Prolonged cardiac activation, stressful events and worry in daily life.

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Chapter 5: *Prolonged Cardiac Effects of Momentary Assessed Stressful Events and Worry Episodes.*

ABSTRACT

***Objective**: Prolonged physiological activation before or after stressors has gained recognition as a decisive element in theories that explain the link between stress and disease, specifically cardiovascular (CV) disease. We hypothesized that increased heart rate (HR) and decreased heart rate variability (HRV) are not only due to concurrent stressful events but also to stressors that occurred in the four preceding hours or were anticipated to occur in the next hour. Further, we expected worry to mediate at least part of these prolonged effects of stressors.*

***Methods**: HR and HRV of 55 female and male teachers were recorded during neutral standardized laboratory tasks. Additionally, ambulatory HR and HRV recordings were performed for 4 days, during which the participants reported the number and duration of worry episodes and stressful events; this was done on an hourly basis using computerized diaries. Multilevel regression models were used, accounting for the effects of biobehavioral variables. These variables included recovery from neutral laboratory stressors assessed in advance, job stress, and negative emotional traits (trait worry, anxiety, depression and hostility).*

***Results**: Compared to neutral periods, stressful events were associated with an HR increase of 2.02 beats/min in the succeeding hour, while worry independently displayed concurrent (2.86 beats/min; 1.15 ms) and prolonged effects in the succeeding hour on HR and HRV (2.85 beats/min; 1.17 ms) and two hours later on HR (2.51 beats/min). These findings were largely independent of effects of emotions, physical activity, posture and biobehavioral factors, such as gender, age, body mass or negative health behavior, and neutral lab stress recovery. Psychological traits and job stress did not predict HR or MSSD levels.*

***Conclusions**: Stressors can have prolonged cardiac effects up to one hour; however, these are not mediated by worry. On the other hand, worry itself can have independent prolonged effects that last even longer, i.e up to two hours. These findings emphasize the importance of worry as a source of excessive cardiac elevations. The prolonged activation by stress and worry are probably mediated by unconscious perseverative processes; this should be addressed in future studies.*

Until recently, research on the effects of stress on disease development has mainly focussed on the immediate effects of psychological stressors on cardiovascular activity (1). However, it has long been recognised (2-4) that *prolonged* cardiovascular responses of stressors and not so much the relatively short responses *during* stressors (i.e. reactivity), strain and wear out the cardiovascular system, to the extent that it may lead to cardiovascular disease. Indeed, several recent studies have shown that delayed cardiac recovery from cognitive (5-9) and physical (10-19) stressors is predictive of adverse cardiac outcomes, such as hypertension, enhanced rest HR and BP, abdominal adiposity, and even overall mortality 3 to 15 years later ((5, 6, 8-11), reviewed in (1)). According to a *prolonged activation model* of the effects of stress on cardiovascular (CV) health (20, 21), the level of CV activation in daily life is not only influenced by simultaneously occurring psychological stressors, but also by more 'distal' stressors such as stressors in the past and anticipated future. In fact, the larger part of increased CV activation may be caused by slow recovery from preceding stressors or anticipatory responses to expected stressors. The present study's first aim was to compare, in daily life, cardiac effects that occur *during* stressors with the prolonged effects of these stressors at various temporal distances *before* and *after* them. Thus, the study tests the hypothesis of prolonged stressor effects of various durations against the reactivity hypothesis that involves effects during stressors only.

For practical reasons, laboratory studies of stress recovery have only tested restricted recovery periods, thereby limiting their ecological validity. Ambulatory studies in natural environments have measured longer time periods (1). These types of studies have suggested that CV stress effects may last any period between 5 minutes and the rest of the day, and may even include the subsequent nocturnal sleep period (1, 22). However, since most of these studies were not primarily interested in prolonged activation, they did not adequately assess clear beginnings and endings of stressors. Thus, they failed to indicate where prolonged activation started, and how long it lasted after the stressor. Without this information, it is difficult to precisely document prolonged activation, to distinguish it from mere reactivity, and to study its determinants.

The latter pertains to another critical issue that has remained largely unaddressed. The ambulatory studies mentioned did not investigate why some stressors lead to prolonged activation while others do not. More specifically, they did not test a psychological mediator of the prolonged physiological effects. We recently proposed (21, 23) that perseverative cognition, such as worry or rumination, may play this mediating role, and thus may prolong physiological activation beyond the actual occurrence of a stressor. When a stressor cannot be readily coped with, perseverative cognitive processes such as worry or rumination will keep the cognitive representation of the stressor active along with its negative emotional and physiological concomitants. As a result, the body will remain in a state of behavioral readiness and physiological activation will be prolonged. In line with this 'perseverative cognition hypothesis' a number of laboratory studies have shown that worry and rumination are associated with increased physiological activity, including higher heart rate (HR), lower heart rate variability (HRV), higher blood pressure (BP) and several effects on immunological and endocrinological parameters (see for a review (23)). Recently, we have shown that some of these effects of worry also occur during daily life. Participants displayed increased HR and decreased HRV

during worry periods compared to neutral periods, and these effects were independent from those of stressors (24). The second research aim of the present study was to test whether worry mediates – at least part of – the prolonged cardiac effects of stressors.

Recent laboratory studies suggest that worry can prolong the CV effects of a (anger- provoking) stressor (25-28). Still, with respect to real life this was shown in only one study which revealed that worry mediated the effects of daily stressors on nocturnal HR and HRV (22). That study was limited in several ways. No exact beginnings and endings of stressors and worry episodes were measured. Therefore, no short-term prolonged activity during the day, including anticipatory activation, was analyzed. Furthermore, potential confounders of the effects of stressors and worry, such as emotional states and physical activity, were not measured. Finally, paper & pencil diaries were used, which carry the danger of unreliable data. For example, questions may be filled in at a later time, causing retrospection to lead to potentially distorted reporting (29). The current study measured stressors more precisely, including their prolonged effects during the day instead of during the nocturnal sleep period, and measured anticipated stressors as well. Additionally, electronic diaries were used, improving reliability by automatically time-locking the reports.

A methodological problem in studying prolonged stress effects of different durations is that for each duration a different statistical test is needed. For example, to compare three recovery durations after daily stressors, of 0, 1 and 2 hours, three tests are necessary. Multiple tests however lead to increased type I errors. The solution chosen here was to *not* take the stressor (the independent variable) as the starting point of analysis, but instead cardiac activity itself (the dependent variable). Thus the question became: Is the average cardiac activity in any given time period not only predicted by stressors occurring *during* that period but also by stressors occurring during several predetermined time periods *preceding* those periods, and even by stressors expected to occur *after* it. The advantage of this approach is that these questions can be answered with a single statistical test, using multiple predictors (see also van Eck et al. (30)). For this purpose we calculated the average HR and HRV during the last 15 minutes of measurement episodes of approximately 60 minutes, partly based on data gathered previously during four days in 73 teachers (24). These 15 minutes were chosen for several reasons. Firstly, 15 minutes was a sufficiently short period to allow the persons to adequately remember and indicate their emotions, posture and physical movement. All of these variables can be related to stressors or worry *and* can influence cardiac activity, and are therefore potential confounders of their effects. Secondly, taking the last 15 minutes also enabled us to examine the *short term* prolonged effects of stressors, that is, stressors that occurred earlier in the same 60 minute measurement period (see methods). In this way, five different durations of prolonged activity were tested: stressors occurring simultaneously with the cardiac assessments (marked '0' in the rest of this article); in the same hour but before the measurements ('-1'); in the previous hour ('-2'); the hour before that ('-3'); and stressors expected by the participant to occur in the next hour ('+1'). Subsequently, the effects of worry during these episodes was measured to test whether worry mediated the prolonged effects of stressors.

Individuals differ to the extent to which they recover from any physical or psychological challenge, independent of its stressfulness, and this individual recovery slope may partly determine their recovery in daily life. For example there could be physical causes for slow recovery, due to an inherited or acquired diminished autonomic function associated for example with physical fitness, obesity, or age. To correct for these differences in the analyses of prolonged daily cardiac activity all participants' typical recovery slopes after neutral stress were assessed in a laboratory session, using a standardized physical stressor (bicycle ergometer) and a neutral cognitive stressor (Stroop task).

The current analyses were partly based on data used in a previous report (24), concerning the comparison of cardiac activity *during* exactly determined stressful episodes and worry episodes. This report used a different statistical approach that could not be combined with the current one. Unlike the present study, the starting point of analysis in that study consisted of the independent variables, that is, the stressors and worry episodes, and the cardiac activity of interest was confined to these episodes. To exclude the possibility that the prolonged effects of interest were due to emotion, physical activity and posture the present study focussed only on cardiac activity during the last 15 minute window of each 60 minute measurement period. To optimize measurement accuracy, these potential behavioral confounders were only assessed during those last 15 minutes, and could therefore not be used in the previous study. Because of the inclusion of physical activity and posture we could analyze all the cardiovascular data instead of only the data collected during low physical activities as was done in the previous study. The results in the present report are new and do only overlap for a small part with results of the previous one. Where this is the case we will state so.

Summarizing, we expected increased HR and decreased HRV to be related to stressors that occur simultaneously as well as in the preceding three 60 minute measurement periods, as well as to stressors anticipated to occur in the next hour. Further, we expected worry to mediate at least part of these prolonged effects of stressors. We used HR and HRV because both chronic high HR and low HRV are risk factors for CVD as well as other organic diseases and overall mortality (31), and because they are easy to measure in daily life without interfering with natural behavior.

Several negative emotional traits (i.e. depression, anxiety, worry, questionnaire-derived as well as interview-derived hostility (32-36)), and stress-related beliefs (e.g. job strain (37)) have been documented as CVD risk factors. We measured these factors to test the possibility that their enhanced CVD risk is due to prolonged cardiac activity related to stressful events or worry, or both. Age, gender, body mass index (BMI), bodily motion, time of day and the consumption of coffee, alcohol and smoking are known to effect HR and/or HVR (38-44); therefore, analyses were corrected for effects of these biobehavioral factors. Due to the hierarchical structure of the data we used multilevel regression models for the analyses.

Methods

Participants

A total of 102 teachers were recruited; 29 dropped out for various reasons (pregnancy, sick leave, allergy for electrodes, use of antidepressants and hypertension medication) or were left out due to insufficient diary recordings. A final total of 73 teachers at 17 secondary schools in the Netherlands were included in this study and were measured between years 2001 and 2003. The sample consisted of 49 men and 24 women aged 24 to 69 (mean=46.7; sd=9.5), who were employed for an average of 34.0 (sd=9.5) hours per week. Eleven persons had valid data for only 48 of the 96 hours due to withdrawal from the project (four subjects), time constraints (two subjects), allergic reaction to the electrodes revealed after 48 hours of measurements (one subject), sudden sick leave (one subject) and device malfunction (three subjects). However, since they had more than 10 diary entries (the required minimum set by us) they were included in the analyses. All teachers gave written informed consent before entrance to the study and received a book token worth 20 Euros for their participation. The study was approved by the university ethics committee.

Procedure

After receiving consent of the management of the schools, we invited the teachers to participate by regular mail. The responders were contacted by phone to schedule the laboratory session and the ambulatory measurements after which they received self-report questionnaires by regular mail. Firstly, the teachers underwent a laboratory session, in which they signed the informed consent, were interviewed (IHAT, see below), and underwent a bike and Stroop task to estimate typical recovery after neutral stress (see below). Within two weeks after, an experimenter fitted the ambulatory ECG device (45) in the morning before the teachers started their regular work activities and instructed them on the use of this device as well as a handheld computer that contained the hourly diary questions including questions about worry episodes and stressful events. They carried both devices for two periods of 48 hours. In between periods, devices were read out and provided with new batteries. At the end of the first 48-hour period the teachers left the devices at school where an experimenter could collect them. The day before the second 48-hour period, the equipment was handed over to the teachers, so that they could fit the equipment themselves after waking up in the morning.

State measurements

Diary format

A Palm^{tm} m100 handheld device (Palm Inc., Santa Clara, CA, USA) was used for the hourly diary. Additionally, we used customized software (Pendragon Forms, version 3.1.; Pendragon Software Corporation, Libertyville, Ill) to implement questions and to transfer responses from the handheld to MS-Access data format. An hourly tone (plus or minus 15 min) was set from 8.00 AM to 10.00 PM on which participants were instructed to fill in the computerized questions. During work a large part of these tones were programmed to occur in between lessons to reduce disturbance during teaching; the interval between two tones could therefore vary from 45 to 75

minutes. When the subjects answered the first question of each entry of the log, the present time was stored to enable comparison between their responses and the cardiac measurements.

Worry episodes and stressful events

The subjects received definitions of worry episodes and stressful events in print before starting the momentary measurements. The word for worry in Dutch is "piekeren". However, unlike the English word "worry" this word can also mean "thinking hard" or "pondering". To make sure that the subjects used the right concept we introduced the word "rumineren" (rumination) which is a seldom used Dutch word, and defined a "rumineer" episode or worry episode as "*when you, for a certain period of time, feel worried or agitated about something. It is a summary-term for processes such as worry, ruminating, keeping on about something, fretting or grumbling about some problem or angry brooding etc. Thus, it is about a chain of negative thoughts that is hard to let go of.*". By using this definition we made sure that the subjects would also report other types of perseverative cognition than only worry, such as angry brooding and rumination. Stressful events were defined as "*all minor and major events due to which you, to any extent, feel tense, irritated, angry, depressed, disappointed or otherwise negatively affected*". Subsequently, on the handheld computer, the participants reported hourly whether a worry episode or a stressful event or both had occurred during the preceding hour. If this was the case they additionally reported on the approximate starting points and duration of the worry episode or the event.

Cardiac activity

Ambulatory cardiac measurements were acquired continuously by the VU-AMS device (version 4.6. TD-FPP, Vrije Universiteit, Amsterdam, the Netherlands). This device has been used extensively and details of its characteristics have been published earlier (46). In the present study the electrogram signal was recorded using disposable pre-gelled Ag-AgCL electrodes (ConMed, New York, USA) that were placed at the jugular notch of the sternum, 4 cm under the left nipple and at the lateral right side. Using this three electrode configuration the inter beat interval time series was available for analysis. The device detects the R-wave of the electrocardiogram and records the time in milliseconds (with one millisecond resolution). From the raw inter beat intervals the device derives and stores 30-second averages of HR (in beats/min) and root mean square of successive differences of inter beat intervals (in milliseconds: MSSD), which we used as an index of HRV. The MSSD has been shown to be a reliable index of cardiac parasympathetic influences (47), and is one of the time domain indices recommended by a task force report on HRV measurement (48). For the current analyses only the cardiac measurements of the last 15 minutes of each hourly period were used.

Mood, activity, and other (bio)behavioral variables

During the last 15 minutes of each hourly measurement period, the subjects reported on the handheld computer to what extent they had felt the following four moods: Angry or irritated, sad or gloomy, tense or restless, and happy or cheerful (not at all, some, a bit, much, very much). They also reported what their main

posture had been in those last 15 minutes (laying, sitting, standing, walking, biking, other), and they reported on consumed units of tobacco, coffee and alcohol (0, 1-2, 2-4, more than 4) in the preceding hour, and on having performed relatively strenuous activities in the preceding hour (not at all, some, a bit, much, very much). A more objective estimate of high activity was obtained with the AMS, which includes an accelerometer sensitive to changes in vertical acceleration. This motility signal was used to distinguish periods with high activity from periods with low activity. High physical activities were identified as motility higher than the 48-hour average plus one SD (indicating high physical activity) in combination with a visually detected simultaneous increase of HR, which was presumably due to this high activity. The percentage of 30-sec periods that were spent in high activity during each 15-minute period, is used as a covariate to control for cardiac differences due to intense movement. Note that for our previous report (24) we analyzed only periods in which participants displayed low activity.

Individual recovery slopes to standard neutral stressors

To assess their 'natural' recovery in reaction to standardized non-stressful tasks participants performed a cognitive and a physical task during a laboratory session. The cognitive task was a standardized Stroop task (49, 50) which was performed on a computer and consisted of four parts. Firstly, they had to read out loud and as quickly as possible the names of four colours printed in black. Secondly, they had to name as quickly as possible the colours of blocks that were printed in four different colours. Thirdly, they had to name as quickly as possible the four colours in which the words are printed while trying to ignore reading the words (of the same four colours). In all three parts, the participants had to name or read 70 items and the researcher timed their achievements with a stopwatch, while urging the subjects to perform faster. Lastly, they had to sit quietly for 5 minutes and read neutral magazines in order to achieve recovery to baseline. The physical stress task consisted of cycling on a bicycle ergometer at the resistance of 40 watt (which is about 80 pedal steps per minute) for 5 minutes after which they had to sit quietly again for 5 minutes (recovery) reading magazines. Both tasks were performed in counterbalanced order after the IHAT interview (see below) and were preceded by a 5-minute (baseline) rest period. These tasks and the interview took place at the teacher's school in a room that was accommodated as a laboratory and that was inaccessible for others during the session.

Negative emotional dispositions and job strain

Trait hostility was measured by the Cook-Medley hostility scale (CM) (51). Nonverbal hostility was measured by the Interpersonal Hostility Assessment Technique (IHAT) (52), which is a rating system based on a structural interview for four subtypes of hostility: direct challenges to the interviewer, indirect challenges, hostile withholding of information or evasion of the question and irritation. In the present study two raters, who were trained by the developers of the test (52), independently assessed all interviews and achieved an intraclass correlation of .86. For the analyses these ratings were averaged across persons. The interview took place just before the standardized stress tasks (see above). Symptoms of depression were measured by the Beck Depression Inventory (BDI) (53). Trait anxiety was assessed by the trait scale of the Spielberger State-Trait Anxiety Inventory (STAI) (54). Trait worry was

measured by the Penn State Worry Questionnaire (PSWQ) (55) and the Worry Domain Questionnaire (WDQ) (56). The PSWQ was developed to measure the tendency for excessive, uncontrollable, pathological worry, while the WDQ quantifies worry across different areas of content. Job strain was measured by the Job Content Questionnaire, which measures job demand and job control in the workplace (57). All these scales are widely used, reliable and valid.

Data processing

The program calculated mean HR and MSSD over the last 15-minute periods of each 60 minute measurement period and these were the dependent variables in the analyses. Before that, we eliminated all (parts of) these periods with outliers in standard deviation, mean, minimum and maximum values of HR, MSSD, IBI and motility. Based on the diary data, all 15-minute periods of cardiac data just before the hourly entries were labelled as 'neutral', or containing a 'worry episode' and/or containing a 'stressor' using the AMS graphical program (45). Additionally, based on the time stored by the handheld device, all episodes were provided with a time code (1=morning until 12.00 hrs, 2=afternoon until 18.00 hrs, 3= evening until sleep), which was used as 'time of day' in the analyses.

To enable prolonged activation estimation a series of independent variables was added, containing diary information of the 45 minutes of the same hour occurring before the 15-minute period (marked x^{-1}, with x referring to either stressful events or worrisome episodes in that period, and with those in the 15 minute period itself marked as x^{0}), as well as diary information of each preceding hour (x^{-2}, x^{-3} and x^{-4}; i.e. up to 4 preceding hours). The word 'hours' should not be taken too literally here. For the hours before x^{1}, we allowed a certain imprecision in duration, because a large part of the diary prompts was given between 40 and 70 minutes after the last prompt (see section on 'State measurements'). However, we excluded 'hours' that were more than 20 minutes apart, due to delayed entry of data by the participant. To prevent counting stressors and worry episodes more than once (i.e. those occurring across 'hours') only the occurrence in the last 'hour' was taken into account. Finally, a total of 1957 episodes (on average 26.81 ± 13.12 episodes per participant) were used in the analyses.

Individualized recovery slopes were analyzed as follows. Each of the baseline and recovery periods during the laboratory stress session were divided into 5 separate 1-minute periods, of which the averages per period were calculated. For the baseline the 4^{th} rest minute after the IHAT interview was taken, because due to circumstances the beginning and end of this period were not completely restful for each participant. Thereafter the area under the curve (AUC) was computed for each participant, for the cognitive and physical task and for HR and MSSD. The following equation was used to compute the recovery excursions (30): Excursion=[0.5*fixed time interval ((cardiovascular measure at time 1)+(2*cardiovascular measure at time 2)+(2*cardiovascular measure at time 3) + . . .+(cardiovascular measure at last time point)) - (baseline cardiovascular measure*the fixed time interval)]; where fixed time interval contained 1-minute averages for HR and MSSD, and each time point (e.g., time 1) represents a HR or MSSD value taken every 60 s, until the end of the 5-min recovery period.

Statistical analysis

The effects of predictor variables on the 15 minute averages of HR and MSSD were estimated using multilevel regression models (58, 59). The choice of multilevel analysis logically arises from the two-level hierarchical structure of the data: 15 minute periods of HR and MSSD measurement (episodes) are nested within subjects, which we refer to as the *episode level* and the *person level*, respectively. However, to allow for an accurate estimation of prolonged effects, it would not be sufficient to account for episodes nested within persons only. For that purpose it had to be guaranteed that episodes were not only successive, but also adjacent. Treating measurements as successive and adjacent which are not adjacent, would possibly lead to a falsely decreased estimation of prolonged effects, considering that a longer period after stressor experience would result in more complete recovery. Hence, an additional third level was included, the *series level*, which refers to a sequence of successive and adjacent (with a maximum of 20 minutes in between endings and beginnings of periods) 60 minute measurement periods (each containing one episode). In our data, this resulted in sequences ranging from 2 (allowing for tests of stressor^{+1}, stressor^{0}, stressor^{-1} and worry^{+1}, worry ^{0}, worry $^{-1}$) to 14 measurement periods (each containing one episode), which is the maximum number of measurement periods per day. Thus, the series level allowed for multiple tests of all durations of prolonged activity within the same day.

Predictor variables measured at episode and person level were entered into the model. Episode level predictor variables included the expected, concurrent (during the 15 minute episode) or past stressful events and worry episodes (i.e. stressor^{+1}, stressor^{0}, stressor^{-1}, stressor^{-2}, stressor^{-3}, stressor^{-4}, worry^{+1}, worry ^{0}, worry $^{-1}$, worry^{-2}, worry $^{-3}$, worry $^{-4}$), mood scores, percentage of high physical activity, reported level of activity, reported posture (all during the 15 minute episode), time of day, and the biobehavioral variables, including smoking and consumption of alcohol and coffee (during the total measurement period of 60 minutes). Person level predictor variables entered into the model, included gender, age, BMI, hostility (CM and IHAT), depression (BDI), anxiety (STAI), trait worry (PSWQ and WDQ), job strain and cardiac recovery after neutral laboratory stress. No variables measured at series level were included.

Predicting HR and MSSD by e.g. stressor^{+1}, stressor^{0}, stressor^{-1}, stressor^{-2}, and so on, implies that the same predictor variable may be used more than once. For instance, stressor^{0} predicting HR, plays the role of stressor^{-1} in predicting the next, adjacent value of HR. As a result, errors in prediction may be correlated (the length of such a sequence of correlated errors will depend on the number of successive and adjacent episodes within a series). This additional source of dependency in the multilevel regression model is taken into account by explicitly modelling the correlation between successive observations, called the autocorrelation. Omitting the autocorrelation would bias the standard errors of the regression coefficients downward and may consequently lead to mistaken rejection of the null hypothesis. Autocorrelation estimates were obtained using an MLwiN macro similar to van Eck (30).

For all variables descriptive statistics were computed. The distribution of MSSD departed from normality. Therefore, prior to model testing, the distribution of this variable was improved by applying a log transformation. Furthermore, the

variables smoking, consumption of alcohol and coffee, were dichotomized into yes/no variables. All independent variables were centered around their grand mean.

A sequence of six models was tested for HR and MSSD each. Firstly, an intercept-only model was fit containing no predictor variables. This model decomposes the variance of the dependent variable into three independent components, pertaining to the episode level, the series level and the person level, and was used as a baseline model. In the second to fifth models, episode level predictor variables were entered in logical rational groups, i.e. stressors and worry and (bio)behavioral variables. In the second model, we examined the effects of the occurrence of concurrent worry episodes ($Worry^{0}$) and stressful events ($Stressor^{0}$) on HR and MSSD. This model partly overlaps with the model from the previous study (24). In the third model, the episode level variables $Stressor^{-1}$ to $Stressor^{-4}$, and $Worry^{-1}$ to$Worry^{-4}$, as well as expectation of stressful events ($Stressor^{+1}$), were entered into the model to assess the prolonged activation effects of stressful events and worry. In the fourth model different emotional states, percentage of high activity, reported level of activity and reported posture were added to the previous model to assess whether the effects of worry episodes and stressful events found in the previous model would still be present. In the fifth model the episode level variables time of day, smoking and consumption of alcohol and coffee were added, as well as the person level variables gender, age and BMI, to study whether the effects of worry episodes, stressful events and the other effects found in the previous model would still be present. In the sixth and final model, we added the person level variables trait worry, depression, hostility and anxiety, and job stress as well as cardiac recovery after neutral laboratory stressors. Additionally, this last model was refined by including the autocorrelation parameter.

To test the hypothesis that the prolonged effects of stressors were mediated by concurrent as well as subsequent worrying, we additionally tested models without worry, and compared these models with the models above including worry. If the prolonged effects of stressors were stronger and more significant without entering the worry episodes, it may be concluded that worry mediates at least partly the effects of these variables (60). Similar tests were run for psychological traits and job stress.

The effects of the predictor variables in all models were considered fixed, since we did not have a specific interest in their random effects (apart from the variance components related to the different levels). Multilevel regression models were fit using the program MLwiN, version 2.02 (61). All models were estimated by the method of maximum likelihood. Hypotheses concerning the significance of fixed effects were tested using one-tailed t-tests, since these hypotheses were explicitly directional. T-values were obtained by dividing the estimated model parameter by its standard error. General model improvement was tested using likelihood-ratio tests (based on deviance values). An alpha level of .05 was used for all statistical tests.

Results

Descriptive statistics

Descriptive statistics of variables on the person, series and episode level are given in Table 1. The mean scores of the questionnaires (PSWQ, WDQ, BDI, STAI, CM) and IHAT ratings were similar to other healthy samples (51, 53, 54, 57, 62-65). Subjects

reported a mean of 1.58 (sd=1.16) stressful events and 1.06 (sd=1.69) worry episodes per day, which translates to 8.7% and 6.1% respectively of all episodes. The duration of worry episodes was larger than the duration of stressful events ($z=3.11$, $p<.01$). Reports of stressful events and worry episodes were clustered within persons, with most subjects reporting two stressful events (15 subjects) and no worry episodes (35 subjects) over the total measurement period (adjusted for a differential total number of episodes per person); additionally, both stressful event and worry episodes were simultaneously reported in 39 episodes. These frequencies are comparable with findings from other studies, i.e. 1.38 and 1.65 for stressful events (66, 67) and .96/day for worry episodes (68). The frequency of worry episodes (corrected for the total number of episodes per person) was related to the total score on the PSWQ ($r=.25$, $p<.05$) , BDI ($r=.44$, $p<.01$) and STAI ($r=.45$, $p<.01$), but not to IHAT, CM, WDQ or job strain scores. Multiple regression analysis showed that the STAI was the best predictor ($F(1,72)=19.76$; $p < .001$). Frequency of stressful events (corrected for the total number of episodes per person) was only related to the STAI ($r=.29$, $p<.05$).

Table 2 shows means and standard deviations of HR and MSSD (antilog value) during 15 minute periods for which $Stressor^{0}$, $Worry^{0}$, $Stressor^{+1}$, $Stressor^{-1}$ to $Stressor^{-4}$ or $Worry^{-1}$ to $Worry^{-4}$ were reported and during periods in which these variables were not reported. In general, according to expectations HR was higher and MSSD lower when stressful events or worry episodes were reported in the preceding hours or anticipated in the next hour. Note that the values given in Table 2 were based on the individual 15 minute periods and p-values of unilevel tests of the displayed differences would be overestimated and were therefore reported only in the multilevel analysis that follows in the next paragraph. Table 3 shows correlations between total scores on trait measurements of hostility (CM and IHAT), depression (BDI), anxiety (STAI), worry (PSWQ and WDQ), job strain (Karasek) and recovery to standard neutral stressors. Because of high interdependence ($r=.83$ for HR and $r=.74$ for MSSD), we used the mean of the AUC estimations of the cognitive task and the physical task (for HR and MSSD separately) in the analyses below. Here too significance tests were not performed because unilevel tests would overestimate p-values.

Prolonged effects on HR

Results of the intercept-only model (not reported in tables) showed that the estimated value of the intraclass correlation at person, at series and at episode level was .38, .18 and .45 respectively, providing evidence for a 3-level hierarchical data structure (with a deviance of 14554.45). Concurrent stressful events ($Stressor^{0}$) and worry episodes ($Worry^{0}$) were added as predictors to the intercept-only model (model 1 Table 4). Only $Worry^{0}$ showed a significant effect on HR ($z=2.26$, $p=.01$) and was associated with a simultaneous increase in HR of 2.48 (CI 1.36-3.59) beats/min. Generally, model 1 fits well in comparison with the intercept-only model ($\chi 2 = 90.83$, $df=2$, $p<.001$).

To assess the prolonged effects of stressful events and worry episodes occurring in the hours before the target 15-minute period and the effects of expecting a stressful event on cardiac activity in this period we added these factors to the model (model 2, Table 4 and Figure 1). Results show that effects of $Worry^{0}$ remained significant (increase in HR of 2.86, CI 1.72-4.00; $z=2.51$, $p=.006$).

Additionally, $Stressor^{-1}$ and $Worry^{-2}$ were associated with an increase of 2.02 (CI .82-3.22; z=1.68, p=.047) and 2.51 (CI 1.50-3.52; z=2.49, p=.006) beats/min, respectively. The effect of $Worry^{-1}$ was marginally significant (increase in HR of 2.85, z=1.53, p=.06, but see model 4), and that of $Stressor^{-2}$ was not significant. The expectation of a stressful event in the succeeding hour ($Stressor^{+1}$) was not significantly related to increased HR. Overall, the fit of model 2 was good in comparison with model 1 ($\chi 2$ = 216.86, df=5, p<.001). Adding stressful events and worry episodes that happened even earlier ($Stressor^{-3}$, $Worry^{-3}$, $Stressor^{-4}$, $Worry^{-4}$) did not add any significant effects, which is why these factors were left out of the models below. An alternative model without the worry variables but with all stressor variables ($Stressor^{+1}$ and $Stressor^{-1}$ to $Stressor^{-4}$) yielded only an effect of $Stressor^{-1}$ (increase in HR of 3.05 (CI 1.29-4.81; z=1.73, p=.04), which was only slightly higher than in the analyses above (2.86 in model 2, Table 4). Thus, the addition of worry had not decreased or diminished any effects of stressful events, which would have supported a mediating role of worry (see also Methods, under 'Statistical analyses').

Concurrent emotional (angry, sad, tense, happy) and physical (percentage of high activity, subjective activity level and posture) states were added to the previous model (model 3, Table 4). One unit increase of happy and tense emotional states (on a scale of 5 units from "not at all" to "very much"; see Methods) was related to increases in HR of .61 (CI .32-.89; z=2.12, p=.02) and .96 (CI .55-1.37; z=2.34, p=.01) beats/min, respectively. Maximal percentage of high activities was associated with a mean increase in HR of 16.76 beats/minute (CI 9.93-11.19; z=16.76, p<.001). Additionally, one unit increase in activity level (on a scale of 5 units from "not at all" to "very much"; see Methods) and posture (on a scale of 6 units from "laying" to "other posture"; see Methods) were related to increases in HR of 3.18 beats/minute (CI 2.86-3.49; z=10.11, p<.001) and 2.45 beats/minute (CI 2.26-2.64; z=12.94, p<.001), respectively. Overall, the fit of model 3 was good in comparison with model 2 ($\chi 2$ = 1550.12, df=7, p<.001). The inclusion of these factors in the model did not markedly change the effects of $Worry^{0}$ and $Worry^{-2}$ which were still associated with a significant increase in HR of 1.79 (CI .90-2.68; z=2.02, p=.02) and 1.70 (CI .55-2.13; z=1.70, p=.04) beats/min, respectively. Even the effect of $Worry^{-1}$ became significant now, being associated with an increase in HR of 2.35 (CI 1.91-4.76; z=2.35, p=.01) beats/min. On the other hand, the effect of $Stressor^{-1}$ became marginally significant (z=1.32, p=.09). On closer inspection, we found this drop in stressor effect to be due to the effects of the variable posture and not due to the inclusion of other physical parameters or the emotional states.

Subsequently, biobehavioral variables and time of day were added to the previous model (model 4, Table 4). Only smoking was related to increases in HR (i.e. 3.55 beats per minute (CI 2.27- 4.84; z=2.77, p=.003). Overall, the fit of model 4 was good in comparison with model 3 ($\chi 2$ = 1496.2, df=7, p<.001). The inclusion of these factors in the model only slightly changed the effect of $Worry^{-2}$, which now became marginally significant (z=1.62, p=.053). The effects of $Worry^{0}$ and $Worry^{-1}$ did not markedly change and were still associated with a significant increase in HR of 1.57 (CI .64-2.49; z=1.70, p=.045) and 3.33 (CI 1.84-4.82; z=2.24, p=.01) beats/min, respectively. An alternative model without the worry variables but with smoking, alcohol and coffee intake showed that only smoking was associated with an increase in HR of 5.56 beats per minute (CI 3.99-7.13; z=3.54, p<.001), which

was higher than the worry variables. An exploratory analysis showed that this effect did not become smaller with the inclusion of worry episodes or stressful events, but with the inclusion of the physical activity variable which indicates percentage of high activity. Apparently, participants became more active when smoking or smokers are more active, but toxic worry effects were not established via the effects of smoking.

Next, variables on the person level were added to the model (not reported in table): trait anxiety, hostility, depression, worry and job strain and AUC of recovery during standard neutral laboratory tasks. As was suggested in Table 3, only AUC of recovery reached significance with an effect of .11 increase in HR (CI . 08 - .15; z=3.39, p<.001, which translates to a maximal increase of 15.72 beats per minute for the maximum score of AUC recovery, that is, the least complete recovery after neutral lab stress. Additionally optimal autocorrelation between the subsequent cardiac measurements was calculated and correction of estimates was performed. Autocorrelation estimation adjustment resulted in a best-fitting autocorrelation of .17 ($\chi 2$ = 81.60, df=1, p<.001), which only slightly changed the effects of $Worry^{0}$ (increase of 2.67 beats/min; CI 1.69-3.65; z=2.73, p=.003), $Worry^{-1}$ (increase of 3.10 beats/min; CI 1.54-4.66; z=1.99, p=.02) and $Worry^{-2}$ (increase of 1.59 beats/min; CI .71-2.47; z=1.82, p=.03).

Prolonged effects on MSSD

The estimated value of the intraclass correlation of MSSD from the intercept-only model (not reported in tables) at person and at series level was .56, .09 and .35 respectively, indicating a 3-level hierarchical data structure (with a deviance of 1940.80). $Stressor^{0}$ and $Worry^{0}$ were added to the intercept-only model (model 1, Table 5). Only $Worry^{0}$ showed a significant effect on MSSD (z=2.89, p=.002) and was associated with a simultaneous decrease in MSSD of -1.14 ms (antilog value; CI -2.19 to -.09). Model 1 fits well compared to the intercept only model ($\chi 2$ = 24.69, df=2, p<.001).

Next, stressful events and worry episodes expected in the hour following the 15 min target period and those occurring in the hours preceding that period were added to the previous model (model 2, Table 4 and Figure 2). Results show that $Worry^{0}$ remained significant (decrease in MSSD of -1.15 ms, antilog value, CI 1.11-1.20, z=3.04, p=.001). Additionally, only $Worry^{-1}$ displayed significant effects (z=2.16, p=.002) and was significantly associated with a decrease in MSSD of -1.17 ms (antilog value: CI -1.10 to 1.24). Overall, the fit of model 2 was good in comparison with model 1 ($\chi 2$ = 30.35, df=5, p<.001). Because adding stressful events and worry episodes that happened even earlier ($Stressor^{-3}$, $Worry^{-3}$, $Stressor^{-4}$, $Worry^{-4}$) did – like with HR - not lead to significant effects, these factors were left out of the models below. Since stressors ($Stressor^{+1}$ and $Stressor^{-1}$ to $Stressor^{-4}$) showed no significant effects, mediation by worry was not tested.

Concurrent emotional (angry, sad, tense, and happy) and physical (percentage high activity, subjective activity level and reports on main posture) states were added to the previous model (model 3, Table 5). Only the physical parameters were significantly associated with decreases in MSSD: percentage of high activities were associated with a maximum mean decrease in MSSD of -1.12 ms (antilog value; CI -2.15 to -.09, z= 3.36, p<.001). Additionally, one unit increase in activity level (on a scale of 5 units from "not at all" to "very much"; see Methods) and posture (on a scale of 6 units from "laying" to "other posture"; see Methods)

were related to decreases in MSSD of -1.07 ms (antilog value; CI -2.09 to -.05, z= 4.44, p<.001) and -1.04 (antilog value; CI -2.05 to -.03, z= 3.90, p<.001) respectively. The inclusion of these variables however did not change the previously found effects of $Worry^0$ and $Worry^{-1}$, which were still significantly associated with decreases in MSSD of -1.12 (antilog value; CI -1.07 to -1.17, z= 2.48, p=.007) and -1.17 (antilog value; CI -1.10 to -1.24, z= 2.16, p=.015). Overall, the fit of model 3 was well in comparison with model 2 ($\chi 2$ = 181.15, df=27, p<.001).

Biobehavioral variables and time of day were added to the previous model (model 4, Table 5). Smoking and coffee intake were related to decreases in MSSD of -1.16 (antilog value; CI –1.23 to -1.09, z= 2.29, p=.01) and -1.05 (antilog value; CI -1.07 to -1.02, z= 1.88, p=.03) ms respectively. Additionally, subjects displayed a decrease in MSSD of -1.03 (antilog value; CI -1.04 to -1.02, z= 2.29, p=.01) ms as the day progressed (on a scale of 3 units from "morning" to "evening"; see Methods). The effects of $Worry^0$ and $Worry^{-1}$ were not changed by addition of these factors and were still associated with a significant decrease in MSSD of -1.11 (antilog value; CI -2.16 to -.06, z= 2.15, p=.02) and -1.19 (antilog value; CI -2.27 to -.11, z= 2.23, p=.01) ms respectively. Overall, model 4 fits well in comparison with model 3 ($\chi 2$ = 158.64, df=7, p<.001).

Next, variables containing trait values of depression, hostility, anxiety, worry and job strain as well as AUC recovery estimated during the Stroop and the bike task were added to the model (not reported in table). As was suggested in Table 3, only AUC of recovery reached significance with an increase of 1.004 ms MSSD (CI .003 – 2.01; z=4.00, p<.001, which translates to a maximal increase of 25.48 ms daily life MSSD for the maximal score of AUC recovery, i.e. the most complete recovery after neutral lab stress.

Autocorrelation estimation adjustment resulted in a best-fitting autocorrelation of .20 ($\chi 2$ = 85.707, df=1, p<.001), which slightly changed the effects of $Worry^0$ (decrease of 1.16 ms; CI -2.21 to -.11; z=2.92, p=.002), $Worry^{-1}$ (decrease of 1.16 ms; CI -2.25 to -.07; z=1.79, p=.04) and $Worry^{-2}$ (decrease of 1.09 ms; CI -2.14 to -.04; z=1.83, p=.03).

Discussion

The present study was designed to examine the prolonged cardiac effects of stressful events and the mediating role of worry episodes. To test this, we analyzed whether cardiac activity in hourly 15 minute periods could be predicted by stressors and worry occurring not only during these periods but also preceding them and stressors expected in the hour succeeding them. Stressful events were associated with an increase in HR up to about one hour before the target periods, which was only minimally mediated by worry. Instead this effect was mediated by an active posture following the stressful event. No stressor effects of longer duration were found, and no stressor effects were found on MSSD. Additionally, no effect of anticipating a stressor in the succeeding hour was found. However, there were substantial and independent concurrent *and* prolonged effects of worry episodes on both HR and MSSD, with durations up to one hour for MSSD and up to two hours for HR. These were in fact the most robust findings of this study, and they were independent of the effects of emotions, physical activity, posture, circadian rhythm and biobehavioral factors, such as gender, age, body mass or negative health behavior. They were also independent of individual differences, such as standardized

individualized recovery from standard neutral laboratory tasks, depression, hostility, anxiety, worry and job strain.

The magnitude of the prolonged effects of worry on HR, that is, about two to three beats/minute, was comparable to effects previously found for *concurrent* worry episodes in laboratory studies (69, 70). The effects of worry on MSSD (slightly more than minus one ms) were less pronounced than found in previous laboratory studies measuring MSSD during worry (71) (decreases of about 4 ms) or (72) (decreases up to 6 ms). To qualify our current findings, several issues are need not to be neglected. Firstly, it is important to emphasize that these previous studies concern reactivity - cardiac activity *during* stress experiences.

The present study shows that worry episodes did not only affect HR *during* their occurrence, but that they, along with stressful events, had prolonged effects up to several hours afterwards. The former effect does not indicate a causal relationship; i.e. it can still be reasoned that high HR and low HRV cause worry and stress perceptions, instead of the other way around. The latter finding that worry is related to cardiac levels up to two hours is specifically relevant for the perseverative cognitions model, since it is a *prospective* finding, indicating that worry episodes *precede*, and thus likely induce, high HR and low HRV. Since these effects of stressors and worry are mutually independent they accumulate to a considerably higher effect on HR and MSSD, both simultaneously and within several hours (Figure 1). Since both chronic high HR and low MSSD are shown to be independent risk factors for cardiovascular disease (73, 74), these findings offer support for the notion that daily worry is a possible factor in generating potentially pathogenic CV activity.

Moreover, although the negative emotional traits and job strain that carry CVD risk (32-37) showed no independent effects, worry, anxiety and depression are associated with a higher number of worry episodes and anxiety was related to a higher number of stressful events. Thus, it is very likely that although they do not directly lead to higher cardiac levels in daily life, they might do so via the cardiac effects of stressful events and worry episodes, leading to prolonged high total physiological load on the organism. It is tempting to view this as a possible underlying mechanism of their CVD risks.

It is intriguing that not so much stressful events but worry episodes are associated with prolonged cardiac activation. There are several possible explanations. Firstly, worry is not something completely different from stressful events. In fact, worry is always about stressful events in the past, the present or the future. Thus, by measuring the effects of worry episodes we aggregated the effects of one or more unsolved stressful events from in the (regretted) past as well as expected in the (feared) future (see also (23)). Moreover, these worries typically involve events that are the emotionally most relevant for the person. In contrast, the effects of stressful events found in this study were confined to those from a limited time period (i.e. those within the time frame 4 hours before to 1 hour after a cardiac measurement period), and are not restricted to the emotionally most relevant. This may explain that the cardiac effects of worry were independent of the stressful events measured in this study and that the cardiac effects of worry are in fact much greater than those of these stressful events, because they pertain to many more events and to much more intense – past and future – stressful events.

Still, the finding that worry itself can have prolonged effects poses a theoretical problem. As emphasized above, the cardiac worry effects of different durations were independent of each other. This means that none of these effects can be mediated by worry on a later time point. If worry itself causes prolonged cardiac effects of a duration up to 2 hours, what is mediating these effects? The finding that prolonged effects of worry are independent of the effects of emotions, biobehavioral and life style variables excludes these factors as candidates. There are some possible clues in the literature indicating that perseverative cognition may partly act in an unconscious fashion and is not reported by the individual. For example, prolonged low HRV was found during sleep as a result of anticipating a stressful oral speech to be held after waking up (75). Prolonged HR and HRV effects were also found following a day of stressful events and worry (22). These findings are noteworthy because the subjects could not have been consciously worrying when asleep. Thus, it is possible that perseverative cognition processes continued during sleep in a more or less unconscious fashion such as during dreaming. However, polysomnographical evidence showed that these effects were not confined to REM periods. Very little is known about the physiological consequences of unconscious processing of stressful information, but considering that a large part of information acquisition and processing is done outside of conscious awareness (76) the involvement of unconscious information processing mechanisms in perseverative cognition is highly plausible. Thus, it is possible that unconscious perseverative processes might - during sleeping as well as waking - result in prolonged physiological effects after termination of conscious worry episodes, and might occur perhaps even completely independent of worry.

Unlike earlier studies (1), including our own (24), which was partially about the same data, we found no clear effects of concurrent stressful events on HR or MSSD ('Stressor^0' effects) in the current study, although the non-significant differences (Table 4) were as expected. Only stressful events in the past hour were related to elevated HR. This dissimilarity with the previous study is likely due to the different type of analyses that was required for testing the different hypotheses (see Introduction). The previous study, focusing exclusively on reactivity during stress, used all available stressful events during all hourly measurements. For reasons explained in the introduction and methods sections, the present study used only the 15 minute periods for reactivity analyses (the stressor^0 and worry^0 effects). Due to this smaller time window, sensitivity to detect stressful events and worry episodes was lower. Furthermore, many entries that potentially contained stressful events were lost because they did not belong to a series of subsequent and adjacent entries needed for the testing of prolonged effects (see Methods). Moreover, in accordance to our previous study (24), it is possible that specific stressful events such as work-related stressful events would have yielded concurrent as well as prolonged effects, but the infrequent reporting of stressful events did not allow enough cases for a thorough analysis of this hypothesis. Interestingly, the finding that the prolonged stressor effect in the current study was partly due to posture, might have been true for the stressor effects in the former study too. However, since posture reporting was restricted to the last 15 minutes of each measurement period, it was not possible to test posture in that study. Finally, in contradiction to our hypotheses we found no effects of anticipating a stressor in the following hour. On the other hand, our previous report shows (24) that worry episodes concerning future issues resulted

in a subsequent increase in HR of 4.79 beats/min. Apparently, these future issues were not expected in the succeeding hour, or alternatively, those expected in the succeeding hour contained many stressors that were not intense enough to elicit detectable cardiac responses.

In this study we used participants' typical recovery slopes after neutral stress in the laboratory to correct for physical causes for slow recovery. Slow recvery could be due to inherited or acquired diminished autonomic function associated for example with physical fitness, obesity, or age. Intriguingly, recovery speed from neutral lab stressors predicted both daily HR and MSSD, independent of the effects of any psychological and physical variables. This is consistent with findings by other studies showing that recovery from neutral stressors prospectively predicts adverse cardiac outcomes (5, 8, 11, 12, 16, 18). Even so, our findings clearly show that this 'neutral recovery' can not explain the prolonged effects of stress and worry.

This study has several limitations. A group of high school teachers participated in the study. They are a highly educated, medium SES subgroup, and the results of this study might not generalize to other groups with lower education and a different SES. It is possible that a selection bias influenced the results. For instance mainly teachers might have responded who did not experience a lot of stress, or perhaps those teachers with the highest work load did not respond due to lack of time. Furthermore, one could argue that in general, worry episodes and stressful events seem to have been reported relatively infrequently (that is, 4.2 and 5.7% respectively of the total number of entries). However, frequencies were comparable with other studies (30, 66, 68) and solid effects – at least for worry - were still found amidst a large pool of neutral periods independent of activity, posture, emotions and biobehavioral variables. Additionally, if worry is a key detrimental process that might lead to CV disease in the long run, we do not expect that worry happens often in a healthy population, but is more likely to happen in a population at risk, such as chronic patients, unemployed people, or low SES groups. Furthermore, results from our previous study (24) indicate that specific stressor and worry characteristics lead to more pronounced cardiac elevations: worry or stress about work or future-related topics were associated with more pronounced cardiac elevations, as well as work-related stressors. However, the infrequent reporting of stressful events and worry episodes in the current study did not allow enough cases for a thorough analysis of this hypothesis.

In conclusion, the findings of this study extend the results of previous studies by showing worry to have prolonged cardiac effects for up to 2 hours independent of effects of emotions, physical activity, posture and biobehavioral factors, such as gender, age, body mass or negative health behavior. Our findings emphasize the importance of worry as a source of potentially toxic cardiac elevations in daily life, but also seem to imply that still other cognitive perseverative processes, probably automatic or unconscious ones, may mediate the prolonged cardiac effects of conscious worry. Given the fact that elevated HR and decreased HRV are predictors of morbidity and all-cause mortality (33), these results indicate that worry may play a considerable role in the risk of effect of psychosocial stress on risk for cardiovascular disease (77). If further substantiated, this role of worry may open up new pathways for interventions to be included in risk reduction programs. For example, findings from a recent study by our group suggested that a simple worry intervention can decrease worry duration (78).

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Table 1: Mean, standard error, range and (positive) percentages for entry level and person level variables.

	n	Mean ± SD	Range	%
Person level:				
Gender	73			67.1% male
Age	73	46.7 ± 9.5	24 - 69	
BMI [a]	72	24.4 ± 3.5	17.2 – 34.1	
PSWQ [b]	73	43.3 ± 10.5	25 – 76	
WDQ [c]	73	21.5 ± 14.9	0 – 74	
BDI [d]	73	6.5 ± 5.7	0 – 24	
IHAT [e]	73	.18 ± .15	0 - .67	
CM [f]	73	35.5 ± 6.0	3 – 27	
STAI [g]	73	36.9 ± 9.1	24 – 58	
Job strain [h]	73	41.21 ± 5.47	7 - 19	
AUC HR bike	61	235.06 ± 37.35	156.5 – 329.3	
AUC HR Stroop	66	214.63 ± 31.25	128.58 – 299.21	
AUC MSSD bike	61	136.38 ± 161.47	-97 - 943	
AUC MSSD Stroop	66	128.08 ± 118.55	-123.75 – 685.75	
Series level:				
$Stressor^{0}$	1949			5.7%
$Worry^{0}$	1949			4.2%
$Stressor^{-1}$	1949			1.2%
$Worry^{-1}$	1949			5.7%
$Stressor^{-2}$	1451			9.4%
$Worry^{-2}$	1452			5.7%
$Stressor^{-3}$	1089			9.6%
$Worry^{-3}$	1089			5.1%
$Stressor^{+1}$	1925			1.5%
Episode level:				
Angry	1938	1.16 ± .46	1-5	
Sad	1936	1.07 ± .28	1-5	
Tense	1938	1.27 ± .50	1-5	
Happy	1936	2.17 ± .83	1-5	
% High activity	1957	.22 ± .32	0-1	
Activity level	1934	1.38 ± .63	1-5	
Posture	1939	2.67 ± 1.06	0-6	
Smoking	1938			6.2%
Alcohol consumption	1768			10.6%
Coffee consumption	1894			19.5%

Time of day	1957		20.5% morning; 44.8% afternoon; 34.7% evening
Frequency stressful events per day		1.58 ± 1.16	
Mean duration stressful events (minutes)		6.85 ± 9.85	
Frequency worry episodes per day		1.06 ± 1.69	
Mean duration worry episodes (minutes)		16.74 ± 19.34	

[a] BDI=Body Mass Index; [b] PSWQ=Penn State Worry Questionnaire; [c] WDQ=Worry Domain Questionnaire; [d] BDI=Beck Depression Inventory; [e] IHAT= Interpersonal Hostility Assessment Technique; [f] CM=Cook-Medley Hostility Questionnaire; [g] STAI=Spielberger Trait Anxiety Inventory; [h] Job strain=high job demands

Table 2: Mean and standard deviations of HR and MSSD (antilog value) during 15 minute periods in which either Stressor^{+1}, Stressor^{0}, Worry^{0}, Stressor^{-1}, Worry^{-1}, Stressor^{-2}, Worry^{-2}, Stressor^{-3} or Worry^{-3} was reported vs periods in which these variables were not reported.

	HR Mean ± SD	MSSD Mean ± SD
Stressor^{0}	77.53 ± 13,46	29.33 ± 1.81
No Stressor^{0}	77.53 ± 12.70	28.17 ± 1.79
Worry^{0}	80.30 ± 14.84	25.07 ± 1.69
No Worry^{0}	77.41 ± 12.63	28.38 ± 1.79
Stressor^{+1}	77.98 ± 12.15	24.90 ± 1.49
no Stressor^{+1}	77.59 ± 12.75	28.26 ± 1.79
Stressor^{-1}	81.40 ± 13.88	29.88 ± 2.05
No Stressor^{-1}	77.41 ± 12.69	28.19 ± 1.78
Worry^{-1}	79.13 ± 10.94	23.09 ± 1.61
No Worry^{-1}	77.51 ± 12.77	28.32 ± 1.79
Stressor^{-2}	77.88 ± 11.95	31.60 ± 1.84
No Stressor^{-2}	77.50 ± 12.81	27.94 ± 1.78
Worry^{-2}	78.44 ± 11.75	28.04 ± 1.72
No Worry^{-2}	77.48 ± 12.79	28.25 ± 1.79
Stressor^{-3}	77.40 ± 11.88	28.67 ± 1.94
No Stressor^{-3}	77.54 ± 12 83	28.19 ± 1.77
Worry^{-3}	78.41 ± 13.69	29.08 ± 1.87
No Worry^{-3}	77 48 ± 12.68	28.19 ± 1.78
Stressor^{-4}	76.11 ± 12.32	30.81 ± 1.85
No Stressor^{-4}	77.41 ± 12.92	28.18 ± 1.77
Worry^{-4}	77.48 ± 12.15	28.41 ± 1.66
No Worry^{-4}	77.27 ± 12.90	28.42 ± 1.78

Table 3: Correlations between mean overall HR and MSSD total scores on trait measurements of hostility (CM and IHAT), depression (BDI), anxiety (STAI), worry (PSWQ and WDQ) and job strain (Karasek).

	HR	MSSD
Hostility (CM) [a]	.10	-.09
Hostility (IHAT) [b]	.08	-.17
Depression (BDI) [c]	-.11	-.03
Anxiety (STAI)_[d]	-.01	.01
Worry (PSWQ) [e]	.08	-.09
Worry (WDQ) [f]	-.08	-.08
Job strain [g]	-.07	.17
AUC HR bike	.34	-.04
AUC HR Stroop	.34	-.08
AUC MSSD bike	-.04	.47
AUC MSSD Stroop	.00	.41

[a] CM=Cook-Medley Hostility Questionnaire
[b] IHAT= Interpersonal Hostility Assessment Technique
[c] BDI=Beck Depression Inventory
[d] STAI=Spielberger Trait Anxiety Inventory
[e] PSWQ=Penn State Worry Questionnaire
[f] WDQ=Worry Domain Questionnaire
[g] Job strain=high job demands

Table 4: Effects of stressful events and worry episodes on heart rate (HR).

	Model 1 Estimate ± SE (p-value)	Model 2 Estimate ± SE (p-value)	Model 3 Estimate ± SE (p-value)	Model 4 Estimate ± SE (p-value)
Fixed effects				
Intercept	77.73 ± 1.00 (<.001)	77.45 ± 1.02 (<.001)	64.29 ± 1.17 (<.001)	62.81 ± 1.60 (<.001)
Stressor^{0}	1.02 ± .94 (.14)	1.18 ± .95 (.11)	.09 ± .83 (.46)	.40 ± .89 (.33)
Stressor^{-1}		2.02 ± 1.20 (.047)	1.25 ± .95 (.09)	1.34 ± 1.01 (.09)
Stressor^{-2}		.15 ± .76 (.43)	-.12 ± .59 (.42)	-.11 ± .62 (.43)
Worry^{0}	2.48 ± 1.12 (.01)	2.86 ± 1.14 (.006)	1.79 ± .89 (.02)	1.57 ± .93 (.05)
Worry^{-1}		2.85 ± 1.86 (.06)	3.34 ± 1.42 (.01)	3.33 ± 1.49 (.01)
Worry^{-2}		2.51 ± 1.01 (.006)	1.34 ± .79 (.04)	1.31 ± .81 (.05)
Stressor^{+1}		-1.15 ± 1.81 (.26)	.32 ± 1.39 (.41)	.27 ± 1.46 (.43)
Angry			.41 ± .47 (.20)	.36 ± .51 (.24)
Sad			-.59 ± .71 (.20)	-.34 ± .75 (.32)
Tense			.96 ± .41 (.01)	.80 ± .45 (.04)
Happy			.61 ± .29 (.02)	.56 ± .31 (.03)
% High activity			10.56 ± .63 (<.001)	10.68 ± .67 (<.001)
Activity level			3.18 ± .31 (<.001)	3.25 ± .34 (<.001)
Posture			2.45 ± .19 (<.001)	2.46 ± .20 (<.001)
Gender				3.24 ± 2.46 (.09)
Age				-.14 ± .12 (.11)
BMI [b]				.37 ± .32 (.12)
Smoking				3.55 ± 1.28 (.003)
Alcohol consumption				0.8 ± .62 (.10)
Coffee consumption				.37 ± .46 (.21)
Time of day [d]				.15 ± .29

				(.30)
Variance components				
Person level:				
Intercept (σ^2_v)	63.33 ± 12.09	64.12 ± 12.24	71.89 ± 13.05	70.40 ± 13.19
Series level:				
Intercept (σ^2_u)	29.28 ± 3.75	29.12 ± 3.77	22.73 ± 2.60	20.06 ± 2.57
Episode level:				
Intercept (σ^2_e)	73.21 ± 2.69	73.08 ± 2.70	38.82 ± 1.48	39.64 ± 1.61
Deviance	14463.62	14246.76	12696.64	11210.44

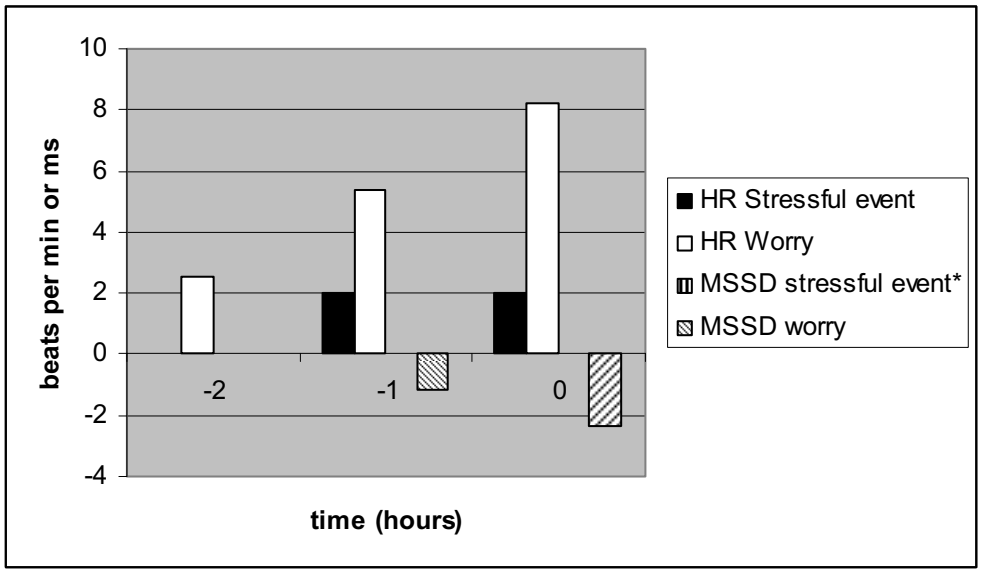
[a] BMI=Body Mass Index
[b] = previous 45 minutes
[c] 0 = non-work day; 1 = work-day
[d] 1 = morning; 2 = afternoon; 3 = evening

Table 5: Effects of stressful events and worry episodes on lnMSSD

	Model 1 Estimate ± SE (p-value)	Model 2 Estimate ± SE (p-value)	Model 3 Estimate ± SE (p-value)	Model 4 Estimate ± SE (p-value)
Fixed effects				
Intercept	3.35 ± .05 (<.001)	3.36 ± .05 (<.001)	3.59 ± .06 (<.001)	3.66 ± .08 (<.001)
Stressor^{0}	-.01 ± .04 (.37)	-.01 ± .04 (.40)	-.001 ± .04 (.49)	-.002 ± .05 (.35)
Stressor^{-1}		-.05 ± .05 (.16)	-.05 ± .05 (.17)	-.06 ± .05 (.11)
Stressor^{-2}		.01 ± .03 (.42)	.004 ± .03 (.45)	-.01 ± .03 (.39)
Worry^{0}	-.13 ± .05 (.002)	-.14 ± .05 (.001)	-.11 ± .05 (.007)	-.10 ± .05 (.02)
Worry^{-1}		-.16 ± .07 (.02)	-.16 ± .07 (.02)	-.18 ± .08 (.01)
Worry^{-2}		-.04 ± .04 (.16)	-.01 ± .04 (.37)	-.01 ± .04 (.39)
Stressor^{+1}		-.04 ± .07 (.28)	-.09 ± .07 (.10)	-.11 ± .08 (.08)
Angry			-.02 ± .03 (.27)	-.01 ± .03 (.34)
Sad			-.02 ± .04 (.33)	-.01 ± .04 (.38)
Tense			-.01 ± .02 (.35)	.01 ± .02 (.41)
Happy			.003 ± .02 (.42)	.01 ± .02 (.27)
% High activity			-.11 ± .03 (<.001)	-.11 ± .04 (.001)
Activity level			-.07 ± .02 (<.001)	-.08 ± .02 (<.001)
Posture			-.04 ± .01 (<.001)	-.04 ± .01 (<.001)
Gender				.08 ± .12 (.26)
Age				-.01 ± .01 (.16)
BMI [b]				-.02 ± .02 (.14)
Smoking				-.15 ± .07 (.01)
Alcohol consumption				-.05 ± .03 (.07)
Coffee consumption				.05 ± .02 (.03)
Time of day [d]				-.03 ± .01

				(.01)
Variance components				
Person level:				
Intercept (σ^2_{u0})	.19 ± .03	.19 ± .03	.19 ± .03	.18 ± .03
Series level:				
Intercept (σ^2_{u0})	.03 ± 0.1	.03 ± .01	.03 ± .01	.03 ± .01
Episode level:				
Intercept (σ^2_e)	.12 ± .004	.12 ± .004	.11 ± .004	.12 ± .005
Deviance	1916.11	1901.18	1704.61	1545.97

Figure 1: Cumulative effects of stressful events and worry episodes at different durations on HR and MSSD [a].



[a] Only significant effects are reported.
* Effects of stressful events on MSSD were not significant and were therefore not reported.

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