Prolonged Cardiac Activation, Stressful Events and Worry in Daily Life

ISBN: 978-90-8891-071-5

Cover: 'fight – flight' by Els Tjong Joe Wai, 2007

The research reported in this thesis was funded by the Netherlands Organisation for Scientific Research-Medical Sciences (NWO-MW).

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PROEFSCHRIFT

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. P.F. van der Heijden,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 27 november 2008
klokke 13.45 uur
door

Suzanne Pieper
geboren te Paramaribo, Suriname
in 1977

Promotiecommissie

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In every life we have some trouble,
but when you worry you make it double.

Bobby McFerrin (1988)

CONTENTS

Chapter 1: *General Introduction*

Cardiovascular disease (CVD) is the leading cause of death in western countries, which is why numerous studies have focussed on mechanisms, risk factors and possible intervention and prevention strategies. In the past decades, the relationship between psychosocial stress factors and cardiovascular disease (CVD) outcomes has been extensively studied (1-3). However, it remains unclear which underlying psychophysiological mechanisms are responsible for the development of CVD and how psychosocial stressors trigger these mechanisms. More precisely, although the physiological pathogenic pathways appear to be well understood, the *psycho*-physiological factors that lead from stressors to these physiological pathways are not. To be able to design successful interventions, it is crucial to have complete knowledge of these pathogenic pathways.

During the past decades, most studies investigating this stress-disease link have focussed on the *reactivity* model. In this model exaggerated cardiovascular (CV) response is a risk factor for the development of CVD. Large and frequent increases in CV response during exposure to stressors would lead to changes in physiological balance, such as increased platelet aggregation and coronary vasoconstriction. These changes would finally lead to various CVD outcomes (4). However, human studies indicated that reactivity has poor power to predict CVD and several authors (5-9) have pointed out that the reactivity model is conceptually insufficient as an explanation for the relationship between stress and disease.

One important insufficiency is that the reactivity model focuses only on states in which a stressor is present and ignores what happens before or after this period. As such, the reactivity model is related to states of such short duration that these states -regardless of their frequency and intensity- cannot explain the development of chronic pathogenic states that lead to CVD. It seems obvious that people whose physiological levels remain elevated for long periods of time following a stressor may be at greater risk than those who show similar reactivity but recover more promptly. Thus, psychological factors may only have a detrimental effect on CV health if resulting in prolonged states of physiological activity rather than in short elevations, however high their magnitude. Thus, the duration of the stress response, rather than its magnitude, seems to be an important element which has been overlooked in the reactivity model.

Indeed, despite the dominance of the reactivity hypothesis, it has long been recognised (10, 11) that *prolonged* CV responses of stressors and not so much the relatively short responses *during* stressors (i.e. reactivity), strain and wear out the CV system to the extent that they may lead to CVD. The *prolonged activity model* states that the duration of the stress response, rather than its magnitude, is an important element in inducing CVD disease (Chapters 2 and 3). Indeed, several studies have shown that delayed cardiac recovery from stressors is predictive of adverse cardiac outcomes (see Chapter 2 for a review (14)). However, these studies mostly focussed on relatively short-term cardiac stress recovery in the laboratory. Laboratory studies are limited with respect to the large time scope that is necessary to enable the ecologically valid study of prolonged activity. On the contrary, ambulatory field studies provide a larger time scope ánd the possibility to measure real-time stressors; therefore, testing prolonged effects of stressors in an ambulatory design is essential for testing the prolonged activation model. However, only a few ambulatory studies have investigated prolonged effects of stressors (see Chapter 2 for a review (14)). For these reasons, the present dissertation focuses on the prolonged cardiac

effects of daily life stressors and compares them to the immediate effects in an ambulatory design.

Additionally, it remains unclear why some stressors lead to prolonged activation, while others do not. It was recently suggested (12-14) (Chapters 2 and 3) that perseverative cognitions, such as worry or rumination prolong physiological activation beyond the actual occurrence of a stressor. When a stressor cannot be readily coped with, perseverative cognitive processes 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 (Chapters 2 and 3). Indeed, recent laboratory studies and one ambulatory study suggest that perseverative cognitions might act directly on somatic disease including CV disease via enhanced activation of the cardiovascular, immune, endocrine and neurovisceral systems (14-22) (Chapters 2-6). Support for this hypothesis is based on only a few laboratory studies. In this dissertation, we investigate the cardiac effects of perseverative cognition in daily life. In our opinion, this is particularly relevant; if we do find that perseverative cognitions induce cardiac effects in daily life, this would open up the possibility of designing an intervention which works specifically on reducing these cognitions.

In general, the present dissertation investigates the prolonged cardiac effects of stressors in daily life and whether perseverative cognitions mediate this relationship. More specifically, three main objectives were investigated.

At first, we reviewed available ambulatory studies for evidence of a relationship between stressors and prolonged CV activation. If prolonged activity is to be an etiological factor it is important to demonstrate that it exists in the first place. We also searched the studies for indications of psychological mechanisms that are responsible for these prolonged effects.

Our second objective was to build the argument that perseverative cognition mediates the health consequences of stressors because it may prolong stress-related affective and physiological activation, both in advance of and following stressors. Additionally, we reviewed evidence that worry, rumination, and anticipatory stress are associated with enhanced cardiovascular, endocrinological, immunological, and neurovisceral activity. Again, it is important to collect evidence, in this case whether perseverative cognition indeed has physiological consequences. If not, it could never have been the topic of the empirical work presented in this dissertation (Chapters 4, 5 and 6), that is, the mediator of stressor effects on health or health parameters.

Thirdly, we conducted an extensive daily life study to investigate the effects of stressful events and worry on simultaneous cardiac activity, prolonged cardiac activity at various durations during the day and prolonged activity during sleep. Since sleep is the primary rest period of most animals including humans, it seems crucial for our model to show prolonged effects during sleep. A previous study from our group suggested that stressors have prolonged effects on sleep and that those effects are mediated by worry (15). We attempted to replicate and expand upon the previous results. We also investigated whether worry mediates prolonged effects of stressful events, as well as negative emotional traits (trait hostility, depression, anxiety and worry) and stress-related factors (job strain). Negative traits and job strain were included because they have been documented previously as risk factors

for CVD (23-28). It is important to investigate whether they have simultaneous as well as prolonged cardiac effects in daily life and during sleep, and whether these effects are mediated by worry.

Thesis outline

Prolonged activity has not often been an explicit research goal of real-life stress studies. Nevertheless**,** a growing number of these studies have provided evidence for prolonged activity as a secondary research goal. In Chapter 2, we review these findings and discuss indications of psychological mechanisms responsible for prolonged effects. In Chapter 3, we plea that perseverative cognition is a mediator of the health consequences of stressors and we review studies that showed an association between worry, rumination, and anticipatory stress on the one hand and enhanced CV, endocrinological, immunological, and neurovisceral activity on the other hand. In Chapter 4, the direct cardiac effects of worry episodes are compared with those of stressful events and neutral events in daily life. Cardiac effects of worry have not been systematically studied in real life. Additionally, we test whether cardiac effects of negative emotional traits (i.e. trait hostility, depression, anxiety and worry) or stress-related beliefs (i.e. job strain) are mediated by momentary worry. In Chapter 5, using a completely different analytical strategy, the hypothesis of prolonged stressor effects in periods of various durations is tested *against* the reactivity hypothesis that involves effects during stressors only; this method enabled us to study whether stressors cause prolonged cardiac activation, how long this activation continues and whether worry effects this process, a question which has not been answered before. In Chapter 6, the effects of daily stressors and worry on cardiac activity during waking and the subsequent nocturnal sleep period are evaluated. This study is a replication of the effects of a previous study (15), which found a relationship between increased daytime stressful events and worry on the one hand and increased mean levels of cardiac activity during daytime and sleep on the other hand. We attempted to replicate these findings in a more elaborate design. In Chapter 7, we provide a summary and general discussion of the integrated results.

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Chapter 2: *Prolonged Stress-Related Cardiovascular Activation: Is There Any?*

ABSTRACT

***Background**: 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. This view is opposed to the conventional reactivity hypothesis that emphasizes responses during stressors.*

***Purpose**: Prolonged activity has not often been an explicit research goal of real-life stress studies. Nevertheless, a growing number of these studies have provided evidence for prolonged activity, as a secondary research goal.*

***Methods**: An overview of this evidence is lacking and is provided in this article.*

***Results**: The combined data from the reviewed studies suggest that discrete and chronic stress sources, as well as negative emotional episodes and dispositions, are related to prolonged CV activity of various durations, including sleep periods. On the other hand, evidence supporting the assumption that prolonged stress-related activation predicts disease is still very modest.*

***Conclusions**: In this article we suggest that future research of prolonged activation should give priority to (a) the establishment of clear beginnings and endings of stressful events, (b) the prediction of disease by prolonged activation, and (c) potential psychological mediators of stress-related prolonged activation. These mediators may include, for example, worry and rumination, or other processes characterized by perseverative cognition, including unconscious processes.*

This chapter was published as *Pieper S, Brosschot JF. Prolonged stress-related cardiovascular activation: is there any? Ann Behav Med 2005;30(2):91-103.*

INTRODUCTION

Psychosocial stress or stress factors have been found to be related to cardiovascular disease (CVD) outcomes such as myocardial infarction (1), coronary artery disease (2,3), stroke (4), and hypertension (5,6). These sources of stress include discrete work-related and domestic events, as well as stressors with a less easily discernable beginning or ending, such as chronic job strain, episodes of depression or anxiety, and stable dispositions to experience a high level of stress, such as hostility or anxiety. They are known to influence many physical diseases, but their influence on CVD is especially well documented. Still, it remains largely unclear which underlying psychophysiological mechanisms are specifically responsible for these CVD outcomes and how psychosocial stressors trigger these mechanisms. More precisely, although the physiological pathogenic pathway appears to be well understood (7,8), the psychophysiological factors that lead from stressors to this pathogenic pathway are not.

Several authors (9,10) have pointed out that the explanatory models for these factors are insufficient. Most theories and studies have focussed on the so-called reactivity model, which suggests that individuals with a tendency to respond to stressful events with increased cardiovascular (CV) reactivity have an increased risk for CVD. Large and frequent increases in CV response would lead to changes in physiological balance, such as increased platelet aggregation and coronary vasoconstriction, which would finally lead to various CVD outcomes. Even though there are animal studies that provide convincing evidence for the reactivity model (11,12), human studies on reactivity have yielded inconsistent results and have had various methodological difficulties, such as lack of stability of the stress response over time and over tasks, inconsistent prediction of CVD, and failure to generalize reactivity in the laboratory to reactivity in daily life (13). Recently, Schwartz and colleagues (10) pointed out that these issues have still not been solved. More important, the reactivity model itself seems to be lacking because it overlooks the duration of the stress response, such as physiological activation after termination of a stressor or in anticipation of a stressor (9,10,14-16). The reactivity hypothesis generally pertains to states of short duration that, even if they are frequent and intense, cannot explain the development of the chronic pathogenic state that leads to CVD (9,14). However, it seems obvious that people whose physiological levels remain elevated for long periods of time following stress may be at greater risk than those who show similar reactivity but recover more promptly. The same goes for people who show anticipatory activation far ahead of a stressor. Thus, psychological factors may only have a detrimental effect on CV health if they result in prolonged states of physiological activity rather than in only short elevations of activity, however high their magnitude. Therefore, the duration of the stress response, rather than its magnitude, may be an important element in causing CVD disease.

Because of the relative novelty of this insight, only a modest amount of CV stress research has explicitly addressed the issue of prolonged activity. However, several studies have measured the duration of stress responses, often as an issue of secondary interest. There is no review available of these potentially important findings with the notable exception of laboratory findings of stress recovery. The latter have been summarized and discussed elsewhere (9,14), and the results suggest that emotional tasks lead to slower recovery than nonemotional tasks (9)

and that recovery is accelerated when there is an opportunity to cope with the source of stress (14).

Laboratory studies are limited with respect to the time scope that is necessary to enable an ecologically valid study of prolonged activity. In contrast, ambulatory field studies provide a larger time scope. In this article we provide a review of findings from ambulatory studies testing the hypothesis that various stress sources can have prolonged CV effects. In addition, we discuss indications from these studies of psychological mechanisms that are responsible for these prolonged effects. Because the stress-disease link has mostly been studied for CVD, and because the reactivity hypothesis is specifically formulated for CV activity, we limited this review to ambulatory field studies that assessed CV variables such as heart rate (HR), blood pressure (BP), and heart rate variability (HRV).

To present an adequate theoretical framework for the review, we first provide a definition and elaborate conceptualization of prolonged activity. Next, we briefly review available evidence for a relationship between prolonged activity and risk for somatic disease. Then, we discuss the few stress-disease theories that have recognized prolonged activation as an essential element. Thereafter, we address possible mechanisms by which psychosocial stressors can bring about prolonged activity. Finally, in the remainder of the article we review and discuss ambulatory field studies that measured prolonged cardiovascular activation.

DEFINITION AND CONCEPTUALIZATION OF PROLONGED ACTIVITY

To avoid confusion, it is important to be clear about what exactly we mean by *prolonged activity*. Therefore, we define three types of prolonged activation, according to the time period in which prolonged activation occurs in relation to the stressor. The first and most frequently studied type is prolonged physiological activity immediately after termination of the stressor, which is often referred to as *recovery*. In ambulatory studies, stressors are often reported over predefined periods (e.g., hours), whereas CV variables or other physiological variables are measured continuously. Some of these studies have in addition analyzed the relationships between these stressors and physiological activity in the subsequent time period. The second type can *reoccur* after initial recovery, when the stressor is so-called mentally re-created -for example when a person ruminates about it at a later point in time (17). This reoccurrence of physiological activity can be found in studies that measured activity during typical restorative periods, such as non-work time, evening, and night. A third type of prolonged activity can take place in *anticipation* of a potential stressor. Anticipatory experience of stress has been occasionally studied but seldom clearly hypothesized as a source of stress-related physiological activity.

In summary, we review psychosocial stressors and stress sources that influence three types of prolonged activity. These three types are defined as (a) slow recovery after stressors or acute prolonged activity, (b) reoccurring prolonged activity after initial recovery, and (c) anticipatory prolonged activity in advance of a stressor. Theoretically, reoccurring as well as anticipatory activity may occur at any time preceding or following a stressful event. We discuss studies that have related prolonged activation to CVD risk in the next section.

PROLONGED ACTIVITY AND RISK FOR CVD: IS THERE EVIDENCE?

Several studies have yielded evidence that prolonged duration of physiological activity during recovery phases is related to CVD outcomes. One study found that slow HR recovery, aggregated over physical and emotional tasks, predicted enhanced rest HR 4 years later when corrected for weight (18). In addition, several studies have shown that prolonged CV activity is an independent or better predictor of disease than reactivity. Delayed systolic BP (SBP) recovery after a cognitive task was found to be more strongly related with hypertension 5 years later than reactivity during the task (19). Similarly, delayed HR recovery during the first minute after physical exercise was found to be predictive of overall mortality 6 years later, independent of reactivity during the exercise and controlled for age, gender, and exercise capacity (20). In addition, slow BP recovery from physical stressors (cold pressor and tourniquet ischemia) was related to elevated BP 3 years later, again after adjustment for reactivity values and controlled for differences due to age, body mass index (BMI), and parental history of hypertension (21). Furthermore, elevated BP during anticipation of physical exercise predicts the development of hypertension 4 years later after adjusting for BP levels during exercise, corrected for smoking, alcohol consumption, physical activity, BMI, and parental history of hypertension (22). In addition, exaggerated anticipatory BP responses to bicycle exercise were cross-sectionally related to incremental increase of left ventricular hypertrophy, which is a risk factor for CVD. This relation remained significant after adjustment for age (23).

Together, these studies seem to provide convincing evidence for a relationship between prolonged stress-related activity and CVD outcomes. An explanation for these findings is that short-term delayed recovery and anticipation reflect a more pervasive and general tendency to recuperate slowly after stress or to anticipate long in advance. Such a tendency might extend the total load on the organism over time, and in that way constitute a risk factor for CVD. Alternatively, prolonged activation might be the consequence of other CVD risk factors and, as such, has no direct effect on disease outcomes. Indeed, delayed CV recovery was found to be related with several of these risk factors, such as parental history of hypertension, low fitness level (for reviews see 24,25), smoking (26), caffeine intake (27), and elevated BMI (28). In the review that follows, we note which factors are controlled. We also discuss several theories in which prolonged activity is an essential element in the relationship between stress and somatic disease.

PROLONGED ACTIVITY AS AN ESSENTIAL ELEMENT IN STRESS-DISEASE THEORIES

As far back as half a century ago, Selye's (29) general adaptation syndrome already included the central element of duration. Even though the importance of prolonged activation was already acknowledged at such an early stage in history of the stress concept, it does not appear to have led to a great deal of attention in later theories and research. There are a few exceptions, however. In the 1980s, Ursin (30) emphasized the crucial role of sustained activation in the effect of psychological stressors on somatic health. In his view, increased physiological activation during a stressful event is experienced as a strain, which the individual is urged to reduce. If the individual would succeed in coping with the stressor (by establishing the expectation to be able to change, eliminate, or avoid it), tonic physiological activation would subsequently be reduced. In contrast, if such an expectation is not

established, the stressful experience would be prolonged and physiological activation would be sustained, which in the long run would be detrimental for physical health. Ursin and Eriksen (31) postulated that activation is sustained by negative outcome expectancies, such as helplessness and hopelessness.

In the late 1990s, several other theorists revived prolonged activation as a cornerstone of stress theory. McEwen (32), in a currently popular theory, proposed the term *allostatic load* to refer to the wear and tear on the body due to repeated efforts to keep it in physiological balance in the face of an external stressor. This theory suggests that there are several types of situations that lead to allostatic load, including repeatedly experiencing novel events causing repeated elevations of stress over long periods of time and failure to habituate or adapt to a specific stressor. According to McEwen, high physiological levels are maintained by a prolonged stress experience.

Linden and colleagues (9) showed that recovery issues seemed to have been neglected in stress studies and that it was necessary to rehabilitate the concept as a subject of crucial theoretical and ecological significance. In their review of laboratory stress studies, they revealed that although recovery was being increasingly measured in stress experiments, it was only being reported in a minority of these cases. They also showed that even in the limited time span typical for laboratory stress experiments, the measurement of recovery yielded findings that were not apparent when only reactivity was taken into account. For example, attenuated recovery but not elevated reactivity was found in persons with a low fitness level, in caregivers, and in anger-provoked participants. The authors postulated that slow recovery after stressors is due to prolonged negative affect.

Sluiter, Frings-Dresen, Meijman, and van der Beek (33) focussed on the relationship between work-related factors and incomplete recovery. They argued that individuals who experienced repeated stressful factors at work needed more time to recover from work-related neuroendocrine reactivity. This process started a cycle in which extra psychophysiological effort had to be exerted to maintain optimal performance at work. In turn, the cycle could lead to long-term health problems. Indeed, they found that this cycle leads to increased cortisol and adrenaline excretion during non-work periods, together with increased reports of feelings of chronic fatigue and health complaints. However, their theory leaves unexplained how extra psychophysiological effort in itself would lead to prolonged activity. Physical effort of comparable intensity does not usually lead to sustained activation of muscles, HR, cortisol, and adrenaline for hours, let alone nights and days. Thus, something more than physical effort alone must cause sustained activation after stressful events.

All theories discussed thus far explicitly contain the duration element and, all except the last one, postulate mediating psychological mechanisms such as negative mood (9), negative outcome expectancy (30), and prolonged stress experience (32). In our opinion, these mechanisms are insufficient to account for prolonged physiological activation. It is unlikely that individuals suffering prolonged stress-related activation are in a continuous state of negative expectation or negative mood. At best, internal or external "reminders," such as worry, rumination, or contextual clues frequently trigger such states. These kinds of mechanisms are not specified in the aforementioned theories. The most elaborated of these hypotheses or models (31,32) correspond closely to general self-regulation theories or systems

theories in which an evaluation mechanism detects a discrepancy between an individual's goals (i.e., set values) and reality (i.e., actual values), which is the direct instigator of the stress response. However, the stress theories discussed provide a *static* model of the stress response mechanism, which is a model that can explain the organism's state at any given period in time. Conversely, prolonged activation is best explained using the *dynamic* aspects of this evaluation mechanism, such as frequency, speed, initiation, and lag between feedback and behavior. The models do not seem to sufficiently address these dynamic aspects.

In conclusion, the notion of prolonged activation as a crucial mediator of the effects of stress on health has been recognized early in the field. However, it is used only in a limited number of stress theories with respect to the size and history of the field. These theories do not sufficiently address the psychological mechanisms responsible for prolonged activation. Recently, attempts have been made to theorize about the nature of these mechanisms and to find empirical support for them. We discuss this in the next section.

PSYCHOLOGICAL MECHANISMS UNDERLYING PROLONGED ACTIVATION

In retrospect, the first studies of psychological mechanisms underlying prolonged activation were not genuine stress experiments but instead were anger reduction experiments. Starting with a set of studies in the early 1960s, Megargee and Hokanson (34) and several other investigators have consistently found, in more than 20 different experiments (14), that anger induction without opportunity to counterreact prolongs CV reactivity. In a review of these findings and the explanations proposed to account for them, Brosschot and Thayer (14) proposed a comprehensive model, partly based on emotion theory. According to this model, angry emotions lead to physiological preparation for action to change the anger-provoking situation. When this situation can not be changed -for example, when the angering object is not present or if social rules prohibit anger expression- the organism remains in a state of behavioral readiness, and the psychophysiological preparation phase is sustained. Most angering instances of normal daily social life do not provide an opportunity to express anger, and so hypothetically this preparation phase will be continued regardless of an individual's tendency to express or inhibit anger. A recent experiment suggests that increased duration of the CV response after anger provocation is related to ruminating about the angering situation. Glynn and colleagues (17) found that BP recovery following an anger provoking stressor was significantly slower than that following a nonemotional stressor although the magnitude of BP responses was comparable among the tasks. When participants were distracted after the anger provocation and thus were less able to ruminate, BP recovered more quickly. Thus, this experiment suggests that rumination (or related cognitive processes) might prolong physiological activation due to stress. In line with this, two recent theoretical reviews (35,36) revealed that worry and rumination are associated with activity of several physiological systems, including the CV, endocrinological, and immunological systems. This is true for experimental as well as dispositional worry and rumination, and for other dispositions toward sustained cognitive and emotional engagement, such as John Henryism coping (37).

Thus, several studies, directly or indirectly, suggested that one possible way in which physiological responses to stressors may be prolonged is by cognitive processes, such as rumination and worry. Theoretically, these processes extend the

duration of the action tendency associated with the negative emotions and concomitant psychophysiological activation. The responsible mechanism in these processes has been named *perseverative cognition* (35) and is usually implicated in several negative emotional states, including anger, depression, and anxiety. The advantage of using the notion of perseverative cognition is that it involves a direct trigger of physiological activation, namely, the representation of the original (or expected) stressor and the repeated reevocation of this representation and concomitant stress experience and physiological activation. In contrast, emotional states and other more ambiguous and general concepts such as negative mood, prolonged stress experience, helplessness, or hopelessness are too ambiguous with respect to this precise mechanism. In our view, this makes perseverative cognition a promising candidate as a predictor of prolonged activation related to stress sources. However, support for this hypothesis is based on only a few laboratory studies. In our review of ambulatory real-life studies in the next section, we examine whether there are cues or suggestions for possible psychological and psychosocial mechanisms responsible for the prolonged effects, including indications of perseverative cognition.

REVIEW OF AMBULATORY STUDIES OF STRESS-RELATED PROLONGED ACTIVITY

We indicate whether the findings of the reviewed studies were controlled for health behavior that might have caused reactivity, as well as prolonged activation, such as smoking, and coffee and alcohol intake. Furthermore, we mention all CV parameters that are reported. The studies to be considered can be divided in four groups according to the time scope of the psychosocial stress sources measured. We distinguish between four types: (a) discrete stressful events (stressors with an easily specifiable beginning and ending); (b) chronic stressors, which are characterized by their continuous presence or high frequency; (c) transient negative affective states that can act as temporal stressors; and (d) dispositions to experience negative emotions, such as neuroticism, trait anger, hostility, depression, and anxiety. The last type implies the largest time scope, in many cases effectively acting as a lifetime stressor. Table 1 shows a summary of the characteristics and findings of all studies discussed in the next sections, categorizing the studies according to their own time scope (i.e., discrete, chronic, transient affective state, emotional disposition) and that of prolonged activation (i.e., recovery, anticipation, reoccurring).

Prolonged Activity Related to Discrete Stressors

Several studies have measured prolonged CV activation after discrete stressors. Catastrophic stressors or personal traumas, such as earthquakes, hurricanes, nuclear accidents, rapes, and child abuse are associated with a range of psychophysiological consequences, including prolonged BP activity for hours to weeks after the incident (38,39). However, these catastrophic events are relatively rare in the life of the average person and therefore are beyond the scope of this article. Brondolo, Karlin, Alexander, Bobrow, and Schwartz (40) showed that a considerably less intense stressor, such as communication of traffic enforcement agents with the public, was related to increased SBP, but not diastolic BP (DBP) or HR, 15 min after termination of communication, as compared to 15 min after communication with coworkers. The results were adjusted for effects of differences in posture, and only periods in which the agents were not communicating were tested for delayed effects. Another study

showed that a high number of stressors experienced during daytime, measured with 60-min diaries, predicted higher HR, but not HRV, during subsequent nocturnal sleep (41). This effect was independent of health behavior, including smoking, coffee intake, and alcohol intake. More distal past stressors may also influence sleep physiology. Ituarte (42) found that an increased number of stressful events over a 6-month period is related to the absence of the typical decline in HR during subsequent nocturnal sleep, especially among persons with low levels of social support. The results were independent of the effects of age, gender, and BMI.

In addition, prolonged activity during sleep can be observed when anticipating a discrete stressor (43). Participants who were anticipating a stressful oral speech task that had to be performed soon after waking up in the morning showed decreased high-frequency power in their HRV, indicating lower vagal tone, during non-REM (NREM) and REM sleep, as well as an increased ratio of low-to-high frequency power of HRV (mainly indicating high sympathetic tone) during NREM sleep. A control group not anticipating the stressor showed a normal increase of vagal tone and low sympathetic tone across successive NREM cycles. Participants were asked to refrain from exercise, alcohol intake, and caffeine intake prior to and during the experiment, and the authors controlled for stress at baseline and the time that participants were awake during the sleep period.

In conclusion, there is evidence that prolonged CV activation can occur prior to or after a discrete stressor, suggesting that the prolonged experience of a past stressor, as well as the mere expectation of a stressor, are related to sustained or recurrent activation, or anticipatory activation. These results could not be attributed to the effects of unhealthy behavior. None of these studies specifically addressed the possible psychological factors causing the observed prolonged activation. However, the results seem to imply that the participants must have been thinking to some degree about the stressors. The finding of prolonged activation during sleep suggests that at least part of these cognitive processes are continued during sleep in an unconscious fashion, such as during dreaming, and that they still result in prolonged CV activity. We discuss these issues in the last section. The next section addresses the question whether there is evidence that more chronic stressors have prolonged activity effects beyond their actual presence.

Prolonged Activity Related to Chronic Stressors

Chronic stressors are characterized by their frequent occurrence or long duration. In theory, prolonged physiological effects of these stressors are relevant for stress-disease theory. Not only do these stressors and the immediate physiological responses to them last longer, but they might also result in longer periods of prolonged activation than discrete stressors because of their pervasiveness and intensity. Despite what their name suggests, chronic stressors are not necessarily of a continuous nature or "always present". From a prolonged activity perspective, it is of high interest whether they have effects in periods in which they are not present.

An important source of chronic stressors is the work environment. The findings for prolonged activation effects of work stressors are inconsistent. One of the leading theoretical work stress models, Karasek's demand-control model (44), in which high job strain is defined by high psychological workload demands combined with low decision latitude, has been studied relatively frequently in ambulatory designs. Van Egeren (45), in a 24-hr study, found that high job strain, compared

with low job strain, was related to higher SBP, but not DBP, at work and during recovery periods at home in the evening, independent of effects of gender, BMI, or caffeine. Similarly, Steptoe, Cropley, and Joekes (46) found that schoolteachers with low job strain showed larger decreases in SBP and DBP, but not HR, during the evening of a work day than the high-job-strain teachers, controlled for age, BMI, and posture. Remarkebly, these teachers did not differ on BP and HR levels during recovery after stressful job-unrelated tasks in the laboratory, which makes it unlikely that slow recovery is a genetically determined or acquired characteristic of individuals who also report high job stress.

In addition to prolonged activity in the evening, prolonged activity in high-strain workers was also observed during non-work days. Schnall, Schwartz, Landsbergis, Warren, and Pickering (47) found these effects in workers from a diverse range of worksites (newspaper department, health agency, stock firm, liquor shop, hospital, warehouse, insurance company). They also demonstrated that these effects were more pronounced in individuals whose high job strain was stable over a long period. Male workers who reported high job strain during 2 work days, 3 years apart, showed higher SBP and DBP at home in the evening and higher SBP during sleep on both time points than workers who reported high job strain at only one time point, which was corrected for the effect of age, BMI, alcohol consumption, and smoking. In a group of general practitioners with high and low job strain, O'Connor, O'Connor, White, and Bundred (48) found results that seem to point toward recurrent prolonged activity. High-job-strain practitioners had higher HRs during the evening following a work day as well as during a non-work day. Although there were no BP differences during the work day and the following evening, during the subsequent non-work day BP was elevated again in high-strain practitioners, with a trend toward further sustained BP during the evening of that non-work day. There were no gender or age differences between the groups. Because high-strain practitioners did not display higher BP during the evening following work, their high BP during the non-work days could not be caused by delayed recovery from work and may indicate a "re-creation" of the work stressors.

In contrast with these findings, several studies found no relationship between high job strain and prolonged CV responses. No such results were found for HR and BP in industrial workers concerning aggregated evening and sleep values (independent of age, gender, BMI, and alcohol) (49); for firefighters regarding HR and BP during non-work day (independent of age, BMI, smoking, alcohol intake, and exercise) (50); in nurses regarding HR and BP during evening, sleep, and non-work day (corrected for age, BMI, posture, alcohol intake, and coffee intake) (51); and between high job demands and prolonged BP physiological responses in schoolteachers during the evening (corrected for age, BMI, and physical activity (52)).

Comparable inconsistent results were found using another leading work stress model, that is, Siegrist's effort-reward imbalance model (53), in which high job strain is defined as a high level of extrinsic efforts or demanding work environment combined with low reward such as esteem rewards or momentary gratification. Male white-collar workers with high job strain compared to those with low job strain displayed elevated SBP and HR at work and in the evening at home and lower HRV during the whole measurement period, namely, during work, evening, sleep, and non-work days. These findings were controlled for age, BMI, activity, posture

changes, smoking, and alcohol consumption (54). In contrast, a group of health professionals and office clerks displayed similar differences in BP, HR, and HRV between high- and low-strain workers at work but not during the evening after work. The effects of gender and smoking were controlled (55).

In addition, other more specific occupational stress sources are related to prolonged activation. In a study of general practitioners (56), high feelings of stress specific to general practitioners, such as constant organizational changes and postgraduate education commitments, were related to elevated SBP and DBP during the work day, elevated SBP during the work day evening, and elevated SBP and DBP during the following non-work day, independent of the effects of age and BMI. In a group of various types of workers, low work-related social support was related to higher HR, corrected for age, gender, BMI, smoking, alcohol, and mean physical strain at work (57), but not to higher BP during work, non-work, and sleep periods. The inconsistencies among the findings for prolonged activation related to work stress are difficult to explain at this point in time. One possibility is that the specific stressors that were measured in these studies do not often lead to prolonged activation during non-work hours, because they do not often lead to worry or rumination during these hours or to other mediators of prolonged activation. Unfortunately, none of the discussed studies have measured possible psychological mediators.

Next to chronic work stressors, there is evidence that chronic domestic stressors can also increase activation during typical recovery periods. High marital distress was associated with higher BP, but not HR, at home during the evening in women employed in a variety of occupations. These differences were not visible at work and were not explained by differences in age, BMI, posture, or caffeine consumption (58). Whether the presence of the source of stress, such as the partner, influenced this result was not reported. Thus, it is unclear whether and to what extent the increased activity is reactivity (responses to the presence of the marital stressor) rather than prolonged activity. This interpretational problem also applies to a study by King (59), who compared BP and HR in middle-age female caregivers of an ill relative with age-matched noncaregivers, for either 1 or 2 days. Caregiving has been shown to be an important chronic stressor with many health consequences (60). Although caregivers and noncaregivers displayed similar BPs at work, caregivers displayed elevated BP at home in the evening, a finding that was independent of age and BMI. During these non-work periods, the caregivers were always in the presence of the care recipient. Again, prolonged activity is hard to distinguish from reactivity because it is not clear whether the caregivers would also show prolonged activity in the absence of the care recipient. In both studies, sleep might have been a good period to detect prolonged activity, but the studies did not assess CV values during sleep.

Another, more general chronic stressor, perceived racism, has also been found to be associated with higher BP during waking periods, but not during sleep. This effect was independent from anger expression styles (61).

Finally, there is evidence that chronic work stress in combination with chronic domestic stress can have a synergistic effect on prolonged activity. Brisson (62) showed that among white-collar women, high job strain and high family load were related to increased SBP and DBP during and after work in the evening and during sleep, compared to workers who exhibited high levels of these types of chronic

stress. These results were independent of age, BMI, smoking, alcohol, and mean physical activity.

In conclusion, there is some evidence that chronic stressors can lead to prolonged activity during periods in which the stressor is absent, although in studies focusing on domestic stressors prolonged activation could not be distinguished from "mere" reactivity. The effects of chronic stressors on prolonged activity were independent of the effects of several confounding variables, such as BMI, age, and physical activity. On the other hand, most studies evaluated the effects of these factors on the overall mean of the studied CV variables, instead of evaluating the effects specific for the different time periods. Therefore, it is not always clear whether prolonged activity effects were truly not due to biobehavioral factors. Furthermore, no reported attempts were made in the studies to measure or analyze personal appraisal of the stressors or psychological responses to the stressors, which could have mediated prolonged activation. Next, we review studies that focussed on the physiological effects of negative affective states.

Prolonged Activity Related to Negative Affective States

Being in a negative affective state can be understood as experiencing a stressor. Several studies measured the effect of these states on prolonged physiological activity. Kamarck and colleagues (63) studied the effects of "emotional affect" and "emotional arousal" on BP and HR in male and female participants. In these participants, 45-min periods of high negative affect compared to periods with low negative affect were related to higher BP in the same period, as well as in the next 45-min period, even after adjusting for negative affect during that next period. High arousal was also related to enhanced BP but only during the same period. These results are independent of posture, physical activity, talking, and caffeine and alcohol intake. Brosschot and Thayer (64) demonstrated that high HR related to negative emotions lasted longer than high HR related to positive emotions. Emotional arousal and physical activity predicted simultaneous HR, whereas prolonged HR activation 5 min later was solely predicted by "negative emotional valence", independent of emotional valence at that point in time and initial HR response. Thus, these two studies suggest that prolonged activity seems to be related to negative emotional valence, and not to high emotional arousal or positive emotional valence. In addition to these short-term effects, Shapiro (65) showed that college students who frequently experience daytime angry or sad emotional states displayed elevated BP, whereas frequently experiencing pleasant or happy states was related to decreased BP during sleep, which was independent of differences due to posture or activity. There was no effect on HR. However, it is not clear from this study whether the BP changes were caused by emotions experienced immediately before sleep or by their accumulation during the preceding day.

To conclude, there is some evidence that episodes of negative affect -or the lack of positive affect- are related to slow recovery as well as prolonged activity during sleep. Even though psychological mediators were not measured in these studies, the results are consistent with the view that prolonged activation is produced by some form of cognitive emotional perseveration that extends beyond the presence of the negative emotion itself. From the perspective of studying the contribution of negative emotions to the development of CVD, it is even more important to know the effects of chronically experiencing these negative

psychological states, or, in other words, having a disposition to experience them. The last review section discusses studies that have focussed on the prolonged effects of several of these emotional dispositions.

Prolonged Activity Related to Negative Emotional Dispositions

Dispositions to experience negative emotions such as hostility, depression, and trait anxiety have been found to be predictive of CV and other diseases (66-69). One explanation is that such negative dispositions could lead to the appraisal of more stressful situations, which could in turn have negative influences on the coping process following the stressors. Thus, these personality dispositions cause longer lifetime exposures to stressors and in fact act as exceptionally chronic stressors. These personality traits can be hypothesized as an even more powerful source of prolonged activation than chronic work stressors or domestic stressors because of their pervasiveness. If this theory proves true, prolonged activation may explain a large part of the disease risks associated with negative dispositions.

There is indeed evidence of prolonged activity in persons with hostile, pessimistic or anxious attitudes. Räikkönen, Matthews, Flory, and Owens (70), who measured university employees during working hours and the subsequent evening, found that high hostility, as well as high levels of pessimism and trait anxiety, were related to continuously elevated BP, but not HR. In contrast, participants low on these traits displayed elevated BP only when actually reporting elevated negative mood. These results were independent of effects of age, posture, location, and physical activity.

Most other relevant studies have related emotional dispositions to high CV activity during sleep. Jamner, Shapiro, Goldstein, and Hug (71) measured HR and BP in paramedics during a 24-hr period including work and sleep, finding that participants with high levels of hostility, in contrast to those with low hostility levels, demonstrated elevated SBP, but not DBP or HR, during waking and sleep. In contrast, high "defensive" participants showed only higher awake DBP levels, but not higher sleep DBP levels, compared to low "defensive" participants. The findings were not controlled for biobehavioral variables. Pasic, Shapiro, Motivala, and Hui (72) found that, independent of effects of gender, age, and BMI, highly hostile participants displayed elevated mean SBP during the 3 hours in the morning preceding awakening compared to participants with low hostility, yet no differences were found during the 3 hours following awakening. Because such differences were not found for anxiety, these results seemed to be limited to hostility. Moreover, Shapiro, Goldstein, and Jamner (73) found a relationship between cynical hostility and prolonged SBP, but not HR or DBP, during waking periods and sleep. This relationship was independent of gender and BMI but only found in African American participants. African American participants scoring high on both anxiety and defensiveness displayed higher DBP during waking periods but not during sleep, which is somewhat in line with the results of Jamner et al. (71).

Kario, Schwartz, Davidson, and Pickering (74) showed higher SBP during sleep, but not during waking time, in men high on anxiety or depression, compared to men low on both these traits. However, this was found only when sleep-to-awake ratio of SBP was used, suggesting that these effects were weak. Women in this study showed only higher waking SBP and pulse rate, not DBP, in relation to higher anxiety. Yet, no differences were found during sleep. These results were corrected

for differences in age, gender and mean activity during sleep and awake measurement periods. In contrast, Schneider, Julius, and Karunas (75) and Van Egeren and colleagues (45,76) did not find differential awake or sleep levels for BP and/or HR related to Type A personality. However, these two studies were conducted before it became broadly established that hostility is the most crucial part of Type A personality in terms of predicting CVD. It is possible that only the hostility element was associated with prolonged CV activity during sleep and not the complete Type A behavior pattern.

Collectively, these results indicate that prolonged activity can be observed in participants with negative emotional dispositions, during waking time as well as during sleep. The sleep findings with these dispositions are even more informative than those with the other stress sources. Earlier, we noted the problem of disentangling stress periods from nonstress or restorative periods in chronic stress. This problem is even more severe during waking for persons with dispositional hostility, depression, or anxiety. In a way, they theoretically experience stressors all the time. However, sleeping might be the only period in which their dispositions are not turning harmless events into potentially disturbing ones, at least not consciously. It is the only period in which we can be sure of the absence of a stress source. Thus, whereas high CV activity during waking may be either reactivity or prolonged activity, high CV levels during sleep must be prolonged activity.

DISCUSSION

We started this article by stating that although prolonged activity is widely acknowledged as an essential part of basic stress-disease theories, it seems to have been largely neglected as an empirical and theoretical research theme for its own sake. To review the available evidence, we collected ambulatory CV studies that measured prolonged activity in relation to various stress sources, whether or not as a primary research aim. This review suggests that there is some evidence for a relationship between prolonged activity and psychosocial factors spread over studies of different types of stress sources. A handful of studies have shown that discrete stressors of various intensities were related to prolonged activity in preparation for and immediately after the stressor and during sleep. Studies focusing on more chronic stressors, such as work-related stressors or caregiving, have found a relationship with prolonged activity during typical recovery periods, such as evening, sleep, and non-work days. However, consistency was lacking with respect to the work-stress findings. Studies have found that negative affective states were related to prolonged activity, immediately after and during sleep. Negative emotional dispositions, which can be viewed as a more chronic form of experiencing a negative affective state, were related to prolonged activity in between episodes of negative states and during sleep.

On the other hand, strong conclusions concerning stress-related prolonged activation are precluded, because of the lack of methodological requirements. These requirements concern the precise identification of prolonged activity and the nature of the mediators of prolonged activation. Firstly, the establishment of clear beginnings and endings of stressful events is lacking in nearly all studies discussed. This is essential because prolonged activity can occur in any period when the stressor is absent, and thus the stress period ought to be established with high precision. In fact, this type of information can be easily reported in the ambulatory

diaries that are already frequently used. It opens the possibility to assess the actual duration of prolonged activity effects. Theoretically, the longer the duration of physiological activation, the more damage will be inflicted on the system. A related problem is that in a number of ambulatory studies, periods such as the evening, sleep, and non-work days were considered as neutral or stress-free periods, with no attempt being made to control for stressors in these periods. This complicates the interpretation of the data, especially in the studies of chronic stressors and emotional dispositions. For example, there was no information available concerning the presence of the stressor during recovery periods, such as in the form of doing work-related chores. Therefore, it is not possible to establish whether these periods are really neutral and stress-free and whether or not prolonged activity during these periods is, in fact, reactivity.

Secondly, it is necessary to correct for various biobehavioral variables that activate physiology, such as physical activity and caffeine/coffee consumption, to be sure that the observed differences are due to prolonged activity. Controlling for these factors can rule out the alternative "health behavior" explanation. Some persons will engage in more unhealthy behavior, such as smoking, drinking alcohol, or drinking coffee, during neutral periods preceding or following stressful events. Their enhanced CV activity in these neutral periods may be the result of this behavior, instead of actual prolonged activity. Although the vast majority of the reviewed studies controlled for one or more of these health behavior variables, only a minority was complete in this respect.

Significantly, none of the studies operationalized and measured potential psychological mediators of the observed prolonged physiological effects. As we proposed earlier in this article, perseverative cognitive processes, such as worry and rumination, form a logical candidate for such a mediating vehicle. Even though such processes were not measured, several findings do suggest their presence. This is especially the case for findings of prolonged activation before or after stressors with a clear-cut beginning and ending. In these cases the stressor is obviously not present during prolonged activation, and it is highly likely that participants are at least busy processing or thinking about the upcoming or past stressor. Of these, most revealing are perhaps those studies that found that CV levels are higher after negative emotional episodes even when the negative affect itself has already worn away (63,64). These findings make clear that prolonged activation cannot easily be attributed to stress-related emotions, but that something more than "mere emotion" mediates these effects, such as perseverative cognition.

It is likely that at least a part of this perseverative cognition is unconscious. This possibility becomes significant when interpreting the findings of prolonged activation during sleep. Prolonged activity during sleep cannot be accounted for by conscious perseverative cognition. There is evidence for a peak in conscious worry frequency in the first part of the night in healthy participants (77), and this is perhaps continued on a less conscious level during subsequent sleep. The possibility of deficient nocturnal recovery of physiological arousal due to a form of cognitive perseveration may be of predominant significance for health because it leads to a situation not unlike being exposed to a permanent stressor. Being continuously physiologically activated by stress without any natural restorative break might eventually cause serious health consequences.

This review is limited by the fact that only studies measuring CV variables were involved. An important reason for this is that the reactivity hypothesis, of which prolonged activity is an extension, was originally formulated to specifically explain the relationship between stress and CVD. A more practical reason is that most available ambulatory studies have focussed on the relationship between stress and CVD. Nonetheless, prolonged activation is obviously not limited to the CV system and CVD but is applicable to various physical systems and their associated diseases, such as the endocrine and immune system, muscle tension, glucose blood level, asthma-related parameters, and so forth. For example, there is empirical evidence that prolonged activity occurs in anticipation of a stressor for cortisol (78) and for cortisol and immune parameters (79). This review of CV ambulatory studies hopefully adds to the insights concerning prolonged activation reached by previous reviews on findings from the laboratory (9,35).

In summary, this article suggests that there is some but not sufficient evidence for a relationship between prolonged CV activity and stress-related psychological factors in ambulatory studies. Future studies are needed that explicitly test the prolonged activation hypothesis with more appropriate methodology and with explicit theories and operationalizations of psychological mediators of stress-related prolonged activation. We suggest that anticipatory activation might be given priority as a research object, given its theoretical importance and the surprisingly small amount of attention it has received as a research object.

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Table 1: Overview of Reviewed Ambulatory Studies and Prolonged Cardiovascular Findings

Stress Source	*Study*	*N*	*Ambulatory Duration*	*Type of Prolonged Activation*	*Specific Stress Factor*	*Prolonged Activation Findings*	*Controlled Biobehavioral Variables*
Discrete	Brondolo et al. (40)	115 (48% men)	8 hr	Recovery	Communication with public	↑ SBP ↕ DBP ↕ HR 15 min after	Posture, activity
	Brosschot et al. (41)	73 (20% men)	± 14 hr	Recovery	Daily stressors	↑ HR ↕ HRV sleep	Smoking, coffee, alcohol
	Ituarte et al. (42)	120 (47% men)	48 hr	Recovery	Stressful events during past 6 months	↑ HR sleep	Age, gender, BMI
	Hall et al. (43)	59 (51% men)	1 night	Anticipatory	Oral speech task after awakening	↓ HF ↑ L/HF sleep	Awaking time, exercise, coffee and alcohol
Chronic	Van Egeren (45)	37 (46% men)	24 hr	Recovery	High demand-control imbalance	↑ SBP ↕ DBP evening after work	BMI, gender, caffeine
	Steptoe et al. (46)	162 (37% men)	13 hr	Recovery	High demand-control imbalance	↑ SBP ↑ DBP ↕ HR evening after work	Gender, age, BMI, posture
	Schnall et al. (47)	195 men	2 x 24 hr	Recovery	High demand-control imbalance measured twice, 3 years apart	↑ SBP ↑ DBP evening after work; ↑ SBP ↕ DBP sleep	Age, BMI, alcohol, smoking
	O'Connor et al. (48)	27 (63% men)	2 x 10-15 hr	Reoccurring	High demand-control imbalance	↕ BP evening after work, ↑ BP non-work day	Age, gender
	Fauvel et al. (49)	70 (22% men)	24 hr		High demand-control imbalance	↕ BP ↕ HR evening after work, sleep	Age, gender, BMI, alcohol
	Steptoe et al. (50)	49 men	2 x 8 hr		High demand-control imbalance	↕ BP↕ HR non-work day	
	Goldstein et al. (51)	138 women	4 x 24 hr		High demand-control imbalance	↕ HR ↕ BP evening after work, sleep, non-work day	Age, BMI, posture, alcohol, caffeine
	Steptoe et al. (52)	104 (36% men)	9 hr		High demand-control imbalance	↕ BP evening after work	Age, BMI, physical activity

	Vrijkotte et al. (54)	109 men	3 x 24 hr	Recovery	High effort-reward imbalance	↓ HRV ↑ SBP ↑ HR ↕ DBP evening after work; ↓ HRV ↕ SBP ↕ HR ↕ DBP sleep, non-work day	Age, BMI, physical activity, posture, smoking, alcohol
	Hanson et al. (55)	70 (44% men)	8-12 hr		High effort-reward imbalance	↕ BP ↕ HR ↕ HRV evening after work	Gender, smoking
	O'Connor et al. (56)	27 (63% men)	2 x 15 hr	Recovery, reoccurring	Stress specific for general practitioners	↑ SBP ↕ DBP evening after work; ↑ SBP ↑ DBP non-work day	Age, BMI
	Unden et al. (57)	148 (79% men)	24 hr (for 93% of the sample)	Recovery	Low work-related social support	↑ HR ↕ BP after work, sleep	Age, gender, BMI, smoking, alcohol, physical strain at work
	Carels et al. (58)	50 women	± 15 hr	Recovery	Marital stress	↑ BP ↕ HR during evening	Age, BMI, posture, caffeine consumption
	King et al. (59)	10 women	1 or 2 days during waking hours	Recovery	Caregiving of ill relative	↑ BP ↕ HR during evening	Age, BMI
	Steffen et al. (61)	69 (43% men)	20 hr		Perceived racism	↕ BP during sleep	Age, gender, BMI
	Brisson et al. (62)	199 women	24 hr	Recovery	↑ Job strain and ↑ family load	↑ SBP ↑ DBP during evening, sleep	Age, BMI, smoking, alcohol, physical activity
Negative affective state	Kamarck et al. (63)	120 (50% men)	2 x 24 hr plus 4 days during waking hours only	Recovery	Negative affect (sad, frustrated, stressed, upset)	↑ BP ↕ HR 45 min later	Gender, race, negative affect at recovery, posture, physical activity, caffeine, alcohol, talking

	Brosschot and Thayer (64)	33 (36% men)	8 hr	Recovery	Arousal and negative valence	↑ HR 5 min later	Age, gender, emotional valence, physical activity at recovery
	Shapiro et al. (65)	197 (50% men)	24 hr	Recovery	Frequent daily anger or sadness	↑ BP ↕ HR during sleep	Posture, activity
Negative emotional dispositions	Räikkönen et al. (70)	100 (50% men)	3 x 8-14 hr	Recovery	Hostility, pessimism, anxiety	Continuously ↑ BP ↕ HR	Age, posture, location, physical activity
	Jamner et al. (71)	33 men	24 hr	Recovery	Hostility	↑ SBP ↕ DBP ↕ HR during sleep	
	Pasic et al. (72)	32 (56% men)	24 hr	Recovery	Hostility Anxiety	↑ SBP ↕ DBP 3 hr preceding awakening -	Gender, age, BMI
	Shapiro et al. (73)	144 (50% men)	24 hr	Recovery	Cynical hostility	↑ SBP ↕ DBP ↕ HR during sleep only in African American	Gender, BMI
	Kario et al. (74)	231 (55% men)	24 hr	Recovery	Anxiety, depression	↑ SBP sleep-to-awake ratio ↕ DBP in men	Age, BMI, physical activity during waking and sleep
	Schneider et al. (75)	33 men	24 hr	Recovery	Type A	↕ HR ↕ BP during sleep	
	Van Egeren and Sparrow (76)	107 (52% men)	2 x 24 hr	Recovery	Type A	↕ HR during sleep	Gender, BMI, caffeine

Note. Parenthetical numbers in the Study column correspond to the reference list numbers. SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; HRV = heart rate variability; BMI = body mass index; HF = high frequency power; L/HF = low to high frequency power; BP = blood pressure; ↑ = higher; ↓ = lower; ↕ = no difference.

Chapter 3: *Expanding Stress Theory: Prolonged Activation and Perseverative Cognition*

ABSTRACT

Several theories of the stress-disease link have incorporated prolonged activation. This article argues that these theories still lack an important element, that is, the cognitive nature of the mechanism that causes stress responses to be sustained. The perception of stress and the initial response to it do not automatically lead to prolonged activation. The active cognitive representations of stressors need to be prolonged in order to extend their physiological concomitants. We call this mediating process perseverative cognition, and it is manifested in phenomena such as worry, rumination, and anticipatory stress. We summarize evidence suggesting that these phenomena are indeed associated with physiological activation, including cardiovascular, endocrinological and immunological parameters. This evidence is still far from sufficient, due to the many methodological insufficiencies in the studies involved. Nevertheless, it showes that cognitive phenomena characterized by perseverative cognition may be candidates to mediate the effects of stress sources on somatic disease.

We also argue that there is a dearth of evidence supporting the role of prolonged activation. A limited number of studies demonstrate prolonged activity related to stressors and emotional episodes, and their methodologies often do not allow unambiguous conclusions. It is even more significant that the crucial assumption that prolonged activation actually leads to pathogenic states and disease has received hardly any attention yet and therefore is still largely unsupported. Only a few studies show that anticipatory responses and slow recovery from stress predict disease states.

This chapter was published as *Brosschot JF, Pieper S, Thayer JF. Expanding stress theory: Prolonged activation and perseverative cognition. Psychoneuroendocrinology 2005;30(10):1043-9.*

PROLONGED ACTIVATION AND STRESS THEORY

Psychological stressors can codetermine the development and course of somatic disease (Krantz and McCeney, 2002). Most stress scientists would agree that a major part of this influence is caused by prolonged physiological activity due to stressors, and not or not alone the activity during stressors. Only prolonged activation can lead to the pathogenic state that eventually leads to organic disease (Linden et al., 1997; Ursin and Eriksen, 2004). Prolonged physiological stress activity comes in three forms: anticipatory responses to (potential) stressors, slow recovery from stressors, and recurrent activity related to past stressors. Prolonged activity, or duration of the stress response, is prominently present in the early stress theory of Selye (1950). However, during the last 50 years stress scientists did not consequently adopt prolonged activation as a major element in their theories and research. Only a few theoretical models have done so. Ursin and co-workers introduced the concept of 'sustained activity' in the early 1980s (Ursin and Murison, 1983). Unfortunately, the implications of this concept did not appear to be sufficiently recognized by others. Much later, in the 1990s, McEwen (1998) launched his allostatic load theory, and Linden et al. (1997), Brosschot and Thayer (1998) and Sluiter et al. (2000) attempted to put stress recovery back on the research agenda.

In this theoretical article, we discuss how prolonged physiological activation can expand stress theory. We explore the possible reasons for the failure of major stress theories to incorporate prolonged activity. Thereafter, we focus on an important lacking element: the cognitive nature of the psychological mediator between stressors and prolonged activation. Finally, we summarize available evidence with respect to some of the major assumptions of the prolonged activation model.

MISSING ELEMENTS IN STRESS THEORY

There are some possible explanations for the failure to include measurements of prolonged activation. One is that studying prolonged activity is more costly, both economically and time wise, than studying activity during stressors or immediately before or after stressors. Also some methodological and statistical issues need to be resolved, especially concerning recovery (Linden et al., 1997). Still, we believe that a more important reason to neglect prolonged activation is related to the natural inclination of researchers to follow the existing theoretical and experimental paradigms, instead of critically examining their premises. For example, a major assumption underlying most of these paradigms involves the 'reactivity hypothesis' that holds that frequent and strong responses to stressors lead to pathogenic wear and tear in organisms and ultimately to disease. The reactivity hypothesis obviously ignores this crucial element of prolonged activation and, not surprisingly, fails to hold up against empirical evidence (Schwartz et al., 2003). In a reactivity model, the shortduration physiological spikes are thought to play the primary pathogenic role. In contrast, a prolonged activation model represents an 'allostatic load' model (McEwen, 1998), which may be conceptualized better in terms of the 'area under the curve'. In such a model, the total amount of stress-induced physiological activation over time, is regarded as the primary pathogenic pathway.

An unfortunate consequence of the dominance of reactivity-based theories is that most researchers still use instruments that fail to capture the most central factor, the duration factor; i.e. stress responses ahead of the stressor and after,

sometimes far ahead and long after. Even though as far back as the 1980s Ursin and co-workers incorporated the notion of negative outcome expectancy in their theory as an important determinant of prolonged activity (Ursin and Murison, 1983), the dominant instruments used in stress research were not focussed on the future. Instead, instruments measuring life events, daily hassles, and various specific stressors such as workrelated stress factors and marital stress factors, all focus on the past. That is, they ask individuals about their experiences in the last week, month or year. At best, they ask about individuals' appraisal of these past experiences, and their interaction with their personality or other dispositional characteristics, such as coping style. None of them, at least not the best known and most widely used, ask about future stressors and anticipation of them. This is astonishing. Any layman would agree that in normal daily life our tense fears and hopes about the future consume at least as much time as those about the past. As the saying goes, 'looking ahead of things is already half the pleasure'. However, looking ahead of stressful events is—at least—half the misery! Consequently, it is likely that anticipatory stress responses account for a large part of stress-related prolonged activation.

Another group of important stress instruments that seem to have neglected prolonged activation involve coping behavior. Apart from the huge conceptual problems with the concept of coping (e.g. Ursin and Eriksen, 2004), it is doubtful if common tests of coping realistically reproduce actual coping behavior. Coping tests usually measure the extent to which individuals exhibit certain coping behaviors, but not the time spent on stressful doubting about which coping strategy to choose. They also do not measure the extent to which individuals are unsure about their choice and will soon terminate one coping endeavour in favour of another, and so on. This pondering, brooding, and feverish vacillation between several coping options are an essential facet of ineffective coping behavior, but it is overlooked by common coping tests. This is especially regrettable because it is this dynamic facet of coping that might be responsible for a large part of prolonged stress activity, as we shall argue below. Ursin and co-workers came close to these dynamics of coping in their Cognitive Activation Theory of Stress (CATS: Ursin and Eriksen, 2004). In this prolonged activation theory, they conceptualise coping as 'positive outcome expectancy', which would only lead to a short stress response, 'training' the biopsychological organism to be more efficient in dealing with future challenges. Non-coping, in their view, is equal to 'negative outcome expectancy' (Fig. 1), 'straining' the organism instead. Still, they did not describe the actual behavioral manifestation of 'negative outcome expectancy', or for that matter, propose a mechanism that prolongs activation.

MEDIATOR OF PROLONGED ACTIVATION: PERSEVERATIVE COGNITION

What prolongs physiological activation, either in advance of a stressor, or afterwards? By lacking the prolonged activation element, the leading stress theories have obstructed the development of a hypothesis of this mediator. Even those theories that incorporated the prolonged activation element (Selye, 1950; Linden et al., 1997; Brosschot and Thayer, 1998; McEwen, 1998; Sluiter et al., 2000; Ursin and Eriksen, 2004) have not explicitly hypothesized a cognitive mechanism that really prolongs activation due to stressors or their perception. For example, although CATS theory (Ursin and Eriksen, 2004) proposes a psychological mediator, that is,

negative expectancy, the theory does not account for the mechanism that causes negative expectancy to be prolonged. It is important to realize that a stressor, or its perception (i.e. negative outcome expectancy) does not lead to prolonged activation in and of itself, but only when the stressor itself or its perception is prolonged. The average physiological response during a stressor is a 'medium sized' biological response, comparable to those occurring during moderate exercise. This kind of response recovers quickly when not instigated otherwise. Thus, something other than metabolic needs keeps on instigating the organism to respond after termination of a psychological stressor. Similarly, huge anticipatory responses far ahead of a stressor can also not be explained by metabolic needs at the moment of anticipation. And finally, modulating stress factors such as perceived uncontrollability, deficient coping styles, low social support and personality dispositions such as hostility, also do not produce prolonged activation of themselves. In short, there must be a mechanism mediating between stressors and stress factors on the one hand and prolonged activation on the other.

Our hypothesis is that perseverative cognition is such a mediator (Brosschot and Thayer, 2003; 2004; see Fig. 1). We have defined perseverative cognition as: 'The repeated or chronic activation of the cognitive representation of stress-related content'. Sources of stress will only lead to prolonged activation when individuals cognitively perseverate about these stress sources, to some extent and for some period. Thus, perseverative cognition might help to convert the immediate psychological and physiological concomitants of life events and daily stressors into prolonged physiological activation of several of the body's systems, which in turn is necessary for the development of a chronic pathogenic state that can lead to disease. As such, perseverative cognition can be thought of as a final psychological pathway by which stress exercises its deleterious effects on the body's systems. It does this by virtue of its propensity to prolong the stressor itself, in a representational form that continues to activate the organism. In terms of CATS theory, negative expectancy is the proposed key factor that produces a physiological activation in the first place, but only when an individual continues to endorse this negative outcome expectation by perseverative cognition, that it will finally lead to prolonged activation. In other words, if one does not worry about the negative outcomes, or maintains an active cognitive representation of it in another way, it will not lead to prolonged activation. What our theory adds to CATS, is the dynamics of this central subjective stress response.

Is there any evidence that perseverative cognition is related to physiological activation and disease outcomes? Perseverative cognition is a central element in cognitive phenomena such as worry and rumination. These phenomena have been major issues in psychopathology and have recently drawn attention in somatic fields too. We have recently reviewed available evidence of worry and rumination-related somatic outcomes (Brosschot and Thayer, 2004). Due to space limits, we will only give a short summary here with the number of studies that reported one or more relevant findings. Trait worry as well as episodes of worry were related to general somatic complaints (two studies), and trait worry predicted a second myocardial infarct (one study). Indirectly, worry is related to poor sleep (e.g. Nicassio et al., 1985), and poor sleep quality in its turn to increased mortality (Dew et al., 2003). Natural episodes of worrying were found to be related to increased cortisol (one study), to high heart rate (two studies) and low heart rate variability (HRV) (one

study). Several laboratory studies showed that experimental worry was related to low HRV (two studies) and that angry rumination was associated with slow blood pressure recovery (four studies). Finally, trait worry and rumination were associated with increased resting blood pressure levels (two studies), less natural killer cells (two studies), higher cardiovascular activity (three studies), and high cortisol values during natural or experimental stressors or during recovery from stressors (one study). In the latter study (Roger and Najarian, 1998) trait rumination was a stronger predictor of cortisol levels than neuroticism, suggesting that a tendency to engage in perseverative cognition represents an independent dimension. Not all of these studies controlled for the effects of health behavior. Worrying or ruminating may have led to for example increased smoking or coffee consumption that may have caused increased physiological activity. Thus, it was not always clear whether and to what extent the prolonged activity related to perseverative cognition was a direct consequence of the cognitive representation of the stressor, as our theory would predict.

PROLONGED ACTIVATION: EVIDENCE FOR ITS EXISTENCE AND ITS DISEASE RISK

The foregoing suggests that perseverative cognition may be a mediator of stress related prolonged activation. However, is there any proof for prolonged activation itself, and even more so, proof that it predicts ill health? Because of its absence in stress theories, prolonged activity has not often been an explicit research goal of scientific inquiry. Not surprisingly therefore, only a relatively small number of laboratory and real life or ambulatory studies have provided evidence for prolonged activity. Recent reviews of laboratory studies revealed that in particular emotional stressors lead to slow recovery after stress (Linden et al., 1997), especially when stressors contain both uncontrollable and social-evaluative elements (Dickerson and Kemeny, 2004). We have recently reviewed evidence of prolonged cardiovascular activation in ambulatory stress studies (Pieper and Brosschot, 2005). We distinguished three types of prolonged activation (anticipatory, recovery and recurrent) related to discrete and chronic stress sources, as well as negative emotional episodes. Natural disasters were excluded as being too uncommon in the life of most people. The combined data from the reviewed studies tentatively suggested that these three sources of stress were related to prolonged cardiovascular activity of various durations, including sleep periods. Endocrinological and immunological real life stress studies are not yet systematically reviewed from the prolonged activation perspective, but a few examples should be mentioned here. For example anticipating a stressor was associated with increased salivary cortisol (Smyth et al., 1998), plasma cortisol (Lacey et al., 2000) and salivary immunoglobulin A (Spangler, 1997), and anticipating a stressful working day was related to higher salivary cortisol awakening response (Kunz-Ebrecht et al., 2004). For more examples the reader is referred to Kristenson et al. (2004). For many of the reviewed studies strong conclusions could not be drawn, since they were hampered by methodological shortcomings with respect to prolonged activation. For example, the exact beginnings and endings of stressors were seldom clear and neutral or rest episodes were not checked for the presence of stressors other than the stressor of interest (e.g. work stress or caregiver stress). Further, not all studies controlled for health behavior such as smoking or drinking, that could act as

alternative causes of prolonged activation. These drawbacks are mostly due to prolonged activity not being the primary focus of study.

Several studies reported prolonged physiological effects of stress sources on sleep. We consider these findings as particularly important because sleep is a major and natural recovery period. A particularly noteworthy example is a study by Hall et al. (2004) who demonstrated that anticipating an oral speech that had to be delivered upon awakening in the morning appeared to increase sympathovagal balance throughout the whole preceding sleep period. If normal daily stressors will be proven to have substantial prolonged physiological effects even during sleep, these effects may account for a considerable part of the effects of stressors on health.

Last but not least, given the existence of prolonged stress-related activity, is there any proof that it actually predicts disease? The answer is yes, but the available evidence is still very meagre. We found five studies, all of which used laboratory stressors that were embedded in larger cardiovascular epidemiological studies. This meagre result is perhaps not surprising given the relatively recent revival of interest in prolonged activity and the costly and time-consuming nature of epidemiological studies. High anticipatory blood pressure responses to a stressor predicted hypertension 4 years later (Everson et al., 1996), and delayed blood pressure recovery from a stressor predicted hypertension 3 and 5 years later (Stewart and France, 2001; Borghi et al., 1986, respectively). Delayed heart rate recovery predicted overall mortality five (Nishime et al., 2000) and 6 years later (Cole et al., 1999) in cardiac patients, and high resting heart rate 5 years later (Treiber et al., 2001), while in the latter study blood pressure recovery did not predict hypertension. Delayed heart rate recovery, but not blood pressure recovery, predicted mortality in atherosclerotic patients 6 years later (Ellis et al., 2004). Importantly, most of these studies corrected for reactivity during the stress task, and for biobehavioral variables such as gender, age, smoking, body mass index, parental history of hypertension and disease severity. On the other hand, only one study (Borghi et al., 1986) used a psychological stressor, while the others used physical stressors, such as a bicycle ergometer, or did not differentiate between the two kinds of stress (e.g. Treiber et al., 2001). Summarizing, evidence for a crucial assumption of the prolonged activation model is still limited. Importantly, prolonged activation values in real life however, and due to a purely psychological stressor (preferably during sleep), have not yet been linked to later development of disease.

CONCLUSION

Prolonged physiological activation is an essential element in a theory of the effects of psychological stress on somatic disease. After having been neglected for nearly half a century, several major stress theories have now incorporated prolonged activation. Nevertheless, an important element seems to be lacking in prolonged activation theory. This element is the cognitive nature of the psychological mediator between stressors or stress-factors and prolonged activation. We argued that stressors or their perception do not automatically lead to prolonged activation. The cognitive representation of stressors needs to be activated in order to extend their physiological concomitants. We call this mediating process perseverative cognition, and it is manifested in phenomena such as worry and rumination, or anticipatory stress. We summarized evidence suggesting that these phenomena are indeed

associated with physiological activation, including cardiovascular, endocrinological and immunological parameters. This evidence is still far from sufficient, due to the many methodological insufficiencies in the studies involved. Nevertheless, it shows that perseverative cognition may be a likely candidate for the mediator of the effects of stress on somatic disease. Therefore, theoretical models of stress and disease should not only account for prolonged activation, but also for its production by cognitive perseverative processes.

We also argued there is a dearth of evidence supporting the role of prolonged activation. Some studies demonstrate prolonged activity related to stressors and emotional episodes. These studies were not primary focussed on the issues above, and therefore lacked methodologies that were adequate for their investigation. Even more important, one crucial assumption underlying prolonged activation theories has received hardly any attention in research yet, and therefore is still largely unsupported. This assumption states that prolonged activation (anticipatory responses and slow recovery) from stress predicts pathogenic states and disease. Only a few studies showed this, but these were human laboratory studies, and nearly all of them pertained to physical stress. Thus, even this little evidence might not generalize to the real world, and not to psychological stress. On the other hand, several studies have demonstrated that need for recovery, which is seen as a subjective index of prolonged activation, mediates the effect of work stress on health complaints and sickness leave (Sluiter et al., 2003), and cardiovascular disease (Van Amelsvoort et al., 2003), effects that seemed reversible by extending rest periods (Schuring et al., 2004). Still, as yet no real life findings are reported showing that slow physiological recovery after psychological stress predicts somatic disease. Finding such evidence in epidemiological studies that preferably use real life psychological stressors would provide an important impetus for testing the prolonged activation theories discussed in this article (Selye, 1950; Linden et al., 1997; Brosschot and Thayer, 1998; McEwen, 1998; Sluiter et al., 2000; Ursin and Eriksen, 2004).

A final important issue about the nature of these processes pertains to sleep. Given the fact that sleep is perhaps the major restorative period in human life, it is at the same time a major 'opportunity' for prolonged activation. The studies mentioned above that show prolonged activation during sleep (e.g. Hall et al., 2004) make clear that at least part of perseverative cognition is not consciously carried out. It is likely that conscious perseveration is not a prerequisite for prolonged physiological activation. At present, little is known about the physiological effects of unconscious processing of distressing information, apart from some studies that show changes in cerebral activity, startle reflexes, skin conductance and the sexual system (Öhman and Mineka, 2001). Studies showing more substantial effects on parameters that are more relevant for somatic disease, such as endocrinological effects or cardiac effects are still rare (Ruiz-Padial et al., 2003). We believe that this is yet another important target for future studies. It is a challenge to show clinically relevant effects of a cognitive process that might be the mediator of prolonged stress responses during a crucial restorative phase: sleep.

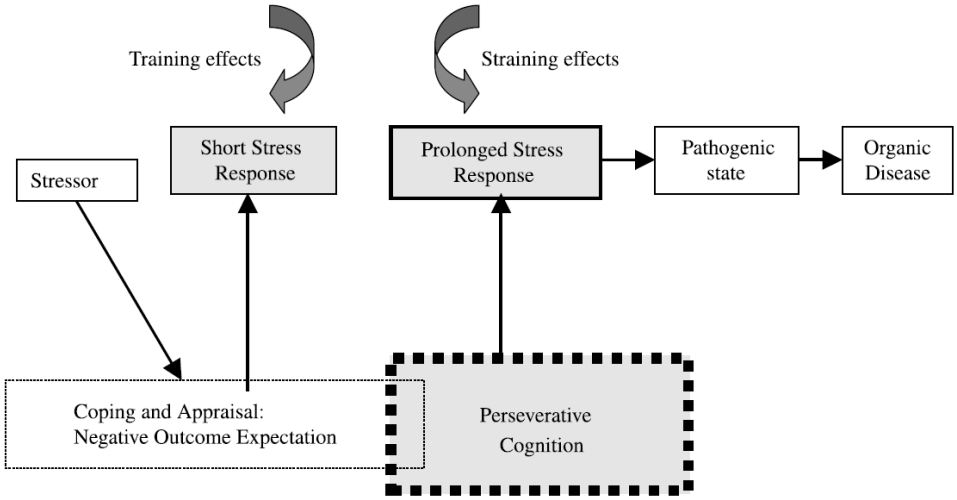

Figure 1: Model of prolonged stress-related activation, including perseverative cognition as a mediator between stress factors and prolonged stress responses.

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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.*

This chapter was published in *Pieper S, Brosschot JF, van der LR, Thayer JF. Cardiac effects of momentary assessed worry episodes and stressful events. Psychosom Med 2007;69(9):901-9.*

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 ($\chi2 = 16.74$, $df=5$, $p<.01$, 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 ($\chi2 = 1.60$, $df=3$, ns), so these parameters were excluded from the model. Generally, model 2 fitted well in comparison with the intercept-only model (model 1: $\chi2 = 47.27$, $df=4$, $p<.01$). 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 ($\chi2 = 2103.8$, $df=7$, $p<.001$). 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 ($\chi2 = 22.70$, $df=22$, 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 ($\chi 2$ = 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 ($\chi 2$ = 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 ($\chi 2$ = 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 ($\chi 2$ = 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 ($\chi 2$ = 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 ($\chi 2$ = 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

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

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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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).

Acknowledgements; The authors thank Dr. J. Berkhof for his autocorrelation macro and for his thorough support.

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

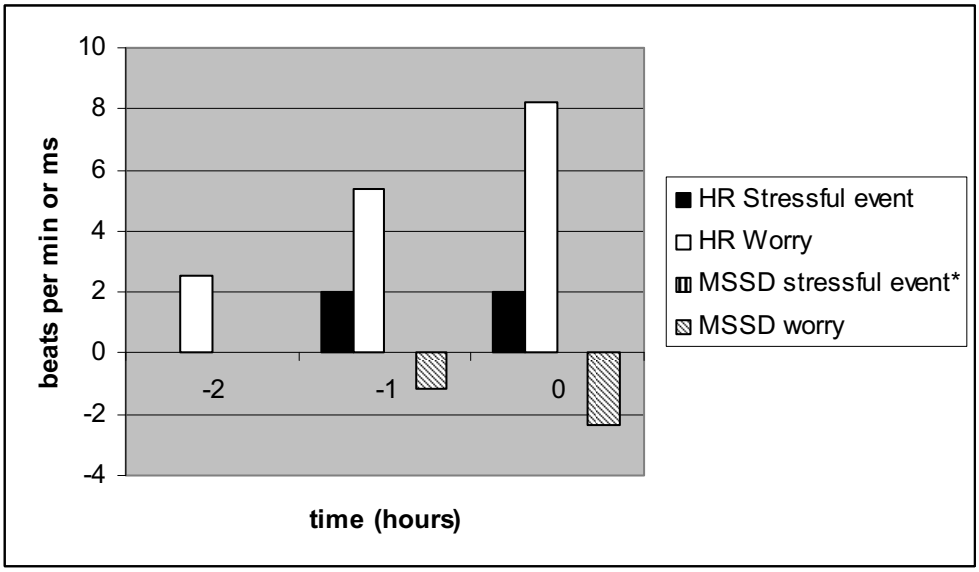
[a] BMI=Body Mass Index
[b] = previous 45 minutes
[c] 0 = non-work day; 1 = work-day
[d] 1 = morning; 2 = afternoon; 3 = evening

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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Chapter 6: *Daytime Stress, Worry and Negative Emotional Traits and Cardiac Activation during Sleep*

ABSTRACT

***Objective**: Prolonged stress-related activity during nocturnal sleep might be a decisive factor in explaining the link between stress and disease, specifically cardiovascular (CV) disease. In a previous study, frequency and duration of stressful events and worry were found to be associated with increased average levels of heart rate (HR) and decreased average levels of heart rate variability (HRV) during one day and the subsequent sleep period; worry duration mediated the effects of stressors. We attempted to replicate these findings using among others, a longer time period, a more precise operationalization of worry and several additional potential explanatory variables.*

***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 employed, 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**: We found associations between frequent daytime stressors and elevated waking and sleep HR, but none for HRV. The effects on HR disappeared when adjusting for biobehavioral factors. Yet, daytime and sleep HR were associated with trait worry and a more incomplete HR recovery to standard neutral laboratory tasks. 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.Other psychological traits and job stress did not predict HR or HRV levels.*

***Conclusions**: Although the previous findings were not replicated in this sample, an independent effect on waking and sleeping HR was found for trait worry. The non-replication is likely due to less stressors and worry periods in the current sample and by the more stringent measure of worry. Alternatively, the effects of stressors and worry are less robust than assumed. It would be worthwhile in future studies to focus on a population with higher stress levels and extend worry measurements with tests of 'just problem solving'.*

During the past decades, the reactivity hypothesis has dominated stress-disease research stating that frequent elevated physiological responses during stressors lead to changes in physiological balance, triggering several pathogenic pathways. Recently however, it has been suggested that CV elevations during stressful events are probably not sufficiently long-lasting to cause chronic pathogenic states (1-4). Prolonged CV activity in absence of a stressor is proposed to be responsible for pathogenic states that can lead to cardiovascular disease. Accordingly, the level of CV activation in real 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. Increased CV activation may be caused by slow recovery from preceding stressors or anticipatory responses to expected stressors. Indeed, several recent studies have shown that delayed cardiac recovery from cognitive (5-9) and physical (10-19) stressors is predictive of 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 (20)). For practical reasons, laboratory stress studies have only tested restricted recovery periods, thereby limiting their ecological validity. Ambulatory studies (20) in natural environments have measured longer time periods. These types of studies have suggested that CV stress effects may last any period between 5 minutes and the rest of the day, including even the subsequent nocturnal sleep period (20). The present study tests whether frequency and duration of stressors and worry are associated not only with increased cardiac activity during the day but also whether they are related to prolonged activity during sleep at night. The possibility of deficient nocturnal recovery of physiological arousal due to a form of stress-related cognitive perseveration may be of potentially major significance for health. If stress-generated physiological arousal does not stop during sleep it leads to a situation not unlike being exposed to a virtually permanent stressor. Continuous physiological activation by stress without any natural restorative break might eventually cause serious health problems.

'Perseverative cognition' including phenomena such as worry or rumination, has been proposed as a mediator of prolonged effects of stress, by causing the continuation of stressful events in the form of cognitive representations of these events (4). These cognitive representations involve negative thoughts and action tendencies analogous to those elicited during an actual stressful event; they are shown to cause similar elevations in physiological arousal in several laboratory studies. Trait worry as well as real-life worry, experimental worry and rumination have been found to be associated with a range of physiological effects 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 (4)). Additionally, trait worry has been related to elevated risk of a second myocardial infarct (21). Moreover, worry and rumination are core elements of psychopathologies such as anxiety disorders and depression that are known to carry elevated CV disease risk (22, 23).

Recently, we have shown that cardiac effects of worry are not restricted to the laboratory but also occur in daily life. During worry episodes participants displayed increased HR and decreased HRV compared to neutral periods, and these effects were independent from those of stressors (24). We also showed (25) that stressors displayed prolonged effects up to one hour after their occurrence. Worry

showed a prolonged effect for up to two hours, which was independent of effects of stressors. All these effects were independent of those of biobehavioral factors. An earlier study by Brosschot, van Dijk and Thayer (26) showed that worry – especially worry duration - mediated the prolonged effects of stressors on daily as well as nocturnal HR and HRV. In addition, daily worry duration on itself had a substantial prolonged effect on nocturnal HR and HRV. It was suggested that sustained worry may 'leak' into nocturnal cognitive activity, which is accompanied by increased autonomic activity. Indeed, worrying has been observed to be most intense during the pre-sleep period; there is evidence for a peak in conscious worry in the first part of the night, just before sleep onset in healthy participants (27). Additionally, there is evidence that anticipatory worry before sleep onset can decrease HRV and REM sleep (28) and that stress and/or worries before sleep can negatively effect slow wave sleep (29, 30). These stressors or worries are perhaps continued on a less conscious level during subsequent sleep. However, this peak was missed in that study, in which stressors and worry episodes occurring after 10PM were not measured (26). Still, stress and worry occurring closer to sleep onset may have much stronger nocturnal cardiac effects, and may mediate the effects of earlier worry during the day and evening. The latter study (26) was limited in several other respects too. Firstly, stressor duration was not measured. Also, the study was confined to only one day and night per subject, while multiple days and nights might yield more reliable results. Furthermore, no distinction was made between work days and leisure days, and potential confounders such as physical activity were not measured. Finally, paper & pencil diaries were used, which carry the risk of filling in questions at a later time when retrospection leads to poorly reported variables (31). Therefore, we designed the present study to replicate the results of the above study (26) accounting for its limitations. The present study measured the frequency of stressors and worry episodes during two working days and two leisure days, including the period after 10PM and during the sleep period. It also measured the duration of stressors and worry episodes, as well as physical activity. Participants used a handheld computer which made it possible to exactly determine if and when they would fill out the questions. In addition, 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 participants' 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).

We tested four hypotheses. *Firstly*, frequency and duration of worry and stressors during daytime and after 10PM are hypothesized to be associated with high HR and low HRV during both waking and subsequent nocturnal sleep. *Secondly*, it was hypothesized that at least part of the increased waking and sleeping cardiac levels of daily stress is mediated by worry during waking time and by late night worry (i.e. after 10PM). HR and HRV were measured because both chronic high HR and low HRV are risk factors for CVD as well as other organic diseases and overall mortality (32), and because they are easy to measure in daily life as well as during sleep without interfering with natural behavior.

Several negative emotional traits (depression, anxiety, worry, questionnaire-derived as well as interview-derived hostility (33-37)), and beliefs concerning work stress (i.e. job strain (38)) have been documented as CVD risk factors. The *third* hypothesis tested is that enhanced CVD risk of several negative traits or job strain (high demand/low control) is due to higher HR or lower HRV especially during sleep. There is some evidence that hostility is associated with enhanced systolic blood pressure during sleep, but no study has measured nocturnal HRV yet. Studies have been either scarce or inconsistent for the other traits and job strain (20). Only one study showed that job strain was related to lower nocturnal HRV (39). The present study also tested a *fourth* hypothesis which holds that these effects of traits are mediated by number and duration of stressors and worry episodes during the day, or by a more pronounced cardiac activity during these stressors or worry episodes. Age, gender, body mass index (BMI), bodily motion, time of day and the consumption of coffee and alcohol and smoking are known to effect HR and/or HVR (40-46); therefore, all analyses were corrected for effects of these biobehavioral factors. Since we measured participants repeatedly during four days and nights, measurements are more alike within participants than between participants. Due to the resulting hierarchical structure of the data we used multilevel regression models for the analyses. Because part of the data (HR and MSSD during waking hours) was used previously (24, 25) to analyze momentary daytime effects of worry and stress only, there is no overlap between the results of the current study and those of earlier ones.

Method

Participants

Subjects in this study were 55 teachers at 17 secondary schools in the Netherlands. The sample consisted of 39 men and 16 women aged 26 to 60 (mean=46.1; sd=8.5). Initially, 102 teachers were willing to participate; 29 dropped out before starting the experiment for various reasons (pregnancy, sick leave, allergy for electrodes not known before starting the experiment, antidepressant or hypertension medication) or were left out due to insufficient diary recordings. 18 Participants provided only valid daytime data and less than 3 hours of data during the night, and were therefore excluded for the analyses. 11 Participants were included in the analyses, although due to several reasons they produced valid data for only 48 of the 96 hours (six subjects withdrew from the project; one subject displayed an allergic reaction to the electrodes after 48 hours of measurements; one left for sudden sick leave; device malfunctioning caused drop-out of three participants). However, since they had more then three diary entries per day (the minimum required by us) they were included in the analyses. Eventually 55 participants were included in the study. All 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 consent of the management of the schools, teachers were recruited via 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 recovery after neutral stress (see below). Within two weeks afterwards, an experimenter fitted the ambulatory ECG device (47) 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. Additionally, they were instructed to fill out a set of questions after waking up in the morning; these included questions about sleep quality and about worry episodes and stressful events after 10PM and during the sleep period.

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 both the hourly diary and the morning diary. We used customized software (Pendragon Forms, version 3.1.; Pendragon Software Corporation, Libertyville, Illinois) to implement questions and to transfer responses from the handheld to MS-Access data format. For the hourly diary, 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. Additionally, subjects were instructed to fill in the questions of the nocturnal diary upon waking up in the morning. Thus, the measurements of stressors and worry covered the whole diurnal period.

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 seldomly used Dutch word. A "rumineer" episode or worry episode was defined 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 apart from 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".

Since stressors and worry episodes occurring during the night take place closer to sleep and their nocturnal cardiac effects may be stronger than those occurring during the day, we distinguished between stressors and worry episodes occurring before 10PM and those occurring after 10PM and during the sleep period. To capture stressors and worry episodes occurring during daytime, the participants reported hourly on the handheld computer 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 duration of the worry episode or the event (<5min, 5-15 min, 15-30 min, 30-45 min, 45-60 min, >60 min). Additionally, they retrospectively filled in the nocturnal diary upon waking up in the morning and reported whether a worry episode and/or a stressful event had occurred after 10PM the preceding night (yes, no) and if so, reported on the duration of that episode or event (<5min, 5-15 min, 15-30 min, 30-45 min, 45-60 min, >60 min).

Mood, activity, and other (bio)behavioral variables

During the last 15 minutes of each hourly measurement period and until 10PM, the subjects reported on the handheld computer to what extent they had felt the following four moods: being angry or irritated, sad or gloomy, tense or restless, and happy or cheerful (not at all, some, a bit, much, very much). Although these emotional states were not continuously measured we assumed that the aggregated 15 minutes samples yielded a valid representation of the occurrence of each of the emotional states during the day. The participants also reported on consumed units of tobacco, coffee and alcohol (0, 1-2, 2-4, more than 4) in the preceding hour, on having performed relatively strenuous activities in the preceding hour (not at all, some, a bit, much, very much) and on having slept or rested during the preceding hour (not at all, some, a bit, much, very much).

A more objective estimate of high activity was obtained with the ambulatory device, 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 standard deviation (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 daytime (for each day separately), is used as a covariate to control for cardiac differences due to intense movement. Note that for a previous report (24) (but not for (25)) we analyzed only periods in which participants displayed low activity.

Additionally, each morning upon waking up the subjects reported on how they evaluated their sleep quality in comparison to a normal night (much worse than normal, worse than normal, similar to normal, better than normal, much better than normal).

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 elsewhere (48). 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 (49), and is one of the time domain indices recommended by a task force report on HRV measurement (50). Additionally, the device 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 at daytime and to detect periods of high activity during the sleeping period, which might reflect waking up.

Individual recovery slopes to standard neutral stressors
To assess their 'natural' recovery in reaction to standardized non-stressful tasks participants performed a cognitive task and a physical task during a laboratory session. The cognitive task was a standardized Stroop task (51, 52) which was performed on a computer and consisted of four parts: firstly, participants had to read out loud and as quickly as possible the names of four colours printed in black. In the second part, they had to name as quickly as possible the colours of blocks that were printed in four different colours. Thirdly, subjects had to name as quickly as possible the four colours in which the words were printed while trying to ignore reading the words (of the same four colours). In part one to three, 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. Finally, 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 exercising on a bicycle ergometer at the resistance of 40 watt (which is about 80 pedal steps per minute) for 5 minutes after which participants had to sit quietly for 5 minutes (recovery) reading magazines. Both the cognitive and physical task 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) (53). Nonverbal hostility was measured by the Interpersonal Hostility Assessment Technique (IHAT) (54), 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 had been trained by the developers of the test (54), 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) (55). Trait anxiety was assessed by the trait scale of the Spielberger State-Trait Anxiety Inventory (STAI) (56). Trait worry was measured by the Penn State Worry Questionnaire (PSWQ) (57) and the Worry Domain Questionnaire (WDQ) (58). 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 (59). All these scales are widely used, reliable and valid.

Data processing

Firstly, we eliminated all parts of cardiac data with outliers in standard deviation, mean, minimum and maximum values of HR, MSSD, IBI and motility. Secondly, we divided the cardiac data in waking period and sleeping period. Waking time was determined as the period between connecting the equipment (or elevating HR in combination with a visible increase of the AMS motility signal in the morning) until the last hourly entry of the day (around 10PM). The sleeping period was the period between 1 hour after going to bed (which was further validated by a visible decrease of the AMS motility signal which is continued during the rest of the night) to one hour before waking up (again validated by visible change to higher activity in the morning) and was confirmed with the subject's reports on sleep duration.

Next, cardiac data were divided into individual periods, by providing labels using the AMS graphical program (23). Cardiac data during waking time were labelled as neutral, worrying and/or stressful, based on the hourly diary data (see also (24, 25)). Additionally, in the resulting periods high activity or low activity periods were labelled. High physical activities were identified as motility higher than the 48-hour average plus one standard deviation (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 is used as a covariate to control for cardiac differences due to intense movement. Additionally, periods of high activity during the sleeping period, which could reflect waking up and moving, were labelled and subsequently removed from the analyses. The AMS graphical program calculated mean HR and MSSD over the resulting labelled periods and these values were aggregated over the waking period and the sleeping period for the four 24-hour periods separately and were used as the dependent variables in the analyses.

Stressor and worry frequency during waking were measured by the number of times the presence of a stressor or worry was reported until 10PM. Stressor and worry duration were estimated for each worry episode by the subjects aided by a set of six time categories (<5min, 5-15 min, 15-30 min, 30-45 min, 45-60 min, >60 min). To facilitate analysis the begin point of these categories was used: 1 min, 5 min, 15 min, 30 min, 45 min, 60 min. The values were counted across entries. Subjects differed with respect to the number of entries that were actually completed (mean=11.25; standard deviation=2.99). Thus, the absolute values were not comparable between the subjects, which was why these variables were divided by the number of completed entries. A similar procedure was performed for reported units of tobacco, coffee and alcohol, as well as emotional states, and reports on

having performed relatively strenuous activities and the percentage of 30-sec periods spent in high activity.

Additionally, the subjects retrospectively filled in the nocturnal diary upon waking up in the morning and reported whether a worry episode and/or a stressful event had occurred after 10PM the preceding night (yes, no) and if so, reported on the duration of the worry episode or the stressful event (<5min, 5-15 min, 15-30 min, 30-45 min, 45-60 min, >60 min). Again, to facilitate analysis the begin point of these categories was used: 1 min, 5 min, 15 min, 30 min, 45 min, 60 min.

Cardiac recovery after neutral laboratory stressors was 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 4th rest minute after the IHAT interview was taken, because due to circumstances for none of the participants the beginning and the end of this period were completely restful. Thereafter the area under the curve (AUC) minus the baseline was computed for each participant, for the cognitive and physical task and for HR and MSSD. The following equation was used derived from the trapezoidal rule (60): 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 seconds, until the end of the 5-min recovery period. A lower value indicates more complete recovery. 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.

Statistical analysis

Multilevel regression models were applied to estimate the effects of frequency and duration of worry and stressors on HR and MSSD during waking and sleep. The choice of multilevel analysis arises from the hierarchical structure of the data: the waking and sleeping averages of HR and MSSD during maximally four 24-hour cycles are nested within subjects. We refer to these two levels as *day level* and *person level*, respectively. Predictor variables measured at these levels were entered into the model. Day level predictor variables used for analysis included stressor and worry frequency and duration during waking and sleeping, type of day (work vs. leisure), percentage high activity, reported level of activity, reported resting during awake period, sleep quality, emotional states and biobehavioral variables, including smoking and consumption of alcohol and coffee. 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 recovery after neutral laboratory stressors for HR and MSSD.

For all variables descriptive statistics were computed. The distribution for MSSD during waking and sleeping was non-normal, as well as frequency and duration of stressors and worry episodes during waking and sleeping, mean coffee intake and smoking, reported level of activity and sleep or rest during waking and mean angry or sad emotional states. Therefore, these variables were log transformed. All independent variables were centered around their grand mean.

A sequence of 4 models was tested separately for HR during waking, HR during sleep, MSSD during waking and MSSD during sleep. Additionally, to prevent errors due to collinearity we tested separate models for frequency and duration (of worry and stressors). Firstly, an intercept-only model was fit containing no predictor variables. This model decomposes the variance of the dependent variable into two independent components, pertaining to the day level and the person level, and was used as a baseline model. In the next model, we examined the effects of stressor and worry frequency (or duration) during waking (or during waking and during sleep). Next, the day variables (type of day, percentage high activity, reported level of activity, reported resting during awake period, sleep quality), biobehavioral variables (including smoking and consumption of alcohol and coffee) and the subject variables (age, gender, BMI and cardiac recovery after neutral laboratory stressors) were entered into the previous model to assess whether the effects of worry and stressors found in that model would still be present, and are thus not mediated by any of these latter variables (61). Next, we added the person level variables (trait worry, depression, hostility and anxiety and job strain) to test their main effects on waking and sleeping cardiac activity and if and to what extent the stressor and worry effects are due to these factors. In the final model, we added mean emotional states during waking, (i.e. being angry, sad, tense, and happy) to analyze whether the effects are mediated by mood.

To test the hypothesis that the prolonged effects of stressors – if any - were mediated by worrying, we additionally tested models without worry, and compared them with the models above including worry. Stronger prolonged effects of stressors that are also more significant without entering worry frequency or duration coulde indicate that worry mediates at least partly the effects of these variables (61). 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 different levels). Multilevel regression models were fit using the program MLwiN, version 2.02 (62). The maximum likelihood method was used for model estimation. Significance of fixed effects of predictor variables was tested by dividing the estimated effect by its standard error. These effects were tested using one-tailed t-tests, since the hypotheses were explicitly directional. 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 and day 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 (53, 55, 56, 59, 63-66).

During waking time, subjects reported a mean of .11 (sd=.13) stressful events per entry, which translates to a total of 1.5 per day if 14 entries (the maximum per day) are completed. These stressful events had a mean duration of 6.86 (sd=9.14) minutes. This duration is calculated only over entries in which stressful events were reported. On the contrary, for the calculation of the values reported in Table 1 entries in which stressful events were not reported, thus with a duration of 0 minutes were also taken into account. The subjects reported a mean of

.08 (sd=.12) worry episodes per entry, which translates to a total of 1.12 per day. The mean duration is 15.63 (sd=18.03) minutes. This duration is calculated only over entries in which worry episodes were reported. On the contrary, for the calculation of the values reported in Table 1 entries in which worry episodes were not reported, thus with a duration of 0 minutes were also taken into account. These frequencies are roughly comparable with findings from other studies, (e.g. 1.38 and 1.65 per day for stressful events (67, 68) and .96 per day for worry episodes (69)) but are lower than those reported in Brosschot et al (26) (stressor: .28 times per hourly entry; worry: .22 times per hourly entry). Additionally, after 10PM they reported a stressful event in 13.3% of the nights, with a mean duration of 6.86 (sd=9.14) minutes and worrying in 21.7% of the nights, with a mean duration of 15.63 (sd=18.03) minutes. As expected HR was higher during waking than during sleep (79.80 vs. 61.79, $t(149)=31.08$, $p<.001$) and MSSD showed the opposite effect (28.33 vs. 36.11, $t(149)=-6.98$, $p<.001$).

Table 2 shows the effects of biobehavioral variables and activity variables on HR and MSSD during waking and sleep. Women had higher sleep HR (64.32 vs. 60.95, $F(1,149)=5.87$, $p=.02$) than men. Older participants (>47.1 years) displayed lower MSSD during waking (25.45 vs. 31.41, $F(1,149)=10.07$, $p=.002$) and during sleep ($F(1,149)=14.92$, $p<.001$) than younger participants. Subjects with lower BMI (<24.3) displayed higher MSSD during waking (31.19 vs. 25.14, $F(1,144)=9.85$, $p=.002$) and during sleep (31.84 vs. 13.72, $F(1,144)=6.31$, $p=.01$) than subjects with a higher BMI. Participants who did not consume coffee during the day had lower waking HR (76.19 vs. 80.49, $F(1,146)=4.81$, $p=.03$) and sleep HR (58.39 vs. 62.44, $F(1,146)=6.20$, $p=.01$) than participants who consumed coffee. Subjects who reported smoking displayed higher daytime HR (84.19 vs. 79.01, $F(1.147)=6.36$, $p=.01$), lower daytime MSSD (21.60 vs. 29.55, $F(1,147)=8.63$, $p=.004$) and higher sleep HR (69.06 vs. 60.55, $F(1,147)=27.60$, $p<.000$). During work days, participants showed higher daytime HR than during leisure days (81.50 vs. 78.54, $F(1,142)=4.12$, $p=.04$).

Table 3 shows the correlations between worry and stressor frequency and duration, negative emotional dispositions, job strain and cardiac recovery after neutral laboratory stressors on the one hand and HR and MSSD during waking and sleep on the other hand. For these correlations (all two-tailed Pearson correlations) the data were aggregated on subject level. Correlations were significant only for the duration of stressful events, trait worry (PSWQ) scores, verbal hostility (IHAT) and cardiac recovery after neutral laboratory stressors. Increased duration of stressful events during the day was positively correlated to increased daytime HR ($r=32$, $p=.02$) and increased nocturnal HR ($r=.30$, $p=.03$). Higher trait worry scores (PSWQ) were related to elevated nocturnal HR ($r=.30$, $p=.02$). Increased verbal hostility (IHAT) scores were related to lower nocturnal MSSD ($r=-.30$, $p=.03$). Finally, a less complete HR recovery was related to both increased daytime ($r=.56$, $p=.00$) and nocturnal HR ($r=.36$, $p=.02$).

Effects on waking cardiac activity

Waking HR

Results of the intercept-only model (deviance 1006.43) for waking HR showed that the estimated value of the intraclass correlation for waking HR at person and at day

level was .66 and .34 respectively, which supports the use of a 2-level hierarchical data structure.

Stressor and worry frequency were added as predictors to the intercept-only model. There were no significant effects of stress and worry, except for a marginal trend of stressor frequency on HR (z=1.51, p=.07). The occurrence of more stressors tended to be associated with an elevated daytime HR of 8.50 (CI 2.85-14.15) beats/min.

However, when including the day variables (type of day, percentage high activity, reported level of activity, reported resting during awake period) cardiac recovery after neutral laboratory stressors and biobehavioral variables (age, gender, BMI, smoking and consumption of alcohol and coffee) in the next model the marginal trend of stressor frequency became non-significant. On closer inspection, we found this stressor effect to be due to the effects of type of day; work days were related to an increase of 4.17 bpm compared to leisure days (CI 3.15-5.18; z=4.10, p<.001). Apart from this, the following variables led to higher HR: more incomplete recovery after neutral stress in the laboratory (.09 bpm per incompletely recovered beat of HR and to a maximum increase of 12.86 bpm for the most incomplete recovery measured; CI .07-.12; z=3.68, p<.001), being female (4.48 bpm increase; CI 2.64-6.32; z=2.44, p=.007) and an increased activity level (18.52 bpm increase; CI 13.96-23.08; z=4.06, p<.001).

Including person level variables trait worry, depression, hostility, anxiety and job strain (Table 4, first column) showed that higher trait worry scores (PSWQ) were related to an increased daytime HR of between .26 bpm for the minimal PSWQ score and 13.26 bpm for the maximal PSWQ score (CI .14-.39; z=2.07, p=.02). No mediation test (hypothesis 4; see Introduction) was performed because there were no effects of worry and the marginal effects of stressors disappeared after adding type of day as reported above.

The same procedure, but now with stressor and worry duration as predictors resulted in largely similar findings as for frequency. When stressor and worry durations were added to the intercept-only model, only stressor duration was significantly associated with an increased daytime HR of 1.99 bpm (which corresponds to a maximal increase of 4.32 bpm, CI .92-3.07; z=1.86, p=.03). Again this effect disappeared when adding the variables mentioned above (Table 4, second column), and closer inspection showed again that this was due to the inclusion of type of day.

Waking MSSD

Similar procedures were followed for lnMSSD (Table 4, third column). Results of the intercept-only model (deviance 35.15) for waking MSSD showed that the estimated value of the intraclass correlation at person and at day level was .81 and .19 respectively, which supports the use of a 2-level hierarchical data structure. Adding stressor and worry frequency as predictors to the intercept-only model did not lead to significant results.

Table 4 (third column) shows the model including day variables (type of day, percentage high activity, reported level of activity, reported resting during awake period) cardiac recovery after neutral laboratory stressors and biobehavioral variables (age, gender, BMI, smoking and consumption of alcohol and coffee) as well as person level variables (trait worry, depression, hostility, anxiety and job

strain). Increasing age (z=2.00, p=.02) and reporting of more anxious symptoms (STAI; z=2.00, p=.02) were associated with decreases in daytime MSSD of -1.01 (antilog value; per year; implying a maximal decrease of 33.33 ms for 60 years old; CI. -2.02 to -.01) and -1.02 (antilog value; per STAI score; implying a maximal decrease of 34.68 ms for the maximal STAI score; CI. -2.03 to -.01) respectively. Addition of emotional states during the day revealed that anger showed a marginal trend (not in Table 4); participants who reported being angry or irritated more frequently, displayed marginally decreased daytime MSSD of –.50 ms (antilog value = 1.66; which corresponds to a maximal decrease in MSSD of -2.10 ms, CI -3.06 to -.26; z=1.49, p=.07**).**

The same procedure but now with stressor and worry duration (Table 4, fourth column) as predictors resulted largely in similar findings as for frequency. Effects of stressor and worry durations did not reach significance. Addition of the biobehavioral variables and trait values mentioned above led to similar results. However, this time one of the effects of angry emotional states was significant (not in Table 4). Participants who reported being angry or irritated more frequently, displayed decreased daytime MSSD of –1.84 (antilog value; which corresponds to a maximal decrease in MSSD of -2.33 ms, CI -3.25 to -.43; z=1.78, p=.04).

Effects on cardiac activity during sleep

Sleep HR

Results of the intercept-only model (deviance 928.35) for HR during sleep showed that the estimated value of the intraclass correlation for sleep HR at person and at day level was .76 and .24 respectively, supporting a 2-level approach. Adding stressor and worry frequency during the day, as well as after 10PM, did not lead to significant effects.

Adding the day variables (type of day, percentage high activity, reported level of activity, reported resting during awake period), cardiac recovery after neutral laboratory stressors and biobehavioral variables (age, gender, BMI, smoking and consumption of alcohol and coffee, as well as sleep quality) lead to the following effects: being female (increase of 5.14 bpm; CI 3.57-6.71; z=3.27, p<.001), increased alcohol intake during daytime (increase of 8.30 bpm; CI 4.72-11.87; z=2.32, p=.01), and slower laboratory recovery (increase from .06 bpm to a maximum increase of 8.52 bpm for the most incomplete recovery; CI .04-.08; z=2.95, p=.002) were related to increases in sleep HR. Adding person level variables trait worry, depression, hostility, anxiety and job strain to the previous model, only led to a significant effect of tendency to worry (PSWQ); increased tendency to worry was associated with increases in sleep HR of .18 bpm (per PSWQ score; implying a maximal decrease of 8.98 bpm for the maximal PSWQ score; CI. .08 to .28).

Finally, the addition of mean emotional states only displayed a significant effect for happy emotions during the day. Participants who reported being happy or cheerful more frequently during daytime displayed a lower sleep HR of 2.46 (which corresponds to a maximal decrease in HR of 6.94 bpm, CI 3.46-1.45; z=2.45, p=.007).

The same procedure but now with stressor and worry *duration* (during daytime and after 10PM) as predictors was performed. When stressor and worry durations were added to the intercept-only model, only stressor duration during

daytime was significantly associated with an increased sleep HR of 2.44 bpm (which corresponds to a maximal increase of 5.28 bpm, CI 1.59-3.28; z=2.88, p=.002). However, this effect disappeared when adding the day variables type of day, percentage high activity, reported level of activity, reported resting during awake period, cardiac recovery after neutral laboratory stressors and biobehavioral variables, including age, gender, BMI, smoking and consumption of alcohol and coffee, as well as sleep quality. On closer inspection, the disappearance of the effect was due to the inclusion of attenuated laboratory recovery (related to increase in HR after 10PM of .06 bpm; to a maximum increase of 8.52 bpm for the most incomplete recovery; CI .04-.08; z=2.73, p=.003). Similar to the findings for frequency (above) being female and increasing alcohol intake during daytime were related to increases in sleep HR of 4.83 (CI 3.21-6.45; z=2.98, p=.001) and 8.81 (CI 5.24-12.37; z=2.47, p=.007) bpm respectively. The inclusion of person level variables (trait worry, depression, hostility, anxiety and job strain) lead to non-significant effects (Table 5, second column).

Finally, the addition of mean emotional states displayed a significant effect for happy emotions only during the day. Participants who reported being happy or cheerful more frequently during daytime, displayed decreased sleep HR of 2.40 (which corresponds to a maximal decrease in HR of 6.81 bpm, CI 3.45-1.35; z=2.29, p=.01).

Sleep MSSD

Similar procedures were followed for lnMSSD. Results of the intercept-only model (deviance 83.12) for waking MSSD showed that the estimated value of the intraclass correlation at person and at day level was .81 and .19 respectively), indicating that the use of a 2-level hierarchical data structure is plausible. Adding stressor and worry frequency as predictors to the intercept-only model did not lead to significant results.

Next, the day variables type of day (percentage high activity, reported level of activity, reported resting during awake period, sleep quality) and biobehavioral variables (age, gender, BMI, smoking and consumption of alcohol and coffee) and cardiac recovery after neutral laboratory stressors were added to the model. Higher age (decrease of -1.02; antilog value, corresponding to a maximal decrease of 34.68 ms; CI -2.03 to -.01; z=2.43, p=.01), increased alcohol intake (decrease of -1.59; antilog value, corresponding to a maximal decrease of 1.06 ms; CI -2.91 to -.27; z=2.14, p=.02) and more reports of a worse quality of sleep (decrease of -1.08; antilog value, corresponding to a maximal decrease of 3.24 ms; CI 2.21 to .04; z=1.85, p=.03) ms respectively.

Next, person level variables (trait worry, depression, hostility, anxiety and job strain) were added to the previous model, but all lead to non-significant effects (Table 5, third column). Similarly, addition of mean emotional states lead to non-significant effects.

The procedure was repeated but now with stressor and worry *duration* (during daytime and after 10PM) as predictors and resulted in similar results. Effects of stressor and worry duration did not lead to significant results. Addition of the biobehavioral variables and trait values mentioned above lead to similar results: higher age (decrease of -1.02 ms, antilog value, corresponding to a maximal decrease of 34.68 ms; CI -2.03 to -.01; z=2.43, p=.01), increased alcohol intake

(decrease of -1.59 ms, antilog value, corresponding to a maximal decrease of 1.06 ms; CI -2.88 to -.04; z=2.30, p=.01) and more reports of a worse quality of sleep (decrease of -1.07 ms, antilog value, corresponding to a maximal decrease of 3.21 ms; CI -2.11 to -.03; z=1.70, p=.04) were related to decreases in MSSD. Additionally, more reports of sleeping or resting during daytime were related to decreases in MSSD of 1.58 (antilog value, corresponding to a maximal decrease of 2.37 ms; CI -2.88 to -.28; z=1.73, p=.04) ms.

Similar to the findings for frequency (see above) the addition of person level variables (trait worry, depression, hostility, anxiety and job strain) as well as the addition of mean emotional states lead to non-significant effects.

Psychological traits

Psychological traits, such as depression and hostility, are important CV disease predictors. The subject-level correlations reported in Table 3 between emotional dispositions and job strain on the one hand and HR and MSSD during waking and sleep on the other hand, indicate that nonverbal hostility (IHAT) is related with daytime MSSD and that tendency to worry (PSWQ) is related to HR after 10PM. However, these relations were not clearly found in the multilevel analyses reported above. It is possible that psychological traits effect HR or MSSD via the effects of biobehavioral variables; however, in the analyses above biobehavioral variables were entered in the model first and may have caused effects of psychological traits to become non-significant. Another reason might be that the above models contain many variables that lower degrees of freedom such that effects of psychological variables become non-significant. For these reasons and in light of the predictive power of these traits in the literature, we tested their effects on daytime CV activity and CV activity during sleep, by adding the predictors (trait worry, depression, hostility, anxiety and job strain) to the null-model. Elevated trait worry (PSWQ) predicted elevated daytime HR of .31 bpm (corresponding to a maximal increase of 15.56 bpm; CI .16 to .45; z=2.12, p=.02) and elevated HR during sleep of .30 bpm (corresponding to a maximal increase of 15.10 bpm; CI .18 to .42; z=2.45, p=.01); these results correspond to the effects found in the analyses above. Additionally, elevated nonverbal hostility (IHAT) was associated with decreased daytime MSSD of 1.78 ms (antilog value; corresponding to a maximal increase of 1.17 bpm; CI -3.17 to -.39; z=1.85, p=.03) and was marginally associated with decreased MSSD during sleep of 1.88 ms (antilog value; corresponding to a maximal increase of 1.24 ms,; CI -3.36 to .40; z=1.61, p=.05). On closer inspection, we found that the effects of nonverbal hostility diminished after adding (increasing) age (related to an increase of 1.02 ms antilog value, CI -2.02 to -.01; z=2.67, p=.004 for daytime MSSD and related to an increase of 1.02 ms antilog value, CI -2.03 to -.01; z=3.43, p=.0003 for MSSD after 10PM).

Unilevel exploratory analyses

In an earlier study we found that stressors and worry during daytime were related to higher HR and lower HRV during daytime and sleep (26). These associations were not replicated in the multilevel analyses above. Since effects of type of day were significant in the multilevel models predicting waking HR (Table 2, column 1 and 2), we expected that subjects reported stressful events and worry at a different frequency during work days and leisure days. Indeed, subjects reported more

stressful events (but not worries) during work days (mean 2.02, sd. 2.03 on work days vs. mean .92, sd. 1.34 on leisure days; $F(1,148)=14.92$, $p=.00$). We explored the possibility that effects of stressful events and worry were significant only on work days, but not leisure days. For this purpose, we added several variables including the interactions between stressful events or worry (during daytime or sleep) and type of day to the related models above including only stressor and worry (frequency or duration). None of these interaction terms reached significance in either of these models. To explore the possibility that effects of stressful events and worry were significant on only one of these days, we looked at bivariate correlations between stressful events, worry (frequency and duration, as well as during daytime and sleep separately) on the one hand and HR and HRV during daytime and sleep on the other hand but now separately for each day. Of all these (total=96) correlations, 9 reached significance, of which only 3 were as expected. Thus these results could be safely attributed to chance alone.

Discussion

This study was designed to examine the effects of worry and stressors on HR and HRV during daytime and the subsequent nocturnal sleep period in order to replicate findings of a previous study (26), in which stressors and worry were related to daily and nocturnal HR and HRV. Contrary to our expectations, we did not find stable associations between increased stressor and worry frequency or their respective durations on the one hand and increased HR or decreased HRV during daytime or sleep on the other hand. We found that stressor duration was related to increased daytime and sleep HR, and we also found a marginal association between stressor frequencies and elevated daytime HR. However, these associations disappeared when correcting for the effects of biobehavioral factors. More specifically, the effect of stressors on waking HR was associated with high HR related to a work day. The association between increased waking stress duration and sleep HR was related to a more incomplete recovery score from tasks in the laboratory.

Additionally, we found that a tendency to worry and nonverbal hostility were related to cardiac activity during daytime and nighttime. In a multilevel test of these associations only an association between trait worry and increased daytime and nighttime HR was yielded. The association between nonverbal hostility and HRV was related to the association between increased age and decreased HRV. Although expected, the association between trait worry and increased daytime and nighttime HR was not mediated by daily stress or worry. Additionally, reports of increased angry or irritated states were related to decreased waking MSSD, whereas reports of increased happy or cheerful states were related to decreased sleep HR. Finally, a more incomplete HR recovery to standard neutral laboratory tasks was associated with elevated HR during daytime and during sleep.

Our previous studies (24, 25), that were partially based on the same sample show that worry and stressors during daily life have simultaneous as well as prolonged (up to two hours) cardiac effects. The present study suggests that these effects do not necessarily generalize to mean cardiac levels during daytime or during sleep. The effects of increased stressor frequency and duration on daytime HR were associated with the effects of a work day on HR; these results are in accordance with our previous study (24), which found that stressful events related to work induced more HR elevations than stressful events related to other topics. In line with

the findings of this study, it is likely that a specific type of worry or stressor elicits prolonged cardiac effects that are pronounced enough to influence mean daytime or sleep levels. However, the infrequent reporting of stressful events did not allow enough cases for a thorough analysis of this hypothesis. It would be fruitful if future studies assessed the prolonged effects of specific stressors or worry episodes. Likely candidates would be worry about work or future issues and stressors related to work (24).

Yet, we were not able to replicate results of the previous study by our group (26), in which daily worry and stressors were found to be related to higher HR and lower HRV during waking and during sleep. Notably, not even late night or nocturnal worry episodes and stressors had significant cardiac effects on sleeping HR and HRV in the present study. We explored the possibility that separate days might display effects that fade away when examining four days together. However, unilevel explorations revealed no noteworthy results, meaning that there was no evidence for the possibility that effects were more pronounced during work days than during leisure days. These differences in findings were possibly due to the less frequent reports of stressful events and worry episodes in the current study. The frequencies and durations for stressful events (.11 events and .75 minutes per hourly entry) and worry episodes (.08 episodes and 1.13 minutes per hourly entry) that were reported in the present study were much lower than those reported in Brosschot et al (26) (stressor: .28 times and 1.20 minutes per hourly entry; worry: .22 times and 2.0 minutes per hourly entry). Possibly, the group of subjects in the present study did not report enough stressful events and worry episodes to influence mean cardiac levels. There are two possible factors that might explain this; the first one is related to the different samples measured and the second is related to a different definition of worry presented to the different subject samples.

Firstly, the study from Brosschot (26) differs from the present study with respect to the sample measured. Brosschot and colleagues measured individuals that were contacted through newspaper ads without obtaining any further individual or demographics data nor applying any exclusion criteria, which could have resulted in the recruitment of a more variable group. One advantage of a variable group is that there is more variance to account for possible effects than a more homogeneous group. The present study, recruited a uniform group of high school teachers, which is a highly educated subgroup with a medium social economic status (SES), and the results might not generalize to other groups with lower education and a different SES. Within this recruitment of teachers, it is possible that a selection bias influenced the results, for instance that mainly teachers responded who did not experience a lot of stress, or that those with the highest work load did not respond due to lack of time. It is also possible that due to their higher educational level their daytime worries were better processed and as a result led to less subconscious cognitive perseveration during sleep. Moreover, compared to the sample by Brosschot et al. (1) this group of teachers displayed a slightly lower trait anxiety (36.5 vs. 40.0 respectively) and trait worry (43.0 vs. 45.6 respectively) score. Considering the relation between these traits, state worry and stress, this might additionally explain why our sample reported stressors and worry less frequently.

Secondly, the definition of worry presented to the subjects in the previous ambulatory study (26) was slightly different from the one that was employed in the present study. Brosschot and colleagues used the Dutch word "piekeren", which has

an extra connotation of "thinking hard", while the present study focussed mainly on the meaning of worry as it is used in English, and thus more exclusively on the emotional negativity of the process. In order to do so, the present study not only used another definition but employed also a not well known Dutch synonym of the word worry, 'rumineren'. It is possible that this led the participants in the present study to only report those worries which go with clear negative emotions and thus overall reporting less 'worrisome' cognitive problem solving attempts, which on themselves might have had cardiac effects. Just "thinking hard" or cognitive problem solving may be an essential element of perseverative cognition (4). Worry has been defined as consisting of thwarted attempts to engage in mental problem solving (70), thus emphasizing the importance of the element of "thinking hard" or cognitive problem solving. Importantly, a recent laboratory study (71) performed by our group after the completion of the current study showed comparable HR and HRV effects during induced worry (about personal worry topics) and a neutral cognitive problem solving task (about self-irrelevant topics), and both were higher compared to a relaxation condition. Moreover, these effects were not explained by differences in negative mood. These results suggest that mere mental activity is responsible for a part of the physiological effects of worry, and not or not only the aspect of negative perseveration or emotionality per se. Therefore, it is possible that an important reason why the present study failed to replicate the findings of Brosschot et al. (1) is the current operationalization of worry. This may have caused a focus away from the element "thinking hard", which not only resulted in lower reporting of worry episodes but also in a lesser overall cardiac effect.

The present study shows that more frequent reports of angry or irritated states were associated with decreased daytime MSSD levels, while more frequent reports of happy or cheerful states were related to decreased HR levels during sleep. These relations were independent of effects of worry, stressful events, biobehavioral variables and trait scores. These results are in line with a finding by Steptoe and coworkers (73), who found that a more complete blood pressure recovery after laboratory mental stress tests was related to increased reports of positive affect during the day. This is also consistent with the results of Brosschot et al. (72), which indicate that negative emotions, but not positive emotions inflict prolonged activation 10 minutes later. Apparently, emotionality has effects independent of worry, that is, conscious perseverative cognition, with especially positive emotionality being beneficial for cardiac health.

It is noteworthy that several important psychological risk factors for CVD, namely hostility, depression, anxiety and job strain (33, 38, 73-77) were not associated with elevated cardiac levels during daytime or sleep. In contrast, the - far less often measured - tendency to worry (measured by the PSWQ) was associated with elevated daytime and sleep HR. The initially apparent effects of nonverbal hostility (IHAT) disappeared when statistically controlling for age, suggesting that elevated age may have been a confounding factor in earlier studies (40). In our recent review (25) we found nocturnal cardiac effects for these negative traits, but not consistently so, that is 2 out of 6 for hostility, 1 out of 3 for anxiety and 1 out of 2 for depression. To our knowledge, only one study has evaluated effects of worry on risk for CVD (34). Thus, our finding for trait worry suggests that prolonged cardiac activity during daytime and sleep mediates the prospective association with CVD as was found by Kubzansky et al. (34). These findings are relevant since

continuous physiological activation during sleep, which should be a natural restorative break, might eventually cause serious health problems. Regarding the limited studies on the CVD risk of worry, our findings stress the importance of including a measure of tendency to worry when studying risk for CVD. Since tendency to worry is a frequently observed aspect of anxiety and depression disorders, it is possible that measuring this factor might reveal an important part of the mechanisms behind the relation between these traits and CVD.

Since the associations between trait worry and elevated daytime and sleep HR are not mediated by states of worry or stress or biobehavioral variables, it remains unexplained which underlying psychological mechanism is responsible for the prolonged cardiac effects of worry. It is possible that a considerable part of the effect of trait worry is due to less conscious forms of perseverative cognition. At least three studies including our own suggest that a part of perseverative cognition may act in an unconscious fashion. Firstly, prolonged low HRV was found during sleep when anticipating a stressful oral speech that had to be performed after waking up (28). The second study showed prolonged cardiac effects during sleep following a day full of stress and worry (26). In the third study, worry showed prolonged cardiac effects up to 2 hours after the worry ended (24). Since in none of these cases conscious worry was possible (1,28) or reported (25), some other forms of perseverative cognition must have mediated these effects. The majority of cognitive processes operate without awareness, i.e. automatically (78, 79) and a considerable part of normal daily emotional processing - including PC - is likely to take place without us being aware (80). Hardly anything is known about the physiological effects of unconscious emotion, except for some brain and some skin conductance effects (81, 82), making this an important unexplored area of stress research.

The present study shows that incomplete recovery from neutral laboratory stressors is associated with elevated HR during daytime and sleep which is a most interesting finding. The literature shows that delayed cardiac recovery from cognitive (5-9) and physical (10-19) stressors is predictive of cardiac outcomes, such as hypertension, enhanced rest HR and blood pressure, abdominal adiposity, and even overall mortality ((5, 6, 8-11), reviewed in (20)). Our results suggest that a more incomplete recovery in the laboratory is associated with cardiac activity in daily life, more specifically elevated daytime and sleep HR. This is in line with results from Trivedi et al. (83) who found that blood pressure recovery in the laboratory predicted daytime and night-time ambulatory blood pressure levels after a work day. Moreover, Moseley and Linden (84) found that laboratory recovery even predicted ambulatory HR and blood pressure 3 years later. Apart from prospective disease risk and relations with physical factors, delayed cardiac recovery in the laboratory is found to relate to psychosocial factors as well. Delayed HR recovery after a treadmill test was observed in rehabilitated cardiac patients who reported an increased level of depressive symptoms (85). Additionally, there are some studies (86, 87) showing that low SES and delayed recovery are related. Others show evidence suggesting that high SES is a protective factor lowering the CVD risk that is induced by an incomplete recovery pattern after laboratory tasks (7, 88). Initially, cardiac recovery after neutral laboratory stressors was included in our analyses to account for individual basic recovery slopes, which are effected by physical characteristics of the individual including among others genetic makeup, fitness and BMI. However, the

effects of incomplete recovery in the laboratory on daytime and sleep HR were independent of age, gender, BMI and other biobehavioral factors measured on an hourly or subject level basis. Together with the findings in previous publications of a relation between delayed recovery and psychosocial factors (85, 86), this suggests that recovery from neutral laboratory stressors might reflect an autonomous factor, which is very likely to be low parasympathetic activity or low vagal tone (32, 89) activity. Rapid lowering of HR after exercise is thought to be accomplished by vagal reactivation after initial deactivation during exercise (90-93), which is why delayed cardiac recovery is seen as a marker for impaired autonomic nervous system functioning, more specifically impaired vagal tone. Apart from its physiological effects (94), vagal tone seems to be involved in the regulation of several psychological functions, such as anger control, attention, emotional regulation (95, 96). Additionally, findings from several studies seem to suggest that decreased depressive symptoms (85), higher SES (86) and improved physical fitness (13) are related to fast recovery and thus might improve impaired vagal functioning and eventually prevent serious health problems.

This study has several methodological limitations. We used the motility and cardiac data to detect and remove waking periods during sleep. There is recent evidence that subjects actually worry when they awaken at night (97). The exclusion of these awake periods from the analyses can possibly explain the lack of effects of worry after 10PM. On the other hand, deletion of awake periods seems to be an appropriate strategy if one is interested in the effects on cardiac levels during sleep only. Only polysomnographic data would have ensured us that all waking periods were deleted. As such, some of our limited effects on cardiac sleep levels might be due to awake periods instead of genuine prolonged effects during sleep. On the other hand, we expect that disturbances in sleep would be reflected in the reported level of sleep quality; statistically controlling for the effects of sleep quality did not change our results and therefore we do not expect that the inclusion of missed awake periods influenced our results. Yet, there is evidence that increased stress or worries before bedtime can increase the amount of awake time during sleep (29). Moreover, there is evidence that subjects actually worry when they awaken at night (97). Consequently, future studies that focus on the effects on physiological levels during actual sleep should be cautious to carefully assess whether participants are awake or not.

There are some additional methodological considerations concerning the measurement of cardiac recovery after neutral laboratory stressors. Firstly, one might argue that attenuated recovery in the laboratory might be influenced by anticipating the next task. Anticipating a stressor in the form of a laboratory task can induce physiological effects (98). However, to minimize these effects the tasks were presented in counterbalanced order. Secondly, the measurement of recovery was dependent on baseline and reactivity, and as such it was not a "clean" measurement of recovery. There is evidence that recovery after laboratory tasks is predictive of CVD outcome independent of reactivity to the same tasks (see for a review (20)). Our purpose was to capture an innate or typical stress curve during recovery, but not to find evidence for the explanatory power of recovery over reactivity or baseline; in our opinion, this can not be done without considering baseline and reactivity**.** Also, one might argue that the duration of this stress recovery period was too small (5 minutes). Since these tasks were relatively simple and of low impact, we

did not expect that a longer duration would be neccessary; also, when an individual does not recover within these 5 minutes this would be reflected in his AUC score. Moreover, Moseley & Linden (84) found that laboratory recovery with a duration of 5 minutes predicted ambulatory BP and HR levels.

In summary, the present study does not replicate cardiac effects of stressful events and worry during waking and nocturnal sleep. The results underscore the value of measuring the tendency to worry and the value of incomplete recovery from neutral laboratory stressors. Additionally, future ambulatory studies should consider the aspect of "thinking hard" when evaluating the effects of perseverative cognitions, since it might be crucially linked with toxic physiological changes.

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

	n	Mean ± SD	Range	%
Person level:				
Gender	55			70,9% Male
Age	55	46.1 ± 8.5	26 - 60	
BMI [a]	54	24.3 ± 3.5	17.2 – 34.1	
PSWQ [b]	55	43.0 ± 10.8	25 – 76	
WDQ [c]	55	22.0 ± 15.8	0 – 74	
BDI [d]	55	6.3 ± 5.5	0 – 24	
IHAT [e]	55	.19 ± .15	.0 - .67	
CM [f]	55	13.4 ± 6.0	3 – 27	
STAI [g]	55	36.4 ± 9.3	24 – 58	
Job strain [h]	55	-.28 ± 1.13	-2.8 – 5.2	
AUCHR	40	227.83 ± 31.67	158.41 – 301.31	
AUCMSSD	40	169.61 ± 32.36	89.15 – 277.20	
Day level:				
HR waking	149	79.80 ± 8.87	49.60 – 100.46	
HR sleep	149	61.79 ± 7.45	42.43 – 92.72	
MSSD waking	149	28.33 ± 11.80	6.52 – 72.20	
MSSD sleep	149	36.11 ± 19.20	6.70 – 126.79	
Frequency worry episodes waking	149	.08 ± .12	0 - .60	
Frequency stressful events waking	149	.11 ± .13	0 - .75	
Duration worry episodes (minutes) waking per entry	149	1.13 ± 3.15	0 – 30.50	
Duration stressful events (minutes) waking per entry	149	.75 ± 1.38	0 – 7.75	
Occurrence worry episodes after 10PM	143			21.7% Worry
Occurrence stressful events after 10PM	143			13.3% Stressful events
Duration worry episode (minutes) after 10PM if worry was reported	142	4.13 ± 11.73	0 - 60	
Duration stressful events (minutes) after 10PM if a	143	2.03 ± 8.07	0 - 60	

stressor was reported				
Type of day	143			52.4% Work
Coffee intake	147	.23 ± .20	0 – 3	
Smoking	148	.09 ± .26	0 - 3	
Alcohol intake	140	.11 ± .13	0 - 3	
Physical activity during waking	149	1.44 ± .34	1 - 5	
Resting during waking	149	1.19 ± .26	1 - 5	
% Physical activity during waking	149	.24 ± .12	0 - 1	
Sleep quality	143	2.85 ± .63	1 - 5	

[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 demand, low control

Table 2: Effect of biobehavioral variables on cardiac activity during waking and sleeping (means and standard deviations)

		Waking		Sleeping	
		HR	MSSD	HR	MSSD
Gender					
	Male	79.52 ± 9.27	28.02 ± 12.27	60.95 ± 6.66	36.52 ± 18.71
	Female	80.65 ± 7.58	29.25 ± 10.35	64.32 ± 9.08	34.89 ± 20.82
Age					
	(<47.1 years)	80.57 ± 9.05	31.41 ± 13.80	60.65 ± 6.72	42.12 ± 22.50
	(>47.1 years)	79.09 ± 8.70	25.45 ± 8.71	62.85 ± 7.97	30.50 ± 13.36
BMI					
	(<24.3)	79.31 ± 9.21	31.19 ± 13.91	61.91 ± 8.55	39.83 ± 22.73
	(>24.3)	80.68 ± 8.40	25.14 ± 8.03	62.14 ± 5.89	31.84 ± 13.72
Coffee intake					
	No	76.19 ± 9.88	29.74 ± 14.38	58.39 ± 6.89	39.60 ± 19.30
	Yes	80.49 ± 8.57	28.06 ± 11.36	62.44 ± 7.36	35.46 ± 19.28
Smoking					
	No	79.01 ± 8.39	29.55 ± 11.49	60.55 ± 6.30	37.38 ± 18.76
	Yes	84.19 ± 10.55	21.60 ± 11.43	69.06 ± 9.74	29.59 ± 21.13
Alcohol intake					
	No	79.33 ± 8.43	28.55 ± 12.23	61.29 ± 7.27	37.09 ± 20.21
	Yes	80.63 ± 9.32	27.88 ± 11.88	62.44 ± 7.74	34.67 ± 18.98
Day					
	Work	81.50 ± 9.46	27.16 ± 10.93	62.46 ± 7.55	35.37 ± 17.96
	Leisure	78.54 ± 7.82	28.71 ± 11.36	61.50 ± 7.14	35.01 ± 16.73
Physical activity during waking					
	(<median)	79.23 ± 8.82	28.08 ± 10.79	62.30 ± 7.80	34.47 ± 19.09
	(>median)	80.35 ± 8.94	28.56 ± 12.77	61.30 ± 7.11	37.69 ± 19.29
Resting during waking					
	(<median)	80.72 ± 8.18	27.91 ± 9.82	62.98 ± 7.58	35.89 ± 17.03
	(>median)	78.96 ± 9.43	28.70 ±	60.69 ± 7.21	36.32 ±

		13.41		21.09
% Physical activity during waking				
(<median)	79.87 ± 8.83	29.03 ± 12.17	60.93 ± 8.32	37.41 ± 20.70
(>median)	79.73 ± 8.97	27.63 ± 11.46	62.63 ± 6.43	34.84 ± 17.63

Table 3: Correlations between worry and stressor variables, trait values and physical activity and cardiac activity during waking and sleeping

	Waking		Sleeping	
	HR	MSSD	HR	MSSD
Stressor frequency waking	.18	.03	.05	.17
Stressor duration waking	.32*	-.08	.30*	.04
Worry frequency waking	-.02	.14	.02	.06
Worry duration waking	.09	.14	.17	-.02
Stressor occurrence during the night	.02	.15	-.06	.21
Stressor duration during the night	.05	.13	.00	.16
Worry occurrence sleep	.09	.07	.05	-.02
Worry duration sleep	.15	-.04	.13	-.11
Hostility (CM) [a]	.03	-.15	.03	-.02
Hostility (IHAT) [b]	.09	-.30*	.21	-.25
Depression (BDI) [c]	-.23	-.11	-.03	-.05
Anxiety (STAI)[d]	.01	-.06	.12	-.03
Worry (PSWQ) [e]	.15	-.15	.30*	-.15
Worry (WDQ) [f]	-.11	-.06	.04	-.08
Job strain [g]	.01	.24	-.14	.25
AUC recovery HR	.56**		.36*	
AUC recovery MSSD		.28		.09

[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 demand, low control

Table 4: Effects of frequency and duration of stressful events and worry episodes on HR and lnMSSD during waking.

	HR		lnMSSD	
	Frequency	Duration	Frequency	Duration
Fixed effects				
Intercept	75.63 ± 1.10	7.53 ± 1.10	3.42 ± .05	3.43 ± .05
Stressor frequency	-1.22 ± 5.77		-.08 ± .26	
Worry frequency	.96 ± 5.30		-.07 ± .24	
Stressor duration		-.62 ± 1.06		.02 ± .05
Worry duration		.68 ± .76		-.00 ± .03
Smoking	5.76 ± 4.98	6.24 ± 5.05	-.32 ± .23	-.32 ± .23
Alcohol consumption	-.98 ± 3.84	-.83 ± 3.79	.25 ± .18	.26 ± .18
Coffee consumption	-7.78 ± 4.76	-7.76 ± 4.71	.40 ± .22	.40 ± .22
Gender	3.15 ± 1.82*	3.02 ± 1.83*	-.06 ± .09	-.06 ± .09
Age	-.17 ± .11	-.16 ± .12	-.01 ± .005*	-.01 ± .005*
BMI [a]	-.28 ± .27	-.27 ± .27	-.01 ± .01	-.01 ± .01
Type of day	4.11 ± 1.01**	4.18 ± 1.01**	-.06 ± .05	-.07 ± .05
% High activity	-4.10 ± 4.14	-4.43 ± 4.08	.16 ± .19	.20 ± .19
Activity level	17.78 ± 4.60**	17.86 ± 4.51**	-.18 ± .21	-.16 ± .21
Resting during awake	-1.09 ± 4.83	-.93 ± 4.76	-.08 ± .22	-.06 ± .22
Hostility (CM) [b]	-.19 ± .24	-.23 ± .24	.02 ± .01	.02 ± .01
Hostility (IHAT) [c]	7.64 ± 7.00	7.60 ± 7.03	-.45 ± .32	-.43 ± .32
Depression (BDI) [d]	-.13 ± .22	-.13 ± .22	-.00 ± .01	-.00 ± .01
Anxiety (STAI)[e]	-.13 ± .17	-.13 ± .17	-.02 ± .01*	-.02 ± .01*
Worry (PSWQ) [f]	.26 ± .13*	.26 ± .13*	.00 ± .01	.00 ± .01
Worry (WDQ) [g]	.00 ± .06	-.01 ± .06	.00 ± .00	.00 ± .00
Job strain [h]	-.30 ± .70	-.31 ± .70	.02 ± .03	.02 ± .03
AUCHR	.09 ± .03**	.10 ± .03**		
AUCMSSD			.003 ± .001	.003 ± .001
Variance components				
Person level:				
Intercept (σ^2_u)	12.93 ± 4.46	13.41 ± 4.53	.03 ± .01	.03 ± .01
Episode level:				
Intercept (σ^2_e)	13.76 ± 2.50	13.41 ± 2.44	.03 ± .01	.03 ± .01
Deviance	573.99	573.07	-24.37	-24.27

[a] BMI=Body Mass Index

[b] CM=Cook-Medley Hostility Questionnaire

[c] IHAT= Interpersonal Hostility Assessment Technique
[d] BDI=Beck Depression Inventory
[e] STAI=Spielberger Trait Anxiety Inventory
[f] PSWQ=Penn State Worry Questionnaire
[g] WDQ=Worry Domain Questionnaire
[h] Job strain=high job demand, low control
** p<.01 based on one-tailed t-tests
* p<.05 based on one-tailed t-tests

Table 5: Effects of frequency and duration of stressful events and worry episodes on HR and lnMSSD during sleep.

	HR		lnMSSD	
	Frequency	Duration	Frequency	Duration
Fixed effects				
Intercept	59.14 ± .92**	59.34 ± .97**	3.62 ± .08**	3.61 ± .08**
Stressor frequency waking	-10.47 ± 5.46		.50 ± .33+	
Worry frequency waking	7.70 ± 5.46		-.38 ± .32	
Stressor frequency night	3.31 ± 2.11		-.02 ± .13	
Worry frequency night	-1.63 ± 1.50		.05 ± .09	
Stressor duration waking		.00 ± 1.01		.05 ± .06
Worry duration waking		1.14 ± .76		-.07 ± .05+
Stressor duration night		1.32 ± 1.22		-.00 ± .07
Worry duration night		-.93 ± 1.00		.02 ± .06
Smoking	5.93 ± 4.25	4.94 ± 4.60	.73 ± .35*	.69 ± .35+
Alcohol consumption	8.74 ± 3.62**	9.72 ± 3.61**	-.47 ± .22*	-.52 ± .22**
Coffee consumption	-.72 ± 4.42	1.18 ± 4.52	-.39 ± .29	-.44 ± .29
Gender	3.86 ± 1.46**	3.90 ± 1.59**	1.15 ± .13	-.15 ± .14
Age	.02 ± .09	.01 ± .10	-.02 ± .01	-.02 ± .01
BMI [a]	-.33 ± .22	-.27 ± .23	-.01 ± .02	-.01 ± .02
Type of day	1.45 ± .99	.90 ± .98	-.07 ± .06	-.05 ± .06
% High activity	1.81 ± 4.10	3.55 ± 4.02	-.22 ± .25	-.26 ± .24
Activity level	-1.56 ± 4.21	-.05 ± 4.18	-.08 ± .26	-.12 ± .26
Resting during awake	-3.38 ± 4.37	-1.07 ± 4.35	-.42 ± .27	-.49 ± .27
Sleep quality	-.70 ± .73	-.61 ± .71	.07 ± .04*	.06 ± .04*
Hostility (CM) [b]	-.32 ± .19	-.28 ± .21	.01 ± .02	.01 ± .02
Hostility (IHAT) [c]	7.84 ± 5.62	9.19 ± 6.10	-.37 ± .50	-.42 ± .51
Depression (BDI) [d]	-.12 ± .18	-.05 ± .19	.00 ± .02	.00 ± .02
Anxiety	.05 ± .15	-.02 ± .15	-.01 ± .01	-.01 ± .01

(STAI)[e]				
Worry (PSWQ)[f]	.18 ± .10*	.14 ± .11	.01 ± .01	.01 ± .01
Worry (WDQ)[g]	.04 ± .05	.06 ± .05	-.00 ± .00	-.00 ± .00
Job strain[h]	-.75 ± .57	-.56 ± .61	.03 ± .05	.02 ± .05
AUCHR	.06 ± .02**	.07 ± .03**		
AUCMSSD			.00 ± .00	.00 ± .00
Variance components				
Person level:				
Intercept (σ^2_u)	5.92 ± 2.74	8.76 ± 3.30	.09 ± .03	.09 ± .03
Episode level:				
Intercept (σ^2_e)	12.76 ± 2.34	11.69 ± 2.15	.04 ± .01	.04 ± .01
Deviance	539.64	541.50	25.48	25.30

[a] BMI=Body Mass Index
[b] CM=Cook-Medley Hostility Questionnaire
[c] IHAT= Interpersonal Hostility Assessment Technique
[d] BDI=Beck Depression Inventory
[e] STAI=Spielberger Trait Anxiety Inventory
[f] PSWQ=Penn State Worry Questionnaire
[g] WDQ=Worry Domain Questionnaire
[h] Job strain=high job demand, low control** p<.01 based on one-tailed t-tests
** p<.01 based on one-tailed t-tests
* p<.05 based on one-tailed t-tests

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Chapter 7: *General Discussion*

The main focus of the present thesis was to study prolonged cardiac effects of stressful events and worry in daily life. In two review papers a theoretical background as well as a review of studies was provided that served as a basis for the empirical study presented here. For the empirical papers we measured cardiac activity in the laboratory and in daily life in a group of high school teachers. Additionally, the participants reported on their experience of stressful events and worry. This resulted in three empirical papers investigating the effects of stressful events and worry on immediate and prolonged cardiac activity, as well as cardiac activity during sleep. This chapter starts with a summary of the main results reported, followed by an overview of the status quo of the prolonged activation hypothesis, in light of which we will discuss our findings. Additionally, this discussion is divided in various subsections focussing on immediate cardiac effects of worry, the possible role of content of worry, the lack of evidence for the suggestion that worry mediates the prolonged cardiac effects of stressors, the prolonged effects of worry, the absence of evidence for an association between worry and average levels during daytime or during sleep, as well as the importance of measuring trait worry in future studies. Furthermore, we discuss methodological considerations and conclude with recommendations for future research.

OVERVIEW OF FINDINGS

This thesis starts by describing a theoretical framework in which prolonged physiological activation before or after stressors is regarded as an important factor in the development of cardiovascular disease (CVD; see Chapters 2 and 3). This contadicts the more conventional reactivity hypothesis which emphasizes activation during stressors and overlooks cardiovascular (CV) activation that continues beyond the presence of a stressor. Hence, the reactivity hypothesis focuses on states of such short duration that, even if frequent and intense, they alone cannot explain the development of chronic pathogenic states leading to CV disease.

In contrast, prolonged activation is viewed as an important element in several disease theories, such as Selye's (sustained preparation causes exhaustion (1)), Ursin's (sustained activity (2)), McEwen's (allostatic load (3)). Indeed, recent studies have suggested that prolonged duration of physiological activity during recovery phases relates to several CVD outcomes (Chapters 2 and 3). However, we argue that most psychological processes postulated to mediate the process of stressors resulting in prolonged activation are insufficient and vague, with the exception of perseverative cognition (4, 5). As a result of this insufficiency, only a small amount of CV stress research has explicitly addressed the relation between stressors and prolonged activity, and not many studies have implicitly tested the issue of possible psychological mediators.

In Chapter 2, we review real life (ambulatory) studies testing the hypothesis that various stress sources can have prolonged CV effects. The review is focussed on real life studies for two reasons. Firstly, a summary and discussion of laboratory findings have been done elsewhere. Secondly, ambulatory field studies enable measurement over a larger time scope, which is crucial for the ecological validity of studying prolonged activity. We conclude that these studies indeed suggest that several stress sources, including discrete and chronic stressors, negative affective states and negative emotional dispositions, are related to prolonged CV activity, although the evidence is still very modest. Additionally, we conclude that potential

psychological mediators of stress-related prolonged activity such as perseverative cognitions were largely overlooked in the reviewed studies.

In Chapter 3 we focus on perseverative cognition as a potential psychological mediator, because it has the capacity to chronically activate the cognitive representation of stress-related content, thereby chronically inducing physical activation. Perseverative cognition is manifested in phenomena such as worry, rumination and anticipatory stress. However, still far from sufficient, evidence is emerging that links these phenomena to physiological activation, including cardiovascular, endocrinological and immunological parameters.

To further investigate the role of perseverative cognitions, we conducted an ambulatory study in which we measured subjects' HR and HRV in daily life during two periods of 48 hours (see Methods Chapters 4, 5 and 6). The participants also completed an hourly set of questions concerning, among others their stress experience and worry behavior during daytime, and each morning after waking up they reported on their stress experience and worry behavior during the night and the nocturnal sleep period. These measurements were preceded by a short laboratory session in which two neutral laboratory stressors were completed to assess the subject's cardiac recovery, as well as a hostility interview. Although the studies reported in Chapters 4, 5 and 6 were partly based on the same data, these reports used such different statistical approaches that the analyses could not be combined (see below).

Following our theoretical framework, we hypothesized that in daily life increased HR and decreased HRV occur not only during stressors, but also during periods of worry in absence of a stressor (Chapter 4). Indeed, our findings indicate that worry has substantial independent effects on HR and HRV in addition to the effects of stressful events. These effects were independent of the effects of biobehavioral variables and psychological traits. 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. Furthermore, we found that these cardiac effects were most pronounced for work-related worry and worry about anticipated future stress. Conventional stress measurements are restricted to the past and neglect anticipation of future stressors. Also, studies measuring anticipatory stress are rare. As such, in the current scientific discourse on including duration of the stress response, the latter finding underscores the importance of studying anticipated stress as source of cardiac effects.

In Chapter 5, we elaborate on these findings by hypothesizing that increased HR and decreased HRV are not only due to concurrent stressful events, but are also effected by stressors occurring before and by stressors that are anticipated. Additionally, we expected that worry would mediate at least part of these effects. The results indicate that stressors have prolonged cardiac effects up to one hour. We did not find evidence for the mediating role of worry, although worry alone displayed even longer lasting prolonged effects, i.e. up to two hours. Since biobehavioral factors, psychological traits and laboratory recovery after neutral stressors cannot explain this association, we reason that unconscious perseverative processes might have mediated the prolonged effects of both stressors and worry.

In Chapter 6 we attempt to extend these findings by showing that accumulated stressful events and worry influence mean levels of daytime and sleep HR and HRV. We argued that the possibility of stressful events or worry inducing

nocturnal physiological arousal is significant for health. Sleep is a typical period to recover from daily life physiological activation. If physiological arousal generated by stress does not stop during sleep it leads to a situation not unlike being exposed to a virtually permanent stressor and this might eventually cause serious health problems. An earlier study by our group (6) showed that worry mediated the prolonged effects of stressors on daily and nocturnal HR and HRV. Furthermore, worry displayed an additional effect on daily and nocturnal HR and HRV independent of those of stressors. The study described in Chapter 6 was designed to replicate these findings, but failed to do so. We did find, though, that a tendency to worry and a more incomplete HR recovery to neutral laboratory stressors were associated with increased daytime and sleep HR, stressing the importance of measuring both variables in future studies.

The results presented in this thesis are discussed below.

STATUS OF THE PROLONGED ACTIVATION HYPOTHESIS

By addressing various elements of the prolonged activation model Chapters 2 and 3 contribute valuably to the field of stress-research. Firstly, we summarized studies that tested the predictive effect of prolonged activation on CVD. Secondly, we were the first to summarize ambulatory studies that tested the prolonged effects of various stress sources. Lastly, possible psychological mechanisms were summarized that might be responsible for the relation between stressors and prolonged activation and focussed specifically on the possible role of perseverative cognitions.

An increasing number of studies have found that the duration of stress response even after simple laboratory stress tasks is predictive of physiological changes. Attenuated blood pressure (BP) recovery after psychological tasks predicted increased BP values in the clinic 3 years afterwards, while reactivity values did not (7). Faster HR recovery after a mental arithmetic and a speech task predicted less thickness of the carotid artery intima-media complex (an index of preclinical atherosclerosis) 2 years later (8). Surprisingly, HR and pre-ejection period (PEP) during these stressors (i.e. reactivity) were not related to carotid thickness, which suggests that elevated reactivity is not necessarily related to negative outcome with regards to atherosclerosis. Furthermore, increased (>195 mm Hg) systolic BP 2 minutes after a laboratory exercise test leads to an increased risk for acute myocardial infarct 13.1 years later, even after correction for cardiac reactivity values. Delayed cardiac recovery is seen as a measure of impaired autonomic nervous system functioning, more specifically impaired vagal tone (9), which seems to suggest that this imbalance is a crucial mediating factor causing these disease states. Thus, in contrast to the reactivity model, which received critical comments on its limited predictive value (10, 11), slow recovery indeed has predictive value with regard to CVD (see above and Chapter 2).

Additionally, in contrast to the limited laboratory-to-life generalizability (12, 13) of cardiovascular reactivity measurements, there is evidence that even small recovery periods in the laboratory are reproducible in daily life. One study suggests that attenuated laboratory BP recovery predicts ambulatory BP levels during daytime and sleep (14). Additionally, another study (15) shows that BP, cardiac output and total peripheral resistance during recovery were related to ambulatory BP independent of resting BP and reactivity values. Our findings presented in Chapters 4 and 5 are in line with these results and contribute to them by showing that

attenuated laboratory HR recovery is predictive of HR levels during 15 minute periods, as well as mean levels during daytime and during sleep. However, not all studies consistently show that recovery is dominant over reactivity in predicting CVD outcomes. For instance, Moseley and Linden (16) found that BP and HR recovery to psychological laboratory tasks in normotensives predicted ambulatory BP and HR 3 years later, but not 10 years. On the other hand, reactivity to these tasks predicted ambulatory HR and BP 3 years later, as well as systolic BP 10 years later. In light of this, and in comparison with the excess amount of reactivity studies, the stability of the recovery effect needs to be replicated in future research.

Apart from the predictive value of delayed recovery, several studies have found psychophysiological factors which lead to physical CVD risk factors that may be mediated by delayed recovery. There is cross-sectional evidence that increased obesity (17, 18), a family history of cardiovascular disease risk (19), social isolation and poor mental health (20) are related to poor diastolic BP recovery in the laboratory. Delayed HR recovery after a treadmill test was observed in rehabilitated cardiac patients who reported an increased level of depressive symptoms (21), which is also a CVD risk factor (22). On the other hand, in line with findings that increased positive affect is associated with reduced risk of mortality (23, 24) reduced mortality (25) and reduced risk of physical disease (26), one study showed that high reporting of positive affect was related to faster BP recovery (27).

Steptoe and colleagues have published a number of papers indicating that the important CVD risk factor of low social economic status (SES) seems to be mediated by delayed recovery and CVD. After behavioral laboratory tasks, subjects with low SES (versus those with high SES) showed less complete cardiovascular recovery of BP and HRV (28), total peripheral resistance (29), HR and pro-inflammatory cytokine interleukin-6 (30), systolic BP (20). Moreover, one study found that delayed HR, BP, PEP and SV recovery values were typical for older subjects and even more pronounced in older subjects with low SES, indicating that high SES can be protective against the effects of increasing age on cardiovascular condition (31). Additionally, delayed BP recovery predicted increased carotid intima-media thickness 3 years later, but only in subjects with low SES (32). Although these studies provide some insight into the possible physiological route from these factors to CVD, we believe that our main comment that the possible psychological route from these factors to delayed recovery is still unclear (formulated in Chapter 2 (5)) remains valid. This is discussed below.

Apart from the above, the psychological concept of need for recovery has received increasing attention. It generally refers to the need for a stress-free period to recuperate from experienced stressors or mental load for example during a work day and to refill ones resources. This "psychological unwinding" is considered to be essential for well-being, work satisfaction and work engagement (33). A more demanding or longer lasting stressful situation will consume more resources and will lead to increased need for recovery. A situation where resources are continuously reduced, will lead to more effort to compensate for lack of resources while trying to adequately work. This accumulative situation is thought to lead to symptoms such as fatigue, disturbances of mood, physiological changes and eventually, burnout, exhaustion, sleep problems and disease (34). Concepts similar to this psychological recovery have been prospectively linked to CVD. Need for recovery was related to more self-reported CVD after 32 months (35). Lack of recovery during free

weekends was related to elevated risk of CVD death after 25.6 years (36). Recently, Geurts and Sonnentag (34) have explicitly formulated processes that can hinder the recovery from load, such as prolonged exposure to work demands and cognitive processes, including perseverative cognitions. However, their research mainly focuses on the psychological effects, but not the direct prolonged physiological effects of related concepts such as ability to psychologically detach from work (37), mental relaxation (38) and non-work experiences that are accompanied by positive feelings such as competence (39). It seems fruitful for future research to study prolonged physiological effects. Moreover, in our view (Chapters 2 and 3) the concept of perseverative cognition is theoretically better suited for a psychological process that can explain prolonged effects of stressors, since it explicates a direct trigger of physiological activation in the form of a mental representation of a stressor, as well as the repeated activation of this representation, and therefore the associated physiological activation and stress experience.

CARDIAC EFFECTS OF WORRY

To be a possible mediator, worry should have cardiac effects independent of the effects of stressors. Several laboratory studies show that worry is associated with simultaneous (that is, during worry itself) physiological effects (Chapter 3). Only one previous study (6) indicates that worry is related to toxic cardiac levels in daily life and results show that worry especially worry duration is related to elevated HR and decreased HRV during daytime, as well as during the nocturnal sleep period. For the study presented in Chapter 3 we measured timing and duration of stressful events more precisely and could therefore accurately match these with simultaneously occurring cardiac activity. Thus, the results replicate and extend the previously attained findings (6) by showing that worry is related to simultaneous HR and HRV levels, and independent from the effects of stressful events. Additionally, the results indicate that worry duration is longer than stressors duration, which indicates that the net cardiac effects of worry might be even more substantial than those of stressful events. Based on these findings we conclude that worry is a noteworthy source of cardiac elevations, even lasting longer than those of stressors.

The results of this study are consistent with experimental findings of worry (Chapter 3) and show that these latter findings are potentially generalizable to the real world. Real world studies, however, are less adequate in clarifying which of the characteristics of worry are actually responsible for its cardiac effects. Only a few laboratory studies have attempted to do this so far. Oathes et al. (40) found that worry was associated with larger corticospinal motor responses than an arithmetic task with high mental load. The authors reason that this finding supports the role of action preparation in worry; this is in line with the idea that perseverative cognitions continuously induce physiological preparation for action intending to change or escape an unwanted situation ('fight – flight') and this action preparation is thought to be associated with physiological activation, which explains why worry induces more physical effects than mere mental activity that is needed for a mental arithmetic task. On the other hand, Verkuil et al. (41) from our group recently found that while worry elicits higher HR and lower HRV than during relaxation, cardiac levels are similar to those elicited during a cognitive problem solving task concerning moral dilemmas that were not personally relevant. This finding seems to contradict the findings by Oathes et al. (40). The cognitive problem solving task used by

Verkuil et al. (41) however, was designed to resemble cognitive activity during worrying (jumping from one problem to the next) without inducing negative emotions related to personal relevance of the presented problems. As such, this task was more complex and therefore required more mental effort than the mental arithmetic task used by Oathes et al. (40). Verkuil et al. (41) conclude the feature of 'prolonging mental load' instead of the prolonged emotional aspects to be responsible for the adverse effects of worry on health.

CONTENT OF WORRY AND CARDIAC EFFECTS

Instead of focussing on the characteristics of worry, we have concentrated on the content of worry. Results reported in Chapter 4 show that cardiac effects were more pronounced during work-related worry and worry about anticipated future stress than during worry about other topics, which is a new finding in the field. The effects of work-relatedness of worry suggest that the reported effects of work stress on CV health (42) might be – at least partially – mediated by immediate effects of worry about work. It leaves unexplained, however, why work-related worries have a stronger cardiac effect than worries related to other problems. The second content-related finding, concerning future-related worries, underscores the importance of measuring anticipatory stress, by indicating that worry about future stressful events is superior to worry about other topics, by inducing a mean HR that is 4.79 beats/min higher. Thus, worrying about stressful events that might happen in the future can cause considerable anticipatory cardiac activation irrespective of its actual later occurrence. This finding is particularly relevant since there is evidence that this is possibly the most frequently occurring form of worry (43), thus again enlarging its effects. This aspect has been neglected in conventional stress measurements (life event questionnaires, work stress, daily hassles), which are restricted to stress in the past neglecting anticipated stressors. The question why future-related worry has stronger effects than past-related worry is perhaps easier to answer than the earlier question about work-related worry. Worry about the future concerns fear, while worry about the past mostly concerns regret and sadness. Fear is known to trigger stronger physiological effects than regret and sadness (44). This finding seems to urge future studies not only to re-evaluate the reactivity principles but also to include stressors that are feared although they need not actually occur.

In Chapter 5 however, we found no cardiac effects of the expectation of a stressor in the succeeding hour. Some factors might explain this non-finding. Firstly, it is possible that the stressors expected in the next hour were not intense enough to elicit cardiac responses. Secondly, it is possible that the future issues that the subjects worried about were not expected in the succeeding hour, but might appear further in the future or might not even appear at all, indicating that "the succeeding hour" was too limited a time-frame or even a falsely designed frame to measure physiological effects. Moreover, stressors expected in the next hour might have already coped with to a large extent, resolving much of the fear that might be responsible for the cardiac worry effects found in Chapter 4. Interestingly, there is experimental evidence supporting this idea. Anticipation of a concrete and unavoidable stressor induced less intense physiological changes than worrying: Hofmann et al. (45) showed that worry was related to higher HR, lower HRV and greater left frontal activity than during baseline, relaxation or anticipation of a stressful speech task. However, anticipation induced higher skin conductance levels

than worry. Nevertheless, since worrying about the future induces such pronounced cardiac effects (Chapter 4) and is a central element of perseverative cognition (62), future studies should focus on the physiological effects of expecting a stressor and apply a less limited time-frame.

A study by Smyth and colleagues (46) showed that anticipating a stressor in the next hour elevated salivary cortisol levels, which seems to contradict our results. However, as discussed in Chapters 4, 5 and 6, participants in our study reported less stressors and worry than other studies, including Smyth's (46). This points to another explanation: too few stressors were expected in the next hour in this sample. Although our results indicate that worrying about possible stressful events in the future can cause considerable anticipatory cardiac activation irrespective of its actual later occurrence, it is clear that there is a need for replication studies to assess the nature of these effects and their generalizability to other subject groups.

WORRY DOES NOT MEDIATE EFFECTS OF STRESSORS

Contrary to our expectations, we did not find evidence that worry mediates substantial effects of stressors, neither concurrent effects (Chapter 4), effects up to one hour (Chapter 5) nor effects on daytime or night-time levels (Chapter 6). At least one previous ambulatory study (6) found that worry duration mediated the effects of stressors on daytime and nocturnal cardiac levels. Results from at least two laboratory studies suggest that slow BP recovery after emotional stress is mediated by worry or rumination (47, 48). The present study could not confirm these findings. However, we argue that worry is always about stressful events, whether in the past, present or future, and certainly not only about those stressful events confined to the limited time periods in the computer diaries. Thus, worry can be about one or more stressful events possibly occurring in a virtually endlessly larger timeframe than the periods in which we measured actually occurring stressors. In fact, it is likely that by measuring worry episodes we measured the (mediated) aggregated effects of those stressful events which typically involve the most relevant stressors for an individual. Furthermore, the small number of stressful events actually measured were general events, including neutral as well as some emotionally upsetting ones. We reason that subjects worried about events that were mainly emotionally upsetting – otherwise why worry about them? Together, these arguments seem to explain why worry did not mediate the effects of stressful events in these studies. In Chapter 6, we further argue that when stressor experiences in daily life are more numerous, and the definition of worry much broader, as in our study (6), it is possible that mediating effects of worry will be found.

WORRY SHOWS PROLONGED CARDIAC EFFECTS

Initially, we expected worry to have a simultaneous and possibly mediating effect but not a prolonged effect of itself. To our surprise, worry displayed a prolonged cardiac effect that lasted up to two hours which was not due to emotions and life style factors, recovery to psychological laboratory tasks or even worry at a later time point. This is an intriguing new result, for several reasons.

Firstly, the finding that worry is related to simultaneous cardiac elevation (Chapter 2) does not indicate a causal relationship, i.e. it may still be reasoned that high HR and low HRV cause worry and stress perceptions, instead of the other way around. On the other hand, the 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.

Secondly, the finding of prolonged effects of worry seem to point to a form of perseverative cognition not yet identified by our theory. Some other studies suggest a possible mechanism that at least a part of perseverative cognition may act in an unconscious fashion during sleep which is not reported by the subject. For example, anticipating a stressful oral speech to be performed after waking up elicited prolonged low HRV during sleep (49). In the study of our group discussed above prolonged HR and HRV effects during sleep were found following a day of stressful events and worry ((6); see Chapters 2, 3 and 6 for further discussion). Conscious worry evidently does not take place during sleep. Moreover, the majority of cognitive processing operates without awareness, i.e. automatically (50, 51), and a considerable part of normal daily emotional processing - including PC - is likely to be unconscious too (52). Hardly anything is known about the physiological effects of unconscious emotion, except for some brain and some skin conductance effects (53, 54). Therefore, future studies should aim at unravelling the works of unconscious processing of stressful information.

WORRY DOES NOT EFFECT AVERAGE CARDIAC LEVELS DURING DAYTIME OR DURING SLEEP

Although worry and stress had simultaneous cardiac effects and even prolonged effects up to two hours, these effects disappeared when evaluating aggregated mean cardiac levels during daytime and sleep. These findings were in contrast with the previously discussed study by Brosschot et al. (6) in which daily worry and stressors were found to be related to higher average HR and lower average HRV during waking. Subjects that were measured for this thesis reported stressful events and worry episodes less frequently than in Brosschot et al. (6). Possibly the stressful events or worry episodes were not enough to influence the subjects' mean cardiac levels. This might be related to their lower levels of trait worry and trait anxiety. Future studies should assess similar hypotheses in samples with higher trait worry and trait anxiety.

Another aspect might be that the two studies presented their subjects with a slightly different definition of worry. Brosschot et al.'s definition included the aspect of "thinking hard" while the present study focussed more on the emotional negativity of the process. When initially designing the study, we believed that "thinking hard" was a side-effect of a mechanism which continuously keeps negative emotions "on-line". The cardiac effects were supposed to be induced by these negative emotions. This change of design might have resulted in an underreporting of less worrisome cognitive problem solving attempts. However, it can also be argued that this element of "thinking hard" is in fact an essential element for perseverative cognition (55). As was discussed above, the study by Verkuil et al. (41) suggests that mere mental activity and negative emotional perseveration induce comparable cardiac effects. It is possible that the results presented in Chapter 6 failed to find effects of worry on mean daytime and sleep cardiac levels due to the focus away from the element of 'thinking hard' and its cardiac effects. Future studies would do well to employ a much broader operationalization of perseverative cognition, including 'just thinking about problems'.

IMPORTANCE OF MEASURING TRAIT WORRY

Unexpectedly, we found that accumulated worry episodes during the day did not result in elevated cardiac levels during daytime or sleep (Chapter 5). Also, despite studies in the literature that found a relation between depression, hostility, anxiety, job stress and elevated somatic disease, we did not find evidence that these traits are related with cardiac elevations during daytime or sleep. Accordingly, the studies evaluating the effects of negative emotional dispositions or job stress on ambulatory cardiac levels during sleep (see Chapter 2 for a review) and the findings in this thesis (Chapter 4: *effect of PSWQ on HR but disappeared after including biobehavioral parameters*, Chapter 5: *no effects*, Chapter 6: *PSWQ effect on nocturnal HR*) together present an ambiguous picture. On the other hand, we found that a tendency to worry (measured by the PSWQ) induced elevated nocturnal HR activity (Chapter 6). To our knowledge, no study has previously showed such an effect of trait worry, and only one study has found effects of trait worry on risk of CVD (56). Interestingly, our other results on the same sample suggest that elevated tendency to worry does not influence HR or HRV during smaller timeframes (less than 2 hours; Chapter 4 and 5). This seems to indicate that prolonged cardiac activity during sleep alone might mediate this prospective association with CVD (45*).* Since these associations are not mediated by worry or stress or biobehavioral variables, it remains unexplained which underlying psychological mechanism is responsible for the prolonged cardiac effects of hostility and worry. Biobehavioral and emotional factors were controlled for in this thesis. One speculative possibility is that persons with a high tendency to worry are more prone to unconscious perseverative cognitions during sleep, but we have yet no evidence to support this. Nevertheless, this finding is particularly relevant for somatic health. Sleep is the most important period for the body to restore from activations inflicted during daytime. Not recovering from physiological elevations induced by stress, might lead to a situation alike being exposed to a permanent stressor. Being continuously physiologically activated without any restorative break might eventually result in serious health problems. Regarding the limited studies on the CVD risk of worry, our findings stress the importance of measuring tendency to worry when studying risk for CVD.

METHODOLOGICAL CONSIDERATIONS

The studies described in this thesis have several methodological aspects that should be considered. These issues are already discussed in detail in the previous chapters. Below, the most crucial methodological considerations are repeated and elaborated on.

Firstly, the studies in Chapters 4, 5 and 6 are based on multiple analyses performed on the same dataset, which might lead to an increased probability of finding effects that do not exist (57). However, because of their different hypotheses the three studies each used a different statistical approach and slightly different data, which could not be tested together. In the first study (Chapter 4) the starting point of the analysis consisted of stressors and worry episodes and their simultaneous cardiac activity. To correct for differences due to high activities, we included only low-impact activities in the analyses. The second study (Chapter 5) focussed only on cardiac activity during the last 15 minute window of each 60

minute measurement period. This was done because we measured several potential behavioral confounders, such as emotion, physical activity and posture, more specifically in the last 15 minute period. Since we could control for these factors, we did not have to confine ourselves to analyzing only low activities and included high physical activities as well. In the last study (Chapter 6), we analyzed mean HR and HRV levels during daytime and during the sleep period, which was again essentially different from the previous studies and included new elements such as stressful events and worry after 10PM and nocturnal cardiac levels. These analyzing strategies were based on our hypotheses that were all specified before conducting the measurements and thus, we do not feel that multiple comparisons lead to increased "change" findings. However, this important aspect urges these findings to be replicated in future studies, in which the different hypotheses are tested in a different sample. Favorably, we should invest in new statistical methods to investigate the hypotheses at the same time in one sample.

Secondly, one might question the clinical relevance of these findings, since worry and stressors were related to small increases of HR and small decreases of HRV. However, the magnitude of these effects is comparable to the effects of other factors associated with CVD, as reported by a recent consensus report on the effects of elevated HR on CVD risk (58). The report cites two studies finding a 15% increased risk for each 5 bpm HR increase. In addition, Cook et al. (59) report that drugs lowering HR by approximately 5 bpm were associated with an approximately 20% decreased risk of mortality. Few studies exist that have examined HRV measurements using a millisecond metric; however, Antelmi et al. (60) 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. It has often been proposed that the effects of worry represent a type of pre-mature aging (61). In addition, the size of the effects for worry and stressful events found in Chapters 4 and 5 were similar in magnitude to those found for smoking in these chapters. 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, as was indeed found in the present study. 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 these changes can accumulate to a level where they start to be potentially pathogenic, especially when combined with the effects of other risk factors, such as smoking, low exercise and hypertension. Thus we feel that the results described in Chapters 4 and 5 are of the same order of magnitude as those that have been shown to be clinically relevant.

Thirdly, the studies in this thesis focus on effects on cardiac parameters, specifically HR and HRV. An important reason for this is that the reactivity hypothesis, of which prolonged activity is an extension, was originally formulated to specifically explain the relationship between stress and CVD. Nevertheless, prolonged activation is not limited to the CV system and is applicable to various bodily systems and their associated diseases, such as the endocrine and immune system, muscle tension, glucose blood level, asthma-related parameters, and so forth. Additionally, there is evidence that perseverative cognitions induce other effects, mainly on somatic complaints, and on endocrinological and immunological parameters (62). Further empirical data on these relations should be gathered and future studies should focus on the mechanisms behind these relations.

Lastly, the sample consisted of high school teachers, who are a highly educated, medium SES subgroup, and the 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 experienced a lot of stress, or the opposite, 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, we did find solid effects of worry and stressors amidst a large pool of neutral episodes which were independent of biobehavioral factors and psychological traits. Additionally, if worry is a key detrimental process that might lead to CV disease in the long run, we do not expect worry to happen 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. Nonetheless, future studies should focus on these populations at risk to assess whether the findings of the present dissertation can be replicated. An interesting issue in studying these populations is whether the load on the organism is related to a high number of worries or on a more pronounced level of cardiac activity during worry.

DIRECTIONS FOR FUTURE RESEARCH

The empirical results from this dissertation indicate suggestions for future research. These suggestions have already been formulated in the chapters above and will be summarized below.

In general, future studies should be directed at replication of the findings, taking into consideration the methodological limitations that are raised. More specifically, various hypotheses should be tested without the disadvantage of multiple testing in separate samples. The results should be replicated in different groups of participants, mainly participants at risk for CVD and participants that experience more stress and worry. The prolonged activation model should be extended to other physiological systems, such as the endocrine and immune system, muscle tension, glucose blood level, asthma-related parameters.

In Chapters 2 and 3, we reasoned that in comparison to numerous ambiguous processes such as negative mood, prolonged stress experience, helplessness, or hopelessness perseverative cognition is best suited to explain prolonged effects of stressors. This is mainly because perseverative cognition involves a direct trigger of physiological activation, namely, the representation of the original (or expected) stressor, the repeated re-evocation of this representation and concomitant stress experience and physiological activation. Nonetheless, we did not find concrete evidence that worry effects the relation between stressors and (prolonged) cardiac activity. Although our empirical evidence shows that perseverative cognition is a factor with significant cardiac effects, future studies should be directed at elucidating other possible psychological mechanisms that could mediate the relation between stressors and prolonged activation. "Need for recovery" (see above) is an elaborate psychological concept, but its physiological effects are -to our knowledge- not studied yet.

Our results as well as results from other studies (40, 41) indicate that different elements of perseverative cognition might be associated with different levels of physiological cardiac activation in such a manner that presenting different

definitions of worry might even lead to different results. This suggestion urges future studies to elucidate these elements and their ability to induce prolonged activation.

Additionally, we found evidence that specific stressor and worry content lead to more pronounced simultaneous cardiac elevations than others: worry or stress about work or future-related topics were associated with pronounced cardiac elevations, as well as work-related stressors. It is possible that worrying about these topics also leads to more pronounced or longer lasting prolonged activation. However, due to the infrequent reports of stressful events and worry episodes we could not assess this hypothesis. It is worthwhile to direct future studies on testing these suggestions more thoroughly in a larger sample. Additionally, worrying about stressful events that might happen in the future is an aspect that has been neglected in conventional stress measurements, which focus on past stressors. Our findings urge future stress studies to include anticipated stressors or fear of future stressors when evaluating stress.

Additionally, since the results indicate that worry has significant immediate and prolonged cardiac effects, future research should focus on intervention studies designed to reduce frequency and duration of worry. Our group has shown that a simple intervention can reduce the duration of worry (63), but this and other strategies need to be further tested before being incorporated in cardiovascular reduction strategies.

Our results indicate that worry induces prolonged cardiac activation which last for up to two hours. Together with other studies this suggests that part of perseverative cognition acts in an unconscious fashion. Since there is almost no knowledge on how unconscious processing of stressful information induces physiological effects, this is a challenging new topic for future research.

In conclusion, the results presented in this dissertation stress the importance of perseverative cognitions for the prolonged activation model. More specifically, they extend evidence on cardiac effects of worry from the laboratory to daily life. The findings of prolonged effects of worry and the tendency to worry call for further research on the role of unconscious perseverative cognitions.

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Samenvatting

Hart- en vaatziekten behoren tot de belangrijkste doodsoorzaken in de westerse wereld. Mede daarom is veel onderzoek gedaan naar achterliggende mechanismen, risicofactoren en mogelijke (preventieve) interventies. Onder andere is de relatie tussen psychosociale stress en hart- en vaatziekten intensief onderzocht. Inmiddels beschikken we over uitgebreide kennis ten aanzien van mogelijke fysiologische mechanismen die maken dat psychosociale stress tot hart- en vaatziekten kan leiden. We weten echter nog weinig over de wijze waarop psychosociale factoren deze fysiologische mechanismen in werking zetten.

In de afgelopen decennia was het *reactivity model* het belangrijkste theoretische uitgangspunt in de meeste onderzoeken. In dit model wordt verondersteld dat een heftige reactie van hart- en vaatstelsel tijdens stress een risicofactor zou zijn voor het ontwikkelen van hart- en vaatziekten. Herhaaldelijke intensieve reacties zouden leiden tot wijzigingen van diverse balansen in de fysiologie van het hart- en vaatsysteem. Deze veranderingen zouden uiteindelijk leiden tot het ontwikkelen van hart- en vaatziekten. Het *reactivity model* dat in het dieronderzoek veelbelovende resultaten boekte, ondervond vanwege niet consistente resultaten uit humaan onderzoek een aantal fundamentele kritieken. Het model zou onder andere conceptueel onvolledig zijn met betrekking tot het verklaren van de relatie tussen stress en ziekte. Het brandpunt ligt bij momenten waarop een stressvolle gebeurtenis plaatsvindt, terwijl, zoals in dit proefschrift in de hoofdstukken 2 en 3 betoogd wordt, de periode daarvoor of daarna over het hoofd wordt gezien. Stressoren zijn gewoonlijk kort van duur en doen zich bij de meeste mensen niet frequent genoeg voor om consequenties voor de gezondheid te hebben. Deze factoren kunnen dus niet verklaren waarom chronische veranderingen in de balans van het hart- en vaatsysteem optreden.

Het lijkt logisch dat degene wiens systeem langdurig verhoogde hartactiviteit laat zien, dus ook na of voor de momenten waarop een stressor zich heeft voorgedaan, een hoger risico loopt op hart- en vaatziekten dan iemand bij wie de hartactiviteit zich meteen na het ervaren van een stressor herstelt. Een alternatief model dat wij voorstellen in dit proefschrift -het *prolonged activation model*- gaat uit van de stelling dat stressoren alleen kunnen leiden tot hart- en vaatziekten als ze in staat zijn verlengde fysiologische effecten te veroorzaken. Hoewel deze ideeën niet nieuw zijn en zelfs centraal staan in een sommige klassieke theorieën over hoe stress tot ziekte kan leiden, is het *prolonged activation model* nog beperkt onderzocht. Een overzicht van dit onderzoek wordt in hoofdstuk 2 gegeven. In dit proefschrift staat derhalve het *prolonged activation model* centraal.

De weinige empirische studies betreffende verlengde effecten van stressoren zijn voor het overgrote deel experimenteel en uitgevoerd in het laboratorium. Een nadeel van deze onderzoeken is dat individuen slechts een korte periode geobserveerd en gemeten kunnen worden, dikwijls met de beperking dat alleen onnatuurlijke stressoren kunnen worden toegepast. Studies in het dagelijkse leven, waarbij individuen rapporteren wanneer ze stressvolle gebeurtenissen meemaken terwijl de hartactiviteit ononderbroken wordt gemeten, bieden de mogelijkheid de verlengde activiteit nauwkeuriger te observeren. Om deze reden wordt in dit proefschrift het

prolonged activation model getoetst in een studie waarbij personen gemeten worden in het dagelijkse leven en de eigen (werk)omgeving.

In hoofdstuk 2 blijkt dat er niet alleen beperkt onderzoek is naar verlengde fysiologische activiteit, maar dat ook de belangrijke vraag nog onbeantwoord is waarom sommige stressoren wel verlengde effecten tot gevolg hebben en anderen niet. Recent heeft onze onderzoeksgroep geopperd dat '*perseverative cognition*' zou zorgen voor verlengde fysiologische effecten nadat een stressor afgelopen is, en ook vaak voordat een stressor mogelijk plaatsvindt. Perseveratieve cognitie is het voortdurend denken aan negatieve gebeurtenissen in het verleden of in de toekomst en omvat fenomenen zoals piekeren, tobben, rumineren of zich zorgen maken. Perseveratieve cognitie zorgt voor het 'vers' houden van het mentale beeld van een stressor alsmede de negatieve emotionele en fysiologische effecten ervan, of deze stressor nu wel of niet plaatsvindt. Tot nu toe verklaart dit '*perseverative cognition model*', dat uiteengezet wordt in de hoofdstukken 2 en 3 als enige waarom sommige stressoren leiden tot verlengde effecten en anderen niet. Daarom bestaat een groot deel van dit proefschrift uit onderzoek naar de effecten van perseveratieve cognitie - met name piekeren- op hartactiviteit.

Samengevat is het doel van dit proefschrift het onderzoek naar de verlengde effecten van stressoren en piekeren op hartactiviteit in het dagelijkse leven. Hiertoe wordt in twee overzichtsartikelen (hoofdstuk 2 en 3) een basis gepresenteerd voor de empirische studie die in de overige hoofdstukken wordt beschreven. In het hierna volgende worden de argumenten en bevindingen per hoofdstuk samengevat.

Hoofdstuk 2 betreft een literatuuronderzoek naar bestaande studies waarin de relatie tussen stressoren en verlengde hartactiviteit in het dagelijkse leven is getoetst. De conclusies van deze studies wijzen uit dat verschillende bronnen van stress gerelateerd zijn aan verlengde effecten. Het beschikbare bewijs is echter, zoals hierboven gezegd, bescheiden. Tevens werden in de bestaande onderzoeken geen mogelijke psychologische factoren geformuleerd, laat staan getoetst, die kunnen verklaren waarom sommige bronnen van stress leiden tot verlengde hartactiviteit en anderen niet.

In hoofdstuk 3 wordt bepleit dat perseveratieve cognitie een mechanisme kan zijn waardoor stress negatieve effecten heeft op het lichaam. Tevens geven we een overzicht van studies die de relatie hebben getoetst tussen verschillende vormen van perseveratieve cognitie en cardiovasculaire, endocriene en immunologische activiteit. Uit de conclusie blijkt dat er bewijs bestaat voor een relatie tussen perseveratieve cognitie en pathologische fysiologische activiteit, maar dat de hoeveelheid bewijs nog verre van voldoende is. Ook zijn er geen studies die hebben onderzocht of perseveratieve cognitie inderdaad verantwoordelijk is voor het effect van stressoren op verlengde fysiologische activiteit.

In de hoofdstukken 4-6 worden verschillende hypothesen getoetst, gebruik makend van een uitgebreide empirische studie. Hiertoe werden 73 docenten uit het voortgezet onderwijs onder andere gedurende twee periodes van 48 uur gemeten. Tegelijkertijd hielden de docenten overdag elk uur bij of ze stressvolle

gebeurtenissen hadden meegemaakt of cognitief hadden ge'persevereerd' (hierna genoemd: piekeren).

In hoofdstuk 4 worden de directe effecten van stressvolle gebeurtenissen en piekeren op gelijktijdige hartactiviteit beschreven. Piekeren blijkt inderdaad in het dagelijks leven samen te gaan met een verhoogde hartactiviteit, onafhankelijk van de (ongeveer even sterke) effecten van stressoren, en ook onafhankelijk van emotionele responsen, 'life style' variabelen zoals koffie en alcohol, en fysieke activiteit. Deze bevinding bij piekeren in het dagelijkse leven kan worden beschouwd als een uitbreiding van de resultaten uit laboratoriumstudies bij gesimuleerde vormen van piekeren. Tevens vonden we dat piekeren over het werk of over een toekomstige gebeurtenis gerelateerd was met de meest uitgesproken effecten op hartactiviteit. De sterkte van de gezamenlijk effecten van piekeren en stressoren komt overeen met die van een belangrijke risicofactor voor hart- en vaatziekte, namelijk roken.

In hoofdstuk 5 wordt een analyse beschreven waarbij verlengde effecten van stressoren en piekeren worden vergeleken met de gelijktijdige effecten. Deze analyse stelde ons in staat te bepalen of stressoren verlengde effecten op hartactiviteit hadden, hoe lang deze verlengde effecten duurden en of perseveratieve cognitie deze effecten veroorzaakte. Stressoren bleken een verlengde hoge hartactiviteit tot gevolg te hebben van maximaal één uur. Deze relatie kon echter niet verklaard worden door de effecten van piekeren, hoewel dat wel door het '*perseverative cognition model*' voorspeld was. Daarentegen leidde piekeren zèlf – onverwacht- tot verlengde verhoogde hartactiviteit die zelfs maximaal twee uur aanhield. Aangezien in die verlengde periode niet werd gepiekerd, redeneren we dat een vorm van onbewuste perseveratieve cognitie deze verlengde effecten veroorzaakt.

Hoofdstuk 6 gaat in op de effecten van stressoren en piekeren op gemiddelde hartactiviteit gedurende de dag en tijdens de slaap. Slaap wordt gezien als een belangrijke periode van herstel. Als negatieve effecten van stressoren niet zouden eindigen tijdens de slaapperiode zou dat betekenen dat men is blootgesteld aan een bijna permanente stressor met uiteindelijk desastreuze fysieke gevolgen. Dit hoofdstuk betreft een meer uitgebreide replicatie van een eerder uitgevoerd onderzoek. Uit dit onderzoek bleek dat meer stressoren en piekeren overdag een verhoogde hartactiviteit overdag en tijdens de slaap veroorzaakten, en dat piekeren verantwoordelijk was voor de effecten van de stressoren. Deze resultaten konden echter niet gerepliceerd worden, wellicht omdat in de huidige groep minder stressoren werden meegemaakt en minder werd gepiekerd dan in het vorige onderzoek. Wel vonden we dat de 'habituele' neiging tot meer en intensiever piekeren (de 'pieker-persoonlijkheid') gerelateerd was met verhoogde hartactiviteit gedurende de dag en tijdens de slaap, en wij benadrukken derhalve het belang deze neiging te betrekken in vervolgonderzoek. Tevens lijkt ook de bevinding dat er verlengde fysiologische effecten gedurende de slaap zijn te wijzen op het bestaan van een onbewuste vorm van cognitief persevereren: in de slaap piekert men immers niet bewust.

Tot slot worden in hoofdstuk 7 de belangrijkste bevindingen van dit proefschrift samengevat, geïntegreerd en besproken en komen onvermijdelijk ook diverse beperkingen aan de orde. We concluderen dat de hierboven genoemde resultaten aangeven dat perseveratieve cognitie, d.w.z. de 'mentale verbeelding' van eerder meegemaakte en in de toekomst gevreesde stressvolle gebeurtenissen en situaties, een belangrijke factor is in het *prolonged activation model*. Het verklaart niet alle verlengde fysiologische effecten van stressoren, maar heeft daarentegen zelf een verlengd fysiologisch effect, dat zelfs langer lijkt dan dat van stressoren. Deze vondst en de effecten van 'piekergeneigdheid' op hartactiviteit gedurende de slaap suggereren dat onderzoek in de toekomst gericht zou moeten worden op de rol van onbewuste perseveratieve cognitie.

Dankwoord

Eindelijk! Het allerallerlaatste stukje… Weliswaar staat alleen mijn naam op de kaft; zonder onderstaande mensen (en dingen) was het me niet gelukt:

In de eerste plaats ben ik de docenten zeer erkentelijk voor hun bijdrage. Ondanks drukke lesroosters en schoolactiviteiten waren jullie enthousiast bereid deel te nemen aan het onderzoek en hebben jullie op bewonderenswaardige wijze geruime tijd de piepende kastjes onder de kleding getolereerd. Dank voor de openheid, bereidwilligheid en hartelijkheid. Zonder jullie inzet was er geen proefschrift.

Rien, dank voor de vele multilevel inspanningen. Een afspraak bij jou gaat meestal niet door, maar uiteindelijk kreeg ik altijd veel meer terug dan dat waar ik je voor nodig had. Het vermogen je in te leven in een probleem waar je niet bekend mee bent, daar een passende analyse voor te vinden, die ook in mooi Engels te verwoorden, je warme persoonlijkheid en oneindige interesse, voor dat alles ben ik je zeer erkentelijk.

Bob Lops van het Empowerment Center; dank voor het geven van de groepssessie. Ik heb ons contact ervaren als bijzonder en wens je succes met het Center.

Studenten Ante Lemkes, Bernadette Rouppe van der Voort, Marije de Bruin en Rogier Poels: jullie inzet, enthousiasme en doorzettingsvermogen vooral tijdens die vroege uurtjes en tijdens het labelen, heb ik enorm gewaardeerd. Jullie werk aan de dataverzameling en -verwerking heeft me een hoop vertraging gescheeld en jullie sprankelende aanwezigheid maakte het trajekt makkelijker vol te houden. Een ieder wens ik het allerbeste met wat je verder gaat doen.

(ex) Collega's van KLIG: jullie aanwezigheid was verkwikkend! In het bijzonder die van Kate, Ismay, Sandra, Geeske, Sasja, mede-piekeraar Bart, Pepijn, Maya en de mensen van de *ondergang*. Dank Pauline voor je ondersteuning bij de laatste loodjes en dank je Elsbeth voor alle keren dat je me uit de brand hebt geholpen.

Dank aan al mijn uitlaatkleppen: melkklopper en bijbehorende koffie, chocola in elke vorm/kleur en de 5 kilo Tikkel verpakkingen van ene Dhr. de Feijter. Voor het tegengaan van de vrij directe negatieve gevolgen van het samenspel van die factoren veel dank aan Marleen, voornamelijk voor de klappen die ik je mocht geven. Door die wekelijkse sessies zijn de cijfers van slachtoffers door zinloos geweld niet nodeloos gestegen. En Massie, helaas geblesseerd, dank voor de zondagochtenden in het Bos en je onvoorwaardelijke steun.

Collega's van Emotional Brain: dank Adriaan voor die afgelopen 2 jaar. Bo, Henk-Jan, Sjaak, Ildiko en eerder Lyna; jullie zijn een fijn team en boden een goede afleiding na avonden vol proefschrift-werk. Dank voor jullie openheid en vrolijkheid. Ildiko, wat ga ik onze samenwerking missen, ze was van veel te korte duur. De andere EB-ers: het was een groot plezier in jullie nabijheid te vertoeven**.** Brenda, ik vergeet onze gesprekken niet; Els volgend jaar weer Dam tot Dam; eend-collega's wat hebben we gelachen; eerste verdieping achter de deur dank voor jullie vieze praatjes; eerste verdieping rechtdoor voor de dropjes, Wadi voor de misverstanden, en niet te vergeten Jos voor je fratsen…

Lieve Wendelien en Anne, met recht zijn jullie mijn paranimfen en ik ben trots dat ik zulke keien naast me heb staan. Anne, maatje van begin tot eind, jij "koor"bal die geen "koor"bal bleek maar een prachtig mooi mens en de beste kamergenoot die ik me kon wensen. Tenminste zo leek het, want "koor"bal Wendelien, het is bijna een wonder dat jij vrijwel naadloos kon aansluiten en zelfs heel goed van pas kwam om in dat kamergenootschap een nuchtere, stimulerende balans te creëren. Ik heb van jullie genoten; dank voor het bijzondere contact waardoor we lief en leed konden delen. Mede door jullie onschatbare mentale steun is dit proefschrift geen poepschrift geworden maar een fantasthesis!

Dank aan alle dierbaren en familie: Bassie – wie kan nou niet van jou houden?- Boezoek en lieve Arlène, Hans en Jannie de Graaf, voor jullie lieve en onvervangbare support rond de kinderen, Erik, Inge, Myrthe en Mike (ons heerlijk zondagochtend gezelschap), Katja, Angelique, Mariska, Alexandra en Ankie (onze relatie is een zeer bijzondere maar hij is onvoorwaardelijk en ik ben daar trots op), Fried, Frederique en Julius (kunnen we ook op vakantie zonder chips en rosé?), verwaarloosde Mylou en Caroline (ik denk nog steeds dat ik terug kom) en Babette (omdat een gesprek met jou me altijd veel motivatie brengt). Mama, voor de correcties in schrift, voor het prachtige voorblad, maar vooral voor de inspirerende persoon die je bent (en ik maar denken dat oma er eentje was). Lang Leve onze internetverbinding… Liefs!

Wilko, dank u voor die bloemen!!! Maar bovenal voor je warme liefde, oneindige support, je geduld, je relativeringsvermogen, voor de geweldige vader die je bent en zoveel meer. Ik ben er trots op dat we het leven samen beleven! Juriaan en Lauren, jullie zijn het mooiste wat me in jaren is overkomen en maken voor mij van iedere dag een FEEST!

Curriculum Vitae

Suzanne Pieper was born on July 24th 1977, a sunny Sunday in Paramaribo, Suriname. She completed her secondary education at the Barlaeus Gymnasium in Amsterdam in 1995. From 1995 until 2000, she studied Psychology at the Vrije Universiteit in Amsterdam and graduated in physiological psychology. During the last year of her studies, she worked as a research assistant for the Netherlands Twin Register. She received a scholarship from the Asthma Fund to perform research on the genetic and environmental factors influencing the relation between asthma and depression at the Institute for Behavioral Genetics (Boulder, Colorado, USA). In December 2000, she started working on the present thesis as a PhD student at the department of Clinical and Health Psychology at Leiden University. Since August 2006 she was employed as a scientific researcher at Emotional Brain, Almere, and co-built a knowledge system containing scientific knowledge on various psychophysiological diseases. She has recently become a postdoctoral researcher at the Centre for Child and Family Studies at Leiden University.