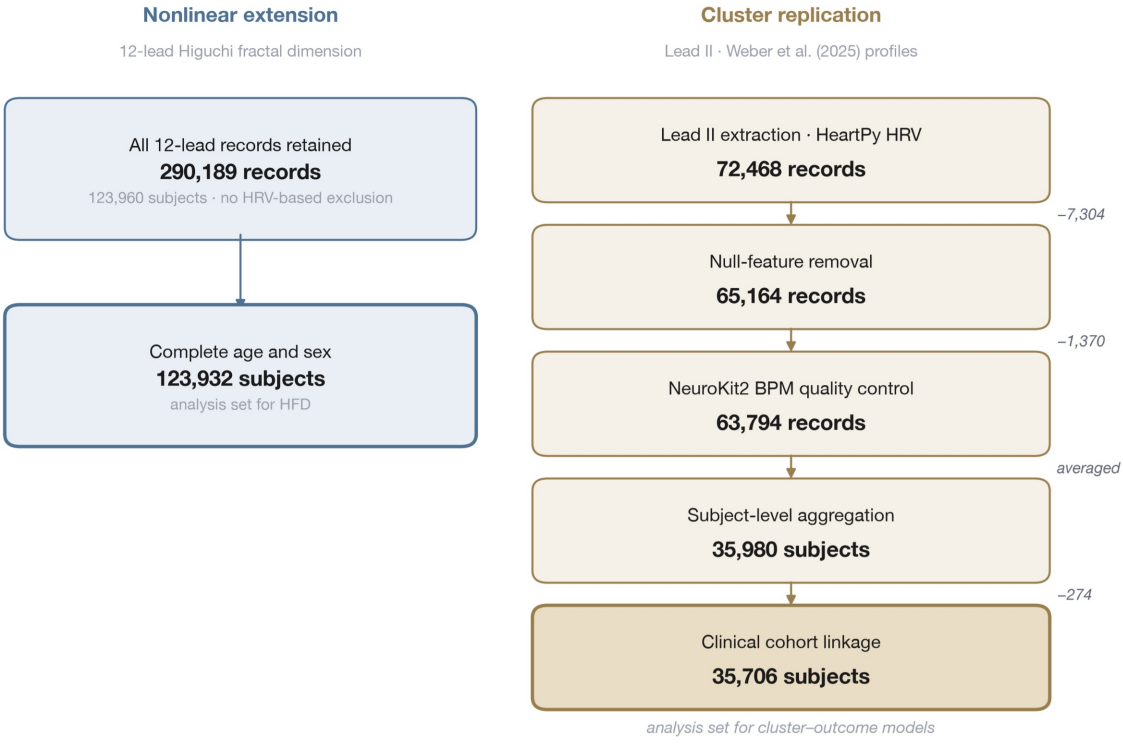
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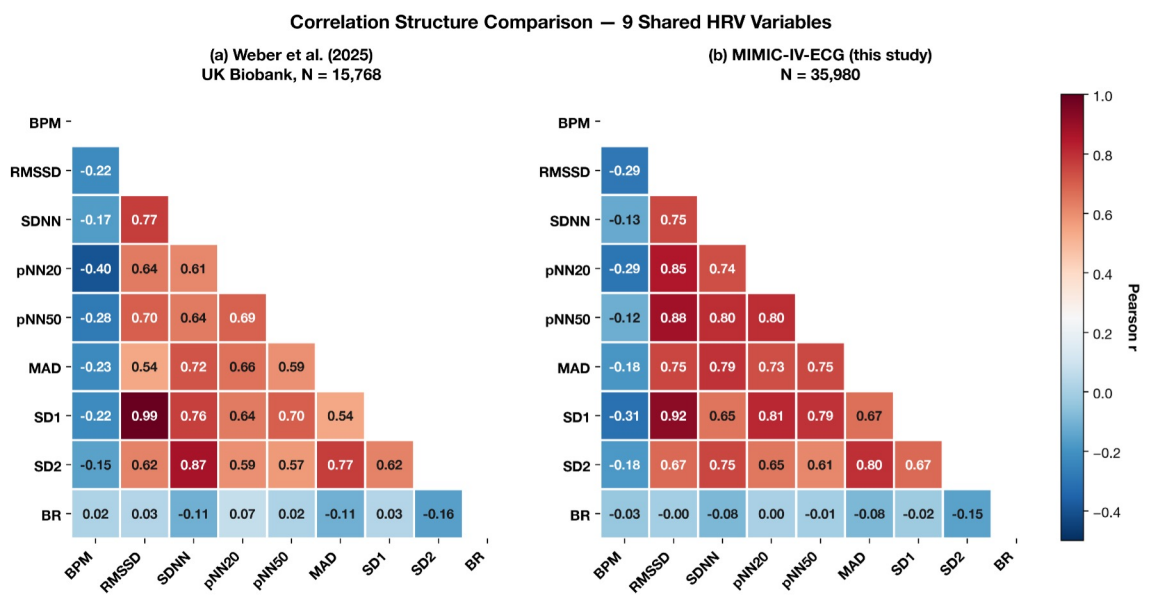
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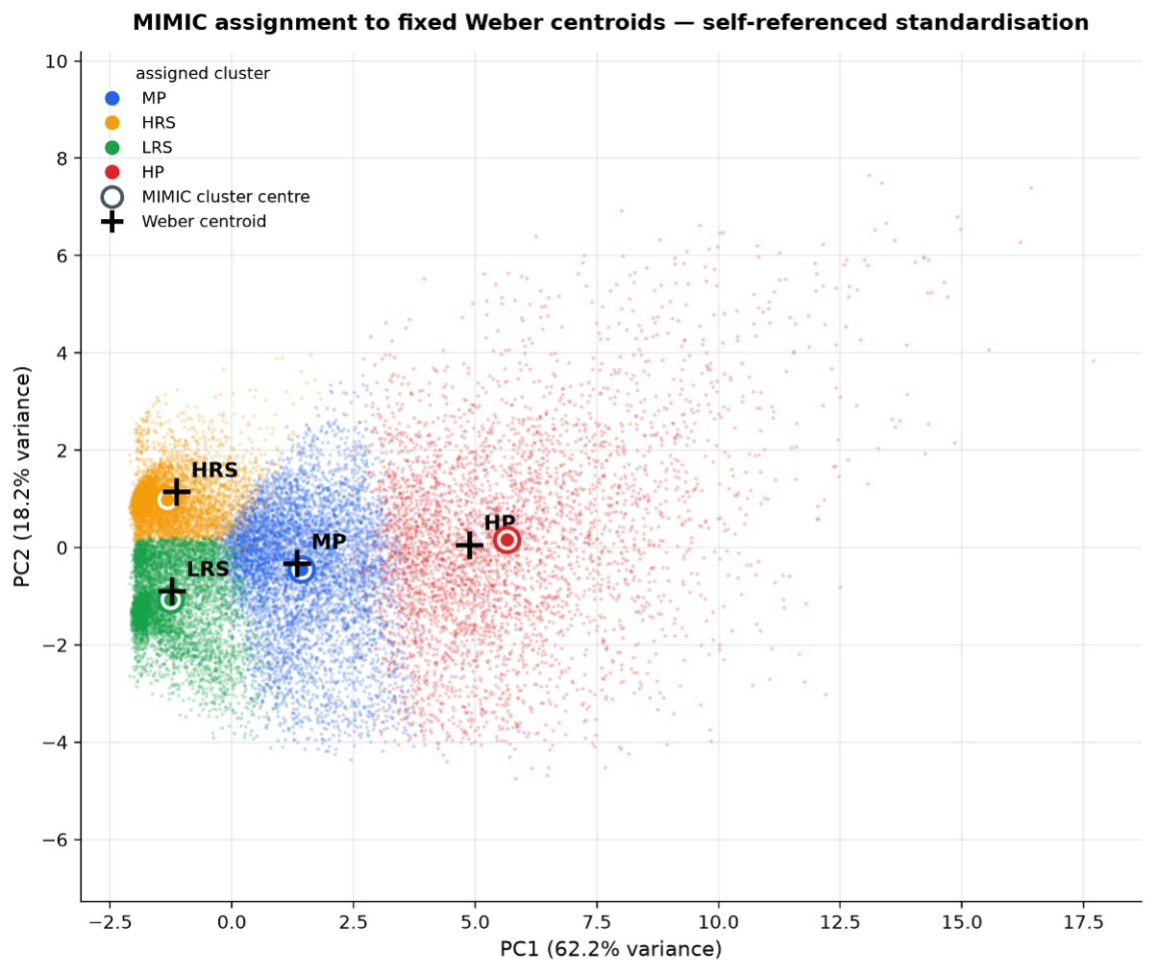
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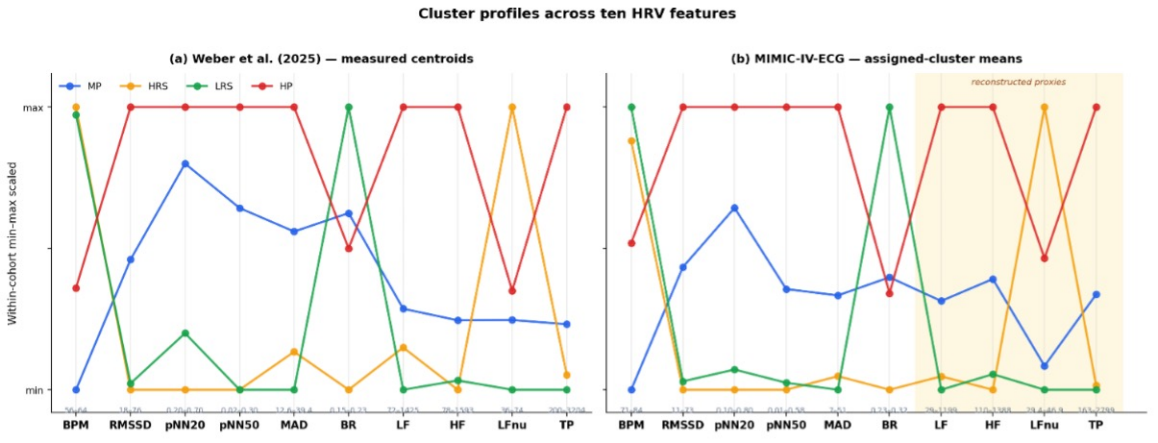

MIMIC-IV-ECG waveforms
Step 0. HRV feature extraction & Quality control
Compatibility check
Step 1. Spectral proxy estimation
Step 2. Subject-level aggregation
Step 3. Fixed-centroid cluster assignment
Mental–health Outcomes & Statistical analysis
Weber et al. (2025)
Published statistics, not re-fitted
Fig. 1: predictor correlations → Step 1
Table 2: cluster centroids → Step 3

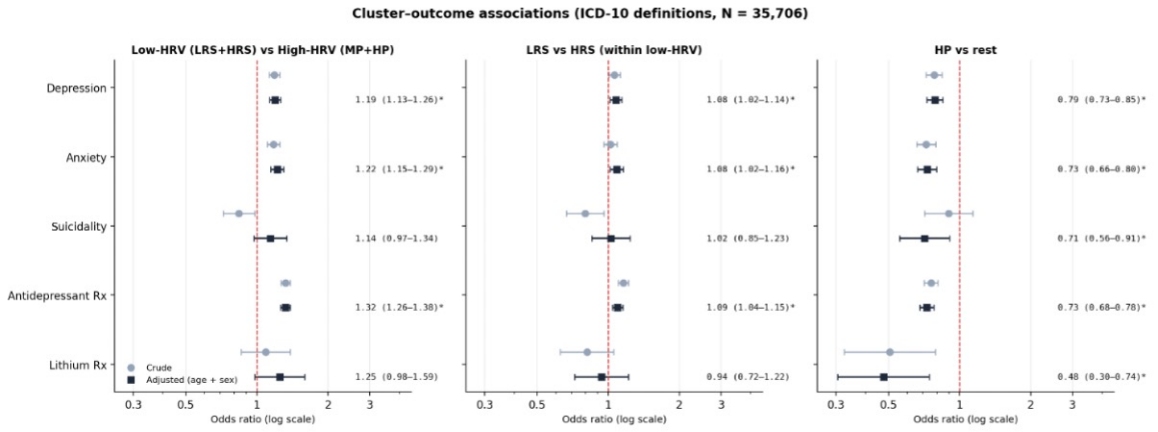
MIMIC-IV-ECG · MIMIC-IV Clinical Database

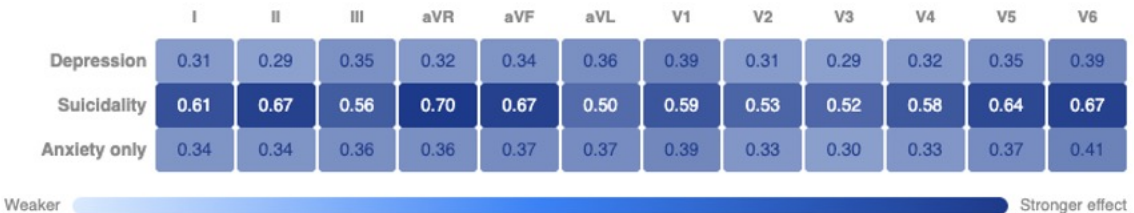



Correlation Structure Comparison — 9 Shared HRV Variables
(a) Weber et al. (2025)
UK Biobank, N = 15,768
(b) MIMIC-IV-ECG (this study)
N = 35,980
BPM
RMSSD
SDNN
pNN20
pNN50
MAD
SD1
SD2
BR
-0.22
-0.17 0.77
-0.40 0.64 0.61
-0.28 0.70 0.64 0.69
-0.23 0.54 0.72 0.66 0.59
-0.22 0.99 0.76 0.64 0.70 0.54
-0.15 0.62 0.87 0.59 0.57 0.77 0.62
0.02 0.03 -0.11 0.07 0.02 -0.11 0.03 -0.16
-0.29
-0.13 0.75
-0.29 0.85 0.74
-0.12 0.88 0.80 0.80
-0.18 0.75 0.79 0.73 0.75
-0.31 0.92 0.65 0.81 0.79 0.67
-0.18 0.67 0.75 0.65 0.61 0.80 0.67
-0.03 -0.00 -0.08 0.00 -0.01 -0.08 -0.02 -0.15
Pearson r
1.0
0.8
0.6
0.4
0.2
0.0
−0.2
−0.4


MIMIC assignment to fixed Weber centroids — self-referenced standardisation
assigned cluster
MP
HRS
LRS
HP
MIMIC cluster centre
Weber centroid
HRS
MP
HP
LRS
PC2 (18.2% variance)
PC1 (62.2% variance)
10
8
6
4
2
0
−2
−4
−6
−2.5
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5


Cluster profiles across ten HRV features
(a) Weber et al. (2025) — measured centroids
(b) MIMIC-IV-ECG — assigned-cluster means
MP
HRS
LRS
HP
reconstructed proxies
Within-cohort min-max scaled
max
min
BPM
RMSSD
pNN20
pNN50
MAD
BR
LF
HF
LFnu
TP


Cluster–outcome associations (ICD-10 definitions, N = 35,706)
Low-HRV (LRS+HRS) vs High-HRV (MP+HP)
LRS vs HRS (within low-HRV)
HP vs rest
Depression
Anxiety
Suicidality
Antidepressant Rx
Lithium Rx
1.19 (1.13–1.26)*
1.22 (1.15–1.29)*
1.14 (0.97–1.34)
1.32 (1.26–1.38)*
1.25 (0.98–1.59)
1.08 (1.02–1.14)*
1.08 (1.02–1.16)*
1.02 (0.85–1.23)
1.09 (1.04–1.15)*
0.94 (0.72–1.22)
0.79 (0.73–0.85)*
0.73 (0.66–0.80)*
0.71 (0.56–0.91)*
0.73 (0.68–0.78)*
0.48 (0.30–0.74)*
Crude
Adjusted (age + sex)
0.3
0.5
1
2
3
Odds ratio (log scale)


I
II
III
aVR
aVF
aVL
V1
V2
V3
V4
V5
V6
Depression
0.31
0.29
0.35
0.32
0.34
0.36
0.39
0.31
0.29
0.32
0.35
0.39
Suicidality
0.61
0.67
0.56
0.70
0.67
0.50
0.59
0.53
0.52
0.58
0.64
0.67
Anxiety only
0.34
0.34
0.36
0.36
0.37
0.37
0.39
0.33
0.30
0.33
0.37
0.41
Weaker
Stronger effect

Profile	N	%	Age, mean	Male, %	BMI, mean	Depression, %	Anxiety, %	Suicidality, %	Antidepressant, %	Lithium, %
MP	6,545	18.3	56.8	38.4	28.8	25.0	17.8	2.7	40.0	1.1
HRS	14,116	39.5	57.7	42.2	28.7	26.6	18.5	2.2	44.5	1.1
LRS	10,932	30.6	62.1	41.4	29.0	27.8	18.8	1.8	48.1	0.9
HP	4,113	11.5	61.4	40.2	28.7	22.1	14.0	1.9	38.1	0.5
All	35,706	100	59.3	41.0	28.8	26.2	17.9	2.1	44.0	0.9

Contrast	Outcome	Crude OR (95% CI)	Adjusted OR (95% CI)	Sig.
Low-HRV (LRS+HRS) vs High-HRV (MP+HP)	Depression	1.19 (1.12–1.25)	1.19 (1.13–1.26)	*
Low-HRV (LRS+HRS) vs High-HRV (MP+HP)	Anxiety	1.18 (1.11–1.25)	1.22 (1.15–1.29)	*
Low-HRV (LRS+HRS) vs High-HRV (MP+HP)	Suicidality	0.84 (0.72–0.98)	1.14 (0.97–1.34)	
Low-HRV (LRS+HRS) vs High-HRV (MP+HP)	Antidepressant Rx	1.32 (1.26–1.38)	1.32 (1.26–1.38)	*
Low-HRV (LRS+HRS) vs High-HRV (MP+HP)	Lithium Rx	1.09 (0.86–1.38)	1.25 (0.98–1.59)	
LRS vs HRS (within low-HRV)	Depression	1.06 (1.00–1.12)	1.08 (1.02–1.14)	*
LRS vs HRS (within low-HRV)	Anxiety	1.02 (0.96–1.09)	1.08 (1.02–1.16)	*
LRS vs HRS (within low-HRV)	Suicidality	0.80 (0.67–0.96)	1.02 (0.85–1.23)	
LRS vs HRS (within low-HRV)	Antidepressant Rx	1.16 (1.10–1.22)	1.09 (1.04–1.15)	*
LRS vs HRS (within low-HRV)	Lithium Rx	0.81 (0.63–1.05)	0.94 (0.72–1.21)	
HP vs rest	Depression	0.78 (0.72–0.84)	0.79 (0.73–0.85)	*
HP vs rest	Anxiety	0.72 (0.66–0.79)	0.73 (0.66–0.80)	*
HP vs rest	Suicidality	0.90 (0.71–1.14)	0.71 (0.56–0.91)	*
HP vs rest	Antidepressant Rx	0.76 (0.71–0.81)	0.73 (0.68–0.78)	*
HP vs rest	Lithium Rx	0.51 (0.33–0.79)	0.48 (0.31–0.74)	*

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table2.jpg
- Table1.jpg