Speed of Heart Rate Recovery in Response to Orthostatic Challenge: 
A Strong Risk Marker of Mortality

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ABSTRACT

**Rationale:** Speed of Heart Rate Recovery (HRR) may serve as an important biomarker of aging and mortality.

**Objective:** To examine whether the speed of HRR following an orthostatic maneuver (i.e. active stand from supine position) predicts mortality.

**Methods and Results:** A longitudinal cohort study involving a nationally representative sample of community dwelling older persons aged 50 years+. 4475 participants completed an active stand at baseline as part of a detailed clinic-based cardiovascular assessment. Beat-to-beat heart rate and blood pressure responses to standing were measured over a two-minute window using a finometer and binned in 10-second intervals. We modeled HRR to the stand by age group, cardiovascular disease burden, and mortality status using a random effects model. Mortality status over a mean follow-up duration of 4 years served as the primary end-point (n=138). Speed of HRR in the immediate 20 seconds after standing was a strong predictor of mortality. A one beat per minute slower between 10 and 20 seconds after standing increased the hazard of mortality by 6% controlling for established risk factors. A clear dose-response relationship was evident. 69 participants in the slowest HRR quartile died over the observation period compared with 14 participants in the fastest HRR quartile. Participants in the slowest recovery quartile were 2.3 times more likely to die compared with those in the fastest recovery quartile.

**Conclusions:** Speed of orthostatic HRR predicts mortality and may aid clinical decision making. Attenuated orthostatic HRR may reflect dysregulation of the parasympathetic branch of the autonomic nervous system.

**Keywords:** Heart rate recovery; mortality; autonomic nervous system; epidemiology.
Nonstandard Abbreviations and Acronyms:

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<th>Abbreviation</th>
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INTRODUCTION

Much recent work has focused on the prognostic value of heart rate recovery (HRR) post-exercise as a risk factor for cardiovascular disease (CVD) and mortality \(^1\)\(^5\). Vagal reactivation plays an integral role in modulating the rate at which the heart rate recovers after exercise, especially during the first 30 seconds \(^6\) and up to two minutes \(^3\). A reduction in vagal tone and an increase in activity of the sympathetic nervous system are associated consistently with an increased risk of cardiovascular events, including sudden death \(^4\),\(^7\),\(^8\) and with all-cause mortality. More recently, the vagus nerve has also been shown to have a reflexive role in modulating pro-inflammatory signaling \(^9\),\(^10\) which may in part contribute to the association with CVD and mortality.

The autonomic nervous system plays a central role in regulation of cardiovascular and humoral responses to orthostasis. Orthostasis evokes a rapid physiological response involving the co-ordinated action of a number of systems including the skeletal-muscle pump, and arterial and cardiopulmonary baroreflexes \(^11\). The orthostatic response reflects a balance between cardiac output and total peripheral resistance modulated by the autonomic nervous system and baroreflexes, and most commonly measured using changes in heart rate and blood pressure. When resting in the supine position, venous and arterial reservoirs are at the same height, but standing up reduces venous return by displacing approximately 500/700 ml (10 ml/kg) of central blood into the peripheral system.

Heart rate increases rapidly in the first few seconds after standing to counteract the gravitational forces acting on blood pressure that propels blood towards the lower extremities (Figure 1). The initial surge in heart rate, which occurs in the first few seconds after standing results from abrupt inhibition of vagal activity \(^12\)-\(^14\). The peak heart rate, which is reached at about 10 seconds after standing is a product of vagal inhibition and (slower acting) sympathetic systems acting in concert. Heart rate declines rapidly after this point as a result of rebounding arterial pressure \(^13\). There is a particularly steep drop in heart rate between 10 and 20 seconds and an age gradient with heart rate and blood pressure responses \(^15\).

With a few exceptions \(^2\) most of the studies examining HRR in response to exercise have been conducted in symptomatic, clinically referred samples so the ecological validity of these findings for the general population remains questionable. Furthermore, there is no standard protocol for measuring HRR \(^16\),\(^17\). Recovery values have been measured at time intervals ranging from 1 to 5 minutes following the cessation of treadmill exercise, and what constitutes a slow HRR has varied from study to study. Few studies have explored the hemodynamics of the HRR during the time period when the speed of recovery towards baseline is at its most pronounced; that is, in the immediate 30 seconds following the cessation of exercise \(^18\). Finally, HRR to orthostasis has not been widely studied despite the fact that the results of at least two studies suggest that shifts in cardiac autonomic balance in response to standing may have promise as predictors of mortality \(^19\),\(^20\).

Given that standing can be easily performed by anyone who is functionally mobile and is a potent cardiovascular stressor that demands the full capabilities of the reflexes that govern cardiovascular function \(^21\), we examined the predictive value of HRR to standing in a large adult population study and further describe a novel measure of autonomic dysregulation.

The Irish Longitudinal Study on Ageing (TILDA) is a population-based nationally representative cohort study of ageing in the Republic of Ireland that measures continuous non-invasive beat-to-beat heart rate and blood pressure responses to orthostatic change in community-dwelling older persons aged 50 and upwards as part of a comprehensive multidisciplinary assessment \(^22\). In this paper we describe the development and validation of a new biomarker of cardiovascular ageing derived from the active stand procedure; specifically the speed of HRR between 10 and 20 seconds after standing, and show that this parameter has clinical relevance as a marker of ageing, cardiovascular disease, and all-cause mortality.
METHODS

Study design and participants.
The Irish Longitudinal Study on Ageing (TILDA) is a large prospective cohort study examining the social, economic and health circumstances of 8,175 community-dwelling older adults, aged 50 years and older, resident in the Republic of Ireland. The sample was generated using a 2-stage clustered sampling process and the Irish Geodirectory as the sampling frame. The Irish Geodirectory is a comprehensive listing of all addresses in the Republic of Ireland which is compiled by the national post service and ordnance survey Ireland. The primary sampling units were 640 geographic regions selected by random selection, stratified on proportion of head of households in the professional class, proportion of the population aged 65 years and older; and geographical location. The second stage involved the selection of a random sample of 40 addresses from within each primary sampling unit, resulting in an initial sample of 25,600 addresses. Addresses were then assessed for eligibility and members of eligible households aged 50 years and over were canvassed to participate. Consequently, the response rate was defined as the proportion of sampled households including an eligible participant from whom an interview was successfully obtained. A response rate of 62.0 percent was achieved at the household level.23 The baseline survey (Wave 1) occurred in 2009/2011.

Respondents completed a computer assisted personal interview (CAPI) (n=8175) in the home. All participants were subsequently invited to undergo a detailed clinic-based health assessment in one of two national centers using trained nursing staff. A total of 5035 people attended the health centre assessment at Wave 1. One hundred and fifteen individuals were unable to complete the active stand and data for a further 445 were excluded due to poor signal quality, incomplete data, or poor compliance with protocol15. This left a final total of 4475 people who completed the active stand procedure. Online Figure 1 presents the flow diagram for study participation.

Ethics statement.
Ethical approval for the study was obtained from the Trinity College Dublin Research Ethics Committee. Signed informed consent was obtained from all participants.

Heart rate and blood pressure measurement.
A detailed description of the active stand protocol employed in TILDA is available elsewhere.24 Briefly, participants who attended the health center completed an active stand from a supine position as part of a detailed cardiovascular health assessment. A pressure cuff was applied to the finger of each participant to measure their phasic blood pressure. Participants rested comfortably in the supine position for 10 minutes prior to performing the stand in a quiet room with an ambient temperature ranging between 21-23°C. Participants were asked to stand in a timely manner (<5 seconds) under the supervision of a nurse and were assisted to stand if this proved necessary.

The zero time point for each individual was set by the clinical nurse at the point where the participant began to rise from the supine position. Beat-to-beat variability in heart rate and blood pressure during the stand were captured using non-invasive digital photoplethysmography (Finometer, Finapres Medical Systems, Arnhem, Netherlands). Data was corrected for hydrostatic changes in finger pressure due to standing using the Height Correction Unit employed by the Finometer device. The following parameters were extracted:
• The supine baseline values of heart rate (HR_b) systolic blood pressure (SBP_b), and diastolic blood pressure (DBP_b) occurring 60 seconds prior to standing.

• Recovery values for heart rate, systolic blood pressure, and diastolic blood pressure at 10 second time intervals between 10-110 seconds after the stand. The full beat-to-beat data traces were filtered using a non-stationary moving average filter. Recovery values at each 10 second time interval represented a moving average ±2.5 seconds around that time point. These values are denoted HR(t), SBP(t), and DBP(t), where t is time in seconds after standing and takes on values of 10-110 seconds.

• Difference from baseline measures were obtained by subtracting values of HR(t) at each time point from the baseline resting heart rate (HR_b). These values are denoted ΔHR(t). This process was repeated for SBP and DBP. These values are denoted ΔSBP(t) and ΔDBP(t).

Endpoints – All-cause mortality.
Mortality status was established through attempts at contact with participants at Wave 2 (approximately 2 years after baseline) and Wave 3 (approximately 4 years after baseline). In total, 549 of the 8175 persons or 6.7% of the sample who were initially recruited were confirmed as deceased by up to a maximum of six year follow-up. Of the 4475 persons who completed the active stand at Wave 1, 141 were confirmed as dead as of 18th December 2015 (i.e. the last interview date for Wave 3 data collection) which is an effective mortality rate of 3.2%.

Time of death was available for 72% (n=102/141) of the deceased from an ‘End of Life’ (EOL) interview that was conducted with the respondent’s surviving kin. Time of death was unavailable for the remaining 27% of the sample because TILDA allows a period of 6 months to elapse before attempting to conduct an EOL interview with the spouse/family of recently deceased cohort members. In these instances, time of death was determined if a family member/spouse of the deceased informed the TILDA fieldwork team of the date of death. In the remaining cases of confirmed deaths, time of death was established using a database operated by funeral directors in Ireland to notify deaths. Respondents were identified on the basis of a name and address match. There were 3 remaining cases where date of death could not be determined. In these instances we imputed date of death as half of the mean between-wave interval after the ‘date of last contact’.

It was not possible to establish whether all participants at Wave 1 were either deceased or still living by Wave 3. Of the sample of 8,175 completing Wave 1 and the subset of 4,475 completing the active stand respectively, 764 (9.3%) and 166 (3.7%) were either lost to follow-up or refused to participate further by Wave 2, and did not participate at Wave 2 and Wave 3. The surveillance interval was not constant for all participants due to unequal intervals between interviews, loss to follow-up, and mortality itself. This interval ranged from 1 day to 5.8 years, with an average of 4 years. One hundred and thirty-eight persons who completed the stand at Wave 1 and were confirmed as subsequently deceased had complete information on all covariates.

Primary predictor variable.
We initially explored variation in HRR across the stand using 3 broad age groups: 50-59, 60-69, and 70 years+. Preliminary investigation of the data revealed that the speed of HRR in the early part of the stand differentiated strongly between age groups; specifically the speed of HRR between 10 and 20 seconds after standing. We extracted an additional parameter to describe the speed of HRR during this time window (described in the statistical analysis section below) and it served as the primary predictor variable in the analysis.

Covariates.
The covariates were chosen based on their association with mortality and speed of HRR in the literature. All of the covariates were measured at baseline during the Wave 1 sweep of data collection. In addition to age, and sex, resting HR (bpm) and resting SBP (mmHg), we control for use of anti-cardiovascular
medications. The international non-proprietary name (INN) for any regularly taken medications was assigned and coded using Anatomic Therapeutic Classification Codes (ATC). Cardiovascular medications were anti-adrenergics (C02), diuretics (C03), beta-blockers (C07), calcium channel blockers (C08), and ACE inhibitors (C09). Medical history, including pre-existing doctor diagnosed CVDs that represent hard end-points (angina, heart attack, congestive heart failure, stroke, and transient ischemic attack) were ascertained during the household interview. Participants with atrial fibrillation were identified as such if they self-reported having an abnormal heart rhythm and this was confirmed from the electrocardiogram recording. These data were then pooled to create a 3-level CVD disease measure: CVD free, one CVD, two+ CVDs, for use in the analysis.

We also include controls for a number of specific co-morbidities that could affect exercise and exertion levels required when actively standing from the supine position. Having ever received a doctor diagnosis of cancer, lung disease, or diabetes, is represented by a series of binary variables in the analysis. Limitations in activities of daily living (ADLs), and instrumental activities of daily living (IADLs) are included as a proxy for the participant’s general physical condition. ADLs included difficulties with: (1) dressing, (2) walking across a room, (3) bathing or showering, (4) eating, such as cutting up food, (5) getting in or out of bed, and (6) using the toilet. IADLs included: (1) difficulties in preparing a hot meal, (2) doing household chores, (3) shopping for groceries, (4) making telephone calls, (5) taking medications, (6) managing money. We summed the number of conditions separately with respect to ADLs and IADLs and the count of these conditions is used in the analysis.

Lifestyle factors included prior smoking history, which is represented as a 3-level variable: never smoked, past smoker, current smoker; Body Mass Index (BMI) (measured weight / measured height m²), and serum lipids. BMI was measured at the clinic visit by trained nursing staff using scientifically approved and calibrated measuring equipment. Participants also provided a blood sample during the course of the health assessment and these were sent for immediate analysis to derive a detailed lipid profile which included high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides. Finally, we also include a control for educational attainment which is represented as a 3-level variable: primary, secondary, tertiary education.

Statistical analysis.
Repeated observations of HR at 10-second intervals within a cross-section allows treatment of the data as a panel (measurement occasions nested within individuals) and fitting of a random effects model using generalized least squares estimation. We explored age related variation in HRR across the stand for different age groups (50-59, 60-69 and 70+ years of age) controlling for sex, existing cardiovascular disease (CVD), and use of cardiovascular medications by fitting the following model (Equation 1) to the data of N individuals, with an individual denoted by i at time j (tij) post-stand:

\[ y_{ij} = \alpha + \beta_j t_{ij} + \gamma X_i + \delta t_{ij} X_i + u_i + e_{ij} \]  

Eq1.

Where \( i = (1, ..., N), j = (1, ..., 11) \) and \( y_{ij} \) represents the difference in HR from baseline (ΔHR) at \( t_{ij} \), \( \alpha \) is the intercept, \( \beta_j \) is the coefficient for each time point at the reference level of each covariate, \( X_i \) represents a vector of individual-level covariates: age group (50-59, 60-69, 70+ years), sex, existing cardiovascular disease (none, one, two or more CVDs), and use of cardiovascular medications (no, yes), and \( \gamma \) is the related row vector of coefficients. A cross-level interaction term between time (\( t_{ij} \)- level 1) and individual-level covariates (\( X_i \) - level 2) is given by \( t_{ij} X_i \) and where \( \delta \) is the related row vector of coefficients. This allows HRR to vary over time by age group and by other covariate groups. The terms \( u_i \) and \( e_{ij} \) are residuals representing an unobserved individual effect and an error term for person \( i \) at time \( j \), sampled from normal distributions with variances \( \tau^2 \) and \( \sigma^2 \) respectively. The model thus contains 77 fixed-effects parameters and 2 random effects parameters. The predictive margins at the means and the associated 95% confidence intervals for the cross-level (time × age group) interaction were derived and plotted.
Visual inspection of the resulting plots revealed that the speed of HRR in the early part of the stand (i.e. initial 20 seconds) was the orthostatic feature that most clearly distinguished younger from older participants. Older people experienced a less vigorous increase in HR upon standing and a slower recovery towards baseline between 10 and 20 seconds relative to those aged 50-59 years. Additional parameters were therefore extracted to represent the speed of HRR during this time frame by subtracting the difference from baseline value of HR at 10 seconds from the value at 20 seconds (Equation 2). This is equivalent to simply calculating the absolute difference in heart rate values between 10 and 20 seconds after standing.

\[
\text{Speed of HRR}_{10\text{secs}|20\text{secs}} = (\Delta HR_{20\text{secs}} - \Delta HR_{10\text{secs}}) \quad \text{Eq2.}
\]

Differences in the rate of change (i.e. slope) across age groups between 10 and 20 seconds following the stand was confirmed by performing significance tests for difference. Because it is clinically difficult to uncouple the speed of HRR from the BP response, parameters were also extracted to represent the speed of the SBP (Equation 3) and DBP recovery occurring at the same time point (Equation 4).

\[
\text{Speed of SBP recovery}_{10\text{secs}|20\text{secs}} = (\Delta SBP_{20\text{secs}} - \Delta SBP_{10\text{secs}}) \quad \text{Eq3.}
\]

\[
\text{Speed of DBP recovery}_{10\text{secs}|20\text{secs}} = (\Delta SBP_{20\text{secs}} - \Delta SBP_{10\text{secs}}) \quad \text{Eq4.}
\]

The bivariate association of each of the parameters extracted from the stand with participants’ age at baseline was examined using Spearman’s rank-order correlation coefficient. This analysis confirmed that the speed of \( HRR_{10\text{secs}|20\text{secs}} \) was the parameter that was most strongly correlated with age. To check clinical relevance, we compared the speed of \( HRR_{10\text{secs}|20\text{secs}} \) in those with and without CVD, and examined its association with the probability of mortality over an average 4 year follow-up.

We also calculated the receiver operating characteristic curves predicting mortality in a series of separate univariate analyses with respect to each of the HR, SBP and DBP parameters extracted from the stand, which was implemented using the ROCTAB 25 procedure in STATA.

We followed the American Heart Association’s recommendations for the evaluation of a novel risk marker 26 to assess the prognostic value of the speed of \( HRR_{10\text{secs}|20\text{secs}} \). Cox proportional hazards models 27 were fitted to the data to determine whether the speed of \( HRR_{10\text{secs}|20\text{secs}} \) was associated with time to death (month and year of death) up to a maximum of 6 years after initial assessment. The crude model (model 1) estimated the impact of a 1 beat per minute change in the speed of \( HRR_{10\text{secs}|20\text{secs}} \) on the hazard of mortality. Model 2 adjusted additionally for a range of covariates measured at baseline: (resting HR, resting SBP, sex, cardiovascular medications, CVDs, cancer, lung disease, diabetes, ADLs, IADLs, smoking status, BMI, serum lipid profile, and educational status) to determine whether the speed of \( HRR_{10\text{secs}|20\text{secs}} \) was independently associated with hazard of mortality in a multivariable model. Model 3 added age and an age squared term to the equation to determine whether the speed of \( HRR_{10\text{secs}|20\text{secs}} \) predicted mortality independently of age.

Discrimination performance was assessed using Harrell’s C index and Somer’s D index. As described by Pennells et al. 28, the C index estimates the probability of concordance between predicted risk and the observed order of events for a randomly selected pair of participants. The D index estimates the mean log hazard ratio for the event of interest for a randomly selected pair of participants; one in the top half and one in the bottom half of the predicted risk distribution. We estimate first the model with the established risk markers then we estimate the model with the established risk markers and the novel risk marker \( (HRR_{10\text{secs}|20\text{secs}}) \) to determine whether it leads to an improvement in prediction. The predictive accuracy of the novel risk marker was further assessed using the net reclassification improvement (NRI) index 29 based on continuous predictions from a binary model predicting probability of mortality at the end of the surveillance period for each individual as described in the online supplementary methods section.
**Missing data and non-response.**

Only 110 participants, 3 (2.3%) of the 141 confirmed deceased, and 107 (2.5%) of the 4227 alive at last contact had one or more missing covariates so we report the results from the complete case analysis. Standard errors of estimates were adjusted to account for the clustered design effect and stratification, and data were weighted using survey weights to account for the fact that respondents who attended the health centre were younger, better educated, and in better health.

**RESULTS**

Mean age of the sample was 62.8 years (SD=9.2), 51.3% were female, and 35.5% were taking cardiovascular medications. Almost 12% of the sample had a doctor diagnosed CVD. The mean $HRR_{10\text{sec}|20\text{sec}}$ was -5.78 bpm (SD=7.06). Table 1 describes the baseline characteristics of the sample and how they vary according to quartiles of $HRR_{10\text{sec}|20\text{sec}}$. For example, mean age of those in the slowest HRR quartile was 67.8 years compared with a mean age of 57.7 years among those in the fastest HRR quartile. Similarly, 49.1% of those in the slowest HRR quartile were taking cardiovascular medications compared with 19.3% of those in the fastest HRR quartile. Figure 1 illustrates the mean unadjusted orthostatic HR, SBP and DBP response to standing for the sample. It shows that HR increases rapidly in the first 10 seconds after standing and then declines quickly between 10 and 20 seconds. This pattern is more or less reversed with respect to SBP and DBP, which fall rapidly in the first 10 seconds but recover quickly between 10 and 20 seconds.

Table 2 summarises the bivariate association between age and the array of HR, SBP and DBP parameters extracted from the stand. The speed of HRR between 10 and 20 seconds ($HRR_{10\text{sec}|20\text{sec}}$) after standing was the parameter that was most strongly correlated with age ($r = 0.40$). It was more strongly correlated with age than any of the difference from baseline measures of HR, SBP, or DBP, or indeed the speed of the $\Delta HR_{10\text{sec}}$ ($r = -0.16$) and $DBP_{10\text{sec}|20\text{sec}}$ recovery ($r = -0.23$). The $\Delta HR_{10\text{sec}}$ was the only other variable extracted from the stand that correlated greater than 0.30 ($r = -0.33$) with age.

Figures 2a – 2d shows that older participants were characterised by a slower heart rate recovery towards baseline in the immediate 20 seconds after standing compared with younger participants in the sample. The speed of $HRR_{10\text{sec}|20\text{sec}}$ was -8.21 bpm for those aged 50-59 years (Figure 2a), -5.25 bpm for those aged 60-69 (Figure 2b), and -2.51 bpm for those aged 70 years and over (Figure 2c). Figure 2d shows the speed of recovery for all age groups simultaneously.

Figures 3a – 3d show slower $HRR_{10\text{sec}|20\text{sec}}$ among those with higher CVD burden. Individuals who were free of CVD at Wave 1 experienced a greater deceleration in heart rate between 10 and 20 seconds after standing (-6.30 bpm – Figure 3a) compared with those who had one CVD (-5.50 bpm – Figure 3b) or two or more CVDs (-4.26 bpm – Figure 3c). Figure 3d shows these relationships simultaneously. Formal statistical tests confirmed that the speed of $HRR_{10\text{sec}|20\text{sec}}$ was significantly faster among those who were CVD free compared with those who had two or more CVDs.

The speed of $HRR_{10\text{sec}|20\text{sec}}$ also distinguished those who completed the stand at baseline and had died over a mean 4 year follow-up. Figures 4a - 4c illustrate this relationship graphically showing that the average $HRR_{10\text{sec}|20\text{sec}}$ at Wave 1 for those who subsequently died was -3.53 bpm compared with an average $HRR_{10\text{sec}|20\text{sec}}$ of -6.30 bpm for those who were still alive at follow-up. The results of the receiver operating characteristic analyses are presented in Online Table 1. The majority of the difference from baseline measures of HR, SBP and DBP did not perform significantly better than chance in predicting mortality. Notably, the area under the curve (AUC) was greatest for the speed of $HRR_{10\text{sec}|20\text{sec}}$ [AUC = 0.69, 95% CI
= 0.64, 0.73], though comparable with the difference from baseline value of heart rate at 10 seconds: \( \Delta HR_{10\text{secs}} \) [AUC = 0.66, 95% CI = 0.62, 0.71].

The speed of \( HRR_{10\text{secs}|20\text{secs}} \) was related to all-cause mortality in univariable and multivariable Cox regression analyses. In the crude analysis (model one), a one bpm slower \( HRR_{10\text{secs}|20\text{secs}} \) was associated with a 10% increase [Hazard Ratio=1.10, 95% CI=1.08, 1.13; \( p<.001 \)] in the risk of all-cause mortality over a mean 4 year follow-up period. The association was robust to adjustment for a broad range of established risk markers measured at baseline (model 2), including resting HR, resting SBP, sex, use of cardiovascular medications, existing CVD burden, lung disease, cancer, diabetes, ADLs, IADLs, smoking, BMI, serum lipids and education [Hazard Ratio=1.09, 95% CI=1.06, 1.13; \( p<.001 \)]. The speed of \( HRR_{10\text{secs}|20\text{secs}} \) remained a significant predictor of all-cause mortality even when adjusted additionally for age and age\(^2\) in model 3 [Hazard Ratio=1.06, 95% CI=1.03, 1.10; \( p<.001 \)].

We observed small incremental gains in the C index [0.810 vs 0.816] and D index [0.620 vs 0.633] when we added speed of \( HRR_{10\text{secs}|20\text{secs}} \) to the model containing the established risk factors predicting mortality. Net reclassification resulted in 78 deaths having greater predicted risk and 60 deaths having lower predicted risk in the model with \( HRR_{10\text{secs}|20\text{secs}} \) compared with the model without. Similarly, 2503 non-deaths had lower predicted risk and 1724 non-deaths had greater predicted risk in the model with \( HRR_{10\text{secs}|20\text{secs}} \) compared to the model without. The continuous NRI was 0.315 [95% CI=0.147, 0.483].

To facilitate exploration of dose-response effects, we calculated the Hazard Ratio and associated 95% confidence intervals for all-cause mortality according to quartiles of \( HRR_{10\text{secs}|20\text{secs}} \). The mean \( HRR_{10\text{secs}|20\text{secs}} \) for those in the fastest recovery quartile was -15.31 bpm. By comparison, the mean \( HRR_{10\text{secs}|20\text{secs}} \) for those in the slowest recovery quartile was positive (+2.11 bpm) which means that on average, these individuals experienced an increase in heart rate between 10 and 20 seconds after standing.

Kaplan Meier survival curves according to quartiles of \( HRR_{10\text{secs}|20\text{secs}} \) are depicted in Figure 5. Table 3 (model 1) shows that in the crude model, those in the slowest quartile of \( HRR_{10\text{secs}|20\text{secs}} \) were 7.0 times [95% CI=3.7, 13.4; \( p<.001 \)] more likely to experience mortality over a mean follow-up duration of four years compared with those in the fastest recovery quartile; and there was a clear dose-response relationship between the speed of \( HRR_{10\text{secs}|20\text{secs}} \) and risk of all-cause mortality. In the full multivariable adjusted model, those in the slowest recovery quartile remained 2.3 times [95% CI=1.1, 4.5; \( p<.05 \)] more likely to experience all-cause mortality compared with those in the fastest recovery quartile.
DISCUSSION

In this large epidemiological study of ageing, the speed of HRR between 10 and 20 seconds \((HRR_{10\text{sec}}|20\text{sec})\) after standing was a clear risk marker for mortality over a mean 4 year follow-up. The reason why this slope parameter performs better than simply using difference from baseline measures at each time point is that it takes account of how far HR rises upon standing and how quickly it recovers towards baseline. To some extent we believe it may be useful to conceive of the slope parameter as a measure of heart rate elasticity as it reflects both the capacity of the system to mount a vigorous response to cardiovascular challenge and to quickly re-establish homeostatic equilibrium. Viewed in this context, an attenuated HRR to the active stand may reflect dysregulation of the parasympathetic branch of the autonomic nervous system as parasympathetic inhibition is largely responsible for the initial surge in HR following the stand \(^{15}\), while parasympathetic reactivation is believed to be responsible for the speed of HRR in the early phase of recovery \(^{30,31}\). Imai et al. \(^{30}\) found that pharmacologic blockade of parasympathetic reactivation using atropine delayed cardiac heart rate deceleration, particularly in the initial 30 seconds of the post-exercise recovery phase.

Consistent with expectations for a powerful risk marker, the speed of \(HRR_{10\text{sec}}|20\text{sec}\) distinguishes between different age groups, demarcates those with existing CVD from those who are CVD-free, and has predictive power as an indicator of all-cause mortality independent of other established risk markers. In the crude analysis, a one beat per minute slower \(HRR_{10\text{sec}}|20\text{sec}\) was associated with a 10% increase in the risk of all-cause mortality over a mean four-year follow-up period. The risk of mortality increased as the speed of \(HRR_{10\text{sec}}|20\text{sec}\) declined. A person in the slowest quartile of \(HRR_{10\text{sec}}|20\text{sec}\) was 7.0 times more likely to die at follow-up compared with those in the fastest recovery quartile. These associations were robust to adjustment for established risk factors, and remained significant even when adjusted for age, though the latter strongly attenuated the associations. What seems clear is that the speed of \(HRR_{10\text{sec}}|20\text{sec}\) has clinical value as a marker of health and may help identify individuals at risk of mortality. Given that we have limited mortality data, the magnitude of the effect sizes would seem to indicate that we have identified a parameter from the stand that has important clinical relevance.

It should be acknowledged that the novel risk marker led to, at most, moderate gains in the discrimination and accuracy of prediction as assessed using measures of concordance (C-index and D-Index) and net reclassification improvement (NRI). This is perhaps not unexpected given that, as a prospective epidemiological study of ageing, the TILDA sample is so well characterised in terms of established risk markers. However, in the context of a clinical setting where all of these covariates are not readily available to the clinician, the speed of \(HRR_{10\text{sec}}|20\text{sec}\) may serve as a useful adjunct to help guide clinical decision making.

Limitations.

Only a small number of cases who completed the stand \((n=138)\) and had full information on covariates had died at follow-up so the confidence intervals around the estimates are large. Despite this, the magnitude of the effect sizes support the use of orthostatic HRR as a robust risk marker. Secondly, information was not available concerning cause of death and the numbers would likely be too small to disaggregate and analyze by disease type. It is entirely possible that the predictive power of \(HRR_{10\text{sec}}|20\text{sec}\) would be higher if we were predicting cardiovascular as opposed to all-cause mortality. Future research with this cohort will be directed towards this end, particularly if we are able to link individual-level clinical data to administrative sources of data (i.e. National Death Registry). Finally, another criticism that could be leveled at the study is that a sizeable proportion of the sample did not attend the health centre assessment, and a sizeable subset of individuals who did attend the health centre assessment did not complete the stand, which may raise concerns about the ecological validity of the findings for the general population. Notwithstanding this caveat, it is important to acknowledge that individuals who attended the health centre...
assessment tended to be younger and in better health compared with those who did not attend. This can be adduced from the fact that the mortality rate was 6.7% in the overall sample compared with 3.2% among those who completed the stand. As the derived estimates were likely to be conservative, we employed survey weights in the analysis to take account of non-participation in the health center component.

Strengths.

The study also has a significant number of strengths. Firstly, it utilizes a large representative sample of the community dwelling older population and a novel measure of cardiovascular functioning (i.e. active stand) that is rare in the context of an epidemiological study. Secondly, beat-to-beat measurement of heart rate and blood pressure affords us the resolution to explore features of the cardiovascular response to standing during a time period (i.e. initial 20 seconds) that is of potential theoretical interest as it is arguably indexing the balance of sympathetic and parasympathetic systems. The study also benefits from the strong in-depth characterization of the sample, which means that we are able to control for a large range of variables that could potentially confound the relationship between our putative measure of cardiovascular ageing and mortality.

Conclusions.

The speed of orthostatic HRR between 10 and 20 seconds identifies those who are at high risk of mortality. This has important clinical applications because the speed of heart rate recovery is a clinical variable that may be useful for population screening. Although HRR is modifiable by, for example, physical activity interventions, whether modifying HRR directly reduces mortality requires further study. Future intervention studies should be designed to explore this possibility.

ACKNOWLEDGEMENTS

We would like to thank the TILDA participants who provided the data for this paper.

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DISCLOSURES

None.
REFERENCES


DOI: 10.1161/CIRCRESAHA.116.308577
FIGURE LEGENDS

**Figure 1:** Mean Heart Rate and Systolic and Diastolic Blood Pressure Values across the Stand (Including Baseline). The hemodynamics of the cardiovascular response to standing among the 4475 TILDA participants who completed the active stand is shown in Figure 1 above. Baseline values for HR and BP are obtained 60 seconds prior to standing. There is a brief initial rise in BP upon standing owing to the strain of the maneuver, but SBP and DBP drops quickly thereafter, reaching a nadir at about 10 seconds and recovering quickly towards baseline between 10 and 20 seconds. HR increases rapidly in the first 10 seconds to counteract the gravitational forces acting on BP, peaks at about 10 seconds and declines rapidly between 10 and 20 seconds.

**Figures 2a - 2d:** Speed of Heart Rate Recovery Following Orthostatic Challenge by Age Group. The hemodynamics of the heart rate response to standing over the two-minute time horizon is presented separately for different age groups: 50-59 (Fig. 2a), 60-69 (Fig. 2b), and 70+ years of age (Fig. 2c). The estimates were derived controlling for sex, existing cardiovascular disease burden, and use of cardiovascular medications. The speed of heart rate recovery between 10 and 20 seconds after standing declines with age. Younger individuals are characterized by a steeper initial rise in heart rate and a faster return towards baseline (i.e. more precipitous drop) during this time period. Figure 2d shows the relationships for all age groups simultaneously. Note that the speed of heart rate recovery between 10-20 seconds is the time point where the difference between age groups is most pronounced. Error bars represent the 95% confidence intervals.

**Figures 3a – 3d:** Speed of Heart Rate Recovery Following Orthostatic Challenge by Cardiovascular Disease Burden. The hemodynamics of the heart rate response to the active stand over the two-minute time horizon is presented separately for those who were free of CVD at Wave 1 (Fig. 3a), for those with one CVD (Fig. 3b) and for those with two or more CVDs (Fig. 3c). The estimates were derived adjusting for, age, sex, and use of cardiovascular medications. Those with higher cardiovascular disease burden are characterised by slower heart rate recovery between 10 and 20 seconds after standing. Figure S1d shows these relationships simultaneously. Error bars represent the 95% confidence intervals.

**Figures 4a - 4c:** Speed of Heart Rate Recovery Following Orthostatic Challenge by Incident Mortality Status. The hemodynamics of the heart rate response to standing over the two-minute time horizon is presented separately for those who completed the stand at wave 1 and were still alive at follow-up (Figure 4a) and those who had died at follow-up (Figure 4b). The estimates were derived controlling for, age, sex, existing cardiovascular disease burden, and use of cardiovascular medications. Respondents who died were characterized by a slower heart rate recovery between 10 and 20 seconds relative to those who were still alive. Figure 3c shows these relationships simultaneously. Error bars represent the 95% confidence intervals.

**Figure 5:** Kaplan Meier Survival Probability Curves According to Quartiles of Heart Rate Recovery between 10-20 Seconds after Standing (n=4365).
NOVELTY AND SIGNIFICANCE

What Is Known?

- Impaired heart rate recovery (HRR) following treadmill stress testing is an established risk factor for cardiovascular and all-cause mortality.

- It is hypothesized that this is due to dysregulation of autonomic balance unmasked by the test.

What New Information Does This Article Contribute?

- Impaired heart rate recovery in the immediate 20 s following an orthostatic maneuver (i.e. active stand from a supine position) predicts all-cause mortality independently of other established risk factors.

- Heart rate monitoring (i.e. with ECG) during active stand is a simpler more cost effective test to determine this autonomic response compared with alternative methods such as treadmill stress testing.

Speed of heart rate recovery (HRR) following physical exertion is an established risk factor for cardiovascular and all-cause mortality and is usually assessed in the clinical setting using treadmill stress testing. This study examines whether the speed of HRR in response to orthostatic challenge (i.e. active stand from a supine position) has clinical value as a marker of risk. The active stand represents a potent cardiovascular stressor that elicits a rapid physiological response involving the coordinated action of a number of systems including the skeletal-muscle pump, and arterial and cardiopulmonary baroreflexes. Peak heart rate is reached about 10 s after standing and declines rapidly thereafter as a result of rebounding arterial pressure. There is a particularly steep drop in heart rate between 10 and 20 s after standing and an age gradient with heart rate and blood pressure responses. We show that speed of HRR during this time window distinguishes those with existing CVD from those who are CVD free, and has predictive power as a marker of all-cause mortality. We hypothesize that speed of HRR during this time window reflects the capability of the system to mount a vigorous response to cardiovascular challenge and to quickly re-establish homeostatic equilibrium.
Table 1: Baseline Characteristics of the Study Population According to Quartiles of Heart Rate Recovery (n=4365)

<table>
<thead>
<tr>
<th></th>
<th>1st quartile (Fastest HRR)</th>
<th>2nd quartile</th>
<th>3rd quartile</th>
<th>4th quartile (Slowest HRR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) or n (%)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD) or n (%)</td>
</tr>
<tr>
<td>Age</td>
<td>57.7 (7.1)</td>
<td>60.3 (7.9)</td>
<td>64.2 (8.9)</td>
<td>67.8 (8.8)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>614 (51.1)</td>
<td>626 (53.6)</td>
<td>586 (52.3)</td>
<td>510 (48.8)</td>
</tr>
<tr>
<td>Resting HR</td>
<td>65.6 (9.5)</td>
<td>64.8 (10.0)</td>
<td>65.3 (10.0)</td>
<td>67.1 (10.8)</td>
</tr>
<tr>
<td>Resting SBP</td>
<td>135.2 (23.0)</td>
<td>136.6 (21.7)</td>
<td>139.3 (23.4)</td>
<td>134.0 (22.2)</td>
</tr>
<tr>
<td>Resting DBP</td>
<td>74.8 (11.7)</td>
<td>73.9 (11.4)</td>
<td>73.6 (11.3)</td>
<td>70.9 (10.8)</td>
</tr>
<tr>
<td>Cardiovascular medications (%)</td>
<td>207 (19.3)</td>
<td>297 (28.6)</td>
<td>412 (40.9)</td>
<td>498 (49.1)</td>
</tr>
<tr>
<td>No CVD (%)</td>
<td>1046 (95.1)</td>
<td>1016 (92.2)</td>
<td>969 (87.0)</td>
<td>902 (80.6)</td>
</tr>
<tr>
<td>One CVD (%)</td>
<td>35 (3.7)</td>
<td>58 (6.0)</td>
<td>100 (10.4)</td>
<td>129 (13.9)</td>
</tr>
<tr>
<td>Two+ CVDs (%)</td>
<td>11 (1.2)</td>
<td>17 (1.9)</td>
<td>22 (2.6)</td>
<td>60 (5.5)</td>
</tr>
<tr>
<td>Cancers (%)</td>
<td>49 (4.3)</td>
<td>50 (4.8)</td>
<td>74 (7.6)</td>
<td>88 (7.8)</td>
</tr>
<tr>
<td>Lung disease (%)</td>
<td>28 (3.4)</td>
<td>31 (3.3)</td>
<td>36 (3.6)</td>
<td>55 (6.2)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>37 (3.5)</td>
<td>49 (4.8)</td>
<td>96 (9.9)</td>
<td>101 (10.2)</td>
</tr>
<tr>
<td>ADLs</td>
<td>0.06 (0.37)</td>
<td>0.08 (0.45)</td>
<td>0.11 (0.42)</td>
<td>0.15 (0.53)</td>
</tr>
<tr>
<td>IADLs</td>
<td>0.04 (0.31)</td>
<td>0.07 (0.48)</td>
<td>0.09 (0.47)</td>
<td>0.12 (0.43)</td>
</tr>
<tr>
<td>Never smoked (%)</td>
<td>558 (48.5)</td>
<td>533 (45.9)</td>
<td>499 (43.2)</td>
<td>410 (34.6)</td>
</tr>
<tr>
<td>Past smoker (%)</td>
<td>427 (39.2)</td>
<td>402 (34.8)</td>
<td>414 (36.5)</td>
<td>474 (41.6)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>107 (12.3)</td>
<td>156 (19.3)</td>
<td>178 (20.3)</td>
<td>207 (23.8)</td>
</tr>
<tr>
<td>BMI</td>
<td>29.1 (4.9)</td>
<td>28.6 (4.8)</td>
<td>28.4 (4.7)</td>
<td>28.5 (5.0)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.76 (1.13)</td>
<td>1.75 (1.19)</td>
<td>1.78 (1.12)</td>
<td>1.78 (1.03)</td>
</tr>
<tr>
<td>Low density lipoprotein (mmol/L)</td>
<td>3.10 (0.92)</td>
<td>3.02 (0.99)</td>
<td>2.86 (0.94)</td>
<td>2.74 (0.92)</td>
</tr>
<tr>
<td>High density lipoprotein (mmol/L)</td>
<td>1.55 (0.42)</td>
<td>1.56 (0.44)</td>
<td>1.51 (0.43)</td>
<td>1.48 (0.39)</td>
</tr>
<tr>
<td>Primary education (%)</td>
<td>156 (23.1)</td>
<td>204 (29.6)</td>
<td>272 (39.3)</td>
<td>289 (46.5)</td>
</tr>
<tr>
<td>Secondary education (%)</td>
<td>505 (53.6)</td>
<td>467 (48.6)</td>
<td>445 (43.3)</td>
<td>426 (37.5)</td>
</tr>
<tr>
<td>Tertiary education (%)</td>
<td>431 (23.3)</td>
<td>420 (21.8)</td>
<td>374 (17.4)</td>
<td>376 (16.1)</td>
</tr>
</tbody>
</table>

N                      | 1092                      | 1091         | 1091         | 1091                       |

*Figures reported in the table are survey weighted means, standard deviations (SD), or percentages*
Table 2: Correlation of HR, SBP, and DBP Parameters Extracted from the Active Stand with Age at Time of Interview

<table>
<thead>
<tr>
<th>HR parameters</th>
<th>r</th>
<th>SBP parameters</th>
<th>r</th>
<th>DBP parameters</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔHR10secs</td>
<td>-0.33</td>
<td>ΔSBP10secs</td>
<td>-0.11</td>
<td>ΔDBP10secs</td>
<td>-0.05</td>
</tr>
<tr>
<td>ΔHR20secs</td>
<td>0.08</td>
<td>ΔSBP20secs</td>
<td>-0.21</td>
<td>ΔDBP20secs</td>
<td>-0.24</td>
</tr>
<tr>
<td>ΔHR30secs</td>
<td>0.03</td>
<td>ΔSBP30secs</td>
<td>-0.16</td>
<td>ΔDBP30secs</td>
<td>-0.23</td>
</tr>
<tr>
<td>ΔHR40secs</td>
<td>-0.02</td>
<td>ΔSBP40secs</td>
<td>-0.13</td>
<td>ΔDBP40secs</td>
<td>-0.23</td>
</tr>
<tr>
<td>ΔHR50secs</td>
<td>-0.04</td>
<td>ΔSBP50secs</td>
<td>-0.07</td>
<td>ΔDBP50secs</td>
<td>-0.18</td>
</tr>
<tr>
<td>ΔHR60secs</td>
<td>-0.05</td>
<td>ΔSBP60secs</td>
<td>-0.03</td>
<td>ΔDBP60secs</td>
<td>-0.15</td>
</tr>
<tr>
<td>ΔHR70secs</td>
<td>-0.08</td>
<td>ΔSBP70secs</td>
<td>0.00</td>
<td>ΔDBP70secs</td>
<td>-0.13</td>
</tr>
<tr>
<td>ΔHR80secs</td>
<td>-0.09</td>
<td>ΔSBP80secs</td>
<td>0.03</td>
<td>ΔDBP80secs</td>
<td>-0.11</td>
</tr>
<tr>
<td>ΔHR90secs</td>
<td>-0.10</td>
<td>ΔSBP90secs</td>
<td>0.05</td>
<td>ΔDBP90secs</td>
<td>-0.10</td>
</tr>
<tr>
<td>ΔHR100secs</td>
<td>-0.13</td>
<td>ΔSBP100secs</td>
<td>0.06</td>
<td>ΔDBP100secs</td>
<td>-0.09</td>
</tr>
<tr>
<td>ΔHR110secs</td>
<td>-0.15</td>
<td>ΔSBP110secs</td>
<td>0.04</td>
<td>ΔDBP110secs</td>
<td>-0.11</td>
</tr>
<tr>
<td>ΔHRR10/20secs</td>
<td>0.40</td>
<td>ΔSBP rec. 10/20</td>
<td>-0.16</td>
<td>ΔDBP rec. 10/20</td>
<td>-0.23</td>
</tr>
</tbody>
</table>

Estimated using Spearman’s rank order correlation coefficient
Table 3: Hazard Ratio for Mortality over a Mean 4 year follow-up duration by Speed of Heart Rate Recovery Quartiles between 10-20 Seconds after Standing in Crude and Multivariable Adjusted Models (n=4365)

<table>
<thead>
<tr>
<th>Quartile 1 (fastest)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Mean (SD)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>REF</td>
<td>-</td>
<td>REF</td>
<td>-</td>
<td>REF</td>
<td>-</td>
<td>-15.31 (4.08)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>1.98</td>
<td>[0.92, 4.27]</td>
<td>1.63</td>
<td>[0.75, 3.52]</td>
<td>1.37</td>
<td>[0.62, 2.98]</td>
<td>-8.24 (1.33)</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>2.95**</td>
<td>[1.43, 6.08]</td>
<td>1.97</td>
<td>[0.95, 4.08]</td>
<td>1.25</td>
<td>[0.60, 2.59]</td>
<td>-3.99 (1.21)</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>7.05***</td>
<td>[3.72, 13.35]</td>
<td>4.32***</td>
<td>[2.20, 8.48]</td>
<td>2.25*</td>
<td>[1.11, 4.53]</td>
<td>+2.11 (4.02)</td>
<td>69</td>
</tr>
</tbody>
</table>

Legend:
- Model 1: Crude
- Model 2: resting HR, resting SBP, sex, cardiovascular medications, CVDs, diabetes, cancer, lung disease, ADLs, IADLs, smoking status, BMI, lipid profile, and educational status
- Model 3: Model 2 + Age, Age²
- REF = reference category
Figure 1: Mean Heart Rate and Systolic and Diastolic Blood Pressure Values across the
Stand (Including Baseline).
Figures 2a - 2d: Speed of Heart Rate Recovery Following Orthostatic Challenge by Age Group

Figure 2a
Recovery = -8.21 bpm

Figure 2b
Recovery = -5.25 bpm

Figure 2c
Recovery = -2.51 bpm

Figure 2d
Recovery for different age groups
Figures 3a – 3d: Speed of Heart Rate Recovery Following Orthostatic Challenge by Cardiovascular Disease Burden
Figures 4a - 4c: Speed of Heart Rate Recovery Following Orthostatic Challenge by Incident Mortality Status

Figure 4a

Figure 4b

Figure 4c
Figure 5: Kaplan Meier Survival Probability Curves According to Quartiles of Heart Rate Recovery between 10-20 Seconds after Standing (n=4365)
Speed of Heart Rate Recovery in Response to Orthostatic Challenge: A Strong Risk Marker of Mortality
Cathal McCrory, Lisa Berkman, Hugh Nolan, Neil O'Leary, Margaret Foley and Rose Anne Kenny

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Data Supplement (unedited) at:
http://circres.ahajournals.org/content/suppl/2016/06/21/CIRCRESAHA.116.308577.DC1
SUPPLEMENTARY MATERIAL

Title: Speed of Heart Rate Recovery in Response to Orthostatic Challenge: A Strong Risk Marker of Mortality

Authors: Cathal McCrory (PhD) 1, Lisa Berkman (PhD) 2, Hugh Nolan (PhD) 1, Neil O’Leary (PhD) 1
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Running Title: Orthostatic Heart Rate Recovery and Mortality.

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Net Reclassification Improvement

The net-reclassification index (NRI) can be interpreted as the net change in the proportion of subjects assigned a more appropriate risk or risk category under the new model. We define the category-free population-weighted NRI as follows:

\[ NRI = NRI_E P(E) + NRI_{NE} P(NE) \]

Here \( P(E) \) is the probability of an event \( E \), in this case death, and the probability of a non-event \( NE \) is given by \( P(NE) = (1 - P(E)) \). These probabilities act as prevalence weighting for calculating the NRI from \( NRI_E \), the NRI for events (deceased) and \( NRI_{NE} \) the NRI for non-events (survivors).

Furthermore we define:

\[ NRI_E = P(q^* > q|E) - P(q^* < q|E) \]
\[ NRI_{NE} = P(q^* < q|NE) - P(q^* > q|NE) \]

The predicted risk from the model with and without the novel risk marker are given by \( q^* \) and \( q \) respectively, and \( P(q^* > q|E) \) is the probability of a higher risk being assigned by the model with the novel risk marker compared to that without given an event \( E \). \( P(q^* < q|E) \) is the probability of a lower risk being assigned by the model with the novel risk marker given an event \( E \) (death). Similarly \( P(q^* < q|NE) \) and \( P(q^* > q|NE) \) represent the probabilities of lower and higher risk respectively from the model with the novel risk marker compared to the model without, given no event (survivor).

We calculated the standard error of \( NRI_E \) and \( NRI_{NE} \) as follows:

\[ SE(NRI_E) = \sqrt{\frac{(P(q^* > q|E) + P(q^* < q|E))P(E) - (NRI_E P(E))^2}{n_E}} \]
\[ SE(NRI_{NE}) = \sqrt{\frac{(P(q^* > q|E) + P(q^* < q|E))P(NE) - (NRI_{NE} P(NE))^2}{n_{NE}}} \]

Then combine for the standard error of the population-weighted NRI

\[ SE_{NRI} = \sqrt{P(E)^2 SE(NRI_E)^2 + (1 - P(E))^2 SE(NRI_{NE})^2} \]

And we compute normal-approximated 95% confidence intervals for the NRI as follows:

\[ (L_{NRI}, U_{NRI}) = (NRI - 1.96 SE_{NRI}, NRI + 1.96 SE_{NRI}) \]
Online Figure I: Flow Diagram for Study Participation

N=8175 respondents at Wave 1

No health centre assessment
N = 3139

N=5035

Unable to complete the active stand
N= 115

N=4920

Poor quality active stand
Incomplete data

N=4475

Poor compliance with protocol
N=445

Missing on covariates
N= 110

N=4365

Alive (at right censoring)
N=4227

Dead
N=138

N=138
Online Table I: Receiver Operating Characteristic Curves Predicting Risk of Mortality for the various Heart Rate, Systolic Blood Pressure and Diastolic Blood Pressure Parameters extracted from the Active Stand.

<table>
<thead>
<tr>
<th>HR parameters</th>
<th>AUC</th>
<th>95% CI</th>
<th>SBP parameters</th>
<th>AUC</th>
<th>95% CI</th>
<th>DBP parameters</th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔHR 10 secs</td>
<td>0.66***</td>
<td>[0.62, 0.71]</td>
<td>ΔSBP 10 secs</td>
<td>0.51</td>
<td>[0.46, 0.56]</td>
<td>ΔDBP 10 secs</td>
<td>0.52</td>
<td>[0.47, 0.57]</td>
</tr>
<tr>
<td>ΔHR 20 secs</td>
<td>0.52</td>
<td>[0.47, 0.57]</td>
<td>ΔSBP 20 secs</td>
<td>0.57**</td>
<td>[0.52, 0.63]</td>
<td>ΔDBP 20 secs</td>
<td>0.56*</td>
<td>[0.51, 0.62]</td>
</tr>
<tr>
<td>ΔHR 30 secs</td>
<td>0.53</td>
<td>[0.48, 0.58]</td>
<td>ΔSBP 30 secs</td>
<td>0.56*</td>
<td>[0.51, 0.62]</td>
<td>ΔDBP 30 secs</td>
<td>0.57**</td>
<td>[0.52, 0.62]</td>
</tr>
<tr>
<td>ΔHR 40 secs</td>
<td>0.51</td>
<td>[0.46, 0.56]</td>
<td>ΔSBP 40 secs</td>
<td>0.57**</td>
<td>[0.52, 0.62]</td>
<td>ΔDBP 40 secs</td>
<td>0.59***</td>
<td>[0.54, 0.64]</td>
</tr>
<tr>
<td>ΔHR 50 secs</td>
<td>0.52</td>
<td>[0.47, 0.57]</td>
<td>ΔSBP 50 secs</td>
<td>0.55*</td>
<td>[0.50, 0.61]</td>
<td>ΔDBP 50 secs</td>
<td>0.57**</td>
<td>[0.52, 0.62]</td>
</tr>
<tr>
<td>ΔHR 60 secs</td>
<td>0.52</td>
<td>[0.47, 0.57]</td>
<td>ΔSBP 60 secs</td>
<td>0.53</td>
<td>[0.48, 0.58]</td>
<td>ΔDBP 60 secs</td>
<td>0.55*</td>
<td>[0.50, 0.60]</td>
</tr>
<tr>
<td>ΔHR 70 secs</td>
<td>0.50</td>
<td>[0.45, 0.55]</td>
<td>ΔSBP 70 secs</td>
<td>0.51</td>
<td>[0.46, 0.57]</td>
<td>ΔDBP 70 secs</td>
<td>0.54</td>
<td>[0.49, 0.59]</td>
</tr>
<tr>
<td>ΔHR 80 secs</td>
<td>0.52</td>
<td>[0.47, 0.57]</td>
<td>ΔSBP 80 secs</td>
<td>0.51</td>
<td>[0.46, 0.56]</td>
<td>ΔDBP 80 secs</td>
<td>0.55</td>
<td>[0.50, 0.60]</td>
</tr>
<tr>
<td>ΔHR 90 secs</td>
<td>0.51</td>
<td>[0.46, 0.56]</td>
<td>ΔSBP 90 secs</td>
<td>0.51</td>
<td>[0.46, 0.56]</td>
<td>ΔDBP 90 secs</td>
<td>0.54</td>
<td>[0.49, 0.59]</td>
</tr>
<tr>
<td>ΔHR 100 secs</td>
<td>0.51</td>
<td>[0.47, 0.56]</td>
<td>ΔSBP 100 secs</td>
<td>0.51</td>
<td>[0.46, 0.57]</td>
<td>ΔDBP 100 secs</td>
<td>0.55</td>
<td>[0.50, 0.60]</td>
</tr>
<tr>
<td>ΔHR 110 secs</td>
<td>0.53</td>
<td>[0.48, 0.58]</td>
<td>ΔSBP 110 secs</td>
<td>0.52</td>
<td>[0.47, 0.57]</td>
<td>ΔDBP 110 secs</td>
<td>0.55</td>
<td>[0.50, 0.60]</td>
</tr>
<tr>
<td>ΔHRR 10/20 secs</td>
<td>0.69***</td>
<td>[0.64, 0.73]</td>
<td>ΔSBP rec10/20 secs</td>
<td>0.60***</td>
<td>[0.55, 0.65]</td>
<td>ΔDBP rec10/20 secs</td>
<td>0.61***</td>
<td>[0.56, 0.66]</td>
</tr>
</tbody>
</table>

AUC = area under the curve
***significant at the 0.001 level; **significant at the 0.01 level; * significant at the 0.05 level