




ORIGINAL RESEARCH

Resting Heartbeat Complexity Predicts All-Cause and Cardiorespiratory Mortality in Middle- to Older-Aged Adults From the UK Biobank

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BACKGROUND: Spontaneous heart rate fluctuations contain rich information related to health and illness in terms of physiological complexity, an accepted indicator of plasticity and adaptability. However, it is challenging to make inferences on complexity from shorter, more practical epochs of data. Distribution entropy (DistEn) is a recently introduced complexity measure that is designed specifically for shorter duration heartbeat recordings. We hypothesized that reduced DistEn predicted increased mortality in a large population cohort.

METHOD AND RESULTS: The prognostic value of DistEn was examined in 7631 middle-older-aged UK Biobank participants who had 2-minute resting ECGs conducted (mean age, 59.5 years; 60.4% women). During a median follow-up period of 7.8 years, 451 (5.9%) participants died. In Cox proportional hazards models with adjustment for demographics, lifestyle factors, physical activity, cardiovascular risks, and comorbidities, for each 1-SD decrease in DistEn, the risk increased by 36%, 56%, and 73% for all-cause, cardiovascular, and respiratory disease-related mortality, respectively. These effect sizes were equivalent to the risk of death from being >5 years older, having been a former smoker, or having diabetes mellitus. Lower DistEn was most predictive of death in those <55 years with a prior myocardial infarction, representing an additional 56% risk for mortality compared with older participants without prior myocardial infarction. These observations remained after controlling for traditional mortality predictors, resting heart rate, and heart rate variability.

CONCLUSIONS: Resting heartbeat complexity from short, resting ECGs was independently associated with mortality in middle- to older-aged adults. These risks appear most pronounced in middle-aged participants with prior MI, and may uniquely contribute to mortality risk screening.

Key Words: autonomic nervous system ■ complexity ■ distribution entropy ■ mortality ■ resting ECG

With the exponential growth in noninvasive, passive monitoring of physiological function, there is burgeoning interest in extracting prognostic information from heart activity.¹ Prior studies have relied on prolonged periods lasting hours² to days,¹ or depended on interventions such as exercise (heart rate recovery or exercise capacity) to derive

prognostic information. However, exercise testing has not always been feasible because of contraindications in physical limitations or comorbidities. In fact, a meta-analysis of large randomized controlled trials found questionable improvement in the prediction of health outcomes using exercise ECGs.³ Thus, convenient passive monitoring of resting heart activity that

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CLINICAL PERSPECTIVE

What Is New?

- Distribution entropy—a measure of heartbeat complexity derived from a 2-minute, resting ECG—predicts mortality independently of resting heart rate and heart rate variability in middle- to older-aged adults.

What Are the Clinical Implications?

- These risks appear most pronounced in middle-aged patients with prior myocardial infarction, and may uniquely contribute to routine mortality risk screening.
- Our findings have the potential to be scaled-up to remote monitoring in wearable devices, and opens up a new avenue of research for resting heartbeat complexity as a vulnerability marker for stress reactivity.

Nonstandard Abbreviations and Acronyms

DistEn	distribution entropy
HRV	heart rate variability
NHS	National Health Service
RHR	resting heart rate
RMSSD	root mean square of successive differences
RRI	RR interval
TDI	Townsend deprivation index
UKB	UK Biobank

is not tightly coupled to a patient's effort is becoming increasingly desirable.

In the past 2 decades, novel analytic tools derived from nonlinear dynamics have harnessed information imbedded in spontaneous physiological fluctuations; these are usually not obtainable through traditional, nonlinear signal processing approaches such as means/medians or frequency- and time-domain analysis of heart rate variability (HRV). One of the predominant nonlinear methods is entropy, a measure of unpredictability or “complexity” of signals.^{4–6} Many have observed a loss/reduction of complexity in disease states,^{6–10} aging, frailty,^{5–7} and death.^{11,12} Population screening tools that can guide clinical decisions demand convenience. Unfortunately, the study of complexity of physiological systems is data intensive. This is further exacerbated by the short time available in most

standard clinical measurements of the heart, eg, during routine screening ECGs at rest.

A recently introduced distribution entropy (DistEn) measure considers a more integrated feature in the fluctuation patterns, thus allowing a reliable assessment of complexity from short recordings. It may fundamentally address the major limitation associated with short physiological recordings.^{13,14} Recent studies have demonstrated its performance in quantifying the impact of diseases on physiological control.^{13–17} However, large-scale longitudinal studies are required to determine the prognostic value of DistEn. We tested for the first time the association between DistEn derived from short, 2-minute resting ECGs and mortality. We assessed whether this was independent of baseline comorbidities and traditional indicators of autonomic function, including RR interval (RRI), resting heart rate (RHR), conventional time-domain HRV, and mean arterial pressure (MAP), in a large cohort from the UK Biobank (UKB).^{18–20}

METHODS

Study Participants

UKB is a large-scale biomedical database and research resource containing genetic, lifestyle, and health information from half a million UK participants. Between late 2009 and 2010, 8039 participants from across the United Kingdom recruited to the UKB undertook a 2-minute resting ECG.²¹ During this baseline assessment, participants also reported their demographics, lifestyle, medical conditions, and medications taken. Individuals were followed up until early 2018, the most up-to-date recording for mortality before data analysis on December 1, 2019. The UKB received National Research Ethics Approval and participants gave written informed consent. This study was conducted under the terms of UKB access for project 40556, and Partners HealthCare institutional review board approval. The data that support the findings of this study are available from the corresponding author on reasonable request.

Preprocessing and Quality Control of Resting ECGs

Resting ECG data collection lasted 2 minutes with the patient in a seated position. Preprocessing steps are summarized in Figure 1A. Under resting conditions, 4 ECG electrodes were placed on the right and left antecubital fossa and wrist; a 3-lead (leads I, II, and III) ECG recording (AM-USB 6.5, Cardiosoft v6.51) at 500 Hz was taken during 2 minutes at rest and stored in xml format by Cardiosoft. Normal R waves were detected using the modified Aristotle algorithm of QRS detection.^{22,23} RRIs >2s or <0.428s [RHR in beats per

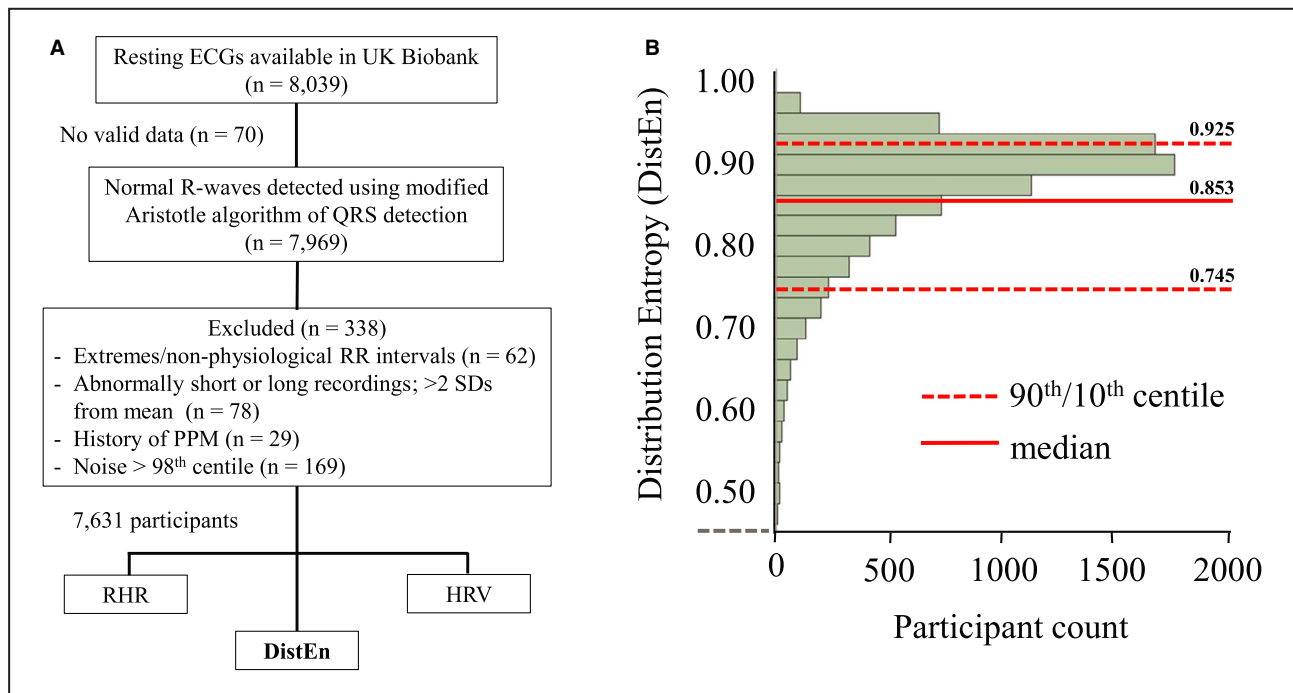


Figure 1. Flowchart of analytical approach and distribution of entropy (DistEn) distribution.

A, Analytic approach for R-wave selective and preprocessing of resting ECGs. **B**, DistEn with median (solid line) and 90th/10th percentiles (upper and lower dashed lines, respectively) by participant count. HRV indicates heart rate variability; PPM, permanent pacemaker; and RHR, resting heart rate.

minute [bpm] <30 or >140] recordings ($n=62$) were excluded from analysis. The majority of records tightly coalesced around the mean duration of 117 seconds ($SD=6$ seconds). We excluded a small number of records ($n=78$) that were >2 SDs from the mean length as they were found to have multiple gaps and/or excess noise. In keeping with prior studies using UKB ECG records,^{24,25} we further removed recordings with artifacts. Noise level was determined by calculating the overall SD of a moving SD with a window length of 3 beats; an overall SD close to zero indicated minimal to no noise, whereas the 98th percentile of SDs was considered excessive and excluded ($n=169$). We excluded an additional 29 patients who were known to have had a pacemaker insertion procedure before ECG assessment. In total, we inspected 1 in 20 raw ECG tracings or RRI profiles at random to ensure quality control and appropriate RRI detection. Data from 7631 participants were entered for analysis (Figure 1A).

RHR and Time-Domain HRV Analysis

RHR in bpm was calculated as the inverse of the mean RRI in milliseconds multiplied by the number of milliseconds per minute (60×1000) for each recording. Using established criteria, the root mean square of successive differences (RMSSDs), SD of NN intervals, and percentage >5, 10, and 20 milliseconds for

differences between adjacent RRIs were calculated as measures of time-domain HRV.^{26,27}

DistEn for Heartbeat Complexity Analysis

A host of entropy measures for assessing physiological complexity have been established in the past decade; conceptually, they all share the same theoretical basis—the system is more complex (or unpredictable) if new information in its output (usually a time series) occurs at a higher rate. To assess such evolution of information in a time series, data are first reconstructed to a higher dimensional state space that is believed to best characterize the dynamic changes in the temporal structure of the fluctuations. A state, defined by a vector in the state space, renders new information if it appears far enough in distance from other states that already appear within the time series. With a threshold parameter for distance, approximate entropy and sample entropy essentially measure the log conditional probability that such a new state emerges.²⁸

For traditional entropy measures, data length of 10 minutes to hours have been used.^{9,12,29,30} If time series were short (eg, 2 minutes in this study), not even a single state would meet this stringent threshold criterion, resulting in a zero probability, and therefore an invalid result. This is a well-known limitation of parameter dependence where the number of states

that survive the threshold criterion can vary widely depending on the threshold parameter chosen. DistEn was developed specifically to handle short time series.^{13,15} It takes full advantage of between-states distances by measuring the distribution pattern instead of hard-coding them as within or beyond the threshold parameter. This strategy appears to be more nuanced because the distribution of the distance (but not the mean/median distance) clearly show different patterns among synthetic time series with different dynamical regimes.¹³ With its established statistical properties, and given the short length of these UKB resting ECGs, we decided to mainly utilize DistEn.

Algorithm for DistEn

For an RRI time series $x=x(i)$, $1 \leq i \leq N$, its m -dimensional state space reconstruction can be obtained by:

$$u_m(i) = \{x(i), x(i + \tau), \dots, x(i + (m - 1)\tau)\}, \quad (1)$$

where $1 \leq i \leq N - m\tau$; τ and m represent the time delay parameter and the dimension parameter, respectively. The Chebyshev distance between a pair of states $u_m(i)$, $u_m(j)$ can be calculated by:

$$d[u_m(i), u_m(j)] = \max_{0 \leq k \leq m-1} (|x(i+k\tau) - x(j+k\tau)|), \quad 1 \leq i, j \leq N - m\tau. \quad (2)$$

Next, a histogram approach with a fixed bin number B is used to estimate the empirical probability density function of the distance matrix $d[u_m(i), u_m(j)]$, $1 \leq i, j \leq N - m\tau$ except the main diagonal (i.e., $i=j$). Using $\{p_t, t=1, 2, \dots, B\}$ to denote the probability of each bin, DistEn is defined by the following formula:

$$\text{DistEn}(m, \tau, B) = -\frac{1}{\log_2(B)} \sum_{t=1}^B p_t \log_2(p_t) \quad (3)$$

Further graphical representation of these methods are shown in Figure S1. The parameters used were as follows: $m=3$, $\tau=1$, and $B=256$ based on our prior studies using similar data.¹³⁻¹⁵ We tested DistEn using a variety of parameters within recommendations and did not see meaningful effects on our results. Figure S2 presents simulation results showing the stability and consistency of DistEn results across data length and parameter selection. DistEn ranges theoretically between 0 and 1, with larger values indicating higher complexity. Figure S2A and S2B show ECG strips over 15 seconds for 2 participants with low and high DistEn but similar heart rate and mean RRI.

Mortality Outcomes

Our primary outcome was all-cause mortality obtained from death certificates within the UK National Health

Service (NHS) Information Center and the NHS Central Register for Scotland. All death certificate details were provided directly to the UKB. Primary cause of death was classified using *International Classification of Diseases, Tenth Revision (ICD-10)*, codes by trained personnel. Secondary outcomes of cause-specific mortality were grouped into cardiovascular- (I00-I99), respiratory- (J00-J99), and cancer- (C00-D48) related primary causes of death.

Assessment of Covariates

Demographics included age, sex, ethnicity, and education. Age at baseline assessment was calculated in years based on their dates of birth. Sex (men/women) and ethnicity were self-reported. Since the majority of participants self-identified as British or "white" European descent (94%), we included ethnicity as European and non-European. Education was college-level (yes/no). For lifestyle factors, we included BMI (calculated as weight [kg] divided by height squared [m²]), alcohol use (<3 drinks per week, ≥ 3 drinks per week), and smoking status (never, former, or current), physical activity (summed metabolic equivalent minutes per week for all activities derived by Cassidy et al³¹). Socioeconomic status was assessed using the Townsend deprivation index (TDI), calculated immediately before the participant joined UKB based on the preceding national census output areas. Each participant was assigned a score corresponding to the output area in which their postcode was located.

Comorbidities relevant to mortality were based on self-report and medications taken at baseline. These included cardiovascular diseases (CVDs), hypertension, high cholesterol, atrial fibrillation (AF)/arrhythmias, diabetes mellitus, angina, myocardial infarction (MI), and peripheral vascular disease. CVD risk was split into low (no risks factors) and high (≥ 3 risk factors) for comparison purposes. Other comorbidities indicative of health status included cancer (yes/no, in response to "has a doctor ever told you that you have had cancer?"), respiratory diseases (chronic obstructive pulmonary disease, asthma, sleep apnea, or pulmonary fibrosis), psychiatric history (depression, anxiety, bipolar, schizophrenia, or suicidal intent), neurological disorders (dementia, Parkinson disease, ischemic/hemorrhagic stroke, epilepsy, or multiple sclerosis head/spinal injuries), musculoskeletal disorders (osteoarthritis, rheumatoid arthritis, or other inflammatory arthropathies), gastrointestinal disorders (ulcers, liver disease, inflammatory bowel disease), renal disorders (kidney failure, dialysis, nephropathies, or pyelonephritis), endocrine disorders (thyroid, parathyroid, hypothalamic/pituitary, or adrenal disorders), hematological disorders (anemia, thrombocytopenia, hemophilia,

sickle cell, or thalassemia), and number of medications taken.

Statistical Analysis

The characteristics of patients who died versus those who survived during follow-up were assessed using *t* tests for continuous variables and chi-square tests for categorical variables. We determined the relationship between DistEn and dichotomized baseline variables (age >65 years versus ≤65 years), sex (men versus women), ethnicity (European versus non-European), college attendance (yes versus no), BMI (>35 versus ≤35), TDI (fourth versus first quartiles), physical activity level (fourth versus first quartiles), CVD risk (high versus low), β-blocker usage, AF/arrhythmias, and pacemaker presence using multivariable regression. Cox proportional hazards models were used to assess the predictive value of DistEn for all-cause and cause-specific mortality: (model A) a core model controlled for demographics; (model B) TDI and lifestyle factors; (model C) cardiovascular risks/diseases; (model D) other comorbidities; and (model E) final adjustment was made for autonomic measures (heart rate, MAP, and RMSSD). We also tested for interactions between DistEn and age, sex, and CVD risk factors. Hazards ratios (HRs) and corresponding 95% CIs represent a 1-SD decrease in DistEn. The proportional hazards assumption was assessed using the global chi-square test in R package *cox.zph* (survival) incorporating methods described by Grambsch and Therneau.³² Efron method was used to handle ties. All other statistical analyses were performed using JMP Pro (version 14, SAS Institute).

RESULTS

Participant Characteristics

Baseline characteristics of 7631 participants (mean age, 59.5 years [SD, 7.6 years]; 4610 [60.4%] women) are summarized in Table 1 based on survival or death from any cause. During a median follow-up of 7.8 years, the 451 participants (5.9%) who died were 3.3 years older at baseline (62.6 versus 59.3 years), more likely men (55% versus 39%), a current smoker (19.7% versus 11.9%), a former smoker (54.7% versus 47.7%), socioeconomically deprived (higher TDI, 0.03 versus -0.44), had lower college attendance (17.4% versus 25.5%), and had more comorbidities and medication usage (5.8 versus 3.8).

DistEn, Baseline Comorbidities, and Cardiovascular Risk

The median value for DistEn was 0.853 (0.877 [SD, 0.078]; range, 0.301–0.975) (Figure 1B). Differences in

values for DistEn by patient characteristics and cardiovascular risk, adjusted for age, sex, ethnicity, and education, where appropriate, are summarized in Table 2. DistEn was moderately lower (ie, lower complexity) in those aged >65 years (effect size -0.16 SD, $P<0.0001$), men (-0.12 SD, $P<0.0001$), non-Europeans (-0.18 SD, $P<0.0001$), low physical activity (lowest quartile; -0.20 SD, $P<0.0001$), and high socioeconomic deprivation (TDI) (highest quartile; 0.25 SD, $P<0.0001$). The difference in DistEn was larger in patients with BMI >35 (-0.41 SD, $P<0.0001$) and those with the highest cardiovascular risk (≥3 risk factors; -0.46 SD, $P<0.0001$). DistEn was marginally lower in those taking β-blockers (0.07 SD, $P=0.046$), but was not different in those with previously reported AF/arrhythmias ($P=0.68$).

Lower DistEn Independently Predicts Incident All-Cause Mortality

DistEn was associated with all-cause mortality using our core Cox proportional hazards model adjusted for demographics (age, sex, ethnicity, and college education) (Table 3; model A). Specifically, for each 1-SD decrease in DistEn, the HR for mortality was 1.36 (95% CI, 1.26–1.46; $P<0.0001$), equivalent to the effect of being 5.5 years older at baseline. After adjusting for lifestyle factors (BMI, deprivation level [TDI], physical activity, alcohol, and smoking), the HR for mortality remained similar (Table 2; model B) (HR, 1.31; 95% CI, 1.21–1.41 [$P<0.0001$]). DistEn remained predictive of mortality after further adjustment for CVDs/risk factors (Table 2; model C) (HR, 1.27; 95% CI, 1.17–1.37 [$P<0.0001$]) and multiple comorbidities (Table 2; model D) (HR, 1.24; 95% CI, 1.14–1.34 [$P<0.0001$]).

Relationship Between DistEn, Autonomic Variables, and Mortality

After controlling for autonomic-related variables (RHR, RMSSD, and MAP), DistEn still remained predictive of mortality (Table 2; model E: HR, 1.22 [95% CI, 1.10–1.35], $P<0.0001$). Full model results are shown in Table S1. This was consistent regardless of which HRV variable was used. To put these results into context, we present fully adjusted model predictions for all-cause mortality for participants with DistEn <0.745 (10th percentile) compared with DistEn >0.925 (90th percentile) in Figure 2A. The lowest decile had a 55% increased risk of all-cause mortality compared with the highest decile; equivalent to being almost 9 years older at baseline, being a former smoker, or having diabetes mellitus at baseline (Table S1).

The mean RHR was 71.3 bpm (SD, 12.6) and significantly lower in those taking β-blockers (58 versus

Table 1. Demographics, Lifestyle, and Clinical Comorbidities at Baseline

	Alive	Died	P Value
	(n=7180)	(n=451)	
	Mean (SD) or n (%)	Mean (SD) or n (%)	
Demographics			
Age at baseline, y	59.3 (7.7)	62.6 (5.9)	<0.0001
Men, %	38.6	55.0	<0.0001
College attendance, %	25.5	17.3	0.0001
Townsend deprivation index	-0.44 (3.2)	0.03 (3.3)	0.003
Ethnic background (European), %	86.7	92.3	0.0006
Lifestyle			
BMI, kg/m ²	29.4 (5.9)	29.9 (6.3)	0.16
Smoking (current), %	12.1	20.1	<0.0001
Smoking (former), %	47.7	54.7	<0.0001
Physical activity (MET-min)*	40.3 (0.3)	36.2 (1.0)	<0.0001
Alcohol (≥3 drinks per wk), %	32.4	32.2	0.90
Cardiovascular disease, %			
Hypertension	47.7	60.5	<0.0001
High cholesterol	18.8	23.1	0.02
Angina	8.9	15.5	<0.0001
Myocardial infarction	4.9	10.9	<0.0001
Diabetes mellitus	9.9	23.5	<0.0001
AF/arrhythmias	2.5	3.8	0.09
Clinical comorbidities			
Medications taken	3.8 (3.4)	5.8 (4.2)	<0.0001
Cancer, %	9.7	26.4	<0.0001
Respiratory, %	30.2	38.8	0.0002
Gastrointestinal, %	9.7	9.4	0.93
Renal, %	1.6	0.4	0.05
Endocrine, %	6.4	4.7	0.14
Musculoskeletal, %	7.6	13.2	0.09
Psychiatric	17.1	18.9	0.34
Neurological, %	7.5	15.7	<0.0001
Hematological, %	1.6	3.1	0.011
Derived ECG metrics			
DistEn	0.856 (0.08)	0.819 (0.11)	<0.0001
RRI, ms	865 (148)	834 (170)	<0.0001
RHR, bpm	71.2 (12.4)	73.7 (15.0)	<0.0001
RMSSD**	2.59 (0.65)	2.36 (0.79)	<0.0001
MAP, mm Hg	105.6 (15.3)	104.5 (15.5)	0.17

UK Biobank participant characteristics at baseline expressed as mean (SD) for continuous variables or percentage for presence of categorical variables. Participants were compared based on survival status (alive/died). Categorical data are presented as percentage of participants present. *P* values from 1-way ANOVA tests for continuous measures and Pearson chi-square tests for categorical data. Physical activity: summed metabolic equivalent (MET) minutes per week for all activities. AF indicates atrial fibrillation; BMI, body mass index; bpm, beats per minute; DistEn, distribution entropy; MAP, mean arterial pressure; RHR, resting heart rate; RMSSD, root mean square of successive differences between normal heartbeats; and RRI, RR interval.

*Square root transformation.

**Log-transformed.

66 bpm, $P<0.0001$). We found DistEn to be negatively correlated with RHR ($r^2=0.11$, $P<0.0001$) and positively correlated with RMSSD ($r^2=0.36$, $P<0.0001$), but had no relationship with MAP ($P>0.05$). A 10-bpm increase

in RHR (HR, 1.14; 95% CI, 1.06–1.22 [$P=0.0002$]), and a 1-SD decrease in RRI (HR, 1.20; 95% CI, 1.09–1.32 [$P=0.0002$]) or RMSSD (HR, 1.22; 95% CI, 1.09–1.35 [$P=0.0003$]), were separately predictive of mortality, but

Table 2. DistEn Differences by Patient Characteristics

	Present	Absent	Difference (SD)	P Value
	Mean (SD)	Mean (SD)		
Age >65 y	0.840 (0.002)	0.854 (0.001)	0.014 (−0.16)	<0.0001
Men	0.843 (0.002)	0.852 (0.002)	0.009 (−0.12)	<0.0001
European ancestry*	0.855 (0.001)	0.840 (0.003)	0.015 (+0.18)	<0.0001
College attendance	0.849 (0.002)	0.846 (0.001)	0.003 (+0.04)	0.10
BMI >35 kg/m ²	0.819 (0.003)	0.852 (0.001)	0.033 (−0.41)	<0.0001
High deprivation**	0.861 (0.002)	0.841 (0.002)	0.020 (−0.25)	<0.0001
Low physical activity***	0.840 (0.002)	0.856 (0.002)	0.015 (−0.20)	<0.0001
High CVD risk****	0.822 (0.003)	0.859 (0.002)	0.037 (−0.46)	<0.0001
β-Blocker usage	0.843 (0.003)	0.849 (0.001)	0.006 (−0.07)	0.046
AF/arrhythmias	0.850 (0.006)	0.848 (0.001)	0.002 (+0.03)	0.68
Pacemaker	0.852 (0.008)	0.848 (0.001)	0.004 (+0.05)	0.64

The difference in mean distribution entropy (DistEn) values and expressed in SDs by the presence/absence of covariates (adjusted for age, sex, ethnicity, and education from body mass index [BMI] onwards). AF indicates atrial fibrillation.

*European vs non-European ancestry.

**Townsend deprivation index (TDI) fourth and first quartiles.

***Metabolic equivalents—minutes first vs fourth quartile.

****Cardiovascular disease (CVD) risk was determined as the sum of the binary covariates hypertension, cholesterol, diabetes mellitus, current smoker, and/or angina or myocardial infarction at baseline; if ≥ 3 , CVD was considered high and if zero, CVD was considered low.

none of these associations remained after inclusion of DistEn (all $P > 0.05$). Table S2 shows model results with all time-domain HRV measures. In a direct comparison between DistEn and RRI survival models (adjusting for age, sex, and education), DistEn was superior across follow-up years. Figure S3C presents concordance index (c-statistic) differences.

DistEn and Cause-Specific Mortality

Of 451 deaths, the following primary causes were seen: 13.3% (60) cardiovascular, 10.0% (44)

respiratory, and 42.8% (193) cancer. In Table 3, the increased risk from low DistEn was highest in model A where the primary cause of death was cardiovascular- (HR, 1.56; 95% CI, 1.30–1.87 [$P < 0.0001$]) or respiratory (HR, 1.73; 95% CI, 1.41–2.11 [$P < 0.0001$]) disease-related; and remained after adjustment for confounders (model B–E, Table 3). DistEn was weakly predictive for cancer-related deaths in our penultimate model (model D: HR, 1.19; 95% CI, 1.03–1.36 [$P = 0.01$]), but this was fully accounted for by inclusion of RHR and HRV measures (model E: HR, 1.06; 95% CI, 0.52–1.27 [$P = 0.55$]).

Table 3. Distribution Entropy of Resting Heartbeats and Risk for All-Cause Mortality and CVD-, Respiratory Disease-, and Cancer-Related Mortality

Model DistEn*	All-Cause	CVD	Respiratory	Cancer
A (Core)	1.36 (1.26–1.46) <0.0001	1.56 (1.29–1.86) <0.0001	1.73 (1.41–2.11) <0.0001	1.24 (1.10–1.41) <0.0001
B (A+lifestyle)	1.31 (1.21–1.41) <0.0001	1.43 (1.17–1.74) 0.0004	1.80 (1.46–2.21) <0.0001	1.22 (1.07–1.39) 0.003
C (B+CVD)	1.27 (1.17–1.37) <0.0001	1.37 (1.12–1.68) 0.003	1.74 (1.41–2.15) <0.0001	1.19 (1.04–1.36) 0.01
D (C+comorbidities)	1.24 (1.14–1.34) <0.0001	1.35 (1.10–1.65) 0.004	1.70 (1.38–2.11) <0.0001	1.19 (1.03–1.36) 0.01
E (D+ANS measures)	1.22 (1.10–1.35) <0.0001	1.46 (1.11–1.91) 0.007	1.75 (1.35–2.26) <0.0001	1.06 (1.13–1.26) 0.55

Cox proportional hazards models. Model A is our core model adjusting for demographics (age, sex, education, and ethnic background). Model B additionally includes lifestyle covariates—alcohol usage, smoking, body mass index, Townsend deprivation index, and summed active metabolic minutes per week. Model C builds on model B by including cardiovascular risks/disease—hypertension, cholesterol, peripheral vascular disease, diabetes mellitus, chronic heart failure, prior myocardial infarction, and arrhythmias. Model D builds on model C by including comorbidities—neurological disease, respiratory diseases, cancer, psychiatric disease, gastrointestinal/hepatic disease, musculoskeletal disorder, endocrine disorders, and hematological disease. Model E builds on model D by including autonomic nervous system (ANS) function indicators—resting heart rate, root mean square of successive differences between normal heartbeats, and mean arterial pressure. CVD indicates cardiovascular disease.

*Results for 1-SD decrease in distribution entropy (DistEn) are presented as hazard ratio (95% CI) and P value.

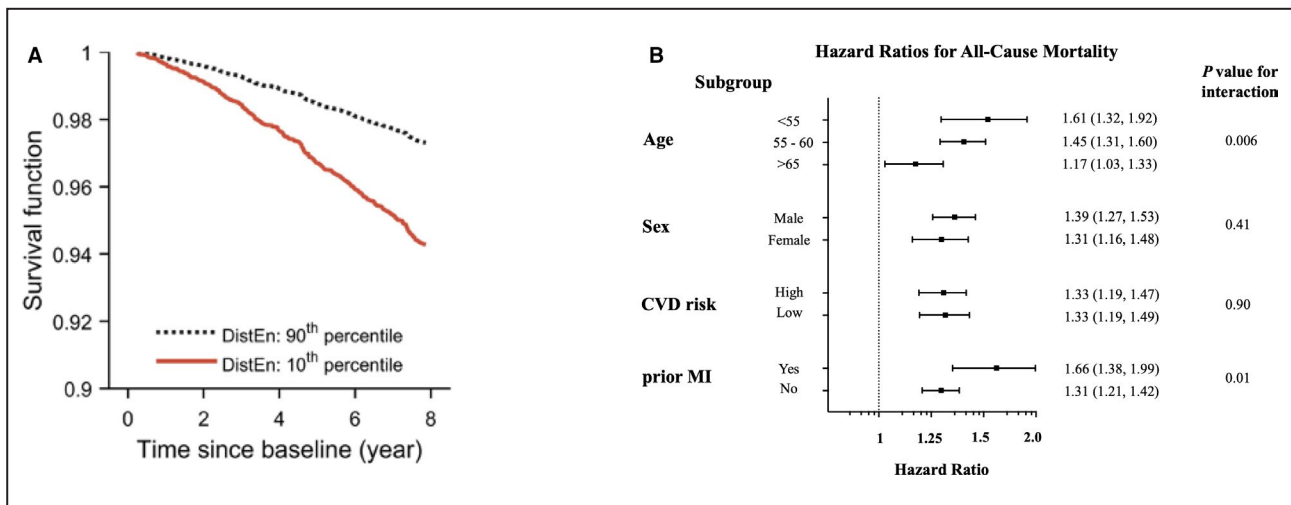


Figure 2. Survival function and subgroup analysis.

A, Survival over time from Cox proportional hazards model for all-cause mortality (model E: fully adjusted) based on those in the 90th (dotted line) and 10th (solid line) percentiles for distribution of entropy (DistEn) from 2 minutes of ECG at rest. **B**, Forrest plot of hazard ratios with 95% CIs for DistEn predicting all-cause mortality based on subgroups of patients. Results presented on logarithmic scale. Cardiovascular disease (CVD) risk was determined high if there were ≥ 3 risk factors and low if there were no risk factors. Prior myocardial infarction (MI) as documented by date of *International Classification of Diseases, Tenth Revision (ICD)* diagnosis before UK Biobank assessment.

Subgroup Analysis and Interactions With DistEn

We did find a significant interaction effect between DistEn and age ($P=0.006$ for interaction) and prior MI ($P=0.01$ for interaction; Figure 2B). For every 1-SD decrease in DistEn in those aged <55 years, there was a higher risk for death (HR, 1.61; 95% CI, 1.32–1.92 [$P<0.0001$]) than those >65 years (HR, 1.17, 95% CI, 1.03–1.33 [$P=0.02$]). Similarly, those with a prior MI (HR, 1.66; 95% CI, 1.38–1.99 [$P<0.0001$]) had a larger risk from every 1-SD decrease in DistEn than those with none (HR, 1.31; 95% CI, 1.21–1.42 [$P<0.0001$]). Taken together, these interactions represented a 56% enhanced risk when comparing those <55 years with a history of MI, versus those >65 years without prior MI.

DISCUSSION

To the best of our knowledge, this is the first large-scale implementation of heartbeat complexity in beat-to-beat recordings to explore its link to incident mortality, after almost a decade of follow-up. The key novel finding from this current study is the ability to derive prognostic information related to mortality using only a 2-minute resting ECG with DistEn, independently of clinically relevant risk factors and autonomic indices such as RHR, HRV, and MAP; this has traditionally not been feasible using other complexity measures.^{13,15,29} In a direct comparison between DistEn and RRI Cox models (adjusting for age, sex,

and education), DistEn was superior across follow-up years. Moreover, DistEn was significantly more predictive of death in younger patients and in those who had already experienced an MI at the time of recording. The observed risks for mortality are clinically meaningful given that these independent findings are readily obtained from resting ECGs, where the effect sizes are comparable to being up to a decade older, having been a former smoker, or having diabetes mellitus.

We should note that complexity is an umbrella term that lacks a clear scientific definition. A variety of algorithms have been established in the past decades, each of which is believed to capture some aspects of this dynamical property. Entropy measures have been widely used in assessing physiological complexity, partially because of their capability in handling limited length data.³³ However, it is generally accepted that many established entropy measures, in fact, quantitate the degree of randomness of a temporal process, which is related to, but is distinct from, complexity. Neither an increase in the randomness nor an increase in regularity necessarily implies an increase in the complexity. In outputs of healthy physiological systems, complexity is characterized by temporal structures that represent a certain optimal balance between variability (randomness) and order (regularity). To demonstrate the conceptual differences between randomness and complexity, a multiscale entropy analysis has been proposed to quantify the profile of entropy as a function of time scale.³⁴ Although the method successfully explained

the seemingly controversial higher entropy values in some diseased states, its application to clinical recordings has been limited because the method also requires longer data for properly profiling the entropy results. Taking full advantage of the state-space characteristic of a temporal process, DistEn can reconcile this complexity-randomness paradox by unravelling the spatial structure of the state space, thus being different from previously established single-scale entropy analyses.¹³

The physiological interpretation of DistEn in heartbeat fluctuations may be partially linked to the autonomic control on the circulatory system. Supporting this hypothesis, we find that DistEn is correlated with RHR and HRV that are known to be influenced by the autonomic nervous system. In particular, RMSSD mostly reflects respiration-related beat-to-beat changes that are measures of parasympathetic involvement in circulatory control, also referred to as respiratory sinus arrhythmia.³⁵ However, at the 2-minute level, RHR is likely influenced by both sympathetic and parasympathetic inputs, and the nonrespiratory sinus arrhythmia aspect may also contribute to beat-to-beat HRV. Therefore, the relationship between RMSSD and aging/disease may be more nuanced than simply a decline in parasympathetic function.³⁶ This may be relevant to our observation that DistEn was lowest in patients with BMI >35 and high CVD risk profile, where there has been a substantial body of evidence supporting the role of the sympathetic/parasympathetic nervous system balance in obesity,^{37,38} hypertension,^{39,40} diabetes mellitus,^{41,42} or a combination in metabolic syndrome.^{37,38} The sympathetic predominance seen in CVD is likely only partially reflected in higher RHR and lower HRV, whereas DistEn's independent predictive value may be indicative of broader mechanisms. For example, DistEn may capture aspects beyond autonomic nervous system activity such as structural^{8,43} and/or electrophysiological properties^{13,15,44} of the heart, metabolic,⁴⁵ or endocrine/neurohormonal factors.^{46,47}

Another interpretation of our results is that complexity, as quantified by DistEn, may be a marker of frailty; it may reflect declines in physiological reserve across multiorgan systems, thus increasing vulnerability to stressors. DistEn applied to short screening ECGs may provide additional information regarding cardiac stress reactivity above that provided by traditional measures of cardiac autonomic function. For example, it has been shown that time domain HRV reflects respiratory sinus arrhythmia, which is predominantly mediated by cardiac vagal outflow at rest.³⁵ In heart failure, myocardial infarction, and stroke, respiratory sinus arrhythmia is usually either blunted or absent. This may partially explain our observation that DistEn is most predictive of cause-specific cardiovascular- and respiratory-related mortality (Table 3). Interestingly, in keeping

with prior studies,^{48,49} RHR and HRV were individually predictive of cancer-related mortality, as was DistEn (Table S2). However, only RHR remained predictive when all 3 measures were included in the same model. Given their shared overlap in reflecting autonomic nervous system output, further studies are needed to understand the role of these measures in cancer-related mortality.

In an effort to understand DistEn in patient subgroups, clinical factors of interest that may influence its value were examined and taken into account. Unsurprisingly, RHR was significantly lower in patients taking β -blockers even after adjustment for demographics, yet there was only a weak effect of β -blocker usage on DistEn (Table 2). History of AF/arrhythmias did not have a significant effect on DistEn. Taken together, this suggests that DistEn is relatively robust to the effects of medications and/or conditions that may affect heartbeats. However, it is unlikely that patients were actively in AF/arrhythmia during the recording period given their paroxysmal nature.⁵⁰ Further work is needed to examine the effects of pacemaker devices and chronic AF on the predictive ability of DistEn for mortality.

Our observation that lower resting heartbeat complexity confers a greater risk of death in younger participants (<55 years), and those having already experienced an MI, is also particularly intriguing. We do note that a similar pattern was also observed for RHR⁴⁸ and HRV during a 2-minute ECG strip analysis.⁴⁵ For example, Goldberger et al⁶ noted in their large, prospective cohort of 30,000 that mortality risk was more pronounced in patients 59 years (similar cutoff to ours) and even in patients <38 years (relative risks between 1.11 and 1.27). Even though complexity is known to decrease with age, it remains unclear whether DistEn observations attenuate with age because of changes in biology or simply because of smaller numbers of older people in our cohort. Complexity changes in heartbeat fluctuations with aging may be masked by increased underlying diseases and medications taken,⁵¹ which was not fully accounted for in this study as well as many other entropy studies. Nevertheless, these observations may be further evidence that hidden mechanisms related to poor health are better captured by low DistEn in younger patients. We postulate that cardiac reactivity to stress, which has an adverse effect on future cardiovascular risk,^{52,53} is perhaps better reflected by DistEn in an age group where there are fewer comorbidities, extrinsic influences of medication, or biological interactions with disease associated with the aging process that attenuate the signal. Those with potential heart damage (eg, post-MI) may exaggerate this response and is better reflected by heartbeat complexity.

Others have begun to explore heartbeat complexity as a novel approach to assessing cardiac stress reactivity,⁵⁴ but more remains to be done to verify these observations and before clinical applications either for screening or risk stratification of patients. For example, validating the DistEn measure with echocardiographic evidence for post-MI structural changes to the heart may shed mechanistic light on why there is such a strong link to mortality. Given the interaction results, one testable hypothesis is that cardiac rehabilitation post-MI in middle age can be tracked using serial DistEn measures alongside multimodal trackers such as motor activity,⁵⁵ with the goal to maintain cardiovascular well-being and increase life expectancy.

Limitations

Despite the strengths of this study, several limitations exist. The interpretation of these results from a clinically meaningful and statistically robust standpoint must be taken. With a large sample size, it can lead to tight CIs, so we have chosen not to make reference only to *P* values, which become less informative in these situations. The resting ECGs are readily obtained and effect sizes are significant, but whether DistEn can be influenced to make a clinical meaningful impact has yet to be tested. While all participants were conducting similar activities in answering questionnaires before their protocolized ECG recordings, we cannot control for the physical and mental state of the participant, in response to the multitude of mental tasks and recall requested of the participants by the UKB.^{18,20} For example, respiratory patterns are known to heavily influence cardiac dynamics.⁵⁶ Patients excluded were of similar age and demographics but they did have slightly more risk factors than those who were included per ECG criteria. This was, however, a relatively small portion (4.2% or 338/7969). While we cannot definitively exclude the possibility that other hidden differences existed in the patients excluded, we are reassured that, if anything, inclusion of participants with potentially slightly more risk factors would likely strengthen the signal from DistEn for mortality, given that DistEn was significantly different in groups separated by the presence/absence of risk factors related to mortality (Table 2). Using the primary cause of death is most definitive, but may miss other contributing diseases that lends caution when interpreting results of the cause-specific models. Finally, the UKB is a single population of mostly Caucasian of European descent, limiting the generalizability of these results to certain parts of the world.

CONCLUSIONS

Resting heartbeat complexity from short, resting ECGs was independently associated with mortality

in middle- to older-aged adults. These risks appear most pronounced in middle-aged patients with prior MI, and may uniquely contribute to routine mortality risk screening. Our findings have the potential to be scaled-up to remote monitoring in smartwatch applications of beat-to-beat heart activity and opens up a new avenue of research for resting heartbeat complexity as a vulnerability marker for stress reactivity.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S2

Figures S1–S3

REFERENCES

- Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, Balasubramanian V, Russo AM, Rajmane A, Cheung L, et al. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med*. 2019;381:1909–1917. DOI: 10.1056/NEJMoa1901183.
- Kinoshita T, Hashimoto K, Yoshioka K, Miwa Y, Yodogawa K, Watanabe E, Nakamura K, Nakagawa M, Nakamura K, Watanabe T, et al. Risk stratification for cardiac mortality using electrocardiographic markers based on 24-hour Holter recordings: the JANIES-SHD study. *J Cardiol*. 2020;75:155–163. DOI: 10.1016/j.jjcc.2019.07.012.
- Jonas DE, Reddy S, Middleton JC, Barclay C, Green J, Baker C, Asher GN. Screening for cardiovascular disease risk with resting or exercise electrocardiography: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018;319:2315. DOI: 10.1001/jama.2018.6897.

4. Pincus SM. Approximate entropy as a measure of system complexity. *Proc Natl Acad Sci*. 1991;88:2297–2301. DOI: 10.1073/pnas.88.6.2297.
5. Lipsitz LA. Loss of “complexity” and aging: potential applications of fractals and chaos theory to senescence. *JAMA*. 1992;267:1806. DOI: 10.1001/jama.1992.03480130122036.
6. Goldberger AL, Peng CK, Lipsitz LA. What is physiologic complexity and how does it change with aging and disease? *Neurobiol Aging*. 2002;23:23–26. DOI: 10.1016/S0197-4580(01)00266-4.
7. Lipsitz LA. Physiological complexity, aging, and the path to frailty. *Sci Aging Knowledge Environ*. 2004;2004:pe16. DOI: 10.1126/sageke.2004.16.pe16.
8. Costa M, Healey JA. Multiscale entropy analysis of complex heart rate dynamics: discrimination of age and heart failure effects. *Comput Cardiol*. 2003;2003:705–708.
9. Gao L, Smielewski P, Czosnyka M, Ercole A. Cerebrovascular signal complexity six hours after intensive care unit admission correlates with outcome after severe traumatic brain injury. *J Neurotrauma*. 2016;33:2011–2018. DOI: 10.1089/neu.2015.4228.
10. Gao L, Smielewski P, Li P, Czosnyka M, Ercole A. Signal information prediction of mortality identifies unique patient subsets after severe traumatic brain injury: a decision-tree analysis approach. *J Neurotrauma*. 2020;37:1011–1019. DOI: 10.1089/neu.2019.6631.
11. Batchinsky AI, Cancio LC, Salinas J, Kuusela T, Cooke WH, Wang JJ, Boehme M, Convertino VA, Holcomb JB. Prehospital loss of R-to-R interval complexity is associated with mortality in trauma patients. *J Trauma*. 2007;63:512–518. DOI: 10.1097/TA.0b013e318142d2f0.
12. Norris PR, Canter JA, Jenkins JM, Moore JH, Williams AE, Morris JA. Personalized medicine: genetic variation and loss of physiologic complexity are associated with mortality in 644 trauma patients. *Ann Surg*. 2009;250:524–530.
13. Li P, Liu C, Li K, Zheng D, Liu C, Hou Y. Assessing the complexity of short-term heartbeat interval series by distribution entropy. *Med Biol Eng Comput*. 2015;53:77–87. DOI: 10.1007/s11517-014-1216-0.
14. Li P, Li K, Liu C, Zheng D, Li Z, Liu C. Detection of coupling in short physiological series by a joint distribution entropy method. *IEEE Trans Biomed Eng*. 2016;63:2231–2242. DOI: 10.1109/TBME.2016.2515543.
15. Karmakar C, Udhayakumar RK, Li P, Venkatesh S, Palaniswami M. Stability, consistency and performance of distribution entropy in analysing short length heart rate variability (HRV) signal. *Front Physiol*. 2017;8:720. DOI: 10.3389/fphys.2017.00720.
16. Lee DY, Choi YS. Multiscale distribution entropy analysis of short-term heart rate variability. *Entropy*. 2018;20:952. DOI: 10.3390/e20120952.
17. Shi M, Zhan C, He H, Jin Y, Wu R, Sun Y, Shen B. Renyi distribution entropy analysis of short-term heart rate variability signals and its application in coronary artery disease detection. *Front Physiol*. 2019;10:1–14. DOI: 10.3389/fphys.2019.00809.
18. Allen NE, Sudlow C, Peakman T, Collins R. Biobank on behalf of U. UK Biobank data: come and get it. *Sci Transl Med*. 2014;6:224ed4. DOI: 10.1126/scitranslmed.3008601.
19. Littlejohns TJ, Sudlow C, Allen NE, Collins R. UK Biobank: opportunities for cardiovascular research. *Eur Heart J*. 2019;40:1158–1166. DOI: 10.1093/eurheartj/ehx254.
20. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Medicine*. 2015;12:e1001779. DOI: 10.1371/journal.pmed.1001779.
21. UK Biobank. UK Biobank Cardio Assessment vol 1.0. 2011. Available at <http://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/Cardio.pdf>. Accessed April 30, 2020.
22. Moody G, Mark RG. Development and evaluation of a 2-lead ECG analysis program. *Comput Cardiol*. 1982;1:39–44.
23. Friesen GM, Jannett TC, Jadallah MA, Yates SL, Quint SR, Nagle HT. A comparison of the noise sensitivity of nine QRS detection algorithms. *IEEE Trans Biomed Eng*. 1990;37:85–98. DOI: 10.1109/10.43620.
24. Verweij N, van de Vegte YJ, van der Harst P. Genetic study links components of the autonomous nervous system to heart-rate profile during exercise. *Nat Commun*. 2018;9. DOI: 10.1038/s41467-018-03395-6.
25. van de Vegte YJ, van der Harst P, Verweij N. Heart rate recovery 10 seconds after cessation of exercise predicts death. *J Am Heart Assoc*. 2018;7. DOI: 10.1161/JAHA.117.008341.
26. Malik M, Bigger JT, Camm AJ, Kleiger RE, Malliani A, Moss AJ, Schwartz PJ. Heart rate variability standards of measurement, physiological interpretation, and clinical use. *Eur Heart J*. 1996;17:354–381. DOI: 10.1093/oxfordjournals.eurheartj.a014868.
27. Gao L, Li P, Hu C, To T, Patxot M, Falvey B, Wong PM, Scheer FAJL, Lin C, Lo M-T, et al. Nocturnal heart rate variability moderates the association between sleep–wake regularity and mood in young adults. *Sleep*. 2019;42:zs034. DOI: 10.1093/sleep/zsz034.
28. Li P. EZ Entropy: a software application for the entropy analysis of physiological time-series. *BioMed Eng OnLine*. 2019;18:30. DOI: 10.1186/s12938-019-0650-5.
29. Gao L, Smielewski P, Czosnyka M, Ercole A. Early asymmetric cardio-cerebral causality and outcome after severe traumatic brain injury. *J Neurotrauma*. 2017;34:2743–2752. DOI: 10.1089/neu.2016.4787.
30. Wallot S, Fusaroli R, Tylén K, Jegindø EM. Using complexity metrics with R-R intervals and bpm heart rate measures. *Front Physiol*. 2013;4:211. DOI: 10.3389/fphys.2013.00211.
31. Cassidy S, Chau JY, Catt M, Bauman A, Trenell MI. Cross-sectional study of diet, physical activity, television viewing and sleep duration in 233 110 adults from the UK Biobank; the behavioural phenotype of cardiovascular disease and type 2 diabetes. *BMJ Open*. 2016;6:e010038.
32. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81:515–526. DOI: 10.1093/biomet/81.3.515.
33. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol*. 2000;278:H2039–2049. DOI: 10.1152/ajpheart.2000.278.6.H2039.
34. Costa M, Goldberger AL, Peng CK. Multiscale entropy analysis of complex physiologic time series. *Phys Rev Lett*. 2002;89:068102. DOI: 10.1103/PhysRevLett.89.068102.
35. Hayano J, Sakakibara Y, Yamada A, Yamada M, Mukai S, Fujinami T, Yokoyama K, Watanabe Y, Takata K. Accuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects. *Am J Cardiol*. 1991;67:199–204. DOI: 10.1016/0002-9149(91)90445-Q.
36. Masi CM, Hawkey LC, Rickett EM, Cacioppo JT. Respiratory sinus arrhythmia and diseases of aging: obesity, diabetes mellitus, and hypertension. *Biol Psychol*. 2007;74:212–223. DOI: 10.1016/j.biopsycho.2006.07.006.
37. Canale MP, Manca di Villahermosa S, Martino G, Rovella V, Noce A, De Lorenzo A, Di Daniele N. Obesity-related metabolic syndrome: mechanisms of sympathetic overactivity. *Int J Endocrinol*. 2013;2013:865965. DOI: 10.1155/2013/865965.
38. Tentolouris N, Liatis S, Katsilambros N. Sympathetic system activity in obesity and metabolic syndrome. *Ann N Y Acad Sci*. 2006;1083:129–152. DOI: 10.1196/annals.1367.010.
39. Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G. Hypertension, blood pressure, and heart rate variability. *Hypertension*. 2003;42:1106–1111. DOI: 10.1161/01.HYP.0000100444.71069.73.
40. Kudat H, Akkaya V, Sozen AB, Salman S, Demirel S, Ozcan M, Atilgan D, Yilmaz MT, Guven O. Heart rate variability in diabetes patients. *J Int Med Res*. 2006;34:291–296. DOI: 10.1177/147323000603400308.
41. Schroeder EB, Chambless LE, Liao D, Prineas RJ, Evans GW, Rosamond WD, Heiss G. Diabetes, glucose, insulin, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care*. 2005;28:668–674. DOI: 10.2337/diacare.28.3.668.
42. Benichou T, Pereira B, Mermillod M, Tauveron I, Pfabigan D, Maqdasy S, Duthel F. Heart rate variability in type 2 diabetes mellitus: a systematic review and meta-analysis. *PLoS One*. 2018;13:e0195166. DOI: 10.1371/journal.pone.0195166.
43. Mukherjee S, Palit SK, Banerjee S, Ariffin MRK, Rondoni L, Bhattacharya DK. Can complexity decrease in congestive heart failure? *Physica A*. 2015;439:93–102. DOI: 10.1016/j.physa.2015.07.030.
44. Staniczenko PPA, Lee CF, Jones NS. Rapidly detecting disorder in rhythmic biological signals: a spectral entropy measure to identify cardiac arrhythmias. *Phys Rev E Stat Nonlin Soft Matter Phys*. 2009;79:011915. DOI: 10.1103/PhysRevE.79.011915.
45. Zivieri R, Pacini N, Finocchio G, Carpentieri M. Rate of entropy model for irreversible processes in living systems. *Sci Rep*. 2017;7:1–9. DOI: 10.1038/s41598-017-09530-5.
46. Pincus SM, Keefe DL. Quantification of hormone pulsatility via an approximate entropy algorithm. *Am J Physiol-Endocrinol Metab*. 1992;262:E741–E754. DOI: 10.1152/ajpendo.1992.262.5.E741.
47. Roelfsema F, Veldhuis JD. Growth-hormone dynamics in healthy adults are related to age and sex, and strongly dependent on body mass index. *Neuroendocrinology*. 2016;103:335–344. DOI: 10.1159/000438904.

48. Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, Schouten EG. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. *Circulation*. 2000;102:1239–1244. DOI: 10.1161/01.CIR.102.11.1239.
49. Seviiri M, Lynch BM, Hodge AM, Yang Y, Liew D, English DR, Giles GG, Milne RL, Dugué PA. Resting heart rate, temporal changes in resting heart rate, and overall and cause-specific mortality. *Heart*. 2018;104:1076–1085. DOI: 10.1136/heartjnl-2017-312251.
50. Gutierrez C, Blanchard DG. Atrial fibrillation: diagnosis and treatment. *AFP*. 2011;83:61–68.
51. Lo MT, Chang YC, Lin C, Young HW, Lin YH, Ho YL, Peng CK, Hu K. Outlier-resilient complexity analysis of heartbeat dynamics. *Sci Rep*. 2015;5:8836. DOI: 10.1038/srep08836.
52. Yoichi C, Andrew S. Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status. *Hypertension*. 2010;55:1026–1032. DOI: 10.1161/HYPERTENSIONAHA.109.146621.
53. Gavin L, Markus S, Elisabeth L, Tye D, Murray E. Stress reactivity and its association with increased cardiovascular risk: a role for the sympathetic nervous system? *Hypertension*. 2010;55:e20. DOI: 10.1161/HYPERTENSIONAHA.110.153841.
54. Brindle RC, Ginty AT, Phillips AC, Fisher JP, McIntyre D, Carroll D. Heart rate complexity: a novel approach to assessing cardiac stress reactivity. *Psychophysiology*. 2016;53:465–472. DOI: 10.1111/psyp.12576.
55. Li P, Lim AS, Gao L, Hu C, Yu L, Bennett DA, Buchman AS, Hu K. More random motor activity fluctuations predict incident frailty, disability, and mortality. *Sci Transl Med*. 2019;11. DOI: 10.1126/scitranslmed.aax1977.
56. Aysin B, Aysin E. Effect of respiration in heart rate variability (HRV) analysis. *Conf Proc IEEE Eng Med Biol Soc*. 2006;2006:1776–1779.

SUPPLEMENTAL MATERIAL

Table S1. Full Cox proportional hazards models for DistEn and all-cause mortality.

	Model 1 Core	Model 2 Lifestyle	Model 3 CVD	Model 4 Comorbidities	Model 5 Autonomic Function
	HR (95% CI) <i>p</i> -value	HR (95% CI) <i>p</i> -value	HR (95% CI) <i>p</i> -value	HR (95% CI) <i>p</i> -value	HR (95% CI) <i>p</i> -value
DistEn^a	1.36 (1.26 - 1.46) <0.0001	1.31 (1.21 - 1.41) <0.0001	1.27 (1.17 - 1.37) <0.0001	1.24 (1.14 - 1.34) <0.0001	1.22 (1.10 - 1.35) <0.0001
Age ^b	1.06 (1.04 - 1.08) <0.0001	1.07 (1.05 - 1.08) <0.0001	1.06 (1.05 - 1.08) <0.0001	1.05 (1.03 - 1.07) <0.0001	1.05 (1.03 - 1.07) <0.0001
Male	1.81 (1.50 - 2.18) <0.0001	1.69 (1.39 - 2.06) <0.0001	1.53 (1.25 - 1.87) <0.0001	1.67 (1.36 - 2.04) <0.0001	1.69 (1.39 - 2.07) <0.0001
European	1.48 (1.04 - 2.12) 0.023	1.51 (1.03 - 2.21) 0.034	1.60 (1.09 - 2.34) 0.008	0.79 (0.61 - 1.01) 0.06	0.78 (0.60 - 1.00) 0.05
Education (College)	0.69 (0.54 - 0.89) 0.002	0.73 (0.57 - 0.94) 0.016	0.76 (0.59- 0.98) 0.033	1.46 (1.00 - 2.14) 0.04	1.47 (1.02 - 2.17) 0.04
BMI (kg/m ²)		0.99 (0.98 - 1.01) 0.497	0.99 (0.97 - 1.00) 0.075	0.99 (1.00 - 1.01) 0.12	0.98 (0.97 - 1.00) 0.09
Townsend Deprivation Index		1.04 (1.01 - 1.07) 0.016	1.04 (1.00 - 1.07) 0.024	1.03 (1.00 - 1.06) 0.06	1.04 (1.01 - 1.07) 0.02
Physical Activity		0.99 (0.99 - 1.00) 0.0004	0.99 (0.99 - 1.00) 0.001	0.99 (0.99 - 1.00) 0.02	0.93 (0.91 - 0.97) 0.02
Smoking (Current)		2.13 (1.59 - 2.86) <0.0001	2.11 (1.58 - 2.84) <0.0001	2.07 (1.54 - 2.78) <0.0001	2.00 (1.51 - 2.63) 0.0001
Smoking (Former)		1.49 (1.19 - 1.88) 0.0006	1.43 (1.14 - 1.80) 0.002	1.42 (1.13 - 1.79) 0.003	1.43 (1.13 - 1.80) 0.003
Alcohol (>3 Drinks per Week)		0.89 (0.68 - 1.16) 0.337	0.94 (0.72 - 1.23) 0.668	1.07 (0.81 - 1.40) 0.89	1.02 (0.82 - 1.25) 0.89
Hypertension			1.04 (0.84 - 1.29) 0.726	0.89 (0.71 - 1.12) 0.32	0.89 (0.71 - 1.12) 0.34
Cholesterol			0.86 (0.69 - 1.09) 0.207	0.78 (0.62 - 0.98) 0.13	0.78 (0.62 - 0.98) 0.03

	Model 1 Core	Model 2 Lifestyle	Model 3 CVD	Model 4 Comorbidities	Model 5 Autonomic Function
	HR (95% CI) <i>p</i> -value	HR (95% CI) <i>p</i> -value	HR (95% CI) <i>p</i> -value	HR (95% CI) <i>p</i> -value	HR (95% CI) <i>p</i> -value
Peripheral Vascular Disease			1.40 (0.52 – 3.80) 0.506	1.52 (0.56 – 4.11) 0.44	1.58 (0.58 – 4.27) 0.37
Diabetes Mellitus			1.86 (1.46 – 2.39) <0.0001	1.59 (1.23 – 2.06) <0.0005	1.54 (1.19 – 1.99) 0.0009
Chronic Heart Failure			2.97 (0.94 – 9.37) 0.064	3.01 (0.94 – 9.67) 0.11	2.84 (0.88 – 9.17) 0.08
AF/Arrhythmia			1.34 (0.82 – 2.19) 0.240	1.19 (0.73 – 1.95) 0.49	1.11 (0.67 – 1.84) 0.69
Myocardial Infarction			1.38 (1.00 – 1.90) 0.046	1.13 (0.82 – 1.57) 0.46	1.19 (0.86 – 1.65) 0.28
Respiratory Diseases				1.17 (0.96– 1.43) 0.12	1.14 (0.93 – 1.39) 0.20
Neurological Diseases				1.65 (1.27 – 2.14) <0.0004	1.59 (1.23 – 2.07) 0.0005
Cancer				2.92 (2.35 – 3.62) <0.0001	2.86 (2.31 – 3.54) <0.0001
Psychiatric Disorders				0.75 (0.58 – 0.98) 0.030	0.76(0.59 – 0.99) 0.04
Gastrointestinal Diseases				0.99 (0.72 – 1.36) 0.962	0.99 (0.72 - 1.36) 0.95
Musculoskeletal Disorders				1.05 (0.79 - 1.39) 0.748	1.06 (0.80 – 1.40) 0.67
Endocrine Disorders				0.73 (0.47 - 1.15) 0.161	0.70 (0.44 – 1.10) 0.12
Hematological Disorders				1.90 (1.10 – 3.27) 0.034	1.95 (1.13 – 3.35) 0.02
Number of Medications Taken				1.08 (1.05 – 1.11) <0.0001	1.08 (1.05 – 1.11) <0.0001

	Model 1 Core	Model 2 Lifestyle	Model 3 CVD	Model 4 Comorbidities	Model 5 Autonomic Function
	HR (95% CI) <i>p</i> -value	HR (95% CI) <i>p</i> -value	HR (95% CI) <i>p</i> -value	HR (95% CI) <i>p</i> -value	HR (95% CI) <i>p</i> -value
RHR (10 bpm increase)					1.10 (0.99 – 1.25) 0.08
RMSSD (1 SD decrease)					1.01 (0.90 – 1.15) 0.80
MAP (1 SD increase)					1.05 (0.95 – 1.16) 0.35

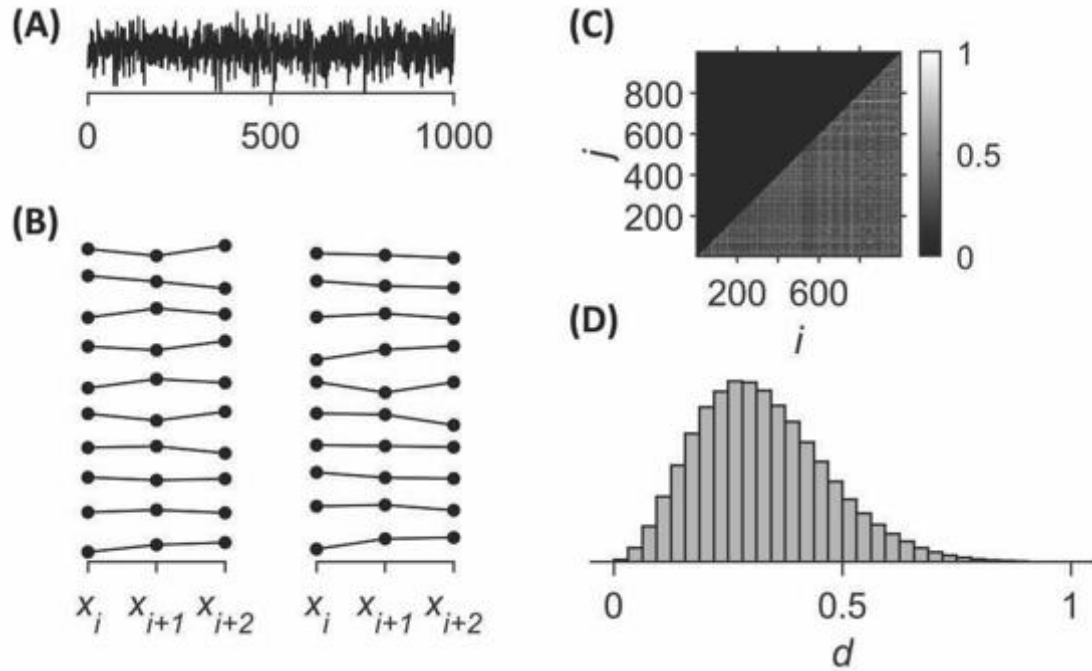
Full Cox proportional hazards models; results presented as hazard ratio (95% confidence interval), and *p* value. Model A is our core model adjusting for demographics (age, sex, education, and ethnic background). Model B additionally includes lifestyle covariates - alcohol usage, smoking, body mass index, Townsend deprivation index and summed active metabolic minutes per week. Model C builds on model B by including CV risks/disease - hypertension, cholesterol, peripheral vascular disease, diabetes mellitus, chronic heart failure, prior myocardial infarction and arrhythmias. Model D builds on C by including comorbidities - neurological disease, respiratory diseases, cancer, psychiatric disease, gastrointestinal/hepatic disease, musculoskeletal disorder, endocrine disorders, and hematological disease. Model E builds on D by including ANS function indicators – RHR, RMSSD and MAP. *DistEn* distribution entropy, *HR* hazard ratio, *SD* standard deviation, *CI* confidence intervals, *CVD* cardiovascular disease, *ANS* autonomic nervous system, *RHR* resting heart rate, *bpm* beats per minute, *RMSSD* root mean square of successive differences between normal heartbeats. ^a per 1-SD decrease, ^b per 1 year increase, ^c per 1 unit increase, ^d per 1 MET-min/week increase, ^e per 1 medication increase, and ^f per 1-SD increase.

Table S2. Associations of RHR and HRV variables with all-cause and cause-specific mortality.

	All-Cause Mortality	Cardiovascular Mortality	Respiratory Mortality	Cancer Mortality
	HR (95% CI) <i>p</i> value	HR (95% CI) <i>p</i> value	HR (95% CI) <i>p</i> value	HR (95% CI) <i>p</i> value
RRI ^a	1.20 (1.09 – 1.32) 0.0002	0.95 (0.73 – 1.24) 0.80	1.25 (0.94 – 1.66) 0.11	1.38 (1.19 – 1.59) 0.0001
RRI ^a (+RMSSD)	1.14 (1.02 – 1.26) 0.02	0.85 (0.63 – 1.14) 0.28	1.16 (0.83 – 1.62) 0.38	1.33 (1.13 – 1.57) 0.0008
RRI ^a (+DistEn)	1.11 (0.98 – 1.20) 0.08	0.80 (0.60 – 1.06) 0.12	1.04 (0.77 – 1.42) 0.78	1.33 (1.13 – 1.56) 0.0005
RHR ^b	1.14 (1.06 – 1.22) 0.0002	0.97 (0.80 – 1.17) 0.80	1.21 (0.98 – 1.49) 0.08	1.26 (1.13 – 1.40) 0.0001
RHR ^b (+RMSSD)	1.10 (1.02 – 1.19) 0.02	0.89 (0.72 – 1.10) 0.28	1.12(0.87 – 1.42) 0.38	1.23 (1.09 – 1.39) 0.0008
RHR ^b (+DistEn)	1.10 (0.99 – 1.21) 0.08	0.85 (0.69 – 1.04) 0.12	1.03 (0.82– 1.29) 0.78	1.23 (1.10 – 1.39) 0.0005
RMSSD ^{†, a}	1.22 (1.09 – 1.35) 0.0003	1.41 (0.96 – 2.05) 0.08	1.39 (0.98 – 1.98) 0.06	1.25 (1.06 – 1.48) 0.009
RMSSD ^{†, a} (+RHR)	1.14 (1.02 – 1.28) 0.02	1.38 (1.00 – 1.90) 0.05	1.36 (0.92 – 2.01) 0.13	1.08 (0.90 – 1.30) 0.41
RMSSD ^{†, a} (+DistEn)	1.01 (0.90 – 1.15) 0.80	0.97 (0.70 – 1.35) 0.87	0.91 (0.64 – 1.29) 0.60	1.17 (0.94 – 1.44) 0.16
SDSD ^{†, a}	1.19 (1.08 – 1.33) 0.0009	1.28 (0.97 – 1.69) 0.08	1.47 (1.03 – 2.11) 0.04	1.25 (1.06 – 1.49) 0.009
SDNN ^{†, a}	1.26 (1.14 – 1.39) 0.0001	1.33 (1.03 – 1.74) 0.03	1.72 (1.23 – 2.40) 0.001	1.23 (1.05 – 1.45) 0.008
pNN5 ^{†, a}	1.23 (1.13 – 1.35) 0.0002	1.30 (1.03 – 1.65) 0.03	1.45 (1.08 – 1.94) 0.01	1.22 (1.06 – 1.40) 0.005
MAP ^c	1.05 (0.95 – 1.16) 0.35	1.02 (0.77 – 1.36) 0.88	0.74 (0.52 – 1.05) 0.10	1.05 (0.90 – 1.22) 0.57

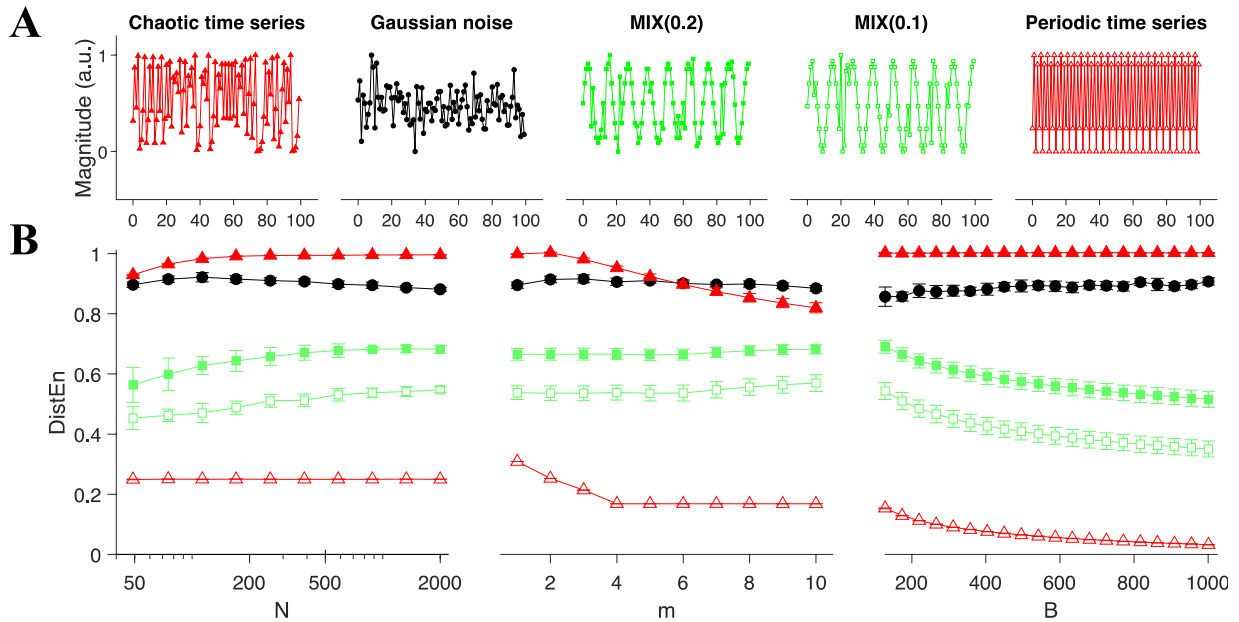
Cox proportional hazards for associations between RHR, time-domain HRV variables, and MAP with all-cause mortality and cause-specific mortality (cardiovascular, respiratory and cancer related mortality) using our fully adjusted Model E. ^afor 1-SD decrease. ^bfor 10bpm increase. ^cfor 1-SD increase. *SD* standard deviation, *HR* hazard ratio, *CI* confidence interval, *RRI* RR interval, *RHR* resting heart rate, *HRV* heart rate variability, *RMSSD* root mean square of the successive differences between normal heartbeats, *SDSD* standard deviation of successive RRI, *SDNN* standard deviations of NN intervals, *pNN5* percentage of successive normal cardiac interbeat intervals greater than 5ms, *MAP* mean arterial pressure. [†]log transformed.

Figure S1. Demonstration and further description of the DistEn algorithm.



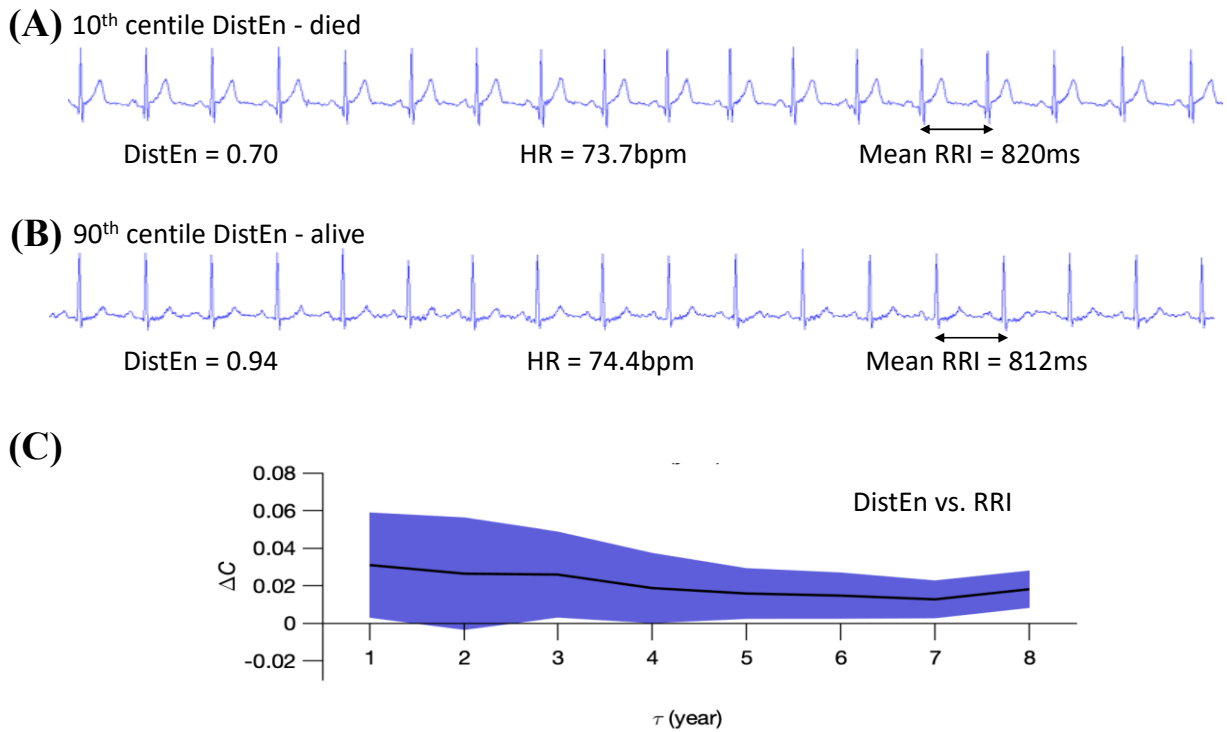
(A) An exemplary time series of 1000 points $\{x(i), 1 \leq i \leq 1000\}$. **(B)** The first 20 vectors $\mathbf{X}(i)=\{u(i), u(i+1), \dots, u(i+m-1)\}, 1 \leq i \leq 20$ in the state space after embedding state-space reconstruction. Here m indicates the embedding dimension which is set as 3. **(C)** The distance matrix $\mathbf{D}=\{d_{ij}\}$ with each element being the Chebychev distance among vectors $\mathbf{X}(i)$ and $\mathbf{X}(j)$ for all $1 \leq i, j \leq N - m$, i.e., $d_{ij} = \max\{|u(i+k) - u(j+k)|, 0 \leq k \leq m-1\}$. **(D)** Probability density of d_{ij} estimated using histogram. If the histogram has B bins, we use $p_t, t = 1, 2, \dots, B$ to denote the probability (frequency) of each bin. To reduce bias, elements with $i = j$ are excluded when estimating the ePDF. Then DistEn can be calculated by the Shannon entropy formula normalized by the theoretical maximum $\log(B)$.

Figure S2. DistEn simulation showing stability and consistency of results across data length and parameter selection.



A: Theoretical time series with known complexity levels were generated to test the performance of DistEn. We simulated chaotic series, Gaussian noise, MIX(p) processes, and a periodic signal. Magnitude of signal in arbitrary units (a.u.) over time in seconds. The Logistic attractor $x(n+1) = \omega \times x(n) \times (1 - x(n))$ was considered with $\omega = 4.0$ for chaotic series and $\omega = 3.5$ for periodic signals (period 4), respectively. The MIX(p) process is generated by a sinusoid signal of length N, with $N \times p$ randomly chosen points being replaced with independent identically distributed random noise. We applied $p = 0.1$ and 0.2 , respectively, to generate two MIX(p) processes with different complexity levels. The Gaussian noise was generated by the random number function (randn) in MATLAB. **B: DistEn as a function of data length N (left panel)**, set at 10 values between 50 to 2,000, in the aforementioned five time series. *Error bars* indicates the standard deviation of 20 results. Note the relative stability i.e. narrow error bars of DistEn, and ability to separate all five signals across varying short signal lengths, N. **DistEn as a function of input parameter, m (middle panel)**: the dimension parameter (1 to 10). DistEn is consistent for MIX(p) signals and separate them well from other signals across the most commonly used 2, 3 or 4 values and beyond. **DistEn as a function of input parameter, B (right panel)**: the number of bins selected (128 to 1024) when m is held constant at 3. Again, note the relative consistency of results for DistEn, and ability to separate all five signals across varying number of bins selected, B.

Figure S3. ECG strips over 15s for two males with similar HR and mean RRI, and direct comparison of DistEn and RRI model performance



(A) Male subject within 10th centile DistEn who died during follow-up **(B)** Male subject within 90th centile DistEn who survived during follow-up. *DistEn* Distribution Entropy; *HR* heart rate; *RRI* RR-interval. Note the difference in the dynamical patterns is not visible to the naked eye, despite differences in nonlinear measures such as DistEn. **(C)** In a direct comparison between DistEn and RRI survival models (adjusting for age, sex and education), DistEn was superior across follow-up years. ΔC , difference in concordance index (c-stat), shaded region represents 95% confidence intervals after 100 iterations.