

Eczema, sleep and daytime functioning in children

by

Danny Camfferman BA, Grad Dip Psych.

A thesis submitted for the Degree of Doctor of Philosophy

Department of Paediatrics

Faculty of Health Sciences

The University of Adelaide

Submitted December 2010

Table of Contents

Table of Contents.....	ii
List of Tables.....	ix
List of Figures.....	xii
Abstract.....	xvi
Declaration.....	xix
Publications in support of thesis.....	xx
Acknowledgements.....	xxi
List of Abbreviations.....	xxii
Chapter 1: Introduction and literature review.....	1
1.1 Introduction.....	1
1.2 Literature review.....	2
1.2.1 The demographic profile of eczematous children with sleep disturbance.....	3
1.2.2 Notable questionnaire studies which focus on the sleep characteristics of children with eczema.....	4
1.2.3 Sleep disturbance in parents of children affected with eczema.....	5
1.2.4 Mechanism assumed to cause sleep disturbance in children with eczema.....	5
1.2.5 Actigraphic studies on children with eczema and sleep.....	6
1.2.6 Biological markers of childhood eczema and sleep.....	7
1.2.7 Polysomnography data on children with eczema.....	8
1.3 Summary of current data on the sleep of children with eczema.....	9

1.4 Body temperature and sleep in humans.....	10
1.4.1 Eczematous skin and body temperature.....	11
1.5 Rhinitis and asthma disturbing sleep in children with eczema.....	12
1.6 Treatment of childhood eczema and sleep.....	14
1.7 Sleep disturbance and quality of life.....	16
1.8 Childhood eczema, sleep, daytime behaviour and cognition.....	17
1.8.1 Eczema, sleep and behaviour in children with eczema.....	18
1.8.2 Eczema, sleep and ADHD in children with eczema.....	19
1.8.3 Sleep and neurocognitive development in children.....	19
1.9 Summary of current literature on eczema, sleep and daytime functioning in children.....	21
Chapter 2: Eczema, asthma, rhinitis, sleep and behaviour in children.....	40
2.1 The contribution of eczema, asthma and rhinitis to sleep disturbance and behaviour in children.....	40
2.2 Method.....	41
2.2.1 Participants and Procedure.....	41
2.2.2 Apparatus.....	41
2.2.3 The Child Health Questionnaire-Parent Form.....	43
2.2.4 The Children's Dermatology Life Quality Index.....	43
2.2.5 The Sleep Disturbance Scale for Children.....	44
2.2.6 The Conner's Parent Rating Scale - Revised (S).....	44

2.3 Statistics.....	45
2.4 Results.....	46
2.4.1 Correlations between atopic disorders and demographic/behavioural variables.....	46
2.4.2 Correlations between eczema, sleep disorder and behaviour.....	47
2.4.3 Structural Equation Modelling Analysis.....	47
2.4.4 Evaluation of the Models generated through Structural Equation Analysis.....	49
2.4.5 Results of Structural Equation Analysis on children with eczema's sleep and behaviour.....	50
2.5 Discussion.....	61
Chapter 3: Polysomnography data on the sleep of eczematous children.....	67
3.1 Rationale for conducting polysomnographic studies on children with eczema.....	67
3.2 Potential measures of eczema severity.....	67
3.2.1 Current methods of measuring eczema severity.....	68
3.2.2 Biological markers of eczema severity.....	69
3.2.3 Urinary Leukotriene E ₄	69
3.3 Method.....	70
3.3.1 Subjects and Procedure.....	70
3.3.2 Apparatus.....	71
3.3.3 Eczema Assessment.....	71

3.3.4 Asthma and Allergic Rhinitis.....	72
3.3.5 Leukotriene E4.....	72
3.3.6 Sleep Disturbance Scale for Children.....	73
3.3.7 Polysomnography.....	74
3.4 Statistics.....	75
3.5 Results.....	76
3.5.1 Comparison of demographics, atopic disorders and sleep variables between children with eczema and controls.....	76
3.5.2 Relationship between atopic disease and polysomnographic sleep data among children with eczema.....	77
3.6 Discussion.....	85
Chapter 4: An examination of the contribution of scratch disturbing sleep in children with eczema	92
4.1 Itch.....	92
4.2 Scratch.....	92
4.2.1 Measuring nocturnal scratch using polysomnography.....	93
4.3 Nocturnal scratching in children with eczema.....	94
4.3.1 Nocturnal scratching in adults with eczema.....	96
4.4 Method.....	98
4.4.1 Actigraphy.....	99
4.4.2 Scratching.....	99

4.5 Results.....	100
4.5.1 Actigraphy data of children with eczema compared to controls.....	100
4.5.3 Relationship between atopic disease and actigraphy data among children with eczema.....	100
4.5.4 Relationship between actigraphy and polysomnography data among children with eczema controlling for frequency that asthma disturbs sleep in the last 12 months and the frequency that rhinitis controls sleep in the last 12 months.....	101
4.5.5 Relationship between the SCORAD, scratching, arousals and sleep stage in children with eczema.....	102
4.6 Discussion.....	109
Chapter 5: Eczema, sleep and body temperature in children.....	116
5.1 Body temperature regulation in humans.....	116
5.2 Circadian rhythms and body temperature in humans.....	117
5.3 Sleep disorders associated with temperature dysfunction.....	119
5.4 The impact of eczema on heat transference in the human body.....	121
5.5 Co-sleeping and thermoregulation in children with eczema.....	122
5.6 Research on the skin of eczema patients and its impact on thermoregulation.....	122
5.7 Rationale for studying skin temperature in children with eczema.....	124
5.8 Method.....	125
5.8.1 Subjects and Apparatus.....	125
5.8.2 Temperature.....	125
5.9 Results.....	126

5.9.1 ANOVA results of nocturnal temperature differences between children with eczema and controls	126
5.8.2 Correlation between sleep and nocturnal mean temperature values.....	126
5.10 Discussion.....	136
Chapter 6: Sleep and daytime functioning in eczematous children: Polysomnography and neurocognitive testing.....	141
6.1 Sleep and Neurocognition.....	141
6.2 Neurocognitive deficits, co-morbid disorders and sleep disturbance in eczematous children.....	143
6.3 Rationale for examining the neurocognitive profile of children with eczema and possible associations with their sleep quality.....	143
6.4 Method.....	144
6.4.1 Neurocognitive assessment.....	144
6.4.2 Attention assessment.....	145
6.4.3 Reading age.....	146
6.4.4 Snoring.....	146
6.5 Results.....	146
6.5.1 Group Comparisons between eczema children and controls on snoring, atopic disorders and sleep variables.....	146
6.5.2 Comparison of neurocognition variables between eczema and control groups.....	146

6.5.3 Relationship between eczema, behaviour and neurocognition among children with eczema.....	147
6.5.4 Correlations between eczema, behaviour and neurocognitive variables among children controlling for snoring and co morbid atopic disease disturbing sleep.....	148
6.5.5 Correlations between polysomnography variables and behavioural ratings of eczematous children, controlling for the frequency of snoring and the frequency that co morbid atopic disease disturbed sleep.....	148
6.5.6 Correlations between polysomnography and neurocognitive variables of eczematous children, controlling for frequency of snoring and the frequency that co morbid atopic disease disturbed sleep.....	148
6.6 Discussion.....	156
Chapter 7: Eczema, sleep and daytime behaviour in children.....	164
7.1 Eczematous children's sleep findings.....	164
7.2 Neurocognition, behaviour and sleep in eczematous children.....	164
7.3 Co-morbid disorders of Asthma and Rhinitis.....	165
7.4 Case study of female eczema patient (aged 7yrs) pre and post treatment.....	165
7.5 Method.....	166
7.6 Results.....	166
7.7 Discussion.....	170
7.8 Future directions for study.....	170
7.9 Conclusion.....	171

List of Tables

Table 1.1: Eczema questionnaire studies reporting sleep information.....	23
Table 1.2: Eczema treatment studies reporting sleep data.....	26
Table 1.3: Questionnaire studies which report the sleep of parents of children with eczema.....	27
Table 1.4: Studies using actigraphy to measure sleep in children with eczema.....	29
Table 1.5: Studies using polysomnography to measure sleep in children with eczema.....	30
Table 2.1: Atopic questionnaire items used to estimate severity and impact on sleep.....	42
Table 2.2: Correlation matrix of eczema, asthma and rhinitis variables.....	51
Table 2.3: Mean (SD) demographic, quality-of-life, sleep and behaviour questionnaire scores for children with eczema and controls together with F-test/Chi-square (χ) results.....	52
Table 2.4: Correlation matrix: atopy variables versus demographic, quality-of-life, sleep and behaviour questionnaire variables in children with eczema.....	53
Table 2.5: Correlation matrix of sleep and behavioural scales and their subscales in children with eczema.....	54
Table 2.6: Results of Structural Equation Modelling (Maximum Likelihood Estimates) in the relationship between Asthma, Eczema, & Rhinitis on Sleep Problems and Behaviour Problems.....	55
Table 3.1: Mean (SD) demographic and sleep scores for children with eczema and controls together with F-test/Chi-square results	78

Table3.2: Correlation matrix: Atopic Disease with Polysomnography variables of children with eczema.....	79
Table 4.1: Mean (SD) demographic, atopic disease and actigraphy variables for children with eczema compared to controls together with F-test/Chi-square results.....	103
Table 4.2: Correlation matrix: Atopic disease severity and their relationship with actigraphic variables.....	104
Table 4.3: Correlation matrix of actigraphy and polysomnography sleep variables of children with eczema controlling for frequency that asthma disturbs sleep in the last 12 months and frequency that rhinitis disturbs sleep in the last 12 months.....	105
Table 4.4: Mean (SD) and F-test results of the nocturnal distribution of scratch-related activity in children with eczema.....	106
Table 4.5: Correlation matrix of eczema severity, polysomnography scratching events in children with eczema.....	107
Table 4.6: Studies of actigraphy and scratch in children with eczema.....	112
Table 4.7: Studies of polysomnography and scratch in children and adults with eczema....	113
Table 5.1: ANOVA results of nocturnal temperature differences between children with eczema and controls.....	127
Table 5.2: Correlation between sleep and nocturnal mean temperature values.....	127
Table 6.1: Mean (SD) of frequency of snoring, atopic disease and sleep scores for children with eczema and controls together with F-test/Chi-square results.....	149

Table 6.2: Correlation matrix: Eczema, Behaviour, IQ, Attention and Reading Age variables of children with eczema co-varied for frequency of snoring, frequency that asthma disturbed sleep in the last 12 months and frequency that rhinitis disturbed sleep in the last 12 months.....	150
Table 6.3: Correlation matrix of the sleep and behavioural variables of children with eczema co-varied for frequency of snoring, frequency that asthma disturbs sleep in the last 12 months and frequency that rhinitis disturbs sleep in the last 12 months.....	151
Table 6.4: Correlation matrix of the sleep and neurocognitive variables of children with eczema co-varied for frequency of snoring, frequency that asthma disturbed sleep in the last 12 months and frequency that rhinitis disturbed sleep in the last 12 months. Attention Total Score and Reading ability are also controlled for age.....	155
Table 7.1: Pre and post treatment data of BMI, snoring, atopic disease severity, sleep questionnaire, actigraphy and polysomnography variables of a 7 year old female with eczema.....	168
Table 7.2: Pre and post treatment data of behavioural and neurocognitive variables of a 7 year old female with eczema.....	169

List of Figures

Figure 2.1: SEM Model for Hypothesised Relationships Between Conditions Sleep and Behaviour.....	56
Figure 2.2: Partial Mediation of Cognition by Asthma, Eczema and Rhinitis Effect on Sleep.....	57
Figure 2.3: Partial Mediation of Hyperactivity by Asthma, Eczema and Rhinitis Effect on Sleep.....	58
Figure 2.4: Partial Mediation of ADHD by Asthma, Eczema and Rhinitis Effect on Sleep.....	59
Figure 2.5: Partial Mediation of Oppositional (Behaviour) by Asthma, Eczema and Rhinitis Effect on Sleep.....	60
Figure 3.1: Minutes of Stage 1 sleep per 30 minute epoch.....	80
Figure 3.2: Minutes of Stage 2 sleep per 30 minute epoch.....	80
Figure 3.3: Minutes of Stage 3 sleep per 30 minute epoch.....	81
Figure 3.4: Minutes of Stage 4 sleep per 30 minute epoch.....	81
Figure 3.5: Minutes of REM sleep per 30 minute epoch.....	82
Figure 3.6: Minutes of Wake After Sleep Onset per 30 minute epoch.....	82
Figure 3.7: Scatterplot of VAS scores of itch severity and Desaturation Nadir in Total Sleep Time in children with eczema.....	83

Figure 3.8: Scatterplot of VAS scores of itch severity and REM % in children with eczema.....83

Figure 3.9: Screenshot of sub cortical respiratory event recorded during polysomnography..84

Figure 4.1: Nocturnal frequency per hour of scratching when awake and scratching when asleep in children with eczema.....106

Figure 4.2: Screenshot of scratch event recorded during polysomnography (Brown and Kalucy, 1979).....108

Figure 4.3: Screenshot of scratch event recorded during polysomnography (Aoki et al., 1991).....108

Figure 5a: Core body temperature of older adults (black) and children (white) over a 24 hour period.....118

Figure 5.1: Right versus left finger temperature control children.....128

Figure 5.2: Right versus left clavicle temperature control children.....128

Figure 5.3: Right versus left finger temperature children with eczema.....129

Figure 5.4: Right versus left clavicle temperature children with eczema.....129

Figure 5.5: Control versus children with eczema right index temperature.....130

Figure 5.6: Control versus children with eczema right clavicle temperature.....130

Figure 5.7: Control versus children with eczema left index temperature.....131

Figure 5.8: Control versus children with eczema left clavicle temperature.....131

Figure 5.9: Control versus children with eczema right index finger minus right clavicle temperature difference.....132

Figure 5.10: Control versus children with eczema left index finger minus left clavicle temperature difference.....132

Figure 5.11: Right versus left distal-proximal gradient (finger minus clavicle) for control children.....133

Figure 5.12: Right versus left distal-proximal gradient (finger minus clavicle) for children with eczema.....133

Figure 5.14: Average index finger (left versus right) temperature for children with eczema and control children.....134

Figure 5.15: Average clavicle (left versus right) temperature for children with eczema and control children.....134

Figure 5.16: Average (left versus right) distal-proximal gradient (finger minus clavicle) for children with eczema and control children.....135

Figure 6.1: Scatterplot of Hyperactivity and Sleep Onset Latency (minutes) in children with eczema.....152

Figure 6.2: Scatterplot of ADHD Index and Sleep Onset Latency (minutes) in children with eczema.....153

Figure 6.3: Scatterplot of Oppositional behaviour and Sleep Onset Latency (minutes) in children with eczema.....154

Abstract

Eczema affects up to 20% of children in western industrialised countries. Chronic childhood eczema has significant morbidity characterised by physical discomfort, emotional distress, reduced child and family quality-of-life and, of particular note, disturbed sleep. Sleep disturbance, characterised by frequent and prolonged arousals, affects up to 60% of children with eczema, increasing to 83% during exacerbation. Even in clinical remission, children with eczema demonstrate more sleep disturbance than healthy children. Disturbed sleep in otherwise healthy children is associated with behavioural and neurocognitive deficits. Preliminary evidence suggests that disturbed sleep in children with eczema is also associated with behavioural deficits while the impact on neuropsychological functioning remains unexplored.

Two major studies were undertaken to examine the sleep of children with eczema and possible secondary deficits due to poor sleep. Parents of children (6-16y) with eczema (n = 77) and healthy controls (n = 30) completed a validated omnibus questionnaire which included items which assessed sleep, behaviour, general health, quality-of-life and additional items assessing eczema, asthma, rhinitis and demographics. Structural Equation Analyses revealed that the effect of eczema on the behavioural variables of Hyperactivity, ADHD Index and Oppositional behaviours were mediated through sleep with no direct effect of eczema on behaviour. A similar relationship between sleep and behaviour was observed for the co morbid atopic disorders of rhinitis and asthma.

In the second study, children (aged 6-16y) with eczema (n = 24) and controls (n = 19) were assessed through polysomnography to provide data on their sleep quality. Eczema severity was evaluated using SCORAD ratings scales and eczematous children provided a urine sample for analysis for Leukotriene E₄, a biological marker of atopic inflammation.

Scratching was assessed using infra-red camera. Distal and Proximal body temperature was measured to ascertain potential deficits in homeostatic processes and actigraphy was employed to record nocturnal activity. To evaluate neurocognitive ability all children underwent IQ testing with eczematous children undergoing additional children attention and reading age measurements.

Polysomnographic data on children with eczema showed that they had a longer REM onset latency, higher percentage stage 3 & 4 sleep, longer Wake After Sleep Onset and a lower Sub Cortical Arousal Index than controls. Higher Leukotriene E₄ levels was strongly associated with longer Wake after Sleep Onset. In addition, Wake after Sleep Onset also exhibited a trend toward higher itch and sleep loss ratings of the SCORAD. Increased Leukotriene E₄ levels also demonstrated associated trends in lower Sleep Efficiency, longer REM Onset Latency, a lower percentage of REM and fewer Stage Shifts. Using infra-red video contiguous with polysomnography, scratching was found to occur during sleep in all sleep stages. The SCORAD variable of Erythema, which is the redness or inflammation of the skin that is the result of dilation of superficial capillaries was found to be strongly associated with nocturnal scratching.

Actigraphic data demonstrated that children with severe eczema had more nocturnal activity and for longer periods of time than either mild to moderate eczema patients or controls. Actigraphy variables were also associated with the frequency that asthma and rhinitis disturbed sleep as well as eczema severity and Leukotriene E₄ levels in children with eczema. The actigraphic variables of Sleep Efficiency and Awakenings were moderately associated with the polysomnographic variables of Total Sleep Time, Sleep Efficiency and Sleep Onset Latency.

Sleep Onset temperatures were similar between eczema and control groups, however the skin temperature profile of children with eczema differed markedly from control subjects thereafter. Distal skin temperature in eczematous children was found to be significantly lower than controls for approximately a third of the night. Overnight trends in eczema subject's Distal temperature indicated that the heat loss usually associated with nocturnal sleep was markedly greater than controls.

Eczema children scored significantly lower on Full Scale IQ, Verbal Comprehension and Perceptual Reasoning scores than controls. On the WISC-IV subtests, scores of similarities, comprehension, picture concepts and letter-number sequencing were also significantly lower in children with eczema than controls. After controlling for the impact of snoring, asthma and rhinitis disturbing sleep, our findings suggest that lower neurocognitive performance in children with eczema is related to their sleep quality.

In conclusion, eczema was found to affect the sleep of children with longer periods of awake during the night and with more nocturnal movement than controls. The sleep architecture of children with eczema was also found to be associated with behavioural and neurocognitive deficits. Nocturnal scratching was found to occur during sleep and further, produce arousal from sleep, however the lack of associations between itch and sleep variables indicate that itch is also not a primary cause of sleep disturbance in children with eczema. The role of skin temperature in nocturnal thermoregulation appears to be disturbed in this patient group with eczema children showing evidence of a greater and more rapid heat loss than controls. It is also suggested that these rapid changes in temperature are associated with sleep disturbance. While the findings of a case study indicating that treatment improving sleep quality is also associated with neurocognitive and behavioural improvements, further study is required to determine the mechanism associating sleep fragmentation with daytime functioning.

Declaration

Name: Danny Camfferman

Program: PhD in Medicine

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue, the Australasian Digital Theses Program (ADTP) and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Signed:.....

Date:.....

Publications in support of thesis

Publications

Camfferman D, Kennedy JD, Gold M, Martin AJ, Lushington K. (2010) Eczema and sleep and its relationship to daytime functioning in children. *Sleep Medicine Reviews*, 14 (6), 359-369.

Camfferman D, Kennedy D, Gold M, Winwood P, Martin AJ, Lushington K. (2010), Eczema and sleep and behaviour in children. *Journal of Clinical Sleep Medicine*, 6 (6), 581-588.

Acknowledgements

First, I would like to thank all the parents and children who participated in the study for their time, interest and compliance, as without their support, this work could not have been possible.

To Yvonne Pamula and staff of the Sleep Disorders Unit at the Women's and Children's Hospital for their help and accommodating me in the use of their facilities.

To Fiona Futo and Margaret Heddle working as research assistants in the Sleep Disorder Unit, for their assistance with recruitment of subjects for this project.

To Kathy Carmen from the Immunology Department for her help in the collection and analyses of the Leukotriene E₄ samples.

To fellow PhD. students Mark Kohler, Andrew Valkulin and Scott Coussens for their help and advice throughout the study.

The final acknowledgement is to my supervisors Assoc. Prof. Kurt Lushington, Dr. Declan Kennedy and Dr. Mike Gold for teaching me research skills that I will endeavour to expand upon in the future.

List of Abbreviations

Acetylcholine (Ach)

Arteriovenous-anastomoses (AVAs)

Attention Deficit Hyperactivity Disorder (ADHD).

Brain-Derived Neurotrophic Factor (BDNF)

Childhood Atopic Dermatitis Impact Scale (CADIS)

Child Health Questionnaire-Parent Form (CHQ-PF-28)

Children's Dermatology Life Quality Index (CDLQI)

Circulatory Temperature Index (CTI)

Dermatitis Family Impact questionnaire (DFI)

Eczema Area Severity Index (EASI)

Immunoglobulin E (IgE)

Infants' Dermatology Quality of Life Index (IDQoLI)

International Study of Asthma and Allergies in Childhood (ISSAC)

Leukotriene E₄ (LTE₄)

Macrophage-Derived Chemokine (MDC)

Nottingham Eczema Severity Score (NESS)

Polysomnography (PSG)

Rapid Eye Movement (REM)

SCORing Atopic Dermatitis (SCORAD)

Socio-Economic Indexes For Areas (SEIFA)

Sleep Disordered Breathing (SDB)

Sleep Disturbance Scale for Children (SDSC)

Suprachiasmatic nucleus (SNC)

T-cell attracting cytokine (CTACK)

Temperature environment (Te)

Temperature rectal (Tr)

Temperature skin (Ts)

The German Health Interview and Examination Survey for Children and Adolescents (KiGGS)

Thymus and Activation Regulated Chemokine (TARC)

Visual Analogue Scale (VAS)

Wechsler Intelligence Scale for Children (WISC-IV)

Chapter 1: Introduction and literature review

1.1 Introduction

Eczema is a cutaneous immune defect that disrupts the skin barrier thereby increasing an individual's susceptibility to infection with bacteria, fungi and viruses.¹ Diagnostic criteria commonly include pruritus, a history of asthma/hayfever, dry skin, erythema, rash onset under two years of age, visible flexural dermatitis and a history of flexural involvement.² Eczema can occur across the lifespan but is particularly prevalent in infancy with 90% of affected children requiring medical review by the fifth year of age.³ The prevalence of childhood eczema varies between countries ranging from 1% - 20%⁴⁻⁹ and is thought to be increasing.^{6, 7, 10-13}

Eczema is common among children with a family history of atopic diseases. Atopic pertains to a hereditary tendency to experience immediate allergic reactions because of the presence of reagin (IgE), an antibody in the skin. IgE attaches to mast cells and basophils and sensitises the skin and other tissues to antigens. In antigen-antibody reactions it triggers the release of histamine and other mediators that cause inflammatory response to antigens in the skin. The abundance of mast cells in the skin, nose and lungs makes these areas susceptible to inflammation type reactions. Late IgE response and IgE dependent presentation of antigen further contribute to the presentation of antigen by Langerhans cells to T cells. Though the inheritance pattern is not clear and a separate atopy gene causing eczema has not been discovered, a polygenic inheritance is most probable. The risk of eczema in the first year of life has been associated with maternal atopic dermatitis and negatively associated with paternal hayfever.¹⁴ Should both parents have had eczema, their offspring will have approximately an 80% chance of acquiring the disease.¹⁵

When chronic, childhood eczema has significant morbidity characterised by physical discomfort,¹⁶ emotional distress,¹⁷ reduced child quality-of-life,¹⁸⁻²¹ reduced family quality-of-life^{22, 23} and, of especial note, disturbed sleep.^{13, 24-29} The ubiquity of disturbed sleep is such that it is a commonly used item in eczema assessment questionnaires (e.g. in the SCORing Atopic Dermatitis (SCORAD)³⁰, the Nottingham Eczema Severity Score³¹ and the Children's Dermatology Life Quality Index (CDLQI)³²). It is estimated that up to 60% of eczematous children have disturbed sleep, increasing to 83% during exacerbation.^{17, 28, 33} Despite its prevalence however, only a small number of studies have directly examined the sleep of children with eczema^{24, 26-29, 31, 33-44} and to date only two have examined the daytime sequelae of disturbed sleep.^{26, 28} This lack of data is an important issue as disturbed sleep in children without eczema is associated with significant daytime deficits including reduced quality-of-life,⁴⁵ behavioural functioning^{46, 47} and neurocognitive performance.⁴⁷⁻⁵⁰ Preliminary evidence suggests that children with eczema have a higher incidence of behavioural deficits^{17, 51, 52} and reduced child and family quality-of-life.^{18-21, 27, 32, 40, 41, 53, 54} In contrast, the impact on neurocognitive performance remains untested. In this review we examine childhood eczema and its putative effects on sleep, quality-of-life and daytime functioning and explore possible links between reduced sleep quality and impaired daytime functioning in this patient group.

1.2 Literature review

Eczema is known in the literature under many names such as atopic eczema, atopic dermatitis, dermatitis, infantile eczema, prurigo besnier, lichen vidal, endogenous eczema, spatexudatives ekzernatoid and neurodermatitus (constitutionalis).⁵⁵ The word "eczema" is derived from the Greek "eczeo" which means "a boiling over". In preparation for this review we entered the keywords (and variants) 'child', 'sleep' and 'eczema' in the PubMed and PsychInfo databases and identified 77 potential studies. Of these, 22 report anecdotal data where problematic sleep

is simply noted: for example, in reviews of symptom management,^{22, 23, 56-70} commented upon in diagnostic interview⁷¹⁻⁷³ and as a treatment gain.^{74, 75} A further 39 report that they collected sleep questionnaire responses but only 22 provide values. Of the latter, 17 report one or more sleep parameter as part of a general investigation into eczema (including parameters such as sleep length, number of arousals, time-in-bed, etc) (see Table 1.1) and a further five report sleep parameters following a treatment intervention (see Table 1.2). As a general observation, sleep was a secondary focus in the majority of questionnaire studies with most relying on a single item which was typically used to assess global sleep quality. We also identified six studies which included the sleep of parents with eczematous children (see Table 1.3). Finally we identified five studies that report actigraphic (see Table 1.4) and a further four that report polysomnographic sleep parameters (see Table 1.5).

The most consistent sleep finding in the questionnaire data is that the sleep of children with eczema is shorter than that of controls and this can be attributed to prolonged nocturnal wakefulness. The percentage of children with eczema reporting sleep loss is often substantial with estimates ranging from 47-60%^{44 23 33} as is nocturnal wakefulness with reports of two hours or more.⁴⁰ For example, Ricci et al.⁴⁰ report in their sample of 45 eczematous children that 17 (38%) averaged 15 - 60 minutes of wakefulness per night, 9 (20%) 60 - 120 minutes and 5 (11%) > 120 minutes. In addition to prolonged wakefulness, children with eczema also tend to report a greater number of awakenings⁴¹ and for some the sleep disturbance is chronic.³¹

1.2.1 The demographic profile of eczematous children with sleep disturbance.

The relationship of age, gender and socio-economic status and sleep disturbance in children with eczema is unclear. Hon et al.⁴⁴ report reduced sleep quality in children with eczema aged < 10 compared to > 10 years. This relationship between age and poor sleep is anticipated in

children with eczema as younger children tend to have more severe symptomology. However, Al-Riyami et al.⁷⁶ report no difference in sleep disturbance in eczematous children aged 6-7 compared to 13-14 years. Likewise, the findings for gender are mixed. Vlaski et al.²⁹ report that eczematous girls compared to boys were slightly more likely to have disturbed sleep while Hon et al.⁴⁴ report no sex difference. Socioeconomic factors are of relevance as urban inhabitants are more often affected compared to the rural population, and in cities a higher prevalence is observed.⁷⁷ A relationship between low socio-economic status and poor sleep in children has been previously reported by Montgomery-Downs et al.⁷⁸ however, no study was found to comment specifically on the relationship of socio-economic status and sleep in children with eczema.

1.2.2 Notable questionnaire studies which focus on the sleep characteristics of children with eczema

To date, only two questionnaire studies have attempted to describe the sleep of children with eczema in detail. Bartlet, Westbroek, et al.²⁶ administered a structured parental interview with a sleep component to 44 U.K. eczematous children and 18 children with other skin conditions, such as psoriasis. Cross tabulation of night waking and scratch ratio indicates that children with a high scratch rate had a higher frequency of night waking. Children with eczema were more likely to have a sleep problem (80% vs. 39%, $p < .001$), have night waking problems (73% vs. 22%, $p < .001$), took longer to resettle during the night, and have a higher scratch rating than the control group (3.2 vs. 1.1, $p < .001$).

Reid and Lewis-Jones²⁸ undertook a similar study using a structured parental interview in 39 U.K. children with eczema. Reid's group report that 75% of children had two or more exacerbations of eczema in the previous six months, each lasting an average of 11 days. Of note is that 59% of the sleep disruptions occurred on exacerbation nights with parents

reporting that their child's sleep was disturbed on 86% of these nights. Furthermore, problems settling to sleep occurred in 76% of children during exacerbation compared to only 26% when eczema was controlled.

1.2.3 Sleep disturbance in parents of children affected with eczema

As anticipated, parental sleep quality is related to the severity of their child's eczema and its subsequent impact on sleep quality.^{18, 27, 79} Increased eczema severity has been associated with parents reporting greater tiredness and exhaustion,^{53, 79} more frequent sleep disruption^{18, 53, 79, 80} and an increased frequency of sleep disturbance due to co-sleeping.^{19, 81} Moore⁸⁰ estimates that mothers of children with moderate to severe eczema lose a median of 39 minutes of sleep per night and fathers 45 minutes. Reduced sleep quality in parents of children with eczema has also been associated with increased work absenteeism and lost productivity²³ and reduced family quality-of-life.^{27, 40, 53, 79-82}

1.2.4 Mechanism assumed to cause sleep disturbance in children with eczema

It is thought that nocturnal itching and subsequent scratching may underlie nocturnal awakenings in children with eczema.^{36, 58, 83} Consistent with this view, higher itch severity ratings⁸³ and, for girls only, higher Immunoglobulin E (IgE) levels⁸⁴ have both been associated with reduced sleep quality. The itch of eczema is thought to be caused by neuropeptide-mediated vasodilation leading to raised skin temperature and erythema,⁸⁵ and scratching is believed to reduce the itch impulse via pain mediated neurological pathways.⁸⁶ At present, it is unknown whether itch intensity or scratch damage has the greater impact on eczema severity; however an itch-scratch cycle is reported in patients with eczema where the scratch response to itch causes skin damage which further precipitates itch. Itch is a subjective and essentially unobservable phenomenon making it difficult to assess during sleep.⁸³ To

address this limitation and better explore the association between scratching and sleep disruption, several groups have combined actigraphy with infrared video monitoring.

1.2.5 Actigraphic studies on children with eczema and sleep

Ebata et al.⁸⁷ examined the nocturnal scratching of 29 Japanese adolescent and young adult inpatients (15-24y) with eczema compared to 5 controls (age unspecified) using actigraphy together with infrared video recordings. Data was collected from 21 of the eczema patients over 63 nights. Actigraphic estimates of movement and infra-red video estimates of total scratch time were highly correlated ($r = .91, p < 0.001$) while total scratch time expressed as a percentage of the total recording time was also shown to increase with disease severity from 1.7% in mild to 5.2% in moderate and 15.4% in severe disease groups. Further and as anticipated, eczema scratch activity was significantly higher in all eczema groups compared to controls.

Benjamin et al.³⁹ also used actigraphy and infrared video evaluated the nocturnal scratching in 14 English children with eczema. This study reported that in addition to typical scratching, eczematous children were also making other complex movements, such as rubbing, that could potentially damage the skin. Children with eczema spent a mean of 46 minutes less time motionless or sleeping at night than controls (Mean \pm SEM) (468 \pm 3 vs. 422 \pm 37). Eczema children were further reported as having 2 to 3 times the amount of scratching or restlessness than controls.

In a further actigraphic study, Bringhurst et al.⁸⁸ also report higher nocturnal movement index scores in 25 eczematous children compared to 17 controls.⁸⁸ They further reported that children with eczema spend more bed-time scratching than controls (15% vs. 2%), 2 to 3 times more restless nocturnal behaviour (5.3% vs. 2%) (all $p < .01$). This group reports that unexpectedly, actigraphy measures were not found to be related to eczema severity measured

with the SCORAD. This finding could be attributed to the deficiencies in using an observer dependant rating scale, though this group also remark on the fluctuating nature of eczema and their finding of considerable variation in night to night activity from the same person.⁸⁸

In summary, actigraphic and infrared video evidence indicates that sleep in children with eczema has significantly more nocturnal movement than that of healthy control children. Studies using both actigraphy and infrared video recordings further report that these two measures of nocturnal movement are strongly associated and in particular, that actigraphy is a reliable measure of nocturnal scratching in children with eczema.

1.2.6 Biological markers of childhood eczema and sleep

Actigraphic measures of scratching have also been correlated with biological markers of eczema severity. Hon et al.³⁷ in 24 Japanese children with eczema (mean age = 11.9 years) explored the relationship between nocturnal movement with SCORAD questionnaire ratings and chemokine markers of skin inflammation.³⁷ Movement activity in the first three hours of sleep was highly correlated with SCORAD ratings of disease severity ($r = 0.52, p < 0.01$) and extent ($r = 0.54, p < 0.01$) while increased movement was also strongly associated with increased chemokine activity including cutaneous T-cell attracting cytokine (CTACK) ($r = 0.56, p < 0.05$), macrophage-derived chemokine (MDC) ($r = 0.63, p < 0.005$) and thymus and activation regulated chemokine (TARC) ($r = 0.54, p < 0.05$).

In a more recent study, Hon et al.⁸⁹ also collected actigraphic data in a further 28 children with eczema (mean age = 11.1 years) and report a strong association between nocturnal scratching and the protein Brain-Derived Neurotrophic Factor (BDNF) which is reduced under high stress⁹⁰ and implicated in eczema severity and flare-up.^{91, 92} Actigraphy data was also reported to be correlated with substance P, a neuropeptide that in association with histamine release from mast cells, causes vasodilation and protein extravasation.⁹¹

1.2.7 Polysomnography data on children with eczema.

Closer scrutiny of childhood eczema's effect on sleep behaviour has been evaluated through polysomnography. Polysomnography is a diagnostic test during which a number of bio-physiologic variables are measured and recorded during sleep. The name is derived from Latin and Greek roots: 'Polys' (many), 'somnus' (sleep) and 'graphein' (to write). The test monitors and records many body functions including brain activity (electroencephalography), eye movement (electrooculography), muscle activity (electromyography), heart rhythm (electrocardiography) and respiratory function during sleep. The data is then staged according to defined criteria as either awake, stage 1 to stage 4 or REM sleep.

Only four studies could be identified which report polysomnographic data in children with eczema (total of index cases = 63 (29 boys and 34 girls), aged 3-15 years). Stores et al.³⁴ collected home-based polysomnography and estimates of scratching frequency using movement probes attached to each forearm in 20 U.K. children with eczema and 20 controls. Stores's group report that sleep in children with eczema was at least four times more disrupted than controls on measures of brief (<2 minutes) (mean (SD not reported) = 0 8.5 vs. 2.0, $p < 0.001$, respectively) and long (>2 minutes) (5.5 vs. 1.0, $p < 0.001$) periods of waking. As well, scratching was highly correlated with the amount of time spent awake after sleep onset ($r = 0.87$, $p < 0.001$). However, while the children with eczema had a lower sleep efficiency than controls (mean (SD not reported) = 92.8% vs. 98.4%, $p < .001$) they nevertheless displayed similar total sleep times, percentage of individual sleep stages and REM onset latencies suggesting that gross sleep architecture is not impaired in children with eczema.

Hon et al.³⁸ collected laboratory-based polysomnography in 20 Hong Kong children with eczema divided into mild to moderate (SCORAD ≤ 40) and severe (SCORAD > 40) groupings compared to 8 controls. Hon and colleagues report that sleep efficiency was

significantly reduced in children with eczema compared to controls (median = 72% vs. 88%, $p = 0.04$). Hon's group also investigated metabolic functioning during sleep (resting energy expenditure, oxygen consumption, and carbon dioxide production). They report no significant group differences for any measure including when values were analysed by sleep stage and no significant relationships between any metabolic and SCORAD parameter. Hon and colleagues conclude that metabolic dysfunction is unlikely to explain either pruritus or sleep disturbance in children with eczema.

Monti et al.³⁶ collected laboratory-based polysomnography in 9 Uruguayan children with mild to moderate eczema. Monti and colleagues report that scratching was observed in every sleep stage with the highest frequency in stage 1, followed by stage 2, REM, stage 4, and stage 3 sleep. The total amount of time that the subjects scratched ranged from 11.0 to 84.6 minutes with a mean (SD) of 30.3 (7.4) minutes. Monti et al. concluded that scratch rather than itch explained disturbed sleep.

Finally, Reuveni et al.³⁵ collected polysomnographic data in 14 Israeli children with eczema in clinical remission and compared them to 9 controls.³⁵ Direct observation, video monitoring and scratch electrodes were also used to estimate nocturnal scratching. Even when in remission, eczema children had more arousals and awakenings than controls (mean \pm SE = 24.1 ± 8.1 vs. 15.4 ± 6.2 per hour respectively, $p = 0.001$), however, scratching accounted for only 15% of the arousals, while the remainder were not associated with any identifiable cause.³⁵

1.3 Summary of current data on the sleep of children with eczema

The consensus findings in the majority of studies and regardless of methodology, i.e. questionnaire, actigraphy or polysomnography, is that the sleep of children with eczema is

characterised by frequent and prolonged awakenings. However, the limited polysomnographic data suggests that while prolonged awakenings are common, nonetheless total sleep times are similar to children without eczema and, in addition, gross sleep architecture is preserved with eczematous and control children demonstrating similar REM onset latency times and sleep stage percentages. Interestingly, eczematous children are further reported to scratch during all stages of sleep with some of the scratching events reported to produce arousal. However, even this curious behaviour accounts for only a relatively small percentage of arousals in this group indicating that other factors are contributing to, or mediating, sleep disturbance in this patient group. The polysomnographic data reported also remains to be expanded in children with eczema and especially in infants with no study having examined children under 3y.

1.4 Body temperature and sleep in humans

Human beings are endothermic which denotes that they are able to thermo-regulate and maintain their body temperature. Within the process of thermo-regulation, a diurnal variation of body temperature has been observed dependent on the periods of sleep and activity.⁹³⁻⁹⁵ The maximum temperature ranges from 10am to 6pm and the minimum from 11pm to 7am.⁹⁶ The regulation of core body temperature occurs as a combination of heat production and heat loss.^{95,97} When heat production is greater than heat loss, core body temperature increases and, conversely, when heat loss exceeds heat production, there is a decrease in core body temperature. Heat loss from the core requires the transference of heat via the blood to various blood vessels located through the skin. The vessels most effective at losing heat are known as arteriovenous-anastomoses (AVAs) and are concentrated in more distal regions of the skin (i.e. hands, feet, nose, lips, ears).⁹⁸ Heat loss from distal skin areas occurs most rapidly when AVAs are maximally dilated.⁹⁵

1.4.1 Eczematous skin and body temperature

It is possible that homeostatic temperature regulation may be impaired in children with eczema. The process of heat loss through distal skin areas may be effected by defects in eczematous skin or by damage produced by eczema. To date only three studies have been undertaken which examined the relationship between eczematous skin and body temperature. Heyer et al.⁹⁹ examined thermoregulation in twenty one adult eczematous subjects compared to twenty three age and sex matched controls under controlled environmental conditions. They examined the response of the skin in one forearm to a standardised 15 minute exposure of the other arm to either a cold or warm bath (17-18 degrees Celsius and 40 - 41 degree Celsius respectively). In controls, the exposure to warmth to one forearm was associated with either no change or a slight decrease in temperature of the other forearm whereas eczema patients responded to warmth on one forearm with either no change or a slight increase in temperature. When controls had their forearm exposed to the cold condition, the other forearm skin temperature either rose slightly or remained fairly static. The eczema patient's response to the cold stimulus on one forearm also differed from controls in that their other forearm either decreased in temperature or remained relatively unchanged.

Samsonov and Bol'shakova¹⁰⁰ examined the heat exchange of 72 adult eczema subjects compared to 25 controls. Heat exchange was measured by the amount of heat entering a purpose built sensor placed on the skin. The sensor was cooled to 10 degrees Celsius below the measured skin temperature and then placed on the skin for 10 minutes. Subjects were separated into groups of severe, moderate and mild eczema severity. Mild and moderate groups had a higher heat exchange than controls and the severe group had a lower heat exchange than controls. The authors propose that mild and moderate eczema increases heat

exchange through inflammation, but severe eczema has altered the heat gradient or damaged the process of heat exchange.

Levin and Loseva¹⁰¹ study examined thermoregulation in 76 adult eczema patients compared to 15 controls using the Circulatory Temperature Index (CTI). CTI refers to the relationship between skin temperature (Ts), rectal temperature (Tr) and the environment (Te). In healthy non-eczema patients an increase in CTI suggests an increase in peripheral circulation to the distal skin and an increase in heat release, while a decrease in CTI suggests a decrease in peripheral circulation to the distal skin and therefore a decrease in heat release. The skin was measured in 12 different parts of the body including; forehead, chin, abdomen, shoulder, upper arm, inner wrist, hand, outer thigh, knee, ankle, and foot. The CTI in controls were in normal ranges for all areas measured. In eczema patients, the CTI was higher in all areas measured when compared to controls, except for the chin, regardless of whether the skin was affected or unaffected by eczema.

In summary, adult patients with eczema exhibit disturbances of various vascular skin functions which impact upon thermoregulation⁹⁹⁻¹⁰² Inflammation of the eczema causes an increase in peripheral blood flow, resulting in the loss of excessive amounts of heat.¹⁰¹ A comparable dysfunction in the thermoregulation of eczematous children may explain why environmental changes in temperature are associated with intense itching and sweating,¹⁰³ increases in flare-ups and scratching¹⁰⁴⁻¹⁰⁶ and problems with sleep initiation and sleep disruption in this patient group.^{85, 97, 107} However, the impact of thermoregulation dysfunction on sleep disturbance in eczematous children remains unexplored.

1.5 Rhinitis and asthma disturbing sleep in children with eczema

The impact of eczema on sleep cannot be fully examined without also acknowledging the broader and potentially confounding contribution of the other atopic disorders namely allergic

rhinitis and asthma. Allergic rhinitis is common in children with a worldwide prevalence rate of up to 40%⁴ and is very common in children with eczema with an estimated prevalence of approximately 60%.¹⁰⁸ Allergic rhinitis and associated symptoms (e.g. rhinorrhea, sneezing, nasal pruritus, postnasal drainage and nasal congestion) may significantly disrupt sleep.¹⁰⁹⁻¹¹³ One report noted that 21% of children with allergic rhinitis have problems with sleep onset,¹¹⁴ while 68% of a combined sample of U.S. adults and children with perennial allergic rhinitis and 48% of the same sample with seasonal allergic rhinitis report disrupted sleep while symptomatic.^{114, 115} Nasal obstruction associated with congestion is also a defined risk factor for sleep disordered breathing.¹¹⁶

Asthma is the most common chronic respiratory disease of childhood affecting up to an estimated 37% of children worldwide⁴ and up to 34% of eczematous children.¹⁰⁸ Children with asthma are more likely to wake at night and spend less time asleep.¹¹⁷⁻¹¹⁹ Indeed, Syabbalo reports that up to 90% of asthmatic children experience nocturnal symptoms severe enough to awaken them from sleep¹²⁰, while Strunk et al. report that 34% of children with asthma experience at least one awakening per night and 14% had up to three or more awakenings per night.¹²¹

Despite the prevalence of rhinitis and asthma, the additional contribution of these factors to disturbed sleep in children with eczema remains unknown. Likewise that additional impact of allergic rhinitis and asthma on daytime behaviour in children with eczema remains unknown. As a corollary, eczema has been associated with an increased risk of snoring^{122, 123} and sleep disordered breathing.⁴³ As such, any examination of childhood eczema and sleep on behaviour and neurocognition should account for sleep disordered breathing.

1.6 Treatment of childhood eczema and sleep

The two most common approaches to treating mild-to-moderate eczema utilise either topical corticosteroids which helps to reduce inflammation and itchiness, or antihistamines due to their symptomatic and anti-inflammatory effects. Corticosteroids and antihistamines both have an effect on sleep. Oral corticosteroids used to treat children are reported to increase night waking but did not increase sleep latency.¹²⁴ First generation antihistamines have a major side effect of sedation, which occurs in 10-50% of patients. These medications induce sleep, adversely affect awakening, reduce alertness and prolong sleep.¹²⁵

Some studies employing various treatments of childhood eczema aimed at improving sleep quality or have used sleep quality to rate the efficacy of the treatment. Stewart and Thomas¹²⁶ examined the efficacy of hypnotherapy on the sleep quality of 20 eczematous children (2-15 y). Sleep was estimated by parents using a 10-point visual analogue scale (VAS). Stewart's group reported that all but one patient showed immediate improvement in sleep and that the majority of children reported better sleep at 4 weeks, (13/16 (81%), $p = 0.003$) which continued up to 2 years after treatment.

Leo et al.¹²⁷ examined the impact of Pimecrolimus cream 1% on skin integrity and sleep disturbance in 19 children with eczema. Sleep was evaluated using questionnaire and actigraphy and skin integrity using the Eczema Area and Severity Index. Although not statistically significant, successful skin treatment was associated with a trend toward improved sleep.

Endo et al.¹²⁸ examined the impact of the antihistamine Azelastine Hydrochloride on the sleep of 40 adolescent and adult eczema inpatients (13-42y) measured with a scratch monitor. They found significant gains in post compared to pre-treatment scratch rate per hour (mean (SD) = 0.22 (0.10) < 0.26 (0.14), $p < .05$), minutes of scratch (6.41 (4.46) < 8.81 (7.71), $p <$

.05), arousal per hour (1.21 (0.88) < 1.45 (1.15), $p < .05$) and awake rate (awake (min)/sleeping time (min)) (0.13 (0.10) < 0.17 (0.15), $p < .05$), but not total sleep time and sleep onset latency.

Bieber et al.¹²⁹ study compared efficacy and safety of 0.1% methylprednisolone aceponate (MPA) ointment with 0.03% tacrolimus ointment for 3 weeks, in 265 children and adolescents (2-15y) with severe to very severe eczema. They noted that methylprednisolone aceponate ointment 0.1% resulted in greater sleep quality gains than tacrolimus ointment 0.3% (10-point VAS scale: mean (SD not reported) = 54.6mm to 5.3mm, $p = 0.04$).¹²⁹

Hon et al.¹³⁰ assessed the clinical efficacy of the immunosuppressant Tacrolimus for itch reduction in 7 children with eczema. The eczema severity was assessed using the SCORAD rating and sleep using actigraphy and patient and parental report. Total SCORAD scores (Median, Interquartile Range) (36.1, 32.8-45.7 vs. 29.4, 24.8 - 45.4) and actigraphy measures (115.0 g/min, 64.8-215.5 vs. 71.5 g/min, 51.0 - 118.0) were significantly reduced over the two week treatment period in conjunction with a reduction in reported sleep disturbance¹³⁰.

Eberlein et al.¹³¹ examined the clinical impact of an emollient containing N-palmitoylethanolamine on sleep in 2,456 German patients (923 children, 1533 adults). They report that after 6 days of treatment, sleep loss was significantly reduced (10-point parental VAS scores mean (SD) = 2.58 (2.69) reduced to 1.36 (1.98), -47%, $p < 0.001$).

Stainer et al.¹³² evaluated the efficacy of sodium cromoglycate on the sleep of 114 English eczematous children (2-12y) using a 0 – 3 range rating scale and report no treatment gains compared to placebo (mean (SD) treatment = 0.98 (0.74) vs. placebo = 0.86 (0.74), $p = ns$).

Schoni et al.¹³³ asked parents of 32 eczematous children (1–16y) to estimate sleep quality on a 5-point rating scale, (5 = severe to 1 = minimal), to evaluate the efficacy of bioresonance as

a treatment for eczema. Schoni and colleagues report that bioresonance did not improve sleep of children with eczema compared to controls (mean (SD) VAS= 3.0 (1.8) vs. 2.6 (1.8), $p =$ ns, respectively).

Finally, Folster-Holst et al.¹³⁴ report that probiotic eczema treatment did not improve sleep scores. In summary, the treatment of childhood eczema appears to be associated with albeit mild but significant improvements in sleep quality, though it must be noted that these studies utilise relatively few subjects and employ different medications.

1.7 Sleep disturbance and Quality of life

Child and family quality-of-life is generally reported to be reduced in children with eczema.^{18-22, 40-42} Holms et al.¹³⁵ examined the quality-of-life in 101 patients with eczema (66 adults and 35 children) compared to 30 healthy controls (23 adults and 7 children). Holm's group report that children with eczema had reduced Dermatology Life Quality Index scores compared to controls (mean rank scores = 15 vs. 35 respectively, $p < .0001$), but similar physical and mental health (SF-36) scores.

Children with eczema are also reported to have a lower quality-of-life when compared to children with other chronic skin conditions. Beattie and Lewis-Jones⁴² compared quality-of-life in children with eczema to those with psoriasis, urticaria and acne. Children ($n = 379$) rated generalised eczema as the second highest rated factor affecting quality-of-life. When parents rated the quality-of-life of children with eczema compared to other chronic diseases such as cerebral palsy, renal disease, cystic fibrosis, urticaria, asthma, psoriasis, epilepsy and diabetes, parents rated generalised eczema as the second highest at reducing quality-of-life after cerebral palsy.⁴²

Sleep disturbance is reported to be a major influence on the quality-of-life of children with eczema. Chamlin et al.¹⁹ report that 10% of their eczematous children rated poor sleep as the factor with the highest impact on quality-of-life and in a later study, moreover, that children with reduced happiness because of eczema were 8.59 times more likely to report disturbed sleep.²³ Hon et al.⁴⁴ examined the factors which contributed most to reduced quality-of-life in children with eczema and report that sleep disturbance was the second highest contributing factor after itch.

Childhood eczema is also reported to impact the quality-of-life and sleep of family members. Ben-Gashir et al.¹⁸ report in 106 English children with eczema first presenting to clinic that sleep was disrupted in 23% of family members. Ricci et al.⁴⁰ report that 75% of parents experienced excessive tiredness due to their child's eczema and that this was the highest ranked problem reported by family members. Two groups have examined sleep in parents of children with moderate to severe eczema and report a mean reduction in parental sleep during their children's eczema flare-up ranging between 0.66 to 2.6 hours per night.^{28, 80} Sleep disturbance is considered by adults with eczematous children to be the most stressful aspect of care^{40, 136} and rated highest on items negatively affecting family quality-of-life.^{40, 79}

1.8 Childhood eczema, sleep, daytime behaviour and cognition

Sleep disturbance in non-eczema children is associated with increased problematic behaviour,^{49, 137-139} ADHD¹⁴⁰⁻¹⁴³ and difficult temperament.¹³⁷ Behavioural deficits are also reported in children with eczema. Daud et al.¹⁷ examined the behaviour of 30 English pre-school children with eczema compared to 20 controls and report that children with eczema are significantly more dependant (15/30 (50%) vs. 2/20 (10%)) and fearful (12/30 (40%) vs. 2/20 (10%)).

Lawson et al.⁵³ collected behavioural data from 41 English families with children with eczema. The aim of this study was to identify the areas of family life most affected and their perceived importance. This group report that 54% of children with eczema displayed behavioural disturbance including being naughty, irritability, bad temper, being easily bored and being hurtful to other family members during eczema flare-ups.⁵³

Schmitt et al.¹⁴⁴ analysed data from a German population database and report that 1,436 children with eczema had a significantly higher prevalence of ADHD when compared to matched controls (5.2% vs. 3.4% respectively). Schmidt and colleagues also propose that the association between eczema and ADHD may be mediated by secondary phenomena including sleep disturbance.

Finally, Sarkar et al.⁵² compared 22 Indian children with eczema with twenty controls and report a significantly higher frequency of behavioural disorders (e.g. child acts too young for his age, cannot concentrate or pay attention for too long, etc) (mean (SD) scale score = 5.9 (2.9) vs. 2.1 (1.4), $p < 0.01$) and conduct disorders (e.g. steals things, frequently disobeys at home, etc) (6.1 (4.0) vs. 0.7 (1.0), $p < 0.01$).⁵² An important question is to what degree sleep disturbance may contribute to these findings of problematic behaviour?

1.8.1 Eczema, sleep and behaviour in children with eczema.

While behavioural and sleep deficits are evident in children with eczema, only two questionnaire studies have explored the possible associations between eczema, sleep and behaviour. Dahl et al.²⁴ measured the sleep and behaviour of 59 American children with eczema using the Child Sleep Behaviour Scale supplemented with 12 additional questions to assess the behavioural symptoms of inadequate sleep. The authors report that children's eczema severity was moderately correlated with difficulty falling asleep ($r = 0.25$, $p < 0.05$) and frequency of nocturnal awakenings ($r = 0.44$, $p < 0.01$). Furthermore, reduced daytime

functioning was associated with greater difficulties in morning waking ($r = 0.41, p < 0.005$), daytime tiredness ($r = 0.33, p < 0.01$), irritability/aggressive behaviours ($r = 0.35, p < 0.01$) and major discipline problems ($r = 0.44, p < 0.001$).²⁴

1.8.2 Eczema, sleep and ADHD in children with eczema

The other notable study examining the association between childhood eczema, sleep and behaviour was conducted by Romanos et al.¹⁴⁵ in 6,484 German eczematous children (aged 3-17 years). Romanos's group report a strong association between eczema and ADHD in a subgroup of children (3-11y) with sleep problems (OR 2.67 & 95% CI 1.51-4.71; $p = 0.001$; $n = 1,112$), but not in children without sleep problems (OR 1.24 & 95% CI 0.83-1.84; $p = .30$; $n = 5,796$). Given the clear consensus in the literature of the association between eczema and sleep disruption, it is surprising that its role in daytime functioning has not been more fully explored.

1.8.3 Sleep, neurological development and neurocognitive ability in children

Associations between sleep, neurological development and neurocognitive ability are well supported in the literature. Human infants sleep more than at any other time in their lifespan. It is also the period of their development which is associated with rapid brain growth and fast growing neurological networks.¹⁴⁶ Neurocognitive abilities and sleep are also associated as learning performances are enhanced following periods of sleep.^{147, 148} In particular, REM sleep appears to have a strong functional relationship with learning and memory. REM sleep is reported to increase following a learning task or exposure to an "enriched" environment known to trigger synaptic remodelling.^{149, 150} Further, REM sleep is related to acetylcholine (ACh) release,¹⁵¹ a neurotransmitter that influences neural development¹⁵² and synaptic remodelling.¹⁵³

Inadequate sleep in non-eczematous children has also been associated with neurocognitive deficits. In otherwise healthy children, both shortened sleep duration and disrupted sleep have been associated with reduced neurocognitive ability,^{46, 48} academic performance,¹⁵⁴ and inattention,^{138, 155} while children with occult sleep disorders such as sleep disordered breathing are reported to demonstrate psychosocial deficits,¹⁵⁶ learning problems,¹⁵⁷ decreased intelligence,¹⁵⁶⁻¹⁵⁸ memory,^{159, 160} attentional capacity^{156, 159, 161} and academic performance.¹⁶²

A recent study by Touchette et al.⁴⁸ suggests that shorter sleep duration in the first three years of life is associated with hyperactivity/impulsivity and lower cognitive performance on neurodevelopmental tests at age six, thereby implying that obtaining insufficient sleep during the first few years of life may have long standing consequences and that brain development is sensitive to sleep loss.¹⁶³ Reports on the sleep of children with eczema indicate that this group also experiences insufficient sleep during the first few years of life and consequently may also suffer long term impairments of their neurocognitive development. This important question remains to be examined as neurocognitive data on children with eczema is relatively absent from the literature.

One recent study which touches on this issue was conducted by Julvez et al.¹⁶⁴ who explored the relationship between Immunoglobulin E levels at the age of six with psychometric measures taken previously at four years of age in 422 Spanish children. Julvez's group proposed that if lower neurocognitive scores were reported prior to the atopy, there must be some underlying neurobiological or developmental connection associated with the development of atopic disorders. Using scores obtained using the McCarthy Scales of Child Abilities and the California Preschool Social Competence Scale, Julvez and colleagues report that lower neurodevelopment was associated with higher frequency of general atopy, asthma and wheeze at the age of four, but not eczema at six years of age.

1.9 Summary of current literature on eczema, sleep and daytime functioning in children

Current evidence suggests that sleep disruption in children with eczema is associated with increased symptom severity and periods of flare-up coinciding with more frequent sleep disturbance and prolonged time taken to return to sleep. However, of note is that even in times of clinical remission, children with eczema demonstrate more sleep disturbances than children without eczema suggesting that reported eczema characteristics may not fully explain sleep deficits. At present our understanding is limited by the paucity of objective sleep and eczema severity data, but biological markers found to be associated with eczema severity may prove to be instructive in future research. Children with eczema are further likely to have additional atopic disorders such as allergic rhinitis and asthma, both of which have been clearly documented to disrupt sleep. These latter conditions need to be considered in future eczema and sleep studies.

There are many potentially negative sequelae of fragmented and disrupted sleep in childhood eczema. Children with eczema and their families report reduced quality-of-life and much of this can be attributed to parental and child sleep disturbance. A further anticipated consequence of a disorder which disrupts sleep is impairment of behaviour and neurocognitive functioning but, to date, only two studies have reported the secondary effects on behaviour and there is a lack of neurocognitive data. In addition as eczema affects very young children and infants, it is potentially possible that sleep disruption at an age of very rapid brain development may be more injurious than a similar degree of sleep disruption in later childhood. This gives impetus to the need to define whether the severity of sleep fragmentation in eczematous children is correlated with daytime decrements and importantly, whether effective treatment resolves them. In conclusion, the impact of eczema on child sleep is significant with possible long-

term impacts on daytime functioning. The importance of managing eczema and addressing sleep problems in this patient group cannot be overestimated.

Table 1.1 Eczema questionnaire studies reporting sleep information.

Author and title	Number and age of participants	Subject selection	Method	Sleep results
Al-Riyami et al. (2003) ⁷⁶ A relatively high prevalence and severity of asthma, allergic rhinitis and atopic eczema in schoolchildren in the Sultanate of Oman.	3,893 (6-7y) 3,174 (13-14y)	Sultanate of Oman public schools	ISAAC	No difference in the prevalence of sleep disturbance in children with eczema aged 6-7 compared to 13-14y (1.7% vs. 1.9%, $p = ns$).
Bartlett et al. (1997) ²⁶ Sleep patterns in children with atopic eczema.	44 (5mths-13y)	UK dermatology clinic	Structured Interview	Cross tabulation of night waking and scratch ratings indicated that children with a high scratch rate had a higher frequency of night waking. Children with eczema were more likely to have a sleep problem (80% vs. 39%, $p < .001$), night waking problems (73% vs. 22%, $p < .001$), take longer to resettle during the night, and a higher scratch rating than the control group (3.2 vs. 1.1, $p < 0.001$).
Chamlin et al. (2005) ²⁷ The price of pruritus: Sleep disturbance and co sleeping in atopic dermatitis.	300 (birth-6y)	US dermatology clinics	CADIS	61% of parents and 68% of children reported that eczema affected how well they slept. 30% of parents reported co-sleeping with their child and of this grouping, 66% reported being bothered by co-sleeping. Children who reported reduced happiness because of eczema were 8.59 times more likely to report disturbed sleep.
Chamlin et al. (2005) ¹⁹ Development of the Childhood Atopic Dermatitis Impact Scale: initial validation of a quality-of-life measure for young children with atopic dermatitis and their families.	270 (< 6y)	2 US dermatology clinics	CADIS	10% of the eczematous children rated poor sleep as the highest ranked impact factor on their quality-of-life.
Chng et al. (2004) ⁴³ Snoring and Atopic Disease: A strong Association.	11,114 (4-7y)	Singaporean pre and primary schools	Author Questionnaire	Children with eczema had an increased risk of snoring (OR = 1.80, 95% CI: 1.28 – 2.54).
Dahl et al (1995) ²⁴ Sleep Disturbances in Children with Atopic Dermatitis	59 (5-12 y)	US hospital	The Child Sleep Behaviour Scale	Compared to normative data, children with eczema had greater difficulty falling asleep (3.9% vs. 10.2%, $p < .001$), less total sleep (< 6h, 3.4%, vs. 0.1%, $p < .001$), more frequent night waking (50% vs. 11%, $p < .001$) and greater difficulty awakening for school (58% vs. 22%, $p < .01$). Difficulty falling asleep was associated with increased itching and scratching ($r = 0.62$, $p < .000$) while eczema severity was associated with increased daytime tiredness ($r = 0.4$, $p < .005$) and irritability ($r = 0.35$, $p < .01$).

Table 1.1 Continued

Author and title	Number (age) participants	Subject selection	Method	Sleep results
Emerson et al. (2000) ³¹ The Nottingham Eczema Severity Score: preliminary refinement of the Rajka and Langeland grading.	290 (1-5y)	4 UK General Practices	NESS	4.8% of eczematous children experienced significant sleep loss for an average of 4 or more nights of per week over the last 12 months. 10.3% of eczematous children reported sleep loss on 1 night per week, 5.5% on 2 to 3 nights per week, 0.3% on 4 to 5 nights per week and 4.5% on 6 or more nights per week.
Hon et al. (2006) ⁸³ Lesson from performing SCORADs in children with atopic dermatitis: subjective symptoms do not correlate well with disease extent or intensity.	182 (<18y)	Hong Kong paediatric dermatology clinic	SCORAD	Higher VAS sleep scores were strongly associated with increased itch severity ratings ($r = 0.57, p = 0.001$).
Hon et al. (2007) ⁸⁴ Are age-specific high serum IgE levels associated with worse symptomatology in children with atopic dermatitis	117 (<18y)	Hong Kong paediatric dermatology clinic	SCORAD	Higher VAS sleep scores were correlated with Immunoglobulin E (IgE) levels in females only ($r = 0.34, p < 0.05$),
Hon et al. (2008) ⁴⁴ Does age or gender influence quality of life in children with atopic dermatitis?	133 (5-16y)	Hong Kong paediatric dermatology clinic	SCORAD NESS	47% of children reported disturbed sleep with similar proportions in girls and boys but more common in children < 10y compared to > 10y (OR = 2.31, 95% CI: 1.05-5.13; $p < 0.05$).
Lewis-Jones et al. (2001) ⁴¹ The Infants' Dermatitis Quality of Life Index	102 (< 4y)	UK Paediatric Dermatology clinic	IDQLI FDI	The three highest scoring questions for the IDQLI were itching and scratching, mood change and sleep disturbance. For the FDI, the highest scoring parameters were parental sleep disturbance, tiredness and exhaustion, and emotional distress. When compared to controls, infants with eczema had a long sleep latency (47% vs. 36%), more frequent awakenings (43% vs. 4.5%) and more miserable mood changes (24.4% vs. 9%) ($p =$ not reported).
Long et al. (1993) ³³ What do members of the National Eczema Society really want?	1944 parents of eczema children	UK National Eczema Society	Author Questionnaire	In children, sleep (60%) was the most common activity affected by eczema.
Reid & Lewis-Jones (1995) ²⁸ Sleep difficulties and their management in preschoolers with atopic eczema.	39 children (mean age = 25 mths)	UK dermatology clinic	Structured Interview child and family sleep	During eczema flare-up, sleep disturbance was reported for 86% of the relevant nights, with an average of 2.7 awakenings per night and with an average parental sleep loss of 2.6 hours per night. The sleep of siblings was disrupted 28% of cases. 67% of parents gave medicine to help their child sleep.

Table 1.1 Continued

Author and title	Number (age) participants	Subject selection	Method	Sleep results
Ricci et al. (2007) ⁴⁰ Atopic dermatitis: quality of life of young Italian children and their families and correlation with severity score.	45 (3-84 mths)	Italian paediatric dermatology clinic	IDQoLI DFI	Parents reported that 38% of the children stayed awake for between .25-1h per night, 20% between 1-2h and 11% > 2h (in the control group, 95% reported <.25h per night).
Romanos et al. ¹⁴⁵ Association of attention-deficit/hyperactivity disorder and atopic eczema modified by sleep disturbance in a large population-based sample.	6,484 (3-17y)	National database on the health of German children and adolescents	Questionnaire & Parental interview	In 3-11y a strong association was observed between eczema and ADHD in children with sleep problems (OR = 2.67 & 95% CI: 1.51-4.71; $p < 0.001$; $n = 1,112$), but not those without sleep problems (OR = 1.24 & 95% CI: 0.83-1.84; $p = ns$; $n = 5,796$).
Vlaski et al. (2006) ¹⁶⁵ Overweight hypothesis in asthma and eczema in young adolescents.	2,926 (13-14y)	Republic of Macedonia public schools	ISAAC	3.8% reported having eczema “ever” and 1.4% reported having an itchy rash that disturbed sleep. Eczematous girls compared to boys were more likely to have disturbed sleep (1.9% vs. 0.9%, $p < 0.05$). The sleep of eczematous children was not associated with BMI (OR = 0.99, 95% CI: 0.37-2.69; $p = ns$).
Zar et al. (2007) ¹³ The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002.	1995: 5178 (13-14y) 2002: 5037 (13-14y)	South African public schools	ISAAC	From 1995 to 2002, children with eczema reported an increase in the limitation of daily activity from sleep disturbance (8.4% vs. 15.7%) and an increase in the prevalence of sleep disturbance (OR = 1.7, 95% CI 1.4-2.06: $p < 0.001$)

NB: CADIS = Childhood Atopic Dermatitis Impact Scale and contains a sleep quality VAS item. CDLQI = Children’s Dermatology Life Quality Index with the single item “Over the last week, how much has your sleep been affected by your sleep problem?”. DFI = Dermatitis Family Impact questionnaire. EASI = Eczema Area Severity Index and contains a sleep quality VAS item. IDQoLI = Infants’ Dermatology Quality of Life Index and contains two sleep items: “Over the last week, how much time on average has it taken to get your child off to sleep at night?” and “Over the last week, what was the total time that your child’s sleep was disturbed on average each night?”. ISAAC = International Study of Asthma and Allergies in Childhood and contains the sleep item: “In the last twelve months, how often, on average, has your child been kept awake by this itchy rash?”. KiGGS = The German Health Interview and Examination Survey for Children and Adolescents (KiGGS) contains a single sleep item “Does your child have sleep problems?”. NESS = Nottingham Eczema Severity Score containing the sleep item “In the last twelve months, how often has your child’s sleep usually been disturbed by itching and scratching?”. SCORAD = the SCORing Atopic Dermatitis scale and contains a sleep quality VAS item. VAS = visual analogue scale. Ns = non-significant.

Table 1.2 Eczema treatment studies reporting sleep data

Author and title	Number (age) participants	Subject selection	Method	Sleep results
Bieber et al. (2007) ¹²⁹ Efficacy and safety of methylprednisolone aceponate ointment 0.1% compared to tacrolimus 0.3% in children and adolescents with an acute flare of severe atopic dermatitis.	265 (2-15y)	25 dermatology centres in Germany, Italy and Spain.	EASI	Methylprednisolone aceponate ointment 0.1% group had greater improvement in sleep quality than the tacrolimus ointment 0.3% group (mean (SD not reported) VAS = 54.6 to 5.3mm, $p = 0.04$).
Eberlein et al. (2008) ¹³¹ Adjuvant treatment of atopic eczema: assessment of an emollient containing N-palmitoylethanolamine (ATOPA study)	2456 (923 <12y and 1533 > 12y)	Brazilian, German, Spanish and Philippine. hospital centres	VAS	After 6 days of drug treatment for eczema patients had improved sleep (mean (SD) VAS = 2.58 (2.69) vs. 1.36 (1.98) mm, $p < 0.001$).
Folster-Holst et al. (2006) ¹³⁴ Prospective, randomized, controlled trial on Lactobacillus rhamnosus in infants with moderate to severe atopic dermatitis.	54 (1-55 mths)	2 German dermatological centres	SCORAD	Treatment did not improve sleep (mean \pm SEM VAS sleep scores = 3.0 \pm 0.6 vs. 3.2 \pm 0.9, ns)
Schoni et al. (1997) ¹³³ Efficacy trial of bioresonance in children with atopic dermatitis	32 (1.5-16.8y)	Swiss hospital	VAS	Treatment did not improve sleep (mean (SD) VAS = 3.0 (1.8) vs. 2.6 (1.8), ns).
Stewart & Thomas (1995) ¹²⁶ Hypnotherapy as a treatment for atopic dermatitis in adults and children.	20 (2-15y)	UK dermatology clinic	VAS	All but one patient showed immediate improvement and the majority of children reported better sleep at 4 weeks (13/16 (81%), $p < 0.005$) and at each assessment up to 2y after treatment (5/5 (100%), $p < 0.001$).

NB: VAS = visual analogue scale, EASI = Eczema Area Severity Index. SCORAD = the SCORing Atopic Dermatitis scale. Ns = non-significant.

Table 1.3 Questionnaire studies which report the sleep of parents of children with eczema.

Author and title	Number (age) participants	Subject selection	Method	Sleep results
Beattie & Lewis-Jones (2006) ⁷⁹ An audit of the impact of a consultation with a paediatric dermatology team on quality of life in infants with atopic eczema and their families: further validation of the Infants' Dermatitis Quality of Life Index and Dermatitis Family Impact score.	203 (mean = 19.8 mths)	UK dermatology clinics	DFI IDQoLI	Parental assessment of eczema severity had moderate to strong associations with both the DFI ($r = 0.394, p < 0.001$) and IDQoLI Index ($r = 0.636, p < 0.0001$) scores. Highest scoring items on the DFI were tiredness/exhaustion in the parents, sleep disturbance of others in the family and emotional distress in the parents. Highest scoring items on the IDQoLI were itching and scratching, problems at bath time and time taken to fall asleep.
Ben-Gashir et al. (2002) ¹⁸ Are quality of family life and disease severity related in childhood atopic dermatitis?	106 (5-10 y)	UK general practices	DFI SCORAD.	Quality of family life was reduced in 48 (45%) cases on the first visit and 38 (36%) cases on the second visit. Each unit increase in children's SCORAD scores was associated with 0.21 units decrease in quality of family life scores. The child's disease severity was related to sleep disturbance in the family on the first clinical visit only (95% CI 0.004 – 0.089, $p < 0.05$).
Chamlin et al. (2005) ²⁷ The price of pruritus: sleep disturbance and co-sleeping in atopic dermatitis.	270 (0-6y)	US dermatology practices	CADIS SCORAD	Parental sleep disturbance because of child's atopic dermatitis was common (61%). Co-sleeping because of the child's skin condition was reported by 30% of families which was of concern to 66% of parents. Child's sleep disturbance was associated with severity of eczema as the never/rarely disturbed sleep eczema group's SCORAD significantly differed from sometimes/often/all the time disturbed sleep eczema group's SCORAD (mean (SD) =19.6 (8.4) vs. 27.5 (12.8), $p < 0.001$).
Fukumizu et al. (2005) ⁸¹ Sleep related night-time crying (yonaki) in Japan: a community-based study.	429 (3-6 mths) 452 (18-21 mths) 440 (36-41 mths)	Japanese public health centre	Author Questionnaire	Chronic eczema was present in 35.7% (5/14) of infants, 81.3% (13/16) of toddlers, and 62.5% (10/16) of preschoolers whose sleep was disturbed by "sleep-related night-time crying". 80% of infants who slept on mattresses and 52% of children who slept in a bed also co-slept with parents with adverse effects on parental sleep.

Table 1.3 Continued

Author and title	Number (age) participants	Subject selection	Method	Sleep results
Lawson et al. (1998) ⁵³ The family impact of childhood atopic dermatitis: the Dermatitis Family Impact Questionnaire	34 (6 - 121 mths)	UK dermatology clinic	DFI	64% of parents reported being exhausted and frustrated due to their child's difficulties in settling to sleep and nocturnal awakening. 29% of parents reported that interpersonal relationships were adversely affected by caring for a child with eczema and that tiredness from sleep loss caused friction in relationships. 68% of families had experienced sleep disturbance in the last week.
Moore et al. (2006) ⁸⁰ Effect of childhood eczema and asthma on parental sleep and well-being: a prospective comparative study.	55 (<17y)	UK dermatology clinic	Author Questionnaire	Mothers of children with eczema lost a median of 39min and fathers 45min of sleep per night. Moderate/strong correlations between the severity of the sleep disturbance and the level of maternal anxiety ($r = 0.58, p < 0.01$), maternal depression ($r = 0.73, p < 0.001$) and parental anxiety ($r = 0.59, p < 0.01$)

N.B. DFI = Dermatitis Family Impact questionnaire. CADIS = Childhood Atopic Dermatitis Impact Scale. IDQoLI = Infants' Dermatology Quality of Life Index. SCORAD = the SCORing Atopic Dermatitis scale.

Table 1.4 Studies using actigraphy to measure sleep in children with eczema.

A Author and title	Number (age) participants	Subject selection	Method	Sleep results
Benjamin et al. (2004) ³⁹ The development of an objective method for measuring scratch in children with atopic dermatitis suitable for clinical use	14 (2-9y)	UK dermatology clinic	Actigraphy Infrared video	Children with eczema spent a mean of 46 minutes less time motionless or sleeping at night than controls (mean \pm SEM) (468 ± 3 vs. 422 ± 37 min). Eczema children are reported to spend more bed-time scratching or restlessness than controls (10% vs. 2%), 2 to 3 times more scratching (4.7% vs. 0%) and restless nocturnal behaviour (5.3% vs. 2%) (all $p < .01$).
Bringhurst et al. (2004) ⁸⁸ Measurement of itch using actigraphy in pediatric and adult populations	33 (20-87y) 25 (2-13y)	UK.Secondary Care Facility	Actigraphy SCORAD	Considerable variation in night-to-night activity and higher nocturnal activity levels in eczema children compared to controls but activity was not related to eczema severity. Increased nocturnal activity was associated with reduced sleep quality in adults but not children.
Ebata et al. (2001) ⁸⁷ Use of a wrist activity monitor for the measurement of nocturnal scratching in patients with atopic dermatitis.	29 (15-44y)	Japanese dermatology clinic	Actigraphy Infrared video	Activity monitor data (the average value of acceleration (AVA) = $10^{-3} \text{ g min}^{-1}$) was strongly correlated with total sleep time ($r = 0.91$, $p < 0.001$). AVA differed significantly between severe (Mean \pm SEM, 44.4 ± 19.1), moderate (23.2 ± 10.9) and mild (8.9 ± 6.0) eczema severity groups (all, $p < 0.001$).
Hon et al (2006) ³⁷ Nocturnal wrist movements are correlated with objective clinical scores and plasma chemokine levels in children with atopic dermatitis.	24 (mean (SD) = 12.6 (3.7)y)	Hong Kong dermatology clinic	Actigraphy SCORAD	Most activity (2-3Hz) occurred in the first 3 hours of sleeping which was significantly correlated with disease severity ($r = .52$, $p < 0.01$) and extent of eczema ($r = .53$, $p < 0.01$). Nocturnal movement was also related with chemokine markers; cutaneous T-cell attracting cytokine (CTACK) ($r = .57$, $p < 0.01$), macrophage-derived chemokine (MDC) ($r = .63$, $p < 0.005$), thymus and activation regulated chemokine (TARC) ($r = .56$, $p < 0.05$).
Leo et al. (2004) ¹²⁷ Effect of pimecrolimus cream 1% on skin condition and sleep disturbance in children with atopic eczema	19 (7-17y)	US dermatology clinics	Actigraphy EASI CDLQI	EASI but not CDLQI scores improved after treatment. CDLQI scores were not correlated with either sleep parameters or pruritus scores. Non-significant trend for improved sleep in the treatment group.

N.B. SCORAD = the SCORing Atopic Dermatitis scale. EASI = Eczema Area Severity Index. CDLQI = Children's Dermatology Life Quality Index.

Table 1.5 Studies using polysomnography to measure sleep in children with eczema.

Author and title	Number (age) participants	Subject selection	Method	Sleep results
Hon et al. (2005) ³⁸ Resting energy expenditure, oxygen consumption and carbon dioxide production during sleep in children with atopic dermatitis.	20 (6.3-12y)	Hong Kong dermatology clinic	Polysomnography SCORAD	Sleep efficiency was lower in severe eczema compared to controls (median: 72% vs. 88%, $p < 0.05$). No differences in metabolic measures in any sleep stage between mild-to-moderate eczema/controls compared to severe eczema.
Monti et al. (1989) ³⁶ Sleep and night-time pruritus in children with atopic dermatitis.	9 (3-15y)	Uruguay dermatology, Clinic	Polysomnography	The highest average scratching frequency corresponded to stage 1, followed by stage 2, REM sleep, stage 4, and stage 3. The sleep characteristics reported of the group included sleep latency in minutes (mean \pm SEM) (14.2 ± 3.5), total wake time (53.9 ± 19.8), wake time after sleep onset in minutes (43.2 ± 19.9), total number of wakes (7.9 ± 2.1) and total sleep time (426.1 ± 20.0).
Reuveni et al. (1999) ³⁵ Sleep fragmentation in children with atopic dermatitis.	14 (mean = 6y)	Israeli dermatology clinic	Polysomnography	Eczema children in remission compared to controls had more frequent arousals (mean (SD), 24.1 (8.1) vs. 15.4, (6.2), $p < 0.001$). However, scratching accounted for only 15% of the arousals, while the remainder were not associated with any identifiable cause. Total sleep time (min.) did not significantly differ in eczema children compared to controls (380.6 (38.3) vs. 367.8 (39.4), $p = ns.$), as did sleep efficiency (88.1% (7.4) vs. 89.8% (6.3), $p = ns.$), sleep onset latency (min.) (15.8 (11.6) vs. 9.1 (8.0), $p = ns.$) and total awake time (min.) (24.9 (25.5) vs. 19.6 (15.7), $p = ns.$).
Stores et al. (1998) ³⁴ Physiological sleep disturbance in children with atopic dermatitis: a case control study.	20 (mean = 9.6y)	UK dermatology clinic	Polysomnography	The eczema group's sleep was at least four times more disrupted than controls on measures of brief (<2 min) (mean = 8.5 vs. 2.0) and long (>2 min) (mean = 5.5 vs. 1.0) periods of waking, and that these periods were associated with scratching episodes. No differences were reported between the eczema and control groups in percentage of sleep stage 1 (5.4 vs. 4.8%), 2 (22.8 vs. 28.3%), 3 + 4 (50.8 vs. 48.0%), REM (18.5 vs. 20.1%) and REM onset latency (129.0 vs. 100.0 minutes).

N.B. SCORAD = the SCORing Atopic Dermatitis scale.

Bibliography

1. McGirt LY, Beck LA. Innate immune defects in atopic dermatitis. *J Allergy Clin Immunol* 2006; 118:202-8.
2. Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis.III. Independent hospital validation *British Journal of Dermatology* 1994; 131:406-16.
3. Hanifin JM. Atopic dermatitis. *J Allergy Clin Immunol* 1984; 73:211-26.
4. Beasley R, Keil U, von Mutius E, Pearce N. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema. *Lancet* 1998; 351:1225-32.
5. Kay J, Gawkrödger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol* 1994; 30:35-9.
6. Johnson MLR, J. Prevalence of dermatologic disease among persons 1-74 years of age PH 5 79--1660 ed. United States. Atlanta, Ga.: Centers for Disease Control; US Dept. of Health, Education and Welfare publication; 1979.
7. Taylor B, Wadsworth J, Wadsworth M, Peckham C. Changes in the reported prevalence of childhood eczema since the 1939-45 war. *Lancet* 1984; 2:1255-7.
8. Hanafin JH, Reed MR. A population-based survey of eczema prevalence in the United States. *Dermatitis* 2007; 82:82-91.
9. Robertson CF, Roberts MF, Kappers JH. Asthma prevalence in Melbourne schoolchildren: have we reached the peak? *Med J Aust* 2004; 180:273-6.
10. Rothe MJ, Grant-Kels JM. Atopic Dermatitis: an update. *J Am Acad Dermatol* 1996; 35:1-13.
11. Ruzicka T, Ring J, Przybilla B. Handbook of atopic eczema. Heidelberg, Germany: Springer Verlag; 1991.
12. Taylor B, Wadsworth J, Wadsworth ME, Peckham CS. Rising incidence of eczema. *Lancet* 1985; 1:464-5.
13. Zar HJ, Ehrlich RI, Workman L, Weinberg EG. The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. *Pediatr Allergy Immunol* 2007; 18:560-5.
14. Sugiyama M, Arakawa H, Ozawa K, Minuzo T, Mochizuki H, Tokuyama K, et al. Early-life risk factors for occurrence of atopic dermatitis during the first year. *Pediatrics* 2007; 119:e716-e23.
15. Uehara M, Kimura C. Descendant history of atopic dermatitis. *Acta Derm Venereol* 1993; 73:62-3.
16. O'Connell EJ. The burden of atopy and asthma in children. *Allergy* 2004; 59:7-11.
17. Daud LR, Garralda ME, David TJ. Psychosocial adjustment in preschool children with atopic eczema. *Arch Dis Child* 1993; 69:670-6.
18. Ben-Gashir MA, Seed PT, Hay RJ. Are quality of family life and disease severity related in childhood atopic dermatitis? *J Eur Acad Dermatol Venereol* 2002; 16:455-62.
19. Chamlin SL, Cella D, Frieden IJ, Williams ML, Mancini AJ, Lai JS, et al. Development of the Childhood Atopic Dermatitis Impact Scale: initial validation of a quality-of-life measure for young children with atopic dermatitis and their families. *J Invest Dermatol* 2005; 125:1106-11.
20. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; 19:210-6.
21. Aziah MS, Rosnah T, Mardziah A, Norzila MZ. Childhood atopic dermatitis: a measurement of quality of life and family impact. *Med J Malaysia* 2002; 57:329-39.
22. Hawkins C. The effects of eczema on children and their families: a review. *Paediatr Nurs* 2005; 17:35-9.

23. Kemp AS. Atopic eczema: its social and financial costs. *J Paediatr Child Health* 1999; 35:229-31.
24. Dahl RE, Bernhisel-Broadbent J, Scanlon-Holdford S, Sampson HA, Lupo M. Sleep disturbances in children with atopic dermatitis. *Arch Pediatr Adolesc Med* 1995; 149:856-60.
25. Aoki T, Kushimoto H, Hishikawa Y, Savin JA. Nocturnal scratching and its relationship to the disturbed sleep of itchy subjects. *Clin Exp Dermatol* 1991; 16:268-72.
26. Bartlett LB, Westbrook R, White JE. Sleep patterns in children with atopic eczema. *Acta Derm Venereol* 1997; 77:446-8.
27. Chamlin SL, Mattson CL, Frieden IJ, Williams ML, Mancini AJ, Cella D, et al. The price of pruritus: sleep disturbance and cosleeping in atopic dermatitis. *Arch Pediatr Adolesc Med* 2005; 159:745-50.
28. Reid P, Lewis-Jones MS. Sleep difficulties and their management in preschoolers with atopic eczema. *Clin Exp Dermatol* 1995; 20:38-41.
29. Vlasky E, Stavric K, Isjanovska R, Seckova L, Kimovska M. Overweight hypothesis in asthma and eczema in young adolescents. *Allergol Immunopathol* 2006; 34:199-205.
30. Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J, Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997; 195:10-9.
31. Emerson RM, Charman CR, Williams HC. The Nottingham Eczema Severity Score: preliminary refinement of the Rajka and Langeland grading. *Br J Dermatol* 2000; 142:288-97.
32. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): Initial validation and practical use. *Br J Dermatol* 1995; 132:942-9.
33. Long CC, Funnell CM, Collard R, Finlay AY. What do members of the National Eczema Society really want? *Clin Exp Dermatol* 1993; 18:516-22.
34. Stores G, Burrows A, Crawford C. Physiological sleep disturbance in children with atopic dermatitis: a case control study. *Pediatr Dermatol* 1998; 15:264-8.
35. Reuveni H, Chapnick G, Tal A, Tarasiuk A. Sleep fragmentation in children with atopic dermatitis. *Arch Pediatr Adolesc Med* 1999; 153:249-53.
36. Monti JM, Vignale R, Monti D. Sleep and nighttime pruritus in children with atopic dermatitis. *Sleep* 1989; 12:309-14.
37. Hon KL, Lam MC, Leung TF, Kam WY, Lee KC, Li MC, et al. Nocturnal wrist movements are correlated with objective clinical scores and plasma chemokine levels in children with atopic dermatitis. *Br J Dermatol* 2006; 154:629-35.
38. Hon KL, Leung TF, Ma KC, Li AM, Wong Y, Yin JA, et al. Resting energy expenditure, oxygen consumption and carbon dioxide production during sleep in children with atopic dermatitis. *J Dermatolog Treat* 2005; 16:22-5.
39. Benjamin K, Waterston K, Russell M, Schofield O, Diffey B, Rees JL. The development of an objective method for measuring scratch in children with atopic dermatitis suitable for clinical use. *J Am Acad Dermatol* 2004; 50:33-40.
40. Ricci G, Bendandi B, Bellini F, Patrizi A, Masi M. Atopic dermatitis: quality of life of young Italian children and their families and correlation with severity score. *Pediatr Allergy Immunol* 2007; 18:245-9.
41. Lewis-Jones MS, Finlay AY, Dykes PJ. The Infant's Dermatitis Quality of Life Index. *Br J Dermatol* 2001; 144:104-10.
42. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol* 2006; 155:145.
43. Chng SY, Goh DY, Wang XS, Tan TN, Ong NB. Snoring and atopic disease: a strong association. *Pediatr Pulmonol* 2004; 38:210-6.
44. Hon KL, Leung TF, Wong KY, Chow CM, Chuh A, Ng PC. Does age or gender

- influence quality of life in children with atopic dermatitis? *Clin Exp Dermatol* 2008; 33:705-9.
45. Baldassari CM, Mitchell RB, Schubert C, Rudnick EF. Pediatric obstructive sleep apnea and quality of life: a meta-analysis. *Otolaryngol Head Neck Surg* 2008; 138:265-73.
 46. Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. *Nature* 2004; 430:78-81.
 47. Sadeh A, Gruber R, Raviv A. Sleep, neurobehavioural functioning, and behavior problems in school-age children. *Child Development* 2002; 73:403-17.
 48. Touchette E, Petit D, Seguin J, Boivin M, Tremblay R, Montplaisir J. Associations between sleep duration patterns and behavioral/cognitive functioning at school entry. *Sleep* 2007; 30:1213-9.
 49. Yokomaku A, Misao K, Omoto F, Yamagishi R, Tanaka K, Takada K, et al. A study of the association between sleep habits and problematic behaviors in preschool children. *Chronobiol Int* 2008; 25:549-64.
 50. Mulvaney SA, Goodwin JL, Morgan WJ, Rosen GR, Quan SF, Kaemingk KL. Behavior Problems Associated with Sleep Disordered Breathing in School-Aged Children--the Tucson Children's Assessment of Sleep Apnea Study. *J Pediatr Psychol* 2006; 31:322-30.
 51. Lawson V, Lewis-Jones MS, Reid P, Owens RG, Finlay AY. Family impact of childhood atopic eczema. *Br J Dermatol* 1995; 133:19.
 52. Sarkar RL, Raj L, Kaur H, Basu S, Kanwar AJ, Jain RK. Psychological disturbances in Indian children with atopic eczema. *J Dermatol* 2004; 31:448-54.
 53. Lawson V, Lewis-Jones MS, Finlay AY, Reid P, Owens RG. The family impact of childhood atopic dermatitis: the Dermatitis Family Impact Questionnaire. *Br J Dermatol* 1998; 138:107-13.
 54. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract* 2006; 60:984-92.
 55. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Dermatology Venereology Suppl (Stockh)* 1980; 92:44-7.
 56. Kiken DA, Silverberg NB. Atopic dermatitis in children, part 1: epidemiology, clinical features, and complications. *Cutis*. 2006; 78:241-7.
 57. Oranje AP, Devilliers AC, Kunz B, Jones SL, DeRaeve L, Van Gysel D, et al. Treatment of patients with atopic dermatitis using wet-wrap dressings with diluted steroids and/or emollients. An expert panel's opinion and review of the literature. *J Eur Acad Dermatol Venereol* 2006; 20:1277-86.
 58. Kelsay K. Management of sleep disturbance associated with atopic dermatitis. *J Allergy Clin Immunol* 2006; 118:198-201.
 59. Kiczuk K, Chodorowska G, Krasowska D. The care of the child with atopic dermatitis. *Ann Univ Mariae Curie Sklodowska* 2004; 59:503-7.
 60. Lawton S. Atopic eczema: nurse-led care - 1. Making the most of the consultation. *J Fam Health Care* 2005; 15:9-10.
 61. Lapidus CS, Kerr PE. Social impact of atopic dermatitis. *Med Health R I* 2001; 84:294-5.
 62. Fennessy M, Coupland S, Popay J, Naysmith K. The epidemiology and experience of atopic eczema during childhood: a discussion paper on the implications of current knowledge for health care, public health policy and research. *J Epidemiol Community Health* 2000; 54:581-9.
 63. Shum KW, Lawton S, Williams HC, Docherty G, Jones J. The British Association of Dermatologists audit of atopic eczema management in secondary care. Phase 2: audit of service process. *Br J Dermatol* 2000; 142:274-8.
 64. Wieland S. Promoting health in children with atopic dermatitis. *Nurse Pract* 1998; 23:96-7.

65. David TJ, Devlin J, Ewing CI. Atopic and seborrheic dermatitis: practical management. *Pediatrician* 1991; 18:211-7.
66. Spergel JM, Paller AS. Atopic Dermatitis and the atopic march. *J Allergy Clin Immunol* 2003; 112:s118-s1127.
67. Lewis-Jones MS. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract* 2006; 60:984-92.
68. Arvola T, Tahvanainen A, Isolauri E. Concerns and expectations of parents with atopic infants. *Pediatr Allergy Immunol* 2000; 11:183-8.
69. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; 4:1-191.
70. Meltzer LJ, Moore M. Sleep disruptions in parents of children and adolescents with chronic illnesses: prevalence, causes, and consequences. *J Pediatr Psychol* 2008; 33:279-91.
71. LeBovidge JS, Kelley SD, Lauretti A, Bailey EP, Timmons KG, Timmons AK, et al. Integrating medical and psychological health care for children with atopic dermatitis. *J Pediatr Psychol* 2007; 32:617-6125.
72. Chamlin SL, Frieden IJ, Williams ML, Chren MM. Effects of Atopic Dermatitis on Young American Children and Their Families. *Pediatrics* 2004; 114:607-11.
73. Lindgren L, Wahlgren CF, Johansson SG, Wiklund I, Nordvall SL. Occurrence and clinical features of sensitization to *Pityrosporum orbiculare* and other allergens in children with atopic dermatitis. *Acta Derm Venereol* 1995; 75:300-4.
74. David TJ, Ferguson AP, Newton RW. Nocturnal Growth hormone release in children with short stature and atopic dermatitis. *Acta Derm Venereol (Stockh)* 1991; 71:229 - 31.
75. David TJ. Short stature in children with atopic eczema. *Acta Derm Venereol Suppl (Stockh)* 1989; 144:41-4.
76. Al-Riyami BM, Al-Rawas OA, Al-Riyami AA, Jasim LG, Mohammed AJ. A relatively high prevalence and severity of asthma, allergic rhinitis and atopic eczema in schoolchildren in the Sultanate of Oman. *Respirology* 2003; 8:69-76.
77. Ruzicka T. Atopic eczema between rationality and irrationality. *Arch Dermatol* 1998; 134:1462-9.
78. Montgomery-Downs HE, Jones VF, Molfese VJ, Gozal D. Snoring in preschoolers: associations with sleepiness, ethnicity, and learning. *Clin Pediatr (Phila)* 2003; 42:719-26.
79. Beattie PE, Lewis-Jones MS. An audit of the impact of a consultation with a paediatric dermatology team on quality of life in infants with atopic eczema and their families : further validation of the Infants' Dermatitis Quality of Life Index and Dermatitis Family Impact score. *Br J Dermatol* 2006; 155:1249-55.
80. Moore K, David TJ, Murray CS, Child F, Arkwright PD. Effect of childhood eczema and asthma on parental sleep and well-being: a prospective comparative study. *Br J Dermatol* 2006; 154:514-8.
81. Fukumizu M, Kaga M, Kohyama J, Hayes MJ. Sleep-related nighttime crying (yonaki) in Japan: a community-based study. *Pediatrics* 2005; 115:217-24.
82. Staab D, Kaufmann R, Brautigam M, Wahn U. Treatment of infants with atopic eczema with pimecrolimus cream 1% improves parents' quality of life: a multicenter, randomized trial. *Pediatr Allergy Immunol* 2005; 16:527-33.
83. Hon KL, Leung TF, Wong Y, Fok TF. Lesson from performing SCORADs in children with atopic dermatitis: subjective symptoms do not correlate well with disease extent or intensity. *Int J Dermatol* 2006; 45:728-30.
84. Hon KL, Lam MC, Leung TF, Wong KY, Chow CM, Fok TF, et al. Are age-specific high serum IgE levels associated with worse symptomology in children with atopic dermatitis? *Int J Dermatol* 2007; 46:1258-68.

85. Beltrani VS. Managing atopic dermatitis. *Dermatol Nurs* 1999; 11:171-6, 9-85; quiz 86-7.
86. Nilsson HJ, Levinsson A, Schouenborg J. Cutaneous field stimulation (CFS): a new powerful method to combat itch. *Pain* 1997; 71:49-55.
87. Ebata T, Iwasaki S, Kamide R, Niimura M. Use of a wrist activity monitor for the measurement of nocturnal scratching in patients with atopic dermatitis. *Br J Dermatol* 2001; 144:305-9.
88. Bringhurst C, Waterston K, Schofield O, Benjamin K, Rees J. Measurement of itch using actigraphy in pediatric and adult populations. *J Am Acad Dermatol* 2004; 51:893-8.
89. Hon KL, Lam MC, Wong KY, Leung TF, Ng PC. Pathophysiology of nocturnal scratching in childhood atopic dermatitis: the role of brain derived neurotrophic factor and substance P. *Br J Dermatol* 2007; 157:922-5.
90. Anisman H, Merali Z, Hayley S. Neurotransmitter, peptide and cytokine processes in relation to depressive disorder: Comorbidity between depression and neurodegenerative disorders. *Prog Neurobiol* 2008; 85:1-74.
91. Hiong HLT. Pruritus in atopic dermatitis - All that you were itching to know. *Bull Med Pract* 2004; 15.
92. Bockelbrink A, Heinrich J, Schafer A, Zutavern A, Borte M, Herbarth O, et al. Atopic eczema in children: another harmful sequel of divorce. *Allergy* 2006; 61:1397-402.
93. Gilbert SS, van den Heuvel CJ, Ferguson SA, Dawson D. Thermoregulation as a sleep signalling system. *Sleep Med Rev* 2004; 8:81-93.
94. Morgan L, Arendt J, Owens D, Folkard S, Hampton S, Deacon S, et al. Effects of the endogenous clock and sleep time on melatonin, insulin, glucose and lipid metabolism. *J Endocrinol* 1998; 157:443-51.
95. Krauchi K, Wirz-Justice A. Circadian rhythm of heat production, heart rate, and skin and core temperature under unmasking conditions in men. *Am J Physiol* 1994; 267:R819-R29.
96. Aschoff JJ. Circadian control of body temperature. In: Hardy JD, Gagge AP, Stowijk AJ, editors. *Physiological and Behavioural Temperature Regulation*. Springfield: Charles C Thomas; 1970. p. 905-19.
97. Krauchi K, Wirz-Justice A. Circadian clues to sleep onset mechanisms. *Neuropharmacol* 2001; 25:S92-S6.
98. Van Someren EJW. More than a marker: Interaction between the circadian regulation of temperature and sleep, age-related changes, and treatment possibilities. *Chronobiol Int* 2000; 17:313-54.
99. Heyer G, Schonberger A, Hornstein OP. Disorders of thermoregulation in adaption to external cold and heat stimuli in patients with atopic eczema. *Hautarzt* 1988; 39:18-22.
100. Samsonov VA, Bol'shakova GM. Body temperature regulation in patients with eczema and neurodermatitis. *Vestn Dermatol Venerol* 1975; 6:25-9.
101. Levin MM, Loseva VA. Temperature index of circulation in patients with eczema. *Vestn Dermatol Venerol* 1974; 2:32-5.
102. Teodosieva E. Changes of temperature of the skin in patients with eczema under the effect of treatment with corticosteroids. *Folia Med* 1969; 11:405-13.
103. Heyer G, Ulmer FJ, Schmitz J, Handwerker HO. Histamine-induced itch and alloknesis (itchy skin) in atopic eczema patients and controls. *Acta Derm Venereol* 1995; 75:348-52.
104. Langan SM, Bourke JF, Silcocks P, Williams HC. An exploratory prospective observational study of environmental factors exacerbating atopic eczema in children. *Br J Dermatol* 2006; 154:979-80.
105. Weiland SK, Husing A, Strachan DP, Rzehak P, Pearce N, Group IPOS. Climate and

- the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. *Occup Environ Med* 2004; 61:609-15.
106. Kramer U, Weidinger S, Darsow U, Mohrenschrager M, Ring J, Behrendt H. Seasonality in symptom severity influenced by temperature or grass pollen: results of a panel study in children with eczema. *J Invest Dermatol* 2005; 124:514-23.
 107. Campbell SS, Broughton RJ. Rapid decline in body temperature before sleep: fluffing the physiological pillow. *Chronobiol Int* 1994; 11:126-31.
 108. Ricci G, Patrizzi A, Baldi E, Menna G, Tabanalelli M, Masi M. Long term follow up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. *J Am Acad Dermatol* 2006; 107:567-74.
 109. Pevernagie DA, De Meyer MM, Claeys S. Sleep, breathing and the nose. *Sleep Med Rev* 2005; 9:437-51.
 110. Craig TJ, McCann JL, Gurevich F, Davies MJ. The correlation between allergic rhinitis and sleep disturbance. *J Allergy Clin Immunol* 2004; 114:S139-S45.
 111. Craig TJ, Teets S, Lehman EB, et al. Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids. *J Allergy Clin Immunol* 1998; 101:633-7.
 112. Craig TJ, Mende C, Hughes K, Kakumanu S, Lehman EB, Chinchilli V. The effect of topical fluticasone on objective sleep testing and the symptoms of rhinitis, sleep, and daytime somnolence in perennial allergic rhinitis. 2003.
 113. Mansfield LE, Diaz G, Posey CR, Flores-Neder J. Sleep disordered breathing and daytime quality of life in children with allergic rhinitis during treatment with intranasal budesonide. *Ann Allergy Asthma Immunol* 2004; 92:240-4.
 114. Shedden A. Impact of nasal congestion on quality of life and work productivity in allergic rhinitis. *Treat Respir Med* 2005; 4:439-46.
 115. Blaiss M, Reigel T, Philpot EA. A study to determine the impact of rhinitis on sufferer's sleep and daily routine [abstract]. *J Allergy Clin Immunol* 2005; 115:S197.
 116. Young T, Finn L, Kim H. Nasal obstruction as a risk factor for sleep-disordered breathing. *J Allergy Clin Immunol* 1997; 99:S757-S62.
 117. Desager KN, Nelen V, Weyler JJ, De Backer WA. Sleep disturbance and daytime symptoms in wheezing school-aged children. *J Sleep Res* 2005; 14:77-82.
 118. Janson C, De Backer W, Gislason T, Plaschke P, Bjornsson E, Hetta J, et al. Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: a population study of young adults in three European countries. *Eur Respir J* 1996; 9:2132-8.
 119. Sulit LG, Storfer-Isser A, Rosen CL, Kirchner HL, Redline S. Associations of obesity, sleep-disordered breathing, and wheezing in children. *Am J Respir Crit Care Med* 2005; 171:659-64.
 120. Syabbalo N. Chronobiology and chronopathophysiology of nocturnal asthma. *Int J Clin Pract* 1997; 51:455-62.
 121. Strunk RC, Sternberg AL, Bacharier LB, Szeffler SJ. Nocturnal awakening caused by asthma in children with mild-to-moderate asthma in the childhood asthma management program. *J Allergy Clin Immunol* 2002; 110:395-403.
 122. Kuehni CE, Strippoli MP, Chauillac ES, Silverman M. Snoring in preschool children: prevalence, severity and risk factors. *Eur Respir J* 2008; 31:326 - 33.
 123. Marshall NS, Almqvist C, Griunstein RR, Marks GB. Predictors for snoring in children with rhinitis at age 5. *Pediatr Pulmonol* 2007; 42:584 - 91.
 124. Harris JC, Carel CA, Rosenburg LA, Joshi P, Leventhal BG. Intermittent high dose corticosteroid treatment in childhood cancer: behavioral and emotional consequences. *J Am Acad Child Adolesc Psychiatry* 1986; 25:120-4.
 125. Nolem TM. Sedative effects of antihistamines: safety, performance and quality of life. *Clin Ther* 1997; 19:39-55.

126. Stewart AC, Thomas SE. Hypnotherapy as a treatment for atopic dermatitis in adults and children. *Br J Dermatol* 1995; 132:778-83.
127. Leo HL, Bender BG, Leung SB, Vu Tran Z, Leung DYM. Effect of pimecrolimus cream 1% on skin condition and sleep disturbance in children with atopic dermatitis. *J Allergy Clin Immunol* 2004; 114:691-3.
128. Endo K, Sano H, Fukuzumi T, Adachi J, Aoki T. Objective scratch monitor evaluation of the effect of an antihistamine on nocturnal scratching in atopic dermatitis. *J Dermatol Sci* 1999; 22:54-61.
129. Bieber T, Vick K, Folster-Holst R, Belloni-Fortina A, Stadtler G, Worm M. Efficacy and safety of methylprednisolone aceponate ointment 0.1% compared to tacrolimus 0.3% in children and adolescents with an acute flare of severe atopic dermatitis. *Allergy* 2007; 62:184-9.
130. Hon KL, Lam MC, Leung TF, Chow CM, Wong E, Leung AK. Assessing itch in children with atopic dermatitis treated with tacrolimus: objective versus subjective assessment. *Adv Ther* 2007; 24:23-8.
131. Eberlein B, Eicke C, Reinhardt HW, Ring J. Adjuvant treatment of atopic eczema: assessment of an emollient containing N-palmitoylethanolamine (ATOPA study). *J Eur Acad Dermatol Venereol* 2008; 22:73-82.
132. Stainer R, Matthews S, S.H. A, McDonald S, Robinson J, Schapira C, et al. Efficacy and acceptability of a new topical skin lotion of sodium cromoglicate (Altoderm) in atopic dermatitis in children aged 2-12 years: a double-blind, randomized, placebo-controlled trial. *Br J Dermatol* 2005; 152:334-41.
133. Schoni MH, Nikolaizik WK, Shoni-Affolter F. Efficacy trial of bioresonance in children with atopic dermatitis. *Int Arch Allergy Immunol* 1997; 112:238-46.
134. Folster-Holst R, Muller F, Schnopp N, Abeck D, Kreiselmaier I, Lenz T, et al. Prospective, randomized, controlled trial on *Lactobacillus rhamnosus* in infants with moderate to severe atopic dermatitis. *Br J Dermatol* 2006; 155:1256-61.
135. Holm EA, Wulf HC, Stegmann, Jemec GBE. Life quality assessment among patients with atopic eczema. *Br J Dermatol* 2006; 154:719-25.
136. David TJ. The investigation and treatment of severe eczema in childhood. *International Medicine Supplement* 1983; 6:17-25.
137. Minde K, Popiel K, Leos N, Falkner S, Parker K, Handley-Derry M. The evaluation and treatment of sleep disturbances in young children. *J Child Psychol Psychiatry* 1993; 34:521-33.
138. Hiscock H, Canterford L, Ukomunne OC, Wake M. Adverse associations of sleep problems in Australian preschoolers: national population study. *Pediatrics* 2007; 119:86-93.
139. Gregory AM, Van der Ende J, Willis TA, Verhulst FC. Parent-reported sleep problems during development and self-reported anxiety/depression, attention problems, and aggressive behavior later in life. *Arch Pediatr Adolesc Med* 2008; 162:330-5.
140. O'Brien LM, Ivanenko A, Crabtree VM, Holbrook CR, Bruner JL, Klaus CJ, et al. Sleep disturbances in children with attention deficit hyperactivity disorder. *Pediatr Res* 2003; 54:237-43.
141. O'Brien LM, Holbrook CR, Mervis CB, Klaus CJ, Bruner JL, Raffield TJ, et al. Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. *Pediatrics* 2003; 111:554-63.
142. Owens JA, Maxim R, Nobile C, McGuinn M, Msall M. Parental and self-report of sleep in children with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med* 2000; 154:549-55.
143. Huang YS, Chen NH, Li HY, Wu YY, Chao CC, Guilleminault C. Sleep disorders in Taiwanese children with attention deficit/hyperactivity disorder. *J Sleep Res* 2004; 13:269-77.

144. Schmitt J, Romanos M, Schmitt NM, al. E. Atopic Eczema and Attention-Deficit/Hyperactivity Disorder in a Population-Based Sample of Children and Adolescents. *JAMA* 2009; 301:724-6.
145. Romanos M, Gerlach M, Warnke A, Schmitt J. Association of attention-deficit/hyperactivity disorder and atopic eczema modified by sleep disturbance in a large population-based sample. *J Epidemiol Community Health* 2009; epub ahead of print.
146. Dang-Vu TT, Desseilles M, Peigneux P, Maquet P. A role for sleep in brain plasticity. *Pediatr Rehabil* 2006; 9:98-118.
147. Mazzoni G, Gori S, Formicola G, Gneri C, Masserani R, Murri L, et al. Word recall correlates with sleep cycles in elderly subjects. *Journal of Sleep Research* 1999; 8:185-8.
148. Meier-Koll A, Bussmann B, Schmidt C, Neuschwander D. Walking through a maze alters the architecture of sleep. *Perceptual and Motor Skills* 1999; 88:1141-59.
149. Mandai O, Guerrien A, Sockeel P, Lecomte P. REM sleep modifications following a Morse code learning session in humans. *Physiology and Behaviour* 1989; 46.
150. Smith C, Lapp L. Increases in number of REMs and REM density in humans following an intensive learning period. *Sleep* 1991; 14.
151. Jones BE. Paradoxical sleep and its chemical/structural substrates in the brain. *Neuroscience* 1990; 40.
152. Lauder JM. Morphogenetic roles of acetylcholine. *Environmental Health Perspectives* 1999; 107:65-9.
153. Rasmusson DD. The role of acetylcholine in cortical synaptic plasticity. *Behavioural Brain Research* 2000; 115:205-18.
154. Buckhalt JA, El-Sheikh M, Keller PS, Kelly RJ. Concurrent and longitudinal relations between children's sleep and cognitive functioning: the moderating role of parent education. *Child Development* 2009; 80:875-92.
155. Willoughby MT, Angold A, Egger HL. Parent-reported attention-deficit/hyperactivity disorder symptomatology and sleep problems in a preschool-age pediatric clinic sample. *J Am Acad Child Adolesc Psychiatry* 2008; 47:1086-94.
156. O'Brien LM, Mervis CB, Holbrook CR, Bruner JL, Klaus CJ, Rutherford J, et al. Neurobehavioral implications of habitual snoring in children. *Pediatrics* 2004; 114:44-9.
157. Montgomery-Downs HE, Crabtree VM, Gozal D. Cognition, sleep and respiration in at-risk children treated for obstructive sleep apnoea. *Eur Respir J* 2005; 25:336-42.
158. Montgomery-Downs HE, Gozal D. Snore-associated sleep fragmentation in infancy: mental development effects and contribution of secondhand cigarette smoke exposure. *Pediatrics* 2006; 117:e496-502.
159. Blunden S, Lushington K, Kennedy D. Cognitive and behavioural performance in children with sleep-related obstructive breathing disorders. *Sleep Med Rev* 2001; 5:447-61.
160. O'Brien LM, Tauman R, Gozal D. Sleep pressure correlates of cognitive and behavioral morbidity in snoring children. *Sleep* 2004; 27:279-82.
161. Chervin RD, Ruzicka DL, Giordani BJ, Weatherly RA, Dillon JE, Hodges EK, et al. Sleep-disordered breathing, behavior, and cognition in children before and after adenotonsillectomy. *Pediatrics* 2006; 117:e769-78.
162. Perez-Chada D, Perez-Lloret S, Videla AJ, Cardinali D, Bergna MA, Fernández-Acquier M, et al. Sleep disordered breathing and daytime sleepiness are associated with poor academic performance in teenagers. A study using the Pediatric Daytime Sleepiness Scale (PDSS). *Sleep* 2007; 30:1698-703.
163. Dahl RE. Sleep and the Developing Brain: Commentary on Touchette et al, Associations between sleep duration patterns and behavioural/cognitive functioning

- at school entry. SLEEP 30 (9); 1213-1219. Sleep 2007; 30:1079-80.
164. Julvez J, Torrent M, Guxens M, Anto JM, Guerra S, Sunyer J. Neuropsychologic status at the age 4 years and atopy in a population-based birth cohort. Allergy 2009; Epub ahead of print.
 165. Vlaski E, Stavric K, Isjanovska R, Seckova L, Kimovska M. Overweight hypothesis in asthma and eczema in young adolescents. Allergol Immunopathol 2006; 34:199-205.

Chapter 2: Eczema, asthma, rhinitis, sleep and behaviour in children

2.1 The contribution of atopic disorders to sleep disturbance and behaviour in children with eczema

The sleep of children with eczema is characterised by poor initiation,^{1,2,3} frequent awakenings^{2,4-8} and prolonged nocturnal wakefulness.⁹⁻¹⁰⁻¹³ In healthy non eczematous children, poor sleep is associated with a range of daytime behavioural deficits.^{14,15-16-24} In children with eczema preliminary results suggest that poor sleep is also associated with daytime deficits including reduced child and family quality-of-life,^{3,25-31} discipline problems³²⁻³⁴ and Attention Deficit Hyperactivity Disorder (ADHD).¹⁵

When examining the relationship between eczema and sleep, it is also important to also consider the potentially confounding impact of asthma and rhinitis in children with eczema³⁵ which themselves are known to affect sleep³⁵⁻³⁷ and behaviour.^{38,39} As this had not been conducted in previous studies, our first task was to confirm previous findings accounting for the impact of asthma and rhinitis. Therefore the aim of this study was to investigate the frequency of sleep problems in children with eczema compared to healthy controls and, after controlling for asthma and rhinitis, and to evaluate its association with daytime behaviour and quality-of-life.

2.2 Method

2.2.1 Participants and Procedure

Parents of children (6-16y) attending Allergy and Dermatology clinics at the Women's and Children's Hospital, a tertiary referral centre for the state of South Australia were recruited for the study. From a potential pool of 107 families with eczematous children approached on clinic days over a six month period, parents of 77 children with eczema volunteered for the study. A further 30 school friends of the eczema children and children recruited through advertisements within the hospital were recruited as controls. Eczema subjects were diagnosed by a Medical Specialist attending Allergy and Dermatology clinics using standardised criteria.⁴⁰ Control subjects were self reported not to have eczema.

An omnibus questionnaire was completed by parents attending the clinic. Parents were also asked to distribute the questionnaire to the parents of controls. Children were excluded if they were obese, had craniofacial abnormalities, cleft palate, neurological disorder, muscular dystrophy, intellectual delay, developmental delay or severe behavioural disorders. The study was approved by the relevant Hospital and University Human Research Ethic committees.

2.2.2 Apparatus

The following demographic data was collected: birth weight, current height and weight, and residential postcode. The latter was used to obtain socio-economic status based on the Australian Bureau of Statistics Socio-Economic Indexes For Areas (SEIFA) (2006).⁴¹

Table 2.1 Atopic questionnaire items used to estimate severity and impact on sleep

Questionnaire	Domain	Question	Response key
CDLQI	Eczema severity	“Over the last week, how itchy, scratchy, sore or painful or has the child’s skin been?”	1 = “not at all” to 4 = “very much”
CDLQI	Impact of eczema on sleep	“Over the previous week how much has the child’s sleep been affected by their skin problem?”	1 = “not at all” to 4 = “very much”
ISAAC	Impact of eczema on sleep	“In the last 12 months, how often has your child’s sleep usually been disturbed by itching and scratching due to their skin problem?”	1 = “sleep is not usually disturbed” to 5 = “6 or more nights per week on average”
ISAAC	Asthma severity	“How many attacks of wheezing has your child had in the last 12 months?”	1 = “none” to 4 = “more than 12”
ISAAC	Impact of Asthma on sleep	“How often, on average, has wheezing disturbed your child’s sleep?”	1 = “never woke with wheezing”, 2 = “less than one night per week” and 3 = “one or more nights per week”
ISAAC	Rhinitis prevalence	“In the last 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or the flu?”	“yes/no”
ISAAC	Rhinitis severity	“In which of the past 12 months did this nose problem occur?”	January to December
ISAAC	Impact of rhinitis on sleep	“How often, on average has your child been kept awake at night by this nose problem?”	1 = “never in the last 12 months”, 2 = “less than one night per week” and 3 = “one or more nights per week”

Nb CDLQI = Children’s Dermatology Life Quality Index⁴² ISAAC = International Study of Asthma and Allergies in Childhood Phase 1 Core questionnaire⁴³

2.2.3 The Child Health Questionnaire-Parent Form

The Child Health Questionnaire-Parent Form (CHQ-PF-28) was used to assess general quality-of-life: including the following subscales Physical Functioning, Role/Social Emotional-Behavioural, Bodily Pain, General Health Perceptions, Change in Health, Parental Impact – Emotional, Family Activities and Family Cohesion. These were rated using a four point scale (1 = “never” to 4 = “always”), apart for the item “In general, how would you rate the child’s health?” which rated the child on a five point scale (1 = “very good” to 5 = “poor”) and “How much bodily pain or discomfort has the child experienced in the last twelve months?” which was rated on a four point scale (1 = “none” to 4 = “severe”).⁴⁴

2.2.4 The Children’s Dermatology Life Quality Index

The Children’s Dermatology Life Quality Index (CDLQI)⁴² was used to further assess eczema severity and quality-of-life. Parents were asked to rate on a four point scale (1 = “not at all” to 4 = “very much”) the impact of the child’s skin problem over the previous week on ten quality-of-life indices. The CDLQI validity and reliability has been established through comparison with other disease-specific instruments.⁴⁵ Of note is that the CDLQI includes a single eczema severity question “Over the last week, how itchy, scratchy, sore or painful has the child’s skin been?” and, as well, a single sleep question, “Over the last week, how much has the child’s sleep been affected by their sleep problem?” both of which have been used as separate variables independent of the CDLQI Complete Scale. Accordingly CDLQI Complete Scale scores and CDLQI scores without the eczema severity question and sleep question are reported.

2.2.5 The Sleep Disturbance Scale for Children

Sleep problems over the previous 12 months were assessed using the Sleep Disturbance Scale for Children (SDSC).⁴⁶ The SDSC contains two items assessing sleep quality using a five point scale (total sleep time 1 = 9-11h to 5 = < 5h; and latency to sleep onset 1 = < 15 min to 5 = > 60 min) and 24 items assessing the frequency of sleep disorder symptoms also rated on a five point scale (1 = never to 5 = always). The SDSC provides normed T-scores (mean = 50 and SD = 10) for six scales entitled: Disorders of Initiating and Maintaining Sleep (e.g. sleep duration, sleep latency, night awakenings, etc), Disorders of Sleep Breathing (e.g. snoring, etc), Disorders of Arousal (e.g. sleepwalking, sleep terrors, nightmares, etc), Disorders of Sleep-Wake Transition (e.g. rhythmic movements, hypnagogic jerks, sleep talking, bruxism, etc), Disorders Of Excessive Daytime Sleepiness (e.g. difficulty waking up, morning tiredness, etc), and Sleep Hyperhydrosis (SHY) (e.g. nocturnal sweating, etc) and a composite Total Sleep Problem score.⁴⁶ The reliability and validity of the SDSC has been well evaluated and supported.⁴⁶

2.2.6 Conner's Parent Rating Scale-Revised (S).

Behavioural problems over the previous 12 months were assessed using the Conner's Parent Rating Scale-Revised (S).⁴⁷ The scale contains 27 statements about the child's behaviour rated on a four point scale (1 = "not true at all" to 4 = "very much true") and provides T-score (mean = 50 and SD = 10) based on an age and gender for four subscales: Oppositional Behaviour (e.g. Defiant, Loses temper, etc), Cognitive problems (e.g. Fails to complete assignments, not reading up to par, etc), Hyperactivity (e.g. Restless in the 'squirmy' sense, excitable, impulsive, etc) and an ADHD Index (e.g. Short attention span, distractibility or attention span a problem, etc).⁴⁷ This well validated measure has been previously used to examine the relationship between child sleep and behaviour.⁴⁸⁻⁵¹

2.3 Statistics

All analyses were conducted using SPSS version 16. An assessment of potential confounding factors between the eczema and control groups including age, gender, socio economic status, asthma⁵², rhinitis⁵³ and the affects of asthma and rhinitis disturbing sleep were undertaken prior to analyses. Group differences were tested using either F-test or Chi-square analyses where appropriate. Pearson-r correlations were used to assess the relationship between subject demographics, sleep factors and behavioural factors in children with eczema. Structural Equation Modelling (SEM) analyses was undertaken to estimate the causal relationship between atopic disorders, sleep and behavioural variables.

2.3.1 Group eczema, asthma and rhinitis covariates

Preliminary analyses of childhood eczema and co-morbid atopic disorders of asthma and rhinitis suggested few associations in the severity of symptoms between atopic disorders within all subjects (see Table 2.2). One significant finding was that the child's age, when eczema first occurred, was associated with the frequency that the child's sleep was disturbed due to wheezing.

Further analyses revealed that children with eczema reported significantly higher asthma and rhinitis severity scores and the frequency with which rhinitis disturbed sleep than controls (see Table 2.3). No significant group differences were observed in gender, age, socio-economic status and the frequency that asthma disturbed sleep. Accordingly, asthma severity, rhinitis severity and frequency that rhinitis disturbed sleep were entered as covariates in subsequent between group analyses. No child was reported to nap in either group and this variable was subsequently removed from analyses.

2.4 Results

Compared to controls, children with eczema had a lower general quality-of-life, more disturbed sleep with significantly higher scores on the Disorders of Initiating and Maintaining Sleep, Excessive Daytime Sleepiness, Total Sleep Disturbance scales and higher scores on the behavioural domains of ADHD and Oppositional behaviours (see Table 2.3).

A higher percentage of children with eczema compared to controls were above the clinical cut-off criteria ($T > 70$) for Disorders of Initiating and Maintaining Sleep [42% (32/77) vs. 7% (2/30)], Disorders Of Excessive Daytime Sleepiness [27% (21/77) vs. 7% (2/30)] and Total Sleep Problem [47% (36/77) vs. 10% (3/30)] and to a lesser extent for Disorders of Sleep Breathing [19% (15/77) vs. 10% (3/30)], Disorders of Arousal [23% (18/77) vs. 7% (2/30)], Sleep–Wake Transition Disorders [13% (10/77) vs. 10% (3/30)] and Sleep Hyperhydrosis T-scores above the clinical cut-off [9% (7/77) vs. 7% (2/30)]. Similarly, on the Conner’s Parent Rating Scale – Revised (S) a higher percentage of children with eczema were above the clinical cut-off in Oppositional Behaviour [18% (14/77) vs. 0% (0/30)], ADHD Index [12% (9/77) vs. 7% (2/30)] and Cognitive Problems [6% (5/77) vs. 3% (1/30)], but no trends were noted in the Hyperactivity scale scores [10% (8/77) vs. 10% (3/30)].

2.4.1 Correlations between atopic disorders and demographic/behavioural variables

The relationship between atopic disorders and demographic/behavioural variables are given in Table 2.4. Younger age, lower socio-economic status and reduced quality-of-life were all associated with increased eczema severity. The greater the severity of eczema, asthma and rhinitis, the more disturbed the sleep. However, the patterns of the effects were different for each disorder. Eczematous children whose sleep was more frequently disturbed by either asthma or rhinitis had higher Disorders of Sleep Breathing scores. Furthermore, eczematous children whose sleep was more frequently disturbed by rhinitis also had elevated Disorders of

Sleep-Wake Transition and Disorders Excessive Daytime Somnolence scores. Eczematous children whose sleep was more frequently disturbed by asthma also had higher Sleep Hyperhydrosis scores. Children whose sleep was more frequently disturbed by eczema had higher Disorders of Initiating and Maintaining Sleep and Disorders of Excessive Daytime Somnolence scores. The frequency that sleep was disturbed by either asthma or rhinitis was not found to correlate with behavioural variables, whereas more frequent sleep disturbance due to eczema was associated with increased Hyperactivity, ADHD and Oppositional behavioural scores.

2.4.2 Correlations between eczema, sleep disorder and behaviour

The relationship between atopic disorders, sleep disorder and behavioural scores in children with eczema are given in Table 2.5. In general the associations were of mild to moderate strength. Eczematous children with higher scores on Disorders of Initiating and Maintaining Sleep also had higher behavioural scores of Hyperactivity, ADHD and Oppositional behaviour. Children with higher disorders of sleep breathing scores also had higher scores of Hyperactivity and Oppositional behaviour. Children with higher Sleep-Wake Transition scores, Disorders of Excessive Daytime Somnolence and Hyperhydrosis scores also had higher scores on all behavioural subscales.

2.4.3 Structural Equation Modelling Analysis

Based on an examination of the literature on outcomes of Eczema, Asthma and Rhinitis on Sleep and behavioural outcomes, we developed SEM models of the interactions between Eczema, Asthma, Rhinitis, Sleep, and Cognitive Problems, Hyperactivity, ADHD Index and Oppositional (behaviour) separately using Amos 17 software.⁵⁴

Figure 2.1 shows the (representative) hypothesised model of the effects of Asthma, Eczema and Rhinitis on Cognitive Problems, to be tested. Figure 1 indicates potential direct and indirect paths (through Sleep Problems) from each condition (Eczema, Asthma and Rhinitis) to the behavioural outcomes of Cognitive Problems, Hyperactivity, ADHD Index and Oppositional. All of these hypothesised Condition/Sleep Problem /Behavioural Outcome models were successfully fitted to the data, and the final form of these models are shown in Figures, 2.2, 2.3, 2.4. & 2.5; Each comprises three exogenous variables i.e. variables which do not appear as a dependent variable in the model and two endogenous variables. Of the former, Asthma was operationalised by two indicators (items Rh1 & Rh2 from the questionnaire); i.e. "...has your child ever had wheezing or whistling in the chest?" and "...how many attacks of this have they had in the last 12 months?" Eczema was also operationalised by two items : "Has your child ever had eczema?" and "Has you child ever had an itchy rash which comes and goes for at least 6 months?". Rhinitis was operationalised by a single item 'Rhinitis Total Score' which is a sum of ratings of the child's nasal condition over the last 24 hours. Sleep Problems was operationalised by six indicators, which were the 't' scores for six subscales of Disorders of Maintaining and Initiating Sleep, Disorders of Sleep Breathing, Disorders of Arousal, Disorders of Sleep-Wake Transition, Disorders of Excessive Daytime Sleepiness and Sleep Hyperhydrosis of the Sleep Disturbance Scale for Children. 't' scores represent scores converted to a 0-100 basis with a mean of 50. The outcome variables of 'Cognitive Problems', 'Hyperactivity', ADHD Index' and 'Oppositional' (behaviours) were variously operationalised by the 't' score total for each variable derived from the Conner's Parent Rating Scale-Revised (S).

2.4.4 Evaluation of the Models generated through Structural Equation Analyses

The fit of the models to the data was assessed with: the chi-square (χ^2) statistic, the Goodness of Fit Index (GFI), Root Mean Square Error of Approximation (RMSEA).⁵⁵ Comparative Fit Index (CFI)⁵⁶ and the Tucker-Lewis Index (TLI). For each of these statistics, values of .90 or higher are acceptable⁵⁷, except for the RMSEA for which values up to .08 indicate an acceptable fit of the model to the data.⁵⁸

Direct Effects models were assessed to test the fit and significance of path coefficients of the direct effects; Asthma, Eczema and Rhinitis → (Behavioural) Outcome (M1 paths). Table 2.6 indicates that M1 models fitted to the data poorly and that none of the path coefficients from (Condition) to (Behaviour) were significant. However the path from Sleep to (Behaviour) was statistically significant in each case except for the Cognitive Problems outcome variable.

The next step was to test the addition of paths from (Condition) to (Behaviour) with paths from (Condition) to Sleep added, i.e. partial mediation of (Condition) by Sleep (M2 models). Table 2.6 indicates that these models fitted to the data very well. However, as with the direct effect (M1) models, no significant effect on Cognitive Problems was evident. The significance of the direct paths of (Condition) → Sleep permitted proceeding to testing full mediation of effects of (Condition) on (Behavioural Outcome) through their effects of Sleep Problems, (M3 models).⁵⁹ Table 2.6 indicates that all M3 models had a good fit to the data, with effects in the expected direction. However X^2 difference tests showed that all M3 models were worse than the M2 models, and in the case of ADHD and Opposition, significantly worse than M2 models.

2.4.5 Results of Structural Equation Analyses on children with eczema's sleep and behaviour

In sum, the confirmatory factor analyses suggest that the three conditions; Asthma, Eczema and Rhinitis have a significant effect on childhood behavioural outcomes including Hyperactivity, ADHD and Oppositional behaviour. This effect is substantially, but not completely, mediated by the effects of these conditions on Sleep Problems. When Disorders of Sleep Breathing was removed from the models, the change in the path coefficient was small (.01 - .09) and did not effect the outcome. The greatest effect between Sleep Problems and behavioural outcomes was seen on Oppositional behaviour followed by Hyperactive behaviour and least on ADHD. Surprisingly, no significant effect on Cognitive Problems was evident

Table 2.2 Correlation matrix of eczema, asthma and rhinitis variables. (significant correlations are bolded) (n=107).

	The child's age when eczema first occurred	In the last 12mnths, the length of time that eczema has been present.	In the last 12mnths, the frequency that the child's sleep usually been disturbed due to their skin problem.
Asthma			
In the last 12 months			
the number of attacks of wheezing the child has had.	-.01	.11	-.01
the frequency that the child's sleep was disturbed due to wheezing.	.31*	-.03	.13
the frequency that the child's wheezing has been severe enough to limit their speech to only one or two words at a time between breaths.	-.18	-.13	.09
the frequency that the child was heard to wheeze or cough during or after active play.	-.05	-.01	.08
Rhinitis			
In the last 12 months			
how many months did the nose problem occur.	-.19	.04	.17
how much did the nose problem interfere with the child's daily activities.	-.02	-.13	.06
how often the child was kept awake by the nose problem.	-.08	-.27	-.01

Nb *denotes $p < .05$, ** $p < .01$, *** $p < .005$, **** $p < .001$ and ***** $p < .0005$. N/A = not applicable.

Table 2.3 Mean (SD) demographic, quality-of-life, sleep and behaviour questionnaire scores for children with eczema and controls together with F-test/Chi-square (χ^2) results.

	Mean (SD)/subject ratio		F-test and chi-square (χ^2) results
	Eczema (n = 77)	Control (n = 30)	
Demographics			
Gender (male/female)	33/44	17/13	$\chi^2 = 1.7$
Age (years)	9.9 (2.8)	9.8 (2.5)	F = 0.0
Body Mass Index	17.9 (2.9)	17.9 (3.1)	F = 0.0
Birth weight (kg)	3.6 (0.6)	3.3 (0.4)	F = 3.6
Socio Economic Status	996.5 (82.2)	984.2 (84.7)	F = 0.5
Atopic Disease			
Eczema severity in the last week	2.7 (0.9)	1.0 (0.0)	F = 103.3*****
Asthma Severity in the last 12mnths	2.0 (1.0)	1.5 (0.8)	F = 5.5*
Rhinitis Severity in the last 12mnths	5.6 (4.5)	1.4 (3.0)	F = 22.3*****
<i>Frequency</i>			
Asthma disturbing sleep in the last 12mnths	1.5 (0.6)	1.3 (0.5)	F = 2.2
Rhinitis disturbing sleep in the last 12mnths	1.6 (0.8)	1.1 (0.3)	F = 10.8***
<i>Medication</i>			
Taken by subjects for Eczema	65/77 (84%)	0/30 (0%)	$\chi^2 = 64.5*****$
Taken by subjects for Asthma	44/77 (57%)	10/30 (33%)	$\chi^2 = 4.9^*$
The following variables were co-varied for asthma and rhinitis severity and frequency that rhinitis disturbed sleep			
Quality-of-Life			
Child-Health Questionnaire - Parent Form 28 (modified)	30.3 (7.9)	23.5 (5.1)	F = 10.7****
Sub-scales			
Physical Functioning	5.0 (2.0)	3.8 (1.3)	F = 3.5
Role/Social Emotional - Behavioural	2.3 (0.9)	1.7 (0.7)	F = 6.1*
Bodily Pain	2.4 (0.9)	1.6 (0.7)	F = 15.8*****
General Health Perceptions	9.1 (2.0)	7.7 (1.7)	F = 7.1**
Change in Health	2.1 (0.8)	1.5 (0.6)	F = 9.6***
Parental Impact – Emotional	4.2 (1.6)	3.0 (1.3)	F = 8.6***
Family Activities	3.5 (1.6)	2.8 (1.0)	F = 1.7
Family Cohesion	1.9 (0.9)	1.4 (0.7)	F = 4.6*
Children's Dermatology Life Quality Index			
CDLQI (Complete Scale)	19.5 (7.5)	N/A	N/A
CDLQI without eczema severity question & sleep question	14.7 (6.0)	N/A	N/A
Sleep Disturbance Scale for Children			
Disorders of Initiating and Maintaining Sleep	70.9 (18.1)	58.1 (12.8)	F = 11.0***
Disorders of Sleep Breathing	59.0 (16.6)	52.4 (10.7)	F = 0.0
Disorders of Arousal	56.4 (14.4)	55.4 (13.3)	F = 0.3
Disorders of Sleep Wake Transition	63.0 (15.8)	54.9 (13.2)	F = 2.9
Disorders of Excessive Daytime Sleepiness	61.9 (17.4)	50.2 (8.0)	F = 7.8**
Sleep Hyperhydrosis	52.2 (11.5)	51.1 (10.8)	F = 0.1
Total Score	70.7 (16.1)	56.0 (11.0)	F = 12.5****
Conner's Parent Rating Scale – Revised (S)			
Cognitive Problems	53.1 (9.9)	49.9 (8.3)	F = 2.5
Hyperactivity	56.4 (12.6)	50.6 (10.8)	F = 3.2
ADHD Index	55.1 (10.7)	49.0 (8.9)	F = 8.2**
Oppositional Behaviour	57.4 (12.6)	50.3 (8.6)	F = 8.0**

Nb *denotes $p < .05$, ** $p < .01$, *** $p < .005$, **** $p < .001$ and ***** $p < .0005$. N/A = not applicable.

Table 2.4 Correlation matrix: atopy variables versus demographic, quality-of-life, sleep and behaviour questionnaire variables in children with eczema (n=77) (significant correlations are bolded).

	Asthma disturbed sleep in the last 12mths	Rhinitis disturbed sleep in the last 12mths	Frequency that eczema disturbed sleep last week	Frequency that eczema disturbed sleep last 12mths
Demographic				
Age	.12	.22	-.33***	-.27*
Birth Weight	.09	.13	.10	.06
Body Mass Index	.02	-.17	-.14	-.14
Socio-Economic Status	-.05	.01	-.26*	-.36***
Atopic Disease				
Asthma severity in the last 12mths	.63****	.52****	.08	.05
Rhinitis severity in the last 12mths	.24*	.56****	.14	.12
Eczema severity in the last week	.08	.09	.71***	.54***
Frequency				
Asthma disturbed sleep in the last 12mths	N/A	.41****	.02	-.01
Rhinitis disturbed sleep in the last 12mths	.41****	N/A	.02	.01
Eczema disturbed sleep in the last week	.02	.02	N/A	.82***
Eczema disturbed sleep in last 12 months	.02	.02	.82***	N/A
Quality-of-Life				
General Quality of Life Measure	.07	.21	.35***	.46***
Children's Dermatology Life Quality Index				
CDLQI (Complete Scale)	.03	.09	.80***	.72***
CDLQI without eczema severity question & sleep question	.03	.16	.81****	.70****
Sleep Disturbance Scale for Children				
Disorders of Initiating and Maintaining Sleep	.18	.25**	.41****	.43****
Disorders of Sleep Breathing	.37****	.53***	.14	.12
Disorders of Arousal	.13	.01	.15	.15
Disorders of Sleep-Wake Transition	.11	.26**	.17	.21*
Disorders of Excessive Daytime Sleepiness	.11	.30***	.45****	.43****
Sleep Hyperhydrosis	.21*	.14	.16	.19*
Total Sleep Problem	.27**	.41****	.48****	.48****
Conner's Parent Rating Scale – Revised (S)				
Cognitive Problems	.07	.05	.13	.12
Hyperactivity	.06	.10	.23*	.27**
ADHD Index	.07	.04	.25*	.26**
Oppositional behaviour	.08	.11	.35****	.39****

Nb *denotes $p < .05$, ** $p < .01$ and *** $p < .005$.

Table 2.5. Correlation matrix of sleep and behavioural scales and their subscales in children with eczema (n=77) (significant correlations are bolded).

Conner's Parent Rating Scale – Revised (S)	Sleep Disorders Scale for Children										
	Eczema Severity in the previous week	Children's Dermatology Life Quality Index	Asthma Severity in the last 12 months	Rhinitis Severity in the Last 12 months	Initiating and Maintaining Sleep	Sleep Breathing	Arousal	Sleep-Wake Transition	Excessive Daytime Sleepiness	Hyperhydrosis	Total Sleep Problem
Cognitive problems	.04	.17	.20*	.00	.10	.17	-.01	.26**	.21*	.26**	.30**
Hyperactivity	.18	.20*	.17	.11	.23*	.21*	.11	.33***	.18	.26**	.34***
ADHD Index	.14	.24*	.12	.02	.19*	.15	.10	.33***	.24*	.25**	.37***
Oppositional Behaviour	.30***	.36***	.11	.02	.34***	.26**	.06	.26**	.43****	.24*	.45****

Nb *denotes $p < .05$, ** $p < .01$ and *** $p < .005$..

Table 2.6: Results of Structural Equation Modelling (Maximum Likelihood Estimates) for the Total Sample (N =107) in the relationship between Asthma, Eczema, & Rhinitis on Sleep Problems and Behaviour Problems

	χ^2	df	GFI	RMSEA	CFI	TLI	χ^2 (df) difference / significance
M1 Direct Effect (Medical) Condition on Cognition	85.22	39	.891	.114	.891	.833	
M 1 Direct Effects Condition on Hyperactivity	77.69	36	.900	.105	.907	.858	
M 1 Direct Effects Condition on ADHD	83.33	36	.894	.114	.896	.842	
M1 Direct Effects Condition on Opposition	83.87	36	.894	.112	.897	.842	
M.2. Direct Effects Condition on Cognition-(Partial Mediation by Sleep)	45.18	33	.933	.050	.973	.955	(M1-M2) 40.06(3) ***
M2 Direct Effects Condition on Hyperactivity-(Partial Mediation by Sleep)	38.00	33	.940	.038	.989	.985	(M1-M2) 39.69 (3) ***
M2 Direct Effects Condition on ADHD-(Partial Mediation by Sleep)	43.38	33	.934	.054	.967	.962	(M1-M2) 39.95(3) ***
M2 Direct Effects Condition on Opposition-(Partial Mediation by Sleep)	43.22	33	.938	.054	.978	.963	(M1-M2) 40.65 (3) ***
M3 Effects Condition on Cognition-(Full Mediation by Sleep)	46.82	36	.931	.053	.971	.963	(M2-M3) -1.44 (0) ns
M3 Effects Condition on Hyperactivity-(Full Mediation by Sleep)	38.83	36	.939	.025	.994	.990	(M2-M3) -0.53 (0) ns
M3 Effects Condition on ADHD-(Full Mediation by Sleep)	46.92	36	.923	.054	.976	.963	(M2-M3) -3.54 (0) *
M3 Effects Condition on Opposition-(Full Mediation by Sleep)	48.78	36	.927	.058	.958	.972	(M2-M3) -5.56 (0) *

Notes; *= $p < .05$; ** $p < .01$; ***= $p < .001$; df = degrees of freedom; GFI = goodness-of-fit index; RMSEA = root mean square error of approximation; CFI = comparative fit index; TLI= Tucker-Lewis Index; χ^2 = Chi-Square Statistic

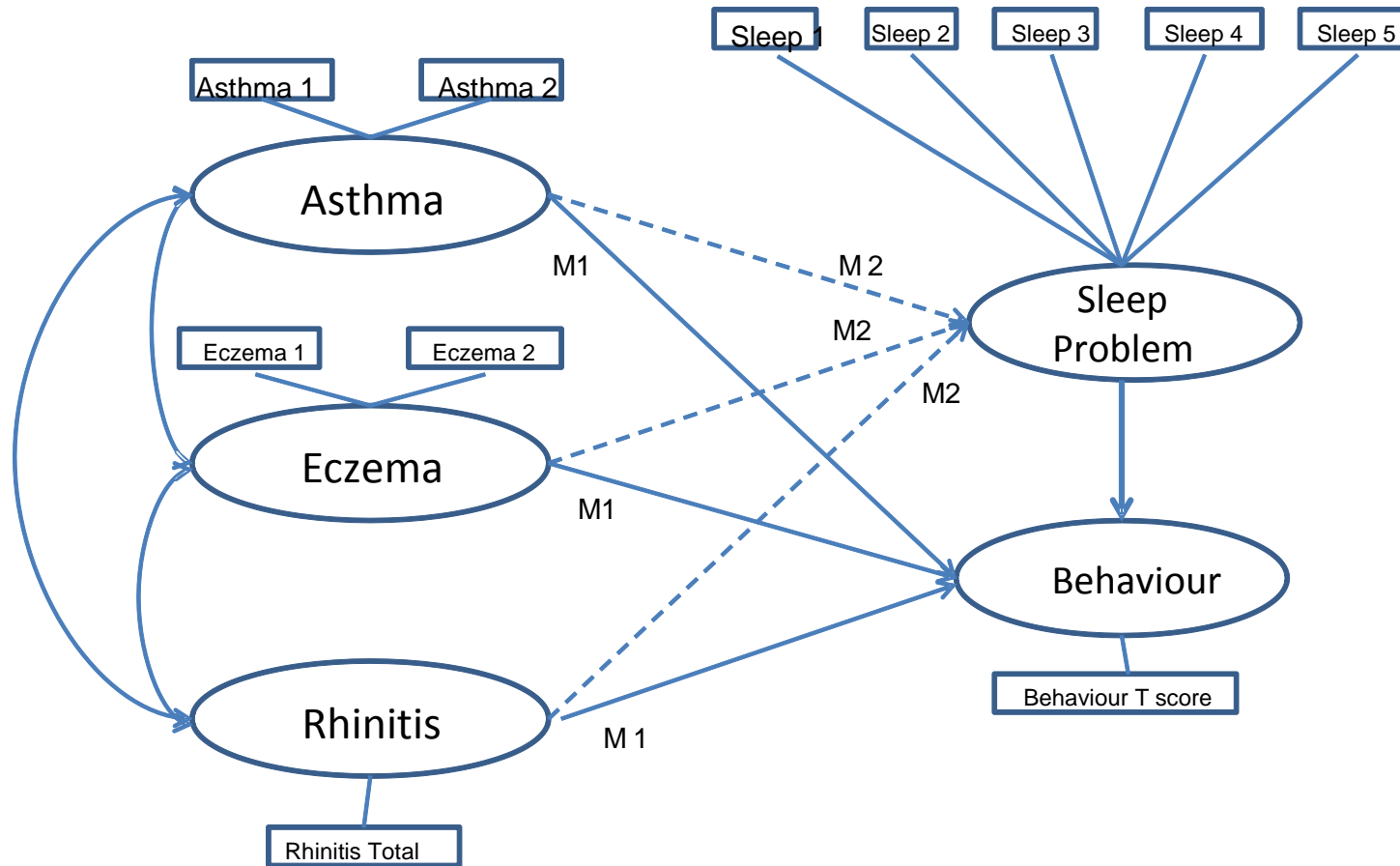


Figure 2.1: SEM Model for Hypothesised Relationships Between Conditions (3), Sleep, & Behaviours (4); Variables, Variable Indicators and Paths
 Note: M1 = Direct Effects, M2 = Indirect Effects (via Sleep)

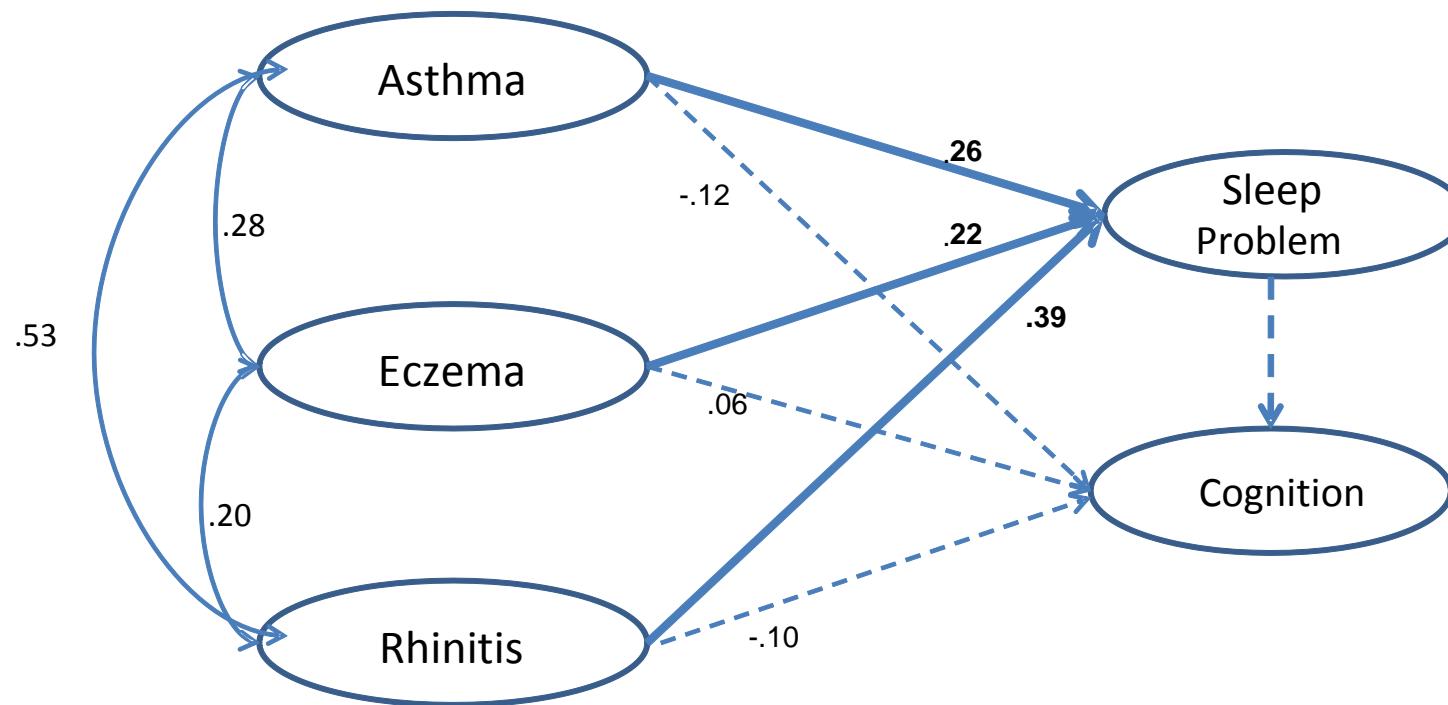


Figure 2.2: Partial Mediation of Cognition by Asthma, Eczema and Rhinitis Effect on Sleep

Note: Dotted paths indicate statistically insignificant path coefficients

[Default Model: CMIN/df = 1.37; CFI= .973; TLI= .933; GFI = .955; RMSEA= .054

Independence Model: CMIN/df = 9.18; CFI= .000; TLI= .000; GFI= .523; RMSEA= .278]

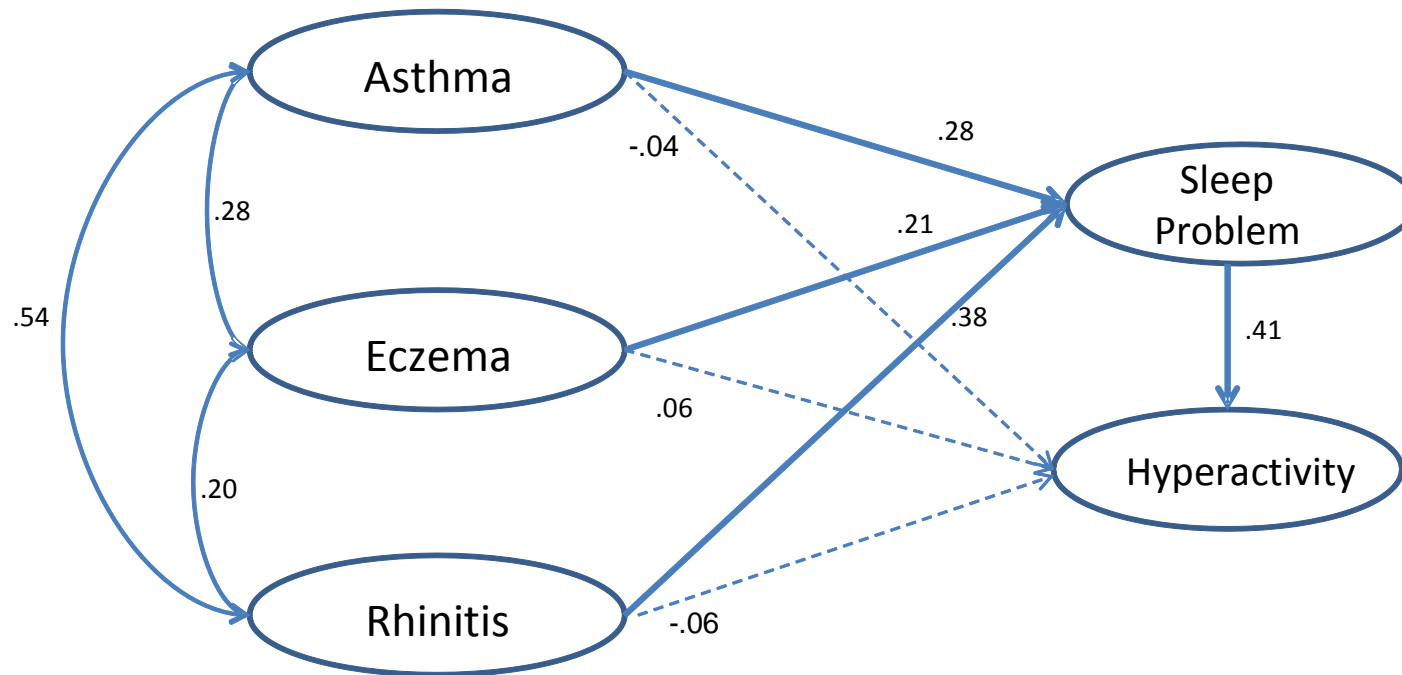


Figure 2.3: Partial Mediation of Hyperactivity by Asthma, Eczema and Rhinitis Effect on Sleep.

Note: Dotted paths are statistically insignificant.

Default Model: CMIN/ Df = 1.85, CFI= .942; TLI= .915; GFI = .900; RMSEA= .085

IndependenceModel: CMIN/df= 10.72; CFI= .000; TLI= .000; GFI= .554; RMSEA=.299

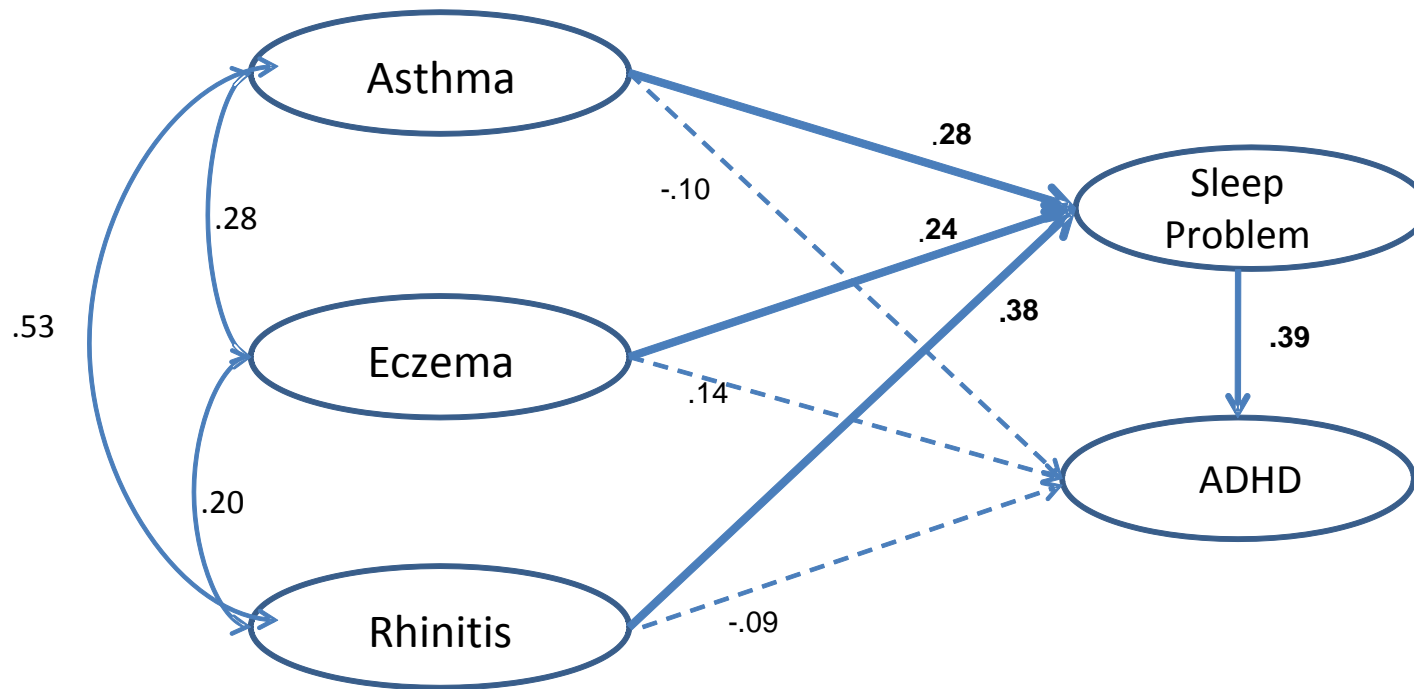


Figure 2.4: Partial Mediation of ADHD by Asthma, Eczema and Rhinitis Effect on Sleep

Note: Dotted paths indicate statistically insignificant path coefficients

[Default Model: CMIN/ df = 1.31; CFI= .977; TL= .933; GFI = 934; RMSEA= .054

Independence Model: CMIN/df= 9.23; CFI= .000; TLI= .000; GFI= 524; RMSEA=217]

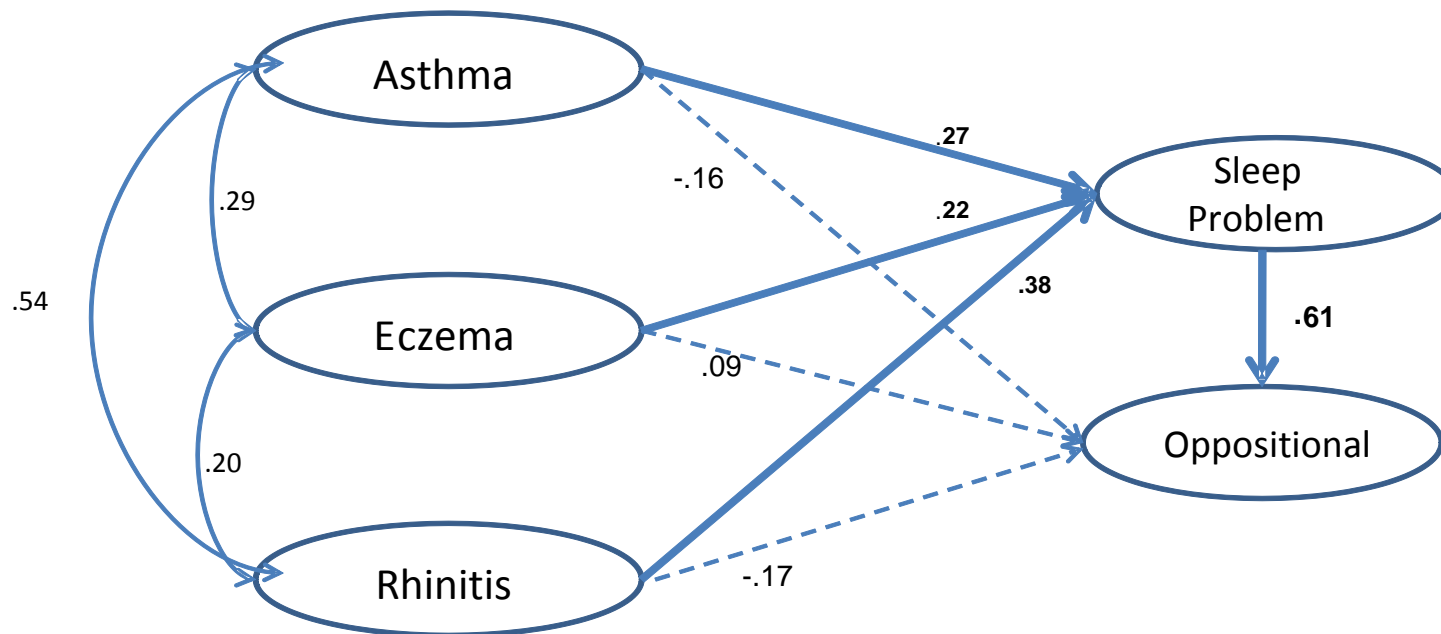


Figure 2.5: Partial Mediation of Oppositional (Behaviour) by Asthma, Eczema and Rhinitis Effect on Sleep

Note: Dotted paths indicate statistically insignificant path coefficients

[Default Model: CMIN/ df = 1.31; CFI= .978 ;TLI= .962; GFI = .934; RMSEA= .054

Independence Model: CMIN/ df = 9.42; CFI= .000; TLI= .000; GFI= .507; RMSEA= .282]

2.5 Discussion

The sleep of children with eczema was characterised, as anticipated, by problems with initially settling and maintaining sleep while their daytime functioning was characterised by excessive daytime sleepiness and higher levels of ADHD and oppositional type behaviours. Subsequent correlation analyses revealed that disturbed sleep due to eczema over the previous week and, likewise, over the previous year were both associated with increased oppositional behaviour and worse quality-of-life. In contradistinction to eczema, asthma and rhinitis were associated with higher Disorders of Sleep Breathing scores but showed no association with any behavioural scores. In summary, the association between sleep disruption and behavioural deficits in eczematous children parallel previous findings in non-eczematous children.^{2, 32, 33, 60, 61}

Structural Equation Modelling was used to test whether there was a direct casual relationship between eczema, asthma, rhinitis and daytime behaviour (i.e. Cognitive Problems, Hyperactivity, Inattention and Oppositional behaviour), or whether this relationship was mediated through sleep. Modelling revealed that the effects of eczema, asthma and rhinitis on behaviour were largely mediated through their respective effects on sleep and of the three atopic conditions, eczema may have a slightly lesser effect. The contribution of Sleep Disordered Breathing was also assessed in the relationship between sleep and behaviour in children with eczema. The contribution of Sleep Disordered Breathing to each sleep and behaviour model was small and did not alter the outcome when removed from the analysis.

In the present study, younger age and lower socio-economic status were both associated with increased eczema severity. An age-related decline in eczema severity is well documented⁶² while the findings for socio-economic status is counter to most groups who report higher frequencies of eczema within families of middle to upper socio-economic groups^{63 64 65 66} but

not all.⁶² Younger age and lower socio-economic status were also associated with more disturbed sleep. The finding for age is consistent with previous research by Hon et al.²⁸ who report reduced sleep quality in children with eczema aged < 10 compared to > 10 years. A relationship between low socio-economic status and poor sleep in children has been previously reported by Montgomery-Downs et al.⁶⁷ but this is the first study to report a relationship in children with eczema.

Consistent with previous research, eczema severity and sleep disturbance in children with eczema were found in this study to be associated with reduced quality-of-life. Sleep disturbance has been rated as the second highest contributing factor to reduced quality-of-life in children with eczema after itch²⁸ while parents with eczematous children report that is the most stressful aspect of care^{29, 68} and rate sleep disturbance highest on items negatively affecting family quality-of-life.^{29, 69}

Limitations of the current study include the reliance on parental report and the low response rate for controls. Concerning the latter, we deliberately sought controls with a similar socio-economic background to patients and, hence asked eczema subjects to recruit peers. Although a higher response rate would have been desirable, nonetheless the two groups had similar demographic profiles and meaningful sleep and behavioural differences were evident.

In conclusion, disturbed sleep remains a common feature in more severe eczematous children when the co-morbid affects of asthma and rhinitis are statistically removed from the relationship and, moreover, disturbed sleep mediates the effects of eczema on behaviour.

Bibliography

1. Reid P, Lewis-Jones MS. Sleep difficulties and their management in preschoolers with atopic eczema. *Clin Exp Dermatol* 1995; 20:38-41.
2. Dahl RE, Bernhisel-Broadbent J, Scanlon-Holdford S, Sampson HA, Lupo M. Sleep disturbances in children with atopic dermatitis. *Arch Pediatr Adolesc Med* 1995; 149:856-60.
3. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol* 2006; 155:145.
4. Reuveni H, Chapnick G, Tal A, Tarasiuk A. Sleep fragmentation in children with atopic dermatitis. *Arch Pediatr Adolesc Med* 1999; 153:249-53.
5. Bartlett LB, Westbrook R, White JE. Sleep patterns in children with atopic eczema. *Acta Derm Venereol* 1997; 77:446-8.
6. Chamlin SL, Mattson CL, Frieden IJ, Williams ML, Mancini AJ, Cella D, et al. The price of pruritus: sleep disturbance and cosleeping in atopic dermatitis. *Arch Pediatr Adolesc Med* 2005; 159:745-50.
7. Chng SY, Goh DY, Wang XS, Tan TN, Ong NB. Snoring and atopic disease: a strong association. *Pediatr Pulmonol* 2004; 38:210-6.
8. Emerson RM, Charman CR, Williams HC. The Nottingham Eczema Severity Score: preliminary refinement of the Rajka and Langeland grading. *Br J Dermatol* 2000; 142:288-97.
9. Stores G, Burrows A, Crawford C. Physiological sleep disturbance in children with atopic dermatitis: a case control study. *Pediatr Dermatol* 1998; 15:264-8.
10. Monti JM, Vignale R, Monti D. Sleep and nighttime pruritus in children with atopic dermatitis. *Sleep* 1989; 12:309-14.
11. Ebata T, Iwasaki S, Kamide R, Niimura M. Use of a wrist activity monitor for the measurement of nocturnal scratching in patients with atopic dermatitis. *Br J Dermatol* 2001; 144:305-9.
12. Benjamin K, Waterston K, Russell M, Schofield O, Diffey B, Rees JL. The development of an objective method for measuring scratch in children with atopic dermatitis suitable for clinical use. *J Am Acad Dermatol* 2004; 50:33-40.
13. Nilsson HJ, Levinsson A, Schouenborg J. Cutaneous field stimulation (CFS): a new powerful method to combat itch. *Pain* 1997; 71:49-55.
14. Hart CN, Palermo TM, Rosen CL. Health-related quality of life among children presenting to a pediatric sleep disorders clinic. *Behav Sleep Med* 2005; 3:4-17.
15. Quach J, Hiscock H, Canterford L, Wake M. Outcomes of child sleep problems over the school-transition period: Australian population longitudinal study. *Pediatrics* 2009; 123:1287-92.
16. Sung V, Hiscock H, Sciberras E, Efron D. Sleep problems in children with attention-deficit/hyperactivity disorder: prevalence and the effect on the child and family. *Arch Pediatr Adolesc Med* 2008; 162:336-42.
17. O'Brien LM, Ivanenko A, Crabtree VM, Holbrook CR, Bruner JL, Klaus CJ, et al. Sleep disturbances in children with attention deficit hyperactivity disorder. *Pediatr Res* 2003; 54:237-43.
18. O'Brien LM, Holbrook CR, Mervis CB, Klaus CJ, Bruner JL, Raffield TJ, et al. Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. *Pediatrics* 2003; 111:554-63.
19. Owens JA, Maxim R, Nobile C, McGuinn M, Msall M. Parental and self-report of sleep in children with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med* 2000; 154:549-55.
20. Chervin RD, Dillon JE, Bassetti C, Ganoczy DA, Pituch KJ. Symptoms of sleep

- disorders, inattention, and hyperactivity in children. *Sleep* 1997; 20:1185-92.
21. Yokomaku A, Misao K, Omoto F, Yamagishi R, Tanaka K, Takada K, et al. A study of the association between sleep habits and problematic behaviors in preschool children. *Chronobiol Int* 2008; 25:549-64.
 22. Minde K, Popiel K, Leos N, Falkner S, Parker K, Handley-Derry M. The evaluation and treatment of sleep disturbances in young children. *J Child Psychol Psychiatry* 1993; 34:521-33.
 23. Hiscock H, Canterford L, Ukomunne OC, Wake M. Adverse associations of sleep problems in Australian preschoolers: national population study. *Pediatrics* 2007; 119:86-93.
 24. Gregory AM, Van der Ende J, Willis TA, Verhulst FC. Parent-reported sleep problems during development and self-reported anxiety/depression, attention problems, and aggressive behavior later in life. *Arch Pediatr Adolesc Med* 2008; 162:330-5.
 25. Ben-Gashir MA, Seed PT, Hay RJ. Are quality of family life and disease severity related in childhood atopic dermatitis? *J Eur Acad Dermatol Venereol* 2002; 16:455-62.
 26. Chamlin SL, Cella D, Frieden IJ, Williams ML, Mancini AJ, Lai JS, et al. Development of the Childhood Atopic Dermatitis Impact Scale: initial validation of a quality-of-life measure for young children with atopic dermatitis and their families. *J Invest Dermatol* 2005; 125:1106-11.
 27. Lewis-Jones MS. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract* 2006; 60:984-92.
 28. Hon KL, Leung TF, Wong KY, Chow CM, Chuh A, Ng PC. Does age or gender influence quality of life in children with atopic dermatitis? *Clin Exp Dermatol* 2008; 33:705-9.
 29. Ricci G, Bendandi B, Bellini F, Patrizi A, Masi M. Atopic dermatitis: quality of life of young Italian children and their families and correlation with severity score. *Pediatr Allergy Immunol* 2007; 18:245-9.
 30. Lewis-Jones MS, Finlay AY, Dykes PJ. The Infant's Dermatitis Quality of Life Index. *Br J Dermatol* 2001; 144:104-10.
 31. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract* 2006; 60:984-92.
 32. Daud LR, Garralda ME, David TJ. Psychosocial adjustment in preschool children with atopic eczema. *Arch Dis Child* 1993; 69:670-6.
 33. Lawson V, Lewis-Jones MS, Reid P, Owens RG, Finlay AY. Family impact of childhood atopic eczema. *Br J Dermatol* 1995; 133:19.
 34. Sarkar RL, Raj L, Kaur H, Basu S, Kanwar AJ, Jain RK. Psychological disturbances in Indian children with atopic eczema. *J Dermatol* 2004; 31:448-54.
 35. Ricci G, Patrizi A, Baldi E, Menna G, Tabanalelli M, Masi M. Long term follow up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. *J Am Acad Dermatol* 2006; 107:567-74.
 36. Syabbalo N. Chronobiology and chronopathophysiology of nocturnal asthma. *Int J Clin Pract* 1997; 51:455-62.
 37. Shedden A. Impact of nasal congestion on quality of life and work productivity in allergic rhinitis. *Treat Respir Med* 2005; 4:439-46.
 38. Fagnano M, van Wijngaarden E, Connolly HV, Carno MA, Forbes-Jones E, Halterman JS. Sleep-disordered breathing and behaviors of inner-city children with asthma. *Pediatrics* 2009; 124:218-25.
 39. Liukkonen K, Virkkula P, Aronen ET, Kirjavainen T, Pitkäranta A. All snoring is not adenoids in young children. *Int J Pediatr Otorhinolaryngol.* 2008; 72:879-84.
 40. Hanifin JM. Basic and clinical aspects of atopic dermatitis. *Ann Allergy* 1984; 52:386-95.

41. Pink B. Socio-Economic Indexes for Areas (SEIFA) - Technical Paper. In: Statistics ABo, ed: Commonwealth of Australia, 2006.
42. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): Initial validation and practical use. *Br J Dermatol* 1995; 132:942-9.
43. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8:483-91.
44. Landgraf JM, Abetz L, Ware JE. The CHQ user's manual. 1st ed. Boston, M.A.: The Health Institute, New England Medical Center.; 1996.
45. Holm EA, Wulf HC, Stegmann, Jemec GBE. Life quality assessment among patients with atopic eczema. *Br J Dermatol* 2006; 154:719-25.
46. Bruni O, Ottaviano S, Guidetti V, Romoli M, Innocenzi M, Cortesi F, et al. The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *J Sleep Res* 1996; 5:251-61.
47. Conners CK. Conner's Parent Rating Scale - Revised. Tonawanda, New York: Multi-Health Systems Inc., 1997.
48. Wei JL, Mayo MS, Smith HJ, Reese M, Weatherly RA. Improved behaviour and sleep after adenotonsillectomy in children with sleep-disordered breathing. *Arch Otolaryngol Head Neck Surg* 2007; 133:974 - 9.
49. Barclay L, Murata P. Adenotonsillectomy improves sleep, behavior in children with sleep disordered breathing. *Arch Otolaryngol Head Neck Surg* 2007; 133:974-9.
50. Cortese S, Maffei C, Konofal E, Lecendreux M, Angriman E, Vincenzi B, et al. Parent reports of sleep/alertness problems and ADHD symptoms in a sample of obese adolescents. *Journal of Psychosomatic Research* 2007; 63:587-90.
51. Constantin E, Kermack A, Nixon G, Tidmarsh L, Ducharme FM, Brouillette RT. Adenotonsillectomy improves sleep, breathing, quality of life but not behavior. *The Journal of Pediatrics* 2007; 150:540-6.e1.
52. Macri F, Rossi FP, Lambiase C, di Castelbianco FB, Frassanito A. Psychological factors in childhood asthma. *Pediatr Pulmonol* 2008; 43:366-70.
53. Nathan RA. The burden on allergic rhinitis. *Allergy Asthma Proc* 2007; 28:3-9.
54. Arbuckle J. Amos 5.0 Computer software. Chicago, Ill: SPSS; 2003.
55. Steiger JH. Structural model evaluation and modification: An interval estimation approach. *Multivariate Behavioral Research* 1990; 25.
56. Bentler PM. Comparative fit indexes in structural models. *Psychological Bulletin* 1990; 107:238-46.
57. Hoyle RH. The structural equation modelling approach: Basic concepts and fundamental issues. In: Hoyle RH, editor. *Structural equation modelling: Concepts, issues and applications*. Thousand Oaks, CA: Sage; 1995.
58. MacCallum RC, Browne, M.W., & Sugawara, H.M. Power analysis and determination of sample size for covariance structure modelling. *Psychological Methods* 1996; 1:130-49.
59. Baron RM, Kenny DA. The Moderator-Mediator Variable Distinction in Social Psychological Research: Conceptual, Strategic, and Statistical considerations. *Journal of Personality & Social Psychology* 1986; 51:1173-82.
60. Elliot BE, Luker K. The experiences of mothers caring for a child with severe atopic eczema. *Journal of Clinical Nursing* 1997; 6:241-47.
61. Absolom CM, Cottrell D, Eldridge SM, Glover MT. Psychological disturbance in atopic eczema: the extent of the problem in school-aged children. *Br J Dermatol* 1997; 137:241-5.
62. Hanifin JM, Reed ML. A population-based survey of eczema prevalence in the United States. *Dermatitis* 2007; 18:82-91.

63. Golding J, Peters TJ. The epidemiology of childhood eczema: I. A population based study of associations. *Paediatr Perinat Epidemiol* 1987; 1:67-79.
64. du Prel X, Krämer U, Behrendt H, Ring J, Oppermann H, Schikowski T, et al. Preschool children's health and its association with parental education and individual living conditions in East and West Germany. *BMC Public Health* 2006; 6:312.
65. Romanos M, Gerlach M, Warnke A, Schmitt J. Association of attention-deficit/hyperactivity disorder and atopic eczema modified by sleep disturbance in a large population-based sample. *J Epidemiol Community Health* 2009; epub ahead of print.
66. McNally NJ, Phillips DR, Williams HC. The problem of atopic eczema: aetiological clues from the environment and lifestyles. *Soc Sci Med* 1998; 46:729-41.
67. Montgomery-Downs HE, Jones VF, Molfese VJ, Gozal D. Snoring in preschoolers: associations with sleepiness, ethnicity, and learning. *Clin Pediatr (Phila)* 2003; 42:719-26.
68. David TJ. The investigation and treatment of severe eczema in childhood. *International Medicine Supplement* 1983; 6:17-25.
69. Beattie PE, Lewis-Jones MS. An audit of the impact of a consultation with a paediatric dermatology team on quality of life in infants with atopic eczema and their families : further validation of the Infants' Dermatitis Quality of Life Index and Dermatitis Family Impact score. *Br J Dermatol* 2006; 155:1249-55.

Chapter 3: Polysomnography data of the sleep of children with eczema

3.1 Rationale for conducting polysomnographic studies on children with eczema

Having established the association between eczema, sleep disturbance and behaviour in our previous study, the next task was to examine this relationship with more precise and comprehensive methods, as the sleep mechanism connecting these features are unclear. First, we examined the sleep of children with eczema using the current gold standard of sleep evaluation, namely polysomnography. To date, only four studies report polysomnographic data in children with eczema (total of index cases = 63 (29 boys and 34 girls), aged 3-15 years). Previous polysomnographic data on eczematous children suggest that while prolonged awakenings are common, total sleep times are nonetheless similar to children without eczema. In addition, eczematous children demonstrate similar REM onset latency times and similar sleep stage percentages when compared to control subjects further indicating that gross sleep architecture is essentially preserved in this patient group. A further consideration was the impact of the co-morbid atopic disorders of asthma and rhinitis which both disturb sleep and were subsequently found to contribute to the behavioural deficits in children with eczema. Hence, any detailed examination on the sleep of eczematous children should also control for the additional impact of asthma and rhinitis.

3.2 Potential measures of eczema severity

A more detailed and accurate measurement of eczema was also sought for further study, however, no laboratory tests or unique signs and symptoms are pathognomonic for eczema alone. Objective methods to record disease activity in eczema could include measurements of skin function, physical properties, circulating factors and photography.¹ Additional proposed methods of assessment include the use of ultrasound,² assessment of transepidermal water

loss,³ measures of erythema,⁴ blood flow,⁵ and assessment of skin surface roughness,⁶ however, these approaches were impractical for our purposes and have been used by very few if any clinical studies assessing patients with eczema.¹

3.2.1 Current methods of measuring eczema severity.

Current diagnostic criteria of eczema are generally a collection of clinical features, with emphasis on the pruritic nature of the rash, its typical distribution and morphology, and its chronic or relapsing course.⁷ Several clinical approaches have been designed to assess the severity and grading of the disease. Some of the more prominent methods include; The SCORAD index which combines information about area of involvement, the “intensity” of six discernable aspects of eczema, and Visual Analogue Scales (VAS) of sleep loss and pruritus.⁸ The Nottingham Eczema Severity Score, which was developed for population based research and grades disease severity through evaluating the three elements of clinical course, disease intensity and extent of examined eczema.⁹ The Six Area, Six Sign severity assessment in which erythema, exudation, excoriation, dryness, cracking and lichenification, each graded on a scale of 0-3 (none to severe) at each of six sites (head, and neck, hands, elbows, feet, legs and trunk).¹⁰ The ADASI scoring system which involves a point counting system of the body areas involved, the severity of the skin changes and the intensity of the itching.¹¹ A further approach utilises a modification of the “rule of nines burn chart” which enabled parents to estimate the active skin involvement of eczema on their children.¹²

All of these rating scales which focus on the symptom severity and extent of affect skin have been shown to be useful in measuring the dynamic nature of eczema. However, a recurrent criticism of eczema rating scales is that the process has a subjective component as it requires an observer to give an estimate and an opinion. Because of the complex and changeable

symptomology of eczema, biological factors which can be used as a comparative measure of eczema severity are sought after to overcome this limitation.

3.2.2 Biological markers of eczema severity

Biological markers of immune/inflammatory responses have been examined which measure eczema activity and may provide important insights into the biomechanics underlying this disorder. Two of the most commonly measured blood serum markers of atopic activity are cytokines and leukotrienes.¹³⁻¹⁶ Cytokines are generally characterised as components of the peripheral immune system.¹⁷ They are a large group of low-molecular weight proteins secreted by various cell types and involved in cell-to-cell communication, co-ordinating antibody and T cell immune interactions, and amplifying immune reactivity. Leukotrienes are potent mediators of allergic inflammation and have a critical role in the pathogenesis of allergic disorders. Leukotrienes increase vascular permeability and dilate skin blood vessels.¹⁸ Strong support for their role in eczema comes from treatment studies using anti-leukotrienes.¹⁹ However, blood serum markers are problematic for serial assessment because children are averse to giving blood samples. Thus, urinary markers are touted as a preferred alternative, being non-invasive and child friendly.¹⁵

3.2.3 Urinary Leukotriene E₄

Urinary Leukotriene E₄ levels are a useful index of whole body cysteinyl leukotriene production in vivo because Leukotriene E₄ is a stable urinary metabolite of Leukotriene C₄ found in the skin of eczema patients.²⁰ Urinary cysteinyl leukotriene levels are strongly associated with eczema severity^{15, 21, 22} and are higher during eczema exacerbation than during remission of the disease.^{21, 23} Some caution is still advised with using Leukotriene E₄ as a measure of eczema severity however, as patients may excrete high levels of Leukotriene E₄ into urine due to other inflammatory disorders, such as asthma or psoriasis.^{15, 23}

In this study, we examined the sleep of children with eczema using polysomnography and measured eczema using a rating assessment method of the SCORAD and a biological marker of atopic inflammation, Leukotriene E₄. The aim of this study is to ascertain how the sleep of children with eczema differs from non-eczema children and to further examine which aspects of their sleep is associated with eczema severity.

3.3 Method

3.3.1 Subjects and Procedure

Parents /Caregivers and their children with eczema (n = 24) (aged 6-16) attending Allergy and Dermatology clinics at the Women's and Children's Hospital, a tertiary referral centre for the state of South Australia, were recruited for the study and compared to controls (n = 19) (aged 6-16 years) who were recruited from advertisements within the hospital. Eczema subjects were diagnosed by a Medical Specialist attending Allergy and Dermatology clinics using standardised criteria.²⁴ Control subjects were self reported not to have eczema. Based on parental report, any child with a history of facial abnormalities or enlarged tonsils that affected breathing, cleft palate, neurological disorder, muscular dystrophy, intellectual delay, developmental delay and behaviour disorder was excluded. The study was approved by the relevant Hospital and University Human Research Ethic committees.

Prior to commencing the study, participants completed an omnibus questionnaire assessing demographic, general health, sleep behaviour and atopic disorders (all parents reported whether their child had asthma or rhinitis with parents of eczema subjects providing additional eczema, asthma and rhinitis severity ratings and sleep disturbance ratings due to eczema, asthma and rhinitis). Children recruited into the study underwent one polysomnography (PSG) study on a non-school night at the Adelaide Women's and Children's Sleep Disorder Unit. Room temperature was kept at 22 degrees Celsius throughout the study.

Care was taken in the placement of the electrodes and apparatus and eczema affected areas was avoided. Prior to the overnight PSG, the child provided a urine sample which was refrigerated at 80 degrees below zero for latter analyses of Leukotriene E₄ (LTE₄), a biological marker of atopic inflammation.

3.3.2 Apparatus

The following demographic information was collected child's birth-weight (kg), and current height (cm) and weight (kg), which were used to generate a Body Mass Index rating.²⁵

Parents residential postcode was utilised to assess a socio-economic status rating using the Australian Bureau of Statistics Socio-Economic Indexes for Areas.²⁶

3.3.3 Eczema Assessment

Children with eczema had their skin disorder assessed using the standardised Scoring of Atopic Dermatitis index (SCORAD) (score range 0-103).²⁷ The SCORAD can be divided into subjective and objective components.²⁸ The objective component of the SCORAD (score range 0-83) combines an assessment of disease extent using the rule of nines method with six clinical features of disease intensity: erythema/darkening, oedema/papulation, oozing/crust, excoriation, lichenification/prurigo and dryness. Dryness is evaluated on non-inflamed skin. The other features are assessed on an average representative area for a given intensity item, each on a scale of 0-3. The subjective component includes two visual analogue scales (VAS) for evaluating the symptoms of itch and sleep loss. A higher score indicates more severe disease. The following cut-off points for objective SCORAD have been suggested for classification of disease severity: mild < 15; moderate 15-40; and severe > 40.^{29,30}

3.3.4 Asthma and Allergic Rhinitis

Eczematous children are also reported to have a high prevalence of asthma,³¹ allergic rhinitis,³¹ and sleep disordered breathing,^{32, 33} all of which are associated with sleep disturbance.³⁴⁻⁴⁸ Accordingly, asthma, rhinitis and sleep disordered breathing needs to be considered in any exploration of the sleep in children with eczema. To determine the incidence of asthma, the parent responded either "yes" or "no" to the question "In the last twelve months has your child had wheezing or whistling in the chest?" To determine the incidence of nasal rhinitis, the parent responded either "yes" or "no" to the question "In the last twelve months, has your child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or flu?" To assess the impact of asthma on sleep, the parent was asked "In the last 12 months, how often, on average, has wheezing disturbed your child's sleep?" with response options of 1 = "never woke with wheezing", 2 = "less than one night per week" and 3 = "one or more nights per week". To assess the impact of rhinitis on sleep the parent was asked "In the last twelve months, how often, on average, has your child been kept awake by this nose problem?" with response options of 1 = "never in the last twelve months", 2 = "less than one night per week" and 3 = "one or more nights per week". All questions used to assess asthma and nasal rhinitis were also used in the International Study of Asthma and Allergies in Childhood (ISSAC) Phase 1 Core questionnaire.⁴⁹

3.3.5 Leukotriene E₄

Urinary Leukotriene E₄ (LTE₄) is a biomarker of total body cysteinyl leukotriene production and excretion.⁵⁰ In humans, basal levels of LTE₄ range from 1-100 pg/mg creatinine.⁵¹ In asthmatics, urinary LTE₄ levels increase to 80-1,000 pg/mg creatinine.⁵ In eczematous children, basal levels of LTE₄ have been reported as (median, quartiles) 140, 66-166 ug/mmol.²² The urine sample provided by children with eczema was analysed for LTE₄ and

creatinine. LTE₄ analyses were conducted using the Leukotriene E₄ EIA kit.⁵¹ All specimens were purified prior to analysis using the Cysteinyl Leukotriene Affinity Sorbent methodology.⁵² The recovery after the purification process was 85.78%. Urine creatinine was measured in spot urine samples as a marker of the effect of hydration on LTE₄ amounts in the sample and producing a LTE₄/creatinine ratio was calculated. Measurements are reported in picogram per milligram of creatinine to control for urine dilution (pg/mg creatinine).

3.3.6 Sleep Disturbance Scale for Children

Sleep problems were assessed using the Sleep Disturbance Scale for Children (SDSC).⁵³ The SDSC contains two items assessing sleep quality using a five point scale (total sleep time 1 = 9-11h to 5 = < 5h; and latency to sleep onset 1 = < 15 min to 5 = > 60 min) and 24 items assessing the frequency of sleep disorder symptoms also rated on a five point scale (1 = never to 5 = always). The SDSC provides normed T-scores (mean = 50 and SD = 10) for six scales: Disorders of Initiating and Maintaining Sleep (e.g. sleep duration, sleep latency, night awakenings, etc), Sleep Breathing Disorders (e.g. snoring, etc), Disorders of Arousal (e.g. sleepwalking, sleep terrors, nightmares, etc) , Sleep-Wake Transition Disorders (e.g. rhythmic movements, hypnagogic jerks, sleep talking, bruxism, etc), Disorders of Excessive Somnolence (e.g. difficulty waking up, morning tiredness, etc), and sleep hyperhydrosis (e.g. nocturnal sweating, etc) and a composite Total Sleep Problem score.⁵³ The reliability and validity of the SDSC has been well evaluated and supported.⁵³ Children with eczema further provided additional questions on the timing of sleep on weekdays and weekends.

3.3.7 Polysomnography

A standard Polysomnography (PSG) montage was used to collect the following measures; electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), intercostal EMG, thermistor (air flow), nasal cannula (nasal pressure), leg leads (limb

movement), respiratory bands (muscular breathing patterns), electrocardiography (ECG) and oximetry (O₂). The signals are digitised and stored using a Compumedics S-Series Sleep System (Melbourne, Australia).

Sleep architecture was scored according to standard criteria⁵⁴ and the following variables were recorded: total sleep time, sleep efficiency, REM (Rapid Eye Movement) onset latency, percentage of stage 1 sleep, percentage of stage 2 sleep, percentage of stage 3 sleep, percentage of stage 4 sleep, percentage of REM, number of sleep stage shifts, Wake After Sleep Onset time (WASO), Arousal Index (AI = arousal per hour), Sub Cortical Arousal Index (sub cortical arousals per hour), Obstructive Apnoea Hypopnoea Index (OAHI), Central Apnoea Hypopnea Index, (CAHI) and nadir oxygen saturation during total sleep time.

An experienced sleep technician blinded to child status scored the studies according to standardized sleep stage⁵⁴ and pediatric criteria.⁵⁵ All respiratory events were ≥ 2 respiratory cycles in duration and associated with a minimum 3% SaO₂ desaturation and/or an arousal within two breaths of event termination. Obstructive apneas were defined as the absence of airflow associated with continued chest and abdominal wall movement. Obstructive hypopneas were defined as a $\geq 50\%$ reduction in the amplitude of respiratory inductance plethysmography and/or airflow signal associated with paradoxical chest/abdominal wall movement. The presence of any other supportive data such as increased intercostal or submental EMG activity was further used to distinguish obstructive from central hypopneas. Central apneas were scored if there was an absence of respiratory effort as determined by respiratory inductance plethysmography and intercostal EMG in association with an absence of airflow. Central apneas were also score if the event lasted ≥ 20 seconds. Central hypopneas were defined as a $\geq 50\%$ reduction in airflow from baseline in association with a $\geq 50\%$

reduction in respiratory effort from baseline. Apnea events that included both central and obstructive components were scored as a mixed apnea. The obstructive apnea/hypopnea index (OAHI) was calculated as the total number of obstructive apneas, mixed apneas and obstructive hypopneas divided by the total sleep time, and expressed as the number of events per hour of sleep. An OAHI ≥ 1 was considered indicative of OSAS. The central apnea/hypopnea index (CAHI) was calculated as the total number of central apneas and central hypopneas divided by the total sleep time and expressed as the number of events per hour of sleep.

Spontaneous and respiratory arousals were scored according to the criteria of the American Sleep Disorders Task Force.⁵⁵ The staging of arousals in the polysomnographic data use the following general criteria; minimum 10 seconds of sleep prior and post arousal (post if greater than 15 seconds), minimum of 3 seconds to maximum 30 seconds duration (15 sec/epoch), when in REM an increase in the chin EMG for a minimum of 1 second.

3.4 Statistics

All analyses were conducted using SPSS version 16. Potential confounding factors such as age, gender, socioeconomic status, the incidence of asthma⁵⁶ and rhinitis.⁵⁷ were evaluated using Chi -square and ANOVA's between the eczema and control groups and undertaken prior to analyses.

3.5 Results

3.5.1 Comparison of demographics, atopic disorders and sleep variables between children with eczema and controls (see Table 3.1).

No significant group differences were observed in potential confounders such as gender, age, BMI, birth weight, SES and prevalence of asthma. Eczematous children were found to have a significantly higher prevalence of rhinitis and because of its association with poor sleep, rhinitis⁵⁷ was included as a co variant in subsequent statistical analyses.

Atopic Disease: Based on suggested SCORAD criteria for classification of disease severity:^{29, 30} mild < 15; moderate 15-40; and severe > 40; 5/24, (21%) of children with eczema were classified as having mild eczema, 12/24 (50%) moderate eczema and 7/24 (29%) severe eczema.

In children with eczema 16/24 (72%) had LTE₄ levels > 100pg/mg. 10/24 (45%) of eczematous children also reported having asthma and of these 8/10 (80%) had LTE₄ levels > 100pg/mg, while 11/24 (50%) of eczematous children also reported having rhinitis and of these 9/11 (82%) had LTE₄ levels > 100pg/mg. A further 7/24 (32%) of children with eczema also reported having both rhinitis and asthma and of these 7/7 (100%) had elevated Leukotriene E₄ levels > 100pg/mg.

Sleep Disturbance Scale for Children (SDSC): Children with eczema had higher scores than controls on the following; Disorders of Initiating and Maintaining Sleep, Sleep Breathing Disorders, Sleep Wake Transitional Disorders, Disorders of Excessive Somnolence and Total Problem Scores. No differences were detected between eczema and controls on measures of Disorders of Arousal and Sleep Hyperhydrosis. Examination of individual SDSC t-scores revealed that a higher percentage of children with eczema compared to controls were above

the clinical cut-off criteria (T-score > 70) for Disorders of Initiating and Maintaining Sleep [54% (13/24) vs. 0% (0/19)], Sleep Breathing Disorders [25% (6/24) vs. 0% (0/19)], Disorders of Arousal [21% (5/24) vs. 0% (0/19)], Sleep Wake Transitional Disorders [33% (8/24) vs. 0% (0/19)], Disorders of Excessive Somnolence [33% (8/24) vs. 0% (0/19)], Sleep Hyperhydrosis [8% (2/24) vs. 4% (1/19)] and Total Sleep Problems [50% (12/24) vs. 0% (0/19)].

Polysomnography: Children with eczema had significantly longer REM onset latency, higher percentages of stage 3 & 4 sleep (see Figures 3.1 - 3.6) and a longer Wake after Sleep Onset time than controls. Controls had more frequent sub cortical arousals than eczema children. WASO times indicated that eczema children were awake on average 84.4 minutes post sleep onset.

3.5.2 Relationship between atopic disease and polysomnographic sleep data among children with eczema (Table 3.2).

The higher the frequency that asthma disturbed sleep in the last 12 months was not found to be significantly associated with sleep variables. The higher the frequency that rhinitis disturbed sleep in the last 12 months was strongly associated with a delayed REM onset latency. A more severe itch severity had moderate associations with a lower percentage of REM sleep and a lower desaturation O₂ nadir in total sleep (see Figures 3.7 & 3.8). Greater sleep loss due to eczema was not found to be significantly associated with sleep variables. A higher SCORAD full score was found to be significantly associated with the frequency of sub cortical arousals. Higher Leukotriene E₄ levels had a strong association with a longer Wake After Sleep Onset.

Table 3.1: Mean (SD) demographic and sleep scores for children with eczema and controls together with F-test/Chi-square results (statistically significant results are bolded).

	Mean (SD) and subject ratio for chi-square		F-test and chi-square (X^2) results
	Eczema (n = 24)	Control (n =19)	
Demographics			
Gender (male/female)	7/17	10/9	(X^2)= 2.4
Age (years)	9.7 (2.5)	9.5 (2.4)	0.0
Body Mass Index	18.4 (3.3)	18.0 (2.2)	0.1
Birth weight (kg)	3.6 (0.6)	3.7 (0.3)	0.2
Socio Economic Status	972.2 (83.3)	991.0 (86.3)	0.5
Atopic Disease			
Asthma	10/14	4/15	(X^2) = 2.1
Rhinitis	11/13	2/17	(X^2) = 6.3*
The following variables were co-varied for subjects having Rhinitis			
Sleep Disturbance Scale for Children			
Disorders of Initiating and Maintaining Sleep	73.9 (19.7)	50.5 (6.4)	15.0***
Sleep Breathing Disorders	57.1 (14.7)	45.3 (1.6)	6.0*
Disorders of Arousal	60.2 (16.8)	50.6 (7.7)	3.0
Sleep Wake Transitional Disorders	71.2 (19.9)	47.9 (7.9)	16.8***
Disorders of Excessive Daytime Somnolence	62.9 (17.2)	46.3 (7.2)	10.2**
Sleep Hyperhydrosis	51.2 (12.8)	47.1 (8.1)	0.8
Total Problem Score	72.1 (18.7)	47.1 (4.2)	22.2***
Sleep - Polysomnography			
Total Sleep Time (min)	419.0 (48.6)	429 (44.2)	0.2
Sleep Onset Latency	38.7 (17.8)	46.2 (26.2)	0.5
Sleep Efficiency	76.0 (8.8)	78.6 (9.3)	0.4
REM onset latency (min)	196.5 (71.7)	139.4 (59.9)	4.3*
%Stage 1	4.8 (4.7)	4.3 (2.0)	0.2
%Stage 2	44.0 (10.6)	46.4 (5.2)	1.7
%Stage 3	7.56 (2.6)	6.47 (1.9)	5.6*
%Stage 4	26.9 (7.4)	23.8 (4.1)	5.5*
% REM	16.7 (5.2)	19.1 (4.0)	1.8
No. of Stage Shifts	108.8 (27.4)	94.0 (20.4)	2.5
Wake After Sleep Onset (min)	84.4 (31.6)	52.8 (24.0)	8.8**
Arousal Index	6.8 (2.4)	6.9 (2.4)	0.4
Sub Cortical Arousal Index	0.3 (0.5)	0.87(0.4)	5.8*
Obstructive Apnoea Hypopnoea Index	0.3 (0.6)	0.3 (0.4)	0.1
Central Apnoea Hypopnea Index	0.4 (1.1)	0.5 (1.1)	0.5
Desaturation O^2 Nadir Total Sleep Time	92.4 (2.3)	93.4 (1.8)	2.1

Nb *denotes $p < .05$, ** $p < .01$, *** $p < .005$ and**** $p < .001$.

Table3.2: Correlation matrix: Atopic Disease with Polysomnography variables of children with eczema (significant correlations are bolded) (n=24).

	Asthma disturbed sleep in the last 12 months	Rhinitis disturbed sleep in the last 12 months	SCORAD – VAS of Itch severity rating	SCORAD – VAS of Sleep loss in the last 3 days	SCORAD (Full Score)	Leukotriene E ₄
Sleep - Polysomnography						
Total Sleep Time	-.16	-.22	-.08	-.42	-.08	-.05
Sleep Onset Latency	-.05	-.08	.20	-.03	.16	-.08
Sleep Efficiency	-.31	-.33	-.17	-.12	.01	-.37
REM onset latency (min)	.39	.56*	.27	-.10	.12	.31
%Stage 1	-.04	.18	.09	-.21	.11	-.10
%Stage 2	.08	.16	.34	.35	.14	.34
%Stage 3	-.09	-.22	-.01	.13	.06	-.26
%Stage 4	.07	-.17	-.23	-.29	-.15	-.10
% Slow Wave Sleep	.03	-.20	-.18	-.19	-.10	-.16
% REM	-.17	-.12	-.43*	-.16	-.20	-.31
No. of Stage Shifts	-.32	-.22	.00	-.13	.21	-.35
Arousal Index	-.12	.07	.17	.03	.26	-.16
Sub Cortical Arousal Index	-.06	-.03	.11	-.09	.57**	-.09
Wake After Sleep Onset (min)	.24	.23	.30	.31	-.13	.57**
Obstructive Apnoea Hypopnoea Index	-.16	.14	.43	.07	.26	.00
Central Apnoea Hypopnea Index	-.13	-.17	.02	-.09	.07	-.20
Desaturation O ₂ Nadir Total Sleep Time	.15	-.14	-.48*	-.35	-.33	-.19

Nb *denotes $p < .05$, ** $p < .01$ and *** $p < .005$ and **** $p < .001$.

Figure 3.1: Minutes of Stage 1 sleep per 30 minute epoch.

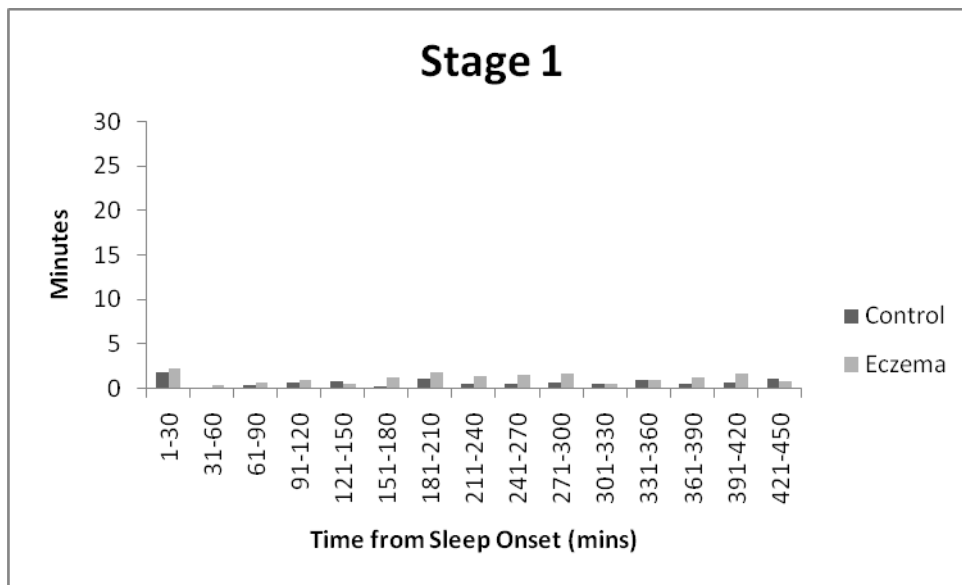


Figure 3.2: Minutes of Stage 2 sleep per 30 minute epoch.

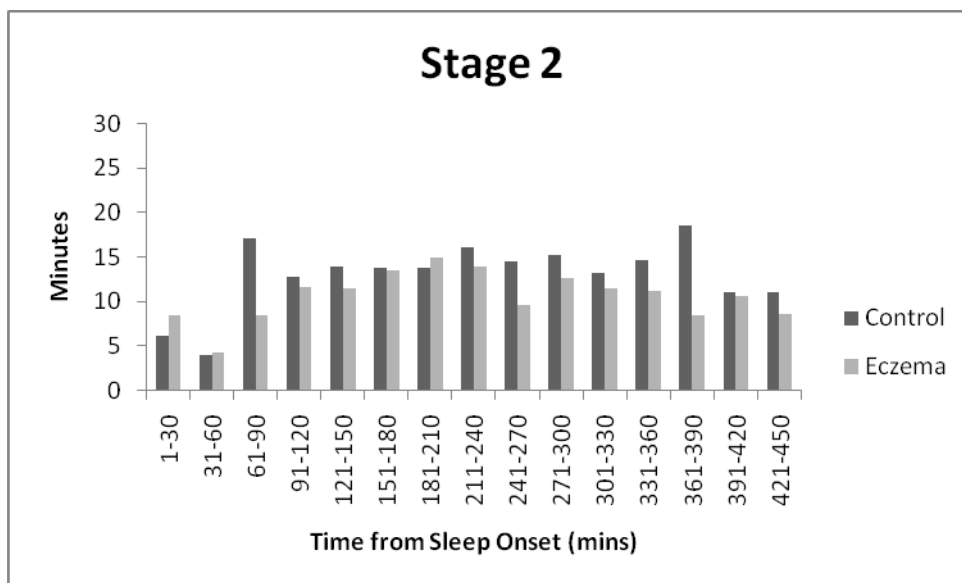


Figure 3.3: Minutes of Stage 3 sleep per 30 minute epoch.

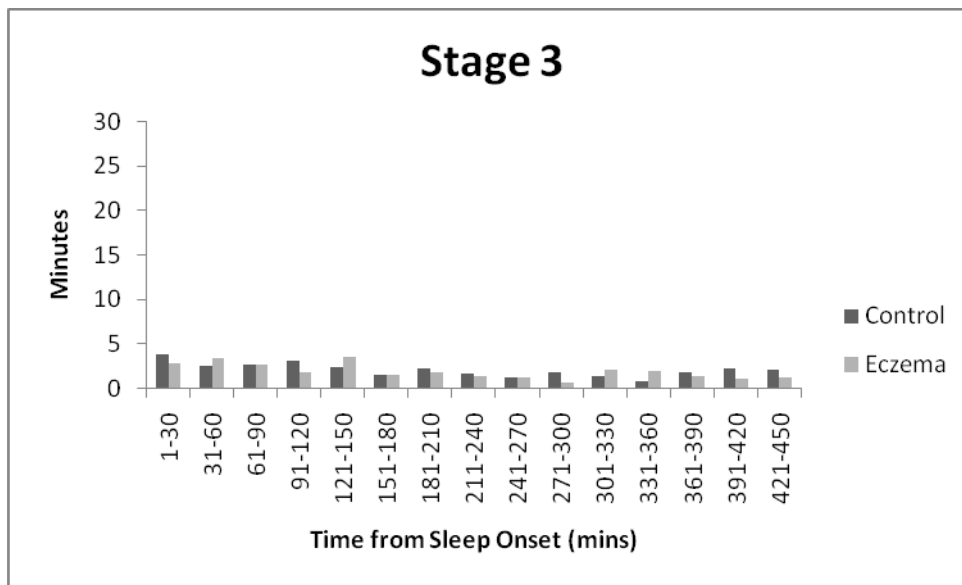


Figure 3.4: Minutes of Stage 4 sleep per 30 minute epoch.

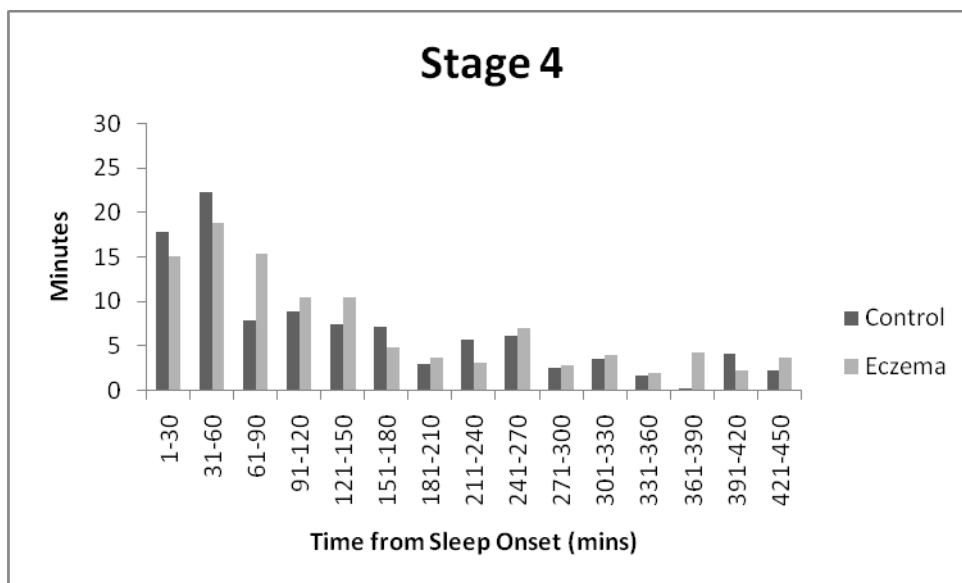


Figure 3.5: Minutes of REM sleep per 30 minute epoch.

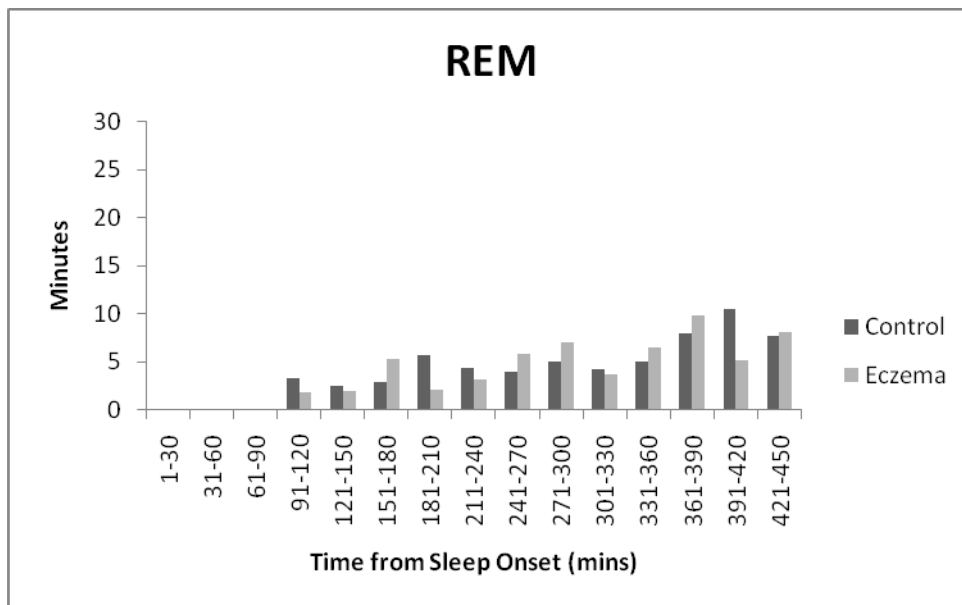


Figure 3.6: Minutes of wake after sleep onset per 30 minute epoch.

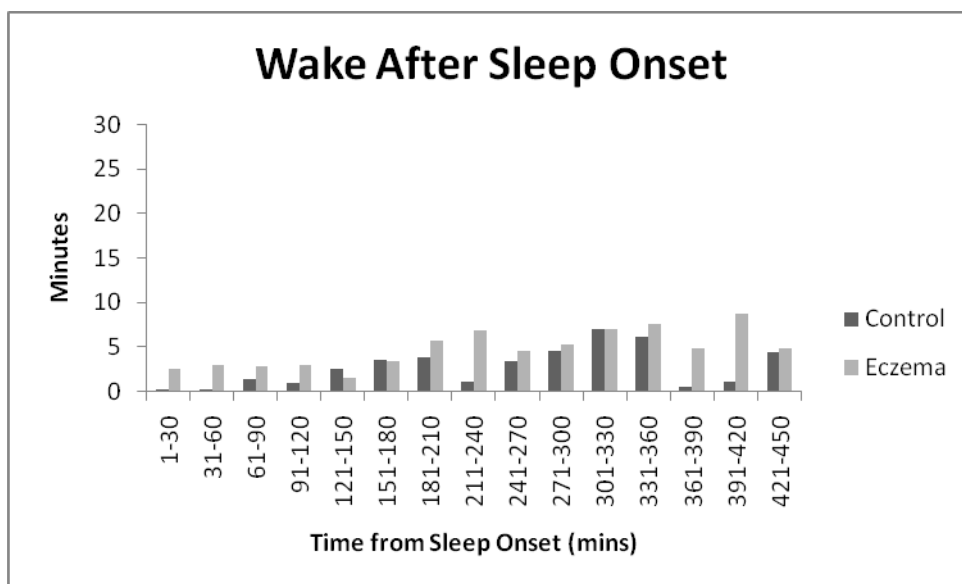


Figure 3.7: Scatterplot of VAS scores of itch severity and Desaturation Nadir in Total Sleep Time in children with eczema.

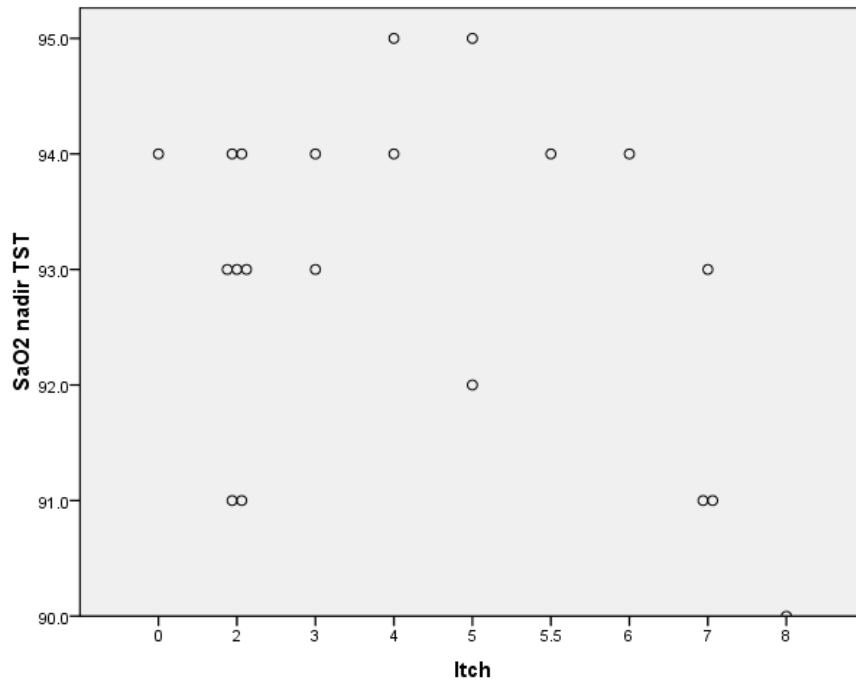


Figure 3.8: Scatterplot of VAS scores of itch severity and REM % in children with eczema.

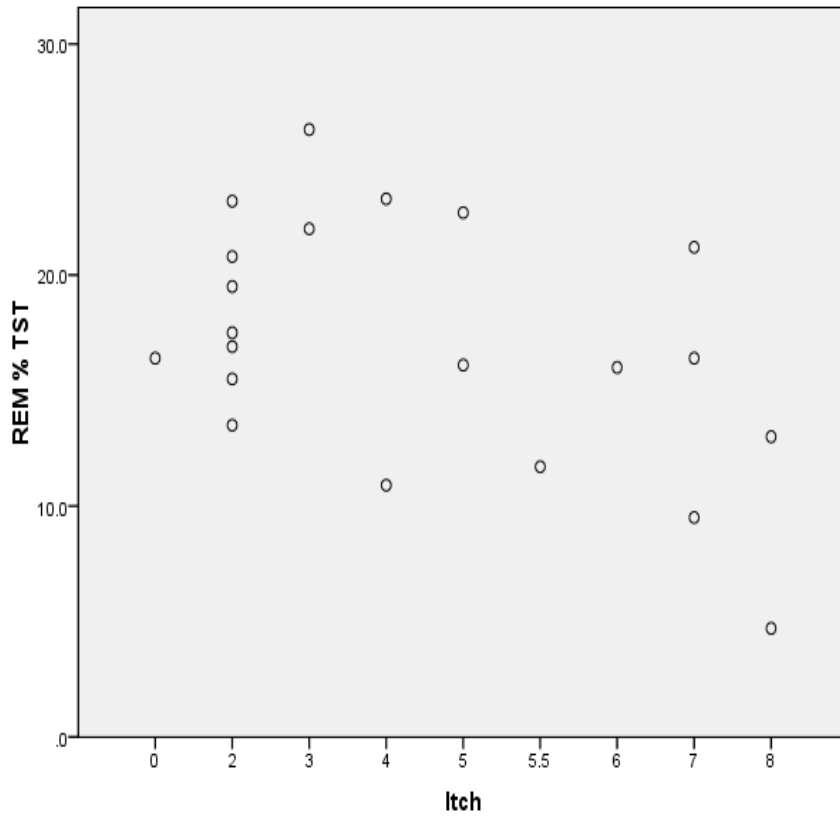
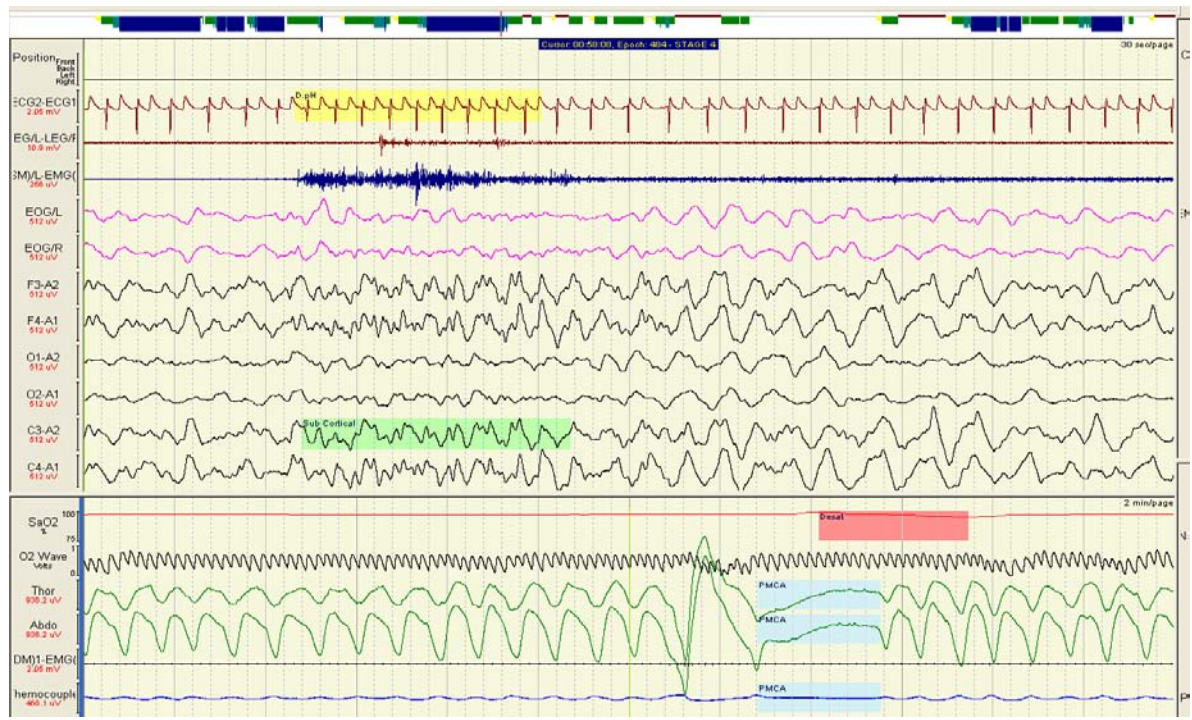


Figure 3.9: Screenshot of sub cortical respiratory event recorded during polysomnography.



3.6 Discussion

In this study, parental report on the sleep of eczema and control subjects exhibited clear differences between the two groups. Eczematous children were more likely to have difficulty in initiating and maintaining sleep (e.g. sleep duration, sleep latency, night awakenings, etc), a higher incidence of sleep disordered breathing (e.g. snoring, etc), a higher incidence of sleep to wake transitional problems (e.g. rhythmic movements, hypnagogic jerks, sleep talking, bruxism, etc), a higher degree of excessive daytime sleepiness (e.g. difficulty waking up, morning tiredness, etc), and the total number of sleep problems. In summary, children with eczema are more likely to awaken during the night and stay awake longer, experience respiratory events during their sleep, move during the night and exhibit daytime behaviours indicative of excessive daytime tiredness more so than controls.

The polysomnographic data further supports the questionnaire profile of the sleep of children with eczema. Children with eczema were found to have a higher percentage of Slow Wave Sleep, a longer REM onset latency and a longer Wake After Sleep Onset time than controls. Longer periods of awake are a commonly reported feature in the sleep profile of eczematous children^{9, 12, 58-60} and may have contributed to eczematous children also having a delayed REM onset. A related finding of itch severity associated with the percentage of REM sleep (see Figure 3.2) could also be a mediating factor between Wake After Sleep Onset and delayed REM onset. However, extended periods of time awake appears to be the foremost characteristic of sleep disturbance in this patient group which suggest that as yet unexamined nocturnal factors, such as body temperature, may be mediating the relationship between eczema and disturbed sleep.

In addition, long periods of Wake After Sleep Onset was moderately associated with ratings

of itch and sleep loss, though the relationships were not statistically significant. Amongst eczema children, this finding could be interpreted as itch not only disturbing sleep but that itch further impeded the child's return to sleep. Interestingly, longer periods of Wake After Sleep Onset was also strongly associated with increased Leukotriene E₄ levels, an indicator of atopic inflammation. Moreover, higher Leukotriene E₄ levels also demonstrated associated trends in lower sleep efficiency, longer REM onset latency, lower percentage of REM and fewer stage shifts. Together, these findings can be interpreted as children with more severe atopic disorders stay awake for longer periods during the night with an additional impact on the latency and percentage of REM sleep.

None of the children in this study were deemed to have clinically significant sleep disordered breathing as all subjects had an OAHl of lower than the criteria used in this study of less than 1 event per hour. The relatively few respiratory events associated with minor oxygen desaturation in this study not accounted for by central or obstructive apnoeas, post arousal respiratory disturbances, etc., are best described as sub cortical respiratory events. The sequence of components for these sub cortical events begin with a sub cortical arousal followed by a single central event, usually the length of a single breath, followed by a large compensatory breath, a minor oxygen desaturation and possibly an arousal (see Figure 3.9). It should be noted that though a moderate relationship was observed between the frequency of sub cortical arousal and the full SCORAD in children with eczema, control subjects had a higher frequency of sub cortical arousals than eczematous children. Furthermore, no differences were detected between eczema and control children in the frequency of arousals during sleep. The finding of approximately 6.8 arousals per hour for both groups could also be viewed as being slightly low for children given that reported normative data of the arousal index of children ranges from (mean, (SD)) 9, (5) to 11, (4).⁶¹⁻⁶³ In addition, the frequency of arousals were not associated with the severity of atopic disorders nor were they associated

with the frequency of respiratory events.

A limiting feature of the present study was the incidence of asthma and rhinitis among children with eczema, primarily because both asthma and rhinitis are also known to disturb sleep.⁶⁴ Of note, was our finding of a higher incidence of rhinitis among children with eczema when compared to healthy non eczematous controls. Further, the affect of asthma and rhinitis on the sleep quality of children with eczema was marked with trends indicating reductions in sleep efficiency and extended REM onset latencies. Clearly, it would be advantageous to study the impact of eczema on sleep without the contribution of co morbid atopic disorders, however, the high incidence of asthma and rhinitis among our target group indicates that it would be difficult to generate an eczema-only-subjects-group for study.

The large number of correlations generated in our analyses would also spawn a higher likelihood of false significant associations. Hence, we present our findings with an appropriate caution. One finding which may fall into this category is the association found between Itch severity and the Desaturation Nadir in Total Sleep Time (see Figure 3.7). Initially, it was suspected that the association may be the result of artefact from using the finger on which the oximetry was attached, to scratch, thus producing minor oximetry dropout. However, closer examination revealed that this was not the case and the nature of this finding remains uncertain.

In conclusion, children with eczema have demonstrated clear differences in their sleep architecture when compared to non eczema children. Moreover, eczematous children exhibited deficits in their sleep quality which were associated with their eczema severity in general, as well as specific attributes indicative of more severe eczema. However, the mechanism as to how sleep is disturbed in this patient group is yet to be determined.

Bibliography

1. Finlay AY. Measurement of disease activity and outcome in atopic dermatitis. *Br J Dermatol* 1996; 135:509-15.
2. Seidenari S, Di Nardo A, Pepe P, al. e. Ultrasound B scanning with image analysis for assessment of allergic patch test reactions. *Contact Dermatitis* 1991; 24:216-22.
3. Werner Y, Lindberg M. Transepidermal water loss in dry and clinically normal skin in patients with atopic dermatitis. *Acta Derm Venereol (Stockh)* 1995; 65:102-5.
4. Pearce A, Edwards C, Hill S, al. e. Portable erythema meter and its application to use in human skin. *Int J Cos Sci* 1990; 12:62-70.
5. Queille-Roussel C, Dutiel L, Padilla JM, al. e. Objective assessment of topical anti-inflammatory drug activity on experimentally induced nickel contact dermatitis: comparison between visual scoring, colorimetry, laser doppler velocimetry and transepidermal water loss. *Skin Pharmacol* 1990; 3:248-55.
6. Graves CJ, Edwards C, Marks R. The occlusive effects of protective gloves on the barrier properties of the stratum corneum. In: Elsner P, Maibach HI, editors. *Irritant Dermatitis-New Clinical and Experimental Aspects*. Karger: Basil; 1994. p. 87-9.
7. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Dermatology Venereology Suppl (Stockh)* 1980; 92:44-7.
8. ETFAD. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology* 1993; 186:23-31.
9. Emerson RM, Charman CR, Williams HC. The Nottingham Eczema Severity Score: preliminary refinement of the Rajka and Langeland grading. *Br J Dermatol* 2000; 142:288-97.
10. Berth-Jones J. Six Area, Six Sign Atopic Dermatitis (SASSAD) Severity score: a system for monitoring disease activity in atopic dermatitis. *Br J Dermatol* 1996; 135:25-30.
11. Bahmer FA, Schafer J, Schubert HJ. Quantification of the extent and the severity of atopic dermatitis; the ADASI score. (Letter). *Archives in Dermatology* 1991; 127:1239-40.
12. Dahl RE, Bernhisel-Broadbent J, Scanlon-Holdford S, Sampson HA, Lupo M. Sleep disturbances in children with atopic dermatitis. *Arch Pediatr Adolesc Med* 1995; 149:856-60.
13. Sugiyama M, Arakawa H, Ozawa K, Minuzo T, Mochizuki H, Tokuyama K, et al. Early-life risk factors for occurrence of atopic dermatitis during the first year. *Pediatrics* 2007; 119:e716-e23.
14. Hon KL, Lam MC, Wong KY, Leung TF, Ng PC. Pathophysiology of nocturnal scratching in childhood atopic dermatitis: the role of brain-derived neurotrophic factor and substance P. *Br J Dermatol* 2007; 157:922-5.
15. Bass JL, Corwin M, Gozal D, Moore C, Nishida H, Parker S, et al. The effect of chronic or intermittent hypoxia on cognition in childhood: a review of the evidence. *Pediatrics* 2004; 114:805-16.
16. Bender BG, Ballard R, Canono B, Murphy JR, Leung DY. Disease severity, scratching and sleep quality in patients with atopic dermatitis. *J Am Acad Dermatol* 2008; 58:415-20.
17. Opp MR. Cytokines and Sleep. *Sleep Med Rev* 2005; 9:355-64.
18. Brain SD, Williams TJ. Leukotrienes and inflammation. *Pharmacol Ther* 1990; 46:57-66.
19. Wedi B, Kapp A. Pathophysiological role of leukotrienes in dermatological diseases. *BioDrugs* 2001; 15:729-43.
20. Talbot SE, Atkins PC, Goetzil FJ, Zweiman B. Accumulation of leukotriene C4 and histamine in human allergic skin reactions. *J Clin Invest* 1985; 76:650-6.

21. Adamek-Guzik T, Guzik TJ, Czerniawska-Mysik G, Korpanty G, Mastalerz L, Radwan J, et al. Urinary Leukotriene levels are increased during exacerbation of atopic eczema/dermatitis syndrome. Relation to clinical status. *Allergy* 2002; 57:732-6.
22. Oymar K, Aksnes L. Increased levels of urinary leukotriene E4 in children with severe atopic eczema/dermatitis syndrome. *Allergy* 2005; 60:86-9.
23. Hishinuma T, Suzuki N, Aiba S, Tagami H, Mizugaki M. Increased urinary leukotriene E4 excretion in patients with atopic dermatitis. *Br J Dermatol* 2001; 144:19-23.
24. Hanifin JM. Basic and clinical aspects of atopic dermatitis. *Ann Allergy* 1984; 52:386-95.
25. Keys A. Indices of relative weight and obesity. *J Chronic Dis.* 1972; 25:329-43.
26. Pink B. Socio-Economic Indexes for Areas (SEIFA) - Technical Paper. In: Statistics ABo, ed: Commonwealth of Australia, 2006.
27. European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD index. *Dermatology* 1993; 186:23-31.
28. Oranje AP, Stalder JF, Taieb A, Tasset C, de Longueville M. Scoring of atopic dermatitis by SCORAD using a training atlas by investigators from different disciplines. ETAC Study Group. *Early Treatment of the Atopic Child. Pediatr Allergy Immunol* 1997; 8:28-34.
29. Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J, Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997; 195:10-9.
30. Holm EA, Wulf HC, Stegmann, Jemec GBE. Life quality assessment among patients with atopic eczema. *Br J Dermatol* 2006; 154:719-25.
31. Ricci G, Patrizzi A, Baldi E, Menna G, Tabanalelli M, Masi M. Long term follow up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. *J Am Acad Dermatol* 2006; 107:567-74.
32. Kuehni CE, Strippoli MP, Chauliac ES, Silverman M. Snoring in preschool children: prevalence, severity and risk factors. *Eur Respir J* 2008; 31:326 - 33.
33. Marshall NS, Almqvist C, Griunstein RR, Marks GB. Predictors for snoring in children with rhinitis at age 5. *Pediatr Pulmonol* 2007; 42:584 - 91.
34. Pevernagie DA, De Meyer MM, Claeys S. Sleep, breathing and the nose. *Sleep Med Rev* 2005; 9:437-51.
35. Craig TJ, McCann JL, Gurevich F, Davies MJ. The correlation between allergic rhinitis and sleep disturbance. *J Allergy Clin Immunol* 2004; 114:S139-S45.
36. Craig TJ, Teets S, Lehman EB, al. e. Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids. *J Allergy Clin Immunol* 1998; 101:633-7.
37. Craig TJ, Mende C, Hughes K, Kakumanu S, Lehman EB, Chinchilli V. The effect of topical fluticasone on objective sleep testing and the symptoms of rhinitis, sleep, and daytime somnolence in perennial allergic rhinitis. 2003.
38. Mansfield LE, Diaz G, Posey CR, Flores-Neder J. Sleep disordered breathing and daytime quality of life in children with allergic rhinitis during treatment with intranasal budesonide. *Ann Allergy Asthma Immunol* 2004; 92:240-4.
39. Desager KN, Nelen V, Weyler JJ, De Backer WA. Sleep disturbance and daytime symptoms in wheezing school-aged children. *J Sleep Res* 2005; 14:77-82.
40. Janson C, De Backer W, Gislason T, Plaschke P, Bjornsson E, Hetta J, et al. Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: a population study of young adults in three European countries. *Eur Respir J* 1996; 9:2132-8.
41. Sulit LG, Storfer-Isser A, Rosen CL, Kirchner HL, Redline S. Associations of obesity, sleep-disordered breathing, and wheezing in children. *Am J Respir Crit Care Med* 2005; 171:659-64.

42. Benninger M, Walner D. Obstructive sleep-disordered breathing in children. *Clin Cornerstone* 2007; 9:S6-12.
43. Blaiss M, Reigel T, Philpot EA. A study to determine the impact of rhinitis on sufferer's sleep and daily routine [abstract]. *J Allergy Clin Immunol* 2005; 115:S197.
44. Shedden A. Impact of nasal congestion on quality of life and work productivity in allergic rhinitis. *Treat Respir Med* 2005; 4:439-46.
45. Young T, Finn L, Kim H. Nasal obstruction as a risk factor for sleep-disordered breathing. *J Allergy Clin Immunol* 1997; 99:S757-S62.
46. Syabbalo N. Chronobiology and chronopathophysiology of nocturnal asthma. *Int J Clin Pract* 1997; 51:455-62.
47. Strunk RC, Sternberg AL, Bacharier LB, Szeffler SJ. Nocturnal awakening caused by asthma in children with mild-to-moderate asthma in the childhood asthma management program. *J Allergy Clin Immunol* 2002; 110:395-403.
48. Chng SY, Goh DY, Wang XS, Tan TN, Ong NB. Snoring and atopic disease: a strong association. *Pediatr Pulmonol* 2004; 38:210-6.
49. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8:483-91.
50. Rabinovitch N. Urinary leukotriene E₄. *Immunol Allergy Clin North Am* 2007; 27:651-64; vii.
51. Leukotriene E₄ EIA Kit Catalog No. 520411. Sydney: Cayman Chemical.
52. Leukotriene E₄ EIA Kit Catalog No. 420509. Sydney: Cayman Chemical.
53. Bruni O, Ottaviano S, Guidetti V, Romoli M, Innocenzi M, Cortesi F, et al. The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *J Sleep Res* 1996; 5:251-61.
54. Rechtschaffen A, Kales A. A Manual of Standardized Terminology, Techniques, and Scoring Systems for Sleep Stages of Human Subjects. Los Angeles: Brain Information/Brain Research Institute UCLA, 1968.
55. Marcus CL, Omlin KJ, Basinki DJ, Bailey SL, Rachal AB, Von Pechmann WS, et al. Normal polysomnographic values for children and adolescents. *Am Rev Respir Dis* 1992; 146:1235-9.
56. Macri F, Rossi FP, Lambiase C, di Castelbianco FB, Frassanito A. Psychological factors in childhood asthma. *Pediatr Pulmonol* 2008; 43:366-70.
57. Nathan RA. The burden on allergic rhinitis. *Allergy Asthma Proc* 2007; 28:3-9.
58. Bartlett LB, Westbrook R, White JE. Sleep patterns in children with atopic eczema. *Acta Derm Venereol* 1997; 77:446-8.
59. Chamlin SL, Mattson CL, Frieden IJ, Williams ML, Mancini AJ, Cella D, et al. The price of pruritus: sleep disturbance and cosleeping in atopic dermatitis. *Arch Pediatr Adolesc Med* 2005; 159:745-50.
60. Stores G, Burrows A, Crawford C. Physiological sleep disturbance in children with atopic dermatitis: a case control study. *Pediatr Dermatol* 1998; 15:264-8.
61. Boselli M, Parrino L, Smerieri A, Terzano MG. Effect of age on EEG arousals in normal sleep. *Sleep* 1998; 21:351-7.
62. Traeger N, Schultz B, Pollock AN, Mason T, Marcus CL, Arens R. Polysomnographic values in children 2-9 years old: additional data and review of the literature. *Pediatr Pulmonol* 2005; 40:22-30.
63. Montgomery-Downs HE, O'Brien LM, Gulliver TE, Gozal D. Polysomnographic characteristics in normal preschool and early school-aged children. *Pediatrics* 2006; 117:741-53.
64. Camfferman D, Kennedy D, Gold M, Winwood P, Lushington K. Eczema and sleep and behaviour in children. *Journal of Clinical Sleep Medicine* 2010; 6:581-8.

Chapter 4: Itch and Scratch and their association with disturbed sleep in children with eczema

4.1 Itch

Itch is a common skin sensation associated with inflammation, dryness, or other skin damage. When functional, the perception of itch is a useful contributor to the body's defence system against injury, but when dysfunctional, it can have substantial effects on behaviour and have serious affects on quality-of-life. Histamine and acetylcholine provoke itch by binding to "itch receptors" and mediators such as neuropeptides, proteases or cytokines, provoke itch indirectly via histamine release.¹ Direct nerve recordings in awake subjects have demonstrated that itch is transmitted by dedicated C neurons, which are distinct from the polymodal nociceptors that are instrumental in pain processing.² These itch neurons can be identified by their lasting response to histamine application, and are characterised by their slow conduction velocities and extensive terminal branching.³ Information on itch is conveyed centrally via the lateral spino-thalamic tract and elicits co-activation of the anterior cingulate cortex, striatum, supplementary motor area, thalamus and inferior parietal lobe, with a left hemisphere predominance.⁴⁻⁷ Measurement of itch presents many difficulties. There is the problem of subjectivity in the sensation to discern strength or severity of the itch,⁸ moreover, there are no adequate animal models with which to qualify itch.⁹

4.2 Scratch

Scratching and rubbing the skin inhibits itch. The term scratching itself is an generic expression used for any action intended to produce abrasive rubbing on the skin surface. Bouts of scratching can start frequently or infrequently, can be long or short, and may be masked by general body movements. The force, amplitude, frequency, and direction of the

strokes vary, and different parts of the body can be scratched at different times or at the same time.¹⁰ Scratching and rubbing the skin stimulate myelinated A neurons via low threshold mechanoreceptors to inhibit neuronal circuits in the grey matter of the spino-thalamic tract. Scratching also activates nociceptors. Nociceptors are sensory receptors that respond to potentially damaging stimuli by activating neuronal circuits to the spinal cord and the brain.¹¹ Activating nociceptors also serves to inhibit neuronal activity of itch via the spino-thalamic tract.^{11, 12}

4.2.1 Measuring nocturnal scratch using actigraphy

Actigraphy is often used to measure the nocturnal scratching in children and adolescents with eczema (see Table 4.7).¹³⁻¹⁶ Felix and Shuster¹⁶ examined the nocturnal activity in 56 adolescent and adult patients with various itch symptomatic skin disorders, including eczema (n = 10), compared to 21 controls. Ankle and wrist movement levels were higher in patients with itchy skin disorders and itch was reported to be associated with the degree of nocturnal limb movement ($r = .88$). Scratching movements were present for approximately 10% of the night in eczema patients.

Ebata et al.¹⁴ examined the nocturnal scratching of 29 Japanese adolescent and young adult inpatients (15-24y) with eczema compared to 5 controls (age unspecified) using actigraphy. Scratch percentage of the night was associated with eczema severity from 1.7% in mild to 5.2% in moderate and 15.4% in severe disease groups and significantly higher in all eczema groups compared to controls.

Benjamin et al.¹⁵ used actigraphy to evaluate the nocturnal scratching in 14 English children with eczema. Children with eczema spent a mean of 46 minutes less time motionless at night than controls (Mean \pm SEM) (468 \pm 3 vs. 422 \pm 37). They further reported that children with eczema spend more bed-time scratching than controls (15% vs. 2%) and 2 to 3 times

more restless nocturnal behaviour (5.3% vs. 2%) (all $p < .01$).

Bringinghurst et al.¹³ also reported higher nocturnal movement index scores in 25 eczematous children compared to 17 controls. Increased nocturnal activity was not found to be associated with perceived poorer sleep quality in children ($r = .48, p = .017$), greater itch ratings ($r = .40, p = .049$) and Full SCORAD ($r = .6, p = .003$). Of note, was this group's finding of considerable variation in the night to night activity of eczema subjects.

Hon et al.¹⁷ used actigraphy to measure nocturnal activity in 24 eczematous children from Hong Kong. Most activity occurred (2-3Hz) in the first 3 hours of sleeping which was significantly correlated with disease severity ($r = .52, p < .01$) and extent of eczema ($r = .53, p < .01$). Nocturnal movement was also related with chemokine markers ; cutaneous T-cell attracting cytokine (CTACK) ($r = .57, p < .01$), macrophage-derived chemokine (MDC) ($r = .63, p < .005$), thymus and activation regulated chemokine (TARC) ($r = .56, p < .05$).

In summary, actigraphic evidence confirm that children with eczema have more nocturnal movement for longer periods of the night than that of healthy control children. The frequency of nocturnal movement was associated with eczema severity and the frequency of scratching events during the night. These findings imply that actigraphy is a reliable measure of nocturnal scratching and sleep in this patient group. However, actigraphic measures have yet to be compared to the gold standard of polysomnography in measuring the nocturnal activity of eczematous children.

4.3 Nocturnal scratching in children with eczema

It is thought that nocturnal itching and subsequent scratching underlie nocturnal awakenings in children with eczema.¹⁸⁻²⁰ However, to date only four studies have examined scratching in children with eczema using polysomnography (see Table 4.7).^{18, 21-23}

Jenney et al.²¹ evaluated oxygen consumption and scratching during sleep in 10 children with eczema (3-14y) compared to 28 healthy controls (5-12y). Nine out of ten eczema subjects scratched while asleep. Scratching was observed (range = 45-105 min of direct visual monitoring) in stage 1, stage 2, stage 3 and REM. Oxygen consumption was also significantly higher in eczema subjects who scratched during sleep, than non-scratching subjects or controls (all values, $p < .001$).

Monti et al.¹⁸ study on the effects of nighttime pruritus on sleep quality in 9 children with eczema reported that scratching produced frequent arousals in this patient group.

Accordingly, sleep maintenance was markedly altered. The highest frequency of scratching episodes occurring in stage 1 sleep, followed by stage 2, REM, stage 4, and stage 3 sleep. REM sleep percentage of the Total Sleep Time was also higher when compared with non-eczematous, healthy controls of the same age.

Reuveni et al.²³ examined the nocturnal activity in 14 children with eczema compared to 9 healthy controls using polysomnography and evaluated the scratching movements of the index finger by mechanical strain gauge and EMG measurement of the extensor digitorum muscle. This group reports that Sleep Onset Latency, Total Sleep Time, and Sleep Efficiency did not differ significantly between the two subject groups, however there was a marked difference in the frequency of arousals between eczema subjects and that of controls (mean, (S.D.) = 24.1, (8.1) vs. 15.4, (6.2), $p < .001$) respectively. Scratching was reported to be associated with arousal from sleep in only 15% of events, with the remainder of arousals having no identifiable cause.

In contrast, Stores et al.²² study on the sleep of 20 eczematous school-age children (6-14y) compared to sex and age matched controls, report that children with eczema spent more time

awake than controls. They further report that the time eczematous children spent scratching was strongly associated with greater nocturnal wakefulness ($r = 0.87, p < .001$).

In summary, three out of the four studies using polysomnography to examine the sleep of eczematous children report that scratch related arousals are more frequent than controls, and of note, that scratching occurs during EEG-defined-sleep.^{18, 21-23} It is this feature that is perhaps most exceptional in this patient group. For example, in healthy children, gross body movements may occur anytime during sleep, but are ordinarily preceded by EEG signs of arousal.²⁴ However, movement during EEG-defined-sleep is considered to be abnormal, particularly movement which includes the fine motor skills required for scratching. More so for movement occurring in REM sleep, where the neurological commands for motor activity are not ordinarily executed. In REM sleep, body movement is normally restricted due to inhibition on the moto-neurons directly innervating musculature.²⁵ It therefore remains to be determined that if scratching during EEG-defined-sleep does occur and if so, whether this behaviour is the main cause of sleep disruption in this patient group.

4.3.1 Nocturnal scratching in adults with eczema

Five polysomnographic studies on adults with eczema also report that scratching occurred during sleep (see Table 4.8).^{8, 26-28} Savin et al.²⁷ examined the sleep of 4 adult patients with eczema using polysomnography. Scratching was reported to occur throughout the night in all sleep stages, often without change of sleep stage. The total length of time that the patients scratched while asleep was between 11.6 and 19.1 minutes. Savin et al.²⁷ proposed that the frequency and the length of the bouts of scratching during sleep offer objective measures of skin itchiness.

In a later study, Savin et al.²⁸ examined the sleep of 15 adult subjects with a variety of skin diseases (eczema, dermatitis herpetiformis, lichen planus, urticaria and psoriasis) using

polysomnography. Bouts of scratching occurred in the following order, beginning with the highest frequency occurring in stage 1, stage 2, REM, stage 3 and 4 sleep. There was no significant difference in the length of scratching bouts starting in the different stages of sleep ($df = 3.42, F = 0.11$). The pattern of scratching during sleep was similar for all the diseases studied. The authors conclude that scratching during sleep seemed to be more related to the physiology of the sleep stages rather than the skin diseases themselves.

Brown and Kalucy²⁹ studied the nocturnal scratch behaviour of 4 adult patients with itchy skin diseases (2 with eczema) using polysomnography. They report that scratching frequently occurred in all four patients throughout the night, in all sleep stages, and particularly in the first half of the night. The authors further report that this group was characterised by a unusually long Sleep Onset Latency, very little stage 3 and stage 4 sleep, and reduced REM sleep in the first half of the night.

Aoki et al.⁸ studied 13 adults with itchy skin diseases (9 subjects with eczema) (18-75y), using polysomnography to assess sleep and paper strain gauges to monitor movement. Scratching bouts were found to occur in stage 1 and stage 2 sleep in all 17 studies, scratching in REM were found in 16 studies and scratching in stage 3 or stage 4 were found in only seven studies. The distribution of the length of scratching bouts were similar, 3-7 seconds, in stage 1, stage 2 and REM, being the most common. In wakefulness, stage 3 and stage 4, scratching bouts of 6-10 seconds were most common. Aoki et al. concluded that the act of scratching leads to a lightening of sleep, if not arousal, and that the longer the scratching bout occurs, the greater the likelihood of subsequent arousal.

Bender et al.²⁶ study on the sleep quality of 20 adults with eczema, examined the relationship between the skin disease and sleep disturbance using polysomnography and actigraphic recording. Actigraphy measures of sleep efficiency and the activity mean were associated

with a higher scratch index and the polysomnography measures of sleep efficiency and activity. This group further reports that scratching was increased with disease severity ($r = .33, p = .008$) and polysomnographic sleep quality ($r = .56, p = .01$) and that most scratching occurred in stage 1 and stage 2 sleep.

Though the occurrence of scratching during sleep is consistently reported in these few studies, some question remains as to the veracity of these findings. Two of these studies submit that their sleep staging protocols confounded their results.^{8,30} Aoki et al.⁸ determined the sleep stage during the scratching bout depending on the sleep stage 40 seconds prior to and 60 seconds after the event. They state that it was impossible to assess the sleep stage during the scratching because of the overlap of activity between the electromyogram and the electroencephalogram. In addition, Bender et al.³⁰ reported that all scratching events occurred only during sustained wakefulness or in association with arousal from sleep, however, their sleep staging protocols required that scratching episodes be assigned to and classified under the specific sleep stage maintained 90 seconds prior to the event.

The use of staging protocols that have the potential to distort findings of patients scratching while asleep, requires that this issue be re-examined. Accordingly, the aims of this study were to examine whether scratching occurred during sleep and to determine whether scratch produces arousal from sleep in children with eczema. A further aim is to examine the efficacy of actigraphy to evaluate the sleep of children with eczema against the gold standard of polysomnography.

4.4 Method

In addition to the method outlined in Chapter 3 (3.3) for polysomnography, the following additional measures and procedures were undertaken to examine contribution of scratch in sleep disturbance in children with eczema. Subjects used in this study are a sub-group of the

subjects used in the Polysomnography study outlined in chapter 3.

4.4.1 Actigraphy

The Actigraph Motionlogger (Ambulatory Monitoring, Ardsley, NY), which is a wrist watch sized device for detecting motion was used to assess periods of wakefulness and sleep.³¹

Wrist actigraphy has been validated in patients with atopic dermatitis as a measure of nocturnal scratching¹³⁻¹⁵ and sleep disturbance.²⁶ Participants wore the activity monitor on the dominant arm during their overnight polysomnography testing. Activity data was analysed using proprietarial software provided with the system. The monitor sampling rate was 32Hz with a lower limit of sensitivity of 0.01g. Actigraphy was set with a bin window of 1 minute epochs.

Primary analyses of the data produced the following variables; Sleep Efficiency, Sleep Percentage, Wake Percentage, Awakenings, Mean Sleep Periods, Mean Wake Periods, Moving during Total Sleep Time percent, Immobile during total Sleep Time percent, Total Activity Score, Mean Score in Inactive Periods, Mean Score in Active Periods and a Movement and Fragmentation Ratio.³²

4.4.2 Scratching

Scratching was observed with an infra red camera which recorded movement as a digital movie file contiguous with polysomnographic data recording. Scratching bouts were classified according to a modification of the criteria described by Ebata et al.³³ In brief, any rhythmical hand or foot movement that resulted in a scratching or rubbing motion to any body part that lasted longer than 3s with bouts containing intervals < 3secs classified as a single episode. We also recorded the sleep stage prior to a scratch-related event, evaluated the number of scratching events during wake periods and the percentage of arousals associated with scratching. The

number of scratch bouts that commenced in sleep and continued or did not continue into wakefulness was calculated. The number of bouts that commenced in wakefulness was also calculated.

4.5 Results

4.5.1 Actigraphy data of children with eczema compared to controls (see Table 4.1).

Actigraphy: Initial analyses indicated a non significant trend that eczema children had more nocturnal activity than controls. Subsequently, children with eczema were divided into two groups, Severe and Mild/Moderate using the suggested cut-off points of the objective SCORAD items for classification of disease severity: severe >40; moderate 15-40; and mild < 15.^{34, 35} Severe eczema children had a higher Total Activity Score than Mild/Moderate eczema children and controls. Mild/Moderate eczema children did not have a higher Total Activity Score than controls. Both the Severe and Mild/Moderate eczema groups had a higher Mean in Inactive periods than controls. The Severe eczema group did not differ from the Mild/Moderate eczema group in the Mean in Inactive periods. The Severe eczema children had a higher Mean in Active Periods than the Mild/Moderate group and the control group. The Mild/Moderate group did not differ from controls in the Mean in Active Periods.

4.5.2 Relationship between atopic disease and actigraphy data among children with eczema (see Table 4.2).

Among children with eczema, a higher asthma severity in the last 12 months was moderately associated with the actigraphy measures of a lower Sleep Percentage, a higher Wake Percentage, longer Mean Awake Periods and a greater Total Activity Score. A greater Rhinitis Severity in the last 12 months was moderately associated with the actigraphy measures of a larger Movement and Fragmentation Ratio. A higher SCORAD VAS of sleep

loss in the last three days due to eczema was moderately associated with more frequent Awakenings. A higher SCORAD Full Scale was moderately associated with a higher Total Activity Score and a higher Mean Score in Inactive Periods. Higher Leukotriene E4 levels were moderately associated with more frequent Awakenings and shorter Mean Sleep Periods.

4.5.3 Relationship between actigraphy and polysomnography data among children with eczema, controlling for frequency that asthma disturbed sleep in the last 12 months and the frequency that rhinitis disturbed sleep in the last 12 months (see Table 4.3).

Significant associations between asthma and rhinitis severity and actigraphy variables (see 4.5.2) required that co morbid atopic disorders be controlled further statistical analyses. A higher actigraphy Sleep Efficiency was moderately associated with the polysomnography variables of a longer Total Sleep Time, a higher Sleep Efficiency and a reduced Sleep Onset Latency. A higher score on the actigraphy variable of Awakenings was moderately associated with the polysomnography variables of more Total Sleep Time and a lower Sleep Onset Latency. The actigraphy variable of Mean Awake Periods had a moderate negative relationship with the polysomnography variable of Sleep Efficiency. The actigraphy variable of Total Activity Score had a moderate negative association with the polysomnography variable of Sleep Efficiency. The actigraphy variable of Mean Score in Inactive Periods had a moderate negative association with the polysomnography variable of Sleep Efficiency. The actigraphy variable of Mean Score in Active Periods had a moderate negative association with the polysomnography variable of Sleep Efficiency.

4.5.4 Nocturnal distribution of scratch related activity in children with eczema (see table 4.4).

The distribution of scratching during sleep did not significantly change over the course of the night (see Figure 4.1). The percentage of scratch events associated with arousals out of the total number of spontaneous arousals in children with eczema ranged from 13% to 59%

(mean, (SD) = .28, (.13) The distribution of scratching while awake did not significantly change over the course of the night, however the trend demonstrated a marked increase towards the middle of the night (4 hours post sleep onset) and tapering off thereafter. The total number of scratching events while awake ranged from 3 to 119, (mean, (SD) = 31.9, (29.3)

4.5.5 Relationship between the SCORAD, scratching, arousals and sleep stage in children with eczema (see Table 4.2)

A noted feature of the SCORAD that demonstrated an association with scratching during sleep that ended in awake and the frequency that scratching occurred in the combined sleep stages of 3&4, was the measure of Erythema. Erythema also appeared to trend of association in the frequency of scratching events that occurred during sleep that did not end in awake and the frequency that scratching occurred in all of the sleep stages and in Wake.

Table 4.1. Mean (SD) demographic, atopic disease and actigraphy variables for children with eczema compared to controls together with F-test/Chi-square results.

	Mean (SD) and subject ratio for chi-square			F-test and chi-square results
	Eczema (Severe) (n = 7)	Eczema (Mild/Moderate) (n = 16)	Control (n =14)	
Actigraphy				
Sleep Efficiency	73.7 (6.0)	78.1 (5.5)	79.0 (7.3)	F = 1.4 S=M, S=C, M=C
Sleep Percentage	81.8 (7.7)	85.9 (5.6)	87.5 (4.1)	F = 2.1 S=M, S=C, M=C
Wake Percentage	18.2 (7.7)	14.1 (5.6)	12.5 (4.1)	F = 2.1 S=M, S=C, M=C
Awakenings	20.9 (5.6)	26.6 (8.4)	21.3 (4.5)	F = 2.6 S=M, S=C, M=C
Mean Sleep Periods (min:sec)	19:11 (6:34)	17:02 (5:11)	19:12 (4:51)	F = 0.7 S=M, S=C, M=C
Mean Awake Periods (min:sec)	04:05 (1:39)	2:51 (1:17)	2:44 (0:48)	F = 2.9 S=M, S=C, M=C
Moving during Total Sleep Time Percent	20.8 (7.1)	17.6 (5.5)	16.3 (4.5)	F = 1.4 S=M, S=C, M=C
Immobile during Total Sleep Time Percent	79.2 (7.1)	82.4 (5.5)	83.7 (4.5)	F = 1.4 S=M, S=C, M=C
Total Activity Score	1.9E4 (16508.3)	9.3E3 (6008.4)	6.7E3 (2528.1)	F = 4.8* S>M, S>C, M=C
Mean Score in Inactive Periods	39.4 (22.8)	17.9 (11.7)	14.5 (5.7)	F = 5.0* S>M, S>C, M=C
Mean Score in Active Periods	1.7E2 (106.3)	95.7 (44.1)	92.4 (35.5)	F = 4.2* S>M, S>C, M=C
Movement and Fragmentation Ratio	43.0 (7.2)	38.9 (12.9)	34.6 (10.8)	F = 1.2 S=M, S=C, M=C

Nb S = Severe, M = Mild/Moderate, C = Control, *denotes $p < .05$, ** $p < .01$, *** $p < .005$, **** $p < .001$ and ***** $p < .0005$.

Table 4.2. Correlation matrix: Atopic disease severity and their relationship with actigraphic variables (significant correlations are bolded) (n=23).

	Asthma Severity in the last 12 months	Rhinitis Severity in the last 12 months	SCORAD - Objective	SCORAD -VAS of sleep loss in the last 3 days	SCORAD - VAS of itch in the last 3 days	SCORAD - Full Scale	Leukotriene E ₄
Actigraphy							
Sleep Efficiency	-0.11	-0.10	-0.11	-0.15	-0.23	-0.23	-0.24
Sleep Percentage	-0.38*	-0.17	-0.16	0.07	-0.14	-0.21	-0.23
Wake Percentage	0.38*	0.17	0.16	-0.07	0.14	0.21	0.23
Awakenings	0.09	0.11	-0.23	0.48*	0.07	-0.10	0.40*
Mean Sleep Periods	-0.10	0.00	0.14	-0.31	-0.07	0.02	-0.39*
Mean Awake Periods	0.38*	0.17	0.18	-0.25	0.09	0.18	0.09
Moving during Total Sleep Time Percent	0.25	0.22	0.12	0.05	0.27	0.19	0.26
Immobile during Total Sleep Time Percent	-0.25	-0.22	-0.12	-0.05	-0.27	-0.19	-0.26
Total Activity Score	0.36*	0.07	0.31	0.15	0.29	0.37*	0.34
Mean Score in Inactive Periods	0.31	0.05	0.33	0.12	0.30	0.39*	0.29
Mean Score in Active Periods	0.32	-0.01	0.32	-0.04	0.20	0.34	0.21
Movement and Fragmentation Ratio	0.16	0.42*	0.02	-0.11	0.17	0.04	0.10

Nb *denotes $p < .05$, ** $p < .01$ and *** $p < .005$.

Table 4.3: Correlation matrix of actigraphy and polysomnography sleep variables of children with eczema controlling for frequency that asthma disturbs sleep in the last 12 months and frequency that rhinitis disturbs sleep in the last 12 months. (n = 23) (significant correlations are bolded).

Actigraphy variables	Sleep Efficiency	Sleep Percentage	Wake Percentage	Awakenings	Mean Sleep Periods (min:sec)	Mean Awake Periods (min:sec)	Moving during Total Sleep Time Percent	Immobile during Total Sleep Time Percent	Total Activity Score	Mean Score in Inactive Periods	Mean Score in Active Periods	Movement and Fragmentation Ratio
Polysomnography variables												
Total Sleep Time	.52*	.23	-.23	.47*	-.21	-.37	-.11	.11	-.35	-.41	-.45	.00
Sleep Efficiency	.54*	.41	-.41	.18	-.03	-.48*	-.34	.34	-.52*	-.55*	-.52*	.23
Sleep Onset Latency	-.50*	-.14	.14	-.58**	.42	.41	-.12	.12	.22	.25	.37	-.07
Arousal Index	-.11	-.01	.01	.32	-.24	-.25	.15	-.15	-.09	-.09	-.13	.28

Nb *denotes $p < .05$, ** $p < .01$, *** $p < .005$ and **** $p < .001$.

Figure 4.1: Nocturnal frequency per hour of scratching when awake and scratching when asleep in children with eczema (n = 16).

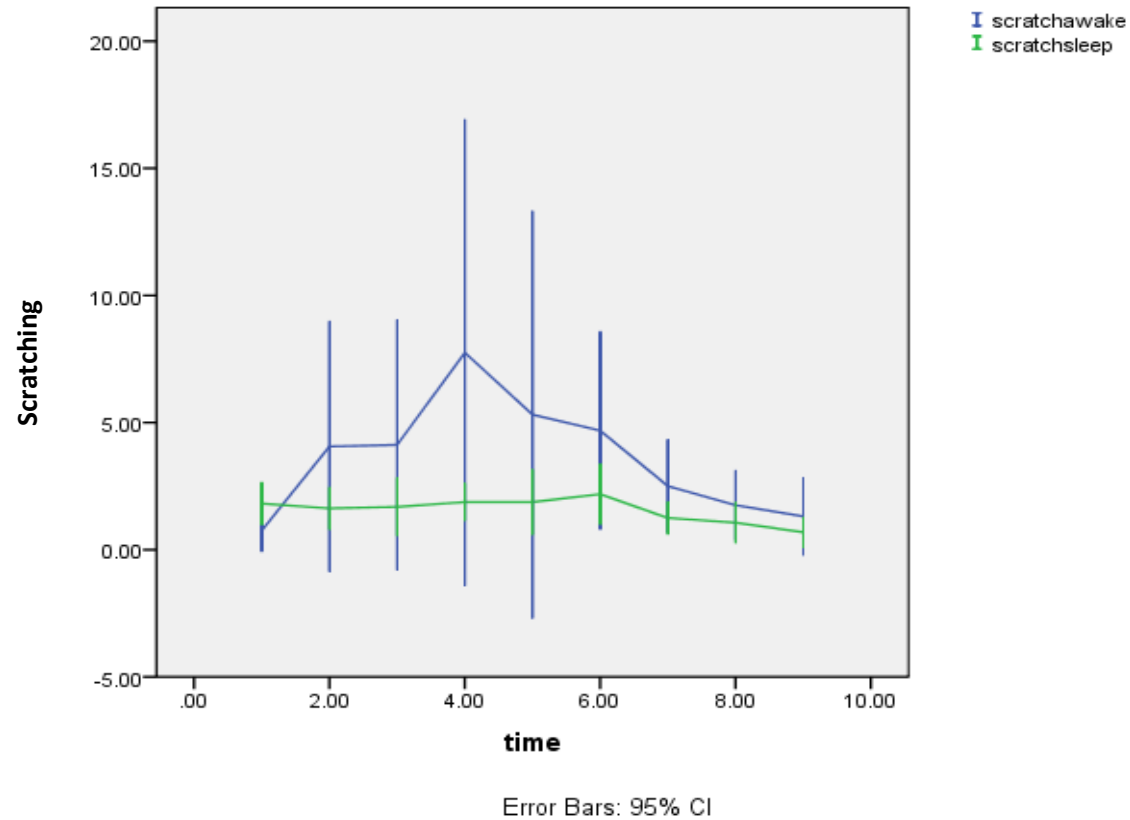


Table 4.4: Mean (SD) and F-test results of the nocturnal distribution of scratch-related activity in children with eczema (n = 16)

Scratch bouts originating in	Time from sleep onset									F - test results
	0-1h	1-2h	2-3h	3-4h	4-5h	5-6h	6-7h	7-8h	8-9h	
Sleep	1.8 (1.6)	1.6 (1.6)	1.6 (1.5)	1.9 (1.4)	1.9 (2.4)	2.2 (2.2)	1.3 (1.2)	1.1 (1.5)	0.7 (1.1)	F = 1.2
Wake	0.8 (1.5)	0.8 (1.5)	4.1 (9.2)	7.8 (17.2)	5.3 (15.0)	4.7 (7.3)	2.5 (3.4)	1.7 (2.5)	1.3 (2.8)	F = 0.9

Nb *denotes $p < .05$, ** $p < .01$ and *** $p < .005$.

Table 4.5 Correlation matrix of eczema severity, polysomnography scratching events in children with eczema. (n = 16)

	SCORAD - Extent%	SCORAD - Erythema	SCORAD - Oedema/Papulation	SCORAD - Oozing/Crust	SCORAD - Excoriation	SCORAD - Lichefication	SCORAD - Xerosis	SCORAD - Intensity	SCORAD Objective Score	SCORAD - VAS of sleep loss in the last 3 days	SCORAD - VAS of itch in the last 3 days	SCORAD Full Score	Leukotriene LTE ₄
Scratching events during sleep that													
end in awake	.19	.57*	.23	.43	.18	-.05	.08	.28	.28	-.07	-.02	.25	.21
did not end in awake	-.06	.41	.33	.19	.08	.06	-.15	.20	.13	.20	.08	.16	.01
Frequency of scratching events during													
Stage 1	.36	.29	.23	.21	.05	-.25	.04	.08	.20	-.08	.10	.18	-.07
Stage 2	-.16	.25	.07	.28	-.09	.09	-.22	.10	.01	.21	.07	.05	-.04
Stage 3+4	-.10	.50*	.31	.17	.20	.12	.05	.29	.19	.41	.00	.21	.28
REM	-.04	.37	.39	.06	.20	.15	-.15	.24	.17	.06	-.03	.16	.09
Wake	.03	.30	.44	-.07	.30	-.03	-.13	.14	.12	-.06	.12	.15	.12

Nb *denotes $p < .05$, ** $p < .01$, *** $p < .005$ and **** $p < .001$.

Figure 4.2 Screenshot of scratch event recorded during polysomnography (Brown and Kalucy, 1975).

NOTE:
This figure is included on page 108
of the print copy of the thesis held in
the University of Adelaide Library.

Figure 4.3 Screenshot of scratch event recorded during polysomnography (Aoki et al. 1991).

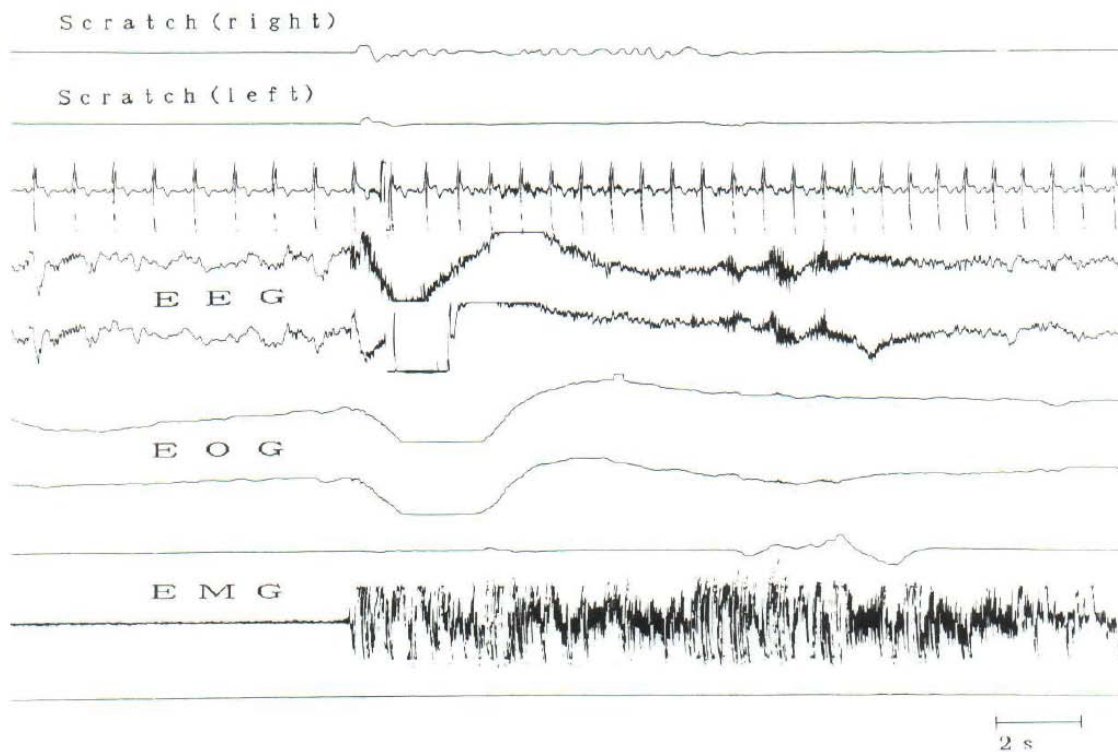


Figure 1. An illustrative recording of a scratch bout, with the right hand, starting in stage 2 of orthodox sleep.

4.6 Discussion

In this study, general actigraphic measures demonstrated significant group differences between eczema and control groups, however all supplementary actigraphic variables show trends depicting more nocturnal movement in the more severe eczema group. Self reported sleep loss due to eczema and higher levels of Leukotriene E4 were also moderately associated with the actigraphic measures of increased frequency of awakenings and shorter mean sleep periods in eczematous children. This finding can be interpreted as children with greater atopic inflammation also had more sleep disruption and greater nocturnal movement. Accordingly, our findings support previous literature of a greater degree of nighttime movement in children with eczema,¹³⁻¹⁵ with eczema severity also associated with the amount of nocturnal activity.¹⁴

Among eczematous children, the frequency that asthma and rhinitis disturbed sleep had a marked association with actigraphy variables suggesting that co morbid atopic disorders may further impact on the degree of nocturnal movement in our patient group. When the frequency that asthma and rhinitis disturbed sleep were statistically controlled for, moderate associations between actigraphic variables of Sleep Efficiency and Awakenings and the polysomnographic variables of Total Sleep Time, Sleep Efficiency and Sleep Onset Latency were prominent. In summary, actigraphy was found to be a reliable measure of nocturnal activity in children with eczema when compared to polysomnography, with moderate associations between the two methods on general measures of sleep quality.

After review of polysomnography and infra-red video recordings, scratching was found to occur during the sleep of children with eczema. Subsequently, support was found for eczematous children's scratching during sleep as reported in both child and adult studies of patients with eczema.^{8, 18, 21, 23, 26-28} A possible explanation for why some studies did not

report scratching during sleep could include researchers looking for movement prior to arousal type events, as it would be expected that a behaviour which disturbs sleep, would precede the arousal. However, this study found that scratching occurred simultaneous to the arousal, confirmed by examples in previous studies (see Figures 4.2 & 4.3).

Within our patient group, the percentage of scratch events associated with arousals out of the total number of spontaneous arousals ranged from 13% to 59%. Accordingly, there were many scratching events that were not associated with arousals. Not all factors which mediate arousal to awakening in children are understood, though children are reported to have a high arousal threshold when compared to adults.³⁶⁻³⁸ For example, Moreira et al.³⁸ found that 75% of normal children aged 2 to 10 years old did not arouse in response to an acoustic stimulus of 100dB, which is the equivalent to the noise of a power lawn mower.³⁸ Furthermore, in children, the arousal threshold is also affected by sleep stage with the lowest arousal threshold occurring during REM sleep and the highest occurring during slow wave sleep.³⁸

Among children with eczema, the distribution of scratching during sleep and when awake did not significantly alter throughout the night. However, the trend of scratching while awake was notably increased in the middle of the night, with the peak of activity occurring at approximately 4 hours after sleep onset. One feature which may mediate the frequency of nocturnal scratching is the degree of erythema of the child's eczema. Erythema is the redness or inflammation of the skin that is the result of increased blood flow to the superficial capillaries. Erythema was also found to be a pronounced feature associated with scratching in this study. In eczematous children, the degree of erythema had the strongest relationship with the frequency of scratching when the subject was either awake or asleep. Whereas the degree of increased blood flow to the superficial capillaries is unlikely to directly encourage more frequent scratch events, it is likely to mediate itch severity and effect skin temperature, which in turn, could stimulate scratching behaviour.

Interestingly, self-reported itch severity was found to have only mild associations with the actigraphy measures of the frequency of Awakening and the Mean Sleep Periods. If itch pressure during sleep had an impact on sleep disturbance, it would be expected that itch would be strongly associated with more awakenings and reduced sleep periods in children with eczema. It is of also of further interest that itch does not have a prominent association with any of the actigraphy measures. Furthermore, ratings of itch severity demonstrate little if any relationship to the frequency of observed scratching events, regardless of wake, sleep or specific to any particular sleep stage.

In conclusion, eczematous children were found to exhibit more frequent nocturnal scratching associated with disease severity. Scratching occurred during EEG-defined wake or sleep and was also seen to be a major cause of sleep disturbance in this patient group accounting for up to 59% of arousals. Surprisingly, itch was not found to be directly related to the frequency of scratch events, but instead scratch appears to be related by the degree of erythema of the eczematous child's skin. Additional physiological features of eczema, such as skin temperature, should be explored as it may be a mediating factor between frequency of scratching, itch and erythema.

Table 4.6: Studies of actigraphy and scratch in children with eczema.

Author (year) and Title	Number (age) participants	Sleep and Scratch Measurement	Sleep Results
Felix and Shuster (1975) ³⁹ A new method for the measurement of itch and the response to treatment	25 Eczema & 31 other skin disorders 21 Controls (patient + control age range = 15-82y)	Sleep = Direct observation Scratch = Bed movement transducer (wrist/ankle meters general movement)	(1) Ankle and wrist movement levels higher in patients, i.e. more restless. (2) Scratching movements present for 10% night in eczema patients.
Ebata et al. (2001) ¹⁴ Use of a wrist activity monitor for the measurement of nocturnal scratching in patients with atopic dermatitis.	29 AD adults (mean = 24.8y) 5 Controls (age not reported)	Sleep = Self-report Scratch = Actigraphy & Infrared camera	(1) Activity levels higher in patients. (2) Patients with more severe disease had higher total scratch time as a percentage of total recording time.
Benjamin et al. (2004) ¹⁵ The development of an objective method for measuring scratch in children with atopic dermatitis suitable for clinical use.	14 AD children (range = 2-9y) 7 Controls (range = 5-7y)	Sleep = Infrared camera (home) Scratch = Actigraphy	(1) Arm and leg activity levels higher in patients. (2) Patients vs. controls (percentage of sleep period time): sleeping (88 vs. 98%), scratching (4.7 vs. 0.0%), restless movement (5.3 vs. 2%) and movement under covers (1.6 vs. 0.0%). (3) Patients had 46 min less sleep. (4) Scratching accompanied by rubbing and writhing.
Bringhurst et al. (2004) ¹³ Measurement of itch using actigraphy in pediatric and adult populations.	15 Eczema & 18 other skin disorder adults (mean = 49y) and 25 eczema children (mean = 5y) 30 Adult (mean = 38y) and 17 child (mean = 7y) controls	Sleep = Self-report Scratch = Actigraphy	(1) Higher activity associated with worse SCORAD scores. (2) Paradoxically, better quality sleep was associated with high activity in children ($r = .48$) but lower quality sleep in adults ($r = -.44$). (3) Frequency of scratching was constant across the night.
Hon et al. (2006) ¹⁷ Nocturnal wrist movements are correlated with objective clinical scores and plasma chemokine levels in children with atopic dermatitis.	24 AD children (mean = 12.6y) 15 Controls (mean = 11.9y)	Sleep = Self-report Scratch = Actigraphy	(1) Activity levels higher in patients. (2) Higher activity levels associated with greater eczema extent and lichenification but not with sleep loss, subjective pruritus and objective SCORAD scores. (3) Frequency of activity: beginning > mid = end of the night.

Table 4.7: Studies of polysomnography and scratch in children and adults with eczema.

Author (year) and Title	Numbers (age) participants	Sleep and Scratch Measurement	Sleep Results
Savin et al. (1973) ²⁷ Scratching during sleep.	4 Eczema adults (mean = 30.5)	Sleep = Polysomnography Scratch = Forearm EMG	(1) Scratching occurred in all sleep stages S1> S2 > REM > S3 > S4 (2) Of the 482 scratching bouts observed, sleep "lightened" in 210 bouts with 42 bouts waking up the patient.
Brown and Kalucy (1975) ⁴⁰ Correlation of neurophysiological and personality data in sleep scratching.	1 Eczema, 1 atopic eczema & 2 other skin disorders adults (mean = 42.7y)	Sleep = Polysomnography Scratch = Forearm EMG	(1) Scratching noted in sleep.
Savin et al. (1975) ²⁸ Further studies of scratching during sleep.	5 Eczema & 10 other skin disorders (age not reported)	Sleep = Polysomnography Scratch = Closed circuit TV & forearm EMG	(1) Scratching S1 > S2 = REM > S3+4. (2) Mean scratch bout durations were similar across sleep stage.
Monti et al. (1989) ¹⁸ Sleep and nighttime pruritus in children with atopic dermatitis.	9 Eczema children (mean = 8.3y)	Sleep = Polysomnography Scratch = Forearm EMG	(1) Scratching S1 > S2 > REM > S4 > S3. (2) Mean total scratch time = 30.3 min. (3) Frequency of scratching: mid > beginning = end of the night.
Aoki et al. (1991) ⁸ Nocturnal scratching and its relationship to the disturbed sleep of itchy subjects.	9 AD, 3 eczema & 1 other skin disorder adult (range = 18-75y)	Sleep = Polysomnography Scratch = Hand strain gauge	(1) Scratching S1 > S2 = S3 = S4 = REM. (2) Mean number of scratch bouts per hour = 7.9. (3) Mean scratch bout duration = 36.3s. (4) Sleep stage lightened after scratch bouts.
Jenney et al. (1995) ²¹ Oxygen consumption during sleep in atopic dermatitis.	10 AD children (median = 7.2y) 10 Controls (median = 9.2y)	Sleep = Polysomnography Scratch = Direct visual observation	(1) Scratching observed (range = 45-105 min of direct visual monitoring) in S1, S2, S3 and REM.
Stores et al. (1998) ²² Physiological sleep disturbance in children with atopic dermatitis: a case control study.	20 AD children (mean = 9.6y) 20 Controls (age matched but values not reported)	Sleep = Polysomnography (home) Scratch = Forearm EMG	(1) Patient mean number of scratching episodes = 61.6. (2) Mean total scratch time = 47.9 min. (3) Percentage of total sleep period patients spent scratching = 7.7%. (4) Higher scratching frequency associated with longer wake after sleep onset.
Reuveni et al. (1999) ²³ Sleep fragmentation in children with atopic dermatitis.	14 AD children (mean = 6y) 9 Controls (mild snorers) (mean = 7y)	Sleep = Polysomnography Scratch = Hand strain gauge and extensor digitorum EMG	(1) Scratching frequency S1 > S2 > REM = S3 =S4. (2) Mean arousal + awakening events per hour patients (24.1) > controls (15.4). (3) Scratching in only 15% of arousals + awakenings. (4) No between group differences in duration of sleep stages and number of deeper to lighter sleep stage shifts.
Bender et al. (2008) ³⁰ Disease severity, scratching and sleep quality in patients with atopic dermatitis.	20 AD adults (18-65y)	Sleep = Polysomnography Scratch = Actigraphy, video & extensor digitorum EMG	(1) Scratching S1 and S2 > S3 = S4 = REM. (2) Higher scratch index associated with worse sleep and more overall body activity. (3) Scratch either occurred during sustained wakefulness or in association with arousal/awakening.

NB S1 = Stage 1, S2 = Stage 2 ,S3 = Stage 3, S4 = Stage 4, REM = Rapid Eye Movement, AD = atopic dermatitis and EMG = electromyography.

Bibliography

1. Stander S, Steinhoff M. Pathophysiology of pruritus in atopic dermatitis: an overview. *Exp Dermatol* 2002; 11:12-24.
2. Twycross R, Greaves MW, Handwerker H, et al. Itch: Scratching more than the surface. *Quarterly Journal of Medicine* 2003; 96:7-26.
3. Schmelz M, Schmidt D, Bickel A, et al. Specific C receptors for itch in human skin. *J Neurosci* 1997; 17:8003-8.
4. Hsieh JC, Hagermark O, Stahle-Backdahl M, et al. Urge to scratch represented in the human cerebral cortex. *J Neurophysiol* 1994; 72:3004-8.
5. Darsow U, Drzezega A, Frisch M, et al. Processing of histamine-inducing itch in the human cerebral cortex: a correlation analysis with dermal reactions. *J Invest Dermatol* 2000; 115:1029-33.
6. Drzezega A, Darsow U, Treede RD. Central activation by histamine-induced itch: analogies to pain processing: a correlational analysis of O-15 H₂O positron emission tomography studies. *Pain* 2001; 92:295-305.
7. Leknes SG, Bantick S, Willis CM, Wilkinson JD, Wise RG, Tracey I. Itch and motivation to scratch: An investigation of the central and peripheral correlates of allergen- and histamine-induced itch in humans. *J Neurophysiol* 2007; 97.
8. Aoki T, Kushimoto H, Hishikawa Y, Savin JA. Nocturnal scratching and its relationship to the disturbed sleep of itchy subjects. *Clin Exp Dermatol* 1991; 16:268-72.
9. Rees JL, Laidlaw A. Pruritus: more scratch than itch. *Clin Exp Dermatol* 1999; 24:490-3.
10. Savin J. The measurement of scratching. *Seminars in Dermatology* 1995; 14:285-9.
11. Woolf CJ, Ma Q. Nociceptors - Noxious Stimuli Detectors. *Neuron* 2007; 55:353-64.
12. Nilsson HJ, Levinsson A, Schouenborg J. Cutaneous field stimulation (CFS): a new powerful method to combat itch. *Pain* 1997; 71:49-55.
13. Bringham C, Waterston K, Schofield O, Benjamin K, Rees J. Measurement of itch using actigraphy in pediatric and adult populations. *J Am Acad Dermatol* 2004; 51:893-8.
14. Ebata T, Iwasaki S, Kamide R, Niimura M. Use of a wrist activity monitor for the measurement of nocturnal scratching in patients with atopic dermatitis. *Br J Dermatol* 2001; 144:305-9.
15. Benjamin K, Waterston K, Russell M, Schofield O, Diffey B, Rees JL. The development of an objective method for measuring scratch in children with atopic dermatitis suitable for clinical use. *J Am Acad Dermatol* 2004; 50:33-40.
16. Felix R, Shuster S. A new method for the measurement of itch and the response to treatment. *British Journal of Dermatology* 1975; 93:303-12.
17. Hon KL, Lam MC, Leung TF, Kam WY, Lee KC, Li MC, et al. Nocturnal wrist movements are correlated with objective clinical scores and plasma chemokine levels in children with atopic dermatitis. *Br J Dermatol* 2006; 154:629-35.
18. Monti JM, Vignale R, Monti D. Sleep and nighttime pruritus in children with atopic dermatitis. *Sleep* 1989; 12:309-14.
19. Kelsay K. Management of sleep disturbance associated with atopic dermatitis. *J Allergy Clin Immunol* 2006; 118:198-201.
20. Hon KL, Leung TF, Wong Y, Fok TF. Lesson from performing SCORADs in children with atopic dermatitis: subjective symptoms do not correlate well with disease extent or intensity. *Int J Dermatol* 2006; 45:728-30.
21. Jenney ME, Childs C, Mabin C, Beswick MV, David TJ. Oxygen consumption during sleep in atopic dermatitis. *Arch Dis Child* 1995; 72:144-6.
22. Stores G, Burrows A, Crawford C. Physiological sleep disturbance in children with atopic dermatitis: a case control study. *Pediatr Dermatol* 1998; 15:264-8.

23. Reuveni H, Chapnick G, Tal A, Tarasiuk A. Sleep fragmentation in children with atopic dermatitis. *Arch Pediatr Adolesc Med* 1999; 153:249-53.
24. Chokroverty S, Hening WA, Walters AS. *Sleep and Movement Disorders: Butterworth Heinmann.*
25. Kryger, Roth, Dement. *Principles and Practice of Sleep Medicine, Second Edition.* 2 ed.
26. Bender BG, Leung SB, Leung DY. Actigraphy assessment of sleep disturbance in patients with atopic dermatitis: an objective life quality measure. *J Allergy Clin Immunol* 2003; 111:598-602.
27. Savin JA, Paterson WD, Oswald I. Scratching during sleep. *Lancet* 1973; 11:296-7.
28. Savin JA, Paterson WD, Oswald I, Adam K. Further studies of scratching during sleep. *Br J Dermatol* 1975; 93:297-302.
29. Brown DG, Kalucy RS. Correlation of neurophysiological and personality data in sleep scratching. *Proceedings of the Royal Society of Medicine* 1975; 68:530-2.
30. Bender BG, Ballard R, Canono B, Murphy JR, Leung DY. Disease severity, scratching, and sleep quality in patients with atopic dermatitis. *J Am Acad Dermatol* 2008; 58:415-20.
31. Cole RJ, Kripke DF, Gruen W, Mullaney DJ, Gillin JC. Automatic sleep/wake identification from wrist activity. *Sleep* 1992; 15:461-9.
32. de Souza L, Benedito-Silva AA, Pires MLN, Poyares D, Tufik S, Calil HM. Further validation of actigraphy for sleep studies. *Sleep* 2003; 26:81-5.
33. Ebata T, Aizawa H, Kamide R, Niimura M. The characteristics of nocturnal scratching in adults with atopic dermatitis. *Br J Dermatol* 1999; 141:82-6.
34. Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J, Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997; 195:10-9.
35. Holm EA, Wulf HC, Stegmann, Jemec GBE. Life quality assessment among patients with atopic eczema. *Br J Dermatol* 2006; 154:719-25.
36. Boselli M, Parrino L, Smerieri A, Terzano MG. Effect of age on EEG arousals in normal sleep. *Sleep* 1998; 21:351-7.
37. Busby KA, Mercier L, Pivik RT. Ontogenetic variations in auditory arousal threshold during sleep. *Psychophysiology* 1994; 31:182-8.
38. Moreira GA, Tufik S, Nery LE, Lutz J, Verfaillie K, Luan X. Acoustic arousal responses in children with obstructive sleep apnea. *Pediatr Pulmonol* 2005; 40: 300-5.
39. Felix R, Shuster S. A new method for the measurement of itch and the response to treatment. *British Journal of Dermatology* 1975; 93:303-12.
40. Brown DG, Kalucy RS. Correlation of neurophysiological and personality data in sleep scratching. *Proceedings of the Royal Society of Medicine* 1975; 68:530-2.

Chapter 5: Eczema, sleep and skin temperature in children

5.1 Body temperature regulation in humans

Human beings are endothermic, which means that they have the ability to regulate their body temperature. Temperature regulation transpires within the interaction of two physiological temperature zones, the core temperature and shell temperature. The core temperature is that of the abdominal, thoracic, and cranial cavities, which contain the vital organs. The core, especially the brain, is homeostatically regulated around a set point of about 37° C with a maximum to minimum temperature range of about 0.9° C. The regulation of core body temperature is maintained through a combination of heat production and heat loss.¹ When heat production is greater than heat loss, core body temperature increases and, conversely, when heat loss exceeds heat production, core body temperature decreases. Temperature input of the core is through heat production by the metabolic activity of the liver, intestines, kidneys, heart and the brain. Hence, most of the body's heat is produced in less than 10% of the central mass which is surrounded by a small proximal skin surface. The poor ratio of the core's body mass to skin surface limits the core's ability for heat transfer with the environment.² However, the core is able to conserve or release heat through the shell.

The shell consists of the skin, subcutaneous tissues and muscles which have a larger mass to surface area ratio, hence it is more proficient in heat transfer. However, the shell is also more effected by the external temperature. Whereas the size of the core remains static, the human body maintains core temperature by changing the size of the shell. The shell size is altered by redirecting blood flow to compensate for external environmental temperature. In a cold environment, the shell is large and acts a buffer to protect the core from dangerous cooling.³ In addition, venous blood returns by way of inner blood vessels located near the arteries that pre-warm the back-streaming blood and protects the core from cooling down. In contrast,

when the environment is hot, the shell is small and the venous blood streams by way of outer veins near the skin surface, thereby enhancing additional heat loss by way of the lower extremities.⁴

Heat loss from the core therefore requires the transference of heated blood to various blood vessels located through the skin.⁵ Increased transference of blood to distal skin regions can be indirectly measured via increases of distal skin temperature. Conversely, when vasoconstriction occurs, the amount of blood flow is restricted causing distal skin temperature to decrease towards ambient air temperature.⁶ The vessels most effective at losing heat are known as arteriovenous-anastomoses (AVAs) and are concentrated in more distal regions of the skin (i.e. hands, feet, nose, lips, ears).⁶ Heat loss from distal skin areas occur most rapidly when AVAs are maximally dilated and have been reported to move about 10,000 times more blood volume per second than capillary blood.⁷

Control of these systems is regulated by the pre-optic area/anterior hypothalamus which is also a key structure in arousal state control. Diverse afferent inputs from cold and warm sensitive neurons are received and processed in this area. The pre-optic area/anterior hypothalamus also generates efferent responses which produce sweating, shivering and changes in vasomotor tone to maintain the core body temperature. The core body temperature is normally maintained within the inter-threshold zone of shivering and sweating.⁸

5.2 Circadian rhythms and body temperature in humans

In addition to maintaining body temperature within a changing environment, humans have a diurnal variation of body temperature dependent on the periods of rest and activity. The mechanisms for changing shell size according to changing ambient temperature also maintains the circadian core body temperature rhythm. The maximum temperature ranges from 10am to 6pm and the minimum from 11pm to 7am (see Figure 5.1).⁹ As the circadian

rhythm of heat loss is phase advanced with respect to heat production, it is probable that the process of heat loss drives the circadian rhythm of core body temperature rather than changes in heat production.^{1,7} It is also consistent with a large body of evidence that a rise in distal peripheral temperature of approximately 0.5° - 1.0° C and a concomitant fall in core body temperature are associated with successful sleep onset.¹⁰⁻¹²

Figure 5a: Core body temperature of older adults (black) and children (white) over a 24 hour period.⁹

NOTE:
This figure is included on page 118
of the print copy of the thesis held in
the University of Adelaide Library.

Distal skin temperatures of the hands and feet therefore exhibit an inverse circadian rhythm in comparison to core body temperature. In addition, the distal skin temperatures are phase advanced by about 100 minutes and their circadian amplitude is about three times higher than that of core body temperature.⁷ In contrast, the proximal skin temperatures (e.g. thigh, infra-clavicular region, stomach, forehead), follow the core body temperature with a similar amplitude.¹³

5.3 Sleep disorders associated with temperature dysfunction

Disease or disorders which disturb circadian temperature mechanisms can also disrupt sleep. For example, studies on adult patients with vascular irregularities have found associations between distal temperature and sleep onset difficulties. Gompper et al.¹⁴ reported that 20 women with primary vascular dysregulation who also had difficulties initiating sleep, were found to have increased vasoconstriction at midday and in the evening compared to 21 controls. Greater vasoconstriction was indicated by lower distal skin temperatures and distal-proximal skin temperature gradients (all, $p < .05$). The authors further report that women with primary vascular dysregulation exhibited a phase delay of distal vasodilation compared to controls (mean, (SD), 38.5 ± 16.65 minutes vs. 3.57 ± 17.28 minutes, $p < .05$).

Rutkove et al.¹⁵ examined the distal foot temperature of 28 patients with diabetes but without diabetic polyneuropathy, 14 patients with isolated small-fibre diabetic polyneuropathy, and 27 patients with more advanced diabetic polyneuropathy compared to 39 controls. No differences were found between groups during wakefulness. During sleep, all of the diabetic subgroups had a reduced mean distal foot temperature ($p < .001$), a reduced maximal temperature ($p < .001$), an increased rate of cooling ($p < .001$), and an increased frequency of variation ($p = .005$) than controls. This group reported that adult patients with diabetic polyneuropathy and even those with only diabetes but no diabetic polyneuropathy, exhibited a nocturnal dysfunction of distal thermoregulation which was likely to contribute to sleep disturbance.

In summing up, diseases which impede blood flow to distal regions are likely to interfere with distal temperatures associated with normal sleep onset latencies.

5.3.1 Experiments on body temperature and sleep

A few studies have explored the outcomes on sleep by manipulating body temperature.

Fronczek et al.¹⁶ manipulated the distal skin temperature of 8 adult subjects with narcolepsy.

The subjects wore a thermo-suit that induced skin temperature to cycle slowly with an amplitude of only 0.4° C within the comfortable range normally observed during sleep.

Proximal skin warming suppressed wakefulness (OR 0.81, CI (0.77 to 0.84), $p < 0.001$) and enhanced slow-wave sleep (OR 1.23 (1.17 to 1.29), $p < 0.001$). In contrast, distal skin warming enhanced wakefulness (OR 1.11 (1.06 to 1.16), $p < 0.001$) and stage 1 sleep (OR 1.22 (1.16 to 1.28), $p < 0.001$). Distal skin cooling led to 160% increase in Slow Wave Sleep, a 50% increase in REM sleep and a 68% decrease in wakefulness, compared to the least beneficial combination of proximal skin cooling and distal skin warming.

Liao, Chiu and Landis¹⁷ examined the affects of a warm footbath on body temperature and sleep outcomes in 15 older adults with self reported sleep disturbance. Body temperature and polysomnographic data was recorded for three consecutive nights. Participants were randomly assigned to receive a 41° C footbath for 40 minutes before sleep onset on night two or night three. The mean distal-proximal skin temperature gradient was significantly elevated on the bathing night compared to the initial baseline night (mean, (SD) = -2.14, (.57) vs. -.42, (.89), $p < .001$). When the first two non-REM periods of the baseline and bathing nights were compared, the percentage of wakefulness was decreased in the second non-REM period on the bathing night (10.3, (8.8) vs. 3.7, (5.0), $p = .01$).

Ebben and Spielman¹⁸ examined the sleep latency of 11 healthy adults, 5 minutes after immersing their hands and feet in either heated water (42° C) or heated to the temperature of the subject's warmest limbs. No differences were found between the two conditions of heated water and the control condition in sleep latency ($t = -.13$, $p = .897$), though both conditions

had a lower sleep onset latency than the initial baseline multiple sleep latency test ($t = 2.78$, $p = .019$ and $t = 2.48$, $p = .032$, respectively).

In summary, studies in which distal and proximal temperatures were manipulated have produced mixed findings with temperature manipulation dependant on the timing of whether a heated or cooling stimulus was applied. However, trends indicate that warming distal skin prior to sleep was related to reductions in sleep onset latency, with a combination of distal skin cooling and proximal skin warming during sleep being associated with enhanced sleep quality.

5.4 The impact of eczema on heat transference in the human body

The skin is the main surface for heat exchange, hence any dermatological dysfunction can interrupt thermoregulation.¹⁹ Patients with eczema also exhibit disturbances of various vascular skin functions which impact upon thermoregulation.⁷⁻¹⁰ Inflammation of eczematous skin causes an increase in peripheral blood flow, resulting in the loss of excessive amounts of heat.²⁰ This increased loss of heat would in turn lead to a fall in core body temperature if not for compensatory mechanisms such as an increase of the size of the shell or an increase of heat output from the core. An increase in heat output would, in turn, cause problems if the child went into a warmer environment, such as going to bed at night. The child would have difficulty dissipating the additional heat as heat loss through the skin would already be at a high level.²¹ The overall dysfunction in the thermoregulation of eczematous children may explain why environmental changes in temperature are associated with intense itching and sweating,²² increases in flare-ups and scratching²³⁻²⁵ and problems with sleep initiation and sleep disruption.^{10, 11, 26}

5.5 Co-sleeping and thermoregulation in children with eczema

Parental strategies in dealing with sleep disturbance may further exacerbate the sleep disturbance in children with eczema. Approximately 30-70% of children with eczema were reported to regularly spend time in the parental bed in comparison to 11-13% of non-eczema children.^{27, 28} A study by Chamlin et al.²⁹ report that 30% of families were co-sleeping with their eczema afflicted child, and that 66% of these parents were bothered by the co-sleeping. Sleep disturbance and co-sleeping were also strongly associated with the severity of the child's eczema and the degree to which parents reported that the eczema affected the family's happiness.²⁹ The relationship between co-sleeping, eczema severity and sleep disturbance may be mediated by temperature. When a young child shares a bed with parents, there is a strong possibility that their body temperature may be higher than when the child is on their own.³⁰

Overheating in bed contributes to sleep disturbances among patients with skin disorders and is associated with increased awakenings, longer total waking time and reduced REM sleep.³¹ Pruritus and scratching may also become a problem at night due to the rise in skin temperature that occurs in a warm bed.²² Overheating in bed would further mediate and blunt the circadian fall in body temperature and delay sleep onset.³¹ Eczematous children are reported to differ from other sleep-disturbed children in sleeping better and scratching less in the second half of the night when both body and environmental temperatures are lower.^{27, 32, 33}

5.6 Research on the skin of eczema patients and its impact on thermoregulation

Few studies have explored the relationship between eczematous skin and its ability to regulate body temperature. Heyer et al.³⁴ examined thermoregulation in 21 adult eczema patients compared to 23 age and sex matched controls. This group studied the response of the skin of one forearm to a standardised 15 minute exposure of the other arm to either a cold or a warm bath (17 degrees - 18 degrees C and 40 degrees - 41 degrees C respectively). In most controls, the

exposure of one forearm to warmth was associated with the skin temperature of the contralateral forearm remaining unchanged or decreasing slightly. In contrast, eczema patients reacted to a warm bath with either no change in the contralateral forearm or a slight increase in temperature. Further, when controls were exposed to cold, the contralateral forearm responded with either a slight rise in skin temperature or an almost indiscernible decrease. In contrast, when eczema patients were exposed to cold, the contralateral forearm exhibited a slight lowering of temperature. Heyer et al. suggests that the abnormal pattern of thermoregulation may reflect an intrinsic disturbance of skin dysfunction due to eczema.

Samsonov and Bol'shakova¹⁹ measured the skin heat exchange of 72 adult subjects with eczema compared to 25 controls. Heat exchange was measured by the amount of heat entering a purpose built sensor over a set time. Measurements were made in three skin areas; affected skin, 2-3 cm away from affected areas and away from affected area on healthy looking skin. The temperature of skin areas to be recorded were first measured with a skin thermometer. The heat exchange sensor was cooled to 10 degrees below the measured skin temperature, placed on the area of the skin to be measured and the temperature recorded for ten minutes. Subjects were separated into three groups depending on eczema severity; severe, moderate and mild. Data from the eczema groups suggest a linear relationship between heat exchange ability and eczema severity. Mild and moderate groups had a higher heat exchange than controls and the severe group had a lower heat exchange than controls. The authors offer that while mild and moderate eczema increases heat exchange through inflammation, severe eczema has altered the heat gradient or damaged the process of heat exchange.

Levin and Loseva²⁰ examined the thermoregulation in 76 adult eczema patients compared to 15 controls using the Circulatory Temperature Index (CTI). CTI refers to the relationship between skin temperature (T_s), rectal temperature (T_r) and the environment (T_e). With this data it is

possible to calculate the difference between skin temperature and the surrounding temperature (external temperature gradient) and also rectal temperature and the skin temperature (internal temperature gradient) for any point on the skin surface.

$$CTI = \frac{T_s - T_e}{T_r - T_s}$$

In normal's, an increase in CTI suggests an increase in peripheral circulation and a release of heat, while a decreased CTI suggests a decrease in peripheral circulation and therefore a decrease in heat release. CTI was measured in 12 different parts of the body including; forehead, chin, stomach, shoulder, upper arm, inner wrist, hand, outer thigh, knee, ankle and foot. All experimental measurements were taken after 20 minutes acclimatisation in a room 21-23 degrees Celsius while in a supine position. The CTI in controls were in normal ranges for all areas measured. In eczema patients, the CTI was higher in all areas measured when compared to controls except for the chin, which had a lower CTI compared to controls. This was true for both affected and non-affected areas. This implies that eczema patients have a higher peripheral circulation and a higher heat release than controls. The CTI in eczema patients was also significantly asymmetric (left side different to the right side in the same area), while in controls the CTI symmetry was not significantly different.

5.7 Rationale for studying skin temperature in children with eczema

Temperature regulation is affected in children with eczema, but the secondary impact on their sleep has yet to be studied. The aim of this study is to examine eczematous children's nocturnal distal and proximal skin temperature and their distal to proximal skin temperature gradient compared to controls. A further aim of this study is to examine the relationship between eczematous children's temperature data and their sleep.

5.8 Method

5.8.1 Subjects and Apparatus

The eczema (n=19) and control (n=15) subjects participating in this study are a sub group of subjects who participated in the polysomnography study outlined in Chapter 3. In addition to the method outlined in Chapter 3 (section 3.3) for polysomnography and Chapter 4 (section 4.4.1) for actigraphy, the following additional measures and procedures were undertaken to examine contribution of body temperature to sleep disturbance in children with eczema.

5.8.2 Temperature

Temperature data was collected using a Mini Logger Series 200 (Respironics, Oregon USA) recording device connected to YSI 400 series thermistor probes. Peripheral skin temperature was measured at four sites simultaneously throughout the night. Temperature was recorded at the left and right clavicle and at the left and right index fingers. The Mini Logger was then taped to the child's clothing on the abdomen. Left and right clavicle temperatures were averaged to produce proximal temperature reading and the left and right index finger temperatures were likewise averaged to produce a distal temperature reading. The averaging of the two sets of sites were done to reduce "noise" inherent in temperature measurement.¹¹ A Distal to Proximal skin temperature Gradient (DPG) was calculated through subtracting the average distal temperature from the average proximal temperature. Room temperature was kept at 22 degrees Celsius throughout the study.

5.9 Results

5.9.1 ANOVA results of nocturnal temperature differences between children with eczema and controls (see Table 5.1 & Figures 5.1 to 5.15).

Temperature: ANOVA Independent T-test comparisons revealed significant group differences in which eczema subjects had a significantly lower Distal temperature at 30 minute bins of 91-120, 121-150, 151-180, 181-210, 211-240 and 421-450 minutes post sleep onset (see Figure 5.14).

5.9.2 Correlation between sleep and nocturnal mean temperature values (see Table 5.2).

A lower Mean Distal temperature was found to have a moderate association with higher scores of Disorders of Sleep-Wake Transition. A lower Mean Distal temperature was also moderately associated with a higher frequency of Spontaneous Arousals in Total Sleep Time. A Higher Distal Proximal Gradient was moderately related to a higher percentage of stage 2 sleep. A higher Distal Proximal Gradient was also associated with a lower frequency of Spontaneous Arousals in Total Sleep Time.

Table 5.1: ANOVA results of nocturnal temperature differences between children with eczema and controls.

Averaged left and right temperature	Time		Group		Time by Group	
	F-test	Partial Eta ²	F-test	Partial Eta ²	F-test	Partial Eta ²
Index Finger (Distal)	1.4	.04	9.2***(a)	.22	1.2	.04
Clavicle (Proximal)	3.5	.10	.02	.00	1.1	.03
Distal-Proximal Gradient	1.6	.05	3.6‡	.14	1.4	.04

NB: Greenhouse-Geisser correction applied to probability estimates. ‡ denotes $p < .07$. (a) Independent T-test comparisons revealed significant group differences at T91-120, T91-150, T151-180, T181-210, T211-240 and T421-450 mins (all $p < .05$).

Table 5.2: Correlation between sleep and nocturnal mean temperature values.

Sleep (n=34)	Temperature (averaged left + right)		
	(Distal) Index Finger	(Proximal) Clavicle	Distal- Proximal Gradient
Sleep Disorders Scale for Children			
Disorders of Initiating and Maintaining Sleep	-.16	.00	-.14
Disorders of Sleep Breathing	-.05	-.16	.07
Disorders of Arousal	-.15	-.01	-.13
Disorders of Sleep-Wake Transition	-.32‡	.01	-.21
Disorders of Excessive Daytime Sleepiness	-.08	.21	-.24
Sleep Hyperhydrosis	-.04	.01	.13
Total Score	-.22	.19	-.28
Actigraphy (n = 32)			
Percentage Time Sleep	-.07	.07	.08
Sleep Efficiency	-.08	.11	.07
Total Activity Score	.28	-.18	.03
Polysomnography			
Total Sleep Time (min)	-.03	-.19	-.29
Wake After Sleep Onset (min)	-.00	.04	.04
Sleep Efficiency	-.08	-.10	-.21
Stage 1%	-.15	.10	.01
Stage 2%	.16	.17	.37*
Stage 3%	.03	-.13	-.07
Stage 4%	-.01	-.17	-.22
REM %	-.18	-.09	-.32
Obstructive Apnoea Hypopnoea Index (per hr)	.21	-.05	.18
Central Apnoea Index (per hr)	-.04	-.22	-.29
Respiratory arousals/TST	-.06	-.14	-.19
Spontaneous arousals/TST	-.39*	-.01	-.35*

NB: ‡Denotes $p < .08$ and * $p < .05$. TST = total sleep time.

Figure 5.1: Right versus left finger temperature control children (n = 15)

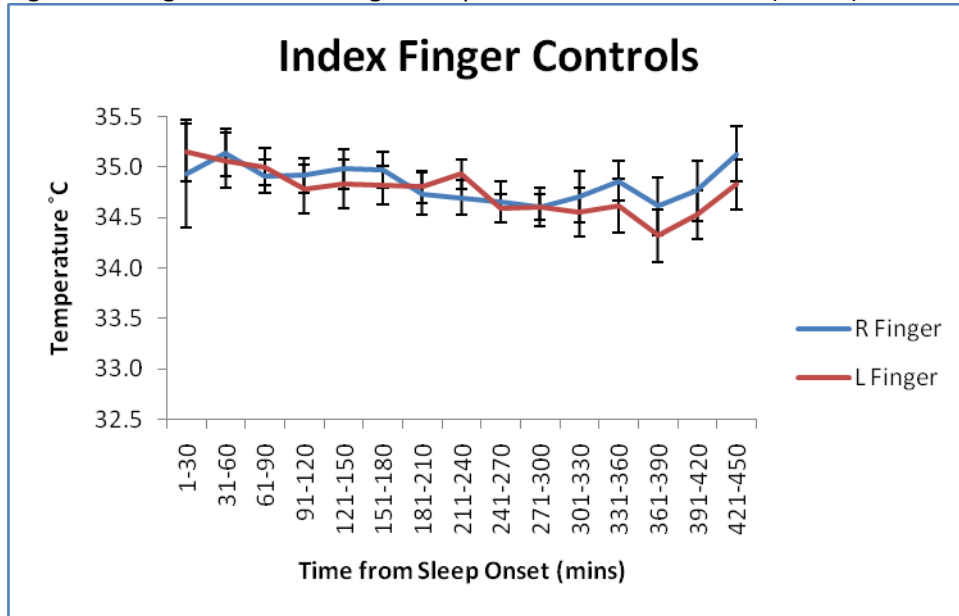


Figure 5.2: Right versus left clavicle temperature control children (n = 15)

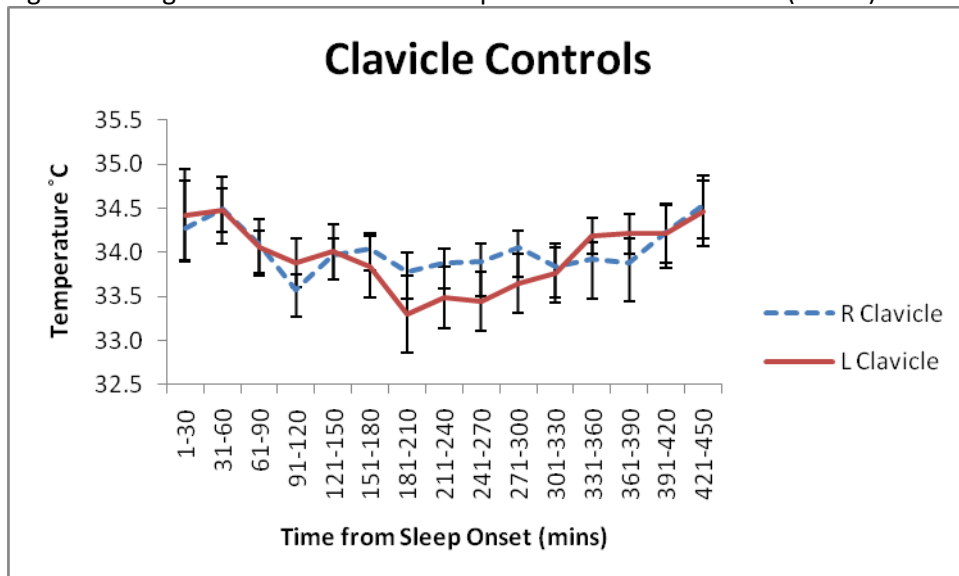


Figure 5.3: Right versus left finger temperature children with eczema (n = 19).

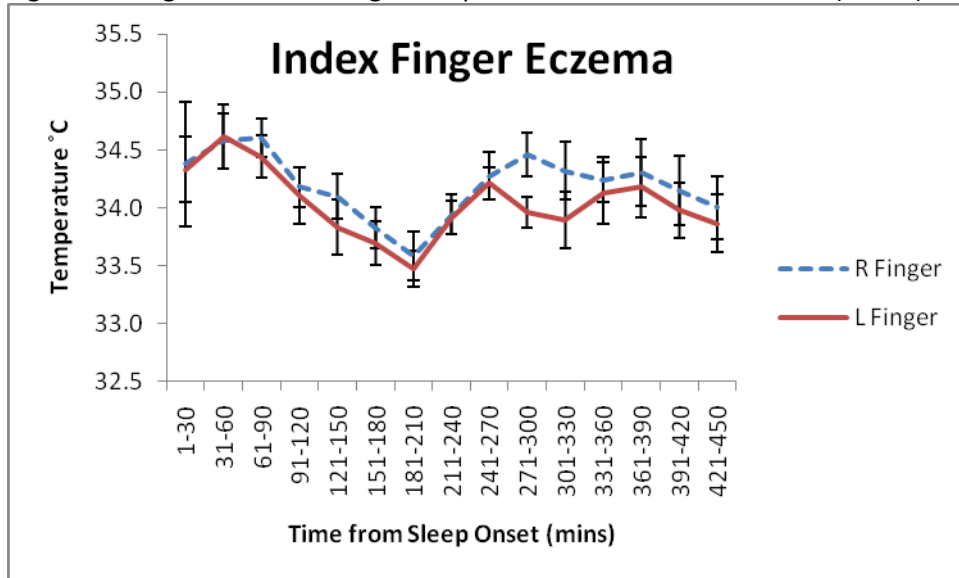


Figure 5.4: Right versus left clavicle temperature children with eczema (n = 19).

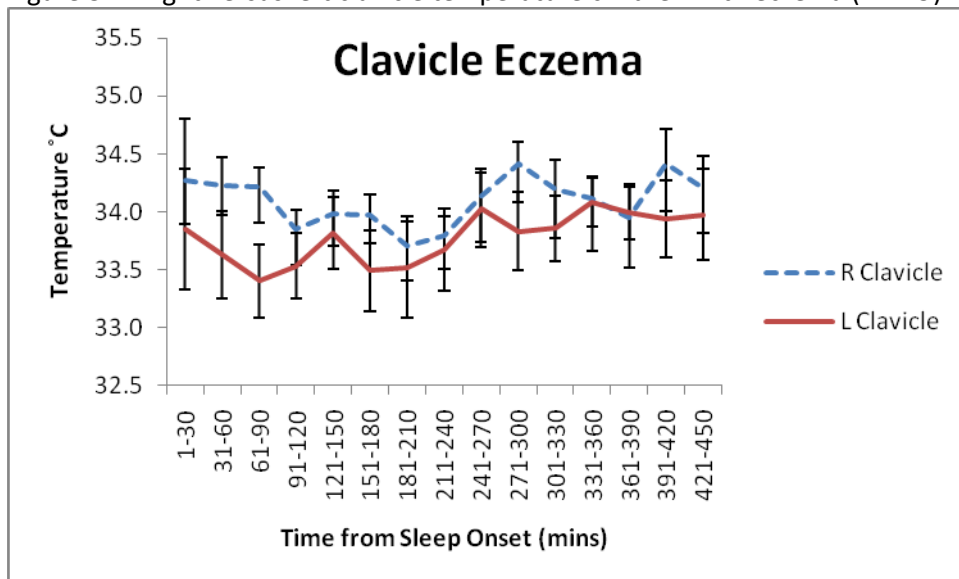


Figure 5.5: Control (n = 15) versus children with eczema (n= 19) right index temperature.

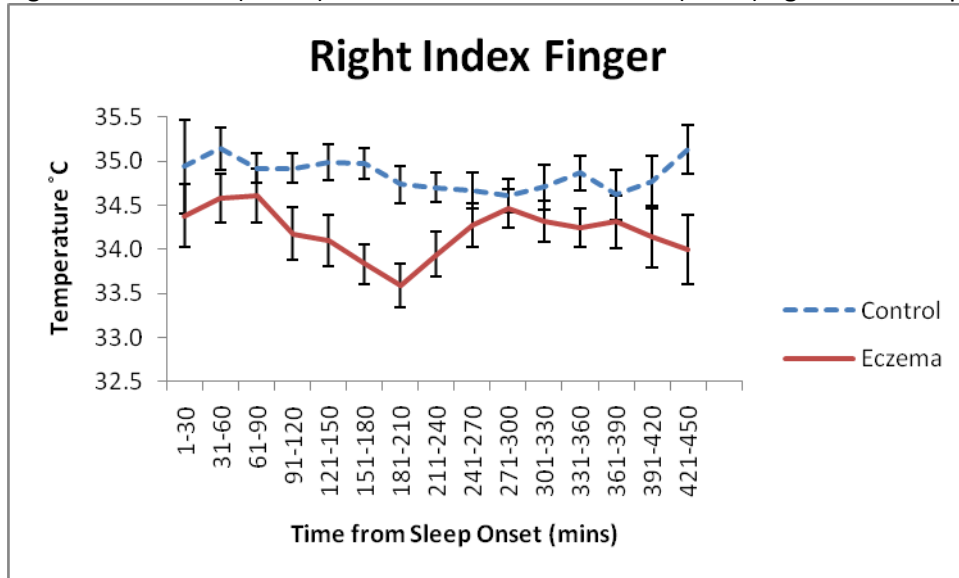


Figure 5.6: Control (n = 15) versus children with eczema (n= 19) right clavicle temperature.

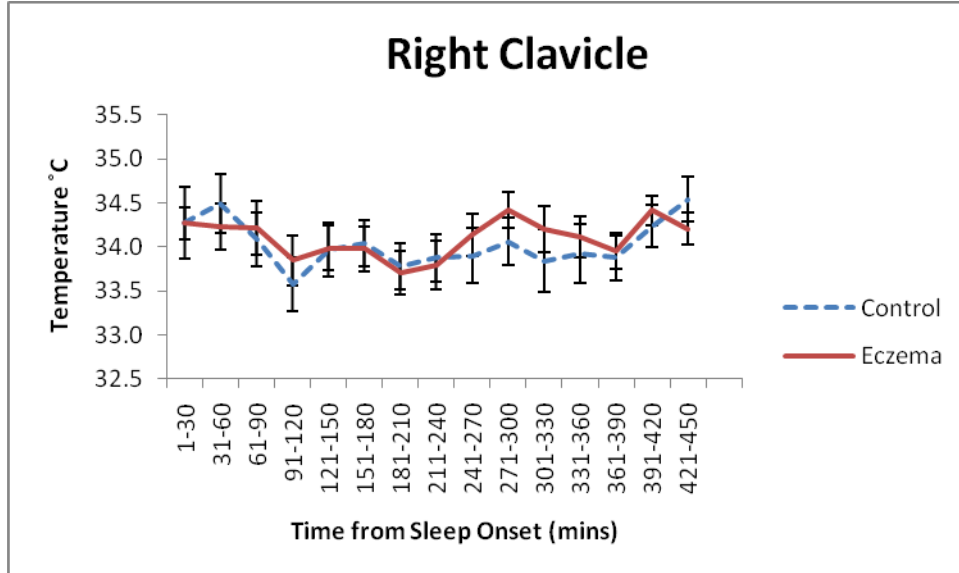


Figure 5.7: Control (n = 15) versus children with eczema (n = 19) left index temperature.

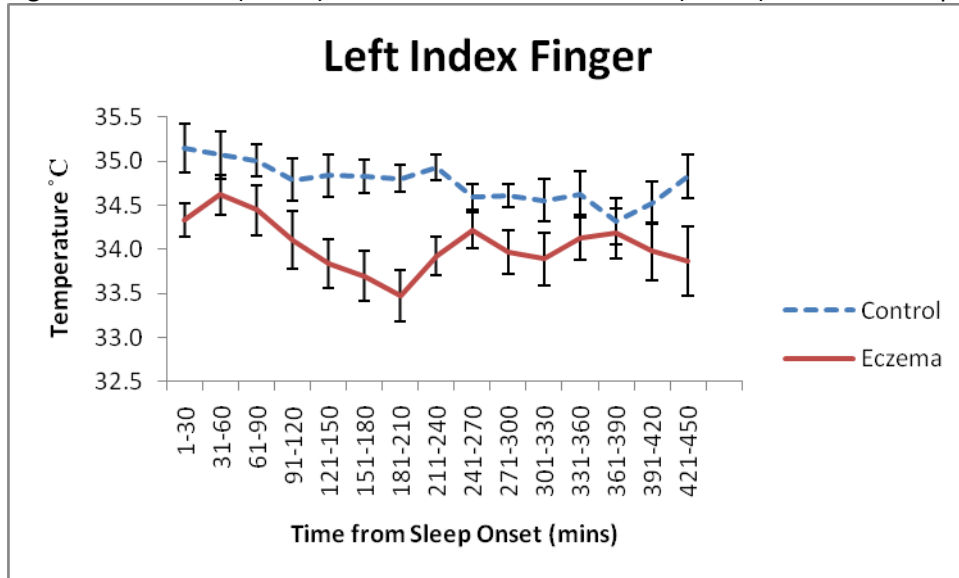


Figure 5.8: Control (n = 15) versus children with eczema (n = 19) left clavicle temperature.

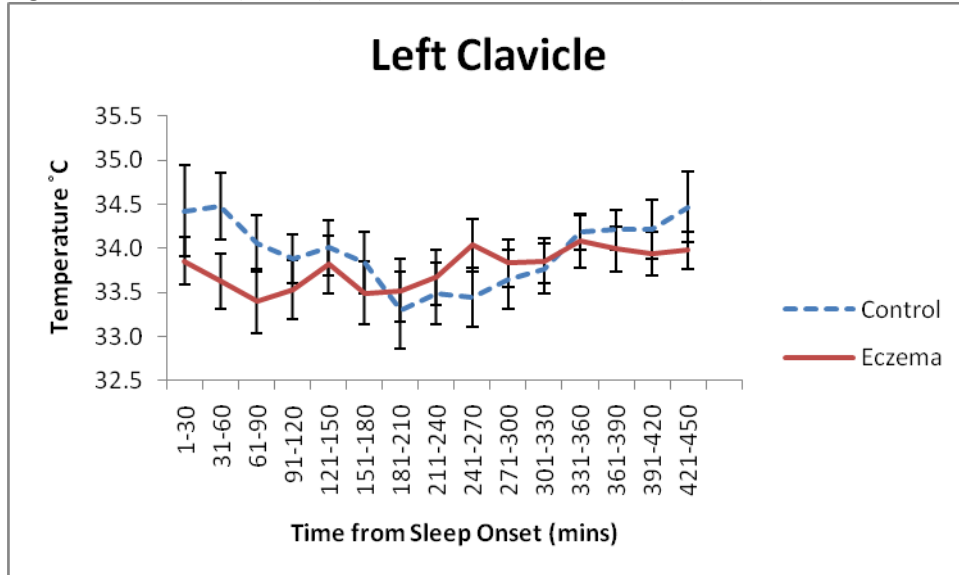


Figure 5.9: Control (n = 15) versus children with eczema (n = 19) right index finger minus right clavicle temperature difference.

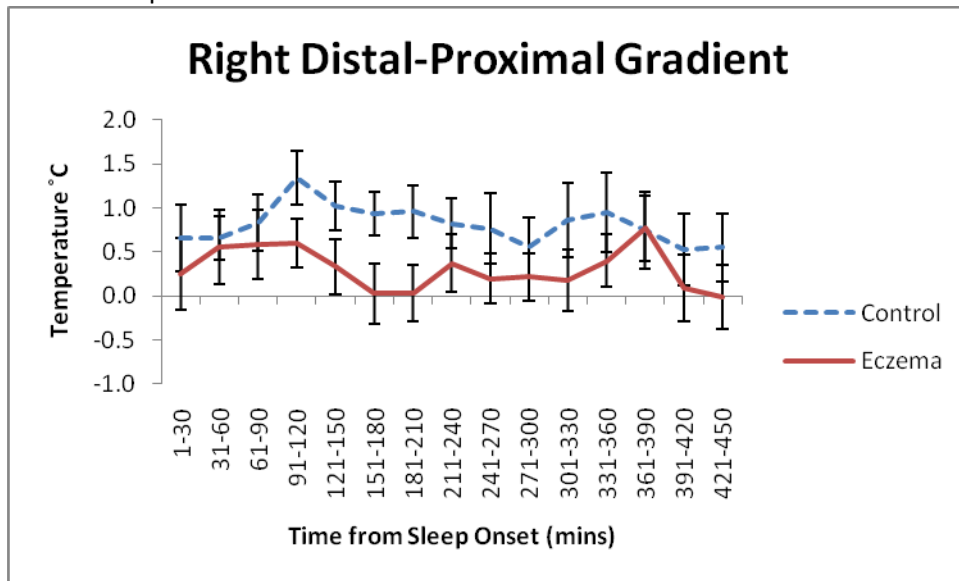


Figure 5.10: Control (n = 15) versus children with eczema (n = 19) left index finger minus left clavicle temperature difference.

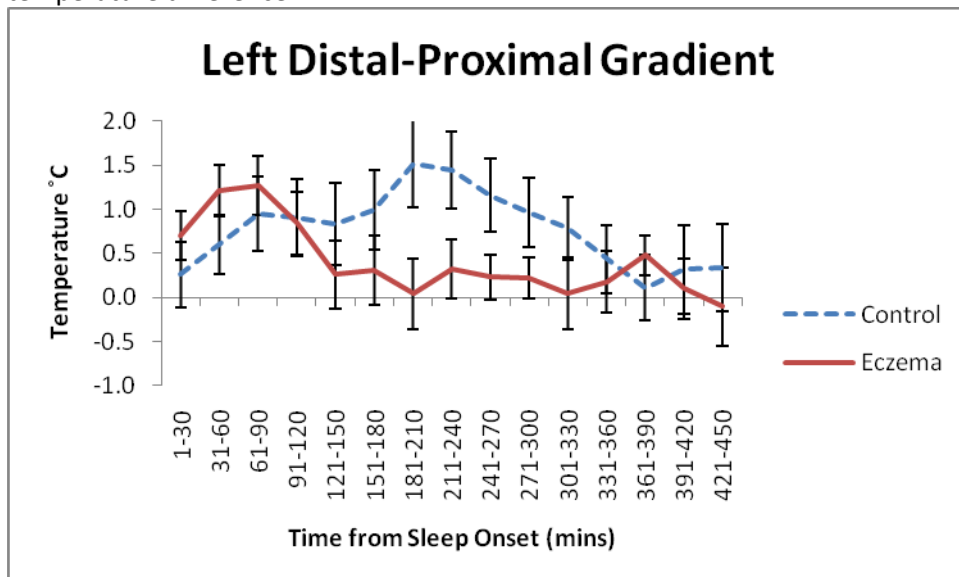


Figure 5.11: Right versus left distal-proximal gradient (finger minus clavicle) for control children (n = 15).

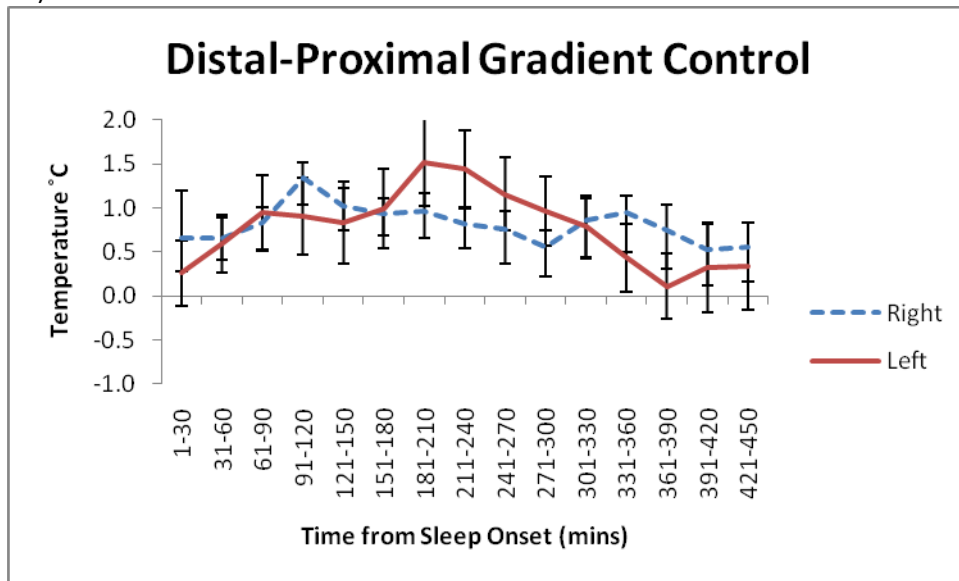


Figure 5.12: Right versus left distal-proximal gradient (finger minus clavicle) for children with eczema (n = 19).

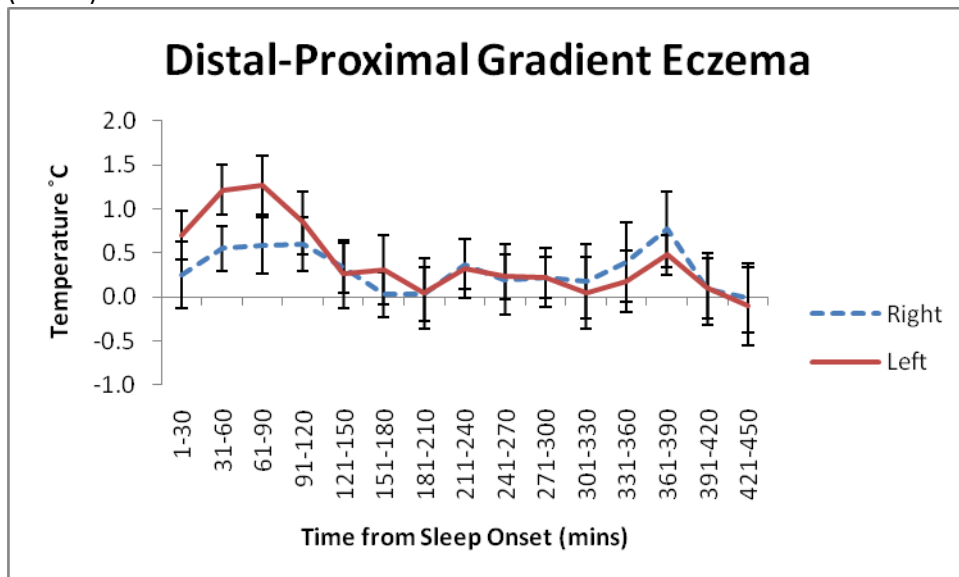


Figure 5.14: Average index finger (left versus right) temperature for children with eczema (n = 19) and control children (n = 15).

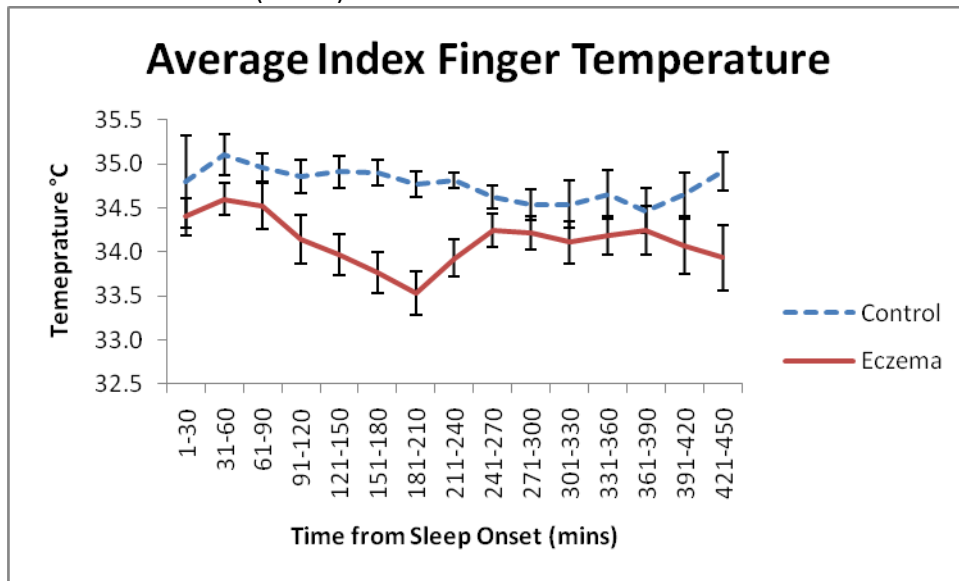


Figure 5.15: Average clavicle (left versus right) temperature for children with eczema (n = 19) and control children (n = 15).

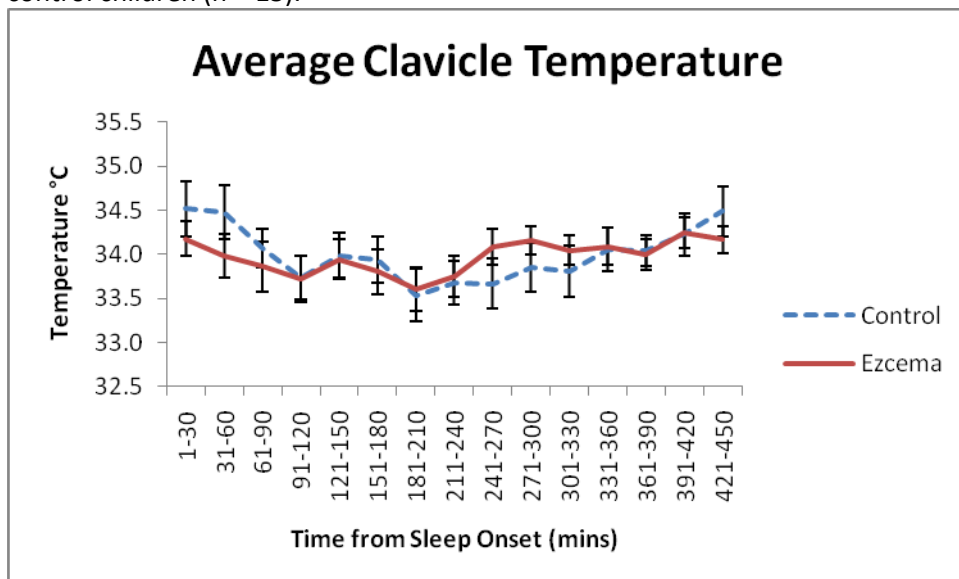
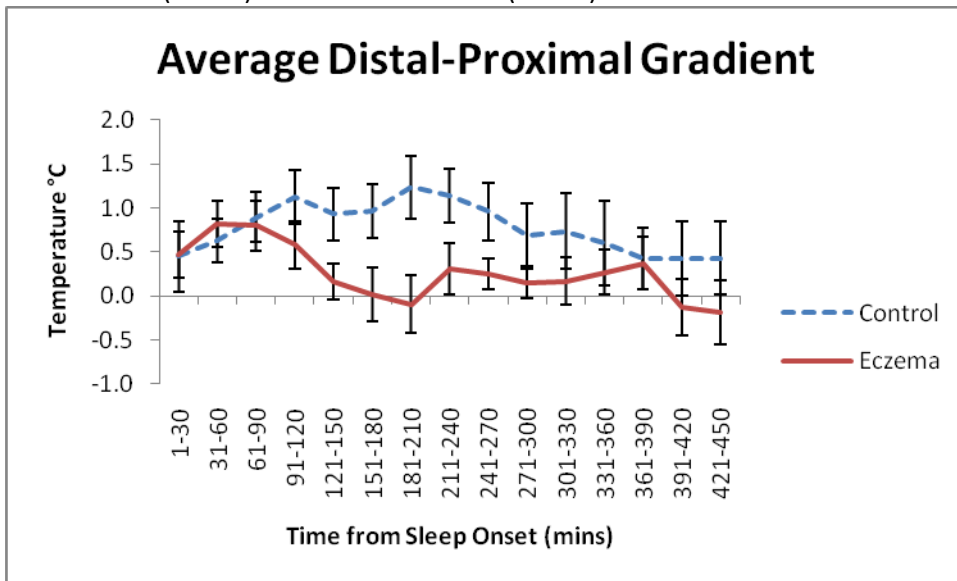


Figure 5.16: Average (left versus right) distal-proximal gradient (finger minus clavicle) for children with eczema (n = 19) and control children (n = 15).



5.10 Discussion

At Sleep Onset, no differences were found between eczema and control groups in Distal temperature, Proximal temperature and the Distal-Proximal temperature Gradient. This finding indicates that eczema and controls had similar skin temperatures at sleep onset and gives additional support to reports that a rise in distal peripheral temperature and a concomitant fall in body temperature are associated with successful sleep onset.^{10, 11}

Within subjects comparisons of the left and right sites of Distal temperature demonstrated that the two sites were not markedly different from each other, regardless of whether the child had eczema or was a control subject (see Figures 5.1 to 5.2). The left and right sites of Proximal temperature were also not markedly different from each other in all subjects (see Figures 5.3 to 5.4). This finding adds support to the reliability of our data and further indicates that skin temperature is relatively consistent on the left and right side of the body in eczema subjects, as well as controls. Accordingly, no support was found for Levin and Loseva²⁰ report that temperature changes were asymmetrical for eczema subjects.

Group differences in skin temperature were detected in Distal temperature over the course of the night. Eczema subjects had a significantly lower Distal temperature between 90 to 240 minutes and 420 to 450 minutes post sleep onset (see Figures 5.5, 5.7 & 5.14). The nocturnal trend of eczema children's Distal temperature further demonstrated a marked decline in finger temperature of approximately 0.9° C (see Figure 5.14). Although not significant, the Distal-Proximal Gradient also indicated temperature differences between eczema and control groups concurrent to those listed in the Distal temperature (5.9, 5.10, 5.11, 5.12 & 5.16). Children with eczema are not likely to produce less heat than controls at this time considering Hon et al.³⁵ report of no nocturnal metabolic differences between eczema and control children during sleep. It is also unlikely that children with eczema were unable to lose heat through the distal skin as

an inability to lose heat would be evidenced by a greater proximal temperature in the eczema group. However, no group differences were found in the Proximal temperature over the course of the night (see Figures 5.6, 5.8 & 5.15). It is more likely that eczema children lost heat more rapidly than controls due to vasodilation.²⁰ Losing heat more rapidly than controls while maintaining their core body temperature, would require that eczematous children generate a larger shell to protect their core from dangerous cooling.³ This would require the shunting of heated blood to more central regions of the body and allowing the distal regions to cool down as evidenced by lower distal temperatures in children with eczema (see Figure 5.14).

Within the context of a circadian rhythm, the distal skin temperatures of hands and feet exhibit an inverse circadian rhythm in comparison to core body temperature and that the amplitude of change in the Distal temperature is about three times higher than the responding changes in core body temperature.⁷ This suggests that the reduction in distal temperature in eczema children is a precursor to an increase in core body temperature of approximately 0.3° C amplitude (see Figure 5.14 & 5.15). A Core temperature increase of 0.3° C is an unexceptional increment in healthy subjects prior to morning arousal. However, the timing of a Core temperature increase in children with eczema is abnormal. In non eczematous children, Distal temperature reduction is phase advanced to circadian elevation of core temperature by about 100 minutes, which is also occurs in eczematous children at 240-300 minutes post sleep onset indicating a markedly premature increase in Core temperature of approximately 5 hours (see Figure 5.15). This finding further suggests that children with eczema have an abnormal circadian temperature rhythm, or more likely considering their normal sleep onset temperature profile, that more rapid heat loss is interfering with their circadian temperature cycle by eczematous children's need to generate more heat in the core. In addition, the temperature profile of eczematous children was found to be related to their sleep quality with the lower average Distal temperature associated with higher ratings of Disorders of Sleep-Wake Transition (e.g. rhythmic movements,

hypnagogic jerks, sleep talking, bruxism, etc), and higher frequencies of spontaneous arousals. This suggests that children with lower nocturnal skin temperature would also have more awakenings and periods of movement at night.

Future study on the relationship between eczema and skin temperature could include the use of a thermal camera to ascertain heat loss from the skin's surface. The degree of skin surface area affected with eczema may be more visible under thermal imaging methods and may further provide an alternative method to evaluate eczema severity. This approach may also answer the question "Does eczema severity determine how much body heat is lost at night?" Other approaches may include methods for controlling heat loss in this patient group and examining whether intervention on eczematous children's reduced Distal temperature is associated with improvements in their sleep quality.

In conclusion, there are marked differences in the thermoregulatory mechanisms of eczema children compared to controls. In general, the Distal temperature of eczematous children is colder and the changes in Distal skin temperature are more dynamic than controls. Furthermore, lower distal temperature is associated with more nocturnal movement disorders and more frequent arousals from sleep. It is also likely that increased heat loss through vasodilation in eczematous children is disturbing their circadian temperature rhythm. From this perspective, it is likely that deficits in thermoregulation, due to eczema's affect on Distal temperature, promote sleep disturbance in this patient group.

Bibliography

1. Aschoff JJ. Circadian control of body temperature. In: Hardy JD, Gagge AP, Stowijk AJ, editors. *Physiological and Behavioural Temperature Regulation*. Springfield: Charles C Thomas; 1970. p. 905-19.
2. Aschoff JJ. Die Extremitäten als Effektoren der physikalischen Temperaturregulation. *Wiener Med Wochenschr* 1958; 19:404-9.
3. Aschoff JJ, editor. *Temperaturregulation. Energiehaushalt und Temperaturregulation [Energy budget and temperature regulation] [in German]*. München: Urban & Schwarzenberg; 1971.
4. Aschoff JJ, Wever R. Kern und Schale im Wärmehaushalt des Menschen [Core and Shell in human energy budget]. *Naturwissenschaften* 1958; 45:477-85.
5. Hales JRS, editor. *Skin arteriovenous anastomoses, their control and role in thermoregulation. Cardiovascular shunts*. Copenhagen: Munksgaard; 1985.
6. Van Someren EJW. More than a marker: Interaction between the circadian regulation of temperature and sleep, age-related changes, and treatment possibilities. *Chronobiol Int* 2000; 17:313-54.
7. Krauchi K, Wirz-Justice A. Circadian rhythm of heat production, heart rate, and skin and core temperature under unmasking conditions in men. *Am J Physiol* 1994; 267:R819-R29.
8. Mekjavik IB, Eiken O. Contribution of thermal and nonthermal factors to the regulation of body temperature in humans. *J Appl Physiol* 2006; 100:2065-72.
9. Duffy JF, Dijk D, Klerman EB, Czeisler CA. Later endogenous circadian temperature nadir relative to an earlier wake time in older people. *Am J Physiol* 1998; 275:1478-87.
10. Campbell SS, Broughton RJ. Rapid decline in body temperature before sleep: fluffing the physiological pillow. *Chronobiol Int* 1994; 11:126-31.
11. Krauchi K, Wirz-Justice A. Circadian clues to sleep onset mechanisms. *Neuropharmacol* 2001; 25:S92-S6.
12. Brown CC. Toe temperature change: A measure of sleep onset? *Waking Sleeping* 1979; 3:353-9.
13. Krauchi K. The thermophysiological cascade leading to sleep initiation in relation to phase of entrainment. *Sleep Med Rev* 2007; 11:439-51.
14. Gompfer B, Bromundt V, Orgul S, Flammer J, Krauchi K. Phase relationship between skin temperature and sleep-wake rhythms in women with vascular dysregulation and controls under real-life conditions. *Chronobiol Int* 2010; 27:1778-9.
15. Rutkove SB, Veves A, Mitsa T, Nie R, Fogerson PM, Garmirian LP, et al. Impaired distal thermoregulation in diabetes and diabetic polyneuropathy. *Diabetes Care* 2009; 32:671-6.
16. Fronczek R, Raymann RJ, Overeem S, Romeijn N, van Dijk JG, Lammers GJ, et al. Manipulation of skin temperature improves nocturnal sleep in narcolepsy. *J Neurol Neurosurg Psychiatry* 2008; 79:1354-7.
17. Liao WC, Chiu MJ, Landis CA. A warm footbath before bedtime and sleep in older Taiwanese with sleep disturbance. *Res Nurse Health* 2008; 31:514-28.
18. Ebben MR, Spielman AJ. The effects of distal skin warming on sleep latency. *Int J Behav Med* 2006; 13:221-8.
19. Samsonov VA, Bol'shakova GM. Body temperature regulation in patients with eczema and neurodermatitis. *Vestn Dermatol Venerol* 1975; 6:25-9.
20. Levin MM, Loseva VA. Temperature index of circulation in patients with eczema. *Vestn Dermatol Venerol* 1974; 2:32-5.
21. Howe AS, Boden B. Heat related illness in athletes. , 35, . *Am J Sports Med* 2007; 35.

22. Heyer G, Ulmer FJ, Schmitz J, Handwerker HO. Histamine-induced itch and alopecia (itchy skin) in atopic eczema patients and controls. *Acta Derm Venereol* 1995; 75:348-52.
23. Langan SM, Bourke JF, Silcocks P, Williams HC. An exploratory prospective observational study of environmental factors exacerbating atopic eczema in children. *Br J Dermatol* 2006; 154:979-80.
24. Weiland SK, Husing A, Strachan DP, Rzehak P, Pearce N, Group IPOS. Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. *Occup Environ Med* 2004; 61:609-15.
25. Kramer U, Weidinger S, Darsow U, Mohrenschrager M, Ring J, Behrendt H. Seasonality in symptom severity influenced by temperature or grass pollen: results of a panel study in children with eczema. *J Invest Dermatol* 2005; 124:514-23.
26. Beltrani VS. Managing atopic dermatitis. *Dermatol Nurs* 1999; 11:171-6, 9-85; quiz 86-7.
27. Bartlett LB, Westbrook R, White JE. Sleep patterns in children with atopic eczema. *Acta Derm Venereol* 1997; 77:446-8.
28. Willinger M, Chia-Wen K, Hoffman HJ, Kessler RC, Conwin MJ. Trends in infant bed sharing in the United States, 1993-2000 *Arch Pediatr Adolesc Med* 2003; 157:43-9.
29. Chamlin SL, Mattson CL, Frieden IJ, Williams ML, Mancini AJ, Cella D, et al. The price of pruritus: sleep disturbance and cosleeping in atopic dermatitis. *Arch Pediatr Adolesc Med* 2005; 159:745-50.
30. Tuffnell CS, Petersen SA, Wailoo MP. Higher rectal temperatures in co-sleeping infants. *Arch Dis Child* 1996; 75:249-50.
31. Molloy HF, Lamont-Gregory E, Idzikowski C, Ryan TJ. Overheating in bed as an important factor in many common dermatoses. *Int J Dermatol* 1993; 32:668-72.
32. Ebata T, Aizawa H, Kamide R, Niimura M. The characteristics of nocturnal scratching in adults with atopic dermatitis. *Br J Dermatol* 1999; 141:82-6.
33. Hon KL, Lam MC, Leung TF, Kam WY, Lee KC, Li MC, et al. Nocturnal wrist movements are correlated with objective clinical scores and plasma chemokine levels in children with atopic dermatitis. *Br J Dermatol* 2006; 154:629-35.
34. Heyer G, Schonberger A, Hornstein OP. Disorders of thermoregulation in adaptation to external cold and heat stimuli in patients with atopic eczema. *Hautarzt* 1988; 39:18-22.
35. Hon KL, Leung TF, Ma KC, Li AM, Wong Y, Yin JA, et al. Resting energy expenditure, oxygen consumption and carbon dioxide production during sleep in children with atopic dermatitis. *J Dermatolog Treat* 2005; 16:22-5.

Chapter 6: Sleep and daytime functioning in eczematous children:

Polysomnography and neurocognitive testing.

6.1 Sleep and Neurocognition

Neurological maturation and a developing sleep-wake system are closely linked in early human development.^{1,2} Infants sleep approximately 16 to 18 hours a day which is more than at any other time in the human lifespan. Infancy is also strongly associated with synaptic plasticity and the rapid development of neural networks. Primary control of the circadian sleep-wake system is located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus which continues to develop throughout the first year of life.^{3,4} Sleep-wake patterns and the consolidation of nocturnal sleep also evolve quickly during this period and are noted as major developmental and health concerns.^{5,6} Associations between sleep quality and cognitive ability are further evident in this early stage of life.^{7,8} Mental performance at 52 weeks of age has been reported to be predicted by the stability and length of a sustained sleep period,⁸ whereas poor quality, fragmented sleep in infants has been associated with lower mental development.⁷

A toddler sleeps less than an infant and requires about 12 to 14 hours sleep a day, which includes a 1-1½ hour afternoon nap. Additional developmental changes include a more established sleep-wake cycle with longer periods of sustained nocturnal sleep and longer periods of sustained wakefulness in the daytime. Healthy toddlers are far more physically active than infants and their sleeping behaviour and the timing of their sleep cycles reflect their maturing central nervous system.⁹ Sleep disturbance in toddlers has been associated with behavioural and cognitive deficits. Touchette et al.¹⁰ report that children with short nocturnal sleep duration before 3.5 years of age have an increased risk of high hyperactivity-impulsivity scores and low cognitive performance at 6 years of age. Bates et al.¹¹ study on

preschool children report that disrupted sleep patterns predicted poorer behavioural adjustment to attending preschool. Finally, Minde et al.¹² report that therapeutic intervention which improved toddlers sleep was associated with improvements in daytime behaviour.

School-age children require approximately eight to ten hours of sleep. At this stage, sleep is well consolidated into a day and night sleep-wake pattern. 75% of an individual's neurological growth, peaking with a neural network density of about 1000 trillion connections, has taken place in the first 6 years of life. Beginning at about 11 years of age, the overall number of neural connections are reduced while some connections are strengthened in a discriminatory process often described as "use it or lose it".¹³ Cognitive ability and behaviour in school-age children are reported to be associated with sleep quality. Studies on school aged children have reported links between poor sleep and cognitive deficits,^{14, 15} lower academic performance,¹⁶ inattention^{17, 18} and a higher incidence of behavioural problems.^{19, 20}

Specific sleep stage also appears to have distinct connections with cognitive attributes. In particular, REM sleep appears to have a strong functional relationship with learning and memory. REM sleep is reported to increase following a learning task or exposure to an "enriched" environment known to trigger synaptic remodelling.^{21, 22} Further, REM sleep is related to acetylcholine (Ach) release,²³ a neurotransmitter that influences neural development²⁴ and synaptic remodelling.²⁵ NREM sleep has also been reported to be associated with cognitive development. Slow wave sleep is associated with reorganisation/specification of neuronal circuits for synapse plasticity occurs²⁶ and is further reported to play a role in the consolidation of memories acquired during wakefulness.²⁷

6.2 Neurocognitive deficits, co-morbid disorders and sleep disturbance in eczematous children

Children with eczema are commonly reported to have disrupted sleep.²⁸⁻³⁴ Consequently, it is likely that neurocognitive deficits associated with poor sleep in non-eczema children may also be present in this patient group. However, the neurocognitive performance of children with eczema has yet to be assessed. A major obstacle in assessing the relationship between eczema, sleep quality and neurocognitive performance in children with eczema is the high incidence of co-morbid disorders, such as rhinitis and asthma, which are also reported to disturb sleep,³⁵⁻³⁷ and are also associated with cognitive deficits^{38, 39} and a higher incidence of behavioural problems.^{40, 41}

Children with eczema are also reported to have an increased risk of sleep disordered breathing.⁴²⁻⁴⁴ Sleep disordered breathing ranges in severity from primary snoring through to complete upper airway obstruction with associated hypoxia and frequent respiratory-related arousals from sleep.⁴⁵ Children with primary snoring are reported to have lower academic performance,⁴⁶ a higher incidence of psychosocial dysfunction⁴⁷ and lower cognitive performance.⁴⁸ In children with sleep disordered breathing, sleep fragmentation has been associated with increased psychosocial deficits,⁴⁹ learning problems⁵⁰ and reduced intelligence,⁴⁹⁻⁵¹ memory,^{52, 53} attentional capacity^{49, 52, 54} and academic performance;⁵⁵ while nocturnal hypoxia secondary to upper airway obstruction has been associated with delayed motor development,⁵⁶ reduced IQ,⁵⁷⁻⁵⁹ reduced attentional capacity^{59, 60} and ADHD symptoms.^{61, 62}

6.3 Rationale for examining the neurocognitive profile of children with eczema and possible associations with their sleep quality.

The aims of the present study are to compare the neurocognitive profile of children with

eczema to controls and further, to examine the relationship between eczema, sleep and neurocognitive performance in eczematous children. In addition, children with eczema are reported to have a higher prevalence of asthma, allergic rhinitis and snoring, all of which are associated neurocognitive deficits. Hence, asthma, rhinitis and snoring needs to be accounted for to evaluate the contribution of eczema on neurocognitive performance.

6.4 Method

In addition to the method outlined in Chapter 2 for the behavioural measures (Conner's Parent Rating Scale – Revised (S)) and Chapter 3 for polysomnography, the following additional measures and procedures were undertaken to examine the neurocognitive ability of children with eczema and its relationship to sleep disturbance in this patient group.

Children recruited into the study underwent one night of polysomnography (PSG) on a non-school day at the Adelaide Women's and Children's Sleep Disorder Unit, followed by neurocognitive testing in the morning. Testing was undertaken in 60-90 minutes bouts to minimise subject fatigue. Children were accompanied by a parent/caregiver who completed behavioural-related questionnaires during the study.

6.4.1 Neurocognitive assessment

The Wechsler Intelligence Scale for Children (WISC-IV)⁶³ standardised for subjects 6-16y was used to measure cognitive ability and estimate IQ. This well-recognised, standardised and normed test provides measures of knowledge, verbal ability, problem solving and memory. The scale comprises of ten core subtests and five supplemental subtests. The supplemental subtests are used to accommodate children in certain rare cases, or to make up for spoiled results which may occur from interruptions or other circumstances. The ten core subtests are used to generate a Full Scale intelligence (IQ) score (FSIQ) as well as four

composite indices: Verbal Comprehension (VCI), Perceptual Reasoning (PR), Processing Speed (PSI) and Working Memory (WMI). Verbal Comprehension assesses children's ability to listen to a question, draw upon learned information from both formal and informal education, reason through an answer, and express their thoughts aloud. Perceptual Reasoning assesses children's ability to examine a problem, draw upon visual-motor and visual-spatial skills, organize their thoughts, create solutions, and then test them. Processing Speed Index assesses children's abilities to focus attention and, as well, to quickly scan and discriminate and sequentially order visual information. Success on the Processing Speed Index subtests requires persistence and planning ability, but is sensitive to motivation, difficulty working under a time pressure, and motor coordination. Finally, Working Memory assesses children's ability to memorize new information, hold it in short-term memory, concentrate, and manipulate that information to produce some result or reasoning processes. It is further important in higher-order thinking, learning, and achievement.

6.4.2 Attention assessment

The Auditory Continuous Performance Test (ACPT) was used to assess attention.⁶⁴ In this test, subjects listen to a tape consisting of a sequence of 96 words, given six times. Within each sequence, the word “dog” is given 20 times to which the subject is to respond by raising their thumb. Three measures were derived from ACPT scores; Inattention errors i.e. the number of missed responses to “dog”, Impulsivity errors i.e. the number of responses to words other than “dog” and Attention i.e. the total error score. Higher ACPT scores indicate poorer performance and the clinical cut-offs are age normed. Only eczematous children were able to be assessed with this measure. Only eczematous children under 12 years of age were tested with this measure.

6.4.3 Reading Age

Standardised reading tests provide a summation or picture of children's reading progress including decoding, word recognition, accuracy, comprehension and fluency. The Schonell Graded Word Reading Test⁶⁵ was used to estimate reading age.^{65, 66} This widely used standardised and normed test requires the child to read out loud from a list of 100 words.⁶⁶ The first words of the list are simple, such as "tree" and "egg", with the degree of difficulty increasing throughout the list towards words such as "bibliography" and "idiosyncrasy". A 100% correct score give the child a reading age of 15 years of age. Only eczematous children under 15 years of age were tested with this measure.

6.4.4 Snoring

Snoring was measured through parental response to the following question. "How often does your child snore during sleep?" The parent responded to the question on a five point scale; 1 = Never, 2 = Occasionally, 3 = Sometimes, 4 = Often and 5 = Always.

6.5 Results

6.5.1 Group Comparisons between eczema children and controls on snoring, atopic disorders and sleep variables (see Table 6.1).

Eczematous children had a significantly higher frequency of snoring and higher prevalence of rhinitis than controls. Because of their associations with poor sleep, snoring⁴²⁻⁴⁴ and rhinitis^{36, 37, 45, 67-77} was co varied for in subsequent analyses between groups.

6.5.2 Comparison of neurocognition variables between eczema and control groups.

WISC-IV: Eczema children had a significantly lower Full Scale IQ scores and significantly lower composite indices of Verbal Comprehension and Perceptual Reasoning scores than

controls. In addition, eczema children had significantly lower WISC-IV subtest scores of word reasoning, similarities, picture concepts and letter-number sequencing than controls.

6.5.3 Relationship between eczema, behaviour and neurocognition among children with eczema (see Table 6.2).

Atopic Disease: Based on suggested SCORAD criteria for classification of disease severity:^{78, 79} mild < 15; moderate 15-40; and severe > 40; 5/24, (21%) of children with eczema were classified as having mild eczema, 12/24 (50%) moderate eczema and 7/24 (29%) severe eczema. In children with eczema 16/24 (67%) had LTE₄ levels > 100pg/mg. 10/24 (42%) of eczematous children also reported having asthma and of these 8/10 (80%) had LTE₄ levels > 100pg/mg, while 11/24 (46%) of eczematous children also reported having rhinitis and of these 9/11 (82%) had LTE₄ levels > 100pg/mg. A further 7/24 (29%) of children with eczema also reported having both rhinitis and asthma and of these 7/7 (100%) had elevated Leukotriene E₄ levels > 100pg/mg.

Behaviour: Examination of the percentage of children above the clinical cut-off (T-score > 70) on the Conner's Parent Rating Scale – Revised (S) revealed a higher percentage of children with eczema with elevated Oppositional behaviour 5/24 (21%) vs. 2/19 (11%) but similar Cognitive problems/Inattention 3/24 (13%) vs. 3/19 (16%); Hyperactivity 3/24 (13%) vs. 3/19 (16%) and ADHD Index 4/24 (17%) vs. 3/19 (16%) scores.

Auditory Continuous Performance Test – Attentional variables were co-varied for age. 4/22 (17 %) of eczema subjects achieved Attention scores of clinical concern (2 eczema subjects were over the age specified for the test and were not included in this analyses). Schonell Graded Word Reading Test – Reading ability was co-varied for age.

6.5.4 Correlations between eczema, behaviour and neurocognitive variables among children, controlling for snoring and co morbid atopic disease disturbing sleep (see Table 6.2).

A higher SCORAD (Full Score) was associated with higher ratings of Oppositional behaviours. A higher SCORAD (Full Score) was also associated with lower Reading Ability.

6.5.5 Correlations between polysomnography variables and behavioural ratings of eczematous children, controlling for the frequency of snoring and the frequency that co morbid atopic disease disturbed sleep (see Table 6.3).

A higher Sleep Efficiency was associated with a lower ratings of Oppositional behaviour. A longer Sleep Onset Latency was associated with higher behavioural ratings of Hyperactivity, ADHD Index scores and Oppositional behaviour (see Figures 6.1, 6.2 & 6.3). A lower percentage of REM sleep was associated with higher ratings of Oppositional behaviour.

6.5.6 Correlations between polysomnography and neurocognitive variables of eczematous children, controlling for frequency of snoring and the frequency that co morbid atopic disease disturbed sleep (see Table 6.4).

A longer Sleep Onset Latency was associated with lower Verbal Comprehension scores. A higher percentage of Stage 2 Sleep was associated with lower Processing Speed scores. A higher percentage of Stage 4 Sleep was associated with a higher Processing Speed scores.

Table 6.1: Mean (SD) of frequency of snoring, atopic disease and sleep scores for children with eczema and controls together with F-test/Chi-square results (statistically significant results are bolded).

	Mean (SD) and subject ratio for chi-square		F-test and chi-square (X^2) results
	Eczema (n = 24)	Control (n =19)	
Snoring	2.3 (1.5)	1.1 (0.2)	F= 13.4***
Atopic Disease			
Incidence of Asthma	10/14	4/15	(X^2) = 2.1
Incidence of Rhinitis	11/13	2/17	(X^2) = 6.3*
The following variables were co-varied for frequency of Snoring and subjects having Rhinitis			
Conner's Parent Rating Scale – Revised (S)			
Cognitive problems/Inattention	56.3 (11.2)	50.6 (12.4)	F = 2.0
Hyperactivity	59.6 (13.8)	52.2 (12.2)	F = 1.0
ADHD Index	60.1 (11.4)	51.7 (13.1)	F = 3.1
Oppositional Behaviour	60.0 (12.1)	51.8 (9.0)	F = 3.5‡
WISC-IV Australian Language Adaptation			
Full Scale IQ	92.2 (15.7)	108.8 (10.1)	F = 5.7*
Verbal Comprehension	92.3 (13.6)	106.2 (10.9)	F = 3.7‡
Vocabulary	8.7 (3.0)	10.2 (2.4)	F = 1.3
Comprehension	8.4 (3.3)	11.2 (2.9)	F = 1.1
Word Reasoning	8.0 (2.7)	12.2 (2.6)	F = 11.6***
Similarities	9.1 (2.6)	12.2 (2.1)	F = 7.1*
Information	8.4 (3.5)	11.1 (2.5)	F = 2.9
Perceptual Reasoning	93.8 (14.9)	110.8 (12.5)	F = 5.7*
Block Design	9.8 (2.4)	12.3 (3.0)	F = 3.2
Picture Concepts	8.0 (3.1)	11.1 (3.0)	F = 4.6*
Matrix Reasoning	9.1 (3.7)	11.8 (2.1)	F = 2.4
Picture Completion	8.6 (4.1)	11.2 (2.4)	F = 1.7
Working Memory	90.2 (17.6)	103.2 (12.8)	F = 2.4
Digit Span	9.3 (3.1)	9.8 (3.0)	F = 0.0
Letter-Number Sequencing	7.4 (4.0)	11.5 (2.0)	F = 7.9***
Arithmetic	8.7 (3.3)	11.0 (2.9)	F = 0.4
Processing Speed	99.7 (14.6)	105.0 (11.1)	F = 1.0
Coding	10.0 (3.2)	10.0 (2.6)	F = 0.0
Symbol Search	9.8 (2.9)	11.6 (2.5)	F = 2.8
Cancellation	8.6 (2.6)	10.4 (3.6)	F = 2.1

Nb ‡denotes $p < .08$, * $p < .05$, ** $p < .01$, *** $p < .005$ and**** $p < .001$.

Table 6.2: Correlation matrix: Eczema, Behaviour, IQ, Attention and Reading Age variables of children with eczema co-varied for frequency of snoring, frequency that asthma disturbed sleep in the last 12 months and frequency that rhinitis disturbed sleep in the last 12 months (significant correlations are bolded) (n=24).

	SCORAD – VAS of Itch severity rating	SCORAD – VAS of Sleep loss in the last 3 days	SCORAD (Full Score)	Leukotriene E ₄
Conner's Parent Rating Scale – Revised (S)				
Cognitive problems/Inattention	.31	.20	.24	.25
Hyperactivity	-.28	-.24	.04	
ADHD Index	.12	.20	.33	
Oppositional behaviour	.23	.42	.46‡	.09
WISC – IV Australian Language Adaptation				
Full Scale IQ	-.04	-.10	-.32	.06
Verbal Comprehension	.04	-.02	-.34	.28
Vocabulary	.05	.08	-.26	.07
Comprehension	-.01	-.17	-.29	.40
Word Reasoning	-.06	-.16	-.25	.43
Similarities	.03	.09	-.30	.16
Information	.15	.01	-.01	.15
Perceptual Reasoning	-.04	-.13	-.23	.03
Block Design	-.15	-.16	-.11	.07
Picture Concepts	.10	-.05	-.20	-.04
Matrix Reasoning	-.11	-.12	-.19	.04
Picture Completion	.04	-.11	-.18	.05
Working Memory	.01	-.08	-.24	.02
Digit Span	-.02	-.11	-.20	.08
Letter-Number Sequencing	.03	-.05	-.21	-.03
Arithmetic	.09	.05	-.05	.08
Processing Speed	-.11	-.10	-.21	-.12
Coding	-.29	-.33	-.25	-.18
Symbol Search	.14	.18	-.12	.02
Cancellation	-.08	-.18	.16	.06
Auditory Continuous Performance Test also co-varied for age (n = 22)				
Inattention	-.04	.17	.42	-.37
Impulsivity	-.25	-.44	-.17	-.40
Attention total score	-.10	.04	.32	-.43
Schonell Graded Word Reading Test also co- varied for age				
Reading Ability	.15	-.11	-.51*	-.08

Nb ‡denotes $p < .08$, * $p < .05$, ** $p < .01$, *** $p < .005$ and **** $p < .001$.

Table 6.3: Correlation matrix of the sleep and behavioural variables of children with eczema co-varied for frequency of snoring, frequency that asthma disturbed sleep in the last 12 months and frequency that rhinitis disturbed sleep in the last 12 months. (n = (24) (significant correlations are bolded).

	Total Sleep Time	Sleep Efficiency	Sleep Onset Latency	REM onset latency (min)	% Stage 1	% Stage 2	% Stage 3	% Stage 4	% Slow Wave Sleep	% REM	No. of Stage Shifts	Arousals in Total Sleep Time	Wake After Sleep Onset (min)	Obstructive Apnoea Hypopnoea Index	Central Apnoea Index
Conner's Parent Rating Scale – Revised (S)															
Cognitive problems/Inattention	-0.19	-0.31	.16	.21	-0.12	.36	-0.16	-0.21	-0.21	-0.24	-0.24	-0.12	.14	.25	.02
Hyperactivity	-0.30	-0.37	.69***	.16	.09	-0.01	-0.16	.10	.04	-0.12	-0.32	-0.06	-0.35	.18	-0.11
ADHD Index	-0.21	-0.27	.51*	.07	.03	.35	-0.21	-0.25	-0.26	-0.28	-0.24	-0.25	-0.14	.36	-0.03
Oppositional behaviour	-0.34	-.41‡	.67**	.14	.10	.37	-0.09	-0.17	-0.16	-.54*	-0.30	-0.24	-0.08	.23	.03

Nb ‡denotes $p < .08$, * $p < .05$, ** $p < .01$, *** $p < .005$ and **** $p < .001$.

Figure 6.1: Scatterplot of Hyperactivity and Sleep Onset Latency (minutes) in children with eczema. (n = 24)

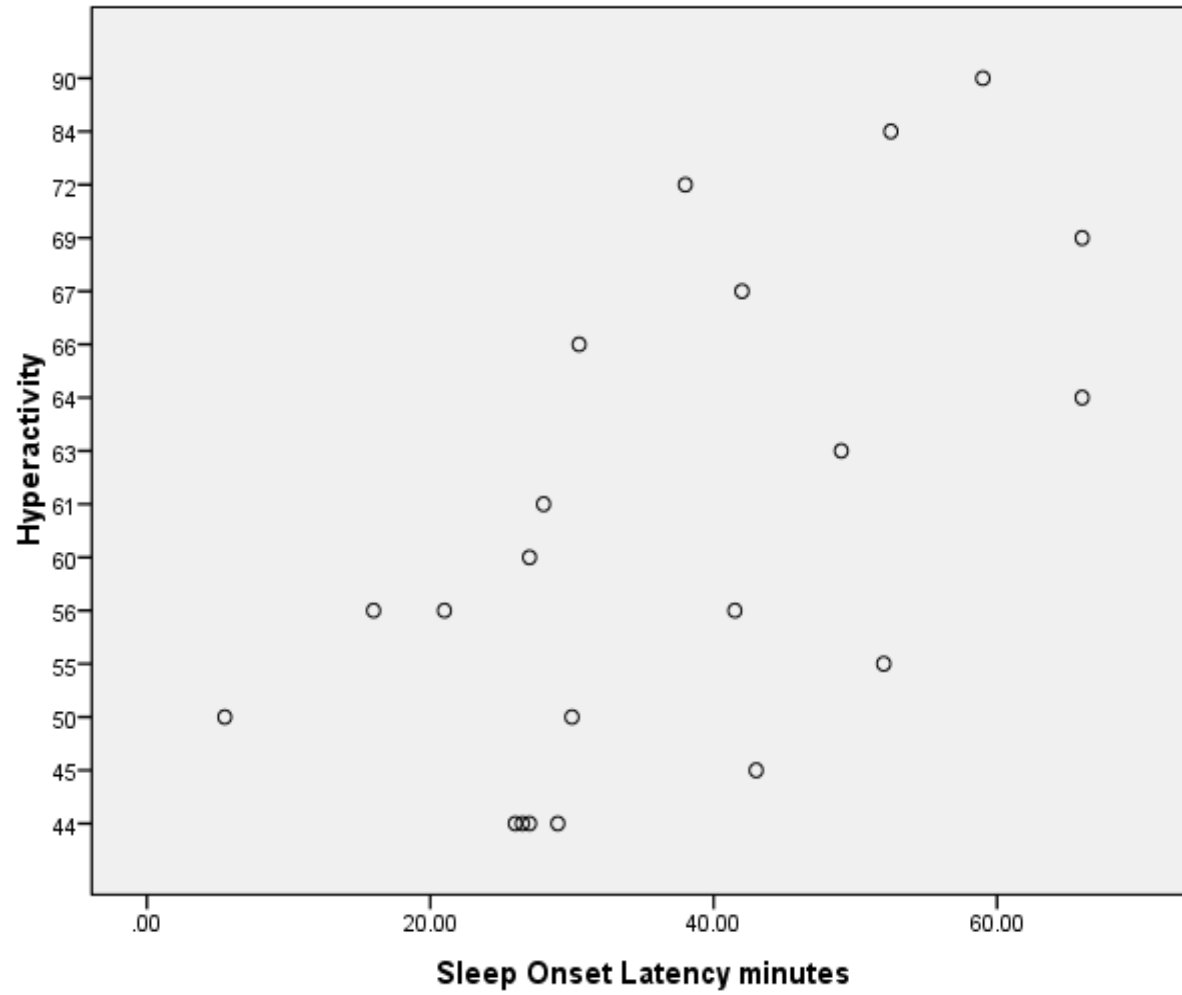


Figure 6.2: Scatterplot of ADHD Index and Sleep Onset Latency (minutes) in children with eczema. (n = 24)

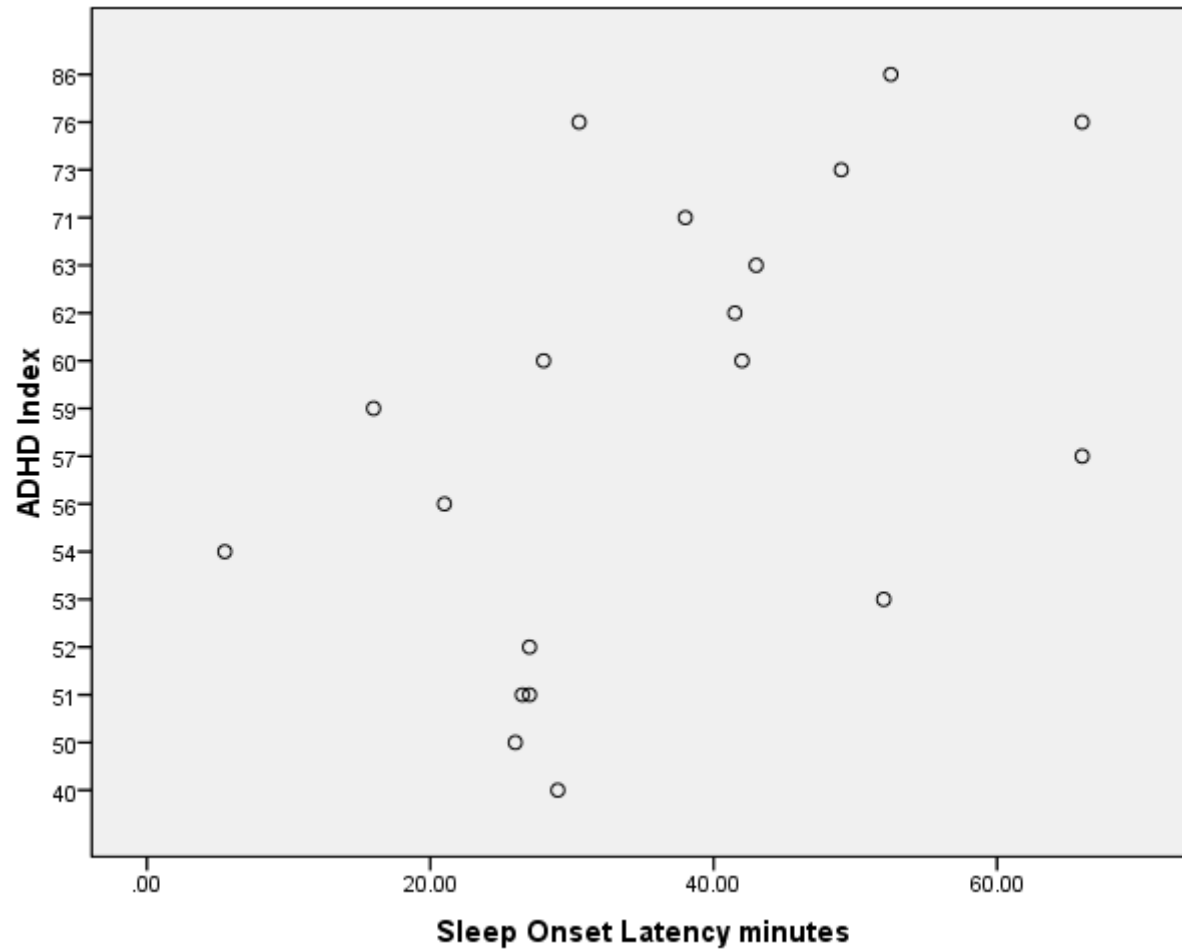


Figure 6.3: Scatterplot of Oppositional behaviour and Sleep Onset Latency (minutes) in children with eczema. (n = 24)

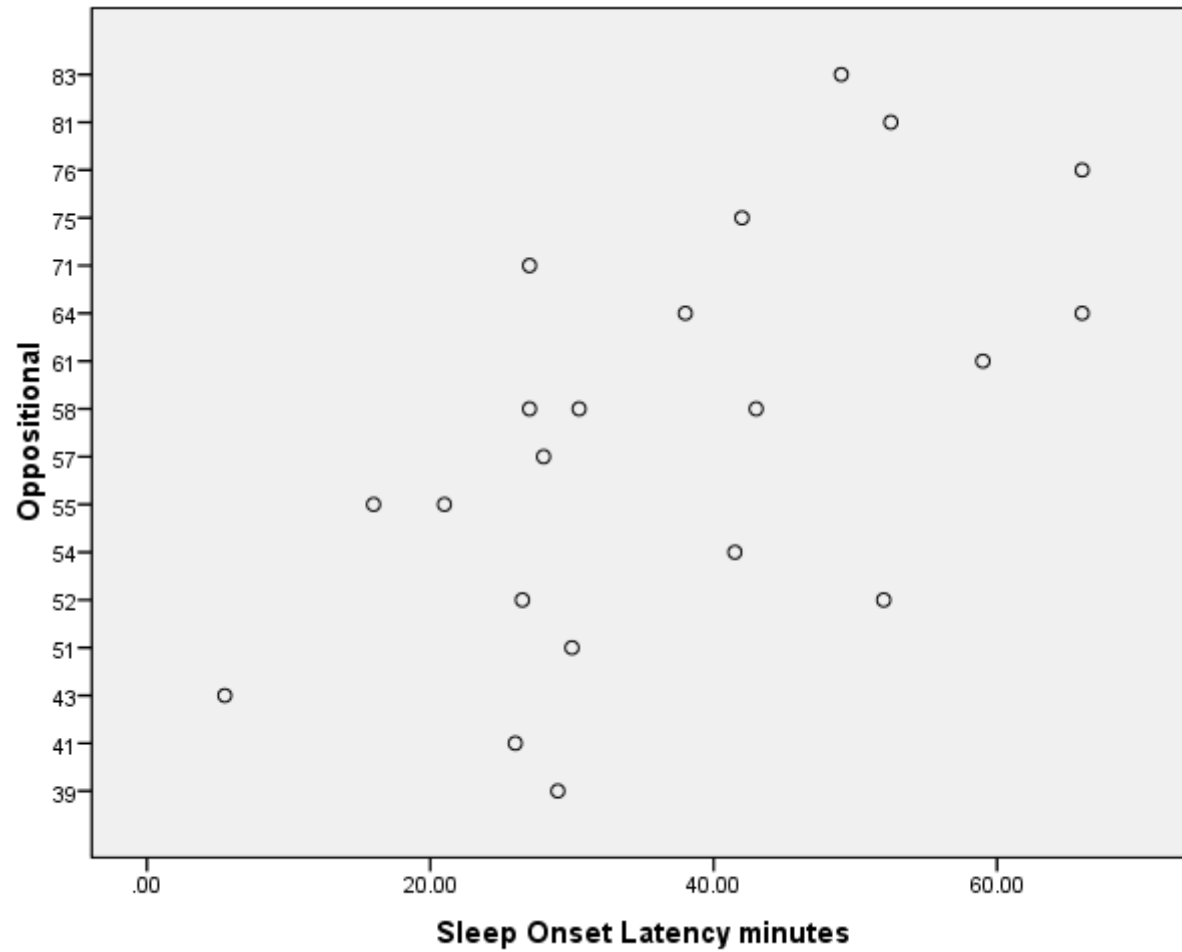


Table 6.4: Correlation matrix of the sleep and neurocognitive variables of children with eczema co-varied for frequency of snoring, frequency that asthma disturbed sleep in the last 12 months and frequency that rhinitis disturbed sleep in the last 12 months. Attention Total Score and Reading ability are also controlled for age. (n = (24) (significant correlations are bolded).

	Total Sleep Time	Sleep Efficiency	Sleep Onset Latency	REM onset latency (min)	% Stage 1	% Stage 2	% Stage 3	% Stage 4	% Slow Wave Sleep	% REM	No. of Stage Shifts	Arousals in Total Sleep Time	Wake After Sleep Onset (min)	Obstructive Apnoea Hypopnoea Index	Central Apnoea Index
Full Scale IQ	.18	.07	-.35	-.31	.26	-.30	-.19	.11	.04	.28	.31	.21	.06	.20	.04
Verbal Comprehension	.38	.23	-.48*	-.23	.22	-.04	-.33	-.12	-.18	.18	.25	.18	.30	.13	.15
Perceptual Reasoning	-.01	-.01	-.03	-.31	.34	-.25	-.13	.00	-.04	.24	.19	-.01	.08	.24	-.15
Processing Speed	.14	-.06	-.41	-.26	-.05	-.42‡	-.02	.47*	.38	.23	.29	.11	-.06	.14	-.12
Working Memory	.03	-.05	-.33	-.20	.29	-.26	-.12	.09	.04	.18	.29	.34	-.05	.07	.20
Auditory Continuous Performance Test also co-varied for age (n = 22)															
Attention Total Score	.04	.24	.25	.31	.25	.02	-.30	-.22	-.26	.14	.06	-.07	-.28	.02	-.07
Schonell Graded Word Reading Test also co-varied for age															
Reading Ability	.41	.25	-.17	-.25	.01	-.26	-.12	.26	.18	.19	.04	.18	-.12	.12	-.03

Nb ‡denotes $p < .08$, * $p < .05$, ** $p < .01$, *** $p < .005$ and **** $p < .001$.

6.6 Discussion

In this study, children with eczema demonstrated that they had a higher incidence of behavioural problems than controls, particularly within the index of Oppositional behaviour. This finding was expected, considering that this group of eczematous children also participated in a larger questionnaire study which found a higher incidence of Oppositional behaviour (see Chapter 2). However, in this study the behavioural measures were examined for their association to a more comprehensive eczema rating scale and to polysomnographic sleep variables. Within this context, an association between behaviour and eczema severity was found with higher eczema severity ratings having a significant moderate relationship to higher Oppositional behaviour ratings. Among polysomnographic variables, a lower Sleep Efficiency was also associated with higher Oppositional behaviour. Of note, Sleep Onset Latency appears to have a strong relationship with behavioural outcomes (see Figure 6.1, 6.2 & 6.3). A longer Sleep Onset Latency was associated with higher Hyperactivity, a higher ADHD Index and higher Oppositional ratings. A lower percentage of REM sleep was also associated with higher Oppositional ratings. This could be interpreted as those children with more severe eczema, had more difficulty in getting to sleep, had poorer sleep quality, less REM and produced secondary deficits in the form of behavioural problems, such as being defiant, losing their temper easily and being irritable.

In addition, the neurocognitive profile of children with eczema was distinctly different from that of control children. Eczematous children's Full Scale IQ scores averaged a substantial 8 points lower than published aged normed peers⁶³ and 16 points lower than our healthy controls. While our controls performed slightly above aged normed peers, this is to be expected once sources of morbidity were screened out using exclusion criteria for physical and psychological disorders.⁸⁰ In general, eczematous children scored lower on tasks within

the composite indices of Verbal Comprehension and Perceptual Reasoning. Verbal Comprehension assessed children's ability to listen to a question, draw upon learned information and reason through the problem to construct a verbal answer, whereas Perceptual Reasoning assessed children's ability to examine a problem, draw upon visual-motor and visual-spatial skills and create solutions. An examination of the unmediated relationship between eczema severity and neurocognitive performance in children did not reveal any statistically significant outcomes, however, trends indicate that higher SCORAD (Full Score) ratings were also associated with lower Verbal Comprehension and lower Perceptual Reasoning scores. The sleep architecture of eczematous children was further found to be related to their neurocognitive profile. A longer Sleep Onset Latency was associated with reduced Verbal Comprehension scores and higher percentage of Stage 2 sleep was associated with reduced Processing Speed scores. In addition, a lower percentage of Stage 4 sleep was further found to be associated with lower Processing Speed scores. In general, among all of the polysomnographic sleep variables tested, trends indicated that a greater Sleep Onset Latency, a greater REM Onset Latency and a higher percentage of Stage 2 sleep, were generally associated with lower scores on WISC-IV measures.

Attention testing also appears to be related to eczema severity with lower Attention ability moderately associated with higher SCORAD (Full Score) ratings. Contrary to this finding was the discovery that higher Leukotriene E4 levels, which are indicative of atopic inflammation, was moderately related to a higher Attention ability. The association between Attention ability and polysomnography sleep variables were generally of a mild to moderate strength, further indicating that poor Attention was associated with a longer Sleep Onset Latency, a longer REM Onset latency, less Slow Wave Sleep and less REM sleep. In summary, Attention ability appears to be negatively affected by childhood eczema and also appears to be related to the sleep architecture of eczematous children.

Reading ability was further found to be significantly associated with eczema severity. When the relationship between Reading ability and polysomnographic variables were examined, a moderate relationship was found between higher Reading ability and more Total Sleep Time. Mild associations were also detected between a higher Reading ability and the following polysomnographic variables; a higher Sleep Efficiency, a shorter Sleep Onset latency, a shorter REM Onset latency, less Stage 2 sleep and more Stage 4 sleep. While it is understood that Reading Ability is in itself the composite of several abilities such as vocabulary, comprehension, spelling, short and long term memory, etc., this ability demonstrates how a fundamental task required by children in their schoolwork is affected by eczema and its secondary sleep deficits.

Children with eczema also presented with a high incidence of co-morbid disorders known to affect sleep quality and which are further associated with deficits in daytime functioning. Most notable was the higher frequency of snoring and higher incidence of rhinitis found among eczema children which needed to be co-varied for in subsequent between groups analyses. The co-morbid disorder of Sleep Disordered Breathing was also a particular concern for this study, largely due to a growing body of literature associating Sleep Disordered Breathing with neurocognitive deficits.⁴⁹⁻⁵⁵ However, apart from a higher frequency of snoring, none of the eczema or control children were found to have nocturnal respiratory disturbances or oxygen desaturation of clinical concern with all subjects were under the clinical cut-off used in this study of an OAH1 of less than 1 event per hour (see Chapter 3 for analyses of respiratory and sleep variables).

Future research on the sleep children with eczema and associated secondary neurocognitive deficits have the potential to answer many general queries in the field of sleep research. One of the pressing issues in current sleep research is trying to disentangle the neurocognitive

outcomes of sleep fragmentation from the neurocognitive outcomes of nocturnal hypoxia. Childhood eczema's impact on sleep may provide a useful model for exploring the affects of sleep disturbance on daytime functioning in contrast to Sleep Disordered Breathing where both sleep fragmentation and hypoxia are commonly present. Further queries may be answered as to how sleep disturbance during early human development affects neurocognitive outcomes. For example, further study on the sleep of eczematous children may resolve whether related neurocognitive deficits are only temporary and are amended once sleep quality is restored, or whether sleep disturbance produces developmental delays, or whether sleep disturbance produces permanent neurocognitive deficits, or a combination of all three.

In conclusion, children with eczema have demonstrated deficits in their behaviour and in their neurocognitive ability. Furthermore, our findings suggest that their poor neurocognitive performance is related to their sleep quality. As to whether improved sleep will also produce improvement in these areas is yet to be examined, however, some research on the effects of disturbed sleep during early child development indicates that neurocognitive deficits may not be totally reversible.¹⁴ In this context, it would be advantageous to prevent or reduce sleep disturbance in this group.

Bibliography

1. Dang-Vu TT, Desseilles M, Peigneux P, Maquet P. A role for sleep in brain plasticity. *Pediatr Rehabil* 2006; 9:98-118.
2. Mignot E. Why we sleep: the temporal organization of recovery. *PLoS Biol* 2008; 6.
3. Rivkees SA. Developing circadian rhythmicity in infants. *Pediatrics* 2003; 112:373-81.
4. Swaab DF. Development of the human hypothalamus. *Neurochem Res* 1995; 20:509-19.
5. Sadeh A. Development of the sleep-wake system and its relationship to children's psychosocial development. In: Tremblay RE, Barr RG, Peters RDV, eds. *Encyclopedia on Early Childhood Development*. Montreal, Quebec: Centre of Excellence for Early Childhood Development, 2003.
6. Anders TF, Halpern LF, Hua J. Sleeping through the night: a developmental perspective. *Pediatrics* 1992; 90:554-60.
7. Scher A. Infant sleep at 10 months of age as a window to cognitive development. *Early Human Development* 2005; 81:289-92.
8. Anders TF, Keener MA, Kraemer H. Sleep-wake state organization, neonatal assessment and development in premature infants during the first year of life II. *Sleep* 1985; 8:193-206.
9. Kinney HC, Brody BA, Kloman AS, Gilles FH. Sequence of central nervous system myelination in human infancy. II. Patterns of myelination in autopsied infants. *J Neuropathol Exp Neurol* 1988; 47:217-34.
10. Touchette E, Petit D, Tremblay RE, Montplaisir JY. Risk factors and consequences of early childhood dyssomnias: New perspectives. *Sleep Med Rev* 2009; 13:355-61.
11. Bates JE, Viken RJ, Alexander DB, Beyers J, Stockton L. Sleep and adjustment in preschool children: sleep diary reports by mothers relate to behavior reports by teachers. *Child Development* 2002; 73:62-74.
12. Minde K, Faucon A, Falkner S. Sleep problems in toddlers: effects of treatment on their daytime behavior. *J Am Acad Child Adolesc Psychiatry* 1994; 33:1114-21.
13. Siegel DJ. *The Developing Mind*. New York: Guilford Press; 1999.
14. Touchette E, Petit D, Seguin J, Boivin M, Tremblay R, Montplaisir J. Associations between sleep duration patterns and behavioral/cognitive functioning at school entry. *Sleep* 2007; 30:1213-9.
15. Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. *Nature* 2004; 430:78-81.
16. Buckhalt JA, El-Sheikh M, Keller PS, Kelly RJ. Concurrent and longitudinal relations between children's sleep and cognitive functioning: the moderating role of parent education. *Child Development* 2009; 80:875-92.
17. Willoughby MT, Angold A, Egger HL. Parent-reported attention-deficit/hyperactivity disorder symptomatology and sleep problems in a preschool-age pediatric clinic sample. *J Am Acad Child Adolesc Psychiatry* 2008; 47:1086-94.
18. Hiscock H, Canterford L, Ukomunne OC, Wake M. Adverse associations of sleep problems in Australian preschoolers: national population study. *Pediatrics* 2007; 119:86-93.
19. Sadeh A, Gruber R, Raviv A. Sleep, neurobehavioral functioning, and behavior problems in school-age children. *Child Development* 2002; 73:403-17.
20. Randazzo AC, Muehlbach MJ, Schweitzer PK, Walsh JK. Cognitive function following acute sleep restriction in children ages 10-14. *Sleep* 1998; 21:861-8.
21. Mandai O, Guerrien A, Sockeel P, Lecomte P. REM sleep modifications following a Morse code learning session in humans. *Physiology and Behaviour* 1989; 46.
22. Smith C, Lapp L. Increases in number of REMs and REM density in humans following

- an intensive learning period. *Sleep* 1991; 14.
23. Jones BE. Paradoxical sleep and its chemical/structural substrates in the brain. *Neuroscience* 1990; 40.
 24. Lauder JM. Morphogenetic roles of acetylcholine. *Environmental Health Perspectives* 1999; 107:65-9.
 25. Rasmusson DD. The role of acetylcholine in cortical synaptic plasticity. *Behavioural Brain Research* 2000; 115:205-18.
 26. Boselli M, Parrino L, Smerieri A, Terzano MG. Effect of age on EEG arousals in normal sleep. *Sleep* 1998; 21:351-7.
 27. Steriade M, Timofeev I. Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. *Neuron* 2003; 37:563-76.
 28. Dahl RE, Bernhisel-Broadbent J, Scanlon-Holdford S, Sampson HA, Lupo M. Sleep disturbances in children with atopic dermatitis. *Arch Pediatr Adolesc Med* 1995; 149:856-60.
 29. Aoki T, Kushimoto H, Hishikawa Y, Savin JA. Nocturnal scratching and its relationship to the disturbed sleep of itchy subjects. *Clin Exp Dermatol* 1991; 16:268-72.
 30. Bartlett LB, Westbrook R, White JE. Sleep patterns in children with atopic eczema. *Acta Derm Venereol* 1997; 77:446-8.
 31. Chamlin SL, Mattson CL, Frieden IJ, Williams ML, Mancini AJ, Cella D, et al. The price of pruritus: sleep disturbance and cosleeping in atopic dermatitis. *Arch Pediatr Adolesc Med* 2005; 159:745-50.
 32. Reid P, Lewis-Jones MS. Sleep difficulties and their management in preschoolers with atopic eczema. *Clin Exp Dermatol* 1995; 20:38-41.
 33. Zar HJ, Ehrlich RI, Workman L, Weinberg EG. The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. *Pediatr Allergy Immunol* 2007; 18:560-5.
 34. Vlasky E, Stavric K, Isjanovska R, Seckova L, Kimovska M. Overweight hypothesis in asthma and eczema in young adolescents. *Allergol Immunopathol* 2006; 34:199-205.
 35. Ricci G, Patrizzi A, Baldi E, Menna G, Tabanalelli M, Masi M. Long term follow up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. *J Am Acad Dermatol* 2006; 107:567-74.
 36. Syabbalo N. Chronobiology and chronopathophysiology of nocturnal asthma. *Int J Clin Pract* 1997; 51:455-62.
 37. Shedden A. Impact of nasal congestion on quality of life and work productivity in allergic rhinitis. *Treat Respir Med* 2005; 4:439-46.
 38. Diette GB, Markson L, Skinner EA, Nguyen TT, Algatt-Bergstrom P, Wu AW. Nocturnal Asthma in children affects school attendance, school performance, and parents' work attendance. *Arch Pediatr Adolesc Med* 2000; 154:923-8.
 39. Brawley A, Silverman B, Kearney S, Guanzon D, Owens M, Bennett H, et al. Allergic rhinitis in children with attention-deficit/hyperactivity disorder. *Ann Allergy Asthma Immunol* 2004; 92:663-7.
 40. Fagnano M, van Wijngaarden E, Connolly HV, Carno MA, Forbes-Jones E, Halterman JS. Sleep-disordered breathing and behaviors of inner-city children with asthma. *Pediatrics* 2009; 124:218-25.
 41. Liukkonen K, Virkkula P, Aronen ET, Kirjavainen T, Pitkäranta A. All snoring is not adenoids in young children. *Int J Pediatr Otorhinolaryngol.* 2008; 72:879-84.
 42. Kuehni CE, Strippoli MP, Chauliac ES, Silverman M. Snoring in preschool children: prevalence, severity and risk factors. *Eur Respir J* 2008; 31:326 - 33.
 43. Marshall NS, Almqvist C, Griunstein RR, Marks GB. Predictors for snoring in children with rhinitis at age 5. *Pediatr Pulmonol* 2007; 42:584 - 91.
 44. Chng SY, Goh DY, Wang XS, Tan TN, Ong NB. Snoring and atopic disease: a strong association. *Pediatr Pulmonol* 2004; 38:210-6.

45. Benninger M, Walner D. Obstructive sleep-disordered breathing in children. *Clin Cornerstone* 2007; 9:S6-12.
46. Urschitz MS, Guenther A, Eggebrecht E, Wolff J, Urschitz-Duprat PM, Schlaud M, et al. Snoring, intermittent hypoxia and academic performance in primary school children. *Am J Respir Crit Care Med* 2003; 168:464-8.
47. Guilleminault C, Winkle R, Korobkin R, Simmons B. Children and nocturnal snoring: evaluation of the effects of sleep related respiratory resistive load and daytime functioning. *Eur J Pediatr* 1982; 139:165-71.
48. Ali NJ, Pitson D, Stradling JR. Sleep disordered breathing: effects of adenotonsillectomy on behaviour and psychological functioning. *Eur J Pediatr* 1996; 155:56-62.
49. O'Brien LM, Mervis CB, Holbrook CR, Bruner JL, Klaus CJ, Rutherford J, et al. Neurobehavioral implications of habitual snoring in children. *Pediatrics* 2004; 114:44-9.
50. Montgomery-Downs HE, Crabtree VM, Gozal D. Cognition, sleep and respiration in at-risk children treated for obstructive sleep apnoea. *Eur Respir J* 2005; 25:336-42.
51. Montgomery-Downs HE, Gozal D. Snore-associated sleep fragmentation in infancy: mental development effects and contribution of secondhand cigarette smoke exposure. *Pediatrics* 2006; 117:e496-502.
52. Blunden S, Lushington K, Kennedy D. Cognitive and behavioural performance in children with sleep-related obstructive breathing disorders. *Sleep Med Rev* 2001; 5:447-61.
53. O'Brien LM, Tauman R, Gozal D. Sleep pressure correlates of cognitive and behavioral morbidity in snoring children. *Sleep* 2004; 27:279-82.
54. Chervin RD, Ruzicka DL, Giordani BJ, Weatherly RA, Dillon JE, Hodges EK, et al. Sleep-disordered breathing, behavior, and cognition in children before and after adenotonsillectomy. *Pediatrics* 2006; 117:e769-78.
55. Perez-Chada D, Perez-Lloret S, Videla AJ, Cardinali D, Bergna MA, Fernández-Acquier M, et al. Sleep disordered breathing and daytime sleepiness are associated with poor academic performance in teenagers. A study using the Pediatric Daytime Sleepiness Scale (PDSS). *Sleep* 2007; 30:1698-703.
56. Aisenberg R, Rosenthal A, Nadas A, Wolf P. Developmental delay in infants with congenital heart disease. *Pediatr Cardiol* 1982; 3:133-7.
57. Silbert A, Wolff PH, Mayer B, Rosenthal A, Nadas AS. Cyanotic heart disease and psychological development. *Pediatrics* 1969; 43:192-200.
58. Wright M, Nolan T. Impact of cyanotic heart disease on school performance. *Arch Dis Child* 1994; 71:64-70.
59. Blunden S, Lushington K, Kennedy D, Martin J, Dawson D. Behavior and neurocognitive performance in children aged 5-10 years who snore compared to controls. *J Clin Exp Neuropsychol* 2000; 22:554-68.
60. O'Dougherty M, Nuechterlein KH, Drew B. Hyperactive and hypoxic children; signal detection, sustained attention, and behavior. *J Abnorm Psychol* 1984; 93:178-91.
61. O'Brien LM, Holbrook CR, Mervis CB, Klaus CJ, Bruner JL, Raffield TJ, et al. Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. *Pediatrics* 2003; 111:554-63.
62. Stradling JR, Thomas G, Warley AR, Williams P, Freeland A. Effect of adenotonsillectomy on nocturnal hypoxaemia, sleep disturbance, and symptoms in snoring children. *Lancet* 1990; 335:249-53.
63. Wechsler D. Wechsler Intelligence Scale for Children - Fourth Edition. San Antonio, T.X.: The Psychological Corporation; 2003.
64. Keith RW. Auditory Continuous Performance Test Examiners Manual. New York: Harcourt Brice & Company; 1994.

65. Schonell FJ, Schonell FE. Diagnostic and Attainment Testing. Edinburgh: Oliver & Boyd; 1950.
66. Schonell FJ, Schonell FE. A Graded Word Reading Test. Edinburgh: Oliver and Boyd; Schonell Graded Word Reading Test (1972 Revised Norms). Edinburgh: Oliver and Boyd; 1950.
67. Pevernagie DA, De Meyer MM, Claeys S. Sleep, breathing and the nose. *Sleep Med Rev* 2005; 9:437-51.
68. Craig TJ, McCann JL, Gurevich F, Davies MJ. The correlation between allergic rhinitis and sleep disturbance. *J Allergy Clin Immunol* 2004; 114:S139-S45.
69. Craig TJ, Teets S, Lehman EB, al. e. Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids. *J Allergy Clin Immunol* 1998; 101:633-7.
70. Craig TJ, Mende C, Hughes K, Kakumanu S, Lehman EB, Chinchilli V. The effect of topical fluticasone on objective sleep testing and the symptoms of rhinitis, sleep, and daytime somnolence in perennial allergic rhinitis. 2003.
71. Mansfield LE, Diaz G, Posey CR, Flores-Neder J. Sleep disordered breathing and daytime quality of life in children with allergic rhinitis during treatment with intranasal budesonide. *Ann Allergy Asthma Immunol* 2004; 92:240-4.
72. Desager KN, Nelen V, Weyler JJ, De Backer WA. Sleep disturbance and daytime symptoms in wheezing school-aged children. *J Sleep Res* 2005; 14:77-82.
73. Janson C, De Backer W, Gislason T, Plaschke P, Bjornsson E, Hetta J, et al. Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: a population study of young adults in three European countries. *Eur Respir J* 1996; 9:2132-8.
74. Sulit LG, Storfer-Isser A, Rosen CL, Kirchner HL, Redline S. Associations of obesity, sleep-disordered breathing, and wheezing in children. *Am J Respir Crit Care Med* 2005; 171:659-64.
75. Blaiss M, Reigel T, Philpot EA. A study to determine the impact of rhinitis on sufferer's sleep and daily routine [abstract]. *J Allergy Clin Immunol* 2005; 115:S197.
76. Young T, Finn L, Kim H. Nasal obstruction as a risk factor for sleep-disordered breathing. *J Allergy Clin Immunol* 1997; 99:S757-S62.
77. Strunk RC, Sternberg AL, Bacharier LB, Szeffler SJ. Nocturnal awakening caused by asthma in children with mild-to-moderate asthma in the childhood asthma management program. *J Allergy Clin Immunol* 2002; 110:395-403.
78. Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J, Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997; 195:10-9.
79. Holm EA, Wulf HC, Stegmann, Jemec GBE. Life quality assessment among patients with atopic eczema. *Br J Dermatol* 2006; 154:719-25.
80. Waber DP, De Moor C, Forbes PW, Almili CR, Botteron KN, Leonard G, et al. The NIH MRI study of normal brain development: Performance of a population based sample of healthy children aged 6 to 18 years on a neuropsychological battery. *J Int Neuropsychol Soc* 2007; 13:729-46.

Chapter 7. Eczema, sleep and daytime functioning in children

7.1 Eczematous children's sleep findings

The present study has demonstrated that children with eczema have disturbed sleep with associated secondary deficits in their daytime functioning. The questionnaire study revealed that children with eczema had difficulty in initiating and maintaining sleep and were excessively sleepy during the daytime. Using polysomnography, children with eczema were found to have a longer REM Onset Latency and longer Wake After Sleep Onset than controls. Scratching was found to occur during EEG defined sleep and often produced arousal from sleep. Using actigraphy, children with more severe eczema were found to be more active than either children with mild to moderate eczema or control subjects during the night.

The skin temperature profile of eczema children was also found to be markedly different from that of healthy controls. At 90 to 240 minutes after sleep onset, the eczematous children's Distal temperature was approximately 1°C below controls, with no significant differences detected between groups in the Proximal temperature or the Distal Proximal Gradient. The nocturnal trend of eczema children's Distal temperature demonstrates a notable decline in skin temperature in contrast to non-eczema controls. Corresponding increases in Proximal temperature after this event further indicated a premature rise in core temperature.

7.2 Neurocognition, behaviour and sleep in eczematous children

Children with eczema also exhibited distinct differences in their neurocognitive profile when compared to controls. Eczematous children's full scale IQ scores were on average, 8 points lower than published aged normed peers¹ and 16 points lower than healthy non-eczema subjects. Furthermore, the neurocognitive profile of eczematous children was associated with their sleep architecture with longer Sleep Onset Latencies associated with lower Verbal

Comprehension scores. In addition, a higher percentage of Stage 2 sleep and a lower percentage of Stage 4 sleep were both associated with lower Processing Speed Scores. Children with eczema were further found to have a higher frequency of behavioural problems. Using Structural Equation Modelling,² behavioural outcomes were found to be mediated through the effects that eczema had on sleep disturbance rather than the direct effects of eczema itself per se.

7.3 Co-morbid disorders of Asthma and Rhinitis

Many eczematous children were found to have the co morbid atopic disorders of asthma and rhinitis, both of which are known to disturb sleep³⁻⁵ and have associated secondary deficits in neurocognitive functioning^{6,7} and behaviour.^{8,9} The impact of asthma and rhinitis was also apparent in the polysomnographic, actigraphic, behavioural and neurocognitive measures in this study. However, once the contribution of asthma and rhinitis disturbing sleep had been statistically controlled for, the contribution of eczema disturbing sleep and producing secondary neurocognitive and behavioural deficits was evident.

7.4 Case study of female eczema patient (aged 7yrs) pre and post treatment

The present findings raise the question as to whether the treatment of eczema will ameliorate nocturnal disturbance and thereby improve neurocognitive performance and daytime behaviour in children. While this type of data is absent from the literature, some inference can be obtained from a recent case study. A 7 1/2 year old girl presented at the dermatology clinic at the Women's and Children's Hospital, Adelaide, South Australia with severe eczema and was treated with a prescribed daily dose of Cyclosporin (also known as cyclosporine, ciclosporin or cyclosporin A). Cyclosporin is an immunosuppressant drug used to reduce the activity of the patient's immune system and has been successfully employed to treat severe

eczema in children.¹⁰

7.5 Method

Prior to commencing treatment, the patient's eczema was evaluated using the SCORAD¹¹. The patient and her parents then undertook procedures outlined in Chapter 2 for completing the questionnaire on her sleep profile (Sleep Disturbance Scale for Children),¹² daytime behaviour (Conner's Parent Rating Scale - Revised (S)),¹³ Chapter 4 for actigraphy and Chapter 6 for neurocognitive testing (Wechsler Intelligence Scale for Children WISC-IV,¹ Auditory Continuous Performance Test¹⁴ & Schonell Graded Word Reading Test^{15, 16}). After 6 months, the subject was re-examined and re-tested using the same measures.

7.6 Results

After six months of treatment, the patient demonstrated an improvement in the majority of measures. Her eczema severity was greatly reduced and her quality-of-life had also markedly improved. The sleep questionnaire data indicated that her sleep breathing had improved and her daytime sleepiness had been reduced. Contrary to expectation, the questionnaire and actigraphy data indicated that her nocturnal awakenings had increased in frequency. However, the majority of actigraphic variables indicated that her sleep had generally improved with a higher sleep efficiency, greater sleep percentage, shorter awake periods and less overall nocturnal movement. A review of the patient's behavioural and neurocognitive data indicated that the patient had improved in majority of variables measured. The behavioural measures of Cognitive problems/Inattention, ADHD Index and Oppositional behaviour had been reduced, though her Hyperactivity index scores were elevated. With regard to her performance on the WISC-IV measures, the patient's improvement was most promising. Apart from minor decrements in the subtests of Arithmetic, Vocabulary, Digit

Span and Symbol Search, she had improved her scores in the majority of subtests and indices. Accordingly, her Full Scale IQ had risen from a score of 89 to 106, despite adjustments made for retesting. Attention and Reading Ability measures were relatively unchanged.

Table 7.1: Pre and post treatment data of BMI, snoring, atopic disease severity, sleep questionnaire, actigraphy and polysomnography variables of a 7 year old female with eczema.

	Condition		Difference	
	Pre-treatment)	Post-treatment		
Body Mass Index	17.0	18.0	+1	improved
Quality -of-Life Index	32	22	- 10	improved
Atopic Disease				
Eczema Severity	58.1	9.4	- 48.7	improved
Asthma Severity	1	1	0	no change
Rhinitis Severity	0	0	0	no change
Sleep Disturbance Scale for Children				
Disorders of Initiating and Maintaining Sleep	73	73		no change
Sleep Breathing Disorders	52	45	- 7	improved
Disorders of Arousal	47	73	+26	worse
Sleep Wake Transitional Disorders	58	66	+8	worse
Disorders of Excessive Daytime Somnolence	92	73	- 19	improved
Sleep Hyperhydrosis	69	69	0	no change
Total Problem Score	80	73	-7	improved
Actigraphy				
Sleep Efficiency (%)	65.8	75.1	+9.3	improved
Sleep Percentage (%)	72.4	77.4	+5	improved
Wake Percentage (%)	27.6	22.6	-6	improved
Awakenings	21	37	+16	worse
Mean Sleep Periods (min:sec)	16:31	11:43	+4:48	worse
Mean Awake Periods (min:sec)	06:17	03:19	+03:02	improved
Moving during Total Sleep Time (%)	27.8	19.1	-8.7	improved
Immobile during Total Sleep Time (%)	72.2	80.9	+8.7	improved
Total Activity Score	47963	20336	-27627	improved
Mean Score in Inactive Periods	100.3	37.3	-63	improved
Mean Score in Active Periods	360.6	195.5	-255.1	improved
Movement and Fragmentation Ratio	42.1	39.1	-3	improved

Table 7.2: Pre and post treatment data of behavioural and neurocognitive variables of a 7 year old female with eczema.

	Condition		Difference	
	Pre-treatment	Post-Treatment)		
Conner's Parent Rating Scale – Revised (S)				
Cognitive problems/Inattention	71	68	-3	improved
Hyperactivity	63	69	+6	worse
ADHD Index	73	71	-2	improved
Oppositional Behaviour	83	64	-19	improved
WISC-IV Australian Language Adaptation				
Full Scale IQ	89	106	+17	improved
Verbal Comprehension	91	98	+7	improved
Vocabulary	9	7	-2	worse
Comprehension	5	9	+4	improved
Word Reasoning	7	10	+3	improved
Similarities	11	11	0	no change
Information	8	8	0	no change
Perceptual Reasoning	84	100	+16	improved
Block Design	7	10	+3	improved
Picture Concepts	9	10	+1	improved
Matrix Reasoning	6	9	+3	improved
Picture Completion	5	9	+4	improved
Working Memory	88	114	+26	improved
Digit Span	12	11	-1	worse
Letter-Number Sequencing	4	13	+9	improved
Arithmetic	12	7	-5	worse
Processing Speed	112	112	0	no change
Coding	8	10	+2	improved
Symbol Search	16	14	-2	worse
Cancellation	11	13	+2	improved
Auditory Continuous Performance Test				
Inattention	2	0	+2	improved
Impulsivity	0	2	-2	worse
Attention Total Score	2	2	0	no change
Schonell				
Reading Ability (yrs old)	8.5	8.5	0	no change

7.7 Discussion

A young eczema patient having improved sleep, neurocognitive ability and behavioural performance post treatment has promising implications for other eczema patients. The implications are that with the appropriate treatment, children with eczema not only have the potential to improve their sleep quality, but that the majority of behavioural and neurocognitive deficits associated with disturbed sleep in this patient group can also be reversed. The findings of the case study also suggests more specific outcomes. They indicate that the majority of daytime deficits due to sleep fragmentation are unlikely to be permanent and that the opportunity to have restorative sleep will amend associated neurocognitive and behavioural deficits. However, it must be restated that this particular treatment for eczematous children is not a overall cure for this disorder and, as this case study aptly illustrates, some sleep deficits in the form of frequent arousals, persist. This finding further infers that the frequency of arousals is not the determining feature of sleep disturbance's contribution to neurocognitive and behavioural outcomes. Furthermore, some inference can be made as to the types of deficits that are affected through sleep fragmentation without hypoxia in children. The skills and abilities measured by the WISC-IV indices of Verbal Comprehension, Perceptual Reasoning and Working Memory and the behavioural measures of Cognitive/Inattention, ADHD Index and Oppositional behaviour appear to be susceptible to the affects of sleep fragmentation. Why these domains are affected by sleep fragmentation and not other domains remains unclear.

7.8 Future directions for study

Additional study is required on the sleep of eczematous children and associated secondary deficits in daytime functioning. In particular, greater subject numbers are required for a more detailed statistical analyses to order to define the specific abilities affected, as opposed to the

broad neurocognitive and behavioural domains identified in this study. This type of approach would also have the potential to give a greater understanding as to the mechanism of how sleep fragmentation affects daytime functioning. Finally, further examination is required on the temperature profile of eczematous children and whether temperature abnormalities persist after treatment.

7.9 Conclusion

In conclusion, eczematous children's poor sleep quality is associated with lower quality-of-life, behavioural problems and neurocognitive deficits, with some indications that these deficits are reversible with an appropriate treatment. For a disorder that can affect up to 20 percent of children in most Western industrialised countries, the secondary outcomes of poor sleep are extraordinary. It is therefore recommended that sleep quality be routinely included into the diagnoses of childhood eczema, and further, that eczematous child's sleep quality should be given prominent consideration in the therapy of this disorder.

Bibliography

1. Wechsler D. Wechsler Intelligence Scale for Children - Fourth Edition. San Antonio, T.X.: The Psychological Corporation; 2003.
2. Steiger JH. Structural model evaluation and modification: An interval estimation approach. *Multivariate Behavioral Research* 1990; 25.
3. Ricci G, Patrizzi A, Baldi E, Menna G, Tabanalelli M, Masi M. Long term follow up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. *J Am Acad Dermatol* 2006; 107:567-74.
4. Syabbalo N. Chronobiology and chronopathophysiology of nocturnal asthma. *Int J Clin Pract* 1997; 51:455-62.
5. Shedden A. Impact of nasal congestion on quality of life and work productivity in allergic rhinitis. *Treat Respir Med* 2005; 4:439-46.
6. Diette GB, Markson L, Skinner EA, Nguyen TT, Algatt-Bergstrom P, Wu AW. Nocturnal Asthma in children affects school attendance, school performance, and parents' work attendance. *Arch Pediatr Adolesc Med* 2000; 154:923-8.
7. Brawley A, Silverman B, Kearney S, Guanzon D, Owens M, Bennett H, et al. Allergic rhinitis in children with attention-deficit/hyperactivity disorder. *Ann Allergy Asthma Immunol* 2004; 92:663-7.
8. Fagnano M, van Wijngaarden E, Connolly HV, Carno MA, Forbes-Jones E, Halterman JS. Sleep-disordered breathing and behaviors of inner-city children with asthma. *Pediatrics* 2009; 124:218-25.
9. Liukkonen K, Virkkula P, Aronen ET, Kirjavainen T, Pitkäranta A. All snoring is not adenoids in young children. *Int J Pediatr Otorhinolaryngol.* 2008; 72:879-84.
10. Lee SS, Tan AWH, Giam YC. Cyclosporin in Severe Atopic Dermatitis. *Annals Academy of Medicine* 2004; 33:311-3.
11. European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD index. *Dermatology* 1993; 186:23-31.
12. Bruni O, Ottaviano S, Guidetti V, Romoli M, Innocenzi M, Cortesi F, et al. The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *J Sleep Res* 1996; 5:251-61.
13. Conners CK. Conner's Parent Rating Scale - Revised. Tonawanda, New York: Multi-Health Systems Inc., 1997.
14. Keith RW. Auditory Continuous Performance Test Examiners Manual. New York: Harcourt Brice & Company; 1994.
15. Schonell FJ, Schonell FE. Diagnostic and Attainment Testing. Edinburgh: Oliver & Boyd; 1950.
16. Schonell FJ, Schonell FE. A Graded Word Reading Test. Edinburgh: Oliver and Boyd; Schonell Graded Word Reading Test (1972 Revised Norms). Edinburgh: Oliver and Boyd; 1950.