Prolonged cardiac activation, stressful events and worry in daily life.
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Chapter 4: *Cardiac Effects of Momentary Assessed Worry Episodes and Stressful Events*

ABSTRACT
Objective: We hypothesized that increased heart rate (HR) and decreased heart rate variability (HRV) occurs not only during stressful events but also during episodes in which stress is cognitively represented, but not necessarily present, i.e. during worry.
Methods: Ambulatory HR and HRV of 73 female and male teachers were recorded for 4 days, during which they reported, on an hourly basis using computerized diaries, the number and characteristics of worry episodes and stressful events. Multilevel regression models were used, controlling for biobehavioral variables.
Results: Compared to neutral periods, worry episodes and stressful events had independent effects on HR (2.00 beats/min and 2.75 beats/min, respectively) and HRV (-1.07ms and –1.05 respectively). Neither psychological traits nor biobehavioral variables influenced these results. Effects were most pronounced for work-related worry on HR (9.16 beats/min) and HRV (-1.19 ms), and for worry about anticipated future stress on HR (4.79 beats/min).
Conclusions: Worry in daily life might have substantial cardiac effects in addition to the effects of stressful events, especially in the form of work-related and anticipatory stress, the latter being a type of stress that has been largely neglected in stress research.

According to the conventional reactivity hypothesis, frequent elevated physiological responses during stressful events lead to changes in physiological balance, triggering several pathogenic pathways. Recently however, it has been repeatedly argued that CV elevations during stressful events are probably not sufficiently long-lasting to cause chronic pathogenic states (1-3). Instead, prolonged CV activity, either before or after the occurrence of a stressful event, is proposed to be responsible (4). This implies that some unmeasured factor before or after stressful events prolongs responses to them. Worry has been mentioned as a candidate for this unmeasured mediator (5). Worry, or rumination (or more formally perseverative cognition) implies the continuation of stressful events in the form of cognitive representations (6). Cognitive representations of stress often act as "real" stressful events, causing real increases in physiological arousal, because they involve negative thoughts and action tendencies that are analogous to those elicited during an actual stressful event. Indeed, trait worry as well as experimental worry and rumination have been found to be associated with a range of physiological effects including CV, endocrinological and immunological effects (6, 7). Trait worry has been related to elevated risk of a second myocardial infarct (8). Moreover, worry and rumination are core elements of psychopathologies with elevated CV disease risk, such as anxiety disorders and depression (9, 10).

In summary, in addition to stressful events, worry might prove to be an important and unexplored source of prolonged CV activation. Only one study has directly compared effects of worry and stress on CV activity before: Brosschot and colleagues (11) found effects of worry on HR and HRV aggregated over one day and one night independently from the effects of stressors. However, timing and duration of worry episodes and stressful events in that study were not precisely measured and could therefore not be matched with *simultaneously* occurring cardiac activity. Thus, the question remains unanswered whether worry has direct cardiac effects in daily life that are independent from stressful events. The present study compared the direct cardiac effects of worry episodes with those of stressful events and neutral events. On four different days (96 hours) momentary assessments were carried out using computerized diaries and heart rate (HR) and heart rate variability (HRV) were measured continuously. High levels of HR or low levels of HRV are risk factors for CVD as well as other organic diseases and overall mortality (12). It was expected that during episodes of both worry and stressful events, compared to neutral episodes, HR would be increased and HRV decreased, and it was tested whether the effects of worry and stress are independent, that is, additive. Several negative traits (i.e. trait hostility and trait worry) as well as negative situations (i.e. high job stress (high demand/low control (13)) have been found to be a risk for CVD. It is possible that the enhanced risk associated with these factors is – at least partly - due to more pronounced HR or more decreased HRV during worry or stress, or with a higher frequency of worry episodes or stressful events having cardiac effects. Therefore, we also tested whether these factors were associated with high HR or low HRV, and whether these effects are mediated by momentary worry. 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 (14-21); therefore, analyses were corrected for effects of these factors. Due to the hierarchical structure of the data we used multilevel regression models for the analyses.

Method

Participants

Subjects in this study were 73 teachers at 17 secondary schools in the Netherlands. 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. Initially, 102 teachers were willing to participate in the monitoring; 29 dropped out before starting the experiment for various reasons (pregnancy, sick leave, allergy for electrodes not known before starting experiment, antidepressant or hypertension medication) or were left out due to insufficient diary recordings. Eventually 73 participants were included in the study and were measured between 2001 and 2003. Eleven persons had valid data for only 48 of the 96 hours, due to withdrawal from the project (four subjects), time constraints (two), allergic reaction to the electrodes revealed after 48 hours of measurements (one), sudden sick leave (one), device malfunction (three). However, since they had more then 10 diary entries (the required minimum) they were included in the analyses. All teachers gave written informed consent and received a book token worth 20 Euros for their participation. The study was approved by the university ethics committee.

Procedure

After receiving approval by the management of the schools, teachers were recruited via regular mail. Participants were contacted by phone to schedule the measurements after which they received self-report questionnaires by regular mail. In a laboratory session the teachers signed the informed consent and underwent a 'hostility'-interview (see below). In the morning before they started their regular work activities an experimenter fitted the ambulatory ECG device (22) 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.

Negative emotional dispositions and job strain

Job strain was measured by the Job Content Questionnaire, which measures job demands and job control in the workplace (13). Trait worry was measured by the Penn State Worry Questionnaire (PSWQ) (23) and the Worry Domain Questionnaire (WDQ) (24). The PSWQ was developed to measure the tendency for excessive, uncontrollable, pathological worry, while the WDQ quantifies worry over different areas of content. Symptoms of depression were measured by the Beck Depression Inventory (BDI) (25). Anxiety was assessed by the trait scale of the Spielberger State-Trait Anxiety Inventory (STAI) (26). Trait hostility was measured by the Cook-Medley hostility scale (CM) (27). All these scales are widely used, reliable and valid. Nonverbal hostility was measured by the Interpersonal Hostility Assessment Technique (IHAT) (28), which is a rating system based on a structured 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 authors of the test (28), independently assessed all interviews and achieved an intraclass correlation of .86. For the analyses these ratings were averaged across persons.

State measurements
      Diary format
For the hourly diary we used a Palm[tm] m100 handheld device (Palm Inc., Santa Clara, CA, USA), together with 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 classes 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 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 besides 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 answered additional questions: About (a) the approximate starting point and duration of the worry episode or the stressful event, (b) the intensity of worry (not at all, some, a bit, much, very much), (c) feeling tense during worry (not at all, some, a bit, much, very much), whether worry was related to (d) work (no, yes) or to (e) a future event (no, yes) and whether (f) worry was difficult to stop (not at all, some, a bit, much, very much); (g) how disturbing or annoying the stressful event was (h) whether the stressful event was related to work (no, yes) and (i) whether the stressful event was about a conflict with others (no, yes). Additionally, they reported on (j) consumed units of tobacco, coffee and alcohol during the preceding hour (0, 1-2, 2-4, more than 4).
      Cardiac activity
Ambulatory HR and HRV were measured 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 elsewhere (29). In

the present study the electrocardiogram 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 only 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: RMSSD), which we used as an index of HRV. The RMSSD has been shown to be a reliable index of cardiac parasympathetic influences (12) and is one of the time domain indices recommended by a task force report on HRV measurement (30). Additionally, the device includes an accelerometer sensitive to changes in vertical acceleration. This motility signal was used to identify and remove episodes with high physical activity (see below).

Data processing
Based on the diary data, episodes were labelled in the cardiac data as neutral, worrying and/or stressful using the AMS graphical program (22). Additionally, based on the time stored by the handheld device, all episodes were provided a time code (1=morning until 12.00 hrs, 2=afternoon until 18.00 hrs, 3= evening until sleep). The program calculated mean HR and RMSSD over the resulting periods. Next, we eliminated all "labels" with outliers in standard deviation, mean, minimum and maximum values of HR, RMSSD, IBI and motility. Before doing this, to ensure that high cardiac activity due to intense movements could not mask the results, the AMS motility signal was used to remove episodes with high physical activity. These episodes were identified as motility higher than the 48-hour average plus one SD of a person (indicating high physical activity) in combination with a visually detected simultaneous increase of HR, which was presumably due to this high activity. Furthermore, we assumed that the subjects were not very accurate in indicating the exact beginning and ending of worry episodes and stressful events. Therefore, the subjects were asked to indicate the beginning and duration of their worry episodes and stressful events using six intervals (<5 min, 5-15 min, 15-30 min, 30-45 min, 45-60 min, >60 min). We excluded neutral periods occurring in the same hour in which worrying or a stressful event occurred from the total number of neutral periods, to ensure that this set of neutral periods was not 'contaminated' by worrying or a stressful event. A final total of 2653 episodes (on average 36.3 ± 13.1 episodes per participant) were used in the analyses.

Statistical analysis
Multilevel regression models (for an introduction see (31, 32)) were applied to estimate the effects of the various predictor variables on HR and RMSSD. The choice of multilevel analysis arises from the hierarchical structure of the data: measurements of HR and RMSSD are nested within subjects. We refer to these two levels as *episode level* and *person level*. Predictor variables measured at both levels were entered into the model. Episode level predictor variables entered into the model included the occurrence of worry episodes and stressful events, time of day and the biobehavioral variables smoking and consumption of alcohol and coffee. Person level predictor variables entered into the model included gender, age, BMI,

trait worry (PSWQ and WDQ), depression (BDI), anxiety (STAI), hostility (CM and IHAT) and job demands.

For all variables descriptive statistics were computed. The distribution for RMSSD was non-normal, therefore this variable was log transformed. Furthermore, smoking, consumption of alcohol and coffee, were dichotomized into yes/no variables. All independent variables were centered around their grand mean.

A sequence of four models was tested for each separate dependent variable. Firstly, an intercept-only model was fit containing no predictor variables (model 1). This model decomposes the variance of the dependent variable into two independent components, pertaining to the episode level and the person level, and was used as a baseline model. In the second model (model 2), we examined the effects of the occurrence of worry episodes and stressful events on HR and RMSSD; additionally, it was evaluated whether these variables had a random effect as well by modelling variation of their slopes across persons. In the third model (model 3), 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, and it was studied whether the effects of worry episodes and stressful events found in model 2 would still be present. In the last model (model 4), we added the person level variables trait worry, depression, hostility and anxiety, as well as their interaction with the episode level variables occurrence of worry episodes and stressful events. The effects of the predictor variables in models 3 and 4 were considered fixed, since we did not have a specific interest in their random effects.

Multilevel regression models were fit using the program MLwiN, version 1.10 (33). The maximum likelihood method was used for model estimation. Fixed effects of predictor variables were tested using one-tailed t-tests, as the hypotheses were explicitly directional random effects, that is, variance components, as well as model improvement in general, were 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 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 (13, 25-27, 34-37). 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 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, e.g. 1.38 and 1.65 for stressful events (38, 39) and .96/day for worry episodes (40). 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). Multiple regression analysis showed that the STAI was the best predictor (F(1,72) = 19.76; p < .001); frequency of stressful events was only related to the STAI (r=.29, p<.05).

Effects on HR

Results of the intercept-only model (model 1) are presented in table 2. The estimated value of the intraclass correlation was 65.28/(66.56+65.28) = .495, providing strong evidence for a 2-level hierarchical data structure. Mean of HR of this sample was 76.37 beats/min (CI 75.40 – 77.34), which is a common ambulatory finding (41, 42).

Worry episodes and stressful events were added as predictors to the intercept-only model (model 2, table 2) and had a significant (fixed) effect on HR (z=3.81, p<.001 and z=1.74, p<.05 respectively). The effects showed that presence of worry episodes and stressful events was associated with an increase in HR of 2.83 (CI 2.09-3.57) and 1.82 (CI .77-2.86) beats/min respectively. Additionally, worry episodes and stressful events had a significant random effect ($\chi 2$ = 16.74, df=5, p<.01, compared to the model with fixed slopes for worry episodes and stressful events only, not reported), indicating that the effects of both predictors (represented by the regression slopes) varied significantly across persons. Parameters for intercept-slope covariances in model 2 were not significant ($\chi 2$ = 1.60, df=3, ns), so these parameters were excluded from the model. Generally, model 2 fitted well in comparison with the intercept-only model (model 1: $\chi 2$ = 47.27, df=4, p<.01). Adding the worry episodes and stressful events as predictors to the latter model resulted in a decrease in intercept variance at the episode level of 2.48. Thus, approximately 3.7% of the variance in HR was explained by the fixed and random effects of these variables.

Biobehavioral variables were added to the previous model (model 3, table 2) to test whether the effects of worry episodes and stressful events would be diminished, which would imply that they were due to one or more of these factors. Results show that smoking had a significant (fixed) effect on HR (z=4.85, p<.001). The effect of this variable was associated with an increase of 5.20 (CI 4.13-6.27) beats/min compared to periods without smoking. Additionally, subjects displayed a decrease in HR as the day progressed with a mean decrease of 1.22 (CI -1.45- -.99; z=5.30, p<.001). Overall, the fit of model 3 was good in comparison with model 2 ($\chi 2$ = 2103.8, df=7, p<.001). The inclusion of biobehavioral factors in the model did not markedly change the effects of worry episodes and stressful events, which were still associated with a significant increase in HR of 2.00 (CI .91-3.09; z=1.84, p<.05) and 2.75 (CI 1.98-3.52; z=3.55, p<.001) beats/min, respectively, compared to neutral periods.

Next, variables containing trait values of worry, depression, hostility and job strain including the interactions between these trait values and the variables indicating the presence of worry episodes and stressful events were added to the model (not reported in table), but these variables did not significantly explain additional variance compared to model 3 ($\chi 2$ = 22.70, df=22, ns). An exploratory model with only psychological traits without worry episodes and stressful events showed that only the effect of trait worry (PSWQ) was significant (CI .11-.38; z=1.81, p<.05), but this effect disappeared (z=1.01, ns) after adding biobehavioral variables.

We explored the effect of specific worry characteristics (within worry episodes), in combination with the biobehavioral variables. Table 3 shows that work-related and future-related worry episodes were associated with an increase in HR of

9.16 (CI 6.99-11.33; z=4.23, p<.001 and 4.79 (CI 3.14-6.44; z=2.90, p<.01) beats/min respectively in comparison to other worry episodes. In comparison to an intercept-only model (not reported) this model fits well (χ2 = 511.14, df=12, p<.001). A similar test of the characteristics of stressful events (not reported) showed that when stressful events were related to work, they were associated with an increase in HR of 2.76 beats/min in comparison to stressful events that were not related to work (CI 1.27-4.08; z=1.91, p<.05). This model also fits well in comparison with an intercept-only model (χ2 = 277.36, df=10, p<.01).

When the fixed effects of predictor variables in the models described above were tested using two-tailed t-tests, stressful events were still significant (p<.001 in model 2 and 3), while worry episodes showed a non-significant tendency to be associated with the increase in HR of 1.82 (p=.08, in model 2) and 2.00 (p=.07, in model 3) beats/min respectively. Additionally work-related and future-related worry episodes were still significant (p<.001 and p=.003 respectively).

Effects on RMSSD

The estimated value of the intraclass correlation of RMSSD from the intercept-only model (model 1, table 4) was .18/(.11+.18) = .62 , indicating a strong 2-level hierarchical data structure. Overall the mean of RMSSD of this sample was 29.52 ms (antilog value; CI 28.47-30.57), which is a common finding in a healthy population (43).

Adding worry episodes and stressful events to the intercept-only model (model 2, table 4) showed that only worry episodes had a significant fixed effect on RMSSD (z=1.77, p<.05). Worry episodes were associated with a decrease of -1.05 (antilog value; CI -2.08 to -.02) ms of RMSSD. Worry episodes also had a random effect, indicating that their effects varied significantly across persons (χ2 = 25.47, df=4, p<.01, compared to the model with fixed slopes for worry episodes and stressful events only (not reported).

Of the biobehavioral effects (model 3, table 4) again only that of smoking was significant (antilog value=-1.16 ms; CI -1.22 to -1.11, z= 3.28, p<.001). Overall model 3 fit well in comparison with model 2 (χ2 = 148.93, df=7, p<.001) and the effect of worry episodes was not markedly changed (antilog value = -1.06 ms; CI -1.04 to -1.10, z=2.28, p<.05). However, the effect of stressful events now became significant (z=1.66, p=.049) and was associated with a decrease of 1.05 ms (antilog value; CI -1.08 to -1.02) compared to neutral periods.

The same model including the psychological traits lead to a non-fitting model as compared to model 3 (χ2 = 12.58, df=22, ns). A model with the traits but without worry episodes and stressful events as predictor variables yielded an effect of hostility (IHAT) (antilog value = -2.14 ms; CI -3.57 to -.71, z=2.14, p<.01), that disappeared when biobehavioral variables were added (z=1.60, ns).

The analyses of worry characteristics showed an effect of work-relatedness (z=1.77, p<.05), indicating a decrease in RMSSD of -1.18 ms (antilog value; CI -1.29 to -1.07) for each unit increase in work-relatedness of worry (table 5). In comparison with an intercept-only model (not reported here) this model has a good fit (χ2 = 89.94, df=12, p<.01). None of the effects of the characteristics of stressful events reached significance.

When the fixed effects of predictor variables in the models described above were tested using two-tailed t-tests, stressful events displayed a non-significant

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tendency to be associated with similar increase in rMSSD (p=.09, in model 3) and worry episodes showed a non-significant tendency to be associated with rMSSD in model 2 (p=.09), while still being significant in model 3 (p=.02). Additionally intensity of worry and work-related worry showed a non-significant tendency to be associated with rMSSD (p=.06 and p=.06 respectively).

Discussion

The purpose of the present study was to examine the cardiac effects of worry episodes during daily life, and to compare these effects with those of stressful events and neutral episodes. The main finding is that worry episodes and stressful events are both, independently, associated with elevated levels of HR and decreased levels of HRV. This appears to support our hypothesis. Strongest were the effects of worry about work on HR and HRV, and the effects of worry about future issues and those of stressful events concerning work on HR. None of these relationships were significantly influenced by biobehavioral factors such as gender, age, body mass or negative health behavior, and they could also not be explained by the effects of several traits, namely worry, depression, anxiety and hostility, or by job strain.

The magnitude of the effects of worry and stress on HR were comparable to effects previously found for worry episodes in laboratory studies (44, 45), that is, increases of about two to three beats/min in comparison to neutral periods. The effect on RMSSD (slightly more than minus one ms) was less pronounced than previously found in a laboratory study measuring RMSSD during worry (46) (decreases of about four ms). Given that both high HR and low HRV are independent risk factors for CV disease (47, 48), these results support the view that daily worry can be a source of pathogenic CV activity in addition to daily stress. The finding that worry episodes and stressful events lead to comparable yet independent elevations of cardiac activity is in agreement with the theory that worry elicits action tendency states and negative cognitions that are similar to those elicited during experience of a stressful event (6). The net cardiac effects of worry might even be much more substantial than those of stressful events because the duration of worry episodes is likely to be much longer than that of stressful events – which was indeed found in the present study. This longer duration of cardiac effects due to worry is consistent with the recently revitalized notion that in order to influence the development or course of CV disease, stress-related activation should be prolonged (2, 4). The number of stressors and worry episodes is typically low for the healthy sample studied and is not likely to lead to disease. However, for subgroups of people these changes can accumulate to a level which begins to be potentially pathogenic, especially when combined with the effects of other risk factors, such as smoking, low exercise and hypertension. It should be noted that the effects of smoking, stress and worry are independent and can therefore be added. For example for heart rate this implies that frequent smokers who experience chronic stress and worrying have a virtually constant increase of up to 10 BPM, independent of other biobehavioral factors. Gillum, Makuc, and Feldman (49) reported that a resting HR of greater than 84 bpm was an independent risk factor for new cardiac events in healthy men and women aged 25 to 74 enrolled in the NHANES study. Additionally, Aronow, Ahn, Mercando, and Epstein (50) reported that a 5 bpm increase in HR was associated with a 1.14 elevated risk of new events in older patients with heart disease and sinus rhythm. Thus HR levels on the magnitude of the present results have been

previously shown to be associated with increased risk for cardiac events in large, prospective studies and thus may be of no small public health consequences.

The finding that the cardiac effects of different psychological traits do not influence the cardiac effects of worry is interesting. Additionally, overall we found no direct effects of these traits on cardiac activity or the few effects disappeared when statistically controlling for biobehavioral variables. The results indicate that these traits do not have a direct pathogenic effect on the cardiac system, despite their empirical relation with elevated risk for CV disease (51-55), which is in contradiction with some (56-58), but not all (59, 60) previous ambulatory findings. Additionally, we did not find that negative traits interacted with worry episodes and stressful events. For example, it is possible that we would have found interactions with *specific* anger provoking events, and with specific anger-related worry, consistent with analogue laboratory studies (61). It is noteworthy that trait anxiety was associated with increased frequency of worry episodes. Thus, trait anxiety apparently has an effect on daily cardiac activity by increasing worrying. However, it should be noted that worry episodes are only moderately predicted by trait measurements of anxiety and worry (62), which again underscores how important state measurements are.

The present study also shows that specific worries are related to more pronounced cardiac elevations. When worrying about their work, the teachers showed a considerably higher HR and lower HRV compared to periods in which they were worrying about other subjects. The magnitude of these effects is even comparable to that of smoking (see tables) which is an established risk factor for CVD. Work-related stressful events were associated with significant albeit somewhat less pronounced HR elevations, but not to different HRV. Job strain has been found to be a risk factor for CVD (47); despite this, the present study did not find that teachers reporting high job stress, that is high demand and low control, displayed elevated cardiac activity in comparison to teachers reporting low job strain nor did they report worry episodes more frequently. The data seem to suggest that increased moment-to-moment worries about work may form an additional source of variance in potentially pathogenic CV changes that is independent of reports of high job stress.

We regard the finding that worry about the future was related to higher HR than worrying about the past or the present of special interest. Elsewhere (4, 5, 8) we have argued that conventional stress measurements (such as life event questionnaires) are restricted to stress in the past, neglecting anticipation of future stressful events. Only very few studies have measured anticipatory stress (38, 39). The current study underscores these criticisms by showing that worry not only adds to the effects of current stressful events but that worry about future stressful events is even superior to worry with other content – except for work-relatedness. The effects of future-related worry are comparable to effects obtained in stress studies in the laboratory (63, 64). This seems to imply that a stressful event that might happen in the future can cause a considerable anticipatory cardiac activation - irrespective of its actual later occurrence.

This study has several limitations. The subjects were a group of high school teachers, which is a highly educated, medium SES subgroup, and these results might not generalize to other groups with lower education and SES. There might also have been a selection bias in the sense that for example teachers responded who

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experienced a lot of stress, or the opposite, that is, that those with the highest work loads did not respond due to a lack of time. Furthermore, it might be argued that worry and stressors were reported relatively infrequently (only 6-9% of the measured diary entries). However, these frequencies are comparable to those found by others (38-40), and we still found solid effects of worry and stressors amidst a large pool of neutral episodes which were independent of biobehavioral factors and psychological traits. Moreover, it could be argued that if worry is a key detrimental process that might lead to CV disease in the long run, one should not expect worry to happen often in a healthy population. For subgroups, such as in the present study for highly anxious persons, the number of worry episodes is clearly higher. This might indicate a possible mechanism underlying the increased risk for CVD of anxiety (6), in which the total load on the organism is related to a high number of worries, rather than, the level of cardiac activity during worry. Additionally, one might argue that effects of the present study are limited since some become non-significant trends when tested with two-tailed t-tests. There are several factors that argue against this. Firstly, the over-reliance on p-values has been criticized in the biomedical literature and it has been recommended that confidence intervals, as we report here, be the primary mode of data presentation in medical journals (65). Confidence intervals and their associated measurements of effect size provide a more informative presentation of the results than just the binary decision of significant or not which detracts from the important role of biomedical research in estimating the magnitude of factors of interest. Importantly, the use of confidence intervals makes the one-tailed versus two-tailed argument moot (66). Relatedly, the effects found in the present study appear to be of the same order of magnitude as others have found to be associated with CVD risk. For example a recent consensus report on the effects of elevated HR on CVD risk (67) cites 2 studies that reported results in the bpm metric. Both studies found that risk increased approximately 15% for each 5 bpm HR increase. In addition, Cook and colleagues (68) report that drugs that lower HR by approximately 5 bpm were associated with an approximately 20% decreased risk of mortality. Fewer studies exist that have examined HRV measurements using a millisecond metric; however Antelmi (14) reported that RMSSD decreased approximately 3.6 ms per decade increase in age and HF power decreased 2.1 ms per decade increase in age. We have often proposed that the effects of worry represent a type of pre-mature aging (69). In addition, the size of the effects found for worry and stressful events were similar to those found for smoking in this study. Thus we feel that the current results are of the same order of magnitude as those that have been shown to be clinically relevant.

In conclusion, the findings of this study extend the findings of laboratory studies of worry by showing that worry during daily life also leads to cardiac effects. Our findings emphasize the importance of worry as a source of cardiac elevations independent of the effect of stressful events. Given the fact that elevated resting HR and decreased resting HRV are both predictors of morbidity and all-cause mortality these findings suggest that part of the large and significant effects of psychosocial stress on the risk for cardiovascular disease found in epidemiological studies such as the InterHeart study (70) are mediated by worrying about psychosocial stress. Although the average effects of worry and stress are not extreme, our analyses found significant inter-individual differences, as indexed by significant random effects in our models, such that the effects for some individuals were quite high.

This suggests that measurements of psychosocial stress and worry in particular may be useful in the identification of persons at particular risk for morbidity and mortality. In addition, our group has shown that a simple worry intervention can decrease the duration of worry and thus might be useful as an adjunct to traditional cardiovascular risk reduction strategies (71). We were also able to identify specific worries, such as worry about work and about the future that lead to even more pronounced effects. The identification of specific topics or domains of worry extends the literature on the CV effects of work stress and underscores the importance of anticipatory stress. The notion that cognitive representations of future stressors can produce significant effects on the cardiovascular system necessitates a re-thinking of the reactivity hypothesis to include stressors that do not actually occur.

Table 1: Mean, standard error, range and (positive) percentages for episode 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	
Episode level:				
Worry	2653			6.1%
Stressful event	2653			8.7%
Smoking	2630			6.7%
Alcohol consumption	2450			10.0%
Coffee consumption	2581			22.0%
Time of day	2653			26.4% morning 42.2% afternoon 31.4% evening
Intensity of worry	165	2.4 ± .6	1-5	
Tense during worry	167	2.1 ± .7	1-5	
Work-related worry	115			68.7% work
Future-related worry	163			31.9% future
Difficult to stop worry	165	2.2 ± .9	1-5	
Frequency worry episodes		1.06 ± 1.69 per day		
Duration worry episodes		16.74 ± 19.34 minutes		
Work-related stress	237			55.3% work
Conflict-related stress	238			69.7% conflict
Disturbance/annoyance	240	2.7 ± .8	1-5	
Frequency stressful events		1.58 ± 1.16 per day		
Duration stressful events		6.85 ± 9.85 minutes		

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

	Model 1 Estimate ± SE (p-value t-test one-sided) [two-sided]	Model 2 Estimate ± SE (p-value t-test one-sided) [two-sided]	Model 3 Estimate ± SE (p-value t-test one-sided) [two-sided]
Fixed effects			
Intercept	76.37 ± .96 (<.001) [<.001]	76.41 ± .96 (<.001) [<.001]	79.26 ± 1.07 (<.001) [<.001]
Stressful event		2.83 ± .74 (<.001) [<.001]	2.75 ± .77 (<.001) [<.001]
Worry		1.82 ± 1.05 (.04) [.08]	2.00 ± 1.09 (.04) [.08]
Smoking			5.20 ± 1.07 (<.001) [<.001]
Alcohol consumption			-.03 ± .59 (.48) [.96]
Coffee consumption			-.76 ± .42 (.04) [.08]
Time of day			-1.22 ± .23 (<.001) [<.001]
Gender			2.74 ± 2.22 (.11) [.22]
Age			-.08 ± .11 (.25) [.50]
BMI [a]			.34 ± .29 (.12) [.24]
Variance components			
Person level:			
Intercept (σ^2_{u0})	65.28 ± 11.18	65.10 ± 11.17	59.72 ± 10.63
Slope worry (σ^2_{u2})		20.55 ± 9.63	20.93 ± 9.92
Slope stress (σ^2_{u1})		10.42 ± 5.58	10.29 ± 5.69
Episode level:			
Intercept (σ^2_e)	66.56 ± 1.85	64.08 ± 1.82	61.50 ± 1.85
Deviance	18923.10	18875.83	16772.03

[a] BMI=Body Mass Index

Table 3: Effects of characteristics of worry episodes on heart rate

	Estimate ± SE (p-value t-test one-sided) (two-sided)
Fixed effects	
Intercept	87.88 ± 3.77 (<.001) [<.001]
Intensity of worry	1.89 ± 1.64 (.12) [.24]
Tense during worry	-1.23 ± 1.63 (.23) [.46]
Work-related worry	9.16 ± 2.17 (<.001) [<.001]
Future-related worry	4.79 ± 1.65 (.002) [.004]
Difficult to stop	-2.14 ± 1.00 (.02) [.04]
Smoking	10.35 ± 3.78 (.003) [.006]
Alcohol consumption	8.68 ± 2.84 (.001) [.002]
Coffee consumption	1.26 ± 1.61 (.27) [.54]
Time of day	-2.54 ± .93 (.003) [.006]
Gender	7.48 ± 3.64 (.02) [.04]
Age	-.17 ± .19 (.19) [.38]
BMI [a]	1.43 ± .59 (.008) [.016]
Variance components	
Person level:	
Intercept (σ^2_{u0})	68.72 ± 21.87
Episode level:	
Intercept (σ^2_{e})	37.80 ± 6.45

[a] BMI=Body Mass Index

Table 4: Effects of worry episodes and stressful events on lnRMSSD

	Model 1 Estimate ± SE (p-value t-test one-sided) (two-sided)	Model 2 Estimate ± SE (p-value t-test one-sided) (two-sided)	Model 3 Estimate ± SE (p-value t-test one-sided) (two-sided)
Fixed effect			
Intercept	3.39 ± .05 (<.001) <.001	3.38 ± .05 (<.001) <.001	3.40 ± .06 (<.001) <.001
Worry		-.05 ± .03 (.05) .10	-.07 ± .03 (.01) .02
Stressful event		-.04 ± .03 (.06) .12	-.05 ± .03 (.049) .098
Smoking			-.15 ± .05 (.001) .003
Alcohol consumption			-.03 ± .02 (.09) .18
Coffee consumption			.04 ± .02 (.02) .04
Time of day			-.01 ± .01 (.31) .62
Gender			.10 ± .12 (.19) .38
Age			-.01 ± .01 (.12) .24
BMI [a]			-.02 ± .02 (.13) .26
Variance components			
Person level:			
Intercept (σ^2_{u0})	.18 ± .03	.18 ± .03	.17 ± .03
Slope worry (σ^2_{u2})		.02 ± .01	.04 ± .02
Slope stress (σ^2_{u1})		.02 ± .01	.02 ± .01
Covariance intercept slope worry		.03 ± .01	.04 ± .01
Cov intercept slope stress		.02 ± .01	.02 ± .01
Episode level:			
Intercept (σ^2_{e})	.11 ± .00	.11 ± .00	.11 ± .00
Deviance	2019.50	1988.69	1839.76

Table 5: Effects of characteristics of worry episodes on lnRMSSD

	Estimate ± SE (p-value t-test one-sided) (two-sided)
Fixed effects	
Intercept	3.24 ± .13 (<.001) [<.001]
Intensity of worry	.13 ± .07 (.03) [.06]
Tense during worry	.03 ± .07 (.36) [.72]
Work-related worry	-.17 ± .09 (.04) [.08]
Future-related worry	-.03 ± .07 (.33) [.66]
Difficult to stop	-.03 ± .04 (.25) [.50]
Smoking	-.47 ± .16 (.002) [.004]
Alcohol consumption	-.19 ± .11 (.05) [.10]
Coffee consumption	-.06 ± .07 (.19) [.38]
Time of day	-2.54 ± .93 (.003) [.006]
Gender	-.12 ± .18 (.26) [.52]
Age	-.01 ± .01 (.31) [.62]
BMI [a]	-.02 ± .03 (.21) [.42]
Variance components	
Person level:	
Intercept (σ^2_{u0})	.20 ± .06
Episode level:	
Intercept (σ^2_e)	.06 ± .01

[a] BMI=Body Mass Index

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