Acute lymphoblastic leukemia (ALL) is the most frequent type of malignancy in childhood and (non-)Hodgkin lymphoma is the most frequent malignancy in adolescence. With the increased survival rates of childhood ALL and of lymphoma, side-effects of treatment become more and more important. High-dose prednisolone or dexamethasone therapy is routinely used in the treatment of both childhood ALL and childhood lymphoma. However, side-effects of these glucocorticoids include suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Adrenal suppression, resulting in inadequate cortisol levels during stress, may lead to life-threatening hypoglycemia and/or hypotension, impaired inflammatory response, and inadequate host defense against infections. The risk of life-threatening situations in patients with HPA axis suppression can be reduced by glucocorticoid coverage (e.g. hydrocortisone) during periods of stress. However, due to the lack of knowledge on the extent of HPA axis suppression during treatment of childhood ALL and lymphoma, stress dose therapy is not standard practice and there is no agreement on the optimal management of adrenal insufficiency.

Studies on long-term effects of exposure to high-dose glucocorticoids early in life have reported an alteration of HPA axis activity later in life. These studies have also caused concern about the long-term neuroendocrine sequelae of high-dose glucocorticoid treatment in childhood ALL and lymphoma. Nevertheless, HPA axis activity in survivors of childhood ALL and lymphoma has not been studied. In addition, there is increasing evidence that cortisol levels are associated with sleep, fatigue, depression and quality of life (QoL). Although childhood cancer survivors frequently report problems with sleep, fatigue, depression and QoL, the potential associations between these impairments and cortisol levels have not been studied in survivors of childhood ALL and lymphoma.

The aim of this thesis was to investigate the neuroendocrine and psychosocial consequences of high-dose glucocorticoid therapy during and after treatment for childhood ALL and lymphoma.

Chapter 1 describes the background of this thesis: childhood ALL and lymphoma, glucocorticoid therapy and its neuroendocrine and psychosocial consequences.

Chapter 2 emphasizes the clinical relevance of the subject of this thesis by illustrating diverse clinical presentations of glucocorticoid-induced adrenal insufficiency in children with a malignancy. In addition, we propose a flowchart for the indication of glucocorticoid coverage.

Chapter 3 discusses the results of a systematic literature review of HPA axis suppression after treatment with glucocorticoid therapy for childhood ALL. The seven included studies (with a total number of 189 participants) show that adrenal insufficiency occurs in nearly all patients in the first days after discontinuation of glucocorticoid treatment for childhood ALL.
The majority of patients recovered within a few weeks, but a small number of patients had prolonged adrenal insufficiency lasting up to 34 weeks. Due to heterogeneity and the suboptimal methodological quality of the included studies, more high-quality research is needed to assess the exact occurrence and duration of HPA axis suppression in order to formulate adequate guidelines for the management of adrenal insufficiency during childhood ALL.

In Chapter 4 we present the results of a prospective multi-center study regarding the occurrence and duration of adrenal insufficiency during induction and maintenance treatment for childhood ALL. The median time to recovery from adrenal insufficiency after induction therapy was 28 days. However, one-third of the patients did not recover from adrenal insufficiency at the end of the follow-up period of 96 days. In addition, ongoing adrenal insufficiency after induction therapy was associated with adrenal insufficiency during maintenance therapy. As the majority of patients recovered within five weeks after cessation of induction therapy, whilst the probability of adrenal recovery for remaining patients after five weeks was low, we recommend glucocorticoid coverage during periods of stress in the first five weeks after induction therapy in all patients. Thereafter, an adrenal function test should be performed in order to determine which patients suffer from prolonged adrenal insufficiency and in which patients stress dose therapy can be discontinued.

The first study that reports on adrenal function during treatment for childhood (non-)Hodgkin lymphoma is presented in Chapter 5. Adrenal insufficiency in childhood lymphoma frequently occurred. In addition, all patients with an insufficient cortisol response to the adrenal stimulation test between courses of glucocorticoids demonstrated prolonged adrenal insufficiency after finishing treatment. Therefore, we recommend to prescribe glucocorticoid coverage during periods of stress between cyclic courses of glucocorticoids and in the first weeks after finishing treatment for childhood lymphoma. An adrenal function test is recommended, e.g. one month after cessation of glucocorticoids, to identify patients who suffer from prolonged adrenal insufficiency and to determine in which patients stress dose schedules can be discontinued. The duration of adrenal insufficiency after cessation of glucocorticoid therapy in children treated for ALL or lymphoma showed considerable inter-individual variation. As described in Chapter 6, we examined the association between genetic variations (polymorphisms) of the glucocorticoid receptor and the duration of adrenal insufficiency. One polymorphism (ER22/23EK) was associated with a shorter duration of adrenal insufficiency, whilst another polymorphism (BclI) was associated with an increased duration of adrenal insufficiency after cessation of induction therapy in childhood ALL.

In order to study the associations between the frequently reported problems with sleep, fatigue, depression and QoL in childhood ALL survivors and cortisol levels, we first had to develop and validate appropriate Dutch questionnaires to measure fatigue in children and sleep in adolescents. Chapter 7 discusses the psychometric properties and the norm-references of the Dutch version of the PedsQL™ Multidimensional Fatigue Scale. This questionnaire demonstrated adequate feasibility, reliability and validity and can be utilized as a
tool to measure fatigue in healthy and chronically ill children aged 2-18 years. **Chapter 8** in addition, describes the psychometric characteristics and the norm-references of the Dutch version of the Adolescent Sleep Habits Questionnaire. This questionnaire demonstrated satisfactory reliability and validity for the total scores and can be utilized for assessing sleep habits in adolescents.

In **Chapter 9** we report on the results of a study regarding sleep, fatigue, depression and QoL after treatment for childhood ALL. Parents rated the ALL survivors as having more disturbed sleep, more fatigue and poorer physical QoL compared to the Dutch norm. ALL survivors themselves, however, reported less sleep problems, less depressive problems, and better psychosocial QoL than the Dutch norm. Discrepancies between parental and self-ratings might be explained by worried parents and/or the adaptive style of the children. Impaired sleep and fatigue were associated with more symptoms of depression and an impaired QoL, indicating a possibility for intervention to improve psychosocial health after surviving childhood ALL.

Although prolonged HPA axis suppression after treatment with high-dose glucocorticoids in childhood ALL has been reported, HPA axis activity in survivors of childhood ALL has never been studied. In **Chapter 10** we present the results of the first study on HPA axis function, in relation to sleep, fatigue and QoL, in survivors of childhood ALL and in healthy children. No differences in cortisol awakening response were observed between ALL survivors and the reference group, but survivors of ALL had higher morning cortisol levels. In addition, ALL survivors had an increased cortisol suppression in response to oral dexamethasone. Higher cortisol levels in childhood ALL survivors were associated with more fatigue and poorer QoL. These findings indicate that the experience of a stressful life event in the past may have caused a long-term dysregulation of the HPA axis in childhood ALL survivors, as reflected in an increased cortisol production and an enhanced negative feedback mechanism.

Previous studies in trauma exposed children did not only demonstrate enhanced cortisol levels, but also increased sympathetic nervous system activity, which in turn may lead to cardiovascular diseases later in life. We therefore assessed the HPA axis regulation and sympathetic nervous system activity in survivors of childhood ALL by evaluating the endocrine and cardiovascular response to a psychosocial stressor, the Trier Social Stress Test for Children (TSST-C), as described in **Chapter 11**. In the total study group, exposure to the TSST-C induced a significant response of perceived stress, saliva cortisol and cardiovascular outcome variables. These responses did not significantly differ between survivors of childhood ALL and healthy controls. These findings indicate that survivors of childhood ALL have an adequate response of the HPA axis and the sympathetic nervous system to social stress.

In conclusion, HPA axis suppression frequently occurs as a result of high-dose glucocorticoid therapy in childhood ALL and lymphoma. Glucocorticoid coverage during periods of stress should be prescribed in the first weeks after cessation of glucocorticoid therapy in all patients, in order to avoid life-threatening complications of HPA axis suppression. Thereafter,
an adrenal function test should be performed in order to determine which patients suffer from prolonged adrenal insufficiency and in which patients stress dose therapy can be discontinued. We identified two polymorphisms of the glucocorticoid receptor gene which play a role in the duration of adrenal insufficiency.

We also demonstrated dysregulation of the HPA axis in survivors of childhood ALL, as reflected in increased morning cortisol levels and enhanced feedback of the HPA axis. This hyperresponsiveness of the HPA axis might be of clinical relevance since high cortisol levels in survivors of ALL are associated with fatigue and an impaired QoL. Although morning cortisol production is increased, survivors of childhood ALL have an adequate response of the HPA axis and the sympathetic nervous system to social stress.