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Endocrine stress responses in critical care nurses : a possible relation to job turnover?

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Abstract: Beide Studien, die den Kern dieser Dissertation bilden, beschäftigen sich mit der Messung der Cortisolkonzentration im Speichel von Menschen am Arbeitsplatz und damit verbundenen Phänomenen. Die Konzentration des ungebundenen Cortisols im Speichel zeigt normalerweise einen Anstieg beim Erwachen, gefolgt von einem kontinuierlichen Abfall über den Tag hinweg. Das Fehlen dieses Musters, also abgeflachte Cortisolkurven wurden bisher außer bei klinisch auffälligen Personengruppen nur in Verbindung mit Arbeitslosigkeit (Ockenfels 1995), einer guten Beziehungsqualität zwischen Müttern und ihren Kindern (Adam 2001) und erhöhtem Arbeitsstress (Caplan 1979) gefunden. Verschiedene Studien haben Personen mit flacher Cortisolkurve identifiziert (Smyth 1997; Stone 2001), ohne dieses Phänomen jedoch erklären zu können. Die erste der beiden Studien hatte zum Ziel, diese Befunde zu replizieren und mit Hilfe moderner Multilevel-Modelle (Rasbash 2000) zu analysieren. Insgesamt wurden 3806 Speichelproben von 123 Ärtzten und Krankenschwestern während Früh-, Spät- und Nachtschichten in einer Abteilung für tertiäre pediatrische Intensivpflege jeweils im 2-Stunden-Rhythmus gesammelt. Die einfache statistische Modellierung der Daten, die auch von den Studien verwendet wurde, die über das Auftreten flacher Cortisolkurven berichteten, bestätigte die bisherigen Befunde: 12% aller Arbeitsschichten wiesen flache Cortisolkurven auf, und 10% aller Individuen zeigten intraindividuell gemittelte flache Kurven. Die Unterschiede auf Ebene der Individuen blieben jedoch nicht länger signifikant, nachdem das Multilevel-Modell um weitere erklärende Variablen, wie z. B. Geschlecht und Aufwachzeit, ergänzt wurde. Diese Ergebnisse weisen darauf hin, das die Cortisolausschüttung im Tagesverlauf einem stabilen Muster folgt, das interindividuell sehr stabil ist. "Flache" Kurven können auf die Variabilität innerhalb der Tagesverläufe eines Individuums oder auf die Variabilität innerhalb der Speichelproben zurückgeführt werden. Die zweite Studie beschäftigte sich mit stressbedingter Cortisolausschüttung. Es sollte überprüft werden, ob die Wahrnehmung von akutem Stress oder endokriner Stressreaktionen den Verbleib von Intensivpflegeschwestern in ihrem Job beeinflussen. Hohe Fluktuation des Personals und die Schwierigkeit, erfahrende Krankenschwestern zu halten, stellt weltweit ein großes Problem für Intensivpflegeabteilungen dar. Als Ursache wird u. a. die permanente Einwirkung von Stress und das dadurch begünstigte Auftreten eines Burnouts gesehen. Verlaufsstudien, die die akut gemessene Stresswahrnehmung mit endokrinen Stressindikatoren verbinden sind rar. In der vorliegenden Studie wurden die Arbeitschichten von 112 qualifizierte Krankenschwestern wurden zu Studienbeginn aufgezeichnet. Als Verbleib definierten wir die Zeit, die seit Studienbeginn bis zum Verlassen des Jobs vergangen war. Die Beobachtungszeit betrug 4,5 Jahre. Als Stressmaße bei Kohorteneintritt wurden 3 verschieden Indikatoren erhoben: 1) die Häufigkeit endokriner Stressreaktionen (Erhöhung der Speichelcortisolkonzentration um mindestens 50% in Bezug auf die Baseline; 2) Mit jeder Speichelprobe wurde auch die subjektive Wahrnehmung des akuten Stresses erfasst; 3) Die Arbeitsbedingungen wurden über einen Fragebogen zu Studienbeginn und mit einem Fragebogen zum Ende jeder Schicht erhoben. Krankenschwestern, deren Häufigkeit endokriner Reaktionen unterhalb des Medians ($< 12.8\%$ aller Proben) lag, verließen ihre Abteilung früher ($p = 0.06$). Zwischen dem Verbleib und der subjektiven Stresswahrnehmung konnte kein Zusammenhang festgestellt werden. Krankenschwestern, deren Beurteilung ihrer Arbeitsbedingungen für den kombinierten Faktor Teamklima, Führungsstil und Arbeitszufriedenheit im untersten Terzil lag, verließen ihre Abteilung signifikant früher als die anderen ($p = 0.03$). The thesis consists of two papers dealing with the measurement of salivary cortisol levels of people at work and several related phenomena. The concentration of free salivary cortisol shows an awakening increase with subsequent decline throughout the day. The absence of this pattern with "flattened" slopes have been observed within non-clinical groups in connection with unemployness (Ockenfels 1995), a good relationship functioning (Adam 2001) and high levels of work stress (Caplan 1979). Several studies have identified individuals with flattened cortisol slopes (Smyth 1997; Stone 2001), without being able to explain this phenomenon. The goal of the first study was designed to replicate these findings using advanced multilevel statistical models (Rasbash 2000). 3806 probes from 123 physicians and nurses during early, late and nightshifts in a tertiary pediatric intensive care unit have been collected at two-hourly intervals. The first model, used by the earlier studies reporting flattened cortisol slope, confirmed their findings: 12% of the shifts showed flattened slopes, and 10% of all individuals had flattened averaged slopes. In the multilevel model, slope terms no longer retained significant between subject variance, after entering appropriate additional explanatory variables such as gender, awakening time. These data suggest that circadian cortisol secretion follows a stable pattern across individuals. "Flattened" slopes arise from between day variance within individuals or from between-samples variance. The second paper explores stress-related cortisol levels. We tried to elucidate whether acute stress perception or endocrine stress reactions are related to retention of critical care nurses. High turnover rates of staff and failure to retain experienced nurses is a major concern for critical care units worldwide. Part of this problem has been attributed to critical care nurses' consistent exposure to stress and ensuing burnout. Empirical data that prospectively relate acutely measured stress perception or endocrine stress reactions to retention are scarce. The working shifts of 112 qualified nurses were scheduled during the cohort entry period. Retention was defined as the time elapsing from cohort entry until leaving the job. Observation time was 4.5 years. Exposure determined at cohort entry was a) the frequency of endocrine stress responses based on two- hourly measurement of salivary cortisol (response defined as increase by at least 50% over baseline); b) the subjective perception of acute stress recorded with each sample; and c) work characteristics as assessed by baseline- and end-of-shift questionnaires. Nurses with below median frequency ($< 12.8\%$ of all samples) tended to leave the unit earlier ($p = 0.06$). No association with retention was found for subjective stress perception. Nurses scoring in the lowest tercile of a factor consisting of perceived team climate, leadership style and job satisfaction left the unit significantly earlier ($p = 0.03$).

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1. Introduction

Turnover rates and low job retention have become a major problem of hospitals in the industrialized world. The difficulty of retaining experienced nurses often leads to shortage of staff, requiring hospitals to close otherwise available beds. An area facing particular difficulties to recruit and to retain qualified staff are critical care units. For more than two decades it has been known that high turnover rates are not only costly but may result in decreased standards of patient care (Price 1981).

Many investigators have addressed potential causes that could drive hospital staff out of their jobs (Yin 2002) (Boyle 1999) (Irvine 1997). A range of organizational factors influencing the intended turnover have been identified. Amongst these are management style, instrumental communication (Boyle 1999) (Leveck 1996) (Yin 2002), group cohesion and the organisation of shift work (Dembicki 1989). In contrast, efforts to promote higher job satisfaction (Boyle 1999) (Leveck 1996) (Shader 2001) and a good climate have been shown to be important factors for retaining staff. A recent systematic review investigating the relationship of reported work stress and retention reported heterogenous effects (Yin 2002). While "stress" appeared to impede the quality of care it did not affect retention (Leveck 1996). A significant but moderate effect was shown by (Shelledy 1992), who stated that high job strain was linked to an increased risk of burnout, which in turn related absenteeism and intention to leave the job and the professional field.

Several major caveats, however, pertain to the existing literature on the relation between job strain and retention in nursing staff. First, studies invariably assessed the intention to quit the job – by means of a cross-sectional study - instead of determining observed turnover. Although intended turnover is a reasonable predictor of actual turnover behavior, prediction quality shows high variability in the related studies particular in relation to long term retention (Steel 1984). Thus, a weak but clinically relevant possible relation between job strain and retention may be blurred by measurement error, or falsely assumed. Second, in nearly all studies stress is assessed by surveys and retrospective investigation and not by acute measurement. This opens the possibility of recall or ascertainment bias – i.e. that some work characteristics are retrospectively attributed to stress, which in reality relate to other work factors. Thus, studies are warranted that relate acutely and repetitively measured subjective stress levels to the real turnover behaviour observed by means of a longitudinal study. Third, it is unknown, whether the subjective stress experience or the biological stress response may account for any relation between job strain and turnover. When investigating biological stress responses in field studies, one possible approach is to study salivary cortisol secretions. Repeated measurements of salivary cortisol during the day provide for assessment of endocrine responses to acute stressors. They also allow assessing of the circadian cortisol secretion – one of the biological responses potentially affected by high levels of job strain.

Two of the aforementioned types of data, namely acute subjective stress assessment and repetitive cortisol assessments, were obtained in a 1997/8 study on critical care nurses in a large pediatric and neonatal tertiary intensive care unit. The original study involved 123 participants from whom nearly 4000 samples were collected. The present investigation adds the five-year follow-up as to job turnover of the original participants. The assessment of cortisol concentrations throughout the working day opens new possibilities in work stress research. The present data allow to investigate a possible relation between the frequency of endocrine stress reactions experienced during a representative work period and the variable “time until leaving the job”. In addition individual characteristics of diurnal cortisol secretion and their relation to turnover can be investigated.

The interpersonal variation in diurnal cortisol secretions has recently been underscored by a re-analysis of several field studies (Smyth 1997) (Stone 2001). While the majority of participants in these studies showed the expected diurnal cortisol secretion with a morning peak after awakening and a steady decline during the day, some individuals showed a flattened cycle with low awakening levels and absent or very moderate decline throughout the day. Previously, observations of a missing diurnal cycle had been reported from clinical populations, e.g. patients with depression (Carroll 1976), fibromyalgia (Crofford 1994) (McCain 1989), chronic fatigue syndrome (MacHale 1998) or severe rheumatoid arthritis (Neeck 1990). Most non-clinical studies, however, failed to find significant associations between personality variables and change in cortisol levels across the day (Schommer 1999) (Smyth 1997). The following exemptions related diurnal cortisol secretion to non-biological data: Ockenfels reported a relation to unemployness (Ockenfels 1995) and Adam a relation to good relationship functioning (Adam 2001). An early study in the field reported flattened diurnal cycles among individuals experiencing high levels of work stress (Caplan 1979). Additionally, lowered morning levels were found in people with burnout (Pruessner 1999). Following the reasoning by Pruessner and coworkers, we hypothesized that high levels of work stress and impending burnout in critical care nurses might lead to flattened diurnal cortisol cycles. Flattened diurnal cortisol cycles in turn might be a risk factor for early quitting of the job.

The present thesis, therefore, requires two separate tasks: first to ascertain the nature of diurnal cortisol secretion in nurses, second to elucidate the relation between job characteristics, repeated subjective and endocrine stress measurements and job retention.

The first paper following the introduction addresses diurnal cortisol secretion. The objective of this paper is to identify an individual's characteristic slope describing the decline of cortisol levels throughout the day. This analysis requires assessing the heterogeneity of observed values by means of multilevel analysis (samples nested within days nested within subjects). In this paper samples not identified as endocrine stress response (about 88% of all samples) are considered. The aim of the first paper was to replicate the findings of individuals with absent or flattened cycle by Stone and coworkers (Stone 2001), in order to use the individuals slope or the presence / absence of flattened cycles as an additional predictor variable possibly relating to retention. The second paper employs explorative survival analysis to relate frequency of subjective stress reactions, frequency of endocrine stress reactions, diurnal characteristics and reported job characteristics to the time until leaving the job.

The presentation of the thesis is organized as follows. After the introduction, definitions of stress and stress in work environments are discussed (Chapter 1.2), including the description of health care work environments. Then, a review of the literature on turnover in the health care sector is provided (Chapter 1.3), followed by a review of the effects on turnover (Chapter 1.4). The next section (1.5) summarizes the nature of the human cortisol metabolism (1.5.1), the literature on the effect of environmental stressors on cortisol levels (1.5.2) and the findings of irregular cortisol patterns in clinical and non-clinical populations (1.5.3). In section 1.6, the design and methods of the underlying study are explained in detail. Additional methods used in the two papers, including multilevel analysis and survival analysis are introduced. Explaining the methods was considered to be important, because of the brevity of the methods section in the presented papers, which were adapted to the requirements of the journals considered for submission.

Chapter 2 presents the first paper, which investigates the intra- and interindividual differences in the diurnal cortisol cycle. Chapter 3 provides the findings on the factors related to job turnover of pediatric critical care nurses. The final chapter summarizes the empirical data and discusses their clinical implications and the remaining questions for future research.

1.1 Human Stress Research

Since Hans Seyle published the first investigations on stress responses in 1936 (Seyle 1936), many definitions and models have been suggested. Scientific discourse as well as lay language knows several definitions of stress as well as number of events that can possibly lead to the experience of stress. Some may confess to being “stressed” when taking an examination, when having to deal with a frustrating work situation, or when experiencing difficulties in their personal relationships. However, individuals may differ as to the perception of the same stressful situation: Some view it as harmful or threatening, others as a challenge. In the following, the concept of “stress” is reviewed to covers those definitions and models that are relevant for the present study.

Characterizing the nature of a stress response, Levine and Ursin (1991) defined four main but distinct characteristics of "stress" (Levine 1991). These are*: 1. The stress stimuli or stressors; 2. The stress experience; 3. The stress response; and 4. The feedback from the stress response*. Unfortunately, many authors using the term “stress” fail to clarify, which of these stages or characteristics is being addressed. Often, the term stress is used for all four categories, sometimes indiscriminately, hereby adding to the confusion around the concept.

More than three decades ago, Lazarus proposed a comprehensive model of stress and coping with stressors (Lazarus 1966). Lazarus regards stress as a state arising from a mismatch between a threat and the resources available to the individual. This general model considers stress being part of a sequential process. The first step in this sequence is the individual’s appraisal of the objective environmental condition (i.e., stressors) as either having no adaptive significance or as being stressful (i.e. presenting a potential threat, danger, change or challenge to one’s well-being or survival). If the individual perceives the environmental condition as stressful, as a result of this appraisal a series of stress-response mechanisms will be set in motion. These comprise integrated *physiological, psychological and behavioral* efforts to adapt to the environmental situation. According to Lazarus, the subjective cognitive appraisal of a situation as challenge, threat harm, or loss – the so called primary appraisal – mediates between the stressor and the individual's stress reaction. The perception of environmental demands, personality characteristics, the individual prior experiences and the subjective evaluation of the person's available resources – the so called secondary appraisal – determine how an individual will cope with the stressor. The theory states that the interaction between a person and his or her environment is dynamic, mutually reciprocal, and bi-directional (Folkman 1985). The term coping includes the cognitive, emotional and behavioral efforts by an individual to master specific external or internal demands.

Lazarus concept omits another perspective on stress responses, which relates to the temporal relation of stress reaction and stressor. Several authors have suggested to differentiate between short-term and long-term stress reactions (Udris 1999) (McEwen 1998b) (Greif 1991a) (Baumann 1998).

1.1.1. Four stages of the stress reaction

The stress stimuli

Whether a stimulus is considered as pleasant or as threatening depends on the individual's prior experience of similar situations, and the predicted expectations of the outcome. Some stimuli would be unanimously regarded as negative, while other stimuli will be perceived as positive by some individuals and as negative by others. For example, students of a class may perceive the same maths exam situation differentially, and this perception may be related to individual states, traits, prior experiences and objective external threats (e.g. scoring a poor mark possibly jeopardizing promotion to the next grade).

The stress appraisal

Given that a particular stimulus, or set of stimuli, is perceived threatening or negative, humans will report this as "stress" (they may chose other wordings, i.e. “Belastung” “Angst”). While many will confess to being “stressed” when interviewed, it is quite challenging to operationalize assessment of this subjective “stress”. Most often the term is used to describe subjective negative experiences, like time pressure and conflicts. The perception of “stress” may increase wakefulness. The individual variance in stress perception is considerable, and the use of the term inconsistent, even within an individual.

The stress response

The first response to a perceived stress stimulus is a general, non-specific response, which at first does not seem to differ from a general, non-specific increase in arousal or wakefulness. However, depending on the degree of perceived potential threat or danger additional neuroendocrine circuits become activated that extent well beyond a simple arousal reaction. Arousal in this context is understood as the brain process that increases the activity of the central nervous system to a higher level. The response is associated with increased brain metabolism and turnover of transmitters, increased muscle tone, specific behaviours, and – in case of a tress response – with vegetative, endocrine, and immunological changes.

The feedback from the stress response

Finally, there is also a certain feedback loop from the peripheral changes back to the brain, the "physical" experience of the stress response. In emotion theory the phenomenon is known as the James-Lange aspect of an emotional experience. A person may sense that he or she is stressed by appreciating an increase in muscles, the heart beating rapidly, and the palms are sweating. However, most of the changes occurring during a stress response escape awareness. While several areas of the brain are quite susceptible to cortisol by means of corticoid-receptors, there is no awareness on the endocrine changes or on other physiological adaptations such as increases in blood pressure or increase contractility.

1.1.2. Psychological, physiological and behavioural stress responses

Psychological stress response

The psychological stress responses can be further categorized into the following two dimensions: 1) subjective experience, for example feelings of distress, anger, anxiety and 2) cognitive function, for example alterations in informational processing and memory (Steptoe 2000) (Chrousos 1998). Under stress, the efficient regulation of action becomes deranged and the successful solution of new problems may prove insurmountable, while the error rate and the danger of accidents increases (Ostell 1991) (Green 1985).

The long term effects of stress include dissatisfaction, resignation, psychosocial disorders and impairments, e.g., depression and reduced self-confidence (Baumann 1998) (Schwarzer 1997). A specific stress reaction is the burnout syndrome, which is characterized by emotional exhaustion, depersonalization and a reduced feeling of self-efficacy (Maslach 2001).

Physiological stress response

Stress leads to an activation of the autonomous nervous system, the immune system and - most important with regard to the present thesis - the endocrine system, particularly hormone release from the hypothalamus-pituitary-adrenal axis (HPA axis) (McEwen 2000) (Birbaumer 1990). Specialized areas in the brain associated with the human stress response include parts of the neocortex, limbic system and brain stem. There are two major systems involved upon eliciting a stress response. The rapid system involves the vegetative nervous system and is characterized by rapid signalling. Activation of this system results in release of catecholamines as the second messengers. *Norepinephrine* (NEp) is the main neurotransmitter in responsible for the heightened arousal that follows exposure to a stressor. Stimulation of this system results in increased heart rate, blood pressure, perspiration, muscle tone and cell metabolism. The half-life time of norepinephrine released into the circulation is only a few minutes. The second – slower – pathway involves activation of nerve cells in the hypothalamus, with the capability to produce hormone releasing factors. Stressful situations stimulate these areas of the hypothalamus resulting in the release of thyroid stimulating hormone, prolactin and beta-endorphins from the pituitary gland. Beta-endorphins are naturally occurring opioids, which elevate one's mood, decrease sensitivity to pain and have been linked to suppression of the immune system. Stimulation of the hypothalamus, in particular of the paraventricular nucleus, also results in the secretion of corticotrophin releasing hormone (CRH). CRH in turn stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH) which is released into the circulation (Ehlert 2000) (Kirschbaum 1999b). ACTH release stimulates the adrenal cortex to secrete cortisol. Cortisol partakes in regulation of the metabolism of carbohydrates, proteins and fat. Hereby, cortisol increases the available energy in the organism and helps to maintain homeostasis. High doses of cortisol have inflammatory as well as anti-allergic functions. This particular propensity of the glucocorticoids gave rise to the view that cortisol may prevent other stress-induced changes from over-shooting, thus helping the organism to re-establish homeostasis (Munck 1984) (Wilckens 1997). The changes in cortisol secretion in response to a stressor are outlined in more detail in chapter 1.5.2.

Among physiological long-term reactions on stress, there are psychosomatic complaints and cardiovascular disease. The process by which prior stress experiences may have long-lasting effects on basal stress-system functioning and also on the functioning of other body systems has been referred to as “allostatic load” (McEwen 1998b). While short-term stress system activation helps to preserve an organism’s stability by preparing it for response to threat (“allostasis”), the conceptual framework of “allostatic load” states that excessive activation of these allostatis mechanisms may in the long term be damaging (“allostatic load”). Chronic stress exposure has been associated with excess activity of the stress system, including a weakened HPA negative feedback mechanism and chronically heightened levels of glucocorticoids (Sapolsky 1996). Chronic stress has also been associated with low basal levels of cortisol (hypocortisolism) and increased risk for autoimmune and inflammatory type disorders due to a weakened ability to contain immunological response (Heim 2000).

Behavioral stress response

Stress also may alter the individual’s behavior. As a consequence of deranged action regulation, fluctuation of performance, with higher error rate and increased danger of accidents can be observed (Ostell 1991) (Green 1985). Other short-term reactions on stress are aggression and withdrawal behaviour. Other stress related reactions to stress include increased tobacco consumption, altered alcohol intake and changes in diet.

(Baumann 1998) (Schwarzer 1997) Finally, individuals may attempt to escape the stressful situation. With respect to the latter, we view job turnover as one possible “behaviour” to escape work-related stress. This long-term stress-response will be further discussed in chapter 1.3.

1.1.3. Summary and implications for the present research

Four characteristics of "stress" can be defined: the stress stimuli, the stress experience, the stress response and the feedback from the stress response. Human stress-response mechanisms comprise of integrated physiological, psychological and behavioral efforts to adapt to the environmental demands. Since short-term and long-term reactions can be differentiated, the study variables in the present work should be categorized according to the reported definitions. The present study has to account for measurement of the psychological experience of stress, for biological indicators of the physiological short-term stress reaction (salivary cortisol level) and for behavioral long-term stress reactions (burnout and turnover behavior).

Table 1.1. Stress reactions in adaptation to stress (Udris 1999) (McEwen 1998b) (Greif 1991a) (Baumann 1998):

Stress reactions	Short term	Medium to long term	Long term successions
Physiological	▪ alterations in autonomic nervous system (increased pulse rate and blood pressure; more adrenaline secretion; higher muscle tension); ▪ alterations in neuroendocrine systems (activation of the HPA axis); ▪ alterations of immune functions	▪ psychosomatic complaints; ▪ cardiovascular disease	▪ atrophy
Psychological	▪ strain; ▪ disappointment; ▪ anger; ▪ anxiety; ▪ exhaustion; ▪ feeling of monotony	▪ dissatisfaction; resignation; ▪ depression; ▪ burnout; ▪ anticipatory anxiety; ▪ not being able to relax after work; ▪ exhaustion	
Behavioral	Individual: ▪ fluctuation in performance; errors; ▪ to omit controlling actions Social: ▪ conflicts; ▪ quarrels; ▪ aggression, withdrawal	Individual: ▪ higher consumption of nicotine, alcohol and medicaments Social: ▪ higher absence rate; ▪ turnover; ▪ passive spare time	

1.2 Stress in work environments

Over the past decade, occupational health psychology has made important progress in delineating the effects of work-related stress on the human organism and to conceptualize the characteristics of work related stress (Greif 1991b) (Karasek 1990). Different theories about stress and the interplay of job related stressors and ressources have been formulated and examined. Pathogenetic, i.e. health impairing conditions, as well as salutogenic, health improving or health constituting conditions, have been focused (Wilckins 1998) (Shigemi 1997) (Kirkcaldy 1995) (Greif 1991a) (Antonovsky 1987) (Antonovsky 1979) (Udris 1991, 1992).

1.2.1. Potential work stressors

Stress research at the workplace deals with the adaptation of the worker to the job's demands. The job-related factors that have been found to influence stress include factors such as heavy workload, poor work conditions, time pressures, unclear work roles, conflict in the workplace, and the emotional demands of work. A widely accepted classification of job-related stressors distinguishes five categories: 1) stressors in the task like excessive work, 2) stressors in the physical environment like noise, 3) time-involving stressors like working time and shift work, 4) social stressors like conflicts, mobbing and 5) specific stressors like mental dysfunction (Ducki 2000) (Udris 1999) (Mohr 1997) (Schwarzer 1997).

It has also been suggested to describe distinct levels of work stressors on the macro-, meso- and micro-level (Ducki 2000) (Semmer 1997). The connections between work and other life areas are located on the macro-level. Organizational burdens like information strategies, payment, working time, belong to the meso-level. The actual task and its regulatory status constitute the micro-level. In the present study, we focussed on the micro- and meso-level of work in a paediatric intensive care unit.

1.2.2. Work stress models

Besides the identification of work related stressors, a multitude of models have been proposed to explain the mechanisms and causes of work-related stress. Organizational stress researchers attempted to apply the cognitive transactional stress model to working situations (Antoni 1989) (McGrath 1981). For example, McGrath follows Lazarus (Lazarus 1991) postulating that stress occurs if a person believes that she or he has insufficient resources to deal with the demands of the environment, particularly if it's very important for the person to meet these demands (McGrath 1981). McGrath suggests that actions in organizations could be seen as interactions between the material/technical system, the social/interpersonal system and the organization member as a personal system (McGrath 1981). Based on the assumption that stress could originate from each of these systems, he differentiates six classes of stress: 1) job-related stress, which occurs from the interaction between individual and material system, for example task-difficulty; 2) role-related stress that arises from the interaction between an individual and the social environment, for example conflicting roles; 3) stress resulting from the behavioural setting (i. e. interaction problems between the material and the social environment like crowding); 4) stress from material environment, for example coldness; 5) stress from the social environment, for example dissent; and 6) stress arising in the individual, for example anxiety, apperception style.

Another widely employed model was postulated by Karasek and became known as the demand-control model (Karasek 1990). The model states that stress-related risk to physical and mental health from stress occurs in workers facing high psychological workload demands combined with low control or decision latitude in meeting those demands. As an example of this constellation, the profession of nursing is mentioned. This holds particularly true for nurses in the pediatric intensive care unit, who are dealing with a critically ill child, often threatened to die or to suffer from major handicap as a consequence from the present condition. The psychological demand on the nurses is paralleled by restricted decision latitude: the doctors, not the nurses bear the final latitude over the relevant treatment decisions.. The demand/control model has proved valuable in understanding the work characteristics associated with coronary heart disease (Schnall 1994), hypertension (Schwartz 1996), mental (Stansfeld 1995), quality of life (Lerner 1994), and other outcomes (van der Doef 1992).

1.2.3. Burnout as a work-related stress response

A specific stress reaction is the burnout syndrome, which is characterized by emotional exhaustion, depersonalization and a reduced feeling of self-efficacy (Maslach 2001). The so-called "professional burnout syndrome" includes symptoms such as cynism and reduced personal accomplishments (Weber 2000), headaches and disturbed sleep patterns (Beer 1992), non-specific pain, reduced attention span, feelings of meaninglessness, apathy, or detachment from work (Misra 1993) (Constantini 1997). Burnout has been frequently observed in caregivers, e.g., social service employees, nurses, or hospital staff (Kilfedder 2001) (Garrett 2001) (Edwards 2000) (Maslach 1996). Teachers showing inappropriate attitudes and responses towards students, loss of idealism, and a desire to change or quit the teaching profession often suffer from burnout too (Pruessner 1999).

Burnout leads to lower productivity and effectiveness at work. Of the three burnout components, exhaustion is closest related to symptoms of stress. Therefore, exhaustion may be more predictive of stress-related health outcomes, like headaches, chronic fatigue, gastrointestinal disorders, muscle tension, hypertension, sleep disturbances and substance abuse Maslach & Leitner 2000 (Maslach 1996) (Melamed 1999) (Shoptaw 1996) (Moss 1989).

1.2.4. Work stress in a health care environment

Work induced stress was reported to be highest in populations of fireworkers (Ehlert 2000), rescue workers (Aardal-Eriksson 1999), skyguides (Zeier 1996) and nurses (Fischer 2000a). Particularly in nursing, the incidence of burnout has shown to be high (Kilfedder 2001) (Garrett 2001) (Edwards 2000) (Maslach 1996). Suicide rate for female nurses in the USA was reported to be significantly higher than the national average (Munro 1998). Numbers of staff absent were above average in health care professions in Germany in 1997 and 1998, due to back pain and psychiatric diseases (DAK-BGW 2000). The study also showed that caregivers with high work induced stress had a higher risk to experience work accidents.

Three typical sources of stress in health care have been identified: 1) Workload according to organisation of work, like high time pressure, frequent disturbances, few information and overload. 2) Low task diversity und few decision latitude, 3) lack of support by supervisor or coworkers (DAK-GBW 2000). Researchers have identified three different sources of stress (Gray-Toft 1981a): the physical environment (work load), the psychological environment (death and dying; uncertainty concerning treatment; inadequate preparation of nurses; lack of support), and the social environment (conflict with physicians; conflict with nurses).

The burnout syndrome has been shown to be highly correlated with workload, time pressure, and role conflicts (Schaufeli 1998). Particularly, conflicts with physicians were highly associated with burnout (Watson 1996). Several studies indicated that blurring of critical care nurses' roles with that of doctors, and subsequent expansion in their skills and activities, covers potential sources of work stress (Ball 1997) (Harris 1994) (Hopkins 1996) (Rudy 1998). In general, collaboration between nurses and doctors turned out to be an important factor for nurses' job satisfaction and evaluation of work (Baggs 1992) (King 1994) (Last 1992). A comparison of 189 critical care nurses and 366 non-critical care nurses revealed that the latter perceived more autonomy. However, relationship with medical staff was more collaborative for critical care nurses and they perceived their jobs to have more value than non critical care nurses (Chaboyer 2001).

Another considerable source of work stress was found in the interaction with patient problems the (psychological, social, and/or physical). This interaction is believed to account for higher levels of chronic stress in human service workers (Maslach 1982). Inadequate preparation in dealing with the emotional needs of the patients and their families as well as death and dying are factors often reported by studies in this field (Watson 1996) (Bratt 2000). Emotional work demands as well as time and performance pressure are presumably high in critical care units, in particular in paediatric critical care (Fischer 2000b).

Stressors that were positively associated with burnout could were job strain, lack of social support, conflicts with other nurses, conflicts with physicians, presence of stressors related to private life, job insecurity, full-time vs. part-time status, low level of perceived job control, hierarchical level, death and dying of patients, feeling unprotected against occupational hazards (Stordeur 1999).

While the continuing emotional burdens linked to caregiving professions and social services are thought to play a pivotal role in the aetiology of this syndrome

(Dressendorfer 1992), leadership dimensions were not significantly related to burnout, once stressors were included in the regression model, explaining 22% of the variance in emotional exhaustion (Stordeur 2001).

1.2.5. Conclusions

Critical care units can be considered one of the most stressful work environments. According to the demand-control model (Karasek 1990), nurses face high psychological workload demands combined with low control or decision latitude in meeting those demands. This constellation is associated with a great risk to physical and mental health. Several studies have independently identified emotional demands and the collaboration with physicians as main sources of stress for nurses.

Prolonged periods of employee burnout have negative implications for the individual, for patients under their care, and for the effectiveness of the organisation and may lead to absenteeism and high job-turnover (Schaufeli 1998). This adds additional cost to critical care services (Song 1997). While there is an abundance of publications on health risks caused by work conditions, the link between work stress and physiological stress responses, in particular cortisol secretion, has not yet been fully elucidated (Steptoe 2000).

1.3 Turnover in health care professions

Employee turnover contributes to shortage of nurses at an organisational level (Price 1981). Turnover and high absence rates are costly and result in decreased standards of patient care (Price 1981). Additionally, they may cause increased pressure on those left on the job.

This chapter gives an overview of studies investigating the causes of turnover in health care units. According to the stress definitions in chapter 1.1, we suggest to view quitting the job as one possible behavioural reaction to long-term stress. However, there are multiple other reasons to quit a job, and it remains unknown to what extent work related stress contributes to the variance in job turnover rates.

1.3.1. Turnover intention

Alexander and colleagues (Alexander 1998) conducted a path model of intention to quit, turnover and associated variables in nurses working in psychiatric units of medical centers. Investigating a sample of 1106 registered nurses, licensed nursing practitioners and nurses' aides, the most significant predictor of turnover was shown to be turnover intention. Following their proposed attitude-decisional-behaviour sequence, six dimensions of job satisfaction, namely work hazards, professional growth opportunities, role clarity, workload, autonomy, relationship with coworkers were significant predictors of the intention to leave. Although the indirect prediction of turnover via the intention was proposed in the model, two dimensions, relationship with coworkers and job hazards, predicted turnover more directly. In other words, nursing personal may consider leaving the job without building long-term prior intention to do so.

The reported study is one of the few studies investigating overt turnover behaviour in nurses. Most studies investigating causes of turnover examine the intention to quit the job instead of turnover behaviour. Agreeing with Alexander and colleagues, a systematic review on the general relationship between intended and actual turnover, reported good prediction quality of intended turnover (r = 0.5). However, correlations ranged from 0.13 to 0.71, showing high variability in the studies analysed (Steel 1984). Other investigators found only moderate correlations between nurses' turnover intention and observed turnover behaviour (Irvine 1995).

In general, the strength of the association between the attitude and the behaviour of turnover varies between studies ((Gauci Borda 1997) Literature Review). Steele (Steel 1984) and Parasuraman (Parasuraman 1989) suggested that these differences are due to unmeasured variables moderating the relationship. Correlations may be influenced by the economic stability of a country (Steel 1984) and the opportunity for other employment (Gauci Borda 1997). However, the most influencing variable seems to be the time interval between measurement of intention and behaviour, since an increased time lag is associated with a decrease of strength of the association (Parasuraman 1989) (Steel 1984). In other words, asking nurses today about their intention to leave may not reflect actual turnover behaviour a year later. These points should kept in mind, when reading the following brief review of the existing literature - since most of the studies investigating effects on turnover in the health care sector actually use turnover intention as the dependent variable.

1.3.2. The role of job satisfaction

As mentioned above, job satisfaction plays an integral role in explaining turnover, with a stronger influence on the intention than the actual behaviour (Alexander 1998). Nurses with high job satisfaction are less likely to quit their job or to express the intention to do so (Leveck 1996) (Ito 2001) (Irvine 1995) (Boyle 1999).

Before demonstrating direct links between several aspects of job satisfaction and turnover intention, the nature of job satisfaction of nurses shall be discussed briefly. The most influential variables explaining of job satisfaction are job stress and nursing leadership (Bratt 2000). In a meta-analysis on 48 studies with a total of 15048 nurses, strong correlations of job satisfaction with stress (r = -0.609) and organisational commitment (r = 0.526) could be found (Blegen 1993). Further, job satisfaction has been shown to be correlated stronger with work content and work environment than with individual difference variables (Irvine 1995). Several aspects of job satisfaction with high prediction power on turnover behaviour are discussed in the following chapter.

1.4 Effects on turnover

Organisational factors identified to influence retention and turnover are a health centre’s reputation and standards, and the goodness-of-fit between the attitude and aims of staff and those of the organization (Cangelosi 1998) (Hatton 1993). An influence of the patient/nurse ratio was reported by Hatton and colleagues (1993). Compared to nurse/patient ratio and the center’s reputation and standards (Dembicki 1989), salary appeared to play a minor role (Hatton 1993). Opportunity for other employment and kinship responsibility affected the intent to stay in a model together with job satisfaction, which had the strongest influence (Gauci Borda 1997).

1.4.1. Management and turnover

According to the literature, turnover intentions are best predicted by the characteristics of management or leading style (Boyle 1999) (Bratt 2000) (Cartledge 2001) (Leveck

1996) (Hatton 1993). A decentralized management style and shift systems that retain flexibility are important factors for maintaining motivation of nurses (Cartledge 2001). Positive perception of organisational democracy was associated with decreased turnover (Hatton 1993). Promoting higher job variety and better staff development, higher schedule flexibility and rotation of work schedule and responsibility were also associated with positive effects (Hatton 1993) (Cangelosi 1998).

Boyle and colleagues (Boyle 1999) investigated 255 staff nurses in intensive care units at 4 urban hospitals. The investigators found that manager's position power and influence over work coordination were directly linked with intent to stay. Boyle and coworkers concluded that managers with leadership styles seeking and appreciating contributions from staff, promote a climate in which information is shared effectively. Such styles further promote decision making at the staff nurse level, exert position power, and influence coordination of work to provide a milieu that maintains a stable cadre of nurses. Several studies agree, that nurses which perceive a high level of autonomy stay longer on their jobs (Alexander 1998) (Ames 1992) (McCloskey 1987) (De Groot 1998). Finally, managers engaged in retaining nursing staff should recognize issues of concern to nurses and develop policies which make nurses feel valued (While 1998).

1.4.2. Social aspects and turnover

Support from other staff could be shown to have positive effects on job stress and job satisfaction and the retention of direct-care staff members in a residential facility for people with multiple disabilities (Hatton 1993). The finding that the correlation between lack of social support and actual turnover behavior was higher as compared to the correlation with turnover intention suggest that lack of support from coworkers is directly related to psychiatric nurses leaving the unit (Alexander 1998). Further factors that affect turnover are low group cohesion, which has been shown to predict increased anticipated turnover (Shader 2001). Group cohesion was also significantly related to turnover in the study reported above (Boyle 1999). Strong cohesion together with positive instrumental communication and high autonomy significantly reduced job stress and increased job satisfaction. Job satisfaction, in turn, was associated with the intent to stay (Boyle 1999).

1.4.3. Work stress and turnover

The description of potential stressors in health professions in chapter 1.2.4 is now extended by reviewing the literature on the relationship between stress experience and turnover. All identified studies share the survey-based assessment of recalled stress perception. Stress is defined as general distress, job strain, or evaluation of work load, death and dying, uncertainty concerning treatment, inadequate preparation of nurses, lack of support, conflict with physicians and conflict with nurses (Goldberg 1978) (Borill 1996) (Gray-Toft 1981a).

Several findings emerge from these studies. First, job stress has been shown influential in the explanation of job satisfaction (Bratt 2000) (Blegen 1993), which in turn, is positively linked with the intent to stay (Boyle 1999). Direct effects of experienced job stress enhancing turnover were reported by Consolvo (Consolvo 1979), Oates and colleagues (1995) and Yin (2000). The latter conducted a systematic review on 129 studies related to nursing turnover from 1978 to 1998 in Taiwanese hospitals. Job stress was among the strongest factors related to nurse's turnover intentions with an overall correlation of $r = 0.21$ (in other words job stress explained approximately 4% of the variance). Less directly, perceived job stress together with work satisfaction predicted anticipated turnover in a study by Shader (Shader 2001).

Validation of the widely accepted Nursing Stress Scale showed that scores correlated negatively with job satisfaction and positively with trait anxiety and turnover (Gray-Toft 1981b).

In contrast, there have been reports that job stress was linked to quality of care (Leveck 1996), but not to intended turnover.

An indirect influence of job stress on turnover was suggested by a study reporting that low job stress, together with increased job independence and job control, improved role clarity, and higher levels of job satisfaction, was associated with lower levels of burnout in respiratory care practitioners (RCPs). Burnout in turn was significantly associated with increase of absenteeism and intent to leave the job or the field (Shelledy 1992). An association between burnout and intended turnover was also found by other investigators (Schaufeli 1998).

The association between job stress and turnover is further supported by a study on schoolteachers. Individuals who experienced a high amount of chronic stress and already reported emotional exhaustion, were more likely to leave their job in the subsequent 12 months (Schwab 1986).

1.4.4. Personal variables and turnover

Several studies lend support the hypothesis that women have higher levels of organisational commitment (Mathieu 1990) (Riordan 1997) and are therefore less likely to express an intent to leave the job than men (Alexander 1998). For example, older nurses (Yang 1989) (De Groot 1998) who are married and who have a lower educational level (Yin 2002) are likely to be more satisfied and stay longer on their jobs.

1.4.5. Conclusion

The most relevant predictor of turnover behaviour is the intention to quit the job, but the prediction power varies across studies. In health care workers, job satisfaction, particularly satisfaction with leading style and coworker relationship, has shown to be the second best predictor followed by the amount of reported job stress. Intent to stay may act as a mediating variable between job satisfaction and turnover (Gauci Borda 1997).

However, and this are relevant implications for the present project, studies on the relationship between job stress and turnover suffer from certain limitations. Besides the operationalisation of turnover as the intent or anticipation, most studies use surveys to assess work-related stress. Answers to questionnaires, however, are prone to recall bias and may not relate to the actual degree of stress, that was directly experienced. In contrast to the assessment of stress on the meso-level, the present study will additionally investigate the effect of directly perceived job stress on a micro-level, according to the definitions reported in chapter 1.2.1 (Ducki 2000) (Semmer 1997). Researchers have confirmed that the reliance on self-report in the diagnosis of stress is a relevant problem (Cotton 1995) that needs to be addressed. There may also be a research induced bias as participants may expect themselves to experience stress in response to certain job characteristics, regardless of the actual stress perception or stress reaction in the situation (Barley 1991). Thus, self-report measures continues to be a major weakness in stress research (Cotton 1995).

Although work stress has been recognized to be major psychological influence on physical and mental health over recent decades, links between cortisol secretion and work stress have not yet been established (Steptoe 2000). One of the first large field studies of this kind was the nurses stress study (Fischer 2000a), which created the data-basis for the present investigation.

1.5 Cortisol secretion

1.5.1. Introduction

Cortisol is the main glucocorticoid hormone in humans produced by the hypothalamic–pituitary–adrenal (HPA) axis. It is secreted in the cortex of the adrenal glands, released both spontaneously (Van Cauter 1998) and in response to various biochemical agents and psychosocial stimuli. The release of cortisol is regulated by the corticotropin releasing hormone (CRH) from the hypothalamus, which elicits release of the adrenocorticotropic hormone (ACTH) of the pituitary gland. ACTH in turn triggers production and release of cortisol from the adrenal gland. Cortisol receptors in various brain regions, including the hypothalamus complete the negative feedback loop (Ehlert 2000) (Kirschbaum 1999a). The corticotrophin release from the hypothalamus is also affected by other situations, which are associated with activation of the vegetative nervous system due to a positive feedback of higher epinephrine levels on the ACTH release.

Most of the circulating cortisol is bound to a specific transport protein, the corticoid binding globulin (CBG), and to albumin. Only 5% to 10 % of the total plasma cortisol is unbound and may exert activity on the target cells (Kirschbaum 1999a). Reaching the target cell, cortisol attaches to the glucocorticoid receptors. The ensuing cascade of intracellular signalling events finally leads to alteration of transcription of certain segments of the genome. The precise effects of this altered gene transcription hinges on the nature of the affected cell. For example in activated immune cells, sufficiently large levels of cortisol suppress transcription of pro-inflammatory cytokines.

Acute elevation of cortisol is observed during stress situations, physical exercises and after external application of ACTH (Kirschbaum 1999a). The existing feedback loop implies, that endogenous cortisol secretion can be suppressed by application of external corticoids e.g. dexamethasone. Pathological and chronic elevation of corticosteroids are found in patients with hypercortisolism (Cushing Syndrome). Causes of hypercortisolism arise from the various points in the HPA axis cascade, e.g. from autonomous tumours of the adrenal cortex, tumours of the pituitary gland or ectopic ACTH-production (e. g. some forms of lung cancer). Pathologically low levels of cortisol are found in patients with hypocortisolism due to primary insufficiency of the adrenal cortex, secondary (pituitary based) insufficiency or tertiary (hypothalamic based) insufficiency of cortisol secretion.

Cortisol may be non-invasively and reliably measured in small samples of human saliva (Kirschbaum 1989) (Kirschbaum 1994a), making it an attractive method for repeated measurement and for collection in naturalistic settings. The method will be explained in detail in chapter 1.6.1.

1.5.2. Effects of stress on cortisol secretion

As reported earlier in this thesis (chapter 1.1.2), acute psychological stressors can activate HPA axis and result in an increased cortisol production. In contrast to other neuronal and endocrine responses the HPA stress response implies a temporary delay to the stressor. After the onset of a psychosocial stressor, ACTH levels start rising within less than 5 min and show peak values shortly after cessation of an acute stressor of about 10 minutes duration (i.e. the Trier Social Stress Test (Kirschbaum 1993)). The cortisol response, however, lags by 5-20 min with maximum cortisol levels in the blood occurring between 10 to 30 min after the stress. Although cortisol exerts a strong feedback action at the level of pituitary, hypothalamus, and hippocampus, prolonged periods of stress can lead to a sustained cortisol secretion of several hours duration (Kirschbaum 1994a).

The transfer of cortisol from plasma to saliva occurs quickly. Within less than a minute, cortisol injected intravenously appears in saliva, and the peak concentration in saliva lags by less than 2-3 min compared to levels measured in blood. Thus, it is not surprising to find similar stress response kinetics in saliva and in blood. Following cessation of stress, however, free cortisol tends to increase further for another 15-20 min, whereas total cortisol levels are unchanged or start to decline. A similar response pattern was observed after meals. Certain discrepancies between salivary and plasma concentrations can be linked to CBG levels influencing the binding of blood cortisol. The use of oral contraceptives for example, leads to an increase of CBG and hence augments the number of binding sites, leaving a smaller amount of unbound cortisol available (Kirschbaum 1994a). In that way, application of drugs like oral contraceptives appears to decrease the response of cortisol on stress, if gauged by the free or unbound fraction of cortisol.

Other variables that moderate salivary cortisol secretion in humans are gender, age, weight, nicotine consumption, eating and drinking, use of medications, pregnancy, menstrual cycle phase, and physical activity (Kirschbaum 1995) (Meulenberg 1990) (Kirschbaum 1999b) (Kudielka 1998) (Stone 2001).

With respect to the present data, it is important to note that increases in cortisol secretion may not only be observed following an acute stressor but also in anticipation of a stressful situation. Increases in cortisol levels have been observed before stressors such as cardiac surgery, dental extraction procedures, academic examinations, and exhaustive exercise (Czeisler 1976) (Hellhammer 1985) (Mason 1973) (Smyth 1997) (Stahl 1992).

Some investigators have reported that positive affect leads to decreased cortisol levels, while negative affect is followed by increased cortisol secretion in response to stressors (Berk 1989) (Hubert 1992) (Smyth 1997).

Although the *short-term effects* of glucocorticoids are essential, it has been hypothesized that the *long-term effects* of repeated and sustained cortisol releases may be damaging. This deleterious effects are mediated by the allostasis mechanisms and include increased blood pressure, and the insulin resistance syndrome (McEwen 1998a).

Important with regard to our present work, individuals suffering from *chronic work stress* showed lowered cortisol stress responses to a laboratory stress task (Klein 1995). Studies of individuals under chronic stress (months to years) show diverging results: some studies reported higher cortisol levels (Sapolsky 1996), others found lower levels (Yehuda 2000) (Heim 2000).

1.5.3. The diurnal cycle of cortisol

When unaffected by physiological adaptation processes of the organism, cortisol organisation shows a characteristic diurnal pattern. The normal cortisol concentration in saliva of humans during the day fluctuates with a 50-100% increase 30 minutes after wake up, referred to as the morning peak. This elevation is followed by a constant decline throughout the day with the lowest levels around the early morning hours

(Kirschbaum 1999b) (Pruessner 1999). A second increase may occur in response to larger meals at lunchtime. This pattern closely parallels the respective changes in plasma with the cortisol peaks being more pronounced (approximately 1.5 fold) in free cortisol compared to total blood cortisol. Awakening seems to represent an endogenous stimulation for the HPA-axis (Linkowski 1999, Van Cauter 1989). Data suggest that measurement of the cortisol response to awakening shows good intra-individual stability over time and that morning cortisol secretion may serve as a marker for HPA activity (Pruessner 1999). The diurnal pattern is established early in life, first emerging at about three months of age (Price 1983).

Because a strong diurnal rhythm in cortisol with a negative slope is the normative or expected pattern, researchers have assumed that an extremely weak, inconsistent or absent diurnal cortisol rhythm would be a sign of HPA dysregulation (Caplan et al., 1979). Other possible markers of HPA activity, for example total levels of cortisol, have rather low intraindividual stability (Coste 1994) (Schulz 1994) and can not differentiate between healthy individuals and those with adrenal insufficiency or Cushing's disease (Laudat 1988).

Cycle and Slope

In clinical populations, evidence of a flattening of the diurnal cortisol rhythm, usually indicated by a smaller drop in cortisol from morning to afternoon or evening (Adam 2001), has been reported for a variety of groups, including depressed adults (Carroll 1976), children with a history of maltreatment and current symptoms of depression (Kaufman 1991) (Hart 1996) and children reared in institutional settings (Carlson 1997). A flattening of the diurnal cortisol rhythm has also been found in several physical disorders, including fibromyalgia (Crofford 1994) (McCain 1989), chronic fatigue syndrome (MacHale 1998) and severe rheumatoid arthritis (Neeck 1990).

Only few studies have systematically examined factors predicting diurnal cortisol patterns in normal adults. Non-clinical deviations from the normative cortisol cycle were linked to shiftwork in nurses, with a delay of several days after changing shifts (Costa 1994) (Jelinkova-Vondrasova 1999). Unemployment has been shown to be correlated with higher morning levels of cortisol and lower evening levels (Ockenfels 1995), causing a very steep slope of the diurnal cycle. In another analysis of these data, individuals who were judged to show flat diurnal cortisol cycles did not differ from individuals with normal or inconsistent cycles on a wide variety of demographic and psychological variables (Smyth 1997). Additionally, another recent study also failed to find significant associations between personality variables and change in cortisol levels across the day (Schommer et al., 1999). Thus, the causes of flattened cortisol cycles remain elusive.

Morning response

Another marker of HPA axis activity, the magnitude of the morning response was shown to be influenced by gender, use of oral contraceptives, persisting pain, burnout or chronic stress (Geiß 1997) (Pruessner 1997) (Pruessner 1999) (Schulz 1998) (Wüst 2000b). Other investigators hypothesized that the morning response could be regarded as a person trait, and reported evidence of influencing genetic factors in their twin study.

Of note to the present investigation is the observed association of the morning response with prolonged psychological stress due to chronic work overload (Schulz 1998) and with burnout (Pruessner 1997). Only few studies investigated the relationship between burnout and cortisol (Pruessner 1999) (Melamed 1999), both reporting evidence of a dysregulation of the HPA axis. One study found basal cortisol levels to be elevated (Melamed 1999), the other showed that morning response were abrogated. The latter finding corroborates earlier reports on lower morning cortisol levels and flatter slope towards lower afternoon levels among individuals experiencing high levels of work stress (Caplan 1979).

Whether or not more subtle individual differences in diurnal cortisol secretion patterns have any psychological, physiological or clinical significance, however, remains elusive.

1.5.4. Conclusions and hypothesis

While the available findings do not point to associations between psychological functioning and diurnal cortisol patterns, there is some evidence that prolonged job strain and burnout are associated with the organization of cortisol levels across the day.

Superimposed upon the rather stable pattern of early morning peaks and subsequent decline of cortisol levels throughout the day are acute stress responses. Data suggest that chronic stress can lead to a lowered cortisol stress response as well as to an altered diurnal cortisol cycle. This alteration appears conflicting: some reports link prolonged exposure to stressors to hypocortisolism (Heim 2000) and others to overactivity (Sapolsky 1996).

Investigations of the diurnal pattern were made using different indicators, like overall level, amplitude of the morning response or slope of diurnal decline. Studies using the latter have reported but not explained flattened cycles. The number of observations and participants varies, repetitive assessment was carried out only in 2 studies and cortisol was measured during two consecutive days only. Thus it still remains controversial, whether the finding of flattened diurnal cycles is a between subject trait variance or whether this variance arises to a large extent from a between day or between sample variance within individuals, superimposed on a relatively stable human circadian cortisol pattern.

The data of our study includes a variety of personal and environmental variables, that can be linked to the occurrence of flattened cycles. Besides the mental and physical health variables, the measures of chronic distress obtained during the 1998 sampling period should provide for further scrutiny of the observed cortisol secretion patterns. If deviations from the expected cycle can be pinned down to environmental events, acute workload, wakeup time, drug intake, then flattened cycles are rather likely to represent the upper boundary of a within subject variance (a state) than an individual trait to be accounted for in the long-term follow up investigating possible causes of job turnover.

1.6 Methodological considerations

Since the methods used in our study are not explained in detail in the forthcoming papers, and because the original study design has been published elsewhere, the following chapter provides a more detailed account of the used methods. Data collection was carried out in the years 1997 and 1998 (Fischer 2000a) (Fischer 2000b). The primary aim of the present thesis was to identify factors being associated with turnover of nurses during the 4 to 5 years follow-up time. These findings are presented in the second paper of the present theses. Leading to the second paper, it was necessary to scrutinize the question of flattened circadian cortisol cycles, since we originally considered to include characteristics of circadian cortisol secretion (estimated morning peak and decline slope) as covariates in the Cox proportional hazard models employed in the second paper. The findings related to circadian cortisol cycles are presented in the first paper.

1.6.1. Underlying study design and methods

The original study was designed as a follow–up study with two 12-days observation periods in two years (1997 and 1998). The study was conducted at a major European paediatric intensive care unit. The unit serves 19 level-III beds and a 14-bed intermediate (level II) neonatal ward. As to the nursing staff, the unit is subdivided into three independent teams located on different floors of the hospital (team IPS-A, IPS-B and NEO). However, all three teams share the same unit management, physicians, guidelines and procedures. In the present study, all nurses and physicians involved in patient care and scheduled for work during the two 12-day periods were eligible. Nurses work in three consecutive 9-h shifts (early, late and night), physicians in day and night shifts only.

Sample collection and processing

To date, assessment of cortisol in saliva is a widely accepted and frequently employed method in psychoneuroendocrinology. It has proven a valid and reliable reflection of the respective unbound hormone in blood (Kirschbaum 1989), (Kirschbaum 1994a). Due to advantages over blood cortisol analyses (e.g., stress-free sampling, laboratory independence, lower costs), saliva cortisol assessment has matured to the method of choice in basic stress research and in field environments. The determination of cortisol in saliva can facilitate stress studies including newborns and infants and replace blood sampling for diagnostic endocrine tests like the dexamethasone suppression test.

In our study the salivary cortisol sampling method was carried out as follows: A pilot study determined the tolerable frequency of saliva collection that could be carried out during work without impending compliance. Participants collected „scheduled“ samples at the beginning of work and then every 2 hrs. Additional „non-scheduled“ samples were collected 15-20 minutes after a task or event that was perceived as stressful. Samples were not collected within 30 minutes of any meal.

Saliva was collected into purpose designed tubes (Salivette, Sarstedt, Chur, Switzerland). These tubes contain a cotton swab which is chewed for 1 min and then returned to the vial. At the end of each shift, samples were centrifuged and the supernatant frozen at –80 C. Specimens were shipped on dry ice for assay. Cortisol levels were determined in duplicate by a time-resolved immunoassay with fluorescence detection (Dressendorfer 1992).To determine the interassay coefficient of variation, aliquots from pooled saliva representing low, medium, and high concentrations were run with each series. The interassay coefficient of variation amounted to < 8% (Kirschbaum, personal communication 1997).

Definitions

Expected Circadian Baseline. Two investigators independently assessed graphed printouts that showed all cortisol results obtained from an individual. They examined whether the resulting curves followed the expected physiologic pattern with high levels shortly after awakening and subsequent decline throughout the day. Potential cortisol responses were identified as values clearly deviated from the expected circadian baseline. To quantify the absolute and relative increase, the expected baseline was interpolated by connecting the last point before the increase and the first observed point after the peak by a straight line. The expected baseline for the first sample of the shift was estimated from the individual’s sample from all other shifts that overlapped in time, considering the time of awakening.

Endocrine Response. A sample was defined as an endocrine response when the measured cortisol concentration exceeded the expected circadian baseline by at least 50% and by at least 2.5 nmol/l. Differences in classification were resolved by consensus with a third investigator who was not involved in the primary classification.

The occurrence rate of endocrine responses was calculated as the number of observed responses by the number of samples. If we had any reason to assume that surges satisfying the criteria for endocrine responses could be attributed to other causes (e.g. postawakening cortisol increases in nurses working night shifts, physical exertion), the peak was not counted as a response.

Collection of psychological variables

Participants recorded sampling time and subjective perception of stress on a five-grade Likert Scale (very low, low, average, high, and very high) with every salivary sample. At the beginning of each shift, participants recorded awakening time, duration and quality of sleep, and prior use of medications, tobacco and alcohol (Tsuda 1996) (Koller 1994; Hakola 1996). At the end of the shift but before leaving the unit, subjects completed a questionnaire assessing the subjective workload. The objective workload was estimated as part of a quality control program by the Swiss Society of Intensive Care Medicine. Nurses determined the number and difficulty of tasks performed for every patient. This allowed the categorization of patients by the required nurse to patient ratio (2:1, 1:1, 1:2, and 1:3). The objective workload per shift was calculated as the ratio of available nurses to required nurses.

Baseline data included age, years of intensive care experience, gender, weight, percentage of employment, use of medications, habitual smoking, and the use of contraceptives or pregnancy. The last two items are known confounders of cortisol reactivity and tend to abate or delay endocrine reactions (Kirschbaum 1995) (Meulenberg 1990). Additional questionnaires assessed the quality of life and the subjective attitude to work.

Table 1.2. Table of Questionnaires

Subject questionnaires

	Number of items
1.) Subjective evaluation of the work situation	
Difficulty	10
Threat	8
Avoidance tendency	8
Positive social consequence	10
Negative social consequence	4
Positive self-evaluation	10
2.) Emotional Evaluation of work situation (EMI)	70
3.) Questions concerning work experiences and life quality (AEQUAS; Swiss study on work environment)[1]	
Team climate	8
Leadership style	8
Job satisfaction	5
Job complexity	3
Job Variation	3
Decision latitude	3
Time management	3
Job conditions	4
4.) SF-36 questionnaire (German version): Mental & physical health	11

Shift questionnaires

1.) Objective workload	
Number of patients and severity of patient illness	2
2.) Subjective workload	
Job difficulty, job quality, personal and work-related conflicts difficulties with coworkers, sudden interruptions of work (e.g. by equipment failure, alarms) and dangerous or threatening patient situations.	8

[1] This questionnaire was applied in 1998 only.

1.6.2. Multilevel analysis

Investigation of diurnal cortisol patterns obtained during several observation days calls for employment of multilevel hierarchical models. The basic structure of the data is samples nested within days nested within participants. To elucidate the question of the existence of a person's trait characteristic circadian rhythm it is necessary to perform appropriate partitioning of the variance to either of the three levels. These issues cannot be resolved using the single level regression algorithms. If data are analyzed on the individual sample level the correlation between samples arising from the nested structure of the data is not appreciated. This leads to a gross overestimation of the power of the analysis. On the other hand, aggregating data to the third level (individual) information would have been lost, leading to lower power of the analysis. If data were not aggregated, with analysis restricted on the shift level only, data values from the individual level would have been weighted in an uncontrolled way. However, disaggregating the analysis to the shift level would inflate the sample size and would lead to significance tests that reject the null-hypothesis far more often than nominal alpha level suggests. In other words: investigators come up with a lot of spurious significances (Hox 1995). To overcome this problems we employed the multilevel hierarchical modelling allowing full random slope and intercept modelling on three observation levels. Modelling is started with a very restricted fixed effects model, in this case modelling log-transformed cortisol values as a function of a morning intercept and a slope-coefficient multiplied with time since awakening, according to the following formula:

$$\text{Cort-log} = \text{intercept} + \beta * \text{time since awakening.}$$

From this starting point, the model is expanded stepwise in a systematic fashion. First, the intercept part is allowed to vary on each of the levels, next the slope parameter β is allowed to vary. Each consecutive model is compared to the previous by the log-likelihood chi-square test. Finally, necessary covariates are included, e.g. accounting for endocrine responses. For the present analysis we employed the MLwin program (version 1.1., London College of Education). This program offers particular advantages as to random modelling. Initial statistical analysis were carried out by the author of the thesis, the final model was calculated by Prof. SV Subramanian, Department of Health and Social Behavior, Harvard School of Public Health, Boston. It should be noted that the advantage of appropriate partitioning of the variance is paralleled by a serious disadvantage of these modelling techniques: The multilevel modelling does not provide for individual estimates (like for example the least square means estimates in mixed regression models). Hence, the multilevel modelling approach used here does not provide for a single "slope" estimate for every participant, that could be used as a covariate in further analyses.

1.7 Final conclusions and hypotheses

The present study examines one possible behavioural consequence of high stress levels at workplace, namely job turnover. Turnover as the main outcome variable will be defined as quitting the job in the work unit during a 4 to 5 years follow-up observation time. Several methods of stress assessment have been combined in the present study: subjective and emotional baseline evaluation of the work situation, including difficulty and threat, objective and subjective workload of an entire work shift and, two-hourly monitoring of stress perception and salivary cortisol stress responses. Additionally, potential sources of stress like team climate, leadership style, job satisfaction, job complexity, job variation, decision latitude, time management and job conditions have been assessed as baseline variables.

Our **first hypothesis** postulated an association between diurnal cortisol cycle and the outcome. Nurses with flattened slopes are expected to report more symptoms of burnout and consequently might be leaving their job earlier. Giving the elusive nature of the "flattened" circadian cortisol slope (Smyth 1997) (Stone 2001), we decided to scrutinize this phenomenon in the existing data-set using more advanced statistical modelling techniques.

The **second hypothesis** concerning turnover was: nurses experiencing higher levels of distress will quit their job earlier than others. Since stress may be defined and measured in different ways (Levine 1991), we further aimed to elucidate, whether the frequency of an individual's endocrine stress reactions or the averaged acute stress perception during work was of any predictive value as to job turnover. Following the existing literature, burnout may be associated with both, flattened cycle/morning response (Pruessner 1999) and lowered stress responses (Klein 1995). Indications of burnout have been shown to predict turnover (Oehler 1992) and may be mediating the stress-turnover relationship.

The comprehensive set of variables covered in the present study, and the longitudinal follow up allows to prospectively identify psychosocial, organizational and task-specific work characteristics as well as individual variables that are related to job turnover.

Since only few studies have examined stress at the workplace with physiological methods, the present study adds an investigation of physiological stress reactions on occupational stress to the predominantly questionnaire based stress research in the workplace.

2. The cortisol paradox: Individual differences in the diurnal cycle of salivary cortisol

2.1 Abstract

Background: Free salivary cortisol levels show an awakening increase with subsequent decline throughout the day. However, several studies have identified subsets of individuals with flattened cortisol slopes. In the present study we aim to replicate these findings in data collected from critical care nurses using advanced multilevel statistical models.

Samples: Salivary samples (n = 3806 samples, 123 physicians and nurses, 92% accrual rate) were collected at two-hourly intervals during work in a tertiary paediatric intensive care unit. Subjects worked early, late and nightshifts. Cortisol peaks representing endocrine stress reactions superimposed on the baseline circadian rhythm were observed in 12.6% of the samples. Two multilevel models were set up: a) a simple hierarchical model as used in the studies suggesting the existence of flattened slopes modelling log-transformed cortisol values as a linear function of daytime, b) a multilevel model nesting samples within days within individuals using a polynomic relation between time since awakening and log-cort values. Additional explanatory variables were entered at the appropriate level.

Results: The first model confirmed previous findings: 12% of the shifts showed flattened slopes, and 10% of all individuals had flattened averaged slopes. In the multilevel model, slope terms no longer retained significant between subject variance, after entering appropriate additional explanatory variables such as gender, awakening time.

Conclusion: These data suggest that circadian cortisol secretion follows a stable pattern across individuals. “Flattened” slopes arise from between day variance within individuals or from between-samples variance.

2.2 Introduction

Cortisol is an essential hormone for regulating vital functions, including glucose and fat metabolism, modulating inflammatory responses, vascular responsiveness and CNS functions. Cortisol assists in the homeostasis of normal, non-stressed activity as well as in the adaptation to stress. In general, cortisol secretion in humans follows a characteristic diurnal rhythm with high morning levels and a steady decline towards a through in the late evening hours. This normative or expected pattern has been reproduced in many studies (Kirschbaum 1999b) (Pruessner 1999) (Van Cauter 1998) (Wüst 2000a). Numerous studies have shown that rapid rises in cortisol are superimposed on the diurnal pattern in response to acute physical or psychosocial stress (Kirschbaum 1989) (Kirschbaum 1994b). More recently, investigators have moved from elucidating the average “normative” pattern towards investigating deviations from this, in particular flattened diurnal cycles with low morning cortisol levels and absent decline during the day (Jelinkova-Vondrasova 1999) (Ockenfels 1995) (Smyth 1997) (Stone 2001).

Flattened cortisol rhythms were first described in clinical populations. These flattened diurnal cycles have been found in patients with depression (Blackburn 1987), chronic fatigue syndrome, or chronic burnout (Melamed 1999). Other investigators showed an association with medical conditions such as asthma (Smyth 1997), severe rheumatoid arthritis (Neeck 1990), and in women with breast cancer (Sephton 2000). In the latter patients, a flat cortisol cycle was associated with shorter survival (Sephton 2000). In non-clinical settings, deviations from the normative cortisol cycle were observed during shiftwork in nurses (Costa 1994) (Hakola 1996) (Shinkai 1993). With a delay of several days, cortisol diurnal rhythms followed shifting of sleep time (Jelinkova-Vondrasova 1999). Steepness of diurnal slopes has also been related to employment status, with unemployed study participants showing had higher morning levels and lower evening levels (Ockenfels 1995). Field research in 70 child-rearing mothers found a strong positive association between the estimated morning peak and the steepness of the diurnal slope (Adam 2001). Hierarchical linear modelling of this data revealed that medical, demographic, contextual (home and work demands) as well as psychological (relationship functioning) variables explained a considerable part of the between-subject variance in morning cortisol levels and slopes (Adam 2001). Using a similar hierarchical modelling approach, Stone and co-workers re-analyzed the data from four large observational field studies with multiple sampling points per day. In all four studies, an upper quintile of individuals with flattened or almost flattened diurnal slopes was identified (Stone 2001). Currently, it remains unknown whether flattened cortisol rhythms are a stable personal trait or a whether they indicate a reaction or adaptation to specific situations.

In the present analysis, we re-evaluated the data from an observational study in staff of a tertiary paediatric critical care unit (Fischer 2000a). Paediatric critical represents one of the most psychologically demanding working environments with frequent exposure to potentially life threatening patient events. In this study, salivary cortisol was collected two-hourly during working hours and after any potentially stressful event. Participants were sampled over several consecutive working days in two subsequent years. The study was characterized by a high accrual rate (94% of all eligible subjects) and a precise documentation of sampling time as well as the individuals awakening time. These features minimized possible biases arising from sampling artefacts or from selection of participants. In addition to salivary cortisol levels, an array of socio-demographic, medical, contextual (including subjective stress-assessment at sampling) and work related variables were assessed.

With the present analysis we aimed to answer the following questions: Do the data from this stress exposed working population corroborate the distribution of diurnal slopes described by Stone and coworkers? What partitioning of the variance is revealed when extending the previous hierarchical modelling (slopes and intercepts within subjects) to a three level model (cortisol values within days within subjects)? Finally, we aimed to identify factors predicting flattened slopes in the two-level hierarchical model by explorative analyses.

2.3 Methods

2.3.1. Design

We performed a prospective cohort-study on critical care staff of a large tertiary paediatric intensive care unit. Salivary cortisol samples were collected two-hourly during two 12-day periods in 1997 and 1998. Questionnaires were used to assess baseline variables (individual level), shift-related variables (shift level) and variables concerning cortisol sampling (sample level). Subjective stress perception was assessed at the sample level and at the day-shift level.

2.3.2. Participants and setting

The unit is a tertiary critical care unit with three wards. Two wards provide level III critical care, one unit is a step-down intermediate neonatal care unit. All nurses as well as physicians involved in the care of patients were eligible. Nurses were performing three 9-hr shifts (morning, day and night shifts), physicians were working in 12.5-hr day- or nightshifts. During nightshifts, senior physicians provided an on-call service. A pilot study determined the tolerable frequency of saliva sampling and the number of questionnaire items that could be included without impeding compliance.

2.3.3. Data collection

Salivary samples

Salivary cortisol was sampled on 12 days in February 1997 and on 12 days in February 1998. Every participating nurse collected „scheduled" samples at the beginning of work and thereafter every 2 h into purpose designed collection tubes (Salivette, Sarstedt, Chur, Switzerland). Additional „non-scheduled" samples were collected 15-20 min after a task or event that was perceived as potentially stressful. Samples were not collected within 30 min of any meal (Kirschbaum 1997). With every sample, nurses recorded the subjective level of actual stress on a five-graded Likert scale. Sampling was carried out on morning, late and night shifts. During 1997 we did not include the intermediate neonatal ward. Sampling was restricted from noon to midnight on the two critical care units in 1998. Based on these schedules, we achieved a 93% accrual rate of all planned samples. On average, participants collected 31 samples. Cortisol levels were determined by a time-resolved immunoassay with fluorescence detection (Dressendorfer 1992). Further details of the design have been described elsewhere (Fischer 2000a).

Endocrine stress responses

All samples collected during an individual shift were plotted against daytime. Two investigators independently reviewed these charts to identify cortisol levels. Investigators were blinded to the results of each other. Cortisol levels that exceeded the projected baseline by at least 50% and by at least 2.5 nmol/l were identified as endocrine responses. Investigators achieved a Cohen's kappa of 0.83 (agreement beyond chance). Cases of divergent assessment were resolved by consensus with a third investigator.

Additional variables

Data concerning individual characteristics was collected as a baseline questionnaire assessing subjective health perception (SF-36 (Bullinger 1998)), subjective and emotional evaluation of work situation, including vital exhaustion (Appels 1987) and socio-demographic data. Shift related factors objective workload (e.g. number of patients) as well as subjective perception of work difficulty (Subjective Difficulty Questionnaire (Zeier 1996)) were recorded at the end of every shift. Further data included duration and quality of sleep prior to coming to work, tobacco and alcohol consumption during the 12 hours preceding the actual working shift and precise awakening time.

2.3.4. Statistical analysis

Slopes and intercepts

All analyses were performed on log-transformed cortisol levels. For all analyses we excluded samples identified as endocrine response. In the first model we regressed log-cort values against time since awakening for every observation day. This resulted in an estimate of the intercept (morning peak) and slope (diurnal decline) for every observation day (shift). Only days with at least three observations were admitted to this analysis. Cortisol samples that were identified as stress responses were excluded from slope calculation. Regressions were carried out using SAS software (SAS, Cary, NC).

For comparison between individuals the shift data was aggregated, and within subject averages for slopes and intercepts were used. For this comparison, only individuals contributing more than two shifts were kept considered. For both, shifts and subjects, the upper quintile for slope values were defined as identifying individuals or shifts with deviations from the typical cycle. These analyses were carried out by SPSS (Version 10.1, SPSS Inc, Chicago, IL). In explorative manner we analysed the influences of proposed predictors on slope and intercept using general linear regression models. Predictors of the upper slope quintile were identified using the logistic regression models. Both models were calculated on the shift data and on the subject data as well.

Multilevel analysis

Multilevel analysis was carried out employing the MLwin software (Version 1.1 (Rasbash 2000)) using a 3-level-model: person, shift and sample level. The basic equation used to explain our data, modelled the log-cort value of each recorded sample as a function of a constant intercept, time since awakening and an error term:

$$\text{cortlog} = \beta_{0ijk} * \text{constant} + \beta_{1ijk} * \text{hours since awakening} + \beta_2 * (\text{hours since awakening}_{ijk})^2$$

This model allows partitioning of the variance between samples into a level 1 (between samples within days), a level 2 variance (between days within subjects) and a level 3 variance (between subjects). The model also allows estimating the circadian slopes and its variation at each level. The level at which most of the variance occurs accounts for the observed differences. Expressed in these terms the hypothesis of individuals with flattened slopes implies that a large proportion of the variance occurs on level 3 and that the 95% confidence interval around the level 3 slope estimate allows for individuals with flat circadian rhythms. On the contrary, a finding of little variation on level 3 and most of the variation occuring on level 2 (between days) or level 1 (within days) would support the notion of a generalizable circadian decline and that observed deviations from this are attributable to between day or within day variances. The models were computed using the likelihood method IGLS (Iterative Generalised Least Squares).

2.4 Results

2.4.1. Study population

A total of 139 (94%) of 147 eligible team members participated in the study. Participants collected 3850 salivary samples during 7145 h of observation. Two hundred and seventy-five samples had to be excluded because undocumented awakening or collection time. The remaining 3531 samples were obtained during 644 shifts (514 day shifts, 130 night shifts). Within these samples, we identified 471 (13.3%) endocrine responses by the method described above. Further characteristics of the population are presented in Tables 2.1. and 2.2.

Table 2.1. Subjective Variables (only subjects with at least 3 observation days)

Subject Variables	
No. of subjects	96
No. of females	78
Mean age (standard deviation)	31.5 (6.2)
No. of shifts per subject	6.24 (3.16)
No. of samples per subject	29.1
No. of physicians	16
No. of smokers	13
No. on oral contraceptives	21
Mean body mass index	22.0 (3.1)
Mean physical health summary score	55.1(5.3)
Mean mental health summary score	48.6 (8.4)
Exhaustion	37.7 (13.91)

Table 2.2. Shift Variables. Data are presented as mean (standard deviation) unless stated otherwise

Shift Variables	**Total**	**Dayshifts only**
No. of shifts (subjects)	644 (124)	514 (115)
No. of samples/shift	4.9 (1.3)	4.9 (1.04)
Mean no. of patients in care	1.60 (.57)	1.52 (.56)
Mean max. of patient in care	2.74 (.761)	2.81 (.73)
Mean wake up time	8:54 am (3.8 hrs)	7:23 am (2hrs)
Mean duration of sleep in hours	7.3 (1.7)	7.2 (1.7)
Mean quality of sleep	3.68 (.9)	3.7 (.9)
Job difficulty (SSF1[1])	40.1 (11.5)	40.6 (11.2)
External disturbances (SSF2)	44.8 (14.6)	45.4 (14.34)
Work load due to not missing help (SSF3)	46.0 (9.9)	46.0 (9.9)
Social conflicts during shift (SSF4)	42.9 (10.7)	43.0 (10.7)
Quality of own work (SSF5)	52.7 (12.9)	52.6 (12.7)

2.4.2. Slopes and intercepts of diurnal rhythms

Using a two-level hierarchical modelling approach similar to the one employed by Stone and coworkers (Stone 2001), we estimated the intercept and slope that provided the best fit for every observed shift. Only shifts with at least three samples that were not identified as endocrine response were considered. Figure 2.1 and 2.2 displays quintiles of the diurnal slopes on the basis of individual shifts (level 1, Figure 2.1) or as the subject average (level 2, Figure 2.2). The 103 shifts scoring in the upper quintile arose from 57 different participants. None of the participants with more than two observed shifts had all of the shifts in the upper quintile. Amongst participants with at least three observed shifts, the highest rate of shifts with slopes in the upper quartile was 6 out of 8 shifts. Ten participants (8% of 112) had more than half of their slopes in the upper quintile. Amongst the 35 participants, who provided at least three observation days in either year, those who had at least one slope in the upper quintile in one year were more likely to have also at least one slope in the upper quintile in the second year (odds ratio = 4.6, 95% confidence interval 1.03-20.7, p = 0.034). Corroborating earlier findings by Adam (Adam 2001), we observed a high negative correlation between the estimated intercept and the estimated slope ($r = -0.79$, $p < 0.001$; see Figure 2.3). The analyses showed that slopes did not differ between early and late shifts (p = 0.56), while intercepts were significantly lower for late shifts (p = 0.003).

Table 2.3 Slopes and intercepts

	Subject level	**Shift level (dayshifts only)**
Mean slope	-0.155 (.06)	-0.1576 (.09)
Mean intercept	2.780 (.54)	2.803 (.80)
Mean slope of upper quintile	-0.069 (.01)	-0,028 (.07)
Mean slope of middle 3 quintiles	-0,156 (.01)	-0,159 (.04)
Mean slope of lower quintile	-0.239 (.01)	-0,285 (.06)

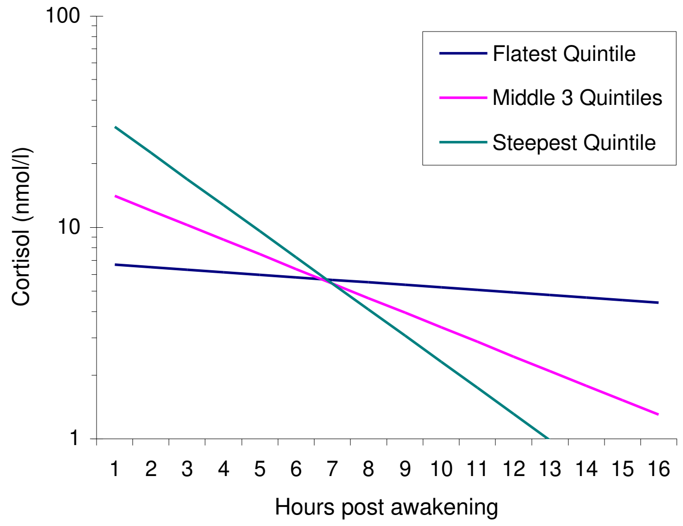

Figure 2.1 Mean slopes of the different quintiles on the shift level

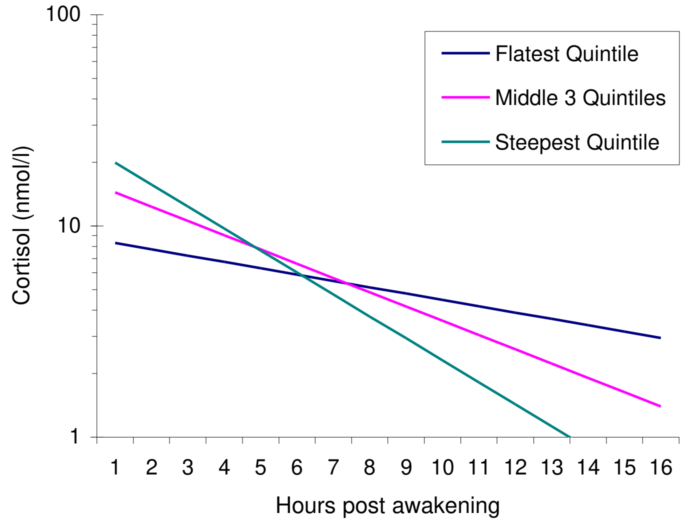

Figure 2.2 Mean slopes of the different quintiles on the subject level

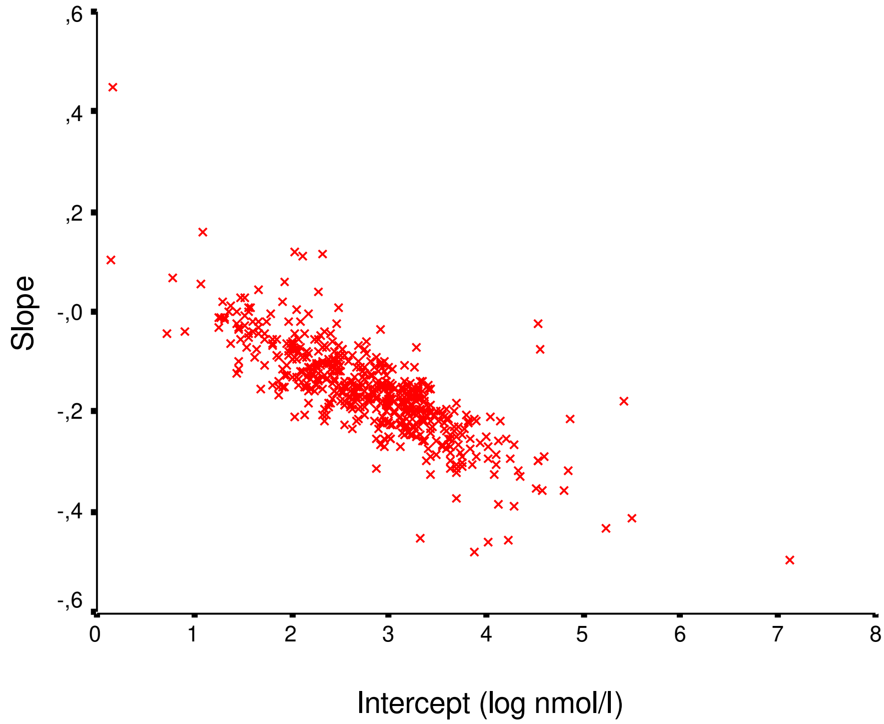

Figure 2.3 Correlation of intercept and slope

2.4.3. Extension to a three-level model

The method of estimating the intercept and the slope for each observation day, with subsequent entering of the obtained estimates into further analysis does not allow full partitioning of the observed variance at all three existing study levels. Because of the observed correlation between estimated slopes and intercepts, it is conceivable that most of the observed variance in slopes actually is a function of the observed variance in intercepts. To account for this, multilevel methods must be employed, that allow for partitioning of the variance between slope and intercept on the basis of individual cortisol measurements. These models nest samples within observation days within subjects. It is conceivable that intercept (an estimate of the morning peak) may vary between subjects and within subjects between days. Likewise, it is conceivable that slopes may vary between subjects and between days. This variation is accounted for by separate variance terms. The overall model fit allows calculating, whether allowing to vary intercept or slope at each level significantly improves the model fit. Once the best model is identified, the various variance terms can be examined for their contribution to the total residual variance.

Our basic multilevel regression included only samples collected during the day that were not identified as endocrine response. First, we modelled the logarithm of cortisol as a function of intercept, our so-called null. Allowing intercept to vary on all levels yielded a first likelihood estimation (-2*log(lh) = 5693.03). Most of the variance could be attributed to the sample level, of course, followed by individual and shift level.

In our next step, we introduced the slope estimate, the time since awakening variable. With the slope fixed on all levels, the random effects could be reduced and the likelihood of the model improved (-2*log(lh) = 3118.51). Allowing slopes to vary between individuals (-2*log(lh) = 3053.37) and between individuals and shifts (-2*log(lh) = 3024.97) further improved the likelihood of the model. However, the estimates of intercept and slope remained almost unchanged. Fixed and random effects of the best model are shown in Table 3.4. Thus, almost all of the variance is attributable on variance of the intercept, especially on the individual (40%) and the sample level (40%) and the shift level (20%). No other variable became significant or models became non-estimable. These results indicate that slope variation on a between-subject level contributes a small portion of the variance in log-cortisol levels, and in this sample does not allow for flat slopes.

Table 3.4 Fixed and random effects in multilevel model. Level 1 represents the sample level, 2 the shift level and 3 the individual level. Intercon stands for the intercept and diffwake stands for the hours since awakening.

Fixed effects

Parameter	Estimate	Standard error
intercon	2.721	0.04353
diffwake	-0.1565	0.004343

Random effects

Level	Parameter	Estimate	Standard error
3	intercon /intercon	0.137	0.02844
3	diffwake /intercon	-0.007536	0.002441
3	diffwake /diffwake	0.001023	0.0002802
2	intercon /intercon	0.07595	0.01995
2	diffwake /intercon	-0.003765	0.002215
2	diffwake /diffwake	0.001035	0.000293
1	intercon /intercon	0.1374	0.005255

likelihood -2*log(lh) = 3024.97

Because the multilevel model does not provide for individual estimates, we employed general linear models to further elucidate relationships between subject or shift variables and the slope. Best regression model explaining the slope contained 5 independent variables ($F = 241.4$, $r = .727$, $df = 5/459$, $p < 0.0001$) in which a higher intercept predicted a steeper slope. Subjects who had endocrine responses, and subjective with higher levels of subjective stress during a shift and waking up early flattened the slope. While these variables are all shift variables, on the subject level only being a woman showed significantly steeper slopes. Testing for autocorrelation was negative (1.456, Durbin-Watson).

Ten percent of the variance in estimated intercepts (shift as the unit of analysis) was explainable by a model containing four variables ($F = 12.6$, $r2 = 0.098$, $df = 4/471$, $p < 0.0001$). Higher intercepts were associated with earlier wake-up times, higher scores on self-reported physical health, higher number of endocrine reactions per shift and being a woman. Adding slope to this model increased the explained variance to 73%.

Finally, we aimed to predict the probability of a shift-slope to fall into the upper quintile. At an entry criterion of $p < 0.1$ most of the aforementioned variables were retained (Table 2.5). The model yielded an area under the receiver operating characteristic curve of 0.94 (95% confidence interval, 0.90-0.97) and a good fit (Hosmer Lemeshov chi-square goodness of fit statistics, $p = 0.99$). The upper quintile was predicted best by low intercept, early awakening, more stress reactions and few samples per shift. Subjective stress wasn't a good predictor for the upper 20%. Being a woman and bad sleep quality had weak prediction power.

Table 2.5 Prediction of upper quintile (Binary Regression Model)

	B	**S.E.**	**Wald**	**df**	**Sig.**	**Exp(B)**
Gender	-1.005	.524	3.688	1	.055	.366
Wake up time	-.313	.101	9.627	1	.002	.731
No. of endocrine reactions	1.232	.276	19.884	1	.000	3.428
Intercept	-4.387	.484	82.085	1	.000	.012
Quality of sleep	-.371	.185	4.015	1	.045	.690
No. of samples per shift	-.658	.209	9.910	1	.002	.518
Constant	16.164	2.136	57.263	1	.000	10471872.392

Area Under the Curve

Test Result Variable(s): Predicted probability

Area	**Std. Error**	**Asymptotic 95% Confidence Interval**	
		Lower Bound	Upper Bound
.939	.018	.904	.973

2.5 Discussion

We reanalyzed an existing dataset to elucidate the observed phenomenon of flattened or positive slopes in circadian salivary cortisol levels. Our dataset was comparable in size to the studies summarized by Stone and coworkers (Stone 2001). In contrast to their data, our participants worked in a highly stressful environment with frequent endocrine stress responses. Our predominantly female study population achieved a high accrual rate (< 93%), thus minimizing selection biases with respect to the population of eligible individuals. All sampling was supervised on site, thus measurement or recording error as to sampling time can be excluded. Our crude analysis revealed a variance in slopes and intercepts that was comparable to the data presented by Stone and coworkers. Like in their data, the upper quintile of our participants had slopes that were only barely negative. Finally, we corroborated the findings by Stone and coworkers by showing a significant within-subject and between-subject variation in slopes.

Having replicated earlier findings, we employed a variety of statistical methods to identify variables accounting for the observed slope-variance. However, it should be kept in mind that on average participants collected around five samples per shift. Maximum likelihood methods will estimate both the intercept and the slope when regressing log-cortisol values against time since awakening. As the number of samples decreases, the fit of maximizing likelihood models becomes more dependent on correctly estimating the intercept.

Our simpler regression models revealed, that intercept explains most of the variance in slopes in our population. Building logistic regression models, we were able to predict with high accuracy which slope would fall into the upper quintile when knowing intercept, time of awakening (absolute daytime), number of endocrine reactions during a shift, number of samples used in the slope regression and, with lower prediction power, quality of sleep and gender. Thus, in our population, most of the “slope paradox” was explainable by other factors, notably the estimated intercept, showing high negative correlations with slope. Although our study did not include an awakening protocol as suggested by Pruessner and coworkers (Pruessner 1997), it is conceivable that our intercept estimate is related to the morning cortisol peak.

Multilevel regression models offer an additional advantage above simple regression models discussed so far. Multilevel regression allows to partition the variance of the error term and to simultaneously account for interactions across levels. Individual cortisol levels obtained during a study provide an excellent example for studying nested layers, since samples nest within diurnal cycles, which in turn nest within individuals. The simplest model with log-cortisol values as the function of fixed intercept and a fixed slope*time term corresponds to an overall mean regression model. Not surprisingly, the obtained estimates did not differ from those obtained by simple regression models on individuals. The advantage of the multilevel model is to allow for systematic introduction of variance at each level and for each term. Our best fitting models allowed the intercept estimate to vary across subjects and within subjects across shifts. Allowing slope to vary across individuals and across shifts further improved the statistical fit of the models. However, in these final models, the remaining error variance was distributed between intercept variance across individuals, intercept variance within individuals across days and intercept variance on the sample level. The model attributed little residual variance to slopes.

How do the two analyses fit together? Multilevel models suggest a fairly constant and stable slope with little variation. Simple regression models explain a large proportion of the variance in slopes by other variables. A prediction model correctly predicts slopes in the upper quintile of the distribution by other variables. Thus, all three models converge in the explanation that the slope paradox finds an explanation by underlying individual, diurnal or situational variables. The most important predictor of the slope is the estimated starting or set point of the circadian rhythm in the morning. In this sample of highly stress exposed individuals, the remaining residual variance in slopes appeared to be small. This indicates that most individuals in our study share a basic decline constant in salivary log-cortisol levels of – 0.157 (+- 0.004) per hour after awakening.

The strength of our study was observation over two years, a high accrual rate, simultaneous recording of other potential explanatory and relating to awakening time. The limitation is a still relatively small number of samples per shift placing mixed with recovery from endocrine responses or some sub-response elevations. This emphasized intercept estimation. While this should have increased variance in slopes, yet most models suggest that the slope variation was explainable by other variables beyond a relatively stable individual slope constant with little between subject heterogeneity. Thus, known factors account for the observation of varying slopes. Once these variables are included in the model, little residual heterogeneity appears to remain. These data somewhat contrast the data published by Stone and coworkers. Most recently, we have therefore exchanged this dataset with Stone and coworkers. Reanalysis of the data using three level full hierarchical modelling as well as advanced mixed models using SAS mixed procedure will be employed. These analyses are forthcoming and will extend the work presented in this thesis. As to the main underlying question regarding prediction of nurses' turnover behaviour, it seems justified not to include individuals slope characteristics in the analysis following in the next chapter.

3. Physiological stress reactions and job turnover rate: A prospective cohort study in critical care nurses.

3.1 Abstract

Context: High turnover rates of staff and failure to retain experienced nurses is a major concern for critical care units worldwide. Part of this problem has been attributed to critical care nurses' consistent exposure to stress and ensuing burnout. Empirical data that prospectively relate acutely measured stress perception or endocrine stress reactions to retention are scarce.

Objective: To elucidate whether acute stress perception or endocrine stress reactions are related to retention of critical care nurses.

Design: Prospective inception cohort study with 4.5 years of follow-up.

Setting: Tertiary paediatric critical care centre with 33 beds.

Participants: Qualified nurses (n = 112) scheduled for working shifts during the cohort entry period.

Interventions: None

Main Outcome Measures: Retention, defined as the time elapsing from cohort entry until leaving the job. Exposure determined at cohort entry was a) the frequency of endocrine stress responses based on two-hourly measurement of salivary cortisol during two 12-day periods in 1997 and 1998 (response defined as increase by at least 50% over baseline); b) the subjective perception of acute stress recorded with each sample; and c) work characteristics as assessed by baseline- and end-of-shift questionnaires.

Results: During 6150 hours of observation participating nurses provided 3278 samples (93% accrual). Ninety-nine nurses collected more than 5 samples. Full datasets, including assessment of work characteristics, were available from 75 nurses. Nurses with below median frequency (< 12.8% of all samples) tended to leave the unit earlier ($p = 0.06$). No association with retention was found for subjective stress perception. Nurses scoring in the lowest tercile of a factor consisting of perceived team climate, leadership style and job satisfaction left the unit significantly earlier ($p = 0.03$).

Conclusion: Micro-social work characteristics presented as the single most important subjective variable associated with retention, above a low frequency of endocrine responses to work-related stress.

3.2 Introduction

High turnover rates of nursing staff are a major problem for intensive care units worldwide (Beckmann 1998) (Cartledge 2001). The difficulty of retaining experienced nurses often leads to shortage of staff, requiring hospitals to close otherwise available beds. Cross-sectional data show an inverse association between the intent to stay and job satisfaction, perceived leadership skills of the managers, group cohesion and instrumental communication (Cartledge 2001) (Boyle 1999) (Leveck 1996). Others have attributed the high turnover rates to persistent exposure to job stress and to burnout (Oates 1995) (Oehler 1992). However, these studies relied on retrospective assessment of perceived stress. To date, there is still a paucity of data assessing subjective stress perception and related biological responses on an acute basis. To our knowledge, there is no longitudinal study with factual job turnover as the outcome and with simultaneous assessment of subjective stress perception, appreciation of work characteristics and biological stress responses as measures of exposure.

We have previously reported on a cross-sectional observational study assessing subjective stress perception and endocrine stress reaction in 112 pediatric intensive care nurses (Fischer 2000a) (Fischer 2000b), who provided 3278 measurement points. The data showed that acute subjective stress perception was poorly related to the occurrence of endocrine stress reactions, the latter being defined as a marked increase in salivary cortisol over circadian baseline levels (Fischer 2000a). The study also found that job experience was unrelated to the frequency of endocrine stress reactions.

Here we report on the 4.5-year follow-up of the original cohort. We aimed to elucidate whether the frequency of an individual's endocrine stress reactions during working hours on the unit, or the averaged acute stress perception, might be related to job turnover. The secondary aim of the study was to prospectively identify psychosocial, organizational and task-specific work characteristics that are related to job retention.

3.3 Methods

3.3.1. Design

This prospective cohort study was conducted on three wards of a tertiary pediatric critical care center. Subjective stress perception and endocrine stress reactions (salivary cortisol) were sampled two-hourly during two 12-day periods in 1997 and 1998. The primary endpoint was the time elapsing until leaving the unit during the 4.5 years of follow-up.

3.3.2. Participants and setting

All nurses employed on the three wards of the paediatric intensive care unit of a university hospital were eligible. The hospital is the tertiary referral centre for Eastern and Southern Switzerland, a region of approximately 3 million people. The unit consists of two level-III bed wards (ward A, 10 beds; ward B, 9 beds) and an intermediate neonatal care unit (ward C, 14 beds). The wards are located within the same building and share attending physicians, residents, technical staff and nursing supervisors. All three wards follow the same procedure guidelines. Patient allocation is carried out by the centre's senior physicians and nursing supervisors. Wards A and B provide the full range of neonatal and paediatric critical care for cardiac, surgical and medical cases. Ward C is a step-down and intermediate care unit for newborns. Nurses working on wards A and B have completed a two-year specialization course in paediatric intensive care or are participating in the units' training program towards this two-year diploma. Nurses working on ward C are specialized paediatric or neonatal nurses. Each ward has its own head nurse, staff nurses and nursing students. There is little staff turnover between the wards. Thus, the variance in perceived psychosocial work characteristics (e.g. group cohesion, managers' leadership skills) arises at least in part from differences between ward teams. All participants gave written informed consent.

3.3.3. Data collection

Salivary samples

The procedures at cohort entry have been described in detail elsewhere (Fischer 2000a). Briefly, we examined subjective stress perception and salivary cortisol levels during two 12-day periods in February 1997 and February 1998. Ward C participated in 1998 only. Sampling was restricted to the interval between noon and midnight on wards A and B in 1998. Every participating nurse collected „scheduled" salivary samples when beginning work and two-hourly thereafter into purpose-designed tubes (Salivette, Sarstedt, Chur, Switzerland). Additional „non-scheduled" samples were obtained 15-20 min after a task or event that was perceived as stressful. Samples were not collected within 30 min of any meal (Kirschbaum 1997). For every sample, the collecting nurse recorded the subjective perception of actual stress prior to sampling on a five-grade

Likert scale. On average, participants collected 31 samples. Sampling was carried out during morning, late and night shifts. The accrual rate of all scheduled samples was 93%. Cortisol levels were determined in duplicate by a time-resolved fluorescence immunoassay (Dressendorfer 1992). A sample was defined as an endocrine response when the cortisol concentration measured exceeded the expected circadian baseline by more than 50% and by at least 2.5 nmol/L. Adjudication of samples as to the presence of endocrine reactions was carried out independently by two investigators, who achieved satisfactory agreement (kappa = 0.74). Further details of the adjudication procedure have been presented elsewhere (Fischer 2000a).

Additional variables

A baseline questionnaire assessed subjective health perception (SF-36), subjective perception of work characteristics, emotional reactions to work (including feelings of exhaustion) and baseline socio-demographic data (Fischer 2000a). In 1998, we added an extensive questionnaire previously used in a Swiss study on work environment (AEQUAS), which had been developed and validated in Switzerland to assess work characteristics in nursing populations to the baseline questionnaire (Elfering 2002). The subscales used in this study for post-hoc tests related to work characteristics were: organizational climate, leadership style, job satisfaction, job complexity, job variation, job conditions, decision latitude, and time management. Apart from subjective stress perception obtained with every sample, nurses completed a questionnaire assessing objective workload characteristics as well as subjective perception of work at the end of every shift.

3.3.4. Statistical analysis

The primary endpoint was the time elapsing until leaving the job. Changing wards was not considered to be equivalent to leaving the unit. The following independent variables were considered: observed frequency of endocrine stress responses, as defined above, mean subjective stress perception, subjective perception of work characteristics and the team membership (A, B, or C). Team membership was coded following the intention-to-treat principle: participants who changed wards after the 1998 collection were analyzed according to the ward membership at baseline. The primary survival analysis followed the Kaplan-Meier method. We used the log-rank test on the median split of the frequency of endocrine stress responses and on the median split of the average subjective stress perception. Post-hoc or hypothesis-generating analyses comprised Cox proportional hazard models. Additional independent variables in these analyses were work characteristics (three factors obtained by principal component analysis from the eight work-characteristic scales), age, subjective level of exhaustion and team membership. Finally, we examined the nature of significant associations (linear, quadratic, U-shaped) by performing log-rank tests on terciles of the variables. No adjustments were made for multiple comparisons in these secondary analyses. All calculations were carried out using SPSS (Version 10.1, SPSS Inc, Chicago, IL).

3.4 Results

Study population: During the two baseline observation periods, 112 of 118 eligible nurses participated (95% accrual rate). Follow-up time was 4.5 years for nurses enrolled in 1997 and 3.5 years for nurses enrolled in 1998. During 775 working shifts (6150 hours of observation) nurses collected 3278 salivary samples. Of these, 403 were identified as endocrine stress responses. The mean absolute increase above baseline amounted to 10.6 nmol/L (range 2.5 – 142 nmol/L), corresponding to a mean relative increase of 219%. The median rate of endocrine responses per participant amounted to 12.8%.

Datasets, including all measures of subjective and endocrine stress perception from at least 5 samples, were available for 99 nurses. Complete datasets, including the assessment of work characteristics (1998 only), were available for 75 subjects. Further details of the study population, stratified by ward, are presented in Table 3.1.

Table 3.1 Study population

	Ward A	**Ward B**	**Ward C**	**F**	**P-Value**	**Post-hoc-tests**
Participants	39	36	24			
Endocrine reaction rate	.14 (.11)	.13 (.10)	.15 (.08)	.200	.819	
Mean stress perception	1.77 (.70)	2.02 (.77)	2.92 (.37)	22.737	**<.001**	A < C; B < C
Team climate	3.64 (.58)	4.40 (.41)	4.49 (.31)	26.661	**<.001**	A < B; A< C
Leadership style	3.81 (.70)	4.28 (.47)	4.48 (.46)	9.345	**<.001**	A < B; A< C
Job satisfaction	4.14 (.94)	4.84 (.93)	5.35 (.84)	1 .777	**<.001**	A < B; A< C
Job complexity	4.11 (.65)	3.98 (.58)	3.88 (.49)	.904	.409	
Job Variation	3.45 (.47)	3.38 (.62)	3.42 (.49)	.113	.893	
Decision latitude	3.76 (.47)	3.92 (.51)	3.71 (.36)	1.530	.224	
Time management	2.08 (.65)	2.21 (.44)	2.22 (.59)	.467	.629	
Job conditions	2.85 (.80)	3.06 (.59)	3.65 (.55)	9.591	**<.001**	A< C; B < C
Factor 1*	-.779 (1.068)	.269 (.703)	.530 (.680)	16.853	**<.001**	A < B; A <C
Factor 2+	.101 (.933)	.052 (1.21)	-.170 (.796)	.490	.614	
Factor 3§	-.381 (1.232)	-.053 (.780)	.476 (.765)	4.930	**.010**	A < C; B < C

* Factor 1 is comprised of: team climate, leadership style and job satisfaction; + Factor 2 consisted of: job complexity, job variation, decision latitude; § Factor 3 included time management and physical job conditions.

Retention: Forty-eight (48%) of the 99 nurses with subjective assessment and salivary cortisol measures left the unit during follow-up, and 30 (40%) of the 75 with full datasets. Participants with above median frequency of endocrine stress responses tended to remain longer than those with below median frequency of endocrine stress responses (log rank test, p = 0.06, Figure 3.1). Average levels of subjective stress perception were not associated with the time elapsing until leaving the unit (log rank test, p = 0.63).

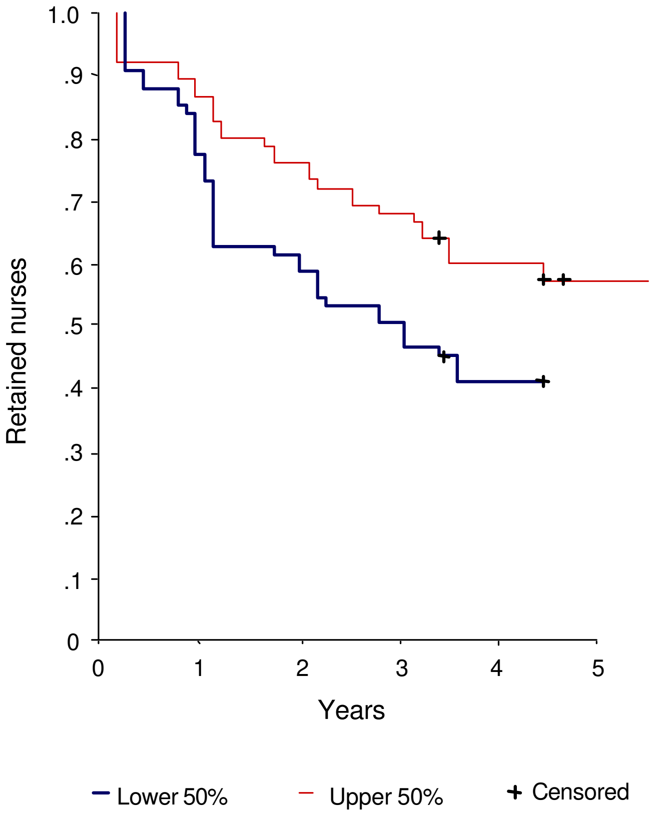

Figure 3.1: Retention of pediatric critical care nurses in relation to endocrine stress reactions. The figure displays the Kaplan-Meier curves for participants with above median frequency of endocrine stress reactions (Upper 50%) and below median frequency of endocrine stress reactions (Lower 50%).

Post-hoc analyses: The secondary analyses revealed that retention times were significantly shorter in ward A than in ward B or C ($p = 0.04$). Teams also differed significantly according to the nurses' perception of work characteristics (Table 3.1). To account for the colinearity between work-characteristic subscales, we extracted three principal components, which explained 65% of the total variance. Factor 1 comprised the subscales of perceived leadership style, team climate, and job satisfaction. Factor 2 consisted of work control, job variation, and job complexity. Factor 3 included time management and material job conditions. Lower scores in either factor indicated the perception of adverse work characteristics. Participants scoring in the lowest tercile on Factor 1 left the unit significantly earlier than other nurses (log rank test $p = 0.03$; Figure 3.2). Cox regression models controlling for frequency of endocrine reactions, and team membership retained Factor 1 ($p = 0.03$). No other work-characteristic variable was significantly associated with retention time (all $p > 0.1$).

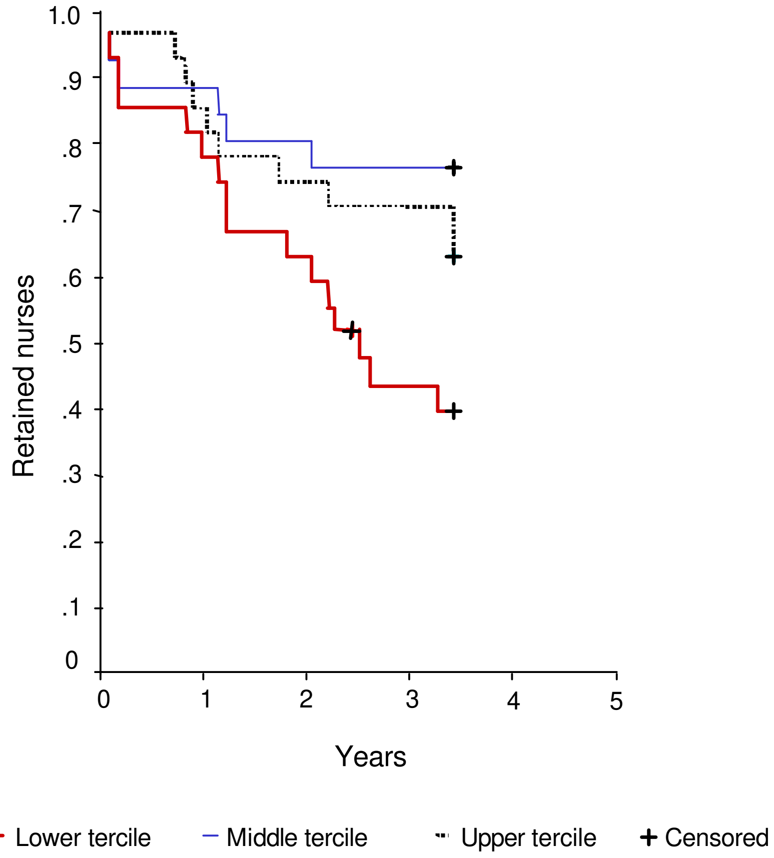

Figure 3.2: Retention in pediatric critical care nurses in relation to work-characteristics. Kaplan-Meier curves show tercile splits on a work-characteristic factor comprising the subscales team climate, perceived leadership style of the manager, and perceived job satisfaction. Lower scores correspond to perceiving job conditions as adverse.

To further elucidate the observed trend towards shorter retention with lower than median frequency of endocrine responses, we introduced a further median split across the scale representing exhaustion. Kaplan-Meyer survival analysis on the resulting two by two analysis (exhaustion x frequency of endocrine reactions) revealed that nurses with below median levels of exhaustion and above median frequency of endocrine reactions were retained in the unit significantly longer (log rank test, $p = 0.041$). This association was retained in Cox regression models controlling for confounding by age. Nurses with below median levels of exhaustion tended to be less likely to show below median frequency of endocrine responses (odds ratio = 0.52, 95% CI 0.23-1.10), indicating a possible association between lower frequencies of endocrine reactions and exhaustion.

3.5 Discussion

In this study, we prospectively followed a cohort of pediatric critical care nurses until they left the unit. At baseline we assessed subjective perception of work characteristics and, using multiple assessments, subjective stress perception and endocrine stress reactions. The main findings of our study were a) that average subjective stress perception was not related to retention, b) that nurses with above average frequency of endocrine stress responses tended to remain longer in the unit, and c) that participants scoring in the lowest tercile on a factor consisting of self-perceived team climate, leadership style and job satisfaction left the unit significantly earlier.

Our study has several important differences compared to previous investigations in this field. First, we assessed the exposure (subjective stress perception, endocrine reaction) by repeated measures at baseline. This method is less prone to recall bias than retrospective attribution of job stress. Second, we prospectively followed nurses until they left the unit. Unlike previous studies, which used “intention to leave” as the dependent variable, we chose to observe the real event of “quitting the job”. Our measurement of job stress was calculated as the average of the perceived job stress from repeated assessments obtained at two-hour intervals during several working shifts. This direct observational method provides an accurate assessment of state perception of task-related stress (e.g. resuscitation, admission of a child after cardiac surgery, death of a child). In contrast, we consider the reported perception of work characteristics as a baseline trait. Consistent with the literature (Cartledge 2001) (Boyle 1999), low scores on a factor consisting of team climate, leadership style and job satisfaction was associated with higher turnover rates. The strength of our study is that the observed differences arose within teams that shared the same environment as to attending physicians, technicians, management and building. Thus, the observed variance is highly likely to have occurred due to differences in the micro-social environment rather than external factors.

Contradicting our initial hypothesis, we found a trend towards a positive association between the frequency of endocrine stress responses and retention time. In our baseline study (Fischer 2000a), we demonstrated that experience did not abate the frequency of endocrine stress, indicating that the frequency of endocrine stress responses might be a rather stable personal trait. Thus, it is unlikely that our finding is a spurious coincidence of experienced nurses having lower frequencies of endocrine responses and being more likely to quit the job. The Kaplan-Meier curves comparing the two groups with lower and higher frequency of endocrine responses suggest that the difference is attributable to a different turnover rate in the first year of follow-up. Post-hoc analysis dividing the study population according to the reported level of exhaustion and the frequency of endocrine responses suggest that the quartile with low exhaustion and above average frequency of endocrine responses may continue to work longer. This finding could suggest a biological explanation of our observation, arising from research in teachers with burnout: Highly exhausted teachers showed impaired salivary cortisol responses to experimental stressors (Pruessner 1997) (Steptoe 2000). It is conceivable that some of the participants who subsequently left the unit were more exhausted during our baseline assessment than others (Appels 2000) (Appels 1991). According to the teachers study, exhausted nurses might mount less marked cortisol increases to the same stressor, thus failing to satisfy our stringent criteria defining a sample as an endocrine stress response.

A limitation to our study is the incompleteness of the work-characteristic data (75 of 98). This reduced our chance to observe statistically significant associations between retention and work-characteristic subscales. Moreover, this also restricted us to Cox regression models containing a maximum of three explanatory variables. Since our primary aim was to elucidate the association between acutely measured subjective stress perceptions or frequency of observed endocrine stress reactions with retention, all results from our secondary post-hoc analyses should be appreciated with appropriate caution. This pertains to the analysis on work characteristics as well as to the subgroup analysis on the interaction of exhaustion and frequency of endocrine stress responses.

In conclusion we demonstrated that perceived job stress - if measured acutely - is not related to job retention. Paediatric critical care nurse participating in this study who had less frequent endocrine stress reactions tended to leave their job earlier. Retention was shorter when nurses perceived team climate, leadership style of managers and personal job satisfaction as poor.

4. General discussion

In this work we assessed salivary cortisol level changes in health care workers both during routine work and stressful job events. This allowed to observe the diurnal patterns of the participants (Chapter 2) as well as their responses to stressful events (Chapter 3). Our main outcome variable was job turnover, defined as the time elapsing from entering the cohort until leaving the job. In the first study paper we focused on the variation of diurnal rhythms of salivary cortisol. The second study paper examined the relation of frequencies of subjective and endocrine stress experiences to turnover in nurses. The basis to both analyses was the same data set of a study in 1997 and 1998 with a total of 147 participants, who collected 3850 salivary samples during 7145 hrs of observation in 881 working shifts (Fischer 2000a) (Fischer 2000b). While varying exclusion criteria somewhat reduced the sample size available for the analyses in either paper, the sample reached good representivity of an individual's cortisol organization.

4.1 The variability of diurnal cortisol patterns

The typical circadian rhythm with increases after awakening and subsequent decline had been previously identified in present dataset (Fischer 2000a). In nurses who changed from early to night shifts, the diurnal rhythm showed little adaption. Over the usual roster of five night duties, a gradual delay of the onset of the morning peak by rd 1 hr per day had been observed. Only nurses who exclusively worked during the night showed an inverse circadian pattern. However, the earlier publication on this dataset was concerned with estimating average patterns and omitted the analysis of within- and between-subject heterogeneity.

In our present study we eliminated night shifts from our data, to reduce potential distortions. Samples that represented endocrine responses were eliminated too. Using the slope regression method, a diurnal cortisol pattern could be shown for nurses and physicians corroborating the findings by Stone and coworkers (Stone 2001). Like these authors, we found a significant within-subject and between-subject variation in slopes.

With a high accrual rate (< 93%) and all sampling supervised on site, we were able to minimize selection biases and measurement or recording error. Thus, our goal to show the cortisol cycle in a naturalistic and even highly stressful work setting was achieved.

According to the methods used by Stone (Stone 2001) we grouped the slopes of each observation shift into quintiles. The upper slope quintile showed significantly flattened cycles compared to the other quintiles. Individuals which had more than 50% of their slopes in the upper quintile could be identified. In contrast to other studies that identified a group of individuals (17%), who failed to exhibit a diurnal cycle during two subsequent observation days (Smyth 1997), none of the participants in the present study (with more than two observed shifts) had all of the shifts in the upper quintile. The highest rate of shifts with slopes in the upper quartile was 6 out of 8 shifts. Ten participants (8% of 112) had more than half of their slopes in the upper quintile. We also showed, that having a slope in the upper quintile in one year was a good predictor of having at least one slope in the upper quintile in the second year, suggesting that characteristics of diurnal cortisol secretion show trait characteristics.

Unlike in the datasets analyzed by Stone (Stone 2001), where no significant associations with the flattened slopes could be found, variables associated with the flattened slopes quintile could be identified in the present study: the slope was weakly associated with being a woman, with bad sleep quality, and with early awakening. However, these associations were rather weak compared to the prediction power of low intercept and high amount of stress reactions. Stone hypothesized that flat cycles could be due to stress-related alterations. Although we controlled for stress responses, eliminating them from our analysis, the remaining samples in the concerned shifts could be affected too. Recently, the flattened cortisol cycle has been shown a predictor of early death in women with breast cancer (Sephton 2000). Thus, the biological relevance of flattened cortisol slopes remains controversial.

In our study, most of the variance in cortisol slopes could be accounted for by the intercept estimate. A low intercept was the best predictor of a flattened slope. If the intercept is considered as the best proxy we had for morning cortisol peaks, our findings simply imply that subjects with high morning cortisol values are more likely to exhibit the expected pattern of diurnal decline than those with mitigated awakening response. In other words, the flattened slope is reflecting a low intercept, better known as morning response. This finding has been recently made by a study investigating cortisol cycles in adult women (Adam 2001). Therefore, it can be stated, that isolated examination of the slope is not useful when investigating the diurnal cortisol pattern.

It is noteworthy, that results and interpretation differed somewhat, if a statistical method was employed that allowed for three-level full random effect models. Using these multilevel models to analyze slope variations simultaneously on the sample, shift and individual level. As reported in chapter 2.5, variation in the diurnal cycle was greater for intercept than for slope. In the multilevel model, slope terms no longer retained between subject variance. These data suggest that circadian cortisol secretion follows a stable pattern across individuals, and that “flattened” slopes are arising from between day variance within individuals or from between-samples variance. This issue, however, is now of intense statistical scrutiny and we are looking forward to the analysis on our dataset being performed in the forthcoming months by Stone and coworkers.

Finally, it should be noted, that our initial goal to show that flattened cycles are related to high burnout levels, could not be achieved. An association between flattened slope quintile and emotional exhaustion could not be found. Thus, our hypothesis that burned out nurses could be identified by their missing diurnal cycle could not be proved.

4.2 Determinants of nurse turnover

Having eliminated the individual's average slope as a meaningful parameter to be included as a predictor for job turnover, the two remaining main independent candidate predictor variables were: 1) the average of subjective stress and 2) the frequency of endocrine stress responses. In addition, job evaluations, emotional exhaustion, the objective and subjective workload as well as personal variables were considered to explain the turnover behavior in nurses.

According to the existing literature, prediction of actual turnover behavior is difficult and the best prediction is made by the intention to quit (Alexander 1998). The few studies investigating factual turnover behaviour found relationship with coworkers and job hazards to be the only predictors besides intention (Alexander 1998). Most studies investigating turnover intention and work related stress found significant associations between both (Consolvo 1979) (Oates 1995), particularly in connection with work satisfaction (Shader 2001). However, the direct linkage between job stress and turnover behaviour has not been established. In addition, none of the studies reported above measurement of subjective stress experience and physiological stress response. The question whether turnover behaviour is predicted more accurately by psychological stress experience or by physiological reaction remains of particular interest, since our previous analysis of the existing dataset showed only moderate accordance between both stress measures. Over 70% of all endocrine responses occurred when participants were not aware of stress (Fischer 2000a). The data from this dataset suggest that on average nurses experienced an endocrine response every second work day/shift (Fischer 2000a).

The first key finding of the present analysis was that subjective stress perception averaged across observation days was not predicting the turnover behavior in the following four years. Comparing a "low stressed" and "high stressed" group of nurses, no differences of turnover behaviour could be found. In our study, the direct monitoring of subjective stress perception in a two-hourly rhythm resulted in a stress measure that was different compared to most of the studies that have previously investigated stress and turnover. Retrospective stress reports using questionnaires are more strongly affected by recall and latent variables, like job satisfaction, group cohesion, instrumental communication and autonomy (Boyle 1999). Our measure of job stress was much more event-related, even though not free from the influences mentioned above. Job stress showed significant correlations with baseline measures of job satisfaction ($r = 0.37$), as well as perception of work conditions ($r = 0.28$), leading style ($r = 0.29$) and team climate ($r = 0.36$). Further, job stress was positively correlated with average work difficulty ($r = 0.35$), perception of threat ($r = 0.30$) and positive appraisal at work ($r = 0.23$).

The finding that neither the averaged stress perception nor the averages of objective and subjective workload measured at the end of each shift were associated with turnover should be kept in mind when designing future studies. The differences in stress assessment methods should be integrated.

A surprising result was the prediction of turnover behaviour by frequency of endocrine stress responses in a direction that was opposite to our initial hypothesis. The group with highest frequency of endocrine responses during several observation days remained significantly longer on the job. However, on hindsight the present findings can be reconciled with some studies mentioned in chapter 1.5.2 that reported hypocortisolism (Yehuda 2000) (Heim 2000) and significantly lowered stress responses (Klein 1995) as a consequence of chronic stress experience. Moreover, people suffering from burnout have been shown to have lowered morning elevations and stress responses (Pruessner 1999) (Steptoe 2000). Thus, it is conceivable that group of nurses in our study with less frequent endocrine responses experienced the same amount of stressful events but due to possible burnout mounted less vigorous cortisol responses. These blunted responses failed to satisfy our criterion of being recorded as endocrine response. This burnout may have been subclinical, since we failed to show an association between frequency of endocrine responses and the emotional exhaustion scale in those individuals, who completed the scale in 1998. However, creating a composite dummy variable of exhaustion and frequency of endocrine reactions revealed that nurses with low or no exhaustion and above frequencies of stress remained in the unit for the longest periods.

The only psychological variable associated with turnover was the combined job factor, including evaluation of climate, leadership and job satisfaction. Nurses who achieved lowest scores on this factor left their job significantly earlier than the others. The influence of the three underlying dimensions is in line with the existing literature on turnover of nurses (Boyle 1999) (Yin 2002) (Hatton 1993). Our study expands previous work by showing the direct associations with observed turnover behaviour. Previously, direct influences had been reported for work hazards and relationship with coworkers (Alexander 1998), the latter probably being comparable to our dimension of team climate.

In conclusion we demonstrated that perceived job stress - if measured acutely - is not related to job retention. We could show a direct association between cortisol secretion and the behaviour of quitting the job. Nurses who had less frequent endocrine stress reactions tended to leave their job earlier. Retention was shorter when nurses perceived team climate, leadership style of managers and personal job satisfaction as poor.

Since our primary aim was to elucidate the association between acutely measured subjective stress perceptions or frequency of observed endocrine stress reactions with retention, the results from our secondary post-hoc analyses should be appreciated with appropriate caution. This pertains to the analysis on work characteristics as well as to the subgroup analysis on the interaction of exhaustion and frequency of endocrine stress responses.

4.3 Open questions for future research

In the present study, a direct link between cortisol values and turnover behavior could be found. The data may be interpreted in a way that nurses with exhaustion left their job earlier during the 4 years of observation. Prolonged periods of employee burnout have negative implications for the individual, for patients under their care, and for the effectiveness of the organisation, especially when leading to absenteeism and turnover (Schaufeli 1998). This adds additional cost to critical care services (Song 1997). Therefore, screening for exhaustion, physical and mental health should be implemented as part of an organizations care for their employees. It remains to be elucidated, whether including assessment of intention to leave may serve as an early warning indicator preceding burnout and factual quitting the job.

Hospital managers should further focus on team climate, leadership style and job satisfaction (Kendall 2000). Attempts to reduce nurse turnover and absenteeism by improving nurses' job satisfaction have included the introduction of case (Loveridge

1988), shared governance (Porter-O'Grady 1987), or implementation of situational leadership (McDaniel 1992).

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