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Inga Kisielienė

Assessment of Endogenous and Exogenous Factors in Children's Atopic Dermatitis and the Impact of the Disease on Quality of Life and Behavioral Difficulties

DOCTORAL DISSERTATION

Medicine and Health Sciences,
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This dissertation was written between 2018 and 2023 at Vilnius University Faculty of Medicine.

Academic supervisor - Prof. Dr. Matilda Bylaitė-Bučinskienė (Vilnius University, Medicine and Health Sciences, Medicine – M 001).

Academic consultant - Prof. Dr. Andreas Wollenberg (Department of Dermatology and Allergy, Augsburg University Hospital, Augsburg, Germany; Department of Dermatology and Allergy, Ludwig-Maximilian University of Munich, Germany; Comprehensive Center for Inflammation Medicine, University of Luebeck, Luebeck, Germany, Medicine and Health Sciences, Medicine – M 001).

This doctoral dissertation will be defended in a public meeting of the Dissertation Defence Panel:

Chairman - Prof. Dr. Ligita Jančorienė (Vilnius university, Medicine and Health Sciences, Medicine – M 001).

Members - Prof. Dr. Brigita Gradauskienė (Lithuanian university of health Sciences, Medicine and Health Sciences, Medicine – M 001);

Assoc. Prof. Dr. Jūratė Grigaitienė (Vilnius University, Medicine and Health Sciences, Medicine – M 001);

Prof. Dr. Māra Rone-Kupfere (Riga Stradins University, Medicine and Health Sciences, Medicine – M 001);

Prof. Dr. Laura Malinauskienė (Vilnius University, Medicine and Health Sciences, Medicine – M 001).

The dissertation shall be defended at a public meeting of the Dissertation Defence Panel at 12:00 on 28 August 2024 in Raudonoji Auditorium of Vilnius University Hospital Santaros klinikos.
Address: Santariškių 2, corpus E, Auditorium E122, Vilnius, Lithuania
Tel: +37052501888; Email: info@santa.lt

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VILNIAUS UNIVERSITETAS

Inga Kisielienė

Vaikų atopinio dermatito endogeninių ir egzogeninių veiksnių bei ligos įtakos gyvenimo kokybei ir elgesio sunkumams vertinimas

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Mokslinė vadovė - prof. dr. Matilda Bylaitė-Bučinskienė (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).

Mokslinis konsultantas - prof. dr. Andreas Wollenberg (Augsburgo universitetinės ligoninės Dermatologijos ir alergijos skyrius, Augsburgas, Vokietija; Miuncheno Liudviko Maksimiliano universiteto Dermatologijos ir alergijos skyrius, Miunchenas, Vokietija; Liubeko universiteto Kompleksinis uždegimų medicinos centras, Liubekas, Vokietija, medicinos ir sveikatos mokslai, medicina – M 001).

Gynimo taryba:

Pirmininkė - prof. dr. Ligita Jančorienė (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).

Nariai - prof. dr. Brigita Gradauskienė (Lietuvos sveikatos mokslų universitetas, medicinos ir sveikatos mokslai, medicina – M 001);

doc. dr. Jūratė Grigaitienė (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001);

prof. dr. Māra Rone-Kupfere (Rigos Stradins universitetas, medicinos ir sveikatos mokslai, medicina – M 001);

prof. dr. Laura Malinauskienė (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).

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Adresas: Santariškų g. 2, E korpusas, E122 auditorija, Vilnius, Lietuva, tel. +370 5 250 1888; el. paštas info@santa.lt

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ABBREVIATIONS

AD, atopic dermatitis

AMPs, antimicrobial peptides

Anti-TPO, anti-thyroid peroxidase antibodies

CBCL /6-18, the 2001 Child Behavior Checklist for Ages 6-18

CDLQI, the Children's Dermatology Life Quality Index

DLQI, Dermatology Life Quality Index

EOS, eosinophils

FA, food allergies

FDLQI, the Family Dermatology Life Quality Index

FLG, filaggrin

EDC, epidermal differentiation complex

HDL, high-density lipoprotein

IDQoL, the Infants' Dermatitis Quality of Life index

IL, interleukin

IgE, immunoglobulin E

JAKI, Janus kinase inhibitor

LDL, low-density lipoprotein

LOR, loricrin gene

LoF, loss-of-function

25(OH)D3, 25-hydroxy vitamin D3

POEM, Patient-Oriented Eczema Measure

PRL, prolactin

QoL, quality of life

SCORAD, the Severity Scoring of Atopic Dermatitis

sIgE, specific IgE

TCS, topical corticosteroids

TEWL, trans-epidermal water loss

TG, triglycerides

Th, T helper cell

TBC, total blood count

TSH, thyroid-stimulating hormone

TSLP, thymic stromal lymphopoietin

UV, ultraviolet

1. INTRODUCTION

1.1. Brief introduction

Atopic dermatitis (AD), also known as ‘‘atopic eczema’’, is the most common chronic and recurrent skin disorder of childhood and is being reported with increasing frequency worldwide. Atopic dermatitis is the most common chronic inflammatory skin disease with a high impact on patients' and relatives' quality of life, with an increasing cumulative lifetime prevalence of up to 20% in developed countries. The main factors of the complex pathophysiology are an altered skin barrier, modified immune system, and skin microbiome dysbiosis, all influenced by gene–gene, and gene–environment interactions. Multiple risk factors have been associated with the development of AD. Recent advances in understanding the role of genetics in this disease have been made, with the discovery of the filaggrin (FLG) gene as the most notable so far. In addition to FLG gene mutations as a risk factor for AD, a positive family history of atopic or allergic disease in either parent, has been shown to confer a greater risk of developing AD.

AD usually presents early in life and is thought to represent the initial step in the “atopic march” which is characterized by the development of other atopic diseases later in life such as asthma, allergic rhinitis, and/or rhinoconjunctivitis, food allergies, and hay fever. Other comorbid diseases that have been associated with AD include an increased risk of viral and bacterial skin infections and neuropsychiatric diseases such as attention-deficit hyperactivity disorders and autistic spectrum disorder. Patients with AD, have also been found to have worse sleep quality and quality of life overall compared to patients without AD (1).

1.2. Aim and objectives

The aim is to analyse the association of exogenous and endogenous factors with AD in children, to assess the impact of the disease on the quality of life of the patient and patient‘s family, to investigate the impact of the disease on the behavioural difficulties of the patients, and to analyse the phenomenon of corticophobia in the parents of children with AD.

Objectives:

1. To investigate the epidemiology and demographic characteristics of children with AD, and to identify endogenous and exogenous factors associated with the manifestation and severity of AD.
2. To assess the quality of life of children with AD and their families, and its relationship with disease severity.
3. To investigate the prevalence and characteristics of behavioural difficulties in children with AD and the factors influencing their occurrence, and to compare the data with a control group of patients.
4. To analyse the concept of corticophobia in the parents of children with AD - prevalence, contributing factors, and its relationship with disease severity.

1.3. Defended statements

1. Abnormalities in serum vitamin D and cortisol levels will be associated with a diagnosis of AD.
2. Childhood AD negatively affects the quality of life of children and their families and it is associated with disease severity.
3. Children with AD may experience behavioural difficulties due to the chronic nature of the disease and the symptoms it may cause (itching, sleep problems).
4. Corticophobia is more common among people with AD and may be related to the severity of the disease, the steroid use, and the level of knowledge about the disease.

1.4. Novelty of the study

There is controversial data about the endogenous and exogenous factors influencing AD disease activity in childhood, such as vitamin D, cortisol, or serum lipids. This analysis will help to highlight the possible additional

external and internal factors that may influence the course of the AD disease and to differentiate what additional laboratory tests could be performed to improve AD management.

The results of this study will provide clinicians with insights into the factors that influence the onset and severity of pediatric AD, how the disease affects the quality of life of the patients and their families, and what impacts children's behavior in our country.

Despite the growing number of studies on quality of life and psychiatric comorbidities in adults with AD, only a few studies have evaluated behavioural difficulties in children and adolescents and their correlation with disease severity. We performed a survey to gather more data from patients and caregivers to help describe the disease burden in Lithuania.

Knowledge of corticophobia of AD patients parents will help clinicians hihhlight potential at-risk patient groups and will allow to improve their treatment adherence.

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2. LITERATURE REVIEW

2.1. Definition and epidemiology

Atopic dermatitis (atopic eczema, neurodermatitis) is one of the most common non-communicable, inflammatory, chronic, or chronically relapsing skin diseases occurring often in families with other atopic diseases (bronchial asthma and/or allergic rhinoconjunctivitis) (2). In Europe and the United States of America, recent data suggests that the prevalence of AD among children is approximately 20% and, among adults, it ranges between 7% and 14%, with substantial variation between countries, and there is considerable evidence that the prevalence is increasing (3). In a study using standardized the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires carried out in Kaunas, Lithuania, in 1994-1995 and 2001-2002 among schoolchildren aged 6-7 years, the prevalence of AD was found to have increased from 1.4% to 3.5% (4). The reason for this increase remains unclear; genetic, immunological, and environmental factors may be important.

The prevalence of AD is believed to be highest in young children: in 60% of affected individuals, onset is in the first year of life, and in 85% – within the first 5 years (5). About one-third of adult cases develop in adulthood. In many instances, AD symptoms end in the teenage years (70-90% by age 10 years), although the disease may relapse in the future. In the remaining 10-30% of patients, the disease persists throughout life (6,7).

2.2. Pathogenesis

AD develops as a result of genes, skin barrier dysfunction, immune dysregulation, and environmental exposures. Each of these factors may be more prevalent in one patient than another (8,9). There are two hypotheses for the pathogenesis of AD. One of them ("outside-in") explains that inadequate skin barrier function and disturbances in keratinocyte differentiation lead to increased penetration of environmental antigens into the skin, activation of the immune system, and sensitisation to allergens. Another hypothesis ("inside-out") suggests that activated T helper 2 (Th2) lymphocytes cause chronic inflammation in the skin (9).

Notably, there may be pathophysiological differences between AD in children and adults (10). Regarding the skin barrier, pediatric AD has more FLG loss-of-function variants and lipid-barrier defects, while adult AD shows more epidermal differentiation and cornification defects (10). Regarding

immune dysregulation, pediatric AD shows the highest skin eosinophil and neutrophil counts and greater induction of T-helper (Th)2, Th9, Th17, interleukin (IL) 31, IL33, and innate immune markers; meanwhile, adult AD is skewed towards Th1 activation (10,11). In both children and adults, AD skin is likely predisposed to pathogen colonization, which may contribute to disease progression (12). Pediatric AD not only predisposes to skin infections but also increases allergen sensitization, including to food and aeroallergens (13).

Taken together, in pediatric AD, microbes, aeroallergens, and pollutants may penetrate the inherently defective skin barrier to trigger dysregulation of the immune system (which may itself be predisposed by genetic defects), causing further skin damage, chronic inflammation, and itch; notably, the right climate and/or commensals may improve some AD (Figure 1)(10).

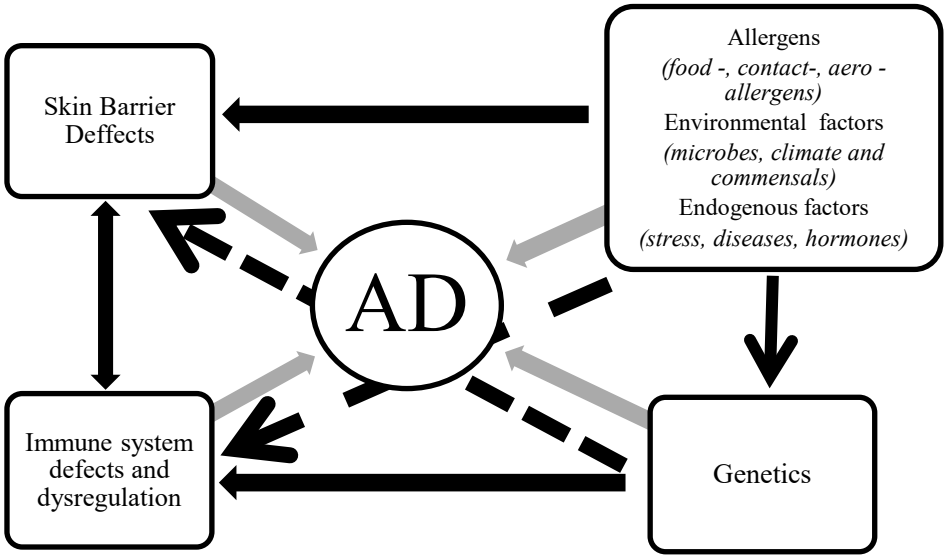

Figure 1. The interplay of genetic and environmental contributors in modulating the immune dysregulation of AD (adapted from Chong et al., 2022 (10)).

2.2.1. Genetics of atopic dermatitis

AD is a disease of defective genetics in an unfavorable environment (10). Thanks to advances in molecular genetics, more than 62 genes and 5 intergenic regions have now been identified in AD (10,14). Some of these genes are responsible for the maintenance of skin barrier function and keratinocyte differentiation, such as filaggrin (FLG), loricrin (LOR), involucrin (IVL), SPINK-5 (SPINK-5), and other proteins, such as the epidermal differentiation complex (EDC). Others are responsible for acquired (IL-4, IL-4RA, IL-13, IL-31, thymic stromal lymphopoietin (TSLP)) and innate immune responses (9).

The epidermal differentiation complex (EDC) is a 2 Mb region of human chromosome 1q21 that is the site of key genes for establishing the skin barrier (ie, FLG). The EDC also controls epithelial tissue development and repair by regulating the terminal differentiation program of KC. Filaggrin is the most studied and implicated gene in AD and is a member of the EDC (10). Mutations in the filaggrin gene have been the most widely described, being found in 10% to 50% of AD patients (9). FLG is associated with AD severity, with about 50% of patients with severe AD having a filaggrin gene mutation (8). FLG mutations cause both barrier defects as well as altered hydration and pH of the stratum corneum, which may modulate the growth of *Staphylococcus aureus* (*S. aureus)* (15). The FLG loss-of-function (LoF) mutation may also predispose to increased allergic sensitization due to the increased ability of allergens to penetrate deeper into skin layers (16). In addition to direct FLG mutations, Th2 cytokines IL4, IL13, and IL31 can suppress FLG expression and/or interfere with keratinocytes differentiation.

While FLG has received the most attention, other EDC genes may be relevant in AD (Table 1). A whole genome sequencing study showed enrichment of rare LoF variants of FLG2, HRNR, LCE2C, LCE4A, LCE5A, RPTN, S100A3, S100A16, SPRR3, SPRR4, TCHH, and TCHHL1 in AD patients. Expression of FLG2 and HRNR are significantly reduced in both lesional and non-lesional skin of patients with AD compared with healthy subjects. Upregulation of S100A7 and S100A8 and downregulation of FLG and the loricrin gene (LOR) have also been observed in AD and may represent abnormal epidermal differentiation and defective defenses favoring the alternative keratinization pathway. Single nucleotide polymorphisms (SNPs) in CLDN1 in AD may compromise tight junctions. Missense mutations in the Transmembrane Protein 79 (or Mattrin) gene (Tmem79/matt) may also predispose humans to AD. Certain genetic variants of LELP1 have been associated with elevated IgE levels, early onset, house dust mite

sensitization, and disease severity in AD. Beyond the EDC, aberrant epidermal serum protease (SP) activity and desmosome instability may contribute to the skin barrier defects of AD.

Epigenetics may contribute to the defective skin barrier of AD. For example, highly methylated KIF3A SNPs are associated with a decreased expression of KIF3A barrier protein in epithelial cells, leading to an increase in TEWL and risk of AD. Meanwhile, transcription factor PPARδ, which regulates inflammation and promotes keratinocyte proliferation and differentiation, is upregulated in lesional AD skin versus non-lesional skin. FABP5, a fatty acid-binding protein expressed in the epidermis, delivers ligands to PPARδ in keratocyte nuclei to enhance transcription. The consensus is that AD is not a monogenic disease. It is caused by a combination of alterations and mutations in several genes (10).

Table 1. Potential genetic contributors to AD (adapted by Chong A, et al., 2022 (10)).

Skin barrier	
Epidermal differentiation complex	FLG, FLG2, HRNR, LCE2C, LCE4A, LCE5A, RPTN, S100A3, S100A7, S100A8, S100A16, SPRR3, SPRR4, TCHH, TCHHL1, CLDN1, Tmem79/matt, LELP1
SP and SP inhibition	SERPINB7, KLK7
Desmosome component	DSC1
Epigenetics	KIF3A methylation, PPARδ upregulation, EMSY upregulation
Immune System	
Innate immunity	TLR2, TLR4, TLR9, NOD1, NOD2, DEFβ1, IFNγ, IFNγR, IRF2, SIDT2, RBBP8NL
Cytokine-related	IL4/4R, IL5, IL7R, IL9, IL10, IL12, IL13, IL18, IL31, TSLP, STAT6
Antigen receptor signaling	CARD14, LRRC32
IgE-related	FcεRIβ, ADAMTSL4
Leukotriene-related	CYSLTR1
Epigenetics	AHR upregulation, reduced IL13 methylation, reduced AcH3K9 acetylation

Abbreviations: *DSC, desmosome component; IFN, interferon; IL, interleukin; LOR, loricrin; FLG, filaggrin; Tmem79/matt, Transmembrane Protein 79; TLR, toll-like receptor.*

2.2.2. Skin barrier dysfunction

The epidermis provides an essential barrier to the external environment, preventing water loss and intrusion of infectious agents and allergens. The basis of barrier defects in AD is due to a deficiency of vital components of the stratum corneum and a lack of keratinocyte differentiation in the epidermis. This leads to reduced protein levels of involucrin, filaggrin, loricrin, claudins, and lipid molecules including ceramide, cholesterol, and fatty acids (10,15). Loss-of-function filaggrin gene mutations and chronic skin inflammation lead to reduced skin hydration (15) and increased water loss as measured by trans-epidermal water loss (TEWL). This holds even when AD skin is normal-appearing. Supporting the role of a defective skin barrier in AD, TEWL is positively correlated with AD severity and may predict AD development (10).

Barrier defects in AD facilitate the penetration of allergens and microbes into the skin (15). A leaky skin barrier may promote allergic sensitization by facilitating allergen uptake. When allergens are captured and processed by epidermal Langerhans cells, they migrate to draining lymph nodes and can interact with naıve T cells to promote helper T cell type 2 (Th2) immunity leading to allergies. Absorption of allergen through the disrupted skin barrier of AD is believed to lead to a Th2 response, immunoglobulin E (IgE) class switching, and clinical allergy (13).

In patients with AD, barrier defects may also be acquired. Th2 cytokines, IL-4, IL-13, and IL-22, which are highly expressed in AD lesions, are also capable of suppressing filaggrin expression, affecting the differentiation of keratinocytes, and contributes to an immune-mediated suppression of barrier function in AD (15). The interplay between the cutaneous immune response and environmental triggers, enhanced by skin barrier defects, results in a vicious cycle of cutaneous inflammation in AD (10).

The role of filaggrin in the prevention of skin infections may be twofold: as a physical barrier, as well as a modulator of *S. aureus* growth. In the skin, filaggrin is broken down into hygroscopic amino acids including urocanic acid (UCA) and pyrrolidone carboxylic acid (PCA). UCA and PCA are components of the natural moisturizing factor (NMF) that hydrate and maintain an acidic pH of the stratum corneum. Acidic pH inhibits the proliferation of *S. aureus*. The most common skin infections in AD are caused by *S. aureus* and *Streptococcus pyogenes* (*S. pyogenes*). Both types of bacterial skin infections may lead to invasive infections in AD. The risk factors for severe or invasive bacterial infections in AD are not fully

understood. It likely involves a complex interaction between host immune response and bacterial virulence (15).

Skin microbiome is part of skin barrier function and may play a role in the pathogenesis of bacterial infections in AD. In a Kong et al. study (17) authors found that microbial community structures at sites of disease predilection were dramatically different in AD patients compared with controls. They found that increased AD severity inversely correlated with decreased microbial diversity, as measured by the Shannon diversity index. The decrease in microbial diversity was also observed in AD patients who did not use any treatment before an eczema flare. On the other hand, AD patients who used topical corticosteroids (TCS) had a significantly higher microbial diversity, even during an eczema flare. Staphylococcus was the predominant species during an AD flare. Interestingly, they also observed a parallel increase in *Streptococcus*, *Propionibacterium*, and *Corynebacterium* species following therapy and during AD flare in patients who did not receive treatment. Representation of the skin commensal *S. epidermidis* also significantly increased during flares. This increase in *S. epidermidis* during AD flare may represent an attempt to control *S. aureus* via the production of their antimicrobial peptides (AMPs) (15,17).

2.2.3. Immune system defects and dysregulation

In AD skin, mechanical injury, allergens, and microbes trigger the skin's innate immune system inciting increased expression of inflammatory cytokines, especially thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. TSLP especially is expressed in high quantities in AD lesions and serves a critical role in activating the Th2 cascade. TSLP, IL-25, and IL-33 collectively trigger the innate lymphoid cell-2 (ILC-2) activation of Th2 cells, IL-5, and IL-13. ILCs are non-T and non-B effector cells that trigger specific cytokines as above. The ILCs also express skin-homing receptors and are activated by IL-33, infiltrating human skin after allergen stimulation.

Antigens are processed directly by Langerhans' cells (LC) and inflammatory dendritic epidermal cells (IDEC) and subsequently presented to Th2 cells. Langerhans' cells, myeloid dendritic cells (DCs), and IDECs in AD also produce chemokines, such as CCL17, CCL18, and CCL22, which further attract additional Th2 cells. These chemokines intensify Th2 and Th22 cytokines, including IL-4, IL-13, IL-31, and IL-22, which in turn have been shown to downregulate terminal differentiation and tight junction proteins, such as filaggrin, loricrin, involucrin, and claudins. These cytokines also

modulate IgE level class switching in B cells and subsequent eosinophil expression. In conjunction with Th2 polarization, which facilitates the binding of *S. aureus*, IL-4, and IL-13 predispose AD patients to *S. aureus* infection by inhibiting the production of AMPs in the cutaneous surface. AD is also characterized by peripheral eosinophilia, with variability in the number of eosinophils in the skin. IL-5 is the cytokine largely responsible for eosinophil recruitment and is typically present in lesional skin (9).

Although it is well recognized that the acute phase of AD is characterized by a strong modulation of Th2 and Th22 immune responses, clinical investigations have revealed other pathways, including Th17/IL-17 and IL-23, that further contribute to disease pathology. Th17 cells, produce IL-17 and, to a lesser extent IL-22, which both regulate AMP S100A7 (psoriasin) production in keratinocytes. IL-17 also induces the production of other inflammatory mediators, contributing to an influx of neutrophils, T-cells, and dendritic cells chemokines. IL-23, a key modulatory cytokine in the production and differentiation of Th17 cells, also induces Th22 differentiation, perhaps explaining its role in AD. The IL-23 receptor is expressed on immune cells, including LCs, DCs, and Th17 cells, and is upregulated in AD skin relative to normal skin (9).

While acute AD pathogenesis is polarized towards Th2 and Th22 immune responses, chronic AD lesions additionally exhibit a substantial Th1 component. The Th1 inflammatory cascade is characterized by the influx of numerous cytokines, including Interferon (IFN) gamma, and IL-12. The defining cytokine of the Th1 pathway, IFN gamma, promotes an intensified cutaneous inflammatory response and keratinocyte apoptosis. IL-12 amplifies this inflammatory process, triggering the proliferation of additional IFN gamma, T cells, and NK cells (9).

2.2.4. Endogenous and exogenous factors

2.2.4.1. Environmental factors

Numerous factors and substances from the environment can irritate the sensitive skin of patients with AD and can elicit eczema flares. They may be physical, like mechanic irritants (e.g. wool, synthetic material), chemical (acids, bleaches, solvents, water), or biological (allergens, microbes) in nature. Exposure to traffic exhaust and tobacco smoke is associated with an increased risk of developing AD. Information on unspecific irritants and their role in aggravating AD is a crucial prerequisite for the long-term management of

patients with AD. Here, also adequate skincare and hygiene procedures in cleansing and dressing have to be discussed with the patient (18).

2.2.4.2. Stress

Scientific articles mention the impact of psychological stress on skin diseases and it should be noted that study results have confirmed a positive connection between a high level of psychological stress and diverse skin conditions and illnesses (e.g. vulgar psoriasis, AD, pruritus, chronic urticaria, human papillomavirus infections/warts, hair loss). When it comes to the effects of psychological stress, the one of most studied skin diseases is AD. Exacerbation of AD symptoms has been seen in patients under the influence of stress, thus implying the fact that emotional factors contribute to the severity of AD symptoms (19,20). Additionally, AD can lead to psychological stress, due to stigmatization, social isolation, and discrimination. Multiple studies have shown that in patients with AD, for example, psychological stress can impair or blunt the hypothalamic-pituitary-adrenal (HPA) axis reactivity but it can overactivated the sympathetic system, which may lead to an increased Th2 response and aggravation of the symptoms (21). The skin actively responds to psychological stress, with the involvement of skin immune cells, hormones, and neurotransmitters. Skin immune cells actively regulate tissue inflammation with their pro-inflammatory and anti-inflammatory effects. Stress-induced skin reactions primarily include cytokine secretion (e.g. interleukin-6, interleukin-1, interferon-g) and activation of skin peripheral corticotropin-releasing hormone (CRH)-proopiomelanocortin (POMC)-adrenocorticotropic hormone (ACTH)-corticosteroids axis, which leads to acute/chronic secretion of corticosteroids in the skin (21). This phenomenon might be mediated by neuroimmunological factors, such as neuropeptides, which can be found in the blood and within the epidermal nerve fibers in close association with epidermal Langerhans cells. Increased levels of nerve growth factor and substance P can be found in the plasma of patients with AD and correlate positively with the disease activity. Enhanced levels of brain-derived growth factor can be detected in the sera and plasma of patients with AD. Brain-derived growth factor has been shown to reduce eosinophil apoptosis while enhancing the chemotaxis of eosinophils in vitro(19). Stress-induced immunomodulation is altered in patients with AD, but the exact mechanisms are not well understood. Impairment of the immune response, with the involvement of many mechanisms, constitutes an important link between stress and illness (21).

2.2.4.3. Vitamin D

There is increasing evidence in the scientific literature that there is a link between hypovitaminosis D and the development of eczema, with vitamin D being involved in the pathogenesis of AD as a protective factor, as it is important for normal immune function and the maintenance of the skin barrier function (22,23). This is supported by the presence of vitamin D receptors (VDRs) on keratinocytes and various cells of the immune system, such as T lymphocytes, B lymphocytes, neutrophils, and macrophages (24). In addition, it has been observed that the symptoms of AD are more pronounced in winter and that the disease is more common in northern latitudes, where exposure to ultraviolet B (UVB) sunlight is shorter and weaker, and the production of vitamin D in the skin is reduced (23). Two recent meta-analyses found significant differences in serum 25-hydroxyvitamin D (25(OH) D) levels, the main circulating form of vitamin D, between pediatric AD (AD) populations and healthy controls, although results varied among included studies (25,26). Studies have found associations between vitamin D levels and sensitization to both food and aeroallergens (27). The causal nature of the observed associations between vitamin D and allergic sensitization is poorly understood and is likely to involve timing, route of sensitization, epithelial barrier characteristics, exposure dose, and other factors(28). Vitamin D activates protective mechanisms in the skin against various micro-organisms and inhibits the inflammatory response of innate and acquired immunity, thereby suppressing inflammatory processes in the skin. In particular, calcitriol, a biologically active metabolite of vitamin D, stimulates keratinocytes to secrete antimicrobial peptides (AMPs), such as cathelicidin and β-defensins, thereby enhancing local skin immunity against micro-organisms, such as *S. aureus* (29). Vitamin D contributes to the normal barrier function of the skin by regulating the synthesis of skin proteins and lipids and by promoting keratinocyte proliferation (30). Calcitriol also activates phagocytosis in macrophages and induces NK cell activity. Vitamin D inhibits inflammatory reactions in several ways: by inhibiting immunoglobulin E (IgE) synthesis in B lymphocytes, by inhibiting the expression of transmembrane receptors (TLRs) in monocytes, by stimulating the release of the anti-inflammatory cytokine IL-10 from mast cells, by inhibiting the activation of dendritic cells and the activity of Th1 cells and by activating regulatory T cells (31).

2.2.4.4. The endocrine factors

Recently, there has been growing interest in the relationship between allergic and autoimmune diseases. Allergy and autoimmunity can be considered two potential outcomes of dysregulated immunity. It has been reported that infantile atopy increases a predisposition to autoimmune disorders, suggesting that these two entities might have immune pathways, common to both pathological conditions, justifying partially the increased prevalence and/or the presence of atopic and autoimmune diseases (32). Genome-wide association studies have shown substantial overlap between susceptibility loci for AD and TH1-mediated autoimmune conditions (33). Furthermore, while TH2-related cytokines dominate in the pathogenesis of acute AD, as is classically seen in atopic inflammation, TH1 and TH17 lymphocytes have also been implicated, particularly in the chronic phase (34,35). These findings, which are most frequently associated with autoimmunity, suggest a potential mechanism underlying the association between AD and autoimmune disease (35). Currently, the mechanisms explaining an association between atopy and autoimmunity (ex. thyroid diseases) are not fully understood (36). Although these conditions have a multifactorial pathogenesis, one generally accepted model is that immune dysregulation, secondary to an infectious process or excessive exposure to an inciting or cross-reactive antigen, promotes a T helper (Th) 1 response leading to progressive inflammation and autoimmunity. Reciprocal counter-regulation of Th1 and Th2 cells predicts that Th1-type autoimmune disease and Th2-mediated allergic disease would occur in mutually exclusive populations of patients (36,37). Last decade observations have identified additional lymphocyte subsets, such as Th17 cells (38), soluble factors such as IL-9 (39), and regulatory T cells (T reg) (40) as a common link between atopy and autoimmunity (36). Autoimmune thyroid diseases are the most common of all autoimmune pathological conditions. Autoimmune phenomena, especially thyroid autoimmunity, have often been associated with other autoimmune diseases, such as chronic urticaria in adults and children (36,41). Recent large cohort studies found an association between AD and the incidence of new-onset autoimmune diseases, such as psoriatic arthritis, Sjogren syndrome, Crohn's disease, vitiligo, alopecia areata, pernicious anemia, ulcerative colitis, rheumatoid arthritis, and hypothyroidism (35). Autoimmune thyroid diseases are the most common of all autoimmune pathological conditions. The findings of the last decade support the idea that the thyroid diseases associated with AD are autoimmune processes. Further studies are needed to explore the

immune dysregulation that may be contributing to the overlap between these pathologic conditions (42). Laboratory tests are integral in the diagnosis and management of most thyroid conditions. Thyroid autoantibodies are frequently tested to diagnose autoimmune thyroid diseases, such as Hashimoto's thyroiditis and Graves' disease. Anti-thyroid peroxidase antibodies (anti-TPO) are found in 5–20% of the general population and are nearly always elevated in patients with Hashimoto's thyroiditis. Thyroid-stimulating hormone (TSH) tests are recommended as first-line screening tests for thyroid dysfunction. Both anti-TPO and TSH are the most commonly recommended tests used to assess the functional status of the thyroid gland (43). However, does environmental factors, such as smoking and socioeconomic status, may be shared? In the study by Ivert et al. (28), adjustment for socioeconomic status did not change the result. In this study, patients with AD were generally diagnosed with autoimmune diseases, especially RA, earlier than controls. This might support the idea of an autoimmune component of AD and/or shared immune pathways and/or shared environmental factors yet to be discovered. A common mechanism of action between AD and autoimmune disease in general is not established.

Additionally, epidemiological studies found that adult eczema can be associated with increased odds of obesity, hypertension, and high cholesterol, which are in part related to increased cigarette smoking, alcohol intake, and sedentary lifestyle (44). Research indicated that dyslipidemia is a type of chronic inflammatory response (45). In particular, elevated triglycerides and low-density lipoprotein cholesterol lead to increased pro-inflammatory signaling and increased expression of TNF-α and interleukin (IL)-6. This supports the interpretation that the presence of a chronic inflammatory state (as indicated by dyslipidemia) is responsible for chronic skin inflammation and provides a possible mechanism for the relationship between AD and hyperlipidemia (45,46). The relationship between dyslipidaemia and AD in children remains unclear.

2.3. Risk factors in atopic dermatitis

In addition to FLG gene mutations as a risk factor for AD, a positive family history of atopic or allergic disease in either parent is a strong risk factor for the development of AD. It is estimated that approximately 70% of patients with AD have a positive family history of AD. Children of one or two affected parents with AD are thought to have a two to threefold, or three to sixfold

increased odds of developing AD, respectively. Children whose mothers had AD are also thought to be at an increased risk for developing AD (1).

Other factors including daycare exposure, level of parental education, socioeconomic status, place of residence (i.e., rural vs. urban setting), smoking, type of delivery during childbirth (i.e., vaginal vs. cesarean section), weight at birth, breast-feeding, being overweight, exposure to hard water, pets and/or dust mites, may influence the risk of developing AD, but the data is varied and inconclusive. Because the microbiota of patients with and without AD are known to be different, it has been suggested that exposure to antibiotics early in life leads to alteration in colonizing organisms, resulting in an increased risk of developing AD. Current data is insufficient to determine if early exposure to antibiotics is associated with an increased risk of developing AD. The relationship between dietary intake and risk for developing AD is not fully understood. It is unclear if maternal dietary restriction, breastfeeding, or timing of food introduction affects the risk of developing AD. A systematic review of sixty studies confirmed the association between AD, food sensitization, and food allergies (FA), with increased AD severity and duration of AD being more strongly associated with FA. Care must be taken when considering strict elimination diets in these patients as there is evidence to support that avoidance may increase the likelihood of developing new, immediate, food reactions in the future (1). It is a common misconception that AD patients especially children diagnosed with AD should avoid routine vaccinations. No evidence recommends vaccinations in infancy and early childhood have an impact on the development of AD or other atopic diseases. All children diagnosed with AD should be vaccinated according to the local or national vaccination plan. Vaccinations should not be administered during acute flares – in those cases, two weeks of well-conducted TCS therapy followed by a normal vaccination procedure are recommended. The only exception from this rule has been the intracutaneous smallpox vaccination with an attenuated live vaccine, which is contraindicated in AD patients due to the risk of life-threatening *eczema vaccinatum* (2).

2.4. Clinical features

Symptoms vary from individual to individual and, while the condition is mild for most, there is a tendency for it to remit and exacerbate unexpectedly (47). The skin lesions, which are usually accompanied by severe pruritus, include infiltrated erythema, erythema with erosions caused by scratching, lichenified areas, and pruriginous papules and nodules. The nummular variant

of childhood resembles nummular eczema in adults. The sites of predilection change over time:

- infants: cheeks, hairy scalp (capillitium), extensor surfaces of the limbs;
- toddlers and schoolchildren: flexor surfaces (elbows, popliteal region, neck);
- adolescents, adults: hand and foot eczema.

Minimal manifestations include dry lip inflammation (cheilitis sicca), inflammatory fissures at the corner of the mouth, infra-nasal erosion, infra-auricular tears, retro-auricular intertrigo, fingertip and toe-tip eczema ("atopic winter feet"), nipple eczema, and pityriasis alba. So-called atopic stigmata are typical skin signs, not pathological in themselves, that indicate an atopic diathesis. These include dry skin, hyperlinearity of the palms and soles, infraorbital double eyelid crease, periorbital halo formation, facial pallor, rarefaction of the lateral portion of the eyebrow, and white dermographism. On highly pigmented skin, the characteristic erythema appears gray ("ashy") rather than red as in Caucasians (2,48).

The differential diagnosis includes other skin diseases such as infections (e.g., scabies), other forms of eczema (allergic contact dermatitis, irritative-toxic eczema, seborrheic eczema), and, in infants, seborrheic dermatitis (2,48).

2.5. Comorbidities of atopic dermatitis

Patients with AD may develop a typical sequence of food allergies, rhinitis, and asthma, which develop at certain ages; some may persist for several years, whereas others may resolve with increasing age. This progression of atopic manifestations from AD to allergic rhinitis to asthma is known as the atopic march (5,49). The risk of developing atopic diseases is complex and the temporal pattern described in the atopic march may not be a simple progression. Atopic diseases can be unrelated disorders that develop sequentially along an atopic pathway or there may be a causal link between eczema and the later-onset atopic respiratory disorders. The development of these diseases is strongly influenced by both genetic and environmental factors. While these disorders share risk factors, the nature and development of the disease can vary among individuals (50).

The symptoms of AD affect the psychological and mental health of patients, mainly due to chronic relapsing disease course, intense pruritus,

unaesthetic appearance of lesions, and sleep disturbances. The mental health of patients with AD has been studied in several countries, and it has already been observed that dermatosis contributes to the development of mental and behavioral disorders (51–55). In a meta-analysis of 16 cross-sectional studies, adult AD was positively associated with higher depression scale scores, parental depression, antidepressant use, and suicidality, and this association was stronger in those with greater disease severity (54). A recent cross-sectional prospective population-based cohort study by Zhang et al. revealed that AD has positive associations with self-reported chronic fatigue syndrome, burnout, depression, social phobia, panic disorder, attention deficit hyperactivity disorder, and eating disorder (55). Depression and anxiety disorders are more common, especially in patients with severe AD (48).

2.6. Quality of life in patients with AD

Atopic dermatitis significantly impairs the quality of life (48). Consequently, the disease often has a major impact on the child and his/her development, social isolation, and psychological problems (47,56). Previous studies demonstrated a higher prevalence of anxiety and depression in patients with AD compared to the general population, which correlated to the severity of AD (57,58). A multicentre study in 13 European countries by Dalgard et al. (57) reported that 10.1% of patients with AD had depression and 15% had anxiety. A meta-analysis by Ronnstad et al. (59) concurred with these findings and demonstrated a positive association with suicidal behaviour. In addition, Cheng CM et al. (60) reported that having AD in adolescence or adulthood predisposes a patient to develop anxiety and depression later in life. However, an acausal relationship has not been established. Stressful events solely may lead to exacerbation of AD. Although one cannot rule out that psychiatric disease is associated with itch sensation, skin barrier damage, and ultimately AD, a more plausible explanation is that the burden from chronic and intermittent disease, itch, disrupted sleep, and social isolation negatively affects mental health (59). Sleep disturbance and the severity of itch and skin pain have been associated with impaired quality of life (58). Itch which is a cardinal symptom in AD can lead to additional problems such as difficulties falling asleep, and subsequent daytime tiredness and irritability. Patients affected with AD experience sleep loss and interference with nearly all aspects of daily life (5). Social stigmatization due to visible skin lesions may also potentially contribute to psychiatric disease burden. Most likely, the combination of pruritus, psychological stress, social isolation, depression, and

anxiety results in a vicious cycle in patients with AD (59). In addition, the child is not the only person affected, as the well-being of the entire family is likely to be disrupted (47). In general, AD patients experience lower QoL compared to healthy controls. This condition is frequently undertreated and dismissed as a nuisance, and it can have a large social/economic and financial effect on the child and family. When treating patients with AD dermatologists should be vigilant for psychiatric symptoms (5).

2.7. Complications of atopic dermatitis

Cutaneous infections are the most common type of complication of AD. Only a few pathogens are responsible; the clinical features are generally characteristic. S. *aureus* is the most common pathogen; it causes both colonization and infection. Colonization with *Malassezia* species is of importance in the head and neck variant of AD; topical antifungal therapy may be considered. Disseminated infection with *herpes simplex* virus, known as *eczema herpeticum*, is a dermatologic emergency. If clinically suspected, this potentially life-threatening disease should be treated immediately with systemically administered acyclovir. The risk of developing eczema herpeticatum is multiplied in patients with severe, untreated AD and those with the IgE-associated (extrinsic) subtype. Disseminated *coxsackie* virus infection (*eczema coxsackie*) may take a similar course on the skin. Other viral dermatoses, such as *molluscum contagiosum* or common warts, may occur in disseminated form in patients with AD (48). Other infectious diseases associated with AD include sinus infections, recurrent ear infections, influenza, pneumonia, varicella zoster, and urinary tract infections (1).

2.8. The diagnosis of atopic dermatitis

2.8.1. Diagnostic criteria of atopic dermatitis

Atopic dermatitis is diagnosed on clinical grounds. Pruritus is a mandatory diagnostic criterion. Along with the symptoms and signs, the patient's history must include information on the age of onset and time course of the condition, the personal andfamily history of atopy, and food allergies (9).

There are several criteria for diagnosing AD. The most popular and best-known are the Hanifin and Rajka AD diagnostic criteria (Table 2), which have been used since 1980. Hanifin and Rajka distinguished 4 major and 23 minor features of AD. The diagnosis of AD needs at least 3 major and 3 minor features (Figure 2)(61). The large number of minor diagnostic criteria makes the Hanifin

and Rajka criteria not very convenient to use in daily practice, especially since some symptoms are not specific to AD, such as white-eyed dermatitis, and others, such as upper lip cheilitis or nipple eczema, although highly specific to AD, are rare (61). Several international groups have proposed modifications of these diagnostic criteria, of which the modification of the Hanifin and Rajka criteria proposed by the United Kingdom Working Party (Figure 3) has become quite widespread (62). They are convenient for use by physicians in other specialties and do not require laboratory tests to confirm the diagnosis. Both the diagnostic criteria proposed by Hanifin and Rajka and the United Kingdom Working Party have been used in medical studies and tested in several different populations. The United Kingdom Working Party criteria are easier to use in practice, but the Hanifin and Rajka criteria are more precise and specific, especially in infants and young children (62–64).

Major criteria:	1. Pruritus. 2. Dermatitis affects flexural surfaces in adults and the face and extensors in infants. 3. Chronic or relapsing dermatitis. 4. Personal or family history of cutaneous or respiratory atopy.
Minor criteria:	**Features of the so-called "atopic facies":** facial pallor or erythema, hypopigmented patches, infraorbital darkening, infraorbital folds or wrinkles, cheilitis, recurrent conjunctivitis, and anterior neck folds.
	Triggers of atopic dermatitis: foods, emotional factors, environmental factors, and skin irritants such as wool, solvents, and sweat.
	Complications of atopic dermatitis: susceptibility to cutaneous viral and bacterial infections, impaired cell-mediated immunity, immediate skin-test reactivity, raised serum IgE, keratoconus, and anterior subcapsular cataracts.
	Others: early age of onset, dry skin, ichthyosis, hyper linear palms, keratosis pilaris (plugged hair follicles of proximal extremities), hand and foot dermatitis, nipple eczema, white dermatographism, and perifollicular accentuation.

Figure 2. Hanifin and Rajka AD criteria. The diagnosis of AD needs at least 3 major and 3 minor criteria (adapted from Rudzki E, et al., 1994 (61)).

Must have:

An itchy skin condition (or parental report of scratching or rubbing in a child)

Plus 3 or more of the following:

1. History of involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles, or around the neck (including cheeks in children under 10).

2. A personal history of asthma or hay fever (or history of atopic disease in a first-degree relative in children under 4).

3. A history of general dry skin in the last year.

4. Visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under 4).

5. Onset under the age of 2 (not used if a child is under 4).

Figure 3. United Kingdom Working Party AD criteria (adapted from Williams HC, et al., 2004 (62)).

2.8.2. Allergen testing in atopic dermatitis

The significance of allergic reactions in the course of AD must be investigated on an individual basis. 80% of patients have an IgE-mediated hypersensitivity to common foods or inhaled allergens such as pollen, animal hair, or house dust mites. Allergy testing (by skin prick test or in vitro test) is particularly indicated in patients with a history of immediate-type reactions in addition to AD, or in those who have delayed eczematous reactions a few hours after contact with allergens (48). Diagnosis of allergy is complicated in general and even more so in children with AD. The clinical course of AD fluctuates with many environmental triggers (allergens, irritants, infection), which can obscure whether allergens, ex. food worsens AD or the removal of the food improves AD. Moreover, children with AD often have high IgE levels to many allergens, which are not clinically relevant. A positive IgE test does not imply clinical relevance or an allergy per se. Diagnosis is made clinically and not based solely on laboratory testing (13).

There are two broad categories of allergy in AD: IgE-mediated and non-IgE-mediated. Although sIgE and skin prick tests are useful to diagnose IgE-mediated reactions, these tests are inappropriate for non-IgE-mediated or

mixed-type immune reactions, such as AD in some cases, food protein-induced allergic proctocolitis, enterocolitis syndrome, or enteropathy (13).

Skin prick tests have an excellent negative predictive value (95%) and a moderate positive predictive value (30%-50%). Specific IgE (sIgE) has a lower sensitivity than skin prick tests but can provide allergen-specific and age-specific predictive cutoffs that can help clinicians determine how likely the test is true or false positive. Referral to a specialist is recommended for the proper interpretation of these tests. Counseling is required about the potential risks of strictly avoiding foods, including worsening food allergy and anaphylaxis, nutritional deficiencies, the cost of the diet and the difficulties in implementing it, anxiety over being allergic to multiple allergens, etc. (13). The mere fact of sensitivity to a certain type of food does not imply a need for abstinence, or for treatment; only clinically relevant food allergies of the immediate type, or very marked late-type reactions, are an indication for the targeted elimination of the allergen. In case of doubt, provocative tests should be carried out under appropriate medical supervision (48).

Patch testing with contact allergens (e.g., external substances) is recommended for the additional demonstration of allergic contact dermatitis, which is hard to distinguish from concomitant AD on clinical grounds alone (48). Atopy patch testing was used in the early 2000s to identify non-IgE and mixed-type food allergens. Previous studies have reported conflicting results about the diagnostic value of atopy path testing for food allergy overall and in patients with AD owing to its nonstandardized methods. Conflicting results across studies may be due to differences in how food allergy was diagnosed (eg, oral food challenge vs skin-prick test, blinding and placebo control for a food challenge and how atopy patch testing was performed (eg, fresh foods vs lyophilized or powdered food, different concentrations (13).

Specific IgG measurement is of no value in the diagnostic evaluation of suspected allergies and should be abandoned (48).

2.9. Treatment of atopic dermatitis

2.9.1. Topical treatment

Disruption of the epidermal barrier (perceived as „dry skin “) is a major characteristic of AD, and basic skin barrier therapy thus plays a central role in treatment, whatever the degree of severity of the condition. Transepidermal water loss is increased in AD. Appropriate topical treatment with emollients can lessen the need for anti-inflammatory drugs such as glucocorticoids.

Emollients are the basis of AD treatment. Emollients usually contain moisturizing agents (to promote hydration of the stratum corneum, e.g. urea or glycerol) and occlusive agents (e.g. lipids or petroleum jelly). Thus, they reduce transepidermal water loss (TEVN), dryness, itching, cracks, or signs of lichenification (18,65). Long-term use of emollients reduces the incidence of eczema relapses, shortens the duration of exacerbations, and reduces the amount of glucocorticoids used (66,67). There is insufficient evidence to show that moisturizers differ in their efficacy and that some emollients are better than others (68,69). To keep the skin hydrated, emollients should be applied at least twice a day immediately after bathing or washing hands. The quantity used is very important. It is recommended to use about 250 g of emollients per week to lubricate the whole body of an adult. A useful rule of thumb is the amount of ointment/cream squeezed from a tube with a 5 mm diameter tip and measured from the distal phalangeal skin fold of the patient's index finger to the tip of the fingertip (about 0.5 g). This amount is sufficient to apply to both palms of an adult, which is approximately 2 % of the surface area of an adult's body (18,67). Basic therapy also includes appropriate skin cleansing: strong alkaline detergents and irritating measures are contraindicated. The main consideration, however, is the quantity of emollient: the most common mistake in topical basic therapy is to use too little of it. The so-called fingertip unit or FTU corresponds to a strand of ointment, 5 mm in diameter, that fits on the tip of an adult’s index finger (approximately 0.5 g). This amount suffices for two adult palms. Adolescents and adults need at least 250 g of emollient per week (48).

2.9.2. Anti-inflammatory treatment

Topical glucocorticosteroids (TCS) remain the main anti-inflammatory drugs for the treatment of AD. Preparations are selected according to their potency and therapeutic index. These drugs are generally applied once daily. Moderately potent topical glucocorticosteroids usually suffice for older children, adolescents, and adults. High- or very-high-potency glucocorticosteroids (class 3, or exceptionally class 4 in adults) may be indicated for the short-term treatment of marked, refractory, lichenified eczematous lesions from school age onward.

Wet wraps enhance the effect of topical glucocorticosteroids. This should be done only for a short period and under medical supervision. Proactive treatment, defined as the long-term, twice-weekly interval therapy of recurrence-prone areas with topical anti-inflammatory drugs after the visible

lesions have healed, lessens the risk of recurrence and lowers the glucocorticoid requirement without increasing the risk of side effects such as skin atrophy. There have been controlled trials of tacrolimus, fluticasone propionate, and methylprednisolone acetate. Tacrolimus ointment is currently the only preparation approved for proactive treatment (48).

Treatment with topical glucocorticoids is problematic on the face, in intertriginous areas, the scrotum, and, in infants and young children, the capillitium as well. In these areas, only low- or intermediate-potency topical glucocorticosteroids should be used, and for no more than a few days.

Topical calcineurin inhibitors (tacrolimus and pimecrolimus) have been approved since 2002 for the anti-inflammatory treatment of AD. Even their prolonged use does not cause skin thinning, steroid-induced rosacea, or perioral dermatitis. Common side effects include transient warmth or a burning sensation, but not more frequent bacterial skin infections. The risk of viral infections appears to be slightly elevated. Topical calcineurin inhibitors do not increase the risk of basal cell carcinoma or lymphoma. Out of basic considerations of safety, effective sun protection is recommended when topical calcineurin inhibitors are used (48,70).

Currently, the mainstay for phototherapy of AD in Europe is narrowband UVB (311–313 nm) and UVA1 (340–400 nm). Until now, no clinical studies have shown an increase in non-melanoma skin cancer with narrowband UVB and UVA1. Taking into account individual tolerability, narrowband UVB has been indicated for chronic moderate forms of AD and is currently preferred to broadband UVB because it is less entheogenic, while high-dose UVA1 has been prescribed for more severe phases. At the beginning of phototherapy, a co-medication of topical steroids and emollients should be considered to prevent a possible flare-up. Phototherapy can improve and even clear AD; it can decrease bacterial colonization and reduce the strength and/or the amount of topical antiinflammatory drugs needed, but the beneficial effects vary from person to person (2).

2.9.3. Systemic treatment

Three substance classes are now available for systemic anti-inflammatory treatment: conventional immunosuppressants, biologic agents, and JAK inhibitors.

Systemic glucocorticosteroids should be used only in exceptional cases and for short periods (from a few days to three weeks) to treat an acute flare (48,70). Cyclosporine is approved for the short- and medium-term treatment of severe AD in patients aged 16 and older and should not be used for more

than two years, preferably as interval therapy every few months. Methotrexate or azathioprine can be used off-label in individual cases for longer-term immunosuppression.

Dupilumab and tralokinumab are monoclonal antibodies for subcutaneous injection. Dupilumab binds the alpha subunit of the IL-4 receptor, blocks IL-4 and IL-13 signaling pathways, and is approved for use from age 6 onward. At least 75% improvement in clinical scores is achieved after 3–4 months of treatment by approximately 50% of patients on monotherapy and 70% of those taking dupilumab in combination with topical glucocorticosteroids. The most common side effects are local reactions at the injection site and ocular symptoms (especially conjunctivitis), which are usually mild and transient (48,71). Tralokinumab binds IL-13 and is currently approved for the treatment of moderate to severe AD from age 12 onward. In phase 3 trials, at least 75% improvement in clinical scores was achieved by approximately 30% of patients after 16 weeks of monotherapy, and by 56% after treatment with tralokinumab in combination with a topical class 3 glucocorticosteroid (48). The main side effects are injection-site reactions and conjunctivitis. No laboratory tests are required before or during treatment with dupilumab and tralokinumab.

Three JAK inhibitors - baricitinib, upadacitinib, and abrocitinib - have been approved to date for the treatment of moderate to severe AD in adults; upadacitinib is also approved for children aged 12 and above (48,70). Janus kinases transduce intracellular signals from cytokine receptors on the cell surface. Depending on their dose and selectivity, JAK inhibitors can act more broadly than antibodies. Baricitinib inhibits JAK1 and JAK2 equally; upadacitinib and abrocitinib are more selective for JAK1, the preferred target of the newer JAK inhibitors for AD. JAK inhibitors are administered orally; they have a short half-life and a rapid onset of action. Response rates for at least 75% improvement in clinical scores in monotherapy are approximately 35% for baricitinib, 60% for abrocitinib, and 75% for upadacitinib (at the highest dose in each case). In comparative studies, more patients displayed clinically relevant improvement in the first days to weeks of treatment with a rocitinib or upadacitinib compared to dupilumab, but the outcomes became increasingly similar the longer the drugs were continued. The side effect profile of JAK inhibitors depends on the particular agent and is more complex and broader than that of biologic agents. Side effects reported in studies of the use of JAK inhibitors to treat AD include an increased frequency of upper respiratory tract infections, herpes simplex, and varicella zoster reactivation. Patients at risk should, therefore, be vaccinated against herpes zoster. Transient nausea has been described more frequently with abrocitinib, and

transient acneiform skin manifestations with upadacitinib. Regular laboratory testing is needed, according to the manufacturers' recommendations. An increased incidence of thromboembolic events, cardiovascular disease, cancer, or serious infections has not been observed in patients with AD. Nevertheless, to minimize the risk of serious adverse events, JAK inhibitors should not be used in persons over age 65, persons at increased risk of serious cardiovascular problems or cancer, or current or past smokers, unless there is no good alternative treatment. Before treatment with JAK inhibitors is started, latent infections such as tuberculosis and hepatitis, marked renal or hepatic dysfunction, and pregnancy must be ruled out (48).

2.9.4. Corticophobia among AD patients and its implications for treatment outcomes

The fear of using TCS (usually called „corticosteroid phobia", „corticophobia") is a frequent concern for patients and their parents (72). The term ''corticosteroid phobia'' describes exaggerated concerns, fears, worries, anxiety, doubts, reservations, reluctance, or scepticism regarding corticosteroid use in patients, their caregivers, or health care professionals. ''Corticophobia'' is an issue across a variety of medical specialties, including respiratory medicine, rheumatology, allergology, and pediatrics. It is of particular importance in dermatology as topical corticosteroids (TCS) are the mainstay of treatment for many skin diseases (73). The prevalence of corticophobia in dermatology patients, especially among patients with atopic eczema or their caregivers can be between 21.0% and 83.7% depending on the authors (74,75). This fear could be the main cause of poor therapeutic adherence and consequently poor treatment response for many patients (only 32% of AD patients seem to adhere to medical instructions). Corticophobia first appeared in 1980-1990 in the context of asthma (76,77) and is now recognized as a very common but poorly understood phenomenon. Use of the term ''phobia'' seems to be a little excessive concerning its psychiatric definition as, according to psychiatrists, a phobia is an intense but unrealistic fear that can interfere with the ability to socialize, work, or go about everyday life, brought on by an object, event or situation. A specific phobia is the fear of a particular situation or object but worries about TCS are not always unfounded. For example, it is true that TCS can pass into the blood stream or can damage the skin by causing permanent thinning. The question, then, is not to qualify a patient's worries and beliefs about TCS as being true or false, but rather to understand to what extent those worries and beliefs have an impact on treatment adherence (72). The evaluation of TCP is thus an essential step in the management of patients with poor adherence (72).

3. METHODS

3.1. Study design and setting

All analyses were performed using data from a one-center cross-sectional prospective study involving a 2-stage sampling process. This study was conducted at Vilnius University Hospital Santaros Klinikos Clinic of Children's Diseases, between December 2020 and December 2022. Children with AD from 1 month to 17 years and healthy children from 6 to 17 years, who came to a dermatovenereologist consultation, were invited to participate in the study. Patients were recruited by consecutive sampling based on their clinic appointment. Of the 318 participants who agreed to take part in the study, 16 did not complete the questionnaires correctly, so the final evaluation involved 302 children in stage 1 of the study. All 55 control group patients and 52 AD patients (a total of 107) were selected to participate in stage 2 of the study.

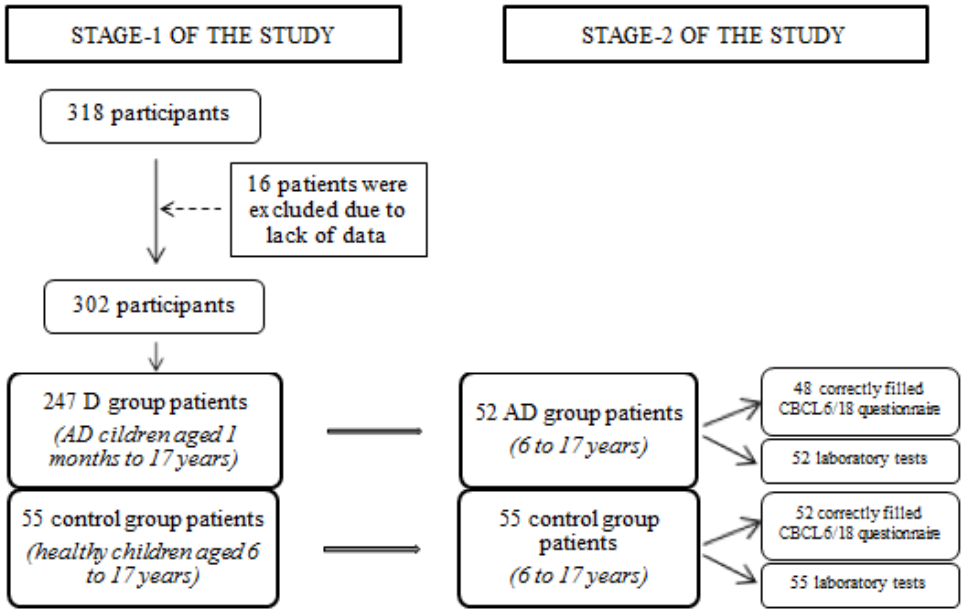

Figure 4. Enrolment in the study

The patients were included in the study according to the following enrolment criteria.

Inclusion criteria for the AD group of stage 1 of the study:

- Children aged from 1 month to 17 years, who were clinically diagnosed with AD according to Hanifin and Rajka's diagnostic criteria for AD.
- Individuals living in Lithuania.

Inclusion criteria for the AD group of stage 2 of the study:

- Children aged 6 to 17 years, who were clinically diagnosed with AD according to Hanifin and Rajka's diagnostic criteria for AD.
- Individuals living in Lithuania.

Inclusion criteria for the control group:

- Children aged 6 to 17 years, with no history of eczema, presented for a general skin examination for moles (naevus).
- Individuals living in Lithuania.

The exclusion criteria:

- Any, other than AD, eczematous and/or itchy skin disease (for example, psoriasis, other types of dermatitis, lichen), which can affect in general or mental health of patients.
- Any severe exacerbated chronic, congenital, or oncological disorders that could affect in general or mental health of patients.
- Participants, who were not able to understand the questionnaires.
- Participants, who declined participation.

3.2. Study organization

Stage 1 was designed to determine the prevalence, risk factors, and quality of life of AD in Lithuanian children. In this stage, an initial cross-sectional sample of children with AD, who came to a dermatovenereologist consultation in Vilnius University hospital Santaros klinikos Children Consultation Department was invited to participate in the survey. Background and quality of life characteristics were obtained through patients and parental questionnaires. All participants had to fill out these questionnaires:

- Original questionnaire.
- Dermatology Life Quality Index (DLQI) according to age:

- The Infants' Dermatitis Quality of Life index (IDQoL), for children under the age of 4 years.
- The Children's Dermatology Life Quality Index (CDLQI), for children aged 4–16 years.
- Dermatology Life Quality Index (DLQI), for aged 16 and above.
- The Family Dermatology Life Quality Index (FDLQI).
- TOPICOP
- Patient-Oriented Eczema Measure (POEM) - only for AD patients, to assess the severity of AD.
- The 2001 Child Behavior Checklist for Ages 6-18 (CBCL 6/18) – for stage 2 participants.

In stage 2, the patients (from stage 1), with diagnosed AD and healthy children, who were from 6 to 17 years old were invited to take part in clinical and laboratory examinations. Participants' skin condition was evaluated by a dermatovenereologist, laboratory biochemical tests from blood serum were taken and additional parents had to fill a the 2001 Child Behavior Checklist for Ages 6-18 (CBCL 6/18) form to evaluate child behavior aspects. The CBCL 6/18 questionnaire was evaluated by a psychologist who had a license to make the CBCL 6/18 assessment. A trained dermatovenereologist used the SCORing AD (SCORAD) index, to assess the severity of AD. The severity groups were defined as follows: SCORAD scores ＜25 (mild AD group), 25-50 (moderate AD group), and >51 (severe AD group).

Original questionnaire

The original questionnaire included 45 questions, created by the authors, for anamnestic, epidemiological data, factors influencing skin condition, skincare habits, and treatments. The format of the questionnaire included multiple-choice questions, yes/no questions, and Likert scales. An example of a questionnaire in the Lithuanian language is in Appendix 1.

Infants' Dermatitis Quality of Life index

The Infants' Dermatitis Quality of Life index (IDQoL) is a dermatitis-specific parent/caregiver proxy measure of the quality of life (QoL) of children under the age of 4 years. It is a 10-item questionnaire with a one-week recall period. The items measure the perceived impact on quality of life of itch and scratch, mood, time to sleep, playing or swimming, family activities, mealtimes, treatment, dressing and undressing, and bath time. An additional question

records the severity of dermatitis as perceived by the parent/caregiver. The IDQoL has been translated into several languages and is frequently used in AD trials and validation aspects have been described (78). An example of a questionnaire in the Lithuanian language is in Appendix 2.

Children's Dermatology Life Quality Index

The Children's Dermatology Life Quality Index (CDLQI) measures the impact of skin conditions on the QoL of children aged 4–16 years. The CDLQI measures the impact over the last week on symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and treatment. One question has a choice of two options depending on whether or not within the last week the child was in school or on holiday. Each question has 4 possible answers. A cartoon version appeals to younger children. The CDLQI has been validated extensively. It is completed in mean in 2 min and has score bands to give meaning to the scores (78). An example of a questionnaire in the Lithuanian language is in Appendix 3.

Dermatology Life Quality Index

Dermatology Life Quality Index (DLQI) is a self-administered, easy, and user-friendly questionnaire with an average completion time of 126 s. It consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their QoL over the last week. It has been validated for dermatology patients aged 16 years and above (79). The questions in the DLQI are classified into 6 heading items: symptoms and feelings (questions 1 and 2), daily activities (questions 3 and 4), leisure (questions 5 and 6), and personal relationships (questions 8 and 9), each item with a maximum score of 6, work and school (question 7) and treatment (question 10), each item with a maximum score of 3 (80). An example of a questionnaire in the Lithuanian language is in Appendix 4.

Family Dermatology Life Quality Index

The Family Dermatology Life Quality Index (FDLQI) is a 10-item questionnaire, with a recall period of one month, assessing the impact on the QoL of adult family members of people of any age with any skin condition. The questionnaire includes the domains of emotional and physical wellbeing, relationships, leisure activities, social life, burden of care, impact on job/study, housework, and expenditure. The FDLQI has been translated into several languages (111) and has been used in various studies involving AD and other

dermatological conditions (78). An example of a questionnaire in the Lithuanian language is in Appendix 5.

TOPICOP

TOPICOP is currently the only validated score to assess TCS phobia (72). For the cause of this study, the TOPICOP questionnaire (72) was translated into Lithuanian, adapted for use by parents of children with AD, and validated. The calculated Cronbach's alpha coefficient of TOPICOP questionnaire was 0.85 (good internal cinsistency, >0.7 is concidered acceptable). Test-retest reliability was assessed using Pearson correlation. All coefficients obtained above 0.7, so that the responses remain stably similar over time and the questionnaire is reliable.The TOPICOP scale comprises 12 questions assessing three domains of TCS phobia, knowledge and beliefs, worries (fears), and behaviour. The questions designed to assess knowledge and beliefs are "TCS makes you fat", „TCS can lead to infections", „TCS passes into the bloodstream", „TCS damages your skin", „TCS will affect my or my child's health in the future", „TCS can lead to asthma". Questions to assess worries/fears are „I am afraid of applying too much TCS", „I don't know of any side effects, but I am still afraid of TCS", „I am afraid of putting TCS cream on certain zones like eyelids where skin I s thinner". And to assess the behaviour domain – „I wait as long as possible before using a TCS to treat my skin/my child's skin", „I need more information about medicines", and „I stop using the TCS as soon as possible" (81). This questionnaire can help researchers and clinicians to better understand what influences therapeutic adherence (72). An example of a questionnaire in the Lithuanian language is in Appendix 6.

Patient-Oriented Eczema Measure (POEM)

The Patient-Oriented Eczema Measure (POEM) is a simple, valid, understandable tool for monitoring disease severity in children and adults with atopic eczema, which was originally developed to help readdress the imbalance between physician and patient-based outcome measures in eczema research. The POEM has been widely recommended as an atopic eczema outcome measure in reviews and national guidelines, being suitable for use in the outpatient clinic, and for audit, epidemiological studies, and clinical trials. Linguistic translations are available on the Patient-Reported Outcome and Quality of Life Instruments Database (http://www.proqolid.org) (82). Patient-Oriented Eczema Measure (POEM) assesses the frequency of 7 AD signs and

symptoms in the past week, including skin manifestations, itch, and sleep disturbance (83). An example of a questionnaire in the Lithuanian language is in Appendix 7.

The Severity Scoring of Atopic Dermatitis (SCORAD)

The severity of eczema symptoms is most commonly assessed using a composite index named SCORAD (scoring atopic dermatitis) developed by Kunz et al. (84). The SCORAD index includes the assessment, by a physician, of objective signs (extent and intensity) and subjective symptoms (pruritus and sleep disturbance) compiled on an analog scale of 0 to 10. It has been extensively tested in trials and validity, reliability, sensitivity, and acceptability testing of this scoring system has been widely published. SCORAD showed itself to be an excellent score for detecting the development of AD (84,85). An example of a SCORAD form in the Lithuanian language is in Appendix 8.

The 2001 Child Behavior Checklist for Ages 6-18

Behavioral difficulties were evaluated using the 2001 Child Behavior Checklist for Ages 6-18 (CBCL 6/18), validated for the Lithuanian language (86). Assessing the emotional and behavioral aspects in scientific studies is challenging because of the subjectivity of symptoms. In this context, using validated instruments allows quantification and comparisons based on established cut-off points, making the evaluation more precise and standardized (87). CBCL 6/18 is one of the most widely used instruments for screening psychological disorders. It is part of the Achenbach System of Empirically Based Assessment (ASEBA), validated by many scientific societies and cultural groups (87). Parents answer a questionnaire consisting of 138 questions, distributed as follows: the first 20 questions relate to social competence, divided into participation in activities, social relationships, and school, while the remaining 118 questions relate to behavioral problems. behavior (86,87). An example of a CBCL 6/18 form in the Lithuanian language is in Appendix 9.

Additionally, for all patients, participating in stage 2 of the study venous blood samples for laboratory analyses on the day of the visit were taken:

- morning (between 8 am and 10 am) basal serum cortisol (reference range 171-536 nmol/l),

- thyroid-stimulating hormone (TSH) (normal range for TSH value: 1-7years 0,7-5,97 mkU/ml; 7-12years 0,6-4,84 mkU/ml; 12 -20 years 0,51-4,30 mkU/ml),
- anti-thyroid peroxidase antibodies (anti-TPO) (normal range for anti-TPO value <34 IU/ml),
- vitamin D (normal range (171-536 nmol/l),
- total immunoglobulin E (IgE) (normal range for 5- 9 years <90 IU/ml; 9-15 years <200 IU/ml),
- total blood count (TBC),
- blood lipids (normal range for cholesterol 2,8-5,2 mmol/l; triglycerides 0-2,3 mmol/l; high density lipoprotein (HDL) women >1,2 mmol/l, men >0,91 mmol/l; low-density lipoprotein (LDL) 2,6-3,5 mmol/l),
- hormone prolactin (PRL) (normal range for women 108,7-557,1 mU/l; men 72,6-407,4 mU/l).

3.3. Ethical statements

Ethical approval for the study was obtained from the Vilnius regional Biomedical Ethics Committee (No. 2020/8-1251-733) on the 25th of August 2020. The study protocol corresponds to the 1975 Declaration of Helsinki revised in 2013. All participants agreed to participate in the study. Informed consent was obtained from the participating parents/caregivers, and assent was obtained from the participating children and adolescents. The consent form was signed by both legal representatives (parents or caregivers), and by children older than 12 years.

3.4. Sample selection for the present analysis

The present analysis included all eligible patients who met all inclusion criteria and none of the exclusion criteria.

3.5. Collected data

The following data was collected and was used for the present analysis within the same time frame of the study:

- Date of birth.
- Gender.
- Anthropometric data (height and weight).

- Demographic data (place of residence, number of family members, pets, skincare habits, factors influencing skin condition).
- Anamnestic data (history of atopic diseases, time of diagnosis of AD, time of onset of AD symptoms, comorbid atopic and chronic diseases, duration of breastfeeding, vaccinations, factors influencing the course of AD).
- Quality of life assessment.
- Disease severity rating scales (POEM, SCORAD).
- Assessment of corticophobia (TOPICOP).
- Behaviour and emotional status by Child Behaviour and Emotional Severity Questionnaire (CBCL 6/18).
- Laboratory tests:
    - morning basal serum cortisol,
    - thyroid-stimulating hormone (TSH),
    - anti-thyroid peroxidase antibodies (anti-TPO),
    - vitamin D,
    - total imunoglobulin E (IgE),
    - complete blood count,
    - total cholesterol,
    - low-density lipoprotein (LDL cholesterol),
    - high-density lipoprotein (HDL cholesterol),
    - triglycerides (TG),
    - prolactin (PRL).

3.6. Data sources and measurements

3.6.1. Anthropometric data

Height and weight were measured by local investigators using calibrated scales and meters.

3.6.2. Laboratory measurement

Levels of basal serum cortisol, TSH, anti-TPO, and vitamin were assessed using the automated immunoassay analyzer Cobas e 411 (Roche Diagnostics CmbH Mannheim, Germany). Total blood count (TBC) was assessed using an automated analyzer XN-L 550 (Sysmex, Japan). Blood lipids by analisator Cobas Integra 400 Plus (Roche Diagnostics CmbH Mannheim, Germany).

3.7. Data definitions and transformations

AD severity was calculated by POEM and SCORAD indexes. Patient-Oriented Eczema Measure (POEM) assesses the frequency of 7 AD signs and symptoms in the past week, including skin manifestations, itch, and sleep disturbance (83). Scores range between 0 and 28, higher scores indicate higher levels of disease activity:

- 0 to 2 clear or almost clear,
- 3 to 7 mild eczema,
- 8 to 16 moderate eczema,
- 17 to 24 severe eczema, and
- 25 to 28 very severe eczema (82).

The SCORAD Index formula is: A/5 + 7B/2 + C. In this formula, A is defined as the extent of the affected area is determined using the 'rule of nines' (maximum score of 100), and B is defined as the intensity of the affected area, including erythema, edema/papulation, oozing/crusts, excoriations, lichenification, and dryness, with each item rated on a scale of 0 to 3 (maximum score of 18) and C is defined as the subjective symptoms, the effects of daytime pruritus and sleep loss rated on an analog scale of 0 to 10 (maximum score of 20). The tool assesses disease severity with a maximum score of 103 and categorizes the severity as mild (<25), moderate (25–50) or severe (>50)(85).

QoL measurements. QoL measurement was calculated according to QoL index questionnaires. Each item in QoL index questionnaires is scored on a four-point Likert scale: 0, not at all⁄not relevant; 1, a little; 2, a lot; and 3, very much. Scores of individual items (0–3) are added to yield a total score (0–30); higher scores mean greater impairment of the patient's QoL. The QoL score is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. Interpretation meanings of QoL index scores:

- no effect at all on the patient's life,
- 2-5 small effects on the patient's life,
- 6-10 moderate effects on the patient's life,
- 11-20 very large effect on patient's life,
- 21-30 extremely large effect on patient's life (79).

Corticophobia measurements were assessed by the TOPICOP questionnaire. Responses were graded on a four-point Likert scale (score

range 0–3: 0 = never, 1 = sometimes, 2 = often and 3 = always; or 0 = totally disagree, 1 = do not agree, 2 = almost agree and 3 = agree) to a maximum of 36 points, with higher values corresponding to more severe topical corticosteroid phobia (72,81). Individual scores for all patients who responded to at least half the items plus one in a dimension were calculated by summing responses to items and then dividing that value by the number of items completed, yielding a maximal score of 36, expressed as a percentage. The mean score for a dimension was the sum of individual scores divided by the maximum possible sum for the included questions, with a resulting score of 0 to 100% of TCS phobia (72). The score can be further categorized into low (≤ 23), intermediate (24--50), and high (>50) (88).

Behavioral difficulties were evaluated using the 2001 Child Behavior Checklist for Ages 6-18 (CBCL 6/18). Parents answer a questionnaire consisting of 138 questions, distributed as follows: the first 20 questions relate to social competence, divided into participation in activities, social relationships, and school, while the remaining 118 questions relate to behavioral problems. The CBCL 6/18 assesses the presence and profile of behavioral disorders, which can be an internalizing profile with a tendency towards depression, anxiety, and somatic disorders, or an externalizing profile with aggressive and rule-breaking behavior (86,87). Questions are classified into eight syndromes: “Anxiety/Depression”, “Isolation” and “Somatic Complaints”, grouped as internalizing problems; “Rule-Breaking Behaviour” and “Aggressive Behaviour”, grouped as externalizing problems. The syndromes “Social Problems”, “Thought Problems” and “Attention Problems” are evaluated separately. The CBCL 6/18 consists of questions that should be answered as “absent/not true” (score = 0), “sometimes/slightly true” (score = 1), or “often true” (score = 2). At the end, it contains open-ended questions for parents. The sum of scores is converted into T-scores according to analyses that are appropriate for each sex and age. A T-score below 64 is normal, between 65 and 69 is borderline, and equal to or above 70 is clinical (89).

The CBCL 6/18 questionnaire was administered by a psychologist licensed to evaluate the CBCL 6/18. The data from t he questionnaires were entered into a specifics of aware that generated T-scores and classified according to the Lithuanian validation. The classification of T-scores varies according to the analyzed scale, with the normal range being >37 for total social competence, >31 for the scales analyzed separately (social, activity, and school), lower than or equal to 69 for emotional and behavioral problems, and 63 for internalizing and externalizing problems (86).

3.8. Statistical analysis

All statistical analysis was performed using the R (v. 4.0.4) program package. The mean, standard deviation (SD), quartiles (Q1 and Q3), median, and the available number of observations of the quantitative variables are presented. Categorical variables are presented as the absolute amount and the percentage. To test hypotheses between the two groups' comparison of the quantitative variables, Student's T-Test or nonparametric Mann-Whitney U test was used as appropriate. To test hypotheses between more than two groups in comparison of the quantitative variables, One-Way Analysis of Variance (ANOVA) or nonparametric Kruskal-Wallis test was used as appropriate. Normality was tested using the Shapiro-Wilks test. To test hypotheses for between-group comparison of the categorical variables, Pearson's Chi-Square or Fisher's exact tests were used as appropriate. To test multiple variables relations to the scores of scales multivariate linear regression was used. A p-value less than 0.05 was considered significant.

The G*Power 3.1.9.4 program was used to determine the sample size for all evaluated hypotheses to ensure the power of 0.9 to detect a desired effect size of 0.5 for all tests comparing the study population with the general population, and 0.65 for the comparisons within various subgroups of the study population. Sample size varies from 86 up to 172 patients depending on the selected analysis type and grouping requirement. Our sample size is 302 in phase 1 and 107 in phase 2 which is considered sufficient to derive reliable statistical estimates for all performed statistical tests. Supplementary analysis was performed using Microsoft Excel. Data was validated by using a standardized data validation plan to avoid including patients with missing data or data that falls outside the predefined plausibility ranges.

4. RESULTS

4.1. Characteristics of study participants

This study included a total of 302 children and their parents/caregivers: 247 children AD patients (125 boys and 121 girls) and 55 non-AD patients (28 boys and 27 girls). Table 2 describes the personal characteristics, demographic and epidemiological data of the participants. The mean age for AD patients was 6.8±4.4 years and 10.5±3.1 years for the control patients in stage 1 of the study, and 10±2.7 years for AD patients and 10.5±3.1 years for the control patients in stage 2. The mean age of parents/caregivers was 37.3±6.5 years. 225 (74%) of families lived in the city, 33 (11%) in the suburb and 37 (12%) in the country area. 257 (85%) responders live in married families, 28 (9%) with cohabiting partners. 11 (4%) of families are divorced and 4 (1%) with single parents. The majority of parents (263 (87%) of mothers and 205 (68%) of fathers) have a university degree. 98 (33%) of parents are smoking, including 29 (10%) mothers and 69 (23%) fathers. However, patients in the control group were more likely to have a pet at home (control group - 35 (70%) vs. AD group 131 (53%), p=0.028).

The fact of breastfeeding (224 (91%) in AD and 44 (85%) in the control group) and duration of breastfeeding, age at initiation of solid food introduction did not differ between the AD and control groups. 169 (69%) in AD and 24 (47.1%) in the control group had a positive family history of atopy ($p<0.05$).

The majority of all children were vaccinated, but only 96 (39%) of AD children were vaccinated with the complete vaccine programme, compared to 50 (96%) of the control group ($p<0.05$). Of the reasons for not receiving the full vaccination, the majority in the AD group (127 (86%)) reported an allergic reaction after the vaccine or an exacerbation of dermatitis, and only 7 (3%) were not advised by doctors. These data show that there is a common fear of vaccine-side reactions among parents of AD patients.

61% of the AD group had at least one atopy disease: 67 (29%) had allergic rhinoconjunctivitis, 99 (43%) had a food allergy, 28 (12%) had allergic asthma. 13 (5%) were diagnosed with all three atopic diseases. AD patients are more likely than control patients, to have food allergies ($p<0.001$) and allergic rhinitis (p=0.022), but not allergic asthma (p=0.188).

189 (77%) of the AD group experienced their first AD symptoms before the age of 1 year. 37% of them had the first symptoms before the age of 3

months, 20% - before the age of 4-5 months, and 20% - between the ages of 6 and 12 months). A total of 218 (89%) AD patients were diagnosed with a disease before the age of 5 years.

In phase 1 of the study, 44 (18%) of the AD children had severe AD, 81 (33%) – had moderate, and 114 (3%) - had mild AD according to objective POEM. 8 (3%) of the AD patients did not complete the POEM questionnaire correctly so the results of these questionnaires were not included. The severity of AD among the 52 AD children in phase 2 was distributed as follows: 19 (37%) children had severe AD, 22 (42%) children had moderate AD, and 11 (2%) children had mild AD as assessed by SCORAD. The difference in results between the POEM and SCORAD groups is because phase 2 included blood laboratory tests, and those with severe AD were more likely to participate in the study.

In summary, there are no differences in parental education, smoking status, place of residence and type of housing, number of siblings and income per family member per month in both the AD group and the control group. However, AD patients are less likely to have pets in their families.The fact and duration of breastfeeding and the timing of introduction of solid foods do not differ between groups, but AD patients have lower vaccination levels, a positive family history of atopy, and a higher incidence of food allergy and allergic rhinitis, but not allergic asthma. Most AD patients were diagnosed before the age of 5 years.

Table 2. Description of the study populations.

Participants' characteristics n (%)	**Children AD group**	**Children control group**	**Parents/caregivers**
Sex			
Male	125 (51%)	28 (51%)	14 (5%)
Female	122 (49%)	27 (49%)	288 (95%)
Age (years)			
Stage 1 of the study	6.8 ±4.4	10.5±3.1	37.3±6.5
Stage 2 of the study	10±2.7	10.5±3.1	N/A

Participants' characteristics n (%)	Children AD group	Children control group	Parents/caregivers	
Place of residence				
City	N/A	N/A	225 (74%)	
Countryside	N/A	N/A	37 (12%)	
Suburb	N/A	N/A	33 (11%)	
N/A	N/A	N/A	3 (1%)	
Marital status				
Married	N/A	N/A	257 (85%)	
Cohabiting partner	N/A	N/A	28 (9%)	
Divorced	N/A	N/A	11 (4%)	
Single	N/A	N/A	4 (1%)	
NA	N/A	N/A	3 (1%)	
Educational level			Mother	Father
University	N/A	N/A	263 (87%)	205 (68%)
Incomplete university	N/A	N/A	7 (2%)	15 (5%)
College	N/A	N/A	23 (8%)	66 (22%)
Secondary school	N/A	N/A	5 (2%)	12 (4%)
Other	N/A	N/A	0 (0%)	1 (0%)
NA	N/A	N/A	5 (2%)	4 (1%)
Smoking habits			Mother	Father
Smoking	N/A	N/A	29 (10%)	69 (23%)
Non-smoking	N/A	N/A	269 (89%)	229 (76%)
NA	N/A	N/A	5 (1%)	5 (1%)

Participants' characteristics n (%)	Children AD group	Children control group	Parents/caregivers	
Type of housing				
Apartment (flat)	136 (55%)	34 (65%)	N/A	N/A
House	98 (40%)	18 (35%)	N/A	N/A
Other	13 (5%)	0 (0%)	N/A	N/A
Monthly income per family member in euros				
<200 Eur	2 (4%)	2 (2%)	N/A	N/A
201-400 Eur	2 (4%)	2 (2%)	N/A	N/A
401-600 Eur	15 (28%)	6 (12%)	N/A	N/A
601-800 Eur	14 (26%)	12 (24%)	N/A	N/A
801-1000 Eur	10 (19%)	8 (16%)	N/A	N/A
>1001 Eur	11 (20%)	21 (41%)	N/A	N/A
Having a pet at home	131 (53%)*	35 (70%)*	N/A	N/A
Child was breastfeeding	224 (91%)	44 (85%)	N/A	N/A
Duration of breastfeeding				
0 months	2 (1%)	0 (0%)	N/A	N/A
≤3 months	37 (15%)	4 (8%)	N/A	N/A
4-5 months	8 (3%)	6 (12%)	N/A	N/A
6-9 months	31 (13%)	4 (8%)	N/A	N/A

Participants' characteristics n (%)	**Children AD group**	**Children control group**	**Parents/caregivers**	
10-12 months	46 (19%)	9 (17%)	N/A	N/A
13-17 months	58 (23%)	16 (31%)	N/A	N/A
18-24 months	12 (5%)	5 (10%)	N/A	N/A
>24 months	30 (12%)	0 (0%)	N/A	N/A
Age of solid food introduction				
≤3 months	3 (6%)	2 (4%)	N/A	N/A
4-5months	20 (38%)	26 (55%)	N/A	N/A
Vaccination				
Yes	96 (39%)*	50 (96%)*	N/A	N/A
No	3 (1%)	2 (4%)	N/A	N/A
Partly	136 (55%)*	0 (0) *	N/A	N/A
Family history of atopy	169 (69%)*	24 (47,1%)*	N/A	N/A
Patients history of atopy				
Food allergy	99 (43%)*	1 (2%)*	N/A	N/A
Allergic asthma	28 (12%)	3 (6%)	N/A	N/A
Allergic rhinoconjunctivitis	67 (29%)*	7 (13%)*	N/A	N/A
All three atopic diseases	13 (5%)	0 (0%)	N/A	N/A

Participants‘ characteristics n (%)	Children AD group	Children control group	Parents/caregivers	
First AD symptoms				
<3 months	91 (37%)	N/A	N/A	N/A
4-5 months	48 (20%)	N/A	N/A	N/A
6-12 months	50 (20%)	N/A	N/A	N/A
1-3 years	32 (13%)	N/A	N/A	N/A
3-5 years	9 (4%)	N/A	N/A	N/A
>5 years	8 (3%)	N/A	N/A	N/A
Severity according to POEM				
Severe	44 (18%)	N/A	N/A	N/A
Moderate	81 (33%)	N/A	N/A	N/A
Mild	114 (46%)	N/A	N/A	N/A
Did nor specified	8 (3%)	N/A	N/A	N/A
Severity according to SCORAD				
Severe	19 (37%)	N/A	N/A	N/A
Moderate	22 (42%)	N/A	N/A	N/A
Mild	11 (2%)	N/A	N/A	N/A

Abbreviations: *N/A, not applicable.*

Note: *data marked with ∗ has p-value <0,05.*

4.2. Skincare, topical treatment features and factors affecting skin condition

4.2.1. Skincare habits

Table 3 summarises skincare habits between the groups. The majority of AD patients baths 1 time (81 (33%)) or 2 times (74 (30%)) per day. 78 (32%) take a bath 1-2 times/week. In the control group 23 (45%) uses baths 1 time/day, 13 (25%) – 3-4 times/week, and 14 (27%) 1-2 times per week. There is no statistically significant difference between the groups when comparing bathing frequency. AD patients are more likely than controls to wash their skin with a special soap for dry skin ($p<0.001$), and more often use bath additives (bath oils) ($p=0.015$). In contrast, the control group is more likely to use regular soap ($p<0.001$).

AD patients do not use emollients frequently enough and use insufficient amounts than recommended. Only 14 (6%) of AD patients reported using the required amount of emollients (>500 ml/month), all others used less than required. As many as 57 (23%) of AD patients consume less than 100 ml of emollients per month. The majority (38 (75%)) of non-AD patients do not apply more than 100 ml of emollient per month.

The frequency of emollient application on the skin during the last 2 weeks varies in the AD group, with 47 (19%) applying 3-4 times a week, 53 (21%) - 1-2 times/week, and 57 (24%) - less than once a week. Only 21 (9%) of AD children apply emollient more than 2 times a day and 31 (13%) twice a day. In contrast, 10 (20%) of the control group apply 1-2 times a week and 9 (18%) less than once a week. However, a relatively high number (31 (61%)) of control group patients did not specify their skin hydration with emollient habits.

Phase 2 participant data showed that AD patients daily apply emollients to the skin ($p<0.001$) and the control group is more likely to apply emollients only when they feel dry skin ($p<0.001$). The reasons for not applying emollient daily were similar between the groups, with 1 (2%) of the patients from AD and control group saying there is no time for daily application, 3 (5%) in AD, and 2 (4%) in control group forgetting to apply. 6 (12%) of AD and 4 (8%) of control patients applies emollients only when a rash appears, and accordingly 8 (15%) and 8 (16%) - only after bathing. There was no statistically significant difference between these data.

Summarising skin care habits, we observed that there is no difference in bathing frequency between the groups, but AD patients use special soaps for dry skin, while the control group uses a regular soap. The AD group is more likely to apply emollients to the skin, but both groups underuse the recommended amount of emollients per month.

Table 3. Skincare characteristics of participants.

Variable	Children AD group	Children Control group
Phase 1 questionnaires (n=302)		
Frequency of bathing		
>2 times/day	2 (1%)	0 (0%)
2 times/day	74 (30%)	1 (2%)
1 time/day	81 (33%)	23 (45%)
3-4 times/week	10 (4%)	13 (25%)
1-2 times/week	78 (32%)	14 (27%)
<1 time/week	2 (1%)	0 (0%)
Types of cleansers		
Bath oil	42 (19%)*	2 (4%)*
Regular soap	25 (11%)*	26 (57%)*
Other	3 (1%)	0 (0%)
Washing only with water without detergents	21 (10%)	2 (4%)
Washing with special soaps for dry skin	185 (84%)*	23 (50%)*
The amount of emollient you use in a month		
<100 ml	57 (23%)*	38 (75%)*
100-200 ml	37 (15%)*	4 (8%)*
201-300 ml	51 (21%)*	0 (0%)*
301-400 ml	37 (15%)*	0 (0%)*
401-500 ml	27 (11%)*	0 (0%)*
>500 ml	14 (6%)*	0 (0%)*
I don't know	24 (10%)	9 (18%)

Variable	Children AD group	Children Control group
How often you have applied an emollient to your child's skin in the last 2 weeks?“		
>2 times/day	21 (9%)	1 (2%)
2 times/day	31 (13%)	0 (0%)
1 time/day	15 (6%)	0 (0%)
3-4 times/week	47 (19%)	0 (0%)
1-2 times/week	53 (21%)	10 (20%)
<1 time/week	57 (24%)	9 (18%)
Did not applied	23 (9%)	31 (61%)
Phase 2 questionnaires (n=107)		
Daily application of emollient	26 (50%)*	1 (2%)*
Applies emollient only when the skin becomes dry	13 (25%)*	38 (76%)*
Applies only then a rash appears	6 (12%)	4 (8%)
Only after bathing	8 (15%)	8 (16%)
Forgets to apply emollient every day	3 (5%)	2 (4%)

Abbreviations: *AD, atopic dermatitis.*
Note: *data marked with * has p-value <0.05.*

4.2.2. Topical skin treatment habits

To investigate medication application routines, we asked parents of children with AD how they apply prescribed topical medications (corticosteroids, calcineurin inhibitors, antibiotics). 114 (51%) of the respondents apply the medicine on top of the moisturizing cream, 42 (19%) applies it on the rash and apply the moisturizing cream on top of or around the rash, 9 (4%) dilute (mix) the medicine with the moisturizing cream, and 8 (4%) choose other application techniques. 49 (22%) choose not to apply prescribed medicines (Figure 5).

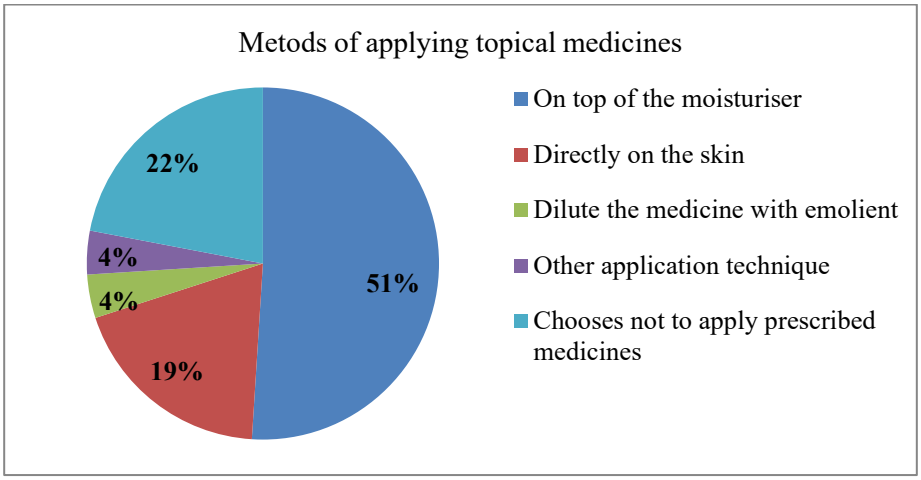

Figure 5. Methods of applying medicines to the skin.

In our questionnaire, we asked respondents where they look for further information about AD. Of the options listed (respondents could choose from more than one answer), the three most common were: from medical professionals 183 (75%), from the internet and chat forums 141 (58%), and from specialist AD websites 112 (46%) (Figure 6). In fact, of the 244 respondents who completed the question on „where they look for more information about the disease", 23 (9%) indicated that they do not look for additional information about AD.

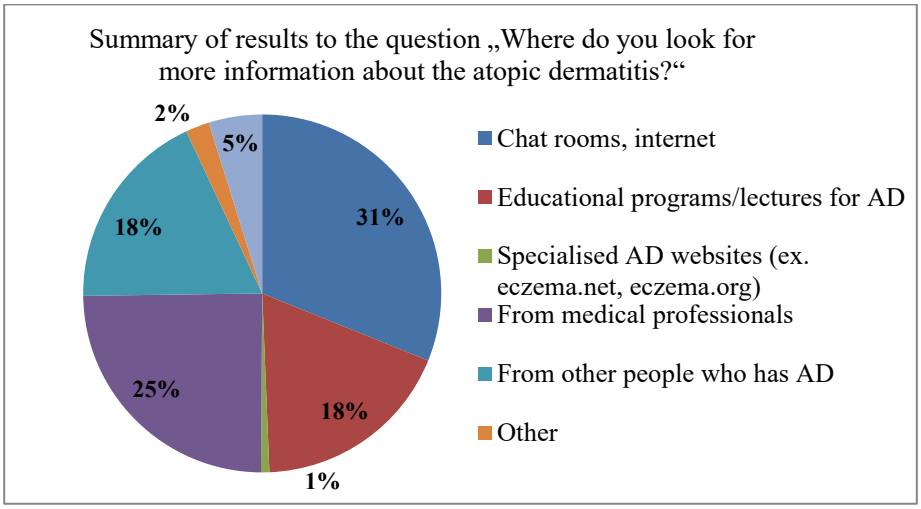

Figure 6. Summary of results to the question „Where do you look for more information about the AD?"

4.2.3. Comparison of physical and environmental factors affecting skin condition (phase 2)

In phase 2 of the study, we asked how the subjects' skin condition changes when they are exposed to different physical stressors. AD patients were more likely to experience improved skin condition during holidays at the seaside 31 (60%) AD group versus 18 (35%) control group), ($p<0.001$) and holidays in warm countries (accordingly 23 (49%) versus 21 (41%), ($p=0.003$).

Although 28 (60%) of the AD and 31 (60%) of the control group reported that infectious diseases do not affect their skin condition, 17 (36%) of AD patients and only 7 (13%) of healthy controls experience worsening of their skin condition due to infectious diseases ($p<0.001$). Clothing also has an impact on the skin condition of people with AD. Although the majority of respondents in both groups reported that clothing has no effect, as many as 17 (41%) of AD respondents reported that woolen clothing and 14 (14%) synthetic clothing worsens their skin condition ($p<0.001$).

17 (38%) of AD patients compared to 7 (14%) controls have their skin condition exacerbated by a swimming pool ($p<0.001$) and accordingly 4 (10%) and 1 (2%) exacerbated by vaccination ($p<0.001$). None of the control group develop skin deterioration after contact with animals, but in 11 (23%) of the AD group, contact with animals causes worsening of skin condition ($p<0.001$). While 50% of atopic patients ($n=22$) and controls ($n=26$) reported that stress has no effect, 21 (48%) of AD patients experience a worsening of their skin condition after stress, compared to 10 (19%) of the control group ($p<0.001$). Similar trends were observed for the effect of season on the skin of the subjects: 31 (60%) of AD and 23 (45%) of control group improved in summer ($p=0.02$), and 31 (61%) and 28 (54%) deteriorated in winter ($p=0.033$).

In summary, AD patients' skin condition improves in summer, during holidays in warm countries or by the sea side. Exacerbating factors for or the skin condition of AD patients include: infectious disease, vaccination, bathing in a swimming pool, wearing woollen or synthetic clothing, contact with an animals. Data on how physical and environmental factors affect the skin of AD and control patients can be seen in Table 4.

Table 4. Comparison of physical and environmental factors affecting skin condition of atopic and control group children (phase 2).

Variable		Children AD group	Children Control group	p-value
During a seaside	No influence	18 (35%)	24 (47%)	<0.001
	Worsens	3 (6%)	0 (0%)	
	Improves	31 (60%)	18 (35%)	
	Don't know	0 (0%)	9 (18%)	
During holidays in warm/sunny countries	No influence	22 (47%)	20 (39%)	0.003
	Worsens	2 (4%)	0 (0%)	
	Improves	23 (49%)	21 (41%)	
	Don't know	0 (0%)	10 (20%)	
Infectious diseases (ex. upper respiratory infection)	No influence	28 (60%)	31 (60%)	<0.001
	Worsens	17 (36%)	7 (13%)	
	Improves	2 (4%)	0 (0%)	
	Don't know	0 (0%)	14 (27%)	
From common non-hypoallergenic hygiene cosmetic products	No influence	23 (50%)	34 (67%)	<0.001
	Worsens	18 (39%)	6 (12%)	
	Improves	5 (11%)	0 (0%)	
	Don't know	0 (0%)	11 (22%)	
Wearing synthetic clothing	No influence	23 (62%)	34 (67%)	<0.001
	Worsens	14 (14%)	6 (12%)	
	Don't know	0 (0%)	11 (22%)	
Wearing woollen clothing	No influence	23 (56%)	32 (63%)	<0.001
	Worsens	17 (41%)	6 (12%)	
	Improves	1 (2%)	0 (0%)	
	Don't know	0 (0%)	13 (25%)	
After eating some food	No influence	18 (39%)	28 (55%)	<0.001
	Worsens	28 (61%)	10 (20%)	
	Don't know	0 (0%)	13 (25%)	

After swimming pool	No influence	25 (56%)	31 (61%)	<0.001
	Worsens	17 (38%)	7 (14%)	
	Improves	3 (7%)	0 (0%)	
	Don't know	0 (0%)	13 (25%)	
After contact with a domestic animal (pet)	No influence	36 (77%)	37 (73%)	<0.001
	Worsens	11 (23%)	0 (0%)	
	Don't know	0 (0%)	14 (27%)	
After vaccination	No influence	36 (88%)	35 (69%)	<0.001
	Worsens	4 (10%)	1 (2%)	
	Improves	1 (2%)	0 (0%)	
	Don’t know	0 (0%)	15 (29%)	
During stress	No influence	22 (50%)	26 (50%)	<0.001
	Worsens	21 (48%)	10 (19%)	
	Improves	1 (2%)	0 (0%)	
	Don’t know	0 (0%)	16 (31%)	
When the skin is sweating	No influence	25 (54%)	29 (57%)	<0.001
	Worsens	19 (41%)	11 (22%)	
	Improves	2 (4%)	0 (0%)	
	Don’t know	0 (0%)	11 (22%)	
During summertime	No influence	15 (29%)	19 (37%)	0.002
	Worsens	6 (12%)	1 (2%)	
	Improves	31 (60%)	23 (45%)	
	Don’t know	0 (0%)	8 (16%)	
During winter time	No influence	17 (33%)	19 (37%)	0.033
	Worsens	31 (61%)	28 (54%)	
	Improves	3 (6%)	0 (0%)	
	Don’t know	0 (0%)	5 (10%)	

Abbreviations: *AD, atopic dermatis*

4.2.4. Comparison of physical and environmental factors affecting skin condition between AD severity groups according to SCORAD (phase 2)

We compared patterns in skincare habits and the influence of other factors on the skin between groups of patients with different severity according to SCORAD of atopic dermatitis and found that severe AD patients are more likely to have a worsening of their skin condition after contact with an animal than mild ($p=0.009$) or moderate ($p=0.041$) AD patients. Patients with severe AD were more likely to have applied emollients daily to their skin 14 (82%) in the severe AD group vs. 6 (30%) mild group), ($p=0.013$) and more often have used topical treatment in the last two weeks (according to 15 (89%) and 4 (40%) compared to mild AD patients ($p=0.011$). The influence of other factors did not differ between the groups (Table 5).

Table 5. Comparison of factors between AD severity groups according to SCORAD.

Variable		Severe		Mild		Moderate		p-value	Mild vs. severe	Mild vs. moderate	Moderate vs. severe
After contact with a domestic animal (pet)	No	8	47%	10	100	10	91%	0.004	0.009	1.000	0.041
After contact with a domestic animal (pet)	Worse	9	53%	0	0	1	9%	0.004	0.009	1.000	0.041
Dailly aplication of emollients	No	3	18%	7	70%	8	57%	0.014	0.013	0.678	0.031
	Yes	1	82%	3	30%	6	43%	0.014	0.013	0.678	0.031
Application of topical medication to the skin during the last two weeks	No	2	11%	4	40%	5	36%	0.024	0.011	0.211	0.195
	Yes	1	89%	4	40%	9	64%	0.024	0.011	0.211	0.195

Abbreviations: *AD, atopic dermatitis.*

4.3. Endogenous factors

In phase 2 of the study, we investigated whether there is an association between endogenous factors such as vitamin D, basal serum cortisol, thyroid-stimulating hormone (TSH) and anti-thyroid peroxidase antibodies (anti-TPO), prolactin levels and pediatric atopic dermatitis and its severity (according to SCORAD index). The analysis included 52 patients with AD and 55 healthy controls (in total 58 females and 47 males) with a mean age of 10.2 ± 2.9 years (range 6-17 years). The subjects' body mass index values were not statistically significantly different and were within the normal range according to the World Health Organisation guidelines. The mean BMI was 20.4 in the AD group and 18.67 in the control group. There were no differences in age, gender, weight, and height between the groups. There were 19 AD patients in the severe AD group, 22 – in the moderate and 19 - in the mild AD group.

The evaluation of the laboratory tests showed a statistically significant difference in the mean values of total immunoglobulin E and cortisol levels. AD patients have higher total IgE and lower cortisol levels. Mean values of count of eosinophils, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, prolactin, TSH, anti-TPO, and 25(OH)D3 did not differ between groups. For more detailed information on the subject groups, refer to Table 6.

Comparing the total count of eosinophils and total IgE, there was a difference between severity groups. Patients with more severe AD had a higher count of total eosinophils ($p=0.039$) and total IgE ($p<0.001$) (refer to Table 8).

In summary, the mean values of eosinophils, total cholesterol, HDL-cholesterol, LDL-cholesterol, LDL-cholesterol, triglycerides, prolactin, TSH, anti-TPO, and 25(OH)D3 did not differ between the groups, but the mean values of total immunoglobulin E were higher and cortisol levels were lower in AD patients. Patients with more severe AD had a higher count of total eosinophils and total IgE.

Table 6. Comparisons of age, weight, height, and laboratory test results between patients with AD and controls in phase 2 of the study.

Variable	Group	Mean±SD	Median (Q1-Q3)	p-value
Age at the time of visit	AD	10.0±2.7	9 (8-11)	0.287
	Control	10.5±3.1	11 (8-13)	0.287
Weight (kg)	AD	46.2±20.2	43.85 (32-51)	0.376
	Control	42.1±16.2	39.35 (28.5-52.9)	0.376
Height (cm)	AD	149.6±16.4	149 (138.2-160)	0.983
	Control	149.5±16.9	148 (136-164)	0.983
Total IgE (IU/ml)	AD	1167.6±2093	264.95 (109.6-	<0.001
	Control	173.0±241.8	66.8 (19.8-219.4)	<0.001
EOS (x10 *9/l)	AD	0.5±0.4	0.33 (0.2-0.6)	0.086
	Control	0.3±0.4	0.25 (0.16-0.3)	0.086
EOS (%)	AD	6.4±4.9	5.3 (2.5-8.4)	0.086
	Control	4.8±4.0	3.9 (2.9-5.5)	0.086
Cholesterol (mmol/l)	AD	4.2±0.6	4.15 (3.8-4.5)	0.057
	Control	4.0±0.7	4.01 (3.6-4.4)	0.057
HDL-cholesterol (mmol/l)	AD	1.6±0.3	1.55 (1.39-1.78)	0.972
	Control	1.6±0.3	1.58 (1.4-1.8)	0.972
LDL-cholesterol (nmol/l)	AD	2.4±0.5	2.4 (2.1-2.8)	0.097
	Control	2.3±0.6	2.24 (1.8-2.6)	0.097
Tryglicerides (mmol/l)	AD	1.0±0.6	0.79 (0.6-1.1)	0.104
	Control	0.8±0.4	0.66 (0.5-0.9)	0.104
Cortisol (nmol/l)	AD	252.9±304.3	200.1 (135.7-	0.047
	Control	351.6±126.1	279.7 (209-373)	0.047

Variable	Group	Mean±SD	Median (Q1-Q3)	p-value
Prolactin (mU/l)	AD	206.8±200.3	155.4 (123.5-	0.198
	Control	237.9±125.7	200.6 (152-263.2)	0.198
Anti-TPO (IU/ml)	AD	28.6±80.7	14.22 (11.4-17.4)	0.430
	Control	15.2±9.6	13.7 (11.6-16.2)	0.430
TSH (mkU/ml)	AD	2.3□1.5	1.98 (1.5-2.5)	0.757
	Control	2.4□1.3	2.02 (1.5-2.9)	0.757
25(OH)D3 (nmol/l)	AD	71.6□22	68 (56.98-81.1)	0.112
	Control	65.6□27.4	62.22 (48.8-79.2)	0.112

Abbreviations: *AD, atopic dermatitis; anti-TPO, anti-thyroid peroxidase antibodies; EOS, eosinophils; HDL-cholesterol, high-density lipoprotein cholesterol; IgE, immunoglobulin E; LDL-cholesterol, low-density lipoprotein cholesterol; SD, standard deviation; TSH- thyroid-stimulating hormone;* 25(OH)D3, *25-hydroxy vitamin D3.*

4.3.1. 25(OH)D3 levels in pediatric AD and control patients

Levels of 25(OH)D3 (vitamin D3) were detected as normal in 18 of 52 (34.6%) patients with AD and 17 of 55 (30.9%) control subjects; insufficient- in 27 (51.9%) versus 21 (38.2%); deficient in 7 (13.5%) versus 17 (30.9 %). Only 1 (1.8%) patient in the control group had vitamin D hypervitaminosis. The mean serum concentration of 25(OH)D3 in 52 patients with AD (71.6±2 nmol/l, was not statistically different (p=0.112) from that of 55 control subjects (65.6±27 nmol/l). We excluded patients who used vitamin D supplements 1 month before the visit. Comparing means, there was no significant difference (p=0.3575) between AD (n=15)(73.6±22.4 nmol/l) and control groups (n=19) (66.8±26.9 nmol/l). Also, there was no difference (p=0.3965) between groups when comparing the means of 25(OH)D3 of patients who did not take vitamin D supplements and were tested during the high-sun season: the mean of 25(OH)D3 in serum in AD group (n=18) was 73.7±20.7 nmol/l versus control group (n=14) – 0.7±41.8 nmol/l. Participants, with AD, who were medically examined during high sun season (from April to September) (n=34) had significantly higher (p=0.0244) mean serum 25(OH)D3 (66.2±27.6 nmol/l) than AD participants with examination during the low-sun season (october-march) (n=18) 71.8±23 nmol/l. However, no

significant difference was found (p=0.197) when comparing the same means in the control group (n=53, 66.2±27.7 nmol/l versus n=2, 49.7±11.3 nmol/l). A comparison of the 25(OH)D3 levels for the different groups of participants is shown in Table 7.

Table 7. Comparison of the 25(OH)D3 levels for the different groups of participants.

Variable	**n**	**Mean±SD**	**p-value**
Total AD	5	71.6±22	p=0.112
Total control	5	65.6±27	p=0.112
AD without supplements	1	73.6±22.4	p=0.357
Control without vit D supplements	1	66.8±26.9	p=0.357
AD without supplementation in the high-sun	1	73.72±20.67	p=0.396
Controls without supplementation in high-sun	1	0.74±41.84	p=0.396
AD during high-sun season	1	71.8±23	p=0.024
AD during low-sun season	3	66.2±27.7	p=0.024
Control during high-sun season	5	66.22±27.65	p=0.197
Control during low-sun season	2	49.3±11.27	p=0.197

Abbreviations: *AD, atopic dermatitis; SD, standard deviatio;* 25(OH)D3, *25-hydroxy vitamin D3; n, number.*

There was no statistically significant difference (p=0.148) in mean 25(OH)D3 scores on the SCORAD index between AD severity groups (Table 8).

In summary, no statistically significant difference between 25(OH)D3 values between AD and healthy control children was found, but children with AD have lower vitamin D levels during the low-sun season. We did not find an association between the severity of AD and 25(OH)D3 levels.

4.3.2. Cortisol levels in pediatric AD and control patients

Morning basal serum cortisol values were observed above the upper limit of the reference range (171-536 nmol/l 7-10 am) in 2 (4%) patients in the AD group (n = 52) and 1 (2%) subject in the control group (n = 55). 14 (27%) of AD and 4 (7%) of control patients had lower values according to the reference

range. The other 36 (69%) patients in the AD group and 50 (91%) subjects in the control group had normal levels of serum cortisol. When the mean values of morning serum cortisol in AD patients (252.9±304.3 nmol/l) and control subjects (351.6±126.1 nmol/l) were compared, there was a statistical difference between the two groups (p=0.047). We compared whether cortisol levels differed between patients in the AD group, who had been treated with topical corticosteroids in the last 2 weeks, and those who had not received these drugs. There was no statistically significant difference in cortisol concentrations between the two groups. The mean cortisol level for treated with topical corticosteroids was 312.6±263.7 nmol/l and for untreated patients – 143.8±76.6 nmol/l (p=0.1808). Were was no difference between cortisol level mean values according to severity by SCORAD groups (Table 8).

In conclusion, we found that serum cortisol was lower in the AD group compared with healthy controls, however, the severity of AD did not affect serum cortisol values in the children with AD group.

4.3.3. Thyroid-stimulating hormone and anti-thyroid peroxidase antibodies levels in pediatric AD and control patients

No statistical difference was found for scores obtained from anti-thyroid peroxidase antibodies (anti-TPO) values between groups: anti-TPO mean value for the AD group was 28.6 ± 80.7 IU/ml, median 14.2 (11.4-17.4) IU/ml and the for the control group – 15.2 ± 96. IU/ml, median 13.7 (11.6-16.2) (p =0.430). The same results were observed in comparing thyroid-stimulating hormone (TSH) results, in the AD group the mean TSH value was 2.3±1.5 mkU/ml, a median of 1.98 (1.5 – 2.5) mkU/ml, and in control group mean 2.4±1.3 mkU/ml, median 2 (1.5-2.9) mkU/ml, p=0.757. Analysis of anti-TPO values showed that two AD patients and one control patient had higher than normal anti-TPO values (p=0.757), however, TSH was in the normal range for those patients. Normal range for TSH value: 1 y.-7y.: 0.7-5.97 mkU/ml; 7y.-12y.: 0.6-484 mkU/ml; 12y.-20 y.: 0.51-4.30 mkU/ml. The normal range for anti-TPO value is <34 IU/ml. Analysis of TSH values showed that 3 patients in AD and 4 patients in the control group had elevated TSH values (p=0.428) (2 of those with AD had elevated anti-TPO values), and 1 in the control group had decreased TSH values (anti-TPO was within normal range). Were was no difference between anti-TPO ant TSH levels mean values according to severity by SCORAD groups (Table 8).

In summary, no statistically significant difference between TSH and Anti-TPO values between AD and healthy control children was found.

4.3.4. Prolactin levels in pediatric AD and control patients

One patient in AD and two control patients had hyperprolactinemia, and one patient in AD had hyperprolactinemia. Mean serum prolactin concentration was 206.8±200.3 mU/l, median 155.4 (123.5 – 246.7) for AD patients and 237.9 ± 125.7 mU/l, median 200.6 (152 – 263.2) for controls (p=0.198). No significant difference was found in prolactin levels between AD severity groups (p=0.168) (Table 8). We found no difference in prolactin levels between children with AD and healthy controls.

Prolactin levels do not seem to play a role in the pathogenesis of AD as its serum levels are comparable with the normal population.

Table 8. Comparison of eosinophils, total IgE, 25(OH)D3, morning cortisol, anti-TPO, TSH, and prolactin levels between AD group according to SCORAD.

Variable	SCORAD group	n	Mean±SD	Median (Q1-Q3)	p-value
Eosinophiles x 10∗9/l	Severe	19	0.63±0.48	0.5 (0.2-1)	0.039
	Moderate	22	0.42±0.43	0.3 (0.1-0.5)	0.039
	Mild	11	0.29±0.23	0.2 (0.2-0.4)	0.039
Total IgE IU/ml	Severe	19	2201.3±2927.8	890.3 (371-2270.0	<0.001
	Moderate	22	713.34±1266	170.6 (69.7-519.4	<0.001
	Mild	11	319.1±393.3	111.3 (28.8-503.1)	<0.001
25(OH)D3 (nmol/l)	Severe	19	65.9±21.3	61.3 (54.1-78.1)	0.148
	Moderate	22	75.1±25.1	69.8 (60.3-90.1)	0.148
	Mild	11	70.3±27.8	66.1 (59.6-74.9)	0.148
Morning cortisol (nmol/l)	Severe	19	254.9±148.8	189.2 (153.3-369.5)	0.844
	Moderate	22	218.8±104.2	200.2 (131.5-272.5)	0.844
	Mild	11	223.5±100.8	224.2 (123.4-269.6)	0.844

Variable	SCORAD group	n	Mean±SD	Median (Q1-Q3)	p-value
Anti-TPO (IU/ml)	Severe	19	15.3±5.2	14.4 (12.2-16.4)	0.968
	Moderate	22	37.5±112.7	14.3 (11.5-17.1)	0.968
	Mild	11	35.4±83.6	13.4 (1.1-19.1)	0.968
TSH (mkU/ml)	Severe	19	2.2±0.7	2.1 (1.8-2.5)	0.268
	Moderate	22	27±1.9	1.8 (1.4-2.4)	0.268
	Mild	11	2.9±2.71	2.1 (1.5-2.9)	0.268
Prolactin (mU/l)	Severe	19	261.6±270	179.0 (140.3-277.7)	0.168
	Moderate	22	192.6±159.9	140.0 (101.5-2137)	0.168
	Mild	11	189.8±87.5	179.8 (131.3-209.8)	0.168

Abbreviations: *anti-TPO, anti-thyroid peroxidase antibodies;* 25(OH)D3, *25-hydroxy vitamin D3.; SD, standard deviatio; TSH- thyroid-stimulating hormon.*

4.4. Quality of life in pediatric atopic dermatitis and control patients

247 of the AD patients and 50 of the control group participants completed the QoL questionnaires correctly. A significant difference was found between the quality of life index (QoLI) score for the AD group (QoLI: 6.3±5.56 points) and controls (QoLI 0.54±1.05 points) (p=<0.001). QoL questionnaires of patients with AD show a moderate impact on their quality of life. Analyzing details of the QoLI questionnaires we found, that children with AD have a great impact on all aspects of life, especially on symptoms and feelings (Q1, Q2), and treatment (Q10). AD significantly affects children's friendships (Q3) and activities (Q4-Q7) compared with control (Table 9).

Table 9. Quality of life index in atopic dermatitis and healthy control patients.

Variable	**AD, mean±SD**	**Controls, mean±SD**	**p-value**
Total QoLI	6.3±5.56	0.52±1.05	<0.001
Q1(how itchy, sore, painful or stinging has your skin been?)	1.4±0.9	0.2±0.4	<0.001
Q2 (how embarrassed or self-conscious have you been because of your skin?)	1.0±0.9	0.1±0.4	<0.001
Q3 (how much has your skin interfered with you going shopping or looking after your home?)	0.6±0.8	0±0.1	<0.001
Q4 (how much has your skin influenced the clothes you wear?)	0.6±0.8	0±0.1	<0.001
Q5 (how much has your skin affected any social or leisure activities?)	0.4±0.8	0±0	<0.001
Q6 (how much has your skin made it difficult for you to do any sport?)	0.4±0.8	0±0	<0.001

Variable	AD, mean±SD	Controls, mean±SD	p-value
Q7 (has your skin prevented you from working or studying?)	0.4±0.7	0±0.1	<0.001
Q8 (how much has your skin created problems with your partner or any of your close friends or relatives?)	0.3±0.6	0±0	<0.001
Q9 (how much has your skin caused any sexual difficulties?)	0.6±0.9	0.1±0.3	<0.001
Q10 (how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time)	0.6±0.8	0.1±0.2	<0.001

Abbreviations*: AD, atopic dermatitis; SD, standard deviation; Q, question, QoLI, quality of life index.*

4.5. Family quality of life in pediatric AD and control patients

The mean Family quality of life index (FDLQI) score for AD patients was 7.1±6.9, indicating a moderate effect on the QoL of the patient‘s family, and the mean FDLQI score for control patients was 2.1±5.9, meaning the low impact on the family‘s QoL ($p<0.001$) (Table 10). The highest scoring items of the FDLQI in the AD group were questions on emotional distress (Q1), time spent for treatment and house-work (Q7, Q8), and increased household expenditure (Q10).

Table 10. FDLQI in atopic dermatitis and healthy control patients.

Variable	**AD, mean±SD**	**Controls, mean±SD**	**p-value**
FDQLI	7.1±6.9	2.1±5.9	<0.001
Q1 (how much emotional distress have you experienced due to your relative/partner's skin disease (e.g. worry, depression, embarrassment, frustration?)	1±1	0.2±0.6	<0.001
Q2 (has your relative/partner's skin disease affected your physical well-being (e.g. tiredness, exhaustion, contribution to poor health, sleep/rest disturbance?)	0.7±0.9	0.2±0.6	<0.001
Q3 (how much has your relative/partner's skin disease affected your relationships with him/her or with other people?)	0.5±0.8	0.2±0.6	0.004
Q4 (how much have you been having problems with other peoples' reactions due to your relative/partner's skin disease (e.g. bullying, staring, need to explain to others about his/her skin problem?)	0.5±0.8	0.1 ±0.6	<0.001
Q5 (how much has your relative/partner's skin disease affected your social life (e.g. going out, visiting or inviting people, attending social gatherings?)	0.4±0.8	0.1±0.6	0.014
Q6 (how much has your relative/partner's skin disease affected your recreation/leisure activities (e.g. holidays, personal hobbies, gym, sports, swimming, watching TV?)	0.5±0.9	0.2±0.6	0.001

Variable	AD, mean±SD	Controls, mean±SD	p-value
Q7 (how much time have you spent on looking after your relative/partner (e.g. putting on creams, giving medicines, or looking after their skin?)	1.1±0.9	0.4±0.7	<0.001
Q8 (how much extra house-work have you had to do because of your relative/partner's skin disease (e.g. cleaning, vacuuming, washing, cooking?)	0.9±0.1	0.2±0.6	<0.001
Q9 (how much has your relative/partner's skin disease affected your job/study (e.g. need to take time off, not able to work, decrease in the number of hours worked, having problems with people at work?)	0.4±0.8	0.1±0.6	<0.001
Q10 (how much has your relative/partner's skin disease increased your routine household expenditure (e.g. travel costs, buying special products, creams, cosmetics?)	1.0±0.9	0.4±0.7	<0.001

***Abbreviations**: AD, atopic dermatitis; FDLQI, family dermatology life quality index; SD, standard deviation; Q, question.*

4.6. Comparison of quality of life between AD severity groups according to POEM

A total of 186 fully completed DLQI and POEM (Patient-Oriented Eczema Measure) questionnaires were analyzed in the AD group. According to POEM, 24 patients had severe, 59 patients had moderate and 103 had mild AD. Our study revealed that the severity of the disease affects patients' QoL negatively. We found, that the mean QoL index for severe AD was 14.3±6.2 (which represents a very large effect), for moderate – 6.9±4.4 (moderate effect), and for mild – 4.4±4.2 (small effect)($p<0.001$), and there were statistically significant differences between groups ($p<0.001$) (Table 11). Quality of life was more affected for severe AD patients compared with mild

and moderate AD almost in all aspects of quality of life. Comparing separated questions in mild versus moderate groups, a significant impact was found in the area of symptoms and feelings (Q1, Q2) and personal relationships (Q8).

Analyzing the POEM and FDLQI data (Table 12. FDLQI and POEM), we also found a significant negative effect on families QoL, with severe AD having a very strong effect (16.3±7.6, $p<0.001$) with moderate and mild AD having a moderate effect (7.6±5.4 and 5±5.9) on QoL. When comparing the results between the individual questions and severity groups, we found that all the data were statistically significant, except for Q 4 (other people's reaction to skin disease), Q5 (effect on social life), Q6 (effect on recreation/leisure activities), Q9 (effect on work/studies) in the mild versus moderate AD groups.

To summarise, we found that AD is directly related to the severity of the disease in many aspects of quality of life of patients and their families.

Table 11. Comparison of QoL index between severity groups scored by POEM.

QoL index	**POEM group**	**Mean score**	**p-value**	**p-value: Mild vs. Severe**	**p-value: Mild vs. Mod.**	**p-value: Mod. vs. Severe**
QoL index	Severe	14.3±6.2	<0.001	<0.001	<0.001	<0.001
	Moderate	6.9±4.4	<0.001	<0.001	<0.001	<0.001
	Mild	4.4±4.2	<0.001	<0.001	<0.001	<0.001
Q1(how itchy, sore, painful or stinging has your skin been?)	Severe	2.5±0.6	<0.001	<0.001	<0.001	<0.001
	Moderate	1.8±0.7	<0.001	<0.001	<0.001	<0.001
	Mild	0.9±0,8	<0.001	<0.001	<0.001	<0.001
Q2 (how embarrassed or self-conscious have you been because of your skin?)	Severe	2.2±0.9	<0.001	<0.001	0.001	<0.001
	Moderate	1.2±0.9	<0.001	<0.001	0.001	<0.001
	Mild	0.7±0.7	<0.001	<0.001	0.001	<0.001

QoL index	POEM group	Mean score	p-value	p-value: Mild vs. Severe	p-value: Mild vs. Mod.	p-value: Mod. vs. Severe
Q3 (how much has your skin interfered with you going shopping or looking after your home?)	Severe	1.3±0.9	<0.001	<0.001	0.198	0.001
	Moderate	0.6±0.8	<0.001	<0.001	0.198	0.001
	Mild	0.5±0.6	<0.001	<0.001	0.198	0.001
Q4 (how much has your skin influenced the clothes you wear?)	Severe	1.2±1.1	0.003	0.014	0.067	0.001
	Moderate	0.4±0.8	0.003	0.014	0.067	0.001
	Mild	0.6±0.7	0.003	0.014	0.067	0.001
Q5 (how much has your skin affected any social or leisure activities?)	Severe	1.2±1.1	<0.001	<0.001	0.456	<0.001
	Moderate	0.4±0.8	<0.001	<0.001	0.456	<0.001
	Mild	0.3±0.6	<0.001	<0.001	0.456	<0.001

Q6 (how much has your skin made it difficult for you to do any sport?)	Severe	1.1±1.1	<0.001	<0.001	0.078	0.001
	Moderate	0.4±0.8	<0.001	<0.001	0.078	0.001
	Mild	0.2±0.5	<0.001	<0.001	0.078	0.001
Q7 (has your skin prevented you from working or studying?)	Severe	0.9±0.8	<0.001	<0.001	0.279	0.003
	Moderate	0.4±0.6	<0.001	<0.001	0.279	0.003
	Mild	0.3±0.6	<0.001	<0.001	0.279	0.003
Q8 (how much has your skin created problems with your partner or any of your close friends or relatives?)	Severe	0.6±0.7	0.012	0.003	0.200	0.065
	Moderate	0.3±0.5	0.012	0.003	0.200	0.065
	Mild	0.2±0,6	0.012	0.003	0.200	0.065
Q9 (how much has your skin caused any sexual difficulties?)	Severe	1.7±1	<0.001	<0.001	<0.001	<0.001
	Moderate	0.8±0.9	<0.001	<0.001	<0.001	<0.001
	Mild	0.4±0.6	<0.001	<0.001	<0.001	<0.001

Q10 (how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?)	Severe	1.6±0.9	<0.001	<0.001	0.043	<0.001
	Moderate	0.6±0.85	<0.001	<0.001	0.043	<0.001
	Mild	0.4±0.6	<0.001	<0.001	0.043	<0.001

Abbreviations: *POEM, The Patient-Oriented Eczema Measure*; *SD, standard deviation; Mod., moderate; Q, question; QoLI, quality of life index.*

Table 12. Comparison of FDLQI between severity groups scored by POEM.

QoL index	POEM group	Mean score	p-value	p-value: Mild vs. Severe	p-value: Mild vs. Mod.	p-value: Mod. vs. Severe
FDLQI	Severe	16.3±7.6	<0.001	<0.001	0.001	<0.001
	Moderate	7.6±5.4	<0.001	<0.001	0.001	<0.001
	Mild	5±5.9	<0.001	<0.001	0.001	<0.001
Q1 (how much emotional distress have you experienced due to your relative/partner's skin disease (e.g. worry, depression, embarrassment, frustration?)	Severe	2.2±0.8	<0.001	<0.001	<0.001	0.001
	Moderate	1.4±0.9	<0.001	<0.001	<0.001	0.001
	Mild	0.6±0.8	<0.001	<0.001	<0.001	0.001
Q2 (has your relative/partner's skin disease affected your physical well-being (e.g. tiredness, exhaustion, contribution to poor health, sleep/rest disturbance?)	Severe	1.9±1	<0.001	<0.001	0.001	<0.001
	Moderate	0.9±0.9	<0.001	<0.001	0.001	<0.001
	Mild	0.5±0.7	<0.001	<0.001	0.001	<0.001
Q3 (how much has your relative/partner's skin disease affected your relationships with him/her or with other people?)	Severe	1.4±1.1	<0.001	<0.001	0.021	<0.001
	Moderate	0.5±0.8	<0.001	<0.001	0.021	<0.001
	Mild	0.3±0.7	<0.001	<0.001	0.021	<0.001
Q4 (how much have you been having problems with other peoples' reactions due to your relative/partner's skin disease (e.g. bullying, staring, need to explain to others about his/her skin problem?)	Severe	1.3±1.1	<0.001	<0.001	0.296	0.001
	Moderate	0.5±0.7	<0.001	<0.001	0.296	0.001
	Mild	0.4±0.6	<0.001	<0.001	0.296	0.001

QoL index	POEM group	Mean score	p-value	p-value: Mild vs. Severe	p-value: Mild vs. Mod.	p-value: Mod. vs. Severe
Q5 (how much has your relative/partner's skin disease affected your social life (e.g. going out, visiting or inviting people, attending social gatherings?)	Severe	1.2±1.3	<0.001	<0.001	0.516	<0.001
	Moderate	0.2±0.6	<0.001	<0.001	0.516	<0.001
	Mild	0.3±0.7	<0.001	<0.001	0.516	<0.001
Q6 (how much has your relative/partner's skin disease affected your recreation/leisure activities (e.g. holidays, personal hobbies, gym, sports, swimming, watching TV?)	Severe	1.7±1.1	<0.001	<0.001	0.610	<0.001
	Moderate	0.4±0.7	<0.001	<0.001	0.610	<0.001
	Mild	0.4±0.7	<0.001	<0.001	0.610	<0.001
Q7 (how much time have you spent on looking after your relative/partner (e.g. putting on creams, giving medicines, or looking after their skin?)	Severe	2.1±0.8	<0.001	<0.001	<0.001	<0.001
	Moderate	1.3±0.8	<0.001	<0.001	<0.001	<0.001
	Mild	0.8±0.7	<0.001	<0.001	<0.001	<0.001
Q8 (how much extra housework have you had to do because of your relative/partner's skin disease (e.g. cleaning, vacuuming, washing, cooking?)	Severe	1.5±1.1	0.001	<0.001	0.033	0.032
	Moderate	1±1	0.001	<0.001	0.033	0.032
	Mild	0.7±1	0.001	<0.001	0.033	0.032
Q9 (how much has your relative/partner's skin disease affected your job/study (e.g. need to take time off, not able to work, decrease in the number of hours worked, having problems with people at work?)	Severe	1.3±1.3	<0.001	<0.001	0.616	0.001
	Moderate	0.3±0.6	<0.001	<0.001	0.616	0.001
	Mild	0.3±0.7	<0.001	<0.001	0.616	0.001

QoL index	POEM group	Mean score	p-value	p-value: Mild vs. Severe	p-value: Mild vs. Mod.	p-value: Mod. vs. Severe
Q10 (how much has your relative/partner's skin disease increased your routine household expenditure (e.g. travel costs, buying special products, creams, cosmetics?)	Severe	1.8±1	<0.001	<0.001	0.003	0.004
	Moderate	1.1±0.8	<0.001	<0.001	0.003	0.004
	Mild	0.8±0.9	<0.001	<0.001	0.003	0.004

Abbreviations*: FDLQI, family dermatology life quality index; POEM, The Patient-Oriented Eczema Measure*; *Mod., moderate; SD, standard deviation; Q, question; QoL, quality of life.*

4.7. Associations between atopic dermatitis and behavior difficulties

101 out of 107 CBCL 6/18 questionnaires were completed correctly, including 48 (48%) children with AD and 53 (52%) children without AD. The mean age was 10±2.7 (median 9 (8-11) years for AD patients and 10.5±3.1 (median 11 (8-13) years for the control patients. The distribution of genders in the groups showed that 26 (49%) in the control group and 20 (42%) in the AD group were boys. Of the adults, who completed the questionnaires, 93 (92%) were mothers and 8 (8%) were fathers. The mean SCORAD score for AD patients was 417.5±20.95. The mean age, sex ratio, and family history of allergy did not differ between controls and patients with AD. Although, the duration of disease was not different between the two AD groups (mild to moderate and severe), however, sleep disturbance and pruritus intensity points were higher in the severe AD group than in the mild to moderate AD group (2.4±2.2 vs. 5.4±2.6, $p<0.001$and 4±2.8 vs. 6.6±2.4, $p=0.001$).

Table 13 shows the mean CBCL 6/18 and T scores for AD patients and controls. The results of the total behavior problem showed that only 1 (2%) subject in the AD group and 2 (4%) subjects in the control group had scored above 70, corresponding to the clinical syndrome. A borderline disorder can be identified in 1 (2%) of the control group patients. The other 47 (98%) AD and 50 (97%) control patients had a total score below 64.

Differences in the overall scores of the three scales between the control and AD groups were found. AD patients have higher internal behavior scale score and T-score (6.6±6.4 vs. 9.6±6.9 and 47.9±9.5 vs. 52.3±10.2, $p=0.01$), anxiety/depression scale score and T-score (2.8±2.7 vs. 4.3±3.5 and 47.7±8.4 vs.52.5±11, $p=0.02$) and somatic problems scale score and T-score (2.1±2.3 vs.3.5±3 and 47.6±8.5 vs.52.7±10.9, $p=0.005$).

The mean total behavior problem score and the mean T-score were higher in the AD group than in the control group (26.1±16.3 vs. 22.2±17.3, and 51.2±9.7 vs. 48.9±10.2), but this difference was not statistically significant ($p=0.134$). However, when the data was stratified by sex and age (6-11 and 12-18 years), there was a statistically significant difference between 6-11 years girls groups. Girls with AD had a higher total behavior problem scale score than girls in the control group (31.8±19.37 vs. 22.4±7.3, $p=0.036$). We also found that in this age (6-11 years) sample, the scores on the social difficulties and thought problem scale for AD girls were higher than those of the control group. The mean score for the social difficulties scale in AD groups was 3.1±2.8 vs. control 1.4±1.2 ($p=0.014$), and in thought problem scales respectively 2.8±2.3 vs. 1.4±1 ($p=0.013$).

In the groups of boys aged 6-11 years and 12-18 years, differences were found only on the somatic problems scale scores, boys with AD had higher results than boys from control groups. The results are ordered as follows: 2.8±2.3 vs. 1.35±1 ($p=0.013$) in the 6-11 years groups and 5.2±4.5 vs. 2±2.7 ($p =0.03$) in the 12-18 years groups. The other clinical range of the CBCL 6/18 scores was not different between the groups. A summary of the results of the CBCL 6/18 questionnaire comparing the data of children with AD and healthy controls is in Table 14.

Table 13. Results of the CBCL 6/18 scores and T-scores in children with AD and control

Syndromes	**Group**	**Mean±SD [Median (Q1-Q3)]**	**T-score Mean±SD [Median (Q1-Q3)]**	**p-value**
Internalizing behavior scale	Control	6.6±6.4 [5.0 (3-8)]	47.9±9.5 [45.6 (42.7-50.5)]	0.010
Internalizing behavior scale	AD	9.6±6.9 [8.5 (4-13)]	52.3±10.2 [50.7 (44.1-57.3)]	0.010
Anxiety/Depression scale	Control	2.8±2.7 [2.0 (1-4.1)]	47.7±8.4 [45.3 (42.1-51.6)]	0.020
Anxiety/Depression scale	AD	4.3±3.5 [3 (2-6.3)]	52.5±11 [48.4 (45.3-58.6)]	0.020
Withdrawn/Depression scale	Control	1.7v±2.5 [1 (0-3)]	49.9±10.9 [46,8 (42,4-55,5)]	0.564
Withdrawn/Depression scale	AD	1.8±2.1 [1 (0-3)]	50.1±9 [46.8 (42.4-55.5)]	0.564
Somatic problem scale	Control	2.1±2.3 [2 (0-3)]	47.6±8.5 [47.3 (40-50.9)]	0.005
Somatic problem scale	AD	3.5±3 [3 (1.8-5)]	52.7±10.9 [50.9 (46.4-58.2)]	0.005
Externalizing behavior scale	Control	5.8±4.6 [5 (2-9)]	49.6±9.3 [48.1 (42-56.2)]	0.819
Externalizing behavior scale	AD	6.1±5.3 [5.0 (2.0-9.3)]	50.4±10.8 [48.1 (42.0-56.7)]	0.819
Rule-breaking behavior scale	Control	1.9±2.0 [1 (0-3)]	50.9±10.7 [46.0 (40.6-56.7)]	0.433
Rule-breaking behavior scale	AD	1.6±1.7 [1 (0-2.3)]	49.0±9.2 [46.0 (40.6-52.7)]	0.433
Aggressive behavior	Control	3.8±3.3[3 (1-6)]	49.0±8.7 [46.8 (41.5-54.8)]	0.520
Aggressive behavior	AD	4.6±4.2 [3.5 (1-7)]	51±11,2 [48.2 (41.5-57.5)]	0.520
Social problem scale	Control	1.9±2.2 [1 (0-3)]	48.8±10.1 [44.7 (40.2-53.8)]	0.104
Social problem scale	AD	2.5±2.2 [2 (1-4)]	51.3±9.8 [49.2 (44.7-58.3)]	0.104
Thought problem scale	Control	1.9±2.4 [1 (0-3)]	49.2±10.1 [45.3 (41-53.9)]	0.279
Thought problem scale	AD	2.3±2.3 [2 (0-3.3)]	50.9±9.9 [49.6 (41.0-54.9)]	0.279
Attention problems	Control	3.5±3.4 [3 (1-5)]	50.2±11.1 [48.7 (42.2-55.2)]	0.856
Attention problems	AD	3.3±2.7 [3 (1.0-4.3)]	49.7±8.7 [48.7 (42.2-52.8)]	0.856
Total behavior problem scale	Control	22.2±17.3 [22 (11-26)]	48.9±10.2 [48.8 (42.3-51.2)]	0.134
Total behavior problem scale	AD	26.1±16.3 [25.5 (12.5-37.5)]	51.2±9.7 [50.9 (43.2-58)]	0.134

Abbreviations: *AD-atopic dermatitis, CBCL 6/18- the 2001 Child Behavior Checklist for Ages 6-18, SD-standard deviation.*

Table 14. Summary of the CBCL 6/18 questionnaire results comparing the data of children with AD and healthy controls

Syndromes	**Results**
Internalizing problems	↑ AD 6-18 years
• Anxiety/Depression	↑ AD 6-18 years
• Isolation (Withdrawn/Depression	-
• Somatic Complaints	↑ AD boys 6-11 years
Externalizing problems	-
• Rule-Breaking Behaviour	-
• Aggressive Behaviour	
Social Problems	↑AD girls 6-11 years
Thought Problems	↑AD girls 6-11 years
Attention Problems	-
Total behavior problem score	↑AD girls 6-11 years

Abbreviations: *AD, atopic dermatitis, CBCL 6/18, Child Behavior Checklist for Ages 6-18.*

We compared the CBCL scale scores and T-scores between different AD severity groups (Table 15). 19 (40%) patients had severe AD and 29 (60%) had mild to moderate AD. Patients with severe AD experienced more sleep disturbances and a greater intensity of itching. Their sleep disturbance and itching scores were higher than those of patients with mild-moderate AD (5.4±2.6 vs 2.4±2.2, $p<0.001$and 6.6±2.4 vs. 4±2.8, $p=0.001$). However, the total behavior problem score and other clinical ranges of the CBCL scores were not significantly different between the severe and mild-to-moderate AD groups.

To test which factors have the highest influence, we tried to model behavioral scales by factors – severity by SCORAD, age, sex, morning cortisol level, duration of disease, intensity of pruritus, and intensity of sleep disturbance. Below we provide the summary in Table 16, which includes all factors and as can be seen, none of them are statistically significant.

In summary, children with AD (from 6 to 18 years) have higher internal behavior, anxiety/depression, and somatic problems scale score and T-score

compared with healthy controls. Girls with AD between 6 and 11 years old have a higher total behavior problem score, social difficulties, and thought problem scales score compared with healthy 6-11 years girls, whereas boys with AD between 6 to 11 years and 12 to 18 years have higher somatic complaints scale scores compared with healthy controls. Patients with severe AD experience more sleep disturbances and a greater intensity of itching compared to mild-moderate AD. In our study population, the AD severity by SCORAD, age, gender, morning cortisol level, duration of illness, intensity of pruritus, and intensity of sleep disturbance did not have a statistically significant effect on the development of behavioral problems.

Table 15. Results of the CBCL scores and T scores in children with severe and mild to moderate atopic dermatitis.

Syndromes	**AD severity according to SCORAD**	**Mean±SD [Median (Q1-Q3)]**	**T-score Mean±SD [Median (Q1-Q3)]**	**p-value**
Internalizing behavior scale	Severe	9.6±7.0 [11.0 (4-13.5)]	52.4±10.3 [54.4 (44.1-58.1)]	0.841
Internalizing behavior scale	Mild-mod.	9.5±7 [8 (4-12)]	52.2±10.3 [50 (44.1-55.9)]	0.841
Anxiety/Depression scale	Severe	4.7±3.9 [3 (1.5-7.5)]	53.9±12.3 [48.4 (43.7-62.6)]	0.648
Anxiety/Depression scale	Mild-mod.	4.0±3.2 [3 (2-5)]	51.7±10.2 [48.4 (45.3-54.7)]	0.648
Withdrawn/Depression scale	Severe	1.4±2.4 [0 (0-2)]	48.6±10.6 [42.4 (42.4-51.1)]	0.095
Withdrawn/Depression scale	Mild-mod.	2.0±1.8 [2 (0-4)]	51.1±7.9 [51.1 (42.4-59.8)]	0.095
Somatic problems scale	Severe	3.5±2.9 [3 (1.5-5)]	52.7±10.5 [50.9 (45.5-58.2)]	0.932
Somatic problems scale	Mild-mod.	3.5±3.1 [3 (2-5)]	52.7±11.4 [50.9 (47.3-58.2)]	0.932
Externalizing behavior scale	Severe	6.8±6.9 [5 (2-11)]	51.7±13.9 [48.1 (42-60.3)]	0.949
Externalizing behavior scale	Mild-mod.	5.7±4.1 [5 (2-9)]	49.6±8.3 [48.1 (42.0-56.2)]	0.949
Rule-breaking behavior scale	Severe	1.5±2.2 [1 (0-2)]	48.5±11.7 [46.0 (40.6-51.3)]	0.252
Rule-breaking behavior scale	Mild-mod.	1.6±1.4 [1 (1-3)]	49.3±7.3 [46 (46-56.7)]	0.252

Syndromes	AD severity according to SCORAD	Mean±SD [Median (Q1-Q3)]	T-score Mean±SD [Median (Q1-Q3)]	p-value
Aggressive behavior scale	Severe	5.3±5.1 [3 (2-8.5)]	53±13.6 (46.8 [44.2-61.4])	0.497
Aggressive behavior scale	Mild-mod.	4.1±3.6 [4 (1-7)]	49.8±9.5 [49.5 (41.5-57.5)]	0.497
Social problem scale	Severe	2.5±2.3 [2 (1-3)]	51.4±10.4 [49.2 (44.7-53.8)]	0.949
Social problem scale	Mild-mod.	2.4±2.1 [2 (1-4)]	51.3±9.6 [49.2 (44.7-58.3)]	0.949
Thought problem scale	Severe	2.5±2.2 [2 (0.5-4)]	51.8±9.6 [49.6 (43.2-58.1)]	0.465
Thought problem scale	Mild-mod.	2.2±2.4 [2 (0-3)]	50.3±10.2 [49.6 (41.0-53.9)]	0.465
Attention problems scale	Severe	4,0±2,9 [3 (2-6.5)]	52±9.4 [48.7 (45.5-60.1)]	0.217
Attention problems scale	Mild-mod.	2.9±2.5 [3 (1-4)]	48.3±8.1 [48.1 (42.2-52)]	0.217
Total behavior problem scale	Severe	27.3±10.3 [27 (11-40.5)]	51.9±11.5 [51.8 (42.3-59.8)]	0.677
Total behavior problem scale	Mild-mod.	25.3±14.4 [25 (13-37)]	50.7±8.5 [50.6 (43.5-57.7)]	0.677
The pruritus intensity score	Severe	6.6±2.4 [6 (5-8.5)]	5.4±2.6 [5 (5-7.5)]	0.001
Pruritus intensity score	Mild-mod.	4±2.8 [3 (2-5)]	2.4±2.2 [2 (1-4)]	0.001

Abbreviations: *AD, atopic dermatitis, mod., moderate; SCORAD, SCORing atopic dermatitis index; SD, standard deviation.*

Table 16. Multivariate linear regression of factors influencing CBCL 6/18 behavioral scales.

Indicator	**Driver**		**p_v**	**r**
Internalizing behavior	(Intercept)	18.861		0.10
Internalizing behavior	SCORAD	0.027	0.83	0.10
Internalizing behavior	Age	-0.162	0.92	0.10
Internalizing behavior	Sex-man	-1.173	0.70	0.10
Internalizing behavior	Morning cortisol level	-0.019	0.14	0.10
Internalizing behavior	Duration of disease	-0.014	0.92	0.10
Internalizing behavior	Intensity of pruritus	-0.568	0.45	0.10
Internalizing behavior	Intensity of sleep	0.473	0.59	0.10
Externalizing behavior	(Intercept)	10.475		0.28
Externalizing behavior	SCORAD	0.164	0.08	0.28
Externalizing behavior	Age	-1.488	0.22	0.28
Externalizing behavior	Sex-man	3.019	0.18	0.28
Externalizing behavior	Morning cortisol level	-0.012	0.22	0.28
Externalizing behavior	Duration of disease	0.075	0.45	0.28
Externalizing behavior	Intensity of pruritus	-0.182	0.74	0.28
Externalizing behavior	Intensity of sleep	-0.409	0.53	0.28
Total behavior	(Intercept)	50.415		0.21
Total behavior	SCORAD	0.314	0.27	0.21
Total behavior	Age	-2.696	0.46	0.21
Total behavior	Sex-man	3.361	0.62	0.21
Total behavior	Morning cortisol level	-0.053	0.06	0.21
Total behavior	Duration of disease	0.085	0.77	0.21
Total behavior	Intensity of pruritus	-1.022	0.54	0.21
Total behavior	Intensity of sleep	-0.230	0.90	0.21

Abbreviations: *SCORAD - SCORing atopic dermatitis index.*

4.8. Evaluation of corticophobia in pediatric patients with atopic dermatitis

In total, we analyzed 296 TOPICOP questionnaires. 244 (82%) questionnaires were completed by parents of children with AD and 52 (18%) by parents in the control group. 283 (96%) of questionnaires were filled by mothers and 13 (4%) by fathers. Girls represented 25 (48%) in the control group and 119 (49%) in the AD group. The mean age of patients was 6.84±4.43 years in AD and 10.5±3.1 years in the control group. The prevalence of corticophobia in our study population was 55% (measured by positive answers to the question „Do you feel anxious or hesitant before applying a corticosteroid cream"). The results of the TOPICOP questionnaire showed that 76 (32%) of the AD group and 5 (14%) of the control group have a high risk of corticophobia, 109 (46%) of the AD group and 18 (50%) of the control group have a medium risk of corticophobia. The remaining 53 (22%) in the AD group and 13 (36%) in the control group are at low risk of corticophobia.

In our study, 126 (55 %) of parents of children with AD felt anxious or hesitant before applying a corticosteroid cream, and 68 (29%) delayed the start of the medication. 14 (5%) of all respondents state that they have never used topical steroids. As many as 281 (98 %) of all surveyed parents (of healthy and AD children) are taking action to minimize the potential side effects of topical glucocorticoids. Respondents use a variety of measures to reduce the side effects of glucocorticoids. The most common choice is the following - 159 (56%) apply only when rashes become very severe and do not improve with moisturizer, 4 (14 %) dilute a topical steroid with moisturizer, 37 (13 %) apply a smaller amount,19 (7 %) apply for a shorter time and 11 (4 %) use other methods.

We wanted to find out which factors lead to a higher risk of corticophobia. We found that corticophobia was not related to the respondents' education, severity of AD according to the POEM, parental gender (mother or father), previous use of topical or systemic steroids, use of steroids in the last two weeks, participation in special educational programs/lectures for AD patients and their relatives. The mean TOPICOP scores between those groups were not statistically different (Table 17). We found that the mean TOPICOP score differed only between the AD and control groups (42.7±44.5 vs. 30.1±19.3, p=0.0481), we therefore suggest that a diagnosis of AD may increase the risk of corticophobia.

Then comparing TOPICOP score with QoL index.

We tested whether there is an association between quality of life and corticophobia in AD patients and found a weak positive correlation between

TOPICOP and the FDLQI, IDLQI and CDLQI questionnaires. All DLQI scores of the impact of AD on the quality of family life (r=0.225), child's life (r=0.192) and infant's life (r=0.222) showed a statistically significant positive correlation with the severity of corticophobia ($p<0.001$; $p=0.022$; $p=0.03$).

In summary, AD patients are at moderate risk of developing corticophobia and a diagnosis of AD may increase the risk of corticophobia . Corticophobia is correlated with AD severity, but is not related to the respondents' education, severity of AD according to the POEM, parental gender (mother or father), previous use of topical or systemic steroids, use of steroids in the last two weeks, participation in special educational programs/lectures for AD patients and their relatives. Patient and family QoL has positive correlation with risk of corticophobia.

Table 17. Possible risk factors for corticophobia.

Variable	Yes (TOPICOP score, percents, mean±SD)	No (TOPICOP score, percents, mean±SD)	p-value
Previous use of topical or systemic steroids	40.1±20.7	40.2±22	p=0.9764
Use of steroids in the last two weeks	41.2±19.1	28.9±22.5	p=0.3978
Participation in special educational programs/lectures for AD patients and their relatives	39.3±20.3	38.6± 17.5	p=0.8789
A university degree	40.8±21.1	38.5±24	p=0.5672
Severe AD according to POEM	45.4±19.6	40.9±21.3	p=0.314
Diagnosis of AD	42.7±44.5	30.1±19.3	p=0.0481
The questionnaire is filled out by the mother	40±21.5	45.4±15.5	p=0.416

Abbreviations: *SD – standard deviation.*

5. DISCUSSION

5.1. Characteristics factors affecting atopic dermatitis and skincare habits of study participants

5.1.1. Characteristics of study participants

The prevalence of atopic dermatitis (AD) is increasing. It commonly presents during early infancy, but may persist or begin later in childhood or even in adulthood. The majority (77%) of our study population develop AD symptoms before age 1 years and 97% - before 5 years of age. These data are consistent with data in other studies (5,90).

Our patients' data show that the percentage of children with anamnesis of atopy in the family is 69%, and it is statistically higher than in controls. Previous foreign studies found a significant association between father/mother having a history of allergic disease and the development of eczema in infants (91), suggesting the involvement of genetic factors in the development of eczema. Consistent with these findings, the present study substantiates a family history of eczema as a risk factor for the development of eczema.

In the present study the anmanestical data of 247 children with AD as well as clinical and laboratory characteristics of 107 children with AD were evaluated. The severity of eczema varies among children with AD. In phase 1 of our study, one-fifth (18%) of the children had severe and one–third (33%) - had moderate AD according to objective POEM. In phase 2 – 37% of AD children had severe AD, 42% - had moderate AD, and 2% - mild AD assessed by SCORAD. The difference in results between the POEM and SCORAD groups is because phase 2 included blood laboratory tests, and those with severe AD were more likely to participate in the study. The severity distribution in phase 1 of our study population was similar to that of the study conducted by other scientists (92,93). The POEM questionnaire has been widely recommended as an atopic eczema outcome measure for use in outpatient clinics epidemiological studies and clinical trials. POEM is more revealing of the subjective symptoms of AD, providing a better understanding of the patient's perspective on the severity of the disease. As the assessment of disease severity does not require an interviewer, it is an excellent instrument for anonymous surveys. In contrast, the SCORAD questionnaire, in addition to the subjective evaluation, includes objective criteria that are assessed by the clinician, making it more suitable for measuring disease progression.

Allergy plays an important immunopathogenic role in 30-50% of young children with AD (94). Of our study population 43% had sensitization to foods, 29% had allergic rhinoconjunctivitis, 12% had allergic asthma, and 55% had all three atopic diseases. Similar results were seen in the study by Akan et al. (92), thefood allergy was determined in 40% of participants. In a study from East Germany, 41.9% of the study population was reported to have allergic sensitization, which was similar to our results (95). In the study by Ricci et al. (93), in which the study population consisted of children with AD aged 6-36 months, the frequency of sensitization to foods and inhalant allergens was reported as 37.1% and 25.9%, respectively, following our results. In our study, the patients who had allergic rhinoconjunctivitis had severe AD more frequently compared with those with mild (p=0,028) and moderate (p=0,027) AD. Park et al. (96) reported a relationship between allergic AD and higher SCORAD scores for young children. In two other studies, food allergen sensitization was found to be more prevalent in patients with a moderate–severe disease compared to those with mild disease (92,97). These data indicate that children with AD with allergic sensitization should be followed more closely, as they may have more severe disease.

It is a common misconception that AD patients especially children diagnosed with AD should avoid routine vaccinations (71,90,98). Our study also observes this problem. Only 39% of AD patients have had a complete vaccination compared to 96% of controls. Of the rest AD patients, 55% have had partial vaccination. No evidence recommends vaccinations in infancy and early childhood have an impact on the development of AD or other atopic diseases. Two multi-centric studies show that the current vaccines do not cause allergic diseases. The International Study of Asthma and Allergies in Childhood (ISAAC) is the most wide-ranging international effort on asthma and atopy research. Phase One used simple core written questionnaires for two age groups (6–7 year old children and 13–14 year old adolescents), and was completed in 156 collaborating centres, in 56 countries; a total of 721,601 children participated (99). Anderson et al. (100) performed a study with data taken from ISAAC to investigate eventual associations between the prevalence of atopic symptoms (asthma, allergic rhinoconjunctivitis, and AD) in 6–7-year-old children and 13–14-year-old adolescents and the rate of immunization against diphtheria, tetanus, pertussis (DTP), measles and tuberculosis. The results indicated a significantly lower prevalence of atopy at 13–14 years of age, in the youngsters that had received DPT and measles vaccine. There were no associations between tuberculosis immunization and atopic diseases. The authors conclude: ‘International variations in childhood

atopic diseases are unlikely to be explained by variations in immunization'. In a prospective cohort study, Gruber et al. (101) followed, from birth to 5 years of age, 943 children from 5 German cities, approximately 40% with a high risk of atopy (2 or more atopic family members or cord IgE X 0.9 kU/L) and 60% randomly selected controls, periodically investigating the prevalence of asthma, rhinoconjunctivitis and AD (follow-up visits at 3, 6, 12, 18 months; 2, 3, 4 and 5 years). They found no statistically significant relationship (at any age) between atopy or allergic diseases and Haemophilus influenzae type b, polio, rubella, pertussis, diphtheria/tetanus vaccination. They concluded that children with a higher vaccination coverage seemed to be transiently better protected against the development of atopy in the first years of life. In conclusion, all children diagnosed with AD should be vaccinated according to the local or national vaccination plan. Vaccinations should not be administered during acute flares – in those cases, two weeks of well-conducted TCS therapy followed by a normal vaccination procedure are recommended (90).

Exposure to tobacco could be associated with an increased risk of developing AD. Our study did not reveal an association between smoking and atopy. A systematic review of 86 studies confirmed the association between smoking and AD in adolescents and adults in all continents of the earth. It remains unclear, however, whether smoking is a provocation factor in AD or whether the burden of AD leads to more frequent smoking habits (90).

The World Health Organization currently recommends exclusive breastfeeding for the first 6 months and continuing to breastfeed, as well as introducing other foods, until 2 years of age. Among the proposed mechanisms by which breastfeeding might protect from or promote allergy is an alteration of the infant's gut microbiome and immune development. Breastfeeding may also alter a child's risk of respiratory infections through maternal antibody transfer or affect the intake of nutrients, such as vitamin D, during infancy (102). In our study, 91% of AD and 85% of control patients were breastfeeded. The duration of breastfeeding was similar with no statistical difference between the groups. The effects of breastfeeding, maternal diet, and the time or the type of introduction of solid food on the development of AD in children are still controversial. Many publications have analyzed different breastfeeding characteristics, including duration of breastfeeding, maternal diet during lactation, or age at complementary food introduction (102). While some reports suggest positive effects in preventing AD by breastfeeding or changing the maternal diet, other studies show insignificant or reverse effects (103). Lodge et al. (104) reviewed 42

observational studies (with 472 488 participants) and found that there was a reduced risk of eczema below the age of 2 years from pooling the 6 cohort studies' estimates comparing exclusive breastfeeding greater than 3–4 months with other feeding types. However, there was no association found between the risk of eczema up to 2 years for the exposure of more vs. less breastfeeding. After 2 years neither the ever breastfeeding nor the more vs. less exposures were associated with eczema. Authors concluded that were is low- to very low-quality evidence that breastfeeding reduces the risk of eczema development up to 2 years of age. After this age, the protective effect was lost. It's important to note, that to have consistent results is difficult, because breast milk varies in composition, and some women alter their diet while breastfeeding, based on varying recommendations. Then looking at studies, that investigate the associations between the timing of the introduction of complementary foods, the study of Nwaru et al. (105) analyzed the results of a cohort of 1924 children followed up for 10 years. The authors concluded that the pattern of infant feeding during the first 6 months does not have a substantial impact on the long-term risk of asthma and atopic diseases in children. Further research is needed to determine sound recommendations about breastfeeding and intorduction of complementary foods for families.

Comparing results, we found that only half of the families with AD have a pet at home, compared with 70% of the control families ($p<0.05$). The choice not to keep animals can be made for many reasons, such as the place where families live, the family's beliefs, an established allergy to animals, or the fear that the allergy will develop and make the course of AD more severe. Numerous studies have reported that prenatal or early-life exposures to mammals, including pets and livestock, are inversely associated with pediatric allergy. Protective associations have been reported for total IgE, atopic sensitization, and clinical disorders such as AD, allergic rhinitis, and asthma. Most reports on livestock exposure have been based in the Alpine areas of Europe, whereas domestic pet studies have been conducted worldwide. The theory that animal exposure is protective for allergy has been linked to the hygiene hypothesis, with the concept that environments with animals are less hygienic, although studies have not identified which specific animal exposure characteristics might afford protection. Hypotheses implicate high levels of allergen exposure, animal transport of outdoor substances into the home, increased physical activity associated with animal ownership, or even decreased stress levels (102). Results have been less consistent for cats than dogs. In the European PASTURE/EFRAIM cohort (106) prenatal exposure to more farm animals, cats, or dogs was associated with significant or borderline

significant decreased ORs for AD by age 2 years. Meta-analyses of Chen et al. (107) suggested inverse relationships between early dog (but not cat) exposure and eczema. Dog exposure has been associated with less risk for allergy, especially allergic sensitization. Inconsistent results may relate to differences in study populations concerning genetic factors, the prevalence of local pet keeping, and unmeasured risk factors associated with pet exposure. Therefore, although not settled, there is no consistent evidence that early pet exposure increases the risk for allergic disorders and some evidence of a protective effect. In recent years, many think that both pet and livestock exposure reflects a complex causal pathway, in which they contribute to normal immune development through their impact on the infant's environmental and human microbiome (102).

5.1.2. Skincare habits

Skin hygiene procedures play an important role in the treatment of AD, especially in infants and young children. AD patients should choose warm baths or showers with mild, oily cleansers as part of their normal skincare routine. Bathing moisturizes the skin, but to maintain moisture, it is necessary to wipe the skin dry all over the body after bathing and immediately apply an emollient within three to five minutes (108). Most patients are suggested to bathe daily. Most experts recommend bathing instead of showering, especially for young children, although there is no convincing scientific evidence. For the time being, it is believed that the method of bathing can be chosen by the patient. Regardless of whether bathing or showering is preferred, it is important that the water temperature is not too high and the bathing time is kept to 20 minutes (18).

AD patients in our study were more likely than controls to use special soaps (respectively 84% vs. 50%, $p<0.001$), to apply emollients more frequently (daily application 50% vs. 25%, $p<0.001$), and to use a higher proportion of emollients (>100 ml/month: 77% vs. 25%, $p<0.001$). The frequency of bathing is similar in both groups, majority of participants go to shower or bath 1 time per day (33% of AD and 45% of control group children, p=0,388). Only several studies have directly compared daily with infrequent bathing in children with AD (109–111). Kim et al. (110) demonstrated that daily bathing using weakly acidic syndets with immediate application of an emollient can reduce skin symptoms in pediatric patients with AD more than infrequent bathing during the summer season. Chiang et al. (111) study quantified cutaneous hydration status after various combination bathing and moisturizing

regimens. The authors concluded that bathing without moisturizer may compromise skin hydration. Bathing followed by moisturizer application provides modest hydration benefits, though less than that of simply applying moisturizer alone. Whereas Koutroulis et al. (109) attempted to determine if there was a relationship between AD severity and bathing habits, especially bathing frequency and duration. They found that bathing frequency and duration were not correlated to AD severity as measured by SCORAD.

The European guidelines on AD recommend daily emollient application, immediately after bathing or showering. The recommended amount of emollient sufficient to achieve optimal effects oscillates around 250 g/week (the quantities of emollients used should be within 100–200 g per week for children and 200–300 g per week for adults)(70). Following these recommendations, we observe that the use of emollients by AD patients in our sample is lower than recommended. 23% of AD patients use <100 ml/month, 36% use 100-300 ml/month, 26% use 301-500 ml/month, and 10% use more than 500 ml/month. It should be emphasized that the cost of quality emollient (low in contact allergens or hazardous substances) therapies often restricts their use because such therapies are considered to be non-prescription drugs. In addition, the daily use of emollients is time-consuming and requires a regular regimen, which is a challenge for both parents and the affected children themselves. Lack of knowledge of how to apply the right amount of emollients to the skin may also be a factor.

5.2. Endogenous factors

5.2.1. Relationship of eosinophils and total IgE levels with pediatric AD

Some studies investigating the relationship between laboratory parameters and disease severity have been conducted, substantiating that systemic expansion of Th2 cell activity leading to release of IL-5, IL-4, IL 13, and IL-3 caused eosinophilia (92,112–114). Eosinophilia in patients with AD is usually assigned as a nonspecific finding. Although eosinophil values were similar in our study between AD and the control groups (0.5±0.4 vs. 0.3±0.4, p=0.086), we found that patients with severe AD had a higher count of eosinophils than those with moderate or mild disease (respectively 0.63±0.48 vs. 0.42±0.43 and 0.29±0.23, p=0.039). In our study, there were higher total IgE levels in the AD patients group (1167.6±2093.1 IU/ml in AD and 173.0±241.8 IU/ml in control group, p<0.001) and there was a difference in total IgE between severe AD and mild or moderate AD groups

(2201.3±2927.8 IU/ml in severe vs. 319.1±393.3 IU/ml in mild and 713.34±1266 IU/ml in moderate AD groups, p<0.001). There are also studies underlining the relation of eosinophil count, total IgE, and disease severity. Similar findings are found in a study by Akan et al. (92), who identified, that patients with AD have elevated eosinophiles count and it was associated with disease severity. Study by Kumar et al. (114) found that both count of eosinophils and total IgE increased significantly in about 66% pediatric patient (aged 0 month to 15 years) and directly correlated with the severity of the AD. Some studies did not find a correlation between objective SCORAD score and total IgE, example study of Akan et al. (92), but this result may be attributed to the younger age of our patients. Park et al. (96) also found no correlation between SCORAD score and serum IgE in the sensitized group of patients with AD. Both of these studies included children who were younger than those of our study population. This result may be related to the immature development of the cytokine system in younger children. It has been demonstrated in recent studies that total IgE increases with age (115). Regarding these results, it seems that total IgE and eosinophils indicate both severe disease and allergic sensitization.

5.2.2. Relationship of dyslipidemia with pediatric AD

Epidemiological studies found that adult eczema can be associated with increased oddsof obesity, hypertension, and high cholesterol, which are in part related to increased cigarette smoking, alcohol intake, and sedentary lifestyle (44). Research indicated that dyslipidemia is a type of chronic inflammatory response (45). In particular, elevated triglycerides and low-density lipoprotein cholesterol lead to increased pro-inflammatory signaling and increased expression of TNF-α and interleukin (IL)-6. In contrast, high-density lipoprotein cholesterol has an antiinflammatory effect, in that it modulates T-cell activation. This supports the interpretation that the presence of a chronic inflammatory state (as indicated by dyslipidemia) is responsible for chronic skin inflammation and provides a possible mechanism for the relationship between AD and hyperlipidemia (45,46). The association between dyslipidemia and AD in children is unclear. A study by Kim et al. (45) indicated that children with AD had significantly higher levels of total cholesterol (173.0 [95% CI: 158.0, 191.0] vs. 194.0 [95% CI: 188.0, 205.5] mg/dL, p < 0.001) and triglycerides (76.0 [95% CI: 55.0, 107.0] vs. 97.0 [95% CI: 65.0, 129.5] mg/dL, p=0.006), but the two groups had similar levels of LDL and HDL. The SCORAD index had significant associations with high

levels of total cholesterol and triglycerides, and a low level of high-density lipoprotein cholesterol. An epidemiological study by Augustin et al. (116) found that dyslipidemia was more often diagnosed in children with atopic eczema to those without AD (prevalence ratio: 1.29; 95% CI:1.12, 1.49; p<0,05). However, in this study patients with AD tend to be more obese, than patients without these diseases. A previously mentioned study by Kim et al. (45) did not specify the weight or body mass index of the subjects, which may influence the blood lipid profile. In our study, we did not find any relationship between dyslipidemia and AD, and with disease severity.

5.2.3. Relationship of 25(OH)D3 levels with pediatric AD

The relationship between vitamin D levels and the severity of AD remains a contentious topic in the existing literature. There is increasing evidence in the scientific literature that there is a link between hypovitaminosis D and the development of eczema, with vitamin D being involved in the pathogenesis of AD as a protective factor, as it is important for normal immune function and the maintenance of the skin barrier function (22,23). Several clinical trials have been carried out in recent decades, but published findings regarding an association between vitamin D status and atopic outcomes are not consistent. A comparison of the results is complicated by differences in the assessment of vitamin D status (e.g. measurements in cord blood or assessment of maternal vitamin D status during pregnancy), in study designs, the age of participants, or the definition of the outcomes. We reviewed clinical trials from the 2018 to 2023 years with similar methodology and compared them with our data. The results are summarised in Table 19. The majority of clinical trials (94,117–121) showed that serum 25-hydroxyvitamin D(25(OH)D) concentrations were statistically significantly lower in AD patients than in healthy subjects ($p<0.05$). Barlianto et al. (117) found a high prevalence of vitamin D deficiency and insufficiency in infants with AD. Similar results are seen in studies by Raj et al. (122), Mohamed et al. (119), Xiang et al. (120), Dogru et al. (121). Li et al. (123) found that only boys with two or more allergic diseases had significantly lower vitamin D levels compared with boys with one allergic disease and girls with two or more allergic diseases. In our study, the mean serum 25(OH)D3 levels were not significantly lower in children with AD when compared to the control group, and similar findings are seen in seven other studies (122,124–129). Differences in results could be due to the relatively small sample size, geographical, genetic and skin type differences . It is also important to mention that children with AD had lower

25(OH)D3 levels during low-sun season compared with AD patients during high-sun season (66.2±27.7 vs. 71.8±23, p=0.0244, indicating that geographical location and exposure to sunlight are important determinants of vitamin D levels, and that its requirements are likely to be higher in children with AD, especially during the low-sun season. A summary of results of the studies investigating the relationship between serum 25-hydroxyvitamin D and AD is in Table 20.

When assessing the severity of disease in patients with AD according to the SCORAD index, the majority of studies showed similar results, with a statistically significantly lower vitamin D level in patients with more severe AD compared with patients with mild AD (120–122,126,127,130). In a study by Sanmartin et al.(131) serum 25(OH)D levels were significantly lower in moderate and severe AD than in mild AD, although this association was only significant for patients with light Fitzpatrick skin type. However, in Shafiq et al. (132) study, similar to ours, there was no significant association between serum level of vitamin D and the severity of AD (r=-0.173). The mean serum vitamin D level in mild AD (25.7±8.1) was higher compared with those with moderate (23.9±8.8) or severe (19.5±8.3) AD, but this difference was not statistically significant (p=0.249). See Table 21 for a summary of the studies on the association of vitamin D levels with the SCORAD index. In our data, we found that AD patients have lower vitamin D levels in the low-sun period than in the high-sun period, while this difference was not found in control group patients. Considering these findings, it would be recommended to check serum vitamin D levels in AD patients during winter and to recommend vitamin D supplementation if necessary.

Table 19. Studies investigating the relationship between serum 25-hydroxyvitamin D and atopic dermatitis (from 2018 to 2023).

Study	Populations	Findings and conclusions
Dogru et al. (121)	Children, n=69 AD, n=70 HC	Mean vit. D levels were lower in patients with AD. A negative correlation between vitamin D levels and disease severity was documented.
Lara-Corrales et al. (127)	Children, n=77	Vit. D levels correlated with AD severity.
Daniluk et al.(126)	Children, n=29 AD, n=22 HC	Low vit. D concentration was observed mainly in patients with severe AD (77.8%), compared to children with mild or moderate AD (25%) or the control group (31.8%).

Study	Populations	Findings and conclusions
Xiang et al.(120)	Children, n=81 AD, n=65 HC	The vit. D levels were significantly lower in children with AD than in normal children. vit. D level negatively correlated with SCORAD scores.
Mohamed et al. (119)	Children, n=100 AD, n=101 HC	Serum 25(OH)D levels were significantly lower in cases with AD than in controls.
Lee et al. (129)	Children, n=135 AD, n=65 HC	The serum levels of 25(OH)D were not statistically different from children without AD. Serum vit. D levels were significantly lower in children with severe AD compared to those with mild-to-moderate AD.
Sanmartin et al.(131)	n=134 AD, n=105 HC	Serum 25(OH)D levels were significantly lower in moderate and severe AD than in mild AD, although this association was only significant for patients with light Fitzpatrick skin type.
Raj et al. (122)	Children, n=35 AD, n=35 HC	No difference in the mean serum vit. D levels between AD patients and controls. An inverse correlation was seen between serum vit. D levels at baseline and the severity of AD.
Imoto et al. (130)	Children, n=152	Patients with sufficient vit. D levels had lower SCORAD values. Considering other factors that could influence the decrease in AD severity after vit. D supplementation, the female gender was associated with a worse treatment response.
Yang et al.(125)	Children, n=4378	Early-life 25(OH)D levels were not linked to the increased risk of developing childhood AD.
Esenboga et al. (133)	Children, n=160 AD, n=79 HC	In infants with AD, disease severity is inversely proportional to vit. D levels.
Ren et al.(124)	Children, adults, n=21,399 AD, n=95,464 HC	Vit. D deficiency or insufficiency did not increase the possibility of childhood AD.
Barlianto et al. (117)	Children, n=36, ≤1 year	There was a high prevalence of vit. D deficiency and insufficiency in infants with AD, and a low vit. D level was correlated with the severity of AD.

Study	Populations	Findings and conclusions
Shafiq et al.(132)	Children and adults, n=41	Levels of serum 25(OH)D were deficient or insufficient in 75.6% of patients and normal in 24.4% of patients. There was no significant association between serum level of vit. D and the severity of AD. The mean serum vit. D level in mild AD (25.7±8.1) was higher compared with those with moderate (23.9±8.8) or severe (19.5±8.3) AD. However, the result was not statistically significant.
Li et al.(123)	Children, n=103 with allergic diseases	Boys with two or more allergic diseases had significantly lower vit. D levels compared with boys with one allergic disease and girls with two or more allergic diseases.
Çiçek et al. (118)	Children, n=96	A negative correlation between serum vit. D levels and the SCORAD index. Low serum vit. D levels may have a more substantial impact on AD severity than atopic conditions and eosinophilia.

Abbreviations: *AD, atopic dermatitis; HC, healthy control; 25(OH)D, serum 25-hydroxyvitamin D; vit. D, vitamin D.*

Table 20. Summary of the studies investigating the relationship between serum 25-hydroxyvitamin D and atopic dermatitis (from 2018 to 2023).

An inverse relationship between high 25(OH)D levels and AD	No significant relationship between 25(OH)D levels and AD
Barlianto et al. (117), Çiçek et al. (118), Li CJ et al.(123) (boys with two or more allergic diseases) , Mohamed et al. (119), Xiang et al.(120), Dogru et al. (121).	Ren et al.(124), Yang et al.(125), Raj et al. (122), Lee et al. (129), Daniluk et al.(126), Lara-Corrales et al. (127).

Table 21. Studies investigating the relationship between serum 25-hydroxyvitamin D and SCORAD (from 2018 to 2023).

An inverse relationship between high 25(OH)D levels and SCORAD	**No significant relationship between 25(OH)D levels and SCORAD**
Sanmartin et al.(131) (*only in light Fitzpatric skin type*), Imoto et al. (130), Barlianto et al. (117), Esenboga et al. (133), Çiçek et al. (118), Raj et al. (122), Lee et al. (129), Xiang et al.(120), Daniluk et al.(126), Lara-Corrales et al. (127), Dogru et al. (121).	Shafiq et al.(132).

5.2.4. Relationship of serum cortisol with pediatric AD

There is great inter-individual variability in neurally mediated responses to psychological stress and AD flare-ups. With the influence of stressful stimuli, physiological activation of some specific areas of the peripheral and central nervous system occurs. The stress response includes stimulation of the hypothalamus and brainstem and also activation of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system. These systems work together with the immune system and are intimately implicated in the pathogenesis of stress-associated illnesses. These compensatory responses of the body involve the production of substances that can be found in serum and saliva. The relationship between stress and the concentrations of cortisol in the serum and saliva has already been described in the literature (134). The evaluation of stress biomarkers would help control skin inflammation by allowing for a more proactive management of AD patients. However, so far, no reliable biomarkers are available to assess the level of stress in AD patients (20). Since the hypothalamic-pituitary-adrenal (HPA) axis is known to help regulate inflammation through the regulation of cortisol, investigators have examined the role of the HPA axis and endogenous cortisol in the outcome of allergic disorders (135). Cortisol is a hormone produced by the adrenal cortex, principally in the second half of the night, and its serum levels are highest between 7 am and 8 am. During the day, cortisol levels drop significantly, and at night only about 10% of the morning cortisol remains in the body. When

exposed to physical or psychological stress, the adrenal glands produce greater amounts of cortisol. This activates the metabolism, which supplies the body with energy and changes the conditions for mental reactions, increasing the activity of other hormones and generating additional energy stimuli to cope with stressful situations. Permanent stress can leave the body exposed to the effects of constantly elevated cortisol levels. It is hypothesized that after long exposure to physical and/or mental stress, the HPA axis becomes less sensitive, resulting in decreased cortisol production by the adrenal glands (134). Several studies have looked at cortisol levels "at rest" in patients with allergic disorders versus nonatopic control patients. Patients with allergic disorders have been noted to have variations in cortisol patterns under natural conditions as well as a differential cortisol response to stress (136–139). A study by Kojima et al. (139) revealed that salivary cortisol responsiveness to the stress of venipuncture is correlated negatively with the severity of AD. Landstar et al. (136) compared serum cortisol levels drawn in the laboratory at 6-time points throughout the day for children with allergic asthma and age-matched nonallergic control subjects. Asthmatic subjects had a lower mean cortisol level than control subjects ($p<0.05$). The study by Afsar et al. (138) data analysis showed no statistical difference in the basal serum cortisol levels ($p=0.383$) between the AD and healthy controls and the SCORAD index was did not correlated with the basal serum cortisol values in AD patients ($p = 0.06$). Tehranchinia et al. (137) observed no statistical difference between the AD patients and healthy controls for basal serum cortisol and ACTH levels. Several studies found a relationship between cortisol levels and the severity of disease. Vinnik et al. (140) showed that all patient serum cortisol levels were within normal ranges; however, AD male cortisol was higher and cortisol levels were found negatively correlated with SCORAD. Nutan et al. (141) half the patients with AD have low basal cortisol levels and this is more marked in patients with severe AD.

We realize that interpretation of our results could be hampered by the fact that cortisol is a stress hormone that can be influenced by several factors and treatment with corticosteroids can be one of the major factors, especially in a pediatric population, because of children's relatively large body surface. The literature provides several studies showing the effects of the use of corticosteroids, on levels of cortisol (139,142–147). Studies from the past decades have found evidence that the use of topical highly potent corticosteroids has systemic effects (142,144), but recent studies have failed to prove this link (139,142–147). A previous study by Weston et al. (144) demonstrated significantly less suppression of the HPA axis by betamethasone dipropionate than clobetasol propionate, despite equal efficacy. Walsh et al. (142) analysis failed to show statistical significance, but a trend with lower mean cortisol levels

at day 4 was seen in patients treated with clobetasol propionate. In contrast, a study by Kojima et al. (139) revealed that salivary cortisol levels showed no correlation with previous use of topical corticosteroids in young children with AD. Patel et al (145) studied the adrenal function in 14 prepubertal children with moderate to severe AD (age 3–10 years). No difference was found in basal serum cortisol levels between children with moderate to severe AD regularly treated with topical corticosteroids compared with controls. A parallel cohort study by Haeck et al. (146) authors have demonstrated that low basal serum cortisol values are not caused by prior use of potent topical corticosteroids in patients with moderate to severe AD. In Ellison et al. (143) study no significant correlation was found between the amount of topical corticosteroids used and basal serum cortisol values. Matsuda et al. (147) showed that AD patients treated with topical steroids had a lower response to ACTH compared to untreated patients ($p<0.001$), although the results were not significantly different between groups. The populations and methodologies of the studies reviewed in our discussion differed, making it difficult to generalize the data. Several studies, like ours, showed that although mean cortisol values were within the normal range (137,138,140,143,145), AD patients had a significantly lower mean value and a higher number of patients had lower than normal serum cortisol levels compared to healthy controls (21,139). Our study, like others, did not find significant changes in mean cortisol levels to disease severity (138), although some authors have found this relationship (140,141). The results of the studies investigating serum cortisol levels in AD are summarised in Table 22.

Table 22. Comparison of studies investigating changes in serum cortisol among AD patients.

Study	Populations	Findings and conclusions
Vinnik et al. (140)	Adults, n=56 with AD, n=49 HC.	All patient serum cortisol levels were within normal ranges. Cortisol levels negatively correlated with the severity of AD. Cortisol level was elevated in male extrinsic AD.
Tehranchinia et al. (137)	Children and adults, n=31 AD, n=31HC, mean age 34.1±19.2 y.	Cortisol levels in the normal range in AD and control patients. No statistical difference was observed between AD and healthy controls for mean basal serum cortisol and ACTH levels.
Nutan et al. (141)	Children, n=62 AD, 6-16 y., mean age 6.95 ±4.50 y.	Half of the patients with AD have low basal cortisol levels and this is more marked in patients with severe AD.

Study	Populations	Findings and conclusions
Afsar et al. (138)	Children, n=36 AD, n=36 HC, 9-16 y.	Normal basal cortisol level with no correlation with disease severity.
Haeck et al. (146)	Adults, n=25 severe AD, n=28 moderate/mild AD, 18–83 y.	The severe AD group had a significantly lower cortisol level than the moderate/mild AD group. AD activity is responsible for low basal cortisol levels.
Matsuda et al. (147)	Children, n=45 severe AD, n=45 HC (selected from asthmatic children), 2-18 y, mean age 8.5 y.	The basal serum cortisol levels as well as the response to ACTH stimulation were significantly lower in the AD than controls. No significant differences in the results between AD patients with daily steroid use and AD patients who did not use steroids for three months.
Patel et al. (145)	Children, n=14 AD, n=14 HC, 3-10 y., median age 6.5 y.	Normal basal cortisol levels. Mild to moderately potent topical corticosteroids did not suppress adrenal glucocorticoid function in this sample of children with AD.

Abbreviations: *AD, atopic dermatitis; HC,* healthy controls; y, years.

5.2.5. Relationship of thyroid-stimulating hormone (TSH) and anti-thyroid peroxidase antibodies (anti-TPO) with pediatric AD

Autoimmune phenomena, especially thyroid autoimmunity, have often been associated with other autoimmune diseases, such as chronic urticaria in adults and children (36,41). However, data in the literature are controversial regarding true associations between atopy and autoimmune disease. Skaaby et al. (148) did not find statistically significant associations between atopic predisposition and autoimmune disorders, although they could not exclude moderate effects of atopy on autoimmune disease. A study by Wu et al. (128) found no significant correlation between AD and AITD. In contrast to previous studies, the recent cohort study by Lusignan et al. (35) found that people with AD were at a significantly increased risk of developing hypothyroidism and other autoimmune diseases. A Swedish case–control study by Ivert et al. (28) found that specialist-diagnosed AD was significantly associated with dermatologic, rheumatologic, and gastrointestinal autoimmune conditions. Notably, AD only in women was associated with dermatomyositis, systemic scleroderma, Hashimoto disease, Graves disease,

multiple sclerosis (MS), and polymyalgia rheumatica. In 2012, Pedullà et al. (149) reported a significant association between AD and autoimmune thyroid disease in children from Naples, Italy. Analysis by Joshi et al. (150) clarifies the link between thyroid dysfunction and AD, showing specifically that Hashimoto disease and Graves disease are associated with AD.

Table 23 provides a summary of the results of studies conducted in the last 25 years investigating the association between TSH and anti-TPO among AD patients. In a study by Handjani et al. (151) patients with AD had a mean value of TSH 2.69 mlU/L (0.37–5.01 mlU/L), and the control group had a mean of 1.90mlU/L (0.98– 2.27mlU/L). There were no significant differences in the serum TSH level among AD and healthy control groups (p-value = 0.080). Giasuddin et al. (152) measured serum TSH levels in 12 patients with psoriasis vulgaris, 9 patients with AD, and 20 controls and found that the mean TSH value was in the normal range in all three groups, and there was no significant difference between groups (p=0.74). Pedulla et al.(153) found that mean serum values of anti-TPO and/or thyroglobulin antibodies (TG Ab) were higher in atopic patients, and thyroid autoimmunity prevalence in atopic was 11.5%, while thyroid autoimmunity prevalence in non-atopic was 2.7% (P = 0.03, OR = 4.68, 95%CI: 1.02-21.38). In Zhang et al. (154) study thyroglobulin antibody (TgAb) positivity was identified as a risk factor for atopic rhinitis, AD, and chronic spontaneous urticaria patients, suggesting the involvement of thyroid autoantibodies in the pathogenesis of atopic reactions. Multivariate regression analysis also confirmed that the presence of TgAb (p=0.004), rather than anti-TPO (p=0.0468), had a significant impact on the occurrence of allergic disease. The mean TSH value was higher (but within the normal range) in the positive TgAb/anti-TPO group compared with the antibodies negative group (p<0.001). Further studies are needed to explore the immune dysregulation that may be contributing to the overlap between these pathologic conditions (42).

Table 23. Comparison of studies investigating changes in TSH and anti-TPO among AD patients.

Study	**Populations**	**Findings and conclusions**
Giasuddin et al. (152)	Children and adults, n=12 with psoriasis, n=9 AD, n=20 HC, 11-47 y.	The mean TSH value was in the normal range in all three groups, and there was no significant difference between groups.

Study	Populations	Findings and conclusions
Handjani et al. (151)	Children and adults, n= 90 (n=30 psoriasis, n=30 AD, n=30 HC), 15-47 y.	There were no significant differences in the serum TSH level among AD and healthy control groups.
Pedulla et al. (153)	Children, n=212 atopic (87 AD and urticaria with confirmed allergy – by IgE, prick tests). n=112 non-AD (urticaria and alopetia areata), 6.3±4.18 y.	A significant association between atopy and thyroid autoimmunity in atopic children with skin disease. The prevalence of thyroid autoimmunity in AD patients was significantly higher than that in HC and the prevalence of thyroid autoimmunity in IgE-mediated AD patients was significantly higher than that in non-IgE–mediated AD patients.
Zhang et al. (154)	Adults, n=217(positive TgAb and/or anti-TPO), n= 217 (negative TgAb and/or anti-TPO), >18 y.	Elevated TgAb and anti-TPO can significantly increase the risk of allergic diseases.

Abbreviations: *AD, atopic dermatitis; anti-TPO, anti-thyroid peroxidase antibodies; HC,* healthy controls; *IgE, immunoglobulin E; TgAb, thyroglobulin antibodies; TSH, thyroid-stimulating hormone; y., years.*

5.2.6. Relationship of prolactin with pediatric AD

The polypeptide hormone prolactin (PRL) is best known as the pituitary modulator of lactation and reproduction. PRL is generated and secreted by the lactotroph cells of the anterior pituitary gland. Strikingly, PRL is also expressed in mammalian skin, where PRL transcripts and protein are most prominently found in the hair follicle, in both mice and humans (155). Prolactin is a polypeptidic neuropeptide produced by lactotroph cells in the anterior pituitary gland and is well known for its lactogenic and mammotrophic effects. It has been hypothesized that forming a ‘prolactin circuit’ between the central nervous system and the skin, prolactin performs as a neuroendocrine modulator of skin epithelial cell proliferation and of the skin immune system (156). PRL plays an important role in immune reactions

and exerts a proliferative effect on human keratinocytes by binding specific sites Binding to specific skin receptors, modulation of cytokine release in the skin, and stimulation of somatomedin release by mesenchymal cells are among the suggested pathways by which prolactin could affect epithelial cell growth in the skin. Its rise in the serum, therefore, may play a role in the hyperproliferation of keratinocytes in vivo, the hallmark of the psoriasis disease process. Epidermal hyperproliferation that is observed in both psoriasis and AD and its underlying mechanisms are not completely understood by now (156).

In our data search, we were only able to find four studies that investigated prolactin changes in AD patients. Previous studies have assessed the association of PRL levels with psoriasis and AD as a hyperproliferative cutaneous disease of multifactorial etiology; however, the results seem contradictory (151,152,157,158). Table 24 summarises studies investigating changes in serum prolactin among AD patients.

A study by Handjani et al. (151) investigated 90 individuals aged between 15 and 47 years which were selected randomly based on the time of referral. The individuals were divided into three groups: psoriatic patients, AD patients, and a control group that included healthy volunteers. None of the patients in the study had raised prolactin, and there was no significant difference in the serum prolactin level between patients with psoriasis and AD and the control group. There was no relationship between the severity of psoriasis and serum levels of prolactin. In a study by Ayanoglu et al. (157), no significant correlation was found between prolactin levels and sex, duration, number of relapses, and scores of AD ($p > 0.05$, Spearman correlation analysis). In the study of Kasperska-Zajac et al. (158), serum concentration of prolactin was measured in 13 female patients with severe intensity of atopic eczema/dermatitis syndrome and compared next with 14 healthy subjects. The study failed to detect any significant differences in serum basal concentration of prolactin among patients and healthy subjects as our results (158).

Giasuddin et al. (152) measured serum PRL levels in 12 patients with psoriasis vulgaris, and found that they were significantly higher than those of 9 patients with AD and 20 controls whereas there was no significant difference between atopic patients and controls.

Table 24. Comparison of studies investigating changes in serum prolactin among AD patients.

Study	Populations	Findings and conclusions
Ayanoglu et al. (157)	Children, n=46 AD, n=60 HC, 0,16-19,5 y.	No significant difference was found in prolactin levels in both groups. No significant correlation was found between prolactin levels and sex, duration, number of relapses, and scores of AD
Handjani et al. (151)	Children and adults, n= 90 (n=30 psoriasis, n=30 AD, n=30 HC), 15-47 years	No significant difference in the serum prolactin levels between patients with psoriasis and AD and the control group.
Kasperska-Zajac et al. (158)	n=13 severe AD, n=14 HC	No significant differences in serum basal concentration of prolactin among patients and healthy subjects.
Giasuddin et al. (152)	Children and adults, n=12 psoriasis, n=9 AD, n=20 HC, 11-47 y.	Serum PRL in psoriasis (25.8±16.1 ng/ml) was significantly higher compared to those in AD (9.1±4.7 ng/ml) and normal control subjects (10.3±5.3 ng/ml).

Abbreviations: *AD, atopic dermatitis; HC, healthy controls; PRL, prolactin; y, years.*

5.3. Quality of life of patients and their family members

To the best of our knowledge, based on a systematic search regarding studies published from 2003 to 2023 this is the first report evaluating QoL in a fairly large sample of Lithuanian pediatric AD patients by using the DLQI and FDLQI questionnaires. The burden of AD on patients' QoL has been previously described in studies outside of Lithuania (56,85,159–161). For summarised results look at Table 25. The mean DLQI score of our respondents was 6.3±5.56, which reflects a moderate effect of AD on patients' QoL. This was consistent with Kim et al. (159) study with a CDLQI score of 6.6. Our results were slightly lower than the mean score of 7.15 reported by Holm et al. (162), 8,7 reported by Ezzedine et al. (161), 7,24 reported by Cheng et al. (85), and 7,6 reported by Sanches-Perez et al. (160), all of which also fall

within the moderate-effect range. A study conducted by Coutaneau et al. (163) revealed that patients with AD experience poor health-related QoL with a mean DLQI score of 10,2, but in our opinion it was influenced by a wider spectrum of population age. The study included children and young adult patients with a mean age of population 11,9±13,1 years. The Marciniak et al. (164) study evaluated the correlation between both mothers' fathers' QoL, assessed using the FDLQI, and the children's QoL, assessed with the IDLQI. We chose to compare the data from this study with ours because in our study 95% (288) of those who completed the questionnaires were mothers. In the current study, the mean FDLQI for mothers was 17.1 ± 5.3 points, which indicates a very large effect on families QoL. Other studies conducted by other authors also confirm a very large effect on families QoL with FDLQI index between 11.8± 5.8 and 16.45 ± 6.56 (165–168). The differences in results could be influenced by the age of the study populations. The studies that found higher FDLQIs looked at populations of children with an average age of up to 5 years. Whereas, the study by Cheng et al., whose subjects were of a similar age range to ours, estimated a moderate effect on families QoL (mean FDLQI 9.97 ±7.99) (85). However, the mean SCORAD index was lower in a recent study (26.58 ±19.77) compared with ours and other studies. We could not find any studies that compared FDLQI and the severity of illness according to the POEM index. The difference between the SCORAD and POEM scales is that the POEM is a subjective self-assessment tool for the severity of disease. We obtained small differences in the analysis of different aspects of FDLQI between SCORAD and POEM and it would be useful to extend the studies in this perspective.

Differences in QoL scores between studies reflect both a variation in disease severity and the subjective nature of QoL impairment, which is undoubtedly influenced by many factors including family and peer relationships, gender, social class, ethnicity, education, and previous life experience. There are differences in the population data of the conducted studies, which may have implications for the data analysis, but overall the data confirm that AD has a negative impact on the patients' and families' QoL and that this issue needs to be integrated into the treatment plan, and that additional psychological support needs to be offered to the patients and their family members. Alternatively, such support may include training programs, cognitive therapy, and others. Our study has some limitations. First, although it was conducted on a fairly large sample of Lithuanian AD patients, it lacks equal distribution around Lithuania. Also, our subjects cannot be considered representative of the whole of Lithuanian AD patients, as they were people

attending dermatological services. Larger studies on population-based samples possibly involving primary care physicians and combining a cumulative life course impairment study with DLQI assessment are needed.

Table 25. Comparison of QoL studies of patients with atopic dermatitis.

Study	**Number of AD patients**	**Age of AD patients, mean score±SD**	**AD severity scale, mean score±SD**	**QoL scale name, mean score±SD**	**FDLQI mean score±SD**
Holm et al., 2016	296	Children, adults	SCORAD, 29.4±14	CDLQI: 7.2±4.6; CDLG/DLQI: 9.8±5.9	-
Kim et al., 2012	415	14.5±10.8 y.	SCORAD, 15.8 ± 8.4	IDLQI: 7.7±5.5; CDLQI: 6.6±6.3; DLQI: 10.7±7.9	-
Ezzedine et al., 2020	400	12-18 y.	POEM (12-14 y.), Mild: 5.6±5.6; Moderate: 12.7±7; Severe:15.9 ± 4.1	CDLQI: 8.7±7.1 (12-14 y.); DLQI: 12.8±11.1 (15-17 y.)	-
Cheng et al., 2019	323	Children, adults	SCORAD, 26.6±19.8	CDLQI: 7.2±6.8	9.9±7.9
Sanchez-Perez J., Dauden-Tello E., 2012	151	9.4±4.5 y.	IGA, Mild: 3.8±3; Moderate: 8.8±4.7; Severe: 14.5±8.2	CDLQI: 7.6±5.7	-
Coutaneau et al., 2014	3914	11.9±13.1 y.	SCORAD, (n=3589), 42.2±17.3	-	-

Study	Number of AD patients	Age of AD patients, mean score±SD	AD severity scale, mean score±SD	QoL scale name, mean score±SD	FDLQI mean score±SD
Marciniak et al., 2017	50	1.2±6.5 months	-	IDLQI:14.1± 4.6 (6–26)	Mothers: 17.1±5.3; Fathers: 14.7±5.8
Kose et al., 2022	122	5.4±2.3 y.	SCORAD, 57.6±11	CDLQI: 7.2±6.8	14.8 ± 4.7
Cheng et al., 2019	155	5.4±2.3 y.	SCORAD, 26.6±9.8	-	9.9±7.9
Pustusek et al., 2016	171	3 months-17 y.	SCORAD, 38.7±16.4	-	13.6±6
Chernysho v et al., 2014	30	23.7±24.6 months	SCORAD, 40.6±11.3	-	11,8±5.8
Kobusiewi cz et al. 2022	88	60.1±56.6 months	SCORAD, 46.6±15.2	-	16.5±6.6

***Abbreviations**: AD, atopic dermatitis; CDLQI, Children's Dermatology Life Quality Index; DLQI, the Dermatology Life Quality Index; FDLQI, the Family Dermatology Life Quality Index; IDQoL, the Infants' Dermatitis Quality of Life index; SD, standard deviation; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring for Atopic Dermatitis; y.-years.*

5.4. Associations between atopic dermatitis and behavior difficulties

Results of our study revealed, that patients with AD (aged 6-18 years) have higher mean scores in total behavior problems, internalizing behavior (anxiety/depression, somatic complaints), and social and thought problems scales compared to controls. Common mental disorders, such as depression and anxiety, show a high prevalence in patients with chronic inflammatory processes underlying physical diseases (51). Depression and anxiety are highly prevalent psychiatric disorders in children and adults with AD (51–53,87,89,169). Moraes et al. (87) observed that nearly half of the patients from their study with AD exhibited CBCL values for internalizing problems in the

clinical range. Muzzolon et al. (89) revealed that children and adolescents with AD present a higher risk for internalizing disorders in comparison with healthy siblings. These data are corroborated in the literature, suggesting that AD may contribute to the development of BD (52,54).

People with severe AD usually have more frequent exacerbations and more severe symptoms. One of the hypotheses is that more severe AD may have a greater impact on patients' mental health than milder AD. Park et al. (169) revealed that children and adolescents with severe AD more frequently have internalizing problems, particularly isolation (withdrawal/depression), somatic complaints, and anxiety problems. Although we found similar differences between AD patients and healthy controls, the results of our CBCL questionnaire were not significantly different when comparing severe and mild-moderate AD groups. However, the results of our study show that patients with severe AD have more sleep disturbances and more itching scores compared to mild-to-moderate AD patients. It is known, that an inadequate quantity and quality of sleep are associated with various impairments in daytime performances and can impair aspects of emotional and cognitive functioning (52). Camfferman et al. (170) found that children with eczema had a significantly higher number of scratching events that originated during wake and sleep and a longer duration of scratching events during sleep, than controls. In a study by Ramirez et al. (171), children with active AD had poorer sleep quality, and the association was strongest among children with more severe disease. These findings are consistent with Fishbein et al. (172), a cross-sectional study of clinic populations that used objective measures of sleep, including actigraphy and polysomnography. The authors found that children with moderate-to-severe AD experience lower sleep efficiency than healthy controls. Similar results were shown by Moraes et al. (87), they observed a higher prevalence of sleep disturbance in patients with AD. Furthermore, when comparing mild and moderate AD groups, the authors found that aggressive behaviour was more common in patients with moderate AD. In contrast, in our study, there were no differences in aggressive behaviour scales between the severe and moderate AD group and the mild and moderate AD group, and the AD and control group. This difference can be explained by the nature of the behaviour. Aggressive behaviour varies according to age and gender, and may be influenced by family or national culture and customs.

We observed, that boys with AD have higher somatic complaints, while the girls - social and thought problems scores in comparison with control. Good control of the disease requires a consistent skincare and treatment

routine, which is applied from infancy. Deviations from the routine almost always lead to the worsening of the disease, as well as the worsening of the symptoms. This is an assumption, but a possible explanation could be that, at least in our country, women are more likely to take care of their skin. Meanwhile, social contact and communication are very important for girls, so these aspects may be more severely affected in the case of an exacerbation of the disease.

Children and adolescents, whether healthy or chronically ill, have the same needs during development. Nevertheless, it is more difficult for a sick child to meet the needs specific to each developmental stage of the child, and at the same time to cope with the stressors of chronic illness.

Symptoms and conversion of the illness can alter the child's and adolescent's mental development, as well as interfere with their interaction with their environment (87). Based on previous studies, the psychological stress caused by AD itself seems to trigger immunological problems and worsen AD symptoms, creating a vicious cycle that can lead to sleep difficulties and psychological and behavioral problems (51,89,173,174). In addition, hormonal disruption found in AD patients can directly cause psychological and behavioral problems (138). We found that the mean cortisol level was statistically lower in the AD group compared to to healthy control group. The hypothalamic-pituitary-adrenal (HPA) axis represents a major immunoregulatory system that plays an important role in balancing the immune response, especially under stressful conditions. Stress-induced immunomodulation is altered in patients with AD, but the exact mechanisms are not well understood. Recent studies have shown that in patients with AD, for example, psychological stress can impair or blunt the HPA axis reactivity but it can over-activate the sympathetic system, which may lead to an increased Th2 response and aggravation of the symptoms. Additionally, AD can lead to psychological stress, due to stigmatization, social isolation, and discrimination (21). Several studies have looked at cortisol levels “at rest” in patients with allergic disorders versus nonatopic control patients. The populations and methodologies of the studies that we reviewed during the literature analysis differed, making it difficult to generalize the data. Several studies, like ours, showed that although mean cortisol values were within the normal range (137,138,140,143,145), AD patients had a significantly lower mean value compared to healthy controls. Our study, like others, did not find significant changes in mean cortisol levels concerning disease severity (138), although some authors have found this relationship (140,141).

In our study, cortisol levels were not an associated risk factor for behavioral problems, and we found only one study that looked at the relationship between cortisol levels and behavioral problems. Afsar et al. (138) did not find a significant correlation between the morning basal cortisol values and anxiety levels in children with AD (the scores were obtained from the State-Trait Anxiety Inventory for Children, (STAI-C), whereas there was a correlation between the morning basal serum cortisol values and the scores of TAI-C in the control group. The differences between our results and those of Afsar et al. may be influenced by the methods used to measure cortisol and the type of previous AD treatment.

Disease duration, but not clinical severity such as SCORAD, was an independent risk factor for having internalizing problems in AD children, in the study by Park et al. (169). This suggests that patients have experienced the psychosocial burden associated with a chronic, persistent course of illness. Our study did not support this hypothesis. None of the tested factors (severity by SCORAD, age, sex, morning cortisol level, duration of disease, intensity of pruritus, and intensity of sleep disturbance) was statistically significant and did not have associations with behavioral problems in our analysis.

In our opinion, the difference in the results shows, that, behavioral difficulties can be the result of a variety of factors, both physiological and individual, related to the disease or the living environment. Their identification requires a long-term and detailed assessment of the patient's history and clinical, physiological, and psychological features.

5.5. Corticophobia

Corticophobia or steroidophobia is a common, worldwide phenomenon in patients with AD, leading to poor local treatment adherence and frequent therapeutic failure. Paradoxically, there is a lack of corticophobia assessment tools available. Corticophobia is a complex phenomenon, and assessing it with binary (yes-or-no) responses is, thus, too simplistic and cannot detect different types of fears and their intensity (72). Analysis of the methodology of studies that investigated corticophobia revealed a higher prevalence of corticophobia in studies that assessed corticophobia with only one question, for example, "Do you feel fear of applying steroid cream? (75). In our study, this trend was consistent. Looking at the prevalence of steroidophobia on a single question „Do you feel anxious or hesitant before applying a corticosteroid cream“ 55% of responders chose a positive answer. The average global TOPICOP score in our population is 43%, replicating the findings of other authors (175–178),

except for Moawad et al. (179) who found lower scores of 18%. The literature analysis shows that different studies identify different factors influencing the development of corticophobia. Some studies replicated our findings that corticophobia was not related to the respondents' education (81), the severity of AD (177,179), or parental gender (175,178), others - found that low level of respondent's education (176) and sex (179), severity of AD (176,178), participation in special educational programs (176,178) are factors associated with steroid phobia (Table 26). Results may be affected by different sample sizes and cultural differences, and therefore large-scale multicentre studies are needed to clarify these results. Adherence to topical treatments among AD patients is a multifactorial issue. Potential barriers to adherence in the pediatric population are caregivers with negative beliefs about treatment, the time-consuming nature of applying topical therapies, or a child who is uncooperative (180). In our study, 29 % of parents delayed the start of the medication. 98 % of all surveyed parents in our study (of healthy and AD children) confirmed that they are taking action to minimize the potential side effects of topical glucocorticoids, such as delaying the beginning of treatment, diluting steroids with moisturizer, applying smaller amounts, and apply for a shorter period, resulting in insufficient treatment effect and poor disease control. Charman et al.(181) found that 72.5% of people worried about using topical corticosteroids on their own or their child's skin, and 24% of people admitted to having been non-compliant with topical corticosteroid treatment because of these worries. Educational tools (eg, action plans, instructions about how to apply topical medications correctly, specialized lectures) may be underutilized in patients with AD. Since AD patients and their caregivers often are not well-versed in how to apply topical medications correctly, efforts to educate patients could potentially increase treatment adherence (180). Nowadays, there is accessible access to medical information in the media, such as newspapers, magazines, and the internet. However, much of this information is not produced by healthcare professionals and may erroneously induce the patient to undergo TCS. A Korean study showed that the internet (49.2%), television or other broadcasting media (45.2%), doctors/healthcare professionals (37.3%), and magazines/newspapers were sources of information associated with steroid phobia (88). In our study, the three most common sources were medical professionals (75%), the internet or chat rooms (58%), and special AD websites (46%). Charman et al. (181) noticed that the most common source of patient information regarding topical corticosteroid safety was the general practitioner, the other common were newspapers and journals, friends and family.

Corticophobia is an ongoing and widespread problem, and the analysis of its causes requires extensive studies. Doctors need to remember to ask about the fear of using steroids for treatment and, once prescribed, to explain the correct use, the possible side effects, and the advantages of this treatment.

Table 26. Factors influencing the development of corticophobia among AD patients.

Article	Study design	Sample size	Mean±SD TOPICOP score (%)	Factors associated with	Factors not associated with steroid
Moawad et al. (179)	Cross-sectional multi-center study	122	18.8 ± 9.5	Mothers vs. fathers	Dermatological condition (psoriasis vs. AD), sex or age of children, family
Saito-Abe et al. (178)	Cross-sectional study	243	40.3 ± 16.9	Younger age of patient	Family history of AD, caretaker
Gonzales et al. (177)	Prospective single-centre	169	37 ± 13.3	Parents of girls, with poor	Age, family history of AD,
Gerner et al. (176)	Cross-sectional study	1343	38.2 ± 19.9	Low parental education	Sex of child with AD, age of the child
Bos et al. (175)	Cross-sectional study	29	44	Parents	Age, sex
Choi et al. (81)	Cross-sectional study	186	38.9±24.4	Female sex	Ethnicity, highest education level,

***Abbreviations**: AD, atopic dermatitis; TCS, topical corticosteroids.*

6. LIMITATIONS

This work has several limitations. This was a single-center study with a relatively small sample size. A larger sample of subjects would provide more accurate statistical data. A cross-sectional study design would help to find the relationship between endogenous and exogenous factors with AD and disease severity. But as a result of the cross-sectional nature, only a single time point is captured. Other study designs could explore the relationship between variables and participants, and answer the correlation question more definitively. A cohort study would better assess the correlation between variables over time for a given individual. Some of the data was collected from a questionnaire survey, so we could not specify additional anamnestic data, such as family history of thyroid disease.

In addition, the average age of the subjects was 10±2.7 years for AD patients and 10.5±3.1 years for the control patients. Some of the internal diseases, such as dyslipidemias, and thyroid diseases are more likely to become apparent at an older age.

Our study had some limitations in identifying the links between AD and behavioral difficulties, overall, it could benefit from broader psychological research/exploration, such as cognitive function and stigma assessment. Also, the data on the participants‘ behavior were obtained through a single source of information, in this case, the main parent who was accompanying the patient during the outpatient visit. Longitudinal studies may verify the persistence of symptoms, as well as the conditions associated with their attenuation or intensification over time.

7. STRENGTHS AND POTENTIAL PERSPECTIVES

Laboratory tests carried out during the study allowed us to investigate the relationship between endogenous factors and the disease. Although not all the factors investigated were related to the severity of the disease, some of the observed parameters (direct correlation of total IgE and eosinophil counts with disease severity, lower serum cortisol levels in AD patients) provided additional insights into the impact of the disease on other body systems than the skin.

This is the first study analyzing the impact of AD on behavioral difficulties in children in Lithuania. The findings add to the knowledge that both the disease itself and its course are related to behavioral difficulties in children. Further comparative studies using common child- and parent-completed indicators would provide additional information on the impact of the disease on quality of life and behavioral difficulties. Recognition of mental disorders in people with AD and effective treatment of mental symptoms could lead to significant improvements in patient's health and quality of life.

8. CONCLUSIONS

1. AD in children is associated with food allergy, rhinoconjunctivitis, higher total IgE, lower serum cortisol and vitamin D levels in the low-sun season compared to non- atopic controls. AD patients' skin is more affected by external factors.
2. AD has a moderate negative impact on the quality of life of affected children and their families and is directly related to the severity of the disease.
3. A higher prevalence of behavioural problems, mainly somatic complain, anxiety and depression has been observed among children with AD (aged 6 to 18 years). We have not identified factors that predispose children to developing behavioural difficulties.
4. Parents of AD patients have a moderate risk of corticophobia, which is related to the diagnosis of AD itself, but unrelated to respondents' education, gender, severity of AD, previous steroid use, and participation in special training programs/reports.

PRACTICAL RECOMMENDATIONS AND FUTURE DIRECTIONS

1. In AD patients, vitamin D levels (especially during periods of low sun exposure), serum cortisol and total IgE, and should be checked if indicated or if the doctor suspects an abnormality.
2. Quality of life questionnaires should be included in the routine assessment of the patient's condition during the consultation, and improving the patient's and family's quality of life should be a central aspect of the development of the consultation and treatment plan.
3. Psychological support therapies should be included in the individual treatment plan and the national guidelines for AD.
4. Further development of information systems for patients (web portals, websites) and physicians, especially general practitioners (lectures at conferences, professional training) is needed to reduce the prevalence of corticophobia, improve treatment adherence, improve immunization rates, and disseminate knowledge about burden of the disease to patients and family members.

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Appendix 1. Original questionnaire for participants

Pildymo data: Identifikacinis numeris: AD_____ Tyrimo N.: ADIK-1

Ši anketa skirta išaiškinti demografinius, aplinkos veiksnius, odos priežiūros ir gydymo įpročius turinčius įtakos sergančių atopiniu dermatitu (AD) pasireiškimui. Pildydami anketą Jūs užtruksite 15-20 minučių. Duomenys bus naudojami tyrėjų atliekamo biomedicininio tyrimo tikslais. Skelbiant duomenis, bus pateikiami tik apibendrinantys analizės rezultatai neminint nei vieno konkretaus paciento. Jei turite klausimų, galite kreiptis į tyrėją gydytoją dermatovenerologę Ingą Kisielienę, el. paštas: sargeviciute@gmail.com, telefonas 860069675. Maloniai prašome atsakyti į kiekvieną klausimą. Dėkojame už nuoširdžius atsakymus.

ANKETA

Informacija apie tėvus/globėjus

1. Jūsų lytis: □ vyras □ moteris
2. Giminystės ryšys su sergančiuoju □ tėtis □ mama □ kita (įrašyti)_____
3. Dabartinis Jūsų amžius (įrašyti)_____
4. Vedybinis statusas □ vienišas/a □ ištekėjęs/si □ išsiskyręs/usi □ našlys/ė □ sugyventinis/ė
5. Tėvų išsilavinimas:
   Tėčio: □ vidurinis □ profesinis □ aukštasis □ nebaigtas aukštasis □ kita (įrašyti)_____
   Mamos: □ vidurinis □ profesinis □ aukštasis □ nebaigtas aukštasis □ kita (įrašyti)_____
6. Darbas: □ dirbantis □ bedarbis □ namų šeiminkė/as □ pensija □ kita (įrašyti)_____
7. Dabartinė gyvenamoji vieta: □ kaimas □ miestas □ priemiestis
8. Būsto tipas: □ butas □ namas/kotedžas
9. Mėnesinės šeimos pajamos per mėnesį (įrašyti)_____
10. Kiek brolių/seserų turi Jūsų vaikas? □ 1 □ 2 □ 3 □ 4 □ kita (įrašyti)_____
11. Ar šiuo metu turite naminių gyvūnų? □ Taip □ Ne
12. Jei taip, kokių? □ katė □ šuo □ žiurkėnas □ kita (įrašyti)_____
13. Ar kuris nors iš tėvų šiuo metu rūko? □ Taip, tėtis □ Taip, mama □ Taip, abu □ Ne
    Jei taip: kiek metų rūkote?
    Tėtis: (įrašyti)____; Mama (įrašyti)_____;
    Cigarečių kiekis per dieną:
    Tėtis: □<10 cig/d □10-20 cig/d □>20 cig/d
    Mama: □<10 cig/d □10-20 cig/d. □>20 cig/d

Informacija apie sergantį atopiniu dermatitu

1. Jūsų vaiko lytis: □ berniukas □ mergaitė
2. Kiek šiuo metu Jūsų vaikui metų? (įrašyti)_____
3. Kelių mėnesių/metų Jūsų vaikui pasireiškė AD simptomai? □<3 mėn. □ 4-5 mėn. □ 6 mėn.-12 mėn. □ 13 mėn.-3 m. □ 4-5 m. □ kita (įrašyti)_____
4. Kelių metų Jūsų vaikui diagnozuotas AD? □<3 mėn. □ 3-5 mėn. □ 6 mėn.-12 mėn. □ 13 mėn. -2 m. □ 3-4 m. □ 5-6 m. □ kita (įrašyti)_____
5. Ar jūsų vaikas serga/sirgo kitomis atopinėmis ligomis (alergine sloga, alergine astma, alergija maistui)? □ Taip □ Ne
6. Jei taip, kokia (galimi keli variantai)? □ alergine astma □ alerginiu rinitu (šienlige) □ alergija maistui
7. Ar Jūsų vaikui yra daryti alerginiai mėginiai? □ Taip □ Ne
8. Jei taip, pažymėkite tyrimus ir kokie rezultatai gauti?
   □ *Odos dūrio*: □ teigiami □ neigiami
   □ *Odos lopo testai*: □ teigiami □ neigiami
   □ *Bendras imunoglobulinas E* (B IgE): □ normalus □ padidėjęs
   □ *Specifiniai IgE (sIgE)*: □ teigiami □ neigiami
   □ *Maisto tolerancijos testas (imunoglobulinas G)*: □ teigiami □ neigiami
   □ *Pasėlis nuo odos bėrimų dėl bakterijų?* □ Taip □ Ne
9. Ar skiepijote vaiką pagal privalomą skiepų kalendorių? □Taip □ Ne □ Nepilnas
10. Jei ne, dėl kokių priežasčių neskiepijote? □ dėl asmeninių įsitikinimų; □ dėl religinių įsitikinimų; □ dėl gretutinių ligų (pvz.: alergijos) □ bijau šalutinių reiškinių □ kita (įrašykite)_____

Informacija apie ligą ir anamnezė

1. Ar kas nors šeimoje sirgo/serga atopiniu dermatitu ir/ar alergine astma ir/ar alerginiu rinitu (šienlige)/ kontaktiniu dermatitu? □ Taip □ Ne
2. Jei taip, kas (galimi keli variantai)? □ Tėtis □ Mama □ Boliai/seserys □ Močiutė □ Senelis
3. Ar Jūsų vaikas serga kitomis lėtinėmis ligomis? □ Taip □ Ne
4. Jei taip, kokiomis? (įrašyti)_____
5. Ar Jūsų vaikas maitintas motinos pienu/ krūtimi? □ Taip □ Ne

Pildymo data: Identifikacinis numeris: AD_____ Tyrimo N.: ADIK-1

6. Jei taip, kiek laiko?
   □ ≤ 3 mėn. □ 4-6 mėn. □ 7-9 mėn.
   □ 10-12 mėn. □ 13-18 mėn. □ 19-24 mėn. □>2 m.
7. Nuo kelių mėnesių pradėjote primaitinti papildomu maistu?
   □ ≤3 mėn. □ 4-5mėn. □ ≥ 6 mėn.
8. Kaip pasikeičia Jūsų vaiko odos būklė paveikus kuriam nors iš žemiau išvardintų veiksnių?

	Pagerėja	Pablogėja	Neturi įtakos
Žiemos metu			
Vasaros metu			
Atostogų metu šiltuose kraštuose			
Atostogų metu prie jūros			
Pavalgius tam tikrų maisto produktų			
Streso metu			
Kitos ligos metu (sloga, karščiavimas)			
Po skiepų			
Suprakaitavus/sušilus			
Po baseino			
Nuo vilnonių rūbų			
Nuo sintetinių rūbų			
Po kontakto su gyvūnais			
Nuo įprastų (ne „hipoalerginių“) higienos/kosmetikos priemonių (pvz.: muilas, skalbimo milteliai)			

Odos priežiūros įpročiai ir gydymas

1. Kaip dažnai per paskutinmėnesį savo vaiką prausėte po dušu/vonioje?
   □ kelis kartus per dieną
   □ vieną kartą per dieną
   □ kelis kartus per savaitę
   □ 1 kartą per savaitę
   □ rečiau nei 1 kartą per savaitę
2. Kokius prausiklius naudojate?
   □ įprastas muilas
   □ specialus sausai odai
   □ nenaudoju
   □ kita (įrašykite)_____
3. Ar nuo gimimo tepėte drėkinantį kremą savo vaikui? □ Taip □ Ne
4. Kaip dažnai per paskutines dvi savaites tepėte drėkinamą kremą savo vaikui?
   □ >2 k/d. □ 1-2 k/d □ kelis kartus/sav. □ kelis kartus per mėnesį □ netepiau
5. Jei netepate kasdien, kokiomis aplinkybėmis patepate?
   □ kai išsausėja, pradeda pleiskanoti
   □ kai atsiranda išbėrimas
   □ po maudynių
   □ kita_____
6. Kokį kremo kiekį apytiksliai sunaudojate per mėnesį tepant savo vaiką?
   □ 100 g □ 200 g □ 300 g □ 400 g □ 500 g
7. Ar dėl vaiko ligos Jums ar Jūsų vaikui buvo skirta dieta (ribojami tam tikri maisto produktai)?
   □Taip □ Ne
8. Ar jūsų vaikui/Jums buvo skirti vaistai bėrimams gydyti? □Taip □ Ne
9. Jei taip, kokie (galimi keli variantai)?
   □ antispetikai (octisept, metileno mėlis, cutasept, kalio permanganato vonelės)
   □ tepami antibiotikai (Fucidin, Baneocin, Fucidin H, Fucicort)
   □ tepami gliukokortikoidai (pvz.: advantan, Cutivate, Elocon, Beloseta)
   □ tepami kalcineurino inhibitoriai (pvz. elidel, protopic)
   □ geriai antibiotikai
   □ geriami I kartos antihistamininiai („migdantys antialerginiai“, pvz.: tavegyl, clemastin)
   □ geriami II kartos antihistaminianiai („nemigdantys antialerginiai“ pvz.: zyrtec, aerius, cetirizin, rupafin, opexa)
   □ geriami/leidžiami gliukokortikoidai (pvz.: prednizolonas, medrolis)
10. Ar per paskutines dvi savaites tepėte savo vaiko odą vaistais? □ Taip □ Ne
11. Jei taip, pažymėkite, kokius vaistus naudojote (galimi keli variantai)?
    □ antispetikus □ tepamus antibiotikus (Fucidin, baneocin, Fucidin H)

□ tepamus gliukokortikoidus (pvz.: advantan, Cutivate, elocon, Beloseta)
□ tepamus kalcineurino inhibitorius (pvz. elidel, protopic)
□ geriamus antibiotikus
□ geriamus antihistamininius (antialerginius)
□ geriamus leidžiamus gliukokortikoidus (pvz.: prednizolonas, medrolis)

12. Kaip tepate paskirtus vaistus (gliukokortikoidus, hormonus)?

□ tepu tiesiai ant bėrimų, prieš tai patepus drėkinančiu kremu

□ tepu tiesiai ant bėrimų, o drėkinamą kremą tepu ant viršaus arba aplink

□ skiedžiu (sumaišau) vaistą su drėkinančiu kremu

□ kita (įrašyti)_____

13. Ar delsėte pradėti gydymą paskirtais gliukokortikoidų (hormonų) tepalais savo vaikui, dėl baimės/abejonės dėl galimų šalutinių reiškinių (odos plonėjimo, patekimo į kraujotaką ir pan.)? □ Taip □ Ne
14. Ar jaučiate nerimą/abejonę dėl paskirto gydymo gliukokortikoidų tepalais (hormonais)? □ Taip □ Ne
15. Jei taip, kokių veiksmų imatės (galimi keli variantai)?

□ tepu mažesnį kiekį □ tepu trumpiau

□ tepu tik tada, kai bėrimai labai paryškėja ir tepant drėkinančiu kremu negerėja

□ skiedžiu su drėkinančiu kremu

□ kita (įrašyti)_____

16. Kiek laikotės Jums rekomenduoto odos priežiūros plano?
□ laikausi visų rekomendacijų;
□ laikausi daugumos rekomendacijų;
□ laikausi kai kurių rekomendacijų;
□ visiškai nesilaikau.
17. Jei nesilaikote/laikotės dalies rekomendacijų, dėl kokių priežasčių (galimi keli variantai)?

□ nepasitikiu gydytojo paskirtu gydymu;

□ bijau šalutinių gydymo reiškinių;

□ nesuprantu paskirto gydymo plano;

□ paskirtas gydymo planas sudėtingas;

□ neturiu laiko laikytis visų paskyrimų;

□ pamirštu; □ kita _____

18. Ar esate girdėję apie proaktyvų, palaikomą AD gydymą? □ Taip □ Ne
19. Jei taip, ar naudojate šį gydymo būdą?

□ Taip □ Ne □ Bandžiau, bet netęsiu

20. Ar duote savo vaikui vitaminų/maisto papildų? □ Taip □ Ne

Jei taip, kokių (galimi keli variantai)? □ Žuvų taukai □ vit. D □ probiotikai/prebiotikai

□ multivitaminai □ kita

Jei taip: □ reguliariai kasdien; □ kelis mėnesius per metus; □ kelias savaites per metus

21. Ar esate gydymui naudoję homeopatines priemones/alternatyvius gydymo būdus? □ Taip □ Ne
22. Jei taip, kokias?
□ žolių mišinius (arbatos, užpilai, tinktūros)
□ specialiai pagamintas granules, žirnelius ir pan. □ kita (įrašykite)_____
23. Ar homeopatinės priemonės padėjo pagerinti Jūsų vaiko simptomus?

□ Taip □ Ne □ Iš dalies □ Nežinau □ Kita___

24. Kur ieškote informacijos apie AD, jo valdymo ir gydymo būdus (galimi keli atsakymo variantai)?

□ internete (forumuose); □ iš mokymo programų/paskaitų skirtų sergantiems AD ir jų artimiesiems (pvz.: egzemos mokykla, odos akademija);

□ specializuotuose puslapiuose, skirtuose sergantiems AD (pvz.: atopinis.lt, egzema.net, eczema.org, fb:egzemosmokykla);

□ iš medikų (farmacininkų, gydytojų, slaugytojų);

□ neieškau; □ kita (įrašyti)_____

Appendix 2. The Infant's Dermatology Life Quality Index (IDLQI)

KŪDIKIO DERMATITO GYVENIMO KOKYBĖS INDEKSAS (IDQOL)

Vardas, pavardė: **Data:** **IDQOL**
Adresas: **BALAS** ☐

Šio lentelės tikslas yra užfiksuoti jūsų kūdikio dermatito būklę. Kiekvienas klausimas susijęs TIK SU PRAĖJUSIA SAVAITE. Prašome atsakyti į kiekvieną klausimą.

Dermatito rimtumas

Kiek rimta, jūsų nuomone, buvo jūsų vaiko dermatito būklė per pastarąją savaitę? T. y., ar labai paraudusi , žvynuota, paveikta uždegimo oda, ar paplitęs.

- Ypač rimta ☐
- Rimta ☐
- Vidutinė ☐
- Pakankamai gera ☐
- Jokia ☐

Gyvenimo kokybės indeksas

1. Kiek laiko per pastarąją savaitę jūsų vaikui **niežėjo ar jis kasėsi odą**?
   - Visą laiką ☐
   - Daug ☐
   - Šiek tiek ☐
   - Nieko ☐

2. Kokia per pastarąją savaitę buvo jūsų vaiko **nuotaika**?
   - Visada verkė
   - Labai sudėtingas ☐
   - Labai irzlus ☐
   - Šiek tiek irzlus ☐
   - Laimingas ☐

3. Kiek apytiksliai **laiko** per pastarąją savaitę prireikė vidutiniškai, **kad jūsų vaikas užmigtų** kiekvieną naktį?
   - Ilgiau nei 2 val. ☐
   - Nuo 1 iki 2 val. ☐
   - Nuo 15 min. iki 1 val. ☐
   - Nuo 0 iki 15 min. ☐

4. Kiek **iš viso laiko** per pastarąją savaitę jūsų vaiko **miegas buvo sutrikdytas** vidutiniškai kiekvieną naktį?
   - 5 val. ar ilgiau ☐
   - Nuo 3 iki 4 val. ☐
   - Nuo 1 iki 2 val. ☐
   - Trumpiau nei 1 val. ☐

5. Kiek per pastarąją savaitę jūsų vaiko egzema trukdė **žaisti ar plaukioti**?
   - Labai daug ☐
   - Daug ☐
   - Šiek tiek ☐
   - Visai nieko ☐

6. Kiek per pastarąją savaitę jūsų vaiko egzema trukdė jūsų vaikui **dalyvauti** arba **mėgautis kita šeimos veikla**?
   - Labai daug ☐
   - Daug ☐
   - Šiek tiek ☐
   - Visai nieko ☐

7. Kiek per pastarąją savaitę dėl egzemos **valgių metu** turėjote problemų su vaiku?
   - Labai daug ☐
   - Daug ☐
   - Šiek tiek ☐
   - Nieko ☐

8. Kiek per pastarąją savaitę buvo problemų su vaiku, kurių sukėlė **gydymas**?
   - Labai daug ☐
   - Daug ☐
   - Šiek tiek ☐
   - Nieko ☐

9. Kiek per pastarąją savaitę jūsų vaiko egzema lėmė tai, kad jūsų vaikui **apsirengti ir nusirengti** buvo **nepatogu**?
   - Labai daug ☐
   - Daug ☐
   - Šiek tiek ☐
   - Nieko ☐

10. Kiek laiko per pastarąją savaitę jūsų vaikui egzema kėlė problemų **maudantis**?
    - Labai daug ☐
    - Daug ☐
    - Šiek tiek ☐
    - Nieko ☐

Prašome patikrinti, ar atsakėte į visus klausimus.

Appendix 3. The Children's Dermatology Life Quality Index (CDLQI)

VAIKŲ DERMATOLGINIS GYVENIMO KOKYBĖS INDEKSAS

Data: Diagnozė: Rezultatas:

Šio klausimyno tikslas – nustatyti kaip Jūsų odos problema įtakojo Jūsų gyvenimą **PER PASKUTINĘ SAVAITĘ.** Prašome pažymėti (X) prie Jums tinkančio atsakymo esančiame langelyje.

1. Kaip stipriai per paskutinę savaitę Jums **niežėjo**, **skaudėjo** ar **degino** odą?
   - ☐ Labai
   - ☐ Vidutiniškai
   - ☐ Mažai
   - ☐ Visai ne

2. Ar labai per paskutinę savaitę **nusiminęs**, **susigėdęs**, **drovus** ar **liūdnas** buvote dėl savo odos?
   - ☐ Labai
   - ☐ Vidutiniškai
   - ☐ Mažai
   - ☐ Visai ne

3. Ar labai per paskutinę savaitę Jūsų odos būklė trukdė **bendrauti su draugais**?
   - ☐ Labai
   - ☐ Vidutiniškai
   - ☐ Mažai
   - ☐ Visai ne

4. Ar labai per paskutinę savaitę pasikeitėte, ar dėvėjote **kitokius** ar **specialius rūbus ar batus** dėl savo odos sutrikimų?
   - ☐ Labai
   - ☐ Vidutiniškai
   - ☐ Mažai
   - ☐ Visai ne

5. Ar labai per paskutinę savaitę Jūsų odos sutrikimai paveikė Jūsų **išėjimą iš namų**, **žaidimus** ar **mėgstamą užsiėmimą**?
   - ☐ Labai
   - ☐ Vidutiniškai
   - ☐ Mažai
   - ☐ Visai ne

6. Ar labai dažnai per paskutinę savaitę Jums teko atsisakyti **plaukimo** ar **kitų sporto šakų** dėl odos sutrikimų?
   - ☐ Labai
   - ☐ Vidutiniškai
   - ☐ Mažai
   - ☐ Visai ne

Lankant mokyklą:

7. Ar labai per paskutinę savaitę Jūsų oda paveikė **mokymąsi**?
   - ☐ Mokyklos nelankiau
   - ☐ Labai
   - ☐ Vidutiniškai
   - ☐ Mažai
   - ☐ Visai ne

Atostogų metu:

7. Ar labai per paskutinę savaitę Jūsų oda paveikė Jūsų **atostogų planus**?
   - ☐ Labai
   - ☐ Vidutiniškai
   - ☐ Mažai
   - ☐ Visai ne

8. Ar daug kartų per paskutinę savaitę dėl Jūsų odos sutrikimų kiti Jus **pravardžiavo, erzino**, **priekabiavo, klausinėjo** ar **nenorėjo** su Jumis **bendrauti**?
   - ☐ Labai
   - ☐ Vidutiniškai
   - ☐ Mažai
   - ☐ Visai ne

9. Ar labai per paskutinę savaitę Jūsų odos sutrikimai paveikė Jūsų **miegą**?
   - ☐ Labai
   - ☐ Vidutiniškai
   - ☐ Mažai
   - ☐ Visai ne

10. Ar labai per paskutinę savaitę Jums trukdė Jūsų odos ligos **gydymas?**
    - ☐ Labai
    - ☐ Vidutiniškai
    - ☐ Mažai
    - ☐ Visai ne

Patikrinkite, ar atsakėtė į visus klausimus. Dėkojame

Appendix 4. Dermatology Life Quality Index (DLQI)

DERMATOLOGINIS GYVENIMO KOKYBĖS INDEKSAS

Ligoninės Nr.: Data: **DLQI**
Pavadinimas: Rezultatas:
Adresas: Diagnozė:

Šio klausimyno tikslas – nustatyti, kaip odos problema paveikė jūsų gyvenimą PASTARĄJĄ SAVAITĘ. Prašome prie kiekvieno klausimo varnele ☑ pažymėti vieną atsakymą.

1. Kiek pastarąją savaitę jūsų oda buvo **niežtinti, opi**, **skausminga** ar **dilginti**?
- Labai stipriai ☐
- Stipriai ☐
- Šiek tiek ☐
- Visai ne ☐

2. Kiek pastarąją savaitę dėl savo odos **varžėtės** ar **drovėjotės**?
- Labai stipriai ☐
- Stipriai ☐
- Šiek tiek ☐
- Visai ne ☐

3. Kaip stipriai pastarąją savaitę dėl jūsų odos būklės jums kilo sunkumų **apsiperkant, tvarkantis namuose** ar **dirbant sode**?
- Labai stipriai ☐
- Stipriai ☐
- Šiek tiek ☐
- Visai ne ☐ Netaikoma ☐

4. Kaip stipriai pastarąją savaitę jūsų odos būklė turėjo įtakos pasirenkant dėvimus **drabužius**?
- Labai stipriai ☐
- Stipriai ☐
- Šiek tiek ☐
- Visai ne ☐ Netaikoma ☐

5. Kaip stipriai pastarąją savaitę jūsų odos būklė turėjo įtakos jūsų **visuomeninei** veiklai ar **laisvalaikio** užsiėmimams?
- Labai stipriai ☐
- Stipriai ☐
- Šiek tiek ☐
- Visai ne ☐ Netaikoma ☐

6. Kaip stipriai pastarąją savaitę patyrėte sunkumų dėl savo odos būklės **sportuodami**?
- Labai stipriai ☐
- Stipriai ☐
- Šiek tiek ☐
- Visai ne ☐ Netaikoma ☐

7. Ar pastarąją savaitę dėl savo odos būklės negalėjote **dirbti** ar **mokytis**?
- Taip ☐
- Ne ☐ Netaikoma ☐

Jei atsakėte „Ne“, kaip stipriai pastarąją savaitę dėl jūsų odos būklės jums kilo problemų **dirbant** ar **mokantis**?
- Daug ☐
- Nedaug ☐
- Visai ne ☐

8. Kaip stipriai pastarąją savaitę dėl jūsų odos būklės jums kilo problemų bendraujant su **partneriu** ar jūsų **artimais draugais** ar **giminaičiais**?
- Labai stipriai ☐
- Stipriai ☐
- Šiek tiek ☐
- Visai ne ☐ Netaikoma ☐

9. Kaip stipriai pastarąją savaitę dėl jūsų odos būklės jums kilo **lytinio gyvenimo** problemų?
- Labai stipriai ☐
- Stipriai ☐
- Šiek tiek ☐
- Visai ne ☐ Netaikoma ☐

10. Kaip stipriai pastarąją savaitę jūsų odos **gydymas** jums kėlė problemų, pvz., dėl jo kilo netvarka namuose arba jis užėmė daug laiko?
- Labai stipriai ☐
- Stipriai ☐
- Šiek tiek ☐
- Visai ne ☐ Netaikoma ☐

Prašome patikrinti, ar atsakėte į VISUS klausimus. Dėkojame.

Lithuanian for Lithuania

Appendix 5. The Family Dermatology Life Quality Index (FDLQI)

Šeimos dermatologijos gyvenimo kokybės indeksas (FDLQI)

Vardas, pavardė: ..... FDLQI balas ☐
Santykis su pacientu: .....
Paciento diagnozė (jeigu žinoma): ..... Data: .....

- Šis klausimynas susijęs su jūsų artimojo / partnerio odos ligos poveikiu jūsų gyvenimo kokybei per pastarąjį mėnesį.
- Atidžiai perskaitykite klausimus ir ties kiekvienu pažymėkite vieną langelį.

1. Kiek emocinių kančių per pastarąjį mėnesį patyrėte dėl jūsų artimojo / partnerio odos ligos (pvz., nerimas, depresija, nepatogumai, nusivylimas)?

Visai nieko / neaktualu ☐ Šiek tiek ☐ Pakankamai ☐ Labai daug ☐

2. Kiek jūsų artimojo / partnerio odos liga per pastarąjį mėnesį paveikė jūsų fizinę gerovę (pvz., nuovargis, išsekimas, prasta sveikata, miego / poilsio sutrikimai)?

Visai nieko / neaktualu ☐ Šiek tiek ☐ Pakankamai ☐ Labai daug ☐

3. Kiek per pastarąjį mėnesį jūsų artimojo / partnerio odos liga paveikė jūsų asmeninį santykį su juo ar kitais žmonėmis?

Visai nieko / neaktualu ☐ Šiek tiek ☐ Pakankamai ☐ Labai daug ☐

4. Kiek per pastarąjį mėnesį turėjote problemų su kitų žmonių reakcijomis dėl artimojo / partnerio odos ligos (pvz., patyčios, spoksojimas, poreikis paaiškinti kitiems apie jo odos problemą)?

Visai nieko / neaktualu ☐ Šiek tiek ☐ Pakankamai ☐ Labai daug ☐

5. Kiek per pastarąjį mėnesį jūsų artimojo / partnerio odos liga paveikė jūsų socialinį gyvenimą (pvz., ėjimas iš namų, kitų žmonių lankymas arba kvietimas, dalyvavimas socialiniuose susibūrimuose)?

Visai nieko / neaktualu ☐ Šiek tiek ☐ Pakankamai ☐ Labai daug ☐

(Verskite lapą)

Appendix 6. TOPICOP questionnaire

Pildymo data: Identifikacinis numeris: AD_____ Tyrimo N.: ADIK-1

BAIMĖS VARTOTI KORTIKOSTEROIDUS ANKETA (TOPICOP©)

Gydytojas paskyrė Jums ar Jūsų vaikui naudoti **tepamus kortikosteroidus**. Mums įdomu, koks Jūsų požiūris į paskirtą gydymą. Pildydami anketą Jūs užtruksite 5 minutes.

Tepami kortikosteroidai patenka į kraujotaką

□ Visiškai nesutinku □ Šiek tiek nesutinku □ Šiek tiek sutinku □ Visiškai sutinku

Tepami kortikosteroidai gali sukelti infekciją

□ Visiškai nesutinku □ Šiek tiek nesutinku □ Šiek tiek sutinku □ Visiškai sutinku

Vartojant tepamus kortikosteroidus auga svoris

□ Visiškai nesutinku □ Šiek tiek nesutinku □ Šiek tiek sutinku □ Visiškai sutinku

Tepami kortikosteroidai pažeidžia odą

□ Visiškai nesutinku □ Šiek tiek nesutinku □ Šiek tiek sutinku □ Visiškai sutinku

Tepami kortikosteroidai turės įtakos mano/mano vaiko sveikatai ateityje

□ Visiškai nesutinku □ Šiek tiek nesutinku □ Šiek tiek sutinku □ Visiškai sutinku

Tepami kortikosteroidai sukelia astmą

□ Visiškai nesutinku □ Šiek tiek nesutinku □ Šiek tiek sutinku □ Visiškai sutinku

Nežinau kokius šalutinius reiškinius sukelia kortikosteroidai, bet vis tiek bijau juos vartoti

□ Visiškai nesutinku □ Šiek tiek nesutinku □ Šiek tiek sutinku □ Visiškai sutinku

Bijau užtepti per daug vaisto

□ Visiškai nesutinku □ Šiek tiek nesutinku □ Šiek tiek sutinku □ Visiškai sutinku

Bijau tepti vaistą tam tikrose odos vietose, pavyzdžiui vokus, kur oda yra plonesnė

□ Visiškai nesutinku □ Šiek tiek nesutinku □ Šiek tiek sutinku □ Visiškai sutinku

Laukiu kiek galiu ilgiau iki pradedant gydymą tepamais kortikosteroidais

□ Visiškai nesutinku □ Šiek tiek nesutinku □ Šiek tiek sutinku □ Visiškai sutinku

Nutraukiu gydymą tepamais kortikosteroidais kaip įmanoma greičiau

□ Visiškai nesutinku □ Šiek tiek nesutinku □ Šiek tiek sutinku □ Visiškai sutinku

Man reikia daugiau informacijos apie tepamus kortikosteroidus

□ Visiškai nesutinku □ Šiek tiek nesutinku □ Šiek tiek sutinku □ Visiškai sutinku

Appendix 7. Patient-Oriented Eczema Measure (POEM)

Pacientams skirta egzemos vertinimo anketa

(angl. *Patient-Oriented Eczema Measure* , POEM)

Pacientas: Data: POEM balų kiekis (Maksimalus 28)

Apibraukite Jums labiausiai tinkantį atsakymo variantą. Klausiame apie Jūsų ar Jūsų vaiko odos būklę per paskutines 7 dienas.

1. Per paskutinę savaitę, kaip labai Jums ar Jūsų vaikui niežėjo odą?

Nė vienos dienos 1-2 dienas 3-4 dienas 5-6 dienas Kasdien

2. Per paskutinę savaitę, kiek naktų Jūsų ar Jūsų vaiko miegas buvo sutrikdytas dėl egzemos?

Nė vienos dienos 1-2 dienas 3-4 dienas 5-6 dienas Kasdien

3. Per paskutinę savaitę, kiek Jūsų ar Jūsų vaiko odos bėrimai kraujavo/stebėjote kraujo ant odos dėl egzemos?

Nė vienos dienos 1-2 dienas 3-4 dienas 5-6 dienas Kasdien

4. Per paskutinę savaitę, kiek Jūsų ar Jūsų vaiko odos bėrimai šlapiavo dėl egzemos?

Nė vienos dienos 1-2 dienas 3-4 dienas 5-6 dienas Kasdien

5. Per paskutinę savaitę, kiek Jūsų ar Jūsų vaiko odos bėrimai sausėjo, stebėjote įtrūkimų odoje dėl egzemos?

Nė vienos dienos 1-2 dienas 3-4 dienas 5-6 dienas Kasdien

6. Per paskutinę savaitę, kiek Jūsų ar Jūsų vaiko odos bėrimai ar oda pleiskanoja, luposi dėl egzemos?

Nė vienos dienos 1-2 dienas 3-4 dienas 5-6 dienas Kasdien

7. Per paskutinę savaitę, kiek Jūsų ar Jūsų vaiko oda buvo sausa, šiurkšti dėl egzemos?

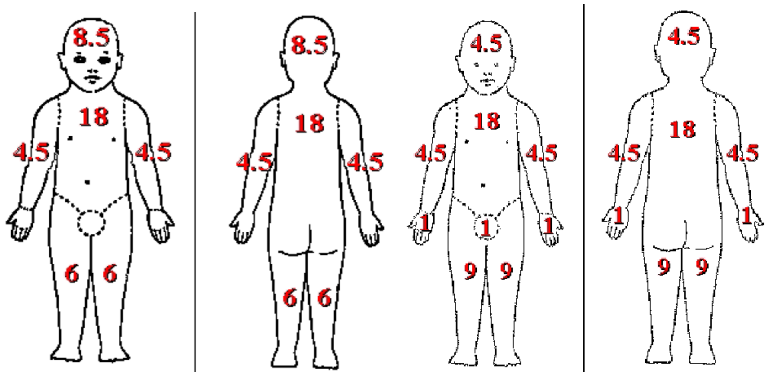
Nė vienos dienos 1-2 dienas 3-4 dienas 5-6 dienas Kasdien

Appendix 8. The Severity Scoring of Atopic Dermatitis (SCORAD)

Pildymo data: Identifikacinis numeris: AD_____ Tyrimo N.: ADIK-1

AD eigos sunkumo laipsnio nustatymas pagal SCORAD indeksą

A. IŠPLITIMAS (piešinėlyje pažymimos pažeistos vietos) Suma



Vaikai iki 2 m. Vaikai virš 2 m.

B. OBJEKTYVŪS SIMPTOMAI Suma

KRITERIJAI	INTENSYVUMAS 0	INTENSYVUMAS 1	INTENSYVUMAS 2	INTENSYVUMAS 3
Sausumas *				
Paraudimas				
Paburkimas				
Šlapiavimas/Šašiukai				
Kąsymosi žymės				
Rambėjimas				

C. SUBJEKTYVŪS SIMPTOMAI (pažymėti skalėje simptomų stiprumą nuo 0 iki 10, kai 0 - nėra simptomų, 10 – stipriausi, kokius yra turėję per paskutines 3 paras)

Niežėjimas ☺ 0 10 ☹

Sutrikęs miegas ☺ 0 10 ☹

Bendras SCORAD A/5+7B/2+C **SUMA**

AD eiga lengva 1-24 AD eiga vidutinio sunkumo 25-50 AD eiga sunki >50

Appendix 9. The 2001 Child Behavior Checklist for Ages 6-18 (CBCL 6/18)

CBCL ID NR·_____

6–18 METŲ VAIKO ELGESIO TYRIMO LAPAS (PILDO TĖVAI)

VAIKO VARDAS, PAVARDĖ		TĖVŲ PROFESIJA, NET JEI JIE ŠIUO METU NEDIRBA *(nurodykite konkrečiai: kariškis, automechanikas, pardavėjas, dėstytojas, namų šeimininkė)*
LYTIS ☐ Berniukas ☐ Mergaitė	**VAIKO AMŽIUS** (metais) **TAUTYBĖ**	**TĖVO** _____
ŠIOS DIENOS DATA 200__m._____mėn.___d.	VAIKO GIMIMO DATA _____m._____mėn.____d.	**MOTINOS** _____
Klasė	Užpildykite šią anketą stengdamiesi kuo tiksliau atskleisti savo požiūrį į vaiko elgesį, net jeigu kiti žmonės su juo nesutiktų. Prie kiekvieno klausimo tam skirtose vietose nesivaržydami rašykite papildomus komentarus.	ŠĮ FORMĄ UŽPILDĖ: ☐ Motina _____ (vardas, pavardė) ☐ Tėvas _____ (vardas, pavardė) ☐ Kiti (ryšys su vaiku) _____

I. Išvardykite sporto šakas, kurias Jūsų vaikas labiausiai mėgsta ir praktikuoja. Pavyzdžiui, plaukimas, čiuožimas, riedlentės, krepšinis, futbolas, žvejyba ir panašiai

☐ Nė viena

	Palyginti su kitais tokio pat amžiaus vaikais, kiek laiko jis/ji tam skiria?				**Palyginti su kitais tokio pat amžiaus vaikais, kaip jam/jai sekasi kiekvienoje sporto šakoje?**			
	Nežinau	Mažiau negu vidutiniškai	Vidutiniškai	Daugiau negu vidutiniškai	Nežinau	Žemiau vidutinio lygio	Vidutiniškai	Aukščiau vidutinio lygio
a._____	☐	☐	☐	☐	☐	☐	☐	☐
b._____	☐	☐	☐	☐	☐	☐	☐	☐
c._____	☐	☐	☐	☐	☐	☐	☐	☐

II. Išvardykite savo vaiko laisvalaikio pomėgius ir nesportinius žaidimus. Pavyzdžiui, kortos, knygos, skambinimas pianinu, amatai ir kt. (ne radijo klausymasis ar TV žiūrėjimas)

☐ Nė vieno

	Palyginkite su kitais tokio pat amžiaus vaikais, kiek laiko jis/ji tam skiria?				**Palyginkite su kitais tokio pat amžiaus vaikais, kaip jam/jai sekasi kiekvienoje srityje?**			
	Nežinau	Mažiau negu vidutiniškai	Vidutiniškai	Daugiau negu vidutiniškai	Nežinau	Žemiau vidutinio lygio	Vidutiniškai	Aukščiau vidutinio lygio
a._____	☐	☐	☐	☐	☐	☐	☐	☐
b._____	☐	☐	☐	☐	☐	☐	☐	☐
c._____	☐	☐	☐	☐	☐	☐	☐	☐

III. Išvardykite komandas, klubus, organizacijas, grupes, kurioms priklauso Jūsų vaikas

☐ Nė vienai

	Palyginti su kitais tokio pat amžiaus vaikais, kiek jis/ji yra jose aktyvus?			
	Nežinau	Mažiau aktyvus	Vidutiniškai	Aktyvesnis
a._____	☐	☐	☐	☐
b._____	☐	☐	☐	☐
c._____	☐	☐	☐	☐

IV. Nurodykite Jūsų vaiko atliekamą darbą arba jo pareigas. Pavyzdžiui, laikraščių išnešiojimas, vaikų priežiūra, darbas parduotuvėje (išvardykite tiek mokamą, tiek nemokamą darbą ir pareigas).

☐ Nė vieno

	Palyginti su kitais tokio pat amžiaus vaikais, kaip jam sekasi juos atlikti?			
	Nežinau	Blogiau	Vidutiniškai	Geriau
a._____	☐	☐	☐	☐
b._____	☐	☐	☐	☐
c._____	☐	☐	☐	☐

V. 1. Kiek artimų draugų apytikriai turi jūsų vaikas? (be seserų ir brolių) ☐ Nė vieno (os) ☐ 1 ☐ 2 ar 3 ☐ 4 ar daugiau

2. Kiek kartų per savaitę su jais susitinka ir bendrauja? (ne mokykloje, ne su broliais ar seserimis) ☐ Ne kiekvieną savaitę ☐ 1 ar 2 ☐ 3 ar daugiau

VI. Palyginti su kitais bendraamžiais, kaip jūsų vaikas:

	Blogiau nei kiti	Taip pat kaip kiti	Geriau nei kiti
a. sutaria su savo broliais ir seserimis	☐	☐	☐
b. sutaria su savo bendraamžiais	☐	☐	☐
c. elgiasi su tėvais	☐	☐	☐
d. dirba ir žaidžia vienas pats	☐	☐	☐

☐ neturi brolių ir seserų

VII. 1. Mokymosi rezultatai

Vaikas nelanko mokyklos, nes_____

Dalykai:

	Visiškai nesiseka	Žemiau vidutinio lygio	Vidutiniškai	Geriau nei vidutiniškai
Skaitymas, lietuvių kalba	☐	☐	☐	☐
Matematika	☐	☐	☐	☐
Istorija ar visuomenės mokslai	☐	☐	☐	☐
Užsienio kalba (_____)	☐	☐	☐	☐
Kitos disciplinos (pvz., kompiuterių kursai, užsienio kalba, verslas). Neįtraukite į sąrašą fizinio lavinimo, darbų pamokų, vairuotojo teisių įgijimo kursų ir pan.				
_____	☐	☐	☐	☐
_____	☐	☐	☐	☐

2. Ar Jūsų vaikas mokosi specialiojoje klasėje arba specialiojoje mokykloje, pagal supaprastintą ir palengvintą programą? ☐ Ne ☐ Taip - kokioje klasėje ar mokykloje?

3. Ar Jūsų vaikas buvo paliktas antriems metams kartoti kurso? ☐ Ne ☐ Taip - kurioje klasėje ir kodėl?

4. Ar Jūsų vaikas turėjo mokymosi ar kokių nors kitokių problemų? ☐ Ne ☐ Taip - prašome apibūdinti

Kada šios problemos iškilo?

Ar šios problemos jau išspręstos? ☐ Ne ☐ Taip - kada?

Ar Jūsų vaikas serga kokia nors liga, turi fizinių arba protinių negalių? ☐ Ne ☐ Taip - prašome apibūdinti

Kas Jums dėl vaiko kelia didžiausią susirūpinimą?

Nurodykite teigiamas savo vaiko savybes

Šiame lape pateikti vaikus ir jaunuolius apibūdinantys teiginiai. Ties kiekvienu teiginiu, kuris apibūdina Jūsų vaiką **dabartiniu metu arba paskutinių šešių mėnesių** laikotarpiu, apibraukite **2**, jei teiginys yra **visiškai teisingas** arba **dažniausiai teisingas** jūsų vaiko atžvilgiu. Apibraukite **1**, jei teiginys **iš dalies arba kartais teisingas.** Apibraukite **0**, jei teiginys **neteisingas** jūsų vaiko atžvilgiu. Prašome įvertinti visus teiginius kuo tiksliau, net jei atrodys kad kai kurie iš jų Jūsų vaikui netinka.

0 – neteisingas; 1 – iš dalies arba kartais teisingas; 2 – labai teisingas arba dažnai teisingas

0 1 2 1. Pagal savo amžių elgiasi pernelyg vaikiškai
0 1 2 2. Vartoja alkoholį be tėvų leidimo (apibūdinkite)_____
0 1 2 3. Dažnai ginčijasi
0 1 2 4. Nesugeba baigti pradėtų darbų
0 1 2 5. Mažai kuo džiaugiasi
0 1 2 6. Tuštinasi ne tualete
0 1 2 7. Giriasi, didžiuojasi prieš kitus
0 1 2 8. Negali susikaupti ir išlikti dėmesingas (-a)
0 1 2 9. Negali atsikratyti tam tikrų minčių. Įkyrios mintys (apibūdinkite)
_____
_____
0 1 2 10. Negali nusėdėti, neramus (-i) arba pernelyg aktyvus (-i)
0 1 2 11. „Prilipęs" (-usi) prie suaugusiųjų, pernelyg nuo jų priklausomas (-a)
0 1 2 12. Skundžiasi, kad yra vienišas (-a)
0 1 2 13. Jaučiasi sutrikęs (-usi), sumišęs (-usi) arba tartum rūke
0 1 2 14. Dažnai verkia
0 1 2 15. Žiauriai elgiasi su gyvūnais
0 1 2 16. Žiaurus (-i), skriaudžia ir žemina kitus
0 1 2 17. Užsisvajoja, paskęsta savo mintyse
0 1 2 18. Tyčia žaloja save arba bando žudytis
0 1 2 19. Reikalauja daug dėmesio sau
0 1 2 20. Gadina savo daiktus
0 1 2 21. Gadina daiktus, kurie priklauso jo/jos šeimai arba kitiems (apibūdinkite)
_____
_____
0 1 2 22. Nepaklusnus (-i) namuose
0 1 2 23. Nepaklusnus (-i) mokykloje
0 1 2 24. Nevalgus (-i)
0 1 2 25. Nesutaria su kitais vaikais
0 1 2 26. Nesijaučia kaltas (-a), kai blogai elgiasi
0 1 2 27. Greitai ima pavyduliauti
0 1 2 28. Pažeidžia taisykles namie, mokykloje, ar kitur
0 1 2 29. Bijo kai kurių gyvūnų, situacijų, vietų ne mokykloje (apibūdinkite)
_____
_____
0 1 2 30. Bijo eiti į mokyklą
0 1 2 31. Bijo, kad gali pagalvoti arba padaryti kažką blogo
0 1 2 32. Mano, kad viską turi padaryti puikiai
0 1 2 33. Jaučia arba skundžiasi, kad jo/jos niekas nemyli
0 1 2 34. Jaučia, kad kiti jį/ją erzina, pykdo
0 1 2 35. Jaučiasi nieko nevertas (-a), niekam tikęs (-usi)
0 1 2 36. Dažnai susižaloja, patenka į bėdą
0 1 2 37. Dažnai įsivelia į muštynes
0 1 2 38. Yra labai erzinamas (-a) kitų
0 1 2 39. Susijęs (-usi) su tais, kurie patenka į bėdą
0 1 2 40. Girdi garsus ar balsus, kurių nėra (apibūdinkite) _____
_____
0 1 2 41. Impulsyvus (-i), neapgalvotai elgiasi
0 1 2 42. Labiau linkęs (-usi) būti vienas (-a), negu su kitais
0 1 2 43. Meluoja arba apgaudinėja
0 1 2 44. Kramto nagus
0 1 2 45. Nervingas (-a), įsitempęs (-usi) ar dirglus(-i)
0 1 2 46. Būdingi nervingi judesiai ar trūkčiojimai (apibūdinkite) _____
_____
0 1 2 47. Sapnuoja košmarus
0 1 2 48. Jo/jos nemėgsta kiti vaikai
0 1 2 49. Būdingi vidurių užkietėjimai, sunkumai tuštinantis
0 1 2 50. Pernelyg bailus (-i), nerimastingas (-a)
0 1 2 51. Svaigsta galva
0 1 2 52. Išgyvena pernelyg stiprų kaltės jausmą
0 1 2 53. Persivalgo
0 1 2 54. Pernelyg pavargsta
0 1 2 55. Turi antsvorio
56. Turi sveikatos problemų be aiškios medicininės priežasties:
0 1 2 a. skausmai arba maudimai (**ne** pilvo ar galvos skausmai)
0 1 2 b. galvos skausmai
0 1 2 c. šleikštulys, silpnumas
0 1 2 d. regos problemos (išskyrus tas ligas, kurioms koreguoti reikalingi akiniai) (apibūdinkite) _____
_____
0 1 2 e. bėrimai ar kitos odos problemos
0 1 2 f. pilvo skausmai ar spazmai
0 1 2 g. vėmimas
0 1 2 h. kiti negalavimai (apibūdinkite)
_____
_____
_____

0 – neteisingas; 1 – iš dalies arba kartais teisingas; 2 – visiškai teisingas arba dažniausiai teisingas

0 1 2 57. Naudoja fizinį smurtą žmonių atžvilgiu
0 1 2 58. Krapšto odą, nosį ar kitas kūno vietas (apibūdinkite) _____
_____
0 1 2 59. Liečia savo lyties organus viešumoje
0 1 2 60. Pernelyg čiupinėja savo lyties organus
0 1 2 61. Mokykloje blogai sekasi atlikti užduotis
0 1 2 62. Būdinga prasta koordinacija, nerangumas
0 1 2 63. Linkęs (-usi) būti su vyresniais vaikais
0 1 2 64. Linkęs (-usi) būti su jaunesniais vaikais
0 1 2 65. Atsisako kalbėtis
0 1 2 66. Nuolat kartoja tuos pačius veiksmus (apibūdinkite) _____
_____
0 1 2 67. Bėga iš namų
0 1 2 68. Dažnai rėkauja
0 1 2 69. Slapukauja, neišsipasakoja
0 1 2 70. Mato daiktus, kurių nėra (apibūdinkite)
_____
_____
0 1 2 71. Varžosi kitų, lengvai sutrikdomas (-a),
0 1 2 72. Padeginėja, sukelia gaisrus
0 1 2 73. Turi seksualinių problemų (apibūdinkite)
_____
_____
0 1 2 74. Maivosi arba vaidina juokdarį (-ę)
0 1 2 75. Jaučiasi nepatogiai, baikštus (-i)
0 1 2 76. Miega mažiau nei daugelis vaikų
0 1 2 77. Dieną ir/arba naktį miega daugiau nei daugelis vaikų (apibūdinkite)
_____
0 1 2 78. Nedėmesingas (-a), lengvai išblaškomas (-a)
0 1 2 79. Turi kalbos problemų (apibūdinkite)
_____
0 1 2 80. Tuščiai spokso
0 1 2 81. Vagiliauja namuose
0 1 2 82. Vagiliauja ne namuose
0 1 2 83. Saugo daiktus, kurie jam/jai nereikalingi (apibūdinkite)_____
_____
0 1 2 84. Būdingas keistas elgesys (apibūdinkite)
_____
0 1 2 85. Būdingos keistos mintys (apibūdinkite)

0 1 2 86. Užsispyręs (-usi), niūrus (-i) arba irzlus (-i),
0 1 2 87. Būdinga staigi nuotaikos ar jausmų kaita
0 1 2 88. Dažnai paniuręs (-usi)
0 1 2 89. Įtarus (-i)
0 1 2 90. Keikiasi arba vartoja nepadorius žodžius
0 1 2 91. Kalba apie savižudybę
0 1 2 92. Miegodamas (-a) kalba ar vaikšto (apibūdinkite) _____
_____
0 1 2 93. Per daug šneka
0 1 2 94. Dažnai erzina kitus
0 1 2 95. Lengvai įtūžta ar yra karšto būdo
0 1 2 96. Per daug galvoja apie seksą
0 1 2 97. Grasina žmonėms
0 1 2 98. Čiulpia nykštį
0 1 2 99. Rūko, kramto arba uosto tabaką
0 1 2 100. Būdinga sutrikęs miegas (apibūdinkite)
_____
_____
0 1 2 101. Dykinėja, praleidžia pamokas
0 1 2 102. Neaktyvus (-i), lėtų judesių, stokoja energijos
0 1 2 103 Nelaimingas (-a), liūdnas (-a), prislėgtas (-a)
0 1 2 104. Neįprastai triukšmingas (-a)
0 1 2 105. Vartoja alkoholį, narkotikus arba vaistus nemedicininiais tikslais (apibūdinkite)
_____
_____
0 1 2 106. Būdingas vandalizmas
0 1 2 107. Apsišlapina dienos metu
0 1 2 108. Šlapinasi į lovą
0 1 2 109. Verkšlena
0 1 2 110. Nori būti priešingos lyties negu yra
0 1 2 111. Atsiskyręs (-usi), nebendrauja su kitais
0 1 2 112. Nerimauja
0 1 2 113. Nurodykite tas savo vaiko problemas, kurios čia nebuvo išvardytos
_____
_____
_____
_____
_____
_____
_____

PARAŠYKITE, KAS JUMS DAR KELIA SUSIRŪPINIMĄ

_____
_____
_____
_____
_____

PRAŠOME ĮSITIKINTI, KAD ĮVERTINOTE VISUS TEIGINIUS

Appendix 10. Authorization for biomedical research

VILNIAUS REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS
sui generis darinys prie VILNIAUS UNIVERSITETO

LEIDIMAS
ATLIKTI BIOMEDICININĮ TYRIMĄ

2020 08 25 Nr.2020/8-1251-733

Tyrimo pavadinimas:

Sergančių atopiniu dermatitu epidemiologinių, rizikos veiksnių ir elgesio sunkumų vertinimas

Protokolo Nr.:	ADIK-1
Versija:	1.1
Data:	2020 08 22
Informuoto asmens sutikimo forma:	2.1 (tėvams) 2020 08 22 2.2 (vaikams >12 m.) 2020 08 22
Pagrindinis tyrėjas:	**Odilija Rudzevičienė** **Matilda Bylaitė Bučinskienė**
Įstaigos pavadinimas: Adresas:	VšĮ Vilniaus universiteto ligoninė Santaros klinikos Santariškių g. 2, Vilnius MB Inovatyvios dermatologijos centras Ateities 31B, Vilnius
Leidimas galioja iki:	**2023 12 31**

Leidimas išduotas Vilniaus regioninio biomedicininių tyrimų etikos komiteto posėdžio (protokolas Nr. 2020/8), vykusio 2020 m. rugpjūčio 25 d. sprendimu.

Pirmininkas prof. dr. (HP) Saulius Vosylius

Viešoji įstaiga
Universiteto g. 3
01513 Vilnius

Duomenys kaupiami ir saugomi
Juridinių asmenų registre
Kodas 211950810

Komiteto duomenys:
M. K. Čiurlionio g. 21, LT- 03101 Vilnius
Tel. (8 5) 268 6998, el. p. rbtek@mf.vu.lt

PUBLICATIONS LIST

Publications related to the topic

1. Kisieliene I, Mainelis A, Rudzeviciene O, Bylaite-Bucinskiene M, Wollenberg A. The Burden of Pediatric Atopic Dermatitis: Quality of Life of Patients and Their Families. Journal of Clinical Medicine , March 2024; 13(6):1700. DOI: 10.3390/jcm13061700
2. Kisieliene I, Aukstuolyte B, Mainelis A, Rudzeviciene O, Bylaite-Bucinskiene M, Wollenberg A. Associations between Atopic Dermatitis and Behavior Difficulties in Children. Medicina (Kaunas, Lithuania) vol. 60,3 492. 17 Mar. 2024, doi:10.3390/medicina60030492

Other publications

1. Patient education program "Eczema School". Zibudaite A, Kisieliene I, Bylaite-Bucinskiene M. Lietuvos bendrosios praktikos gydytojas. Kaunas: Vitae Litera. 2019, t. 23, Nr. 5, p. 304-308. [DB: Index Copernicus]
2. Kisieliene I, Grigaitiene J, Kucinskiene V, Malinauskiene L, Chomiciene A, Blaziene A, Sitkauskiene B, Staikuniene J, Bylaite-Bucinskiene M. Atopinio dermatito diagnostikos ir gydymo rekomendacijos: mokomoji knyga / Vilniaus universitetas; Lietuvos sveikatos mokslų universitetas. Lietuvos dermatovenerologų draugija. Lietuvos alergologų ir klinikinių imunologų draugija; [Sudarė Inga Kisieliene; Recenzentai: Regina Ėmužytė, Aistė Beliauskienė]. Vilnius: [s.n.], 2019. 80 p.
3. Ulianskaite G, Mackeviciute J, Malevic A, Kisieliene I, Bylaite-Bucinskiene M. Prevalence, severity and clinical features of atopic dermatitis in children and adults in Lithuania. Lietuvos bendrosios praktikos gydytojas. Kaunas: Vitae Litera. ISSN 1392-3218. 2020, t. 24, Nr. 4, p. 231-235.
4. Siaudinyte M, Urbonaite R, Kisieliene I, Vanseviciute-Petkeviciene R. Differential diagnosis of Paget's disease of the breast. Literature review and clinical case series. Lietuvos akušerija ir ginekologija : L.A.G.D. ISSN 1392-5091. 2021, 24, 1, p. 69-78. (Profesinis tobulėjimas). DOI: 10.37499/LAG.579. [DB: Index Copernicus]
5. Petruskeviciute E, Kisieliene I. The clinical effects of oral vitamin D supplementation in patients with atopic eczema. Sveikatos mokslai. Vilnius : Sveikatos mokslai. ISSN 1392-6373. eISSN 2335-867X. 2022,

t. 32, Nr. 1, p. 11-15. DOI: 10.35988/sm-hs.2022.002. [DB: Index Copernicus]
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PRESENTATIONS LIST

Presentation related to the topic

1. Oral presentation „The relationship of endogenous factors to atopic dermatitis in children: a pilot study“. International conference „ Joint Meeting EAA-ISGA-ICEM“; 24-27 August 2022, Vilnius.
2. Oral presentation „The relationship of epidemiological and endogenous factors to pediatric atopic dermatitis in Lithuania“. International conference „Dialogs of dermatology“, 3-4 May 2023, Vilnius.
3. Poster presentation „The relationship of basal serum cortisol, prolactin, TSH and vitamin D levels to pediatric patients with atopic dermatitis“. 25th world congress of dermatology. Dermatology beyond borders. Science. Care. Communities, 3-8 July 2023, Singapore.
4. Poster presentation. „Epidemiology‘s associated factors and quality of life of atopic dermatitis in Lithuanian children“. 25th world congress of dermatology. Dermatology beyond borders. Science. Care. Communities, 3-8 July 2023, Singapore.

Other Presentations

1. Oral presentation „The relationship of endogenous factors to atopic dermatitis in children: a pilot study“. International conference „ Joint Meeting EAA-ISGA-ICEM“ ; 24-27 August 2022, Vilnius.
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4. Poster presentation. „Epidemiology‘s associated factors and quality of life of atopic dermatitis in Lithuanian children“. 25th world congress of dermatology. Dermatology beyond borders. Science. Care. Communities, 3-8 July 2023, Singapore.

5. Oral presentation „Infectious disease management in atopic dermatitis". International Conference "Dermatovenereology Update 2019"; 12 April 2019 , Vilnius, Lithuania.
6. Poster presentation "The impact of educational programme on "corticophobia" in Lithuania among atopic dermatitis patients and their parents". International Congress "19th European Society of Paediatric Dermatology Meeting/19th ESPD Annual Meeting", 2-4 May 2019, Dubrovnik, Croatia.
7. Oral presentation "Impact of an educational programme in the management of atopic eczema in Lithuania". International Congress "34th Nordic Congress of Dermatology & Venereology/34th Nordic Congress of Dermatology & Venereology 2019"; 8-10 May 2019; Gothenburg, Sweden.
8. Oral presentation "Can the onset and recurrence of atopic dermatitis be prevented". Republican Conference "Dermatovenerology News 2020"; 11 September 2020, Vilnius, Lithuania.
9. Oral presentation "Atopic dermatitis - facts and controversies: vitamin D, hormones and other factors". LDVD Republican Conference "Dermatovenerology News 2021" - "Skin Health Window" ; 4 June 2021, Vilnius, Lithuania.
10. Oral presentation "Treatment of perioral and atopic facial dermatitis in children". LDVD International Scientific-Practical Conference 2022 "Modern Dermatovenerology: looking forward to tomorrow" ;29 April 2022, Vilnius, Lithuania.
11. Oral presentation "The significance of corticophobia and solutions in the treatment of pediatric atopic dermatitis". Scientific-practical conference "Winter Seminars in Dermatovenerology 2023"; 24 November 2023.
12. Oral presentation "Features and experience in the treatment of adolescent atopic dermatitis". Conference "Allergology and Clinical Immunology/2024"; 15 March 2024, Vilnius, Lithuania
13. Oral presentation „Overview of systemic treatment of atopic dermatitis - what is relevant in practice?“ International Scientific and Practical Conference of LDVD "Remember, Improve, Realize"; 26 April 2023, Vilnius, Lithuania.

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SUMMARY (SANTRAUKA)

SANTRUMPŲ SĄRAŠAS

AD, atopinis dermatitas

Anti-TPO, skydliaukės peroksidazės antikūnai

CBCL 6/18, angl. *The 2001 Child Behavior Checklist for Ages 6–18*, 2001 m. vaikų elgesio klausimynas, skirtas 6–18 metų vaikams

CDLQI, angl. *Children's Dermatology Life Quality Index*, Vaikų dermatologinis gyvenimo kokybės indeksas

DLQI, angl. *Dermatology Life Quality Index*, Dermatologinis gyvenimo kokybės indeksas

DTL, didelio tankio lipoproteinas

FDLQI, angl. *the Family Dermatology Life Quality Index*, Šeimos dermatologinis gyvenimo kokybės indeksas

GK, gyvenimo kokybė

GKI, gyvenimo kokybės indeksas

IDQI, angl. *Infants Dermatology Life Quality Index*, Kūdikių dermatologinis gyvenimo kokybės indeksas

IgE, imunoglobulinas E

POEM, angl. *Patient-Oriented Eczema Measure*, Į pacientą orientuota priemonė egzemai vertinti

PRL, prolaktinas

SCORAD, angl. *The Severity Scoring of Atopic Dermatitis*, Atopinio dermatito eigos sunkumo laipsnio nustatymo indeksas

MTL, mažo tankio lipoproteinas

TG, trigliceridai

TSH, skydliaukę stimuliuojantis hormonas

ĮVADAS

Atopinis dermatitas, dar vadinamas atopine egzema, yra lėtinė uždegiminė odos liga, kuria serga kūdikiai, vaikai ir suaugusieji; liga neigiamai veikia socialinį gyvenimą, psichinę sveikatą, ligonio ir jo šeimos narių gyvenimo kokybę. Atopiniu dermatitu dažnai serga asmenys, kurių šeimoje yra sergančių kitomis su atopija siejamomis ligomis: alergine bronchine astma ir (arba) rinokonjunktyvitu, ir (arba) alergija maistui. Daugelyje pasaulio šalių sergamumas atopiniu dermatitu siekia 5–20 proc. vaikų ir 2–8 proc. suaugusiųjų populiacijose. Ši liga vystosi dėl genų, aplinkos poveikio, odos barjerinės funkcijos sutrikimo, imuninės sistemos disreguliacijos. Su atopiniu dermatitu susijusios gretutinės ligos apima padidėjusią virusinių ir bakterinių odos infekcijų riziką, neuropsichiatrinius sutrikimus, tokius kaip dėmesio ir aktyvumo sutrikimas, autizmo spektro sutrikimas. Taip pat nustatyta, kad sergančiųjų atopiniu dermatitu miego ir gyvenimo kokybė yra prastesnė, palyginti su tų, kurie šia uždegimine odos liga neserga (1).

1. TIKSLAS IR UŽDAVINIAI

Tikslas – išanalizuoti egzogeninių ir endogeninių veiksnių ryšį su vaikų atopiniu dermatitu (AD), įvertinti ligos poveikį paciento ir jo šeimos gyvenimo kokybei, ištirti ligos įtaką pacientų elgesio sunkumams, išanalizuoti AD sergančių vaikų tėvų (globėjų) kortikofobijos reiškinį.

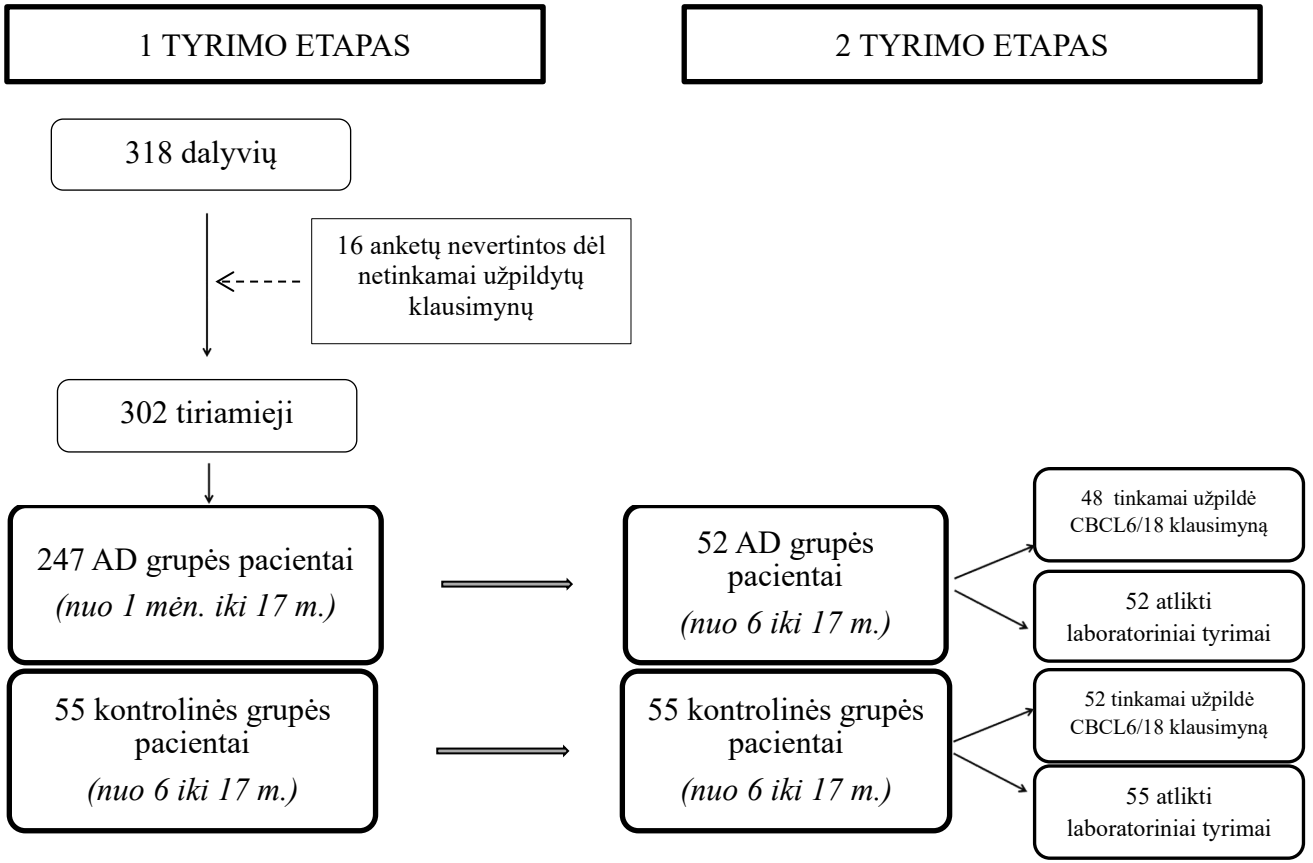
Uždaviniai:

1. Ištirti AD sergančių vaikų epidemiologinę ir demografinę charakteristiką, nustatyti endogeninius ir egzogeninius veiksnius, susijusius su AD pasireiškimu ir sunkumo laipsniu.
2. Įvertinti AD sergančių vaikų ir jų šeimos gyvenimo kokybę, jos sąsają su ligos sunkumo laipsniu.
3. Ištirti AD sergančių vaikų elgesio sunkumų paplitimą ir ypatumus, taip pat juos skatinančius veiksnius, duomenis palyginti su kontroline grupe.
4. Išanalizuoti sergančiųjų AD kortikofobijos reiškinį: paplitimą, lemiančius veiksnius, sąsają su ligos sunkumu.

2. METODAI

2.1. Tyrimo organizavimas

Atliktas vieno centro skerspjūvio prospektyvinis tyrimas dviem etapais. Tyrimas vyko Vilniaus universiteto ligoninės Santaros klinikų Vaikų ligų klinikoje nuo 2020 m. gruodžio mėnesio iki 2022 m. gruodžio mėnesio. Dalyvauti tyrime buvo kviečiami AD sergantys vaikai nuo 1 mėnesio iki 17 metų amžiaus ir sveiki vaikai nuo 6 iki 17 metų amžiaus. Pacientai buvo atrinkti nuosekliosios atrankos būdu pagal dermatovenerologo suteiktas konsultacijas Vaikų ligų klinikoje. Iš 318 sutikusių dalyvauti tyrime 16 netinkamai užpildė klausimyną, todėl pirmame etape buvo tiriami 302 vaikai. Antrame etape sutiko dalyvauti visi 55 kontrolinės grupės ir 52 AD grupės pacientai (iš viso 107). Tyrimo etapų schema pateikta 1 paveiksle.



1 paveikslas. Tyrimo etapų schema.

Pacientai buvo įtraukti į tyrimą pagal toliau aprašomus kriterijus.

Įtraukimo į AD grupę kriterijai pirmame etape:

– Nuo 1 mėnesio iki 17 metų amžiaus vaikai, kuriems kliniškai diagnozuotas AD pagal Hanifino ir Rajkos kriterijus.

– Lietuvos gyventojai.

Įtraukimo į AD grupę kriterijai antrame etape:

– Nuo 6 iki 17 metų amžiaus vaikai, kuriems kliniškai diagnozuotas AD pagal Hanifino ir Rajkos kriterijus.

– Lietuvos gyventojai.

Įtraukimo į kontrolinę grupę kriterijai:

– Nuo 6 iki 17 metų amžiaus vaikai, kuriems nenustatyta egzema ir kurie į dermatovenerologo apžiūrą buvo atvykę dėl apgamų.

– Lietuvos gyventojai.

Atmetimo kriterijai:

– Sergantieji bet kuria, išskyrus AD, egzemine ir (arba) niežulį sukeliančia odos liga (pavyzdžiui, kito tipo dermatitas, kerpligė, psoriazė), galinčia paveikti bendrą ar psichinę sveikatą.

– Sergantieji bet kuria sunkia paūmėjusia lėtine, įgimta ar onkologine liga, galinčia paveikti bendrą ar psichinę sveikatą.

– Dalyviai, kurie netinkamai užpildė klausimynų.

– Pakviesti, bet atsisakę dalyvauti tyrime pacientai.

Visi tyrimo dalyviai turėjo užpildyti toliau nurodomas anketas.

– Originalus klausimynas, autorių sukurtas siekiant išsiaiškinti epidemiologines, demografines charakteristikas, odos priežiūros ir gydymo ypatumus, poveikį odos būklei darančius veiksnius.

– Dermatologinis gyvenimo kokybės indeksas (GKI) pagal amžių:

  – Kūdikių dermatologinis gyvenimo kokybės indeksas (angl. *Infants Dermatology Life Quality Index*, IDQI), skirtas vaikams iki 4 metų amžiaus.

  – Vaikų dermatologinis gyvenimo kokybės indeksas (angl. *Children's Dermatology Life Quality Index*, CDLQI), skirtas 4–16 metų amžiaus vaikams.

  – Dermatologinis gyvenimo kokybės indeksas (angl. *Dermatology Life Quality Index*, DLQI), skirtas asmenims nuo 16 metų amžiaus.

– Šeimos dermatologinis gyvenimo kokybės indeksas (angl. *The Family Dermatology Life Quality Index*, FDLQI).

– Kortikofobijos vertinimo klausimynas TOPICOP®.

– Į pacientą orientuota priemonė egzemai vertinti (angl. *Patient-Oriented Eczema Measure*, POEM).

Į antrą tyrimo etapą buvo pakviesti pirmame dalyvavę AD grupės pacientai ir sveiki vaikai, kurių amžius buvo 6–17 metų. Tiriamųjų klinikinė būklė buvo įvertinta gydytojo dermatovenerologo, atlikti laboratoriniai biocheminiai kraujo serumo tyrimai, taip pat vienas iš tėvų (globėjų) užpildė 2001 m. vaikų elgesio klausimyną, skirtą 6–18 metų vaikams (angl. *The 2001 Child Behavior Checklist for Ages 6–18*, CBCL 6/18).

2.2. Atitiktis bioetikos reikalavimams

2020 m. rugpjūčio 25 d. tyrimui buvo gautas Vilniaus regioninės biomedicinos etikos komisijos etinis pritarimas (Nr. 2020/8–1251–733). Visi pacientai sutiko dalyvauti tyrime. Tiriamųjų tėvai (globėjai) pasirašė informuoto asmens sutikimo formą, vaikai (nuo 12 metų) pasirašė pritarimo dalyvauti biomedicininiame tyrime formą.

2.3. Tiriamųjų atranka

Dalyvauti tyrime buvo atrinkti visi tinkami pacientai, tai yra tie, kurie atitiko visus įtraukimo į tyrimą kriterijus ir neatitiko nė vieno atmetimo kriterijaus.

2.4. Rinkti duomenys

Per tyrimo laikotarpį buvo surinkti ir analizei panaudoti duomenys:

– Gimimo data.

– Lytis.

– Antropometriniai duomenys (ūgis ir svoris).

– Demografiniai ir geografiniai duomenys (gyvenamoji vieta, šeimos narių skaičius, naminiai gyvūnai, odos priežiūros įpročiai, odos būklę lemiantys veiksniai).

– Anamnestiniai duomenys (atopinių ligų anamnezė, AD diagnozės nustatymo laikas, AD simptomų atsiradimo laikas, gretutinės atopinės ir lėtinės ligos, žindymo trukmė, skiepai, poveikį AD eigai darantys veiksniai).

– Gyvenimo kokybės vertinimas.

– Ligos sunkumo vertinimo skalės (POEM, SCORAD).

– Kortikofobijos vertinimas (TOPICOP).

– Elgesys ir emocinė būklė pagal 2001 m. vaikų elgesio klausimyną, skirtą 6–18 metų vaikams (CBCL 6/18).

– Laboratoriniai tyrimai:

- o rytinis kortizolio kiekis serume,
- o skydliaukę stimuliuojantis hormonas (TTH),
- o skydliaukės peroksidazės antikūnai (anti-TPO),
- o vitaminas D,
- o bendrojo imunoglobulino E (IgE) kiekis,
- o bendrasis kraujo tyrimas,
- o bendrojo cholesterolio kiekis,
- o mažo tankio lipoproteinai (MTL),
- o didelio tankio lipoproteinai (DTL),
- o trigliceridai (TG),
- o prolaktinas (PRL).

2.5. Duomenų apibrėžtys ir transformacijos

AD sunkumo laipsnis apskaičiuotas pagal ligos eigos sunkumo laipsnio nustatymo (angl. *The Severity Scoring of Atopic Dermatitis,* SCORAD) ir POEM indeksus.

SCORAD indeksas apskaičiuotas pagal formulę A/5 + 7B/2 + C, kurioje A apibrėžia pažeistos srities plotą (didžiausias balas – 100), B – objektyvius simptomus, tai yra eritemą, edemą, šlapiavimą, nukasymą, lichenifikaciją ir sausumą, kiekvieną elementą vertinant pagal skalę nuo 0 iki 3 (didžiausias balas – 18), o C – subjektyvius simptomus, tai yra niežulį ir miego sutrikimus, kurie vertinami pagal skalę nuo 0 iki 10 (didžiausias balas – 20). Didžiausias balų skaičius yra 103, o AD pagal sunkumo laipsnį skirstomas į lengvos eigos (< 25 balai), vidutinio sunkumo eigos (25–50 balų), sunkios eigos (> 50 balų) (2).

Pagal POEM buvo vertinamas 7 AD požymių ir simptomų dažnumas pastarąją savaitę, įskaitant bėrimo tipą, niežulį ir miego sutrikimus (73). Balų skaičius svyruoja nuo 0 iki 28 ir yra vertinamas taip: nuo 0 iki 2 – egzemos nėra arba beveik nėra, nuo 3 iki 7 – lengva egzema, nuo 8 iki 16 – vidutinio sunkumo egzema, nuo 17 iki 24 – sunki egzema, nuo 25 iki 28 – labai sunki egzema (3).

Gyvenimo kokybės (GK) balas buvo apskaičiuotas pagal gyvenimo kokybės klausimynus. Kiekvienas klausimynų punktas vertintas pagal 4 balų Likerto skalę: 0 – visai nesvarbu, 1 – šiek tiek svarbu, 2 – svarbu, 3 – labai svarbu. GK balas apskaičiuotas sumuojant kiekvieno klausimo balus. Galutinė balų suma rodo ligos

poveikį gyvenimo kokybei: 0–1 jokio poveikio, 2–5 nedidelis poveikis, 6–10 vidutinis, 11–20 didelis, 21–30 labai didelis AD poveikis gyvenimo kokybei (4).

Kortikofobija buvo vertinama pagal TOPICOP® klausimyną. Atsakymai įvertinti pagal 4 balų Likerto skalę (balų intervalas nuo 0 iki 3, kur 0 = niekada, 1 = kartais, 2 = dažnai, 3 = visada; arba 0 = visiškai nesutinku, 1 = nelabai sutinku, 2 = beveik sutinku, 3 = visiškai sutinku). Kortikofobijos rizika (procentais) apskaičiuota balų sumą dalijant iš maksimalios galimos balų sumos (36) ir dauginant iš 100 proc. Maža kortikofobijos rizika yra ≤ 23 proc., vidutinio sunkumo 24–50 proc., didelė rizika > 50 proc. (5).

Elgesio sunkumai buvo vertinami pagal 2001 m. vaikų elgesio klausimyną, skirtą 6–18 metų vaikams (CBCL 6/18). Klausimynas padeda nustatyti, ar yra elgesio sutrikimų, ir išskiria 8 sindromus (nerimastingumo / depresiškumo, užsisklendimo / depresiškumo, somatinių skundų, socialinių sunkumų, mąstymo sunkumų, dėmesio sunkumų, taisyklių laužymo, agresyvaus elgesio). Sindromas čia suprantamas kaip sąvoka, apibrėžianti vienu metu iškylančių sunkumų grupę, bet nebūtinai tapatinamas su liga (6).

Balų suma pateikiama pirminiais ir T balais pagal lyčiai ir amžiui tinkamą analizę. Mažesnis nei 64 T balas yra normalus, nuo 65 iki 69 – ribinis, 70 arba daugiau – klinikinis (7).

2.6. Statistinė analizė

Statistinė analizė atlikta naudojant R (v. 4.0.4) programos paketą. Pateikiamas kiekybinių kintamųjų vidurkis, standartinis nuokrypis (SD), kvartiliai (Q1 ir Q3), mediana ir stebėjimų skaičius. Kategoriniai kintamieji pateikiami kaip absoliutus dydis ir procentinė dalis. Siekiant patikrinti hipotezes dėl kiekybinių kintamųjų palyginimo tarp dviejų grupių, atitinkamai naudotas Stjudento T testas arba neparametrinis Mano ir Vitnio U (angl. *Mann–Whitney U*) kriterijus. Norint patikrinti hipotezes dėl kiekybinių kintamųjų palyginimo tarp daugiau nei dviejų grupių, atitinkamai naudota vienfaktorinė dispersinė analizė (angl. *Analysis of Variance* – ANOVA) arba neparametrinis Kruskalo ir Voliso (angl. *Kruskal–Wallis*) testas. Normalumas buvo tikrinamas naudojant Šapiro ir Vilko (angl. *Shapiro–Wilk*) kriterijų. Norint patikrinti hipotezes dėl kategorinių kintamųjų palyginimo tarp grupių, atitinkamai buvo naudojami Pirsono chi kvadrato (x^2) arba Fišerio tikslieji (angl. *Fischer's exact test*) testai. Siekiant patikrinti kelių kintamųjų sąsajas su skalės rezultatais, naudota daugialypė tiesinė regresija. Reikšminga buvo laikoma p reikšmė, mažesnė nei 0,05.

3. REZULTATAI

3.1. Tiriamųjų charakteristika

Tyrime iš viso dalyvavo 302 vaikai: 247 sergantys AD (125 berniukai ir 121 mergaitė) ir 55 sveiki (28 berniukai ir 27 mergaitės). 1 lentelėje aprašyti demografiniai ir epidemiologiniai tiriamųjų duomenys. Vidutinis AD grupės pacientų amžius pirmame tyrimo etape buvo 6,8 ± 4,4 metų, kontrolinės grupės vaikų 10,5 ± 3,1 metų, antrame etape atitinkamai 10 ± 2 ir 10,5 ± 3,1 metų. Tėvų (globėjų) amžiaus vidurkis buvo 37,3 ± 49 metai. 225 (74 proc.) šeimos gyveno mieste, 257 (85 proc.) respondentai gyveno susituokusiose šeimose. Dauguma tėvų (globėjų), iš jų 263 (87 proc.) motinos ir 205 (68 proc.) tėvai, turėjo aukštąjį išsilavinimą. Rūkantys buvo 98 (33 proc.) tėvai (globėjai), iš jų 29 (10 proc.) motinos ir 69 (23 proc.) tėvai. Tarp kontrolinės grupės pacientų buvo daugiau turinčių naminį gyvūną ($p = 0,028$).

Žindymo faktas ir trukmė, taip pat amžius, nuo kurio vaikas maitinamas kietuoju maistu, AD ir kontrolinėje grupėse nesiskyrė. 169 (69 proc.) sergantiesiems AD ir 24 (47,1 proc.) kontrolinės grupės vaikams buvo nustatyta teigiama šeiminė atopinių ligų anamnezė ($p < 0,05$).

Dauguma abiejų grupių vaikų buvo skiepyti, tačiau tik 96 (39 proc.) AD grupei priklausantys vaikai buvo gavę visus skiepus pagal rekomenduojamą skiepijimo kalendorių, palyginti su 50 (96 proc.) kontrolinės grupės vaikų ($p < 0,05$). Iš priežasčių, dėl kurių tiriamieji nebuvo gavę visų skiepų, dauguma AD grupės tėvų (globėjų) (127 (86 proc.) nurodė alerginę reakciją po skiepo arba dermatito paūmėjimą, tik 7 (3 proc.) vaikams tęsti skiepų nepatarė gydytojai. Šie duomenys rodo, kad tarp AD pacientų tėvų (globėjų) yra paplitusi šalutinių vakcinos reakcijų baimė.

61 proc. AD grupės pacientų sirgo bent viena atopine liga: 67 (29 proc.) – alerginiu rinokonjunktyvitu, 99 (43 proc.) – alergija maistui, 28 (12 proc.) – alergine astma, o 13 (5 proc.) buvo diagnozuotos visos trys atopinės ligos. AD grupėje daugiau vaikų nei kontrolinėje turėjo alergiją maistui ($p = 0,001$) ir sirgo alerginiu rinitu ($p = 0,022$), bet ne alergine astma ($p = 0,188$).

189 (77 proc.) AD grupės pacientams pirmi ligos simptomai pasireiškė iki 1 metų amžiaus (iš jų 37 proc. – iki 3 mėnesių, 20 proc. – 4 ar 5 mėnesių, 20 proc. – nuo 6 iki 12 mėnesių). Iš viso 218 (89 proc.) AD grupės pacientų liga buvo diagnozuota iki 5 metų amžiaus.

Pirmame tyrimo etape 44 (18 proc.) AD grupės pacientai sirgo sunkiu, 81 (33 proc.) – vidutinio sunkumo, 114 (3 proc.) – lengvu AD pagal objektyvų

POEM. 8 (3 proc.) AD grupės pacientai netinkamai užpildė POEM klausimyną, todėl jų rezultatai nebuvo įtraukti į tyrimą. Antrame etape AD sunkumo laipsnis tarp 52 sergančių vaikų pasiskirstė taip: 19 (37 proc.) sirgo sunkiu, 22 (42 proc.) – vidutinio sunkumo, 11 (2 proc.) – lengvu AD pagal SCORAD. Rezultatų skirtumas tarp POEM ir SCORAD grupių atsirado dėl to, kad antrame etape buvo atliekami laboratoriniai kraujo tyrimai, o tyrime dalyvavo daugiau sunkiu AD sergančių vaikų.

1 lentelė. Demografiniai ir klinikiniai tiriamųjų ypatumai.

Charakteristika, n (proc.)	**AD grupės vaikai**	**Kontrolinės grupės vaikai**	**Tėvai (globėjai)**	
Lytis				
Vyriškoji	125 (51 proc.)	28 (51 proc.)	14 (5 proc.)	
Moteriškoji	122 (49 proc.)	27 (49 proc.)	288 (95 proc.)	
Amžius (metai)				
1 tyrimo etapas	6,8 ± 4,4	10,5 ± 3,1	37,3 ± 6,49	
2 tyrimo etapas	10 ± 2,7	10,5 ± 3,1	N/A	
Gyvenamoji vieta				
Miestas	N/A	N/A	225 (74 proc.)	
Kaimas	N/A	N/A	37 (12 proc.)	
Gyvenvietė	N/A	N/A	33 (11 proc.)	
Neatsakė	N/A	N/A	3 (1 proc.)	
Šeiminė padėtis				
Sutuoktiniai	N/A	N/A	257 (85 proc.)	
Sugyventiniai	N/A	N/A	28 (9 proc.)	
Išsiskyrę	N/A	N/A	11 (4 proc.)	
Vieniši	N/A	N/A	4 (1 proc.)	
Neatsakė	N/A	N/A	3 (1 proc.)	
Išsilavinimas			Motina	Tėvas
Aukštasis	N/A	N/A	263 (87 proc.)	205 (68 proc.)
Nebaigtas aukštasis	N/A	N/A	7 (2 proc.)	15 (5 proc.)
Aukštesnysis	N/A	N/A	23 (8 proc.)	66 (22 proc.)
Vidurinis	N/A	N/A	5 (2 proc.)	12 (4 proc.)
Kita	N/A	N/A	0 (0 proc.)	1 (0 proc.)
Neatsakė	N/A	N/A	5 (2 proc.)	4 (1 proc.)
Rūkymas			Motina	Tėvas
Rūkantys	N/A	N/A	29 (10 proc.)	69 (23 proc.)
Nerūkantys	N/A	N/A	269 (89 proc.)	229 (76 proc.)
Neatsakė	N/A	N/A	5 (1 proc.)	5 (1 proc.)
Būsto tipas				
Butas	136 (55 proc.)	34 (65 proc.)	N/A	N/A
Namas	98 (40 proc.)	18 (35 proc.)	N/A	N/A
Kita	13 (5 proc.)	0 (0 proc.)	N/A	N/A

Charakteristika, n (proc.)	**AD grupės vaikai**	**Kontrolinės grupės vaikai**	**Tėvai (globėjai)**	
Mėnesio pajamos žmogui				
≤ 200 Eur	2 (4 proc.)	2 (2 proc.)	N/A	N/A
201–400 Eur	2 (4 proc.)	2 (2 proc.)	N/A	N/A
401–600 Eur	15 (28 proc.)	6 (12 proc.)	N/A	N/A
601–800 Eur	14 (26 proc.)	12 (24 proc.)	N/A	N/A
801–1000 Eur	10 (19 proc.)	8 (16 proc.)	N/A	N/A
> 1000 Eur	11 (20 proc.)	21 (41 proc.)	N/A	N/A
Naminis gyvūnas	131 (53 proc.)*	35 (70 proc.)*	N/A	N/A
Žindymas	224 (91 proc.)	44 (85 proc.)	N/A	N/A
Žindymo trukmė				
0 mėnesių	2 (1 proc.)	0 (0 proc.)	N/A	N/A
≤ 3 mėnesiai	37 (15 proc.)	4 (8 proc.)	N/A	N/A
4–5 mėnesiai	8 (3 proc.)	6 (12 proc.)	N/A	N/A
6–9 mėnesiai	31 (13 proc.)	4 (8 proc.)	N/A	N/A
10–12 mėnesių	46 (19 proc.)	9 (17 proc.)	N/A	N/A
13–18 mėnesių	58 (23 proc.)	16 (31 proc.)	N/A	N/A
19–24 mėnesiai	12 (5 proc.)	5 (10 proc.)	N/A	N/A
> 24 mėnesiai	30 (12 proc.)	0 (0 proc.)	N/A	N/A
Amžius, nuo kurio vaikas maitinamas kietuoju maistu				
≤ 3 mėnesiai	3 (6 proc.)	2 (4 proc.)	N/A	N/A
4–5 mėnesiai	20 (38 proc.)	26 (55 proc.)	N/A	N/A
≥ 6 mėnesiai	29 (56 proc.)	19 (40 proc.)	N/A	N/A
Skiepai				
Skieptytas	96 (39 proc.)*	50 (96 proc.)*	N/A	N/A
Neskiepytas	3 (1 proc.)	2 (4 proc.)	N/A	N/A
Skiepytas iš dalies	136 (55 proc.)*	0 (0) *	N/A	N/A
Atopinės ligos šeimoje	169 (69 proc.)*	24 (47 proc.)*	N/A	N/A
Atopinės ligos, nustatytos vaikui				
Alergija maistui	99 (43 proc.)*	1 (2 proc.)*	N/A	N/A
Astma	28 (12 proc.)	3 (6 proc.)	N/A	N/A
Alerginis rinitas	67 (29 proc.)*	7 (13 proc.)*	N/A	N/A
Visos trys alerginės ligos	13 (5 proc.)	0 (0 proc.)	N/A	N/A
Pirmieji AD simptomai				
≤ 3 mėnesiai	91 (37 proc.)	N/A	N/A	N/A
4–5 mėnesiai	48 (20 proc.)	N/A	N/A	N/A
6–12 mėnesių	50 (20 proc.)	N/A	N/A	N/A
1–3 metai	32 (13 proc.)	N/A	N/A	N/A
3–5 metai	9 (4 proc.)	N/A	N/A	N/A
> 5 metai	8 (3 proc.)	N/A	N/A	N/A
Ligos sunkumo laipsnis pagal POEM				
Sunkus	44 (18 proc.)	N/A	N/A	N/A
Vidutinis	81 (33 proc.)	N/A	N/A	N/A
Lengvas	114 (46 proc.)	N/A	N/A	N/A
Nežinomas	8 (3 proc.)	N/A	N/A	N/A

Charakteristika, n (proc.)	AD grupės vaikai	Kontrolinės grupės vaikai	Tėvai (globėjai)	
Ligos sunkumo laipsnis pagal SCORAD				
Sunkus	19 (37 proc.)	N/A	N/A	N/A
Vidutinis	22 (42 proc.)	N/A	N/A	N/A
Lengvas	11 (2 proc.)	N/A	N/A	N/A

Paaiškinimai: *N/A, netaikoma.*

Pastaba. *∗ Pažymėtų duomenų p reikšmė < 0,05.*

3.2. Odos priežiūra, vietinio gydymo ypatumai, odos būklei svarbūs veiksniai

3.2.1. Odos priežiūros įpročiai

2 lentelėje apibendrinti grupių odos priežiūros įpročiai. Dauguma AD grupės pacientų prausėsi 1 kartą (81 (33 proc.) arba 2 kartus (74 (30 proc.) per dieną. Lyginant maudymosi dažnumą, statistiškai reikšmingo skirtumo tarp grupių nenustatyta. Sergantieji AD dažniau nei kontrolinės grupės pacientai prausėsi specialiu muilu sausai odai ($p < 0,001$), dažniau naudojo vonios priedus (vonios aliejus) ($p = 0,015$).

Sergantieji AD nepakankamai dažnai naudojo emolientus ir tepė mažesnį jų kiekį, nei rekomenduojama. Tik 14 (6 proc.) AD grupės pacientų nurodė naudojantys reikiamą emolientų kiekį (> 500 ml/mėn.), visi kiti tepė mažesnį. Net 57 (23 proc.) AD grupės pacientai sunaudojo iki 100 ml emolientų per mėnesį.

Sergantieji AD per pastarąsias dvi savaites emolientais odą tepė skirtingai dažnai: 47 (19 proc.) tai darė 3 ar 4 kartus per savaitę, 53 (21 proc.) – 1 ar 2 kartus per savaitę, 57 (24 proc.) – rečiau nei kartą per savaitę. Tik 21 (9 proc.) AD grupės pacientas emolientą naudojo daugiau nei 2 kartus per dieną, o 31 (13 proc.) – 2 kartus per dieną. Palyginti 10 (20 proc.) kontrolinės grupės pacientų odą emolientais tepė 1 ar 2 kartus per savaitę, o 9 (18 proc.) – rečiau nei kartą per savaitę. Tačiau didelė dalis (31 (61 proc.) kontrolinės grupės pacientų odos drėkinimo emolientais įpročių nenurodė.

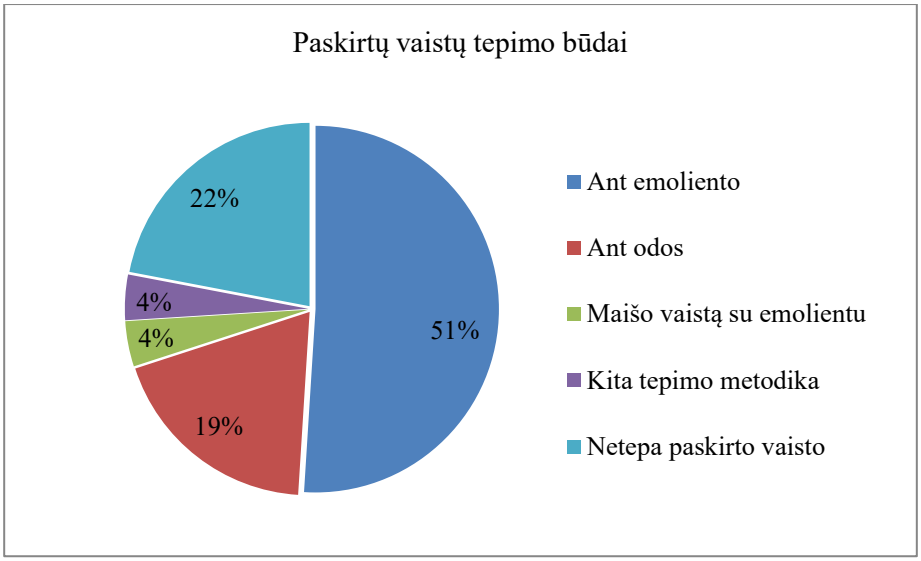
2 lentelė. Tiriamųjų odos priežiūros charakteristika.

Charakteristika	**AD grupės vaikai**	**Kontrolinės grupės vaikai**
1 tyrimo etapo klausimynai (n = 302)		
Maudymosi dažnumas		
> 2 kartai per dieną	2 (1 proc.)	0 (0 proc.)
2 kartai per dieną	74 (30 proc.)	1 (2 proc.)
1 kartas per dieną	81 (33 proc.)	23 (45 proc.)
3–4 kartai per savaitę	10 (4 proc.)	13 (25 proc.)
1–2 kartai per savaitę	78 (32 proc.)	14 (27 proc.)
< 1 kartas per savaitę	2 (1 proc.)	0 (0 proc.)
Prausiklio tipas		
Vonios aliejus	42 (19 proc.)∗	2 (4 proc.)∗
Įprastas muilas	25 (11 proc.)∗	26 (57 proc.)∗
Kita	3 (1 proc.)	0 (0 proc.)
Prausia tik vandeniu	21 (10 proc.)	2 (4 proc.)
Specialus muilas sausai odai	185 (84 proc.)∗	23 (50 proc.)∗
Per mėnesį sunaudojamas emolionto kiekis		
< 100 ml	57 (23 proc.)∗	38 (75 proc.)∗
100–200 ml	37 (15 proc.)∗	4 (8 proc.)∗
201–300 ml	51 (21 proc.)∗	0 (0 proc.)∗
301–400 ml	37 (15 proc.)∗	0 (0 proc.)∗
401–500 ml	27 (11 proc.)∗	0 (0 proc.)∗
> 500 ml	14 (6 proc.)∗	0 (0 proc.)∗
Nežino	24 (10 proc.)	9 (18 proc.)
Kaip dažnai tepėte savo vaiko odą emolientu per paskutines dvi savaites?		
> 2 kartus per dieną	21 (9 proc.)	1 (2 proc.)
2 kartus per dieną	31 (13 proc.)	0 (0 proc.)
1 kartą per dieną	15 (6 proc.)	0 (0 proc.)
3–4 kartus per savaitę	47 (19 proc.)	0 (0 proc.)
1 kartą per savaitę	53 (21 proc.)	10 (20 proc.)
< 1 kartą per savaitę	57 (24 proc.)	9 (18 proc.)
Emolientu odos netepa	23 (9 proc.)	31 (61 proc.)

Pastaba. *∗ Pažymėtų duomenų p reikšmė < 0,05.*

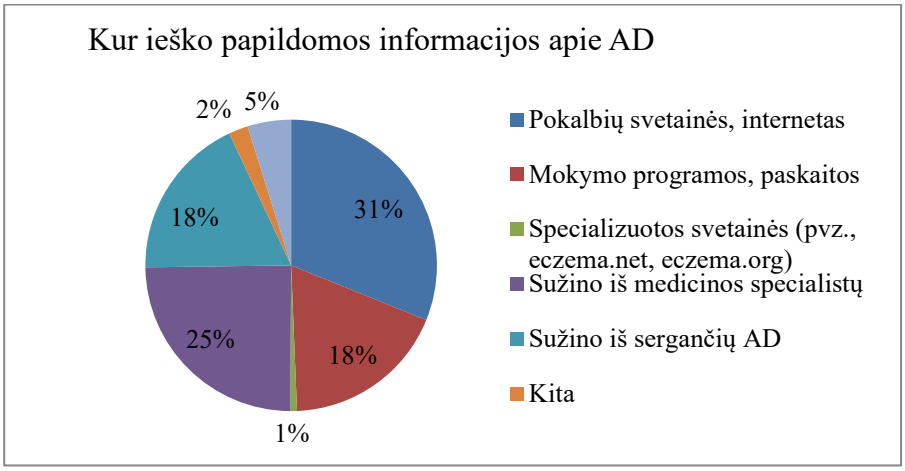
3.2.2. Vietinio odos gydymo ypatumai

AD sergančių vaikų tėvų (globėjų) buvo klausiama, kaip jie tepa paskirtus vietinio poveikio vaistus (kortikosteroidus, kalcineurino inhibitorius, antibiotikus). 114 (51 proc.) respondentų vaistus tepė ant odos, prieš tai pateptos drėkinamuoju kremu, kitaip tariant – ant emoliento. 42 (19 proc.) vaistus tepė ant išbertos odos, o drėkinamąjį kremą – ant vaisto, 9 (4 proc.) vaistus maišė su drėkinamuoju kremu, 8 (4 proc.) rinkosi kitus tepimo būdus, 49 (22 proc.) paskirtų vaistų nenaudojo (2 paveikslas).



2 paveikslas. Paskirtų vaistų tepimo būdai.

Respondentų taip pat buvo klausiama, kur jie ieško papildomos informacijos apie AD. Iš išvardytų atsakymo variantų trys dažniausi buvo šie: sužino iš medicinos specialistų – 183 (75 proc.), internete ir pokalbių svetainėse – 141 (58 proc.), specializuotose interneto svetainėse – 112 (46 proc.). Iš 244 į klausimą atsakiusių respondentų 23 (9 proc.) nurodė, kad papildomos informacijos apie AD neieško (3 paveikslas).



3 paveikslas. Informacijos apie atopinį dermatitą šaltiniai.

3.2.2. Odos būklei svarbių fizinių ir aplinkos veiksnių palyginimas (2 etapas)

Antrame tyrimo etape buvo klausiama, kaip keičiasi odos būklė dėl įvairių fizinių veiksnių. AD grupės pacientams odos būklė dažniau pagerėjo atostogaujant prie jūros (31 (60 proc.), palyginti su kontroline grupe (18 (35 proc.) ($p < 0,001$), taip pat atostogaujant šiltuose kraštuose (atitinkamai 23 (49 proc.), palyginti su 21 (41 proc.) ($p = 0,003$). Nors 28 (60 proc.) sergantieji AD ir 31 (60 proc.) kontrolinės grupės tiriamasis nurodė, kad infekcinės ligos nėra reikšmingos jų odos būklei, tačiau 17 (36 proc.) AD grupės pacientų ir tik 7 (14 proc.) kontrolinės grupės vaikams odos būklė pablogėjo sergant infekcine liga ($p < 0,001$). Apranga taip pat buvo svarbi sergančiųjų AD odos būklei. Nors dauguma abiejų grupių respondentų atsakė, kad drabužiai jokio poveikio nedaro, net 17 (41 proc.) AD grupės pacientų nurodė, kad odos būklę blogina vilnoniai drabužiai, o 14 (14 proc.) tai patyrė dėl sintetinių drabužių ($p < 0,001$). AD grupėje 17 (38 proc.) vaikų, palyginti su 7 (14 proc.) kontrolinės grupės, odos būklė paūmėjo po baseino ($p < 0,001$), atitinkamai 4 (10 proc.) ir 1 (2 proc.) – po skiepų ($p < 0,001$). Niekam iš kontrolinės grupės odos būklė neblogėjo po kontakto su gyvūnais, tačiau blogėjo 11 (23 proc.) AD sergančių vaikų ($p < 0,001$).

Nors 50 proc. sergančiųjų AD ($n = 22$) ir tokia pat dalis kontrolinės grupės respondentų ($n = 26$) atsakė, kad stresas nedaro jokio poveikio, 21 (48 proc.) AD grupės pacientui po streso odos būklė blogėjo, palyginti su 10 (19 proc.)

kontrolinės grupės vaikų ($p < 0,001$). Panaši tendencija pastebėta vertinant sezono poveikį tiriamųjų odai: vasarą 31 (60 proc.) AD grupės pacientui ir 23 (45 proc.) kontrolinės grupės vaikams odos būklė pagerėjo ($p = 0,02$), o žiemą atitinkamai 31 (61 proc.) ir 28 (54 proc.) pablogėjo ($p = 0,033$).

3.2.4. Odos būklei svarbių fizinių ir aplinkos veiksnių palyginimas tarp SCORAD sunkumo grupių (2 etapas)

Lyginant skirtingo sunkumo laipsnio pagal SCORAD indeksą AD pacientų odos priežiūros įpročius ir svarbius veiksnius nustatyta, kad sunkaus laipsnio AD sergančių vaikų odos būklė po kontakto su gyvūnu blogėjo dažniau nei lengvo ($p = 0,009$) ar vidutinio sunkumo ($p = 0,041$) AD pacientų. Sunkiu AD sergantys tiriamieji dažniau kasdien tepė odą emolientais ($p = 0,013$) ir dažniau naudojo vietinio poveikio priemones per pastarąsias dvi savaites ($p = 0,011$), palyginti su tais, kurie sirgo lengvu AD.

3.3. Endogeniniai veiksniai

Antrame etape buvo tiriama endogeninių veiksnių – tokių kaip vitaminas D, kortizolis serume, skydliaukę stimuliuojantis hormonas (TSH), skydliaukės peroksidazės antikūnai (anti-TPO), prolaktinas – sąsaja su vaikų AD ir jo sunkumo laipsniu pagal SCORAD indeksą. Analizuoti 52 sergantieji AD ir 55 kontrolinės grupės vaikai (iš viso 58 mergaitės ir 47 berniukai), kurių vidutinis amžius buvo $10,2 \pm 2,9$ metų (intervalas 6–17 metų). Tiriamųjų kūno masės indeksas (KMI) statistiškai reikšmingai nesiskyrė ir buvo normalus pagal Pasaulio sveikatos organizacijos rekomendacijas. Vidutinis KMI AD grupėje buvo 20,4, o kontrolinėje – 18,67. Amžiaus, lyties, svorio ir ūgio skirtumų tarp grupių nenustatyta. Sunkaus laipsnio AD pacientų buvo 19, vidutinio sunkumo – 22, lengvo – 11.

Įvertinus laboratorinius tyrimus nustatytas statistiškai reikšmingas bendrojo imunoglobulino E (IgE) ir kortizolio kiekio vidurkių skirtumas. AD grupės pacientų bendrojo IgE kiekis buvo didesnis, o kortizolio mažesnis. Eozinofilų (EOS), bendrojo cholesterolio, DTL cholesterolio, MTL cholesterolio, trigliceridų, prolaktino, TSH, anti-TPO ir 25(OH)D3 vidutinės vertės tarp grupių nesiskyrė. Išsami informacija apie tiriamųjų grupes pateikta 3 lentelėje. Sergantiems sunkesnio laipsnio AD nustatytas didesnis eozinofilų ($p = 0,039$) ir bendrojo IgE ($p < 0,001$) skaičius.

3 lentelė. AD ir kontrolinės grupių amžiaus, svorio, ūgio, laboratorinių tyrimų rezultatų palyginimas antrame etape.

Charakteristika	Grupė	Vidurkis ± SD	Mediana (Q1–Q3)	p reikšmė
Amžius (metai)	AD	10,0 ± 2,7	9 (8–11)	0,287
	Kontrolinė	10,5 ± 3,1	11 (8–13)	0,287
Svoris (kg)	AD	46,2 ± 20,2	43,85 (32–51)	0,376
	Kontrolinė	42,1 ± 16,2	39,35 (28,5–52,9)	0,376
Ūgis (cm)	AD	149,6 ± 16,4	149 (138,2–160)	0,983
	Kontrolinė	149,5 ± 16,9	148 (136–164)	0,983
Bendrasis IgE (IU/ml)	AD	1167,6 ± 2093,1	264,95 (109,6–1208)	< 0,001
	Kontrolinė	173,0 ± 241,8	66,8 (19,8–219,4)	< 0,001
EOS (x10 *9/l)	AD	0,5 ± 0,4	0,33 (0,2–0,6)	0,086
	Kontrolinė	0,3 ± 0,4	0,25 (0,16–0,3)	0,086
EOS (proc.)	AD	6,4 ± 4,9	5,3 (2,5–8,4)	0,086
	Kontrolinė	4,8 ± 4,0	3,9 (2,9–5,5)	0,086
Cholesterolis (mmol/l)	AD	4,2 ± 0,6	4,15 (3,8–4,5)	0,057
	Kontrolinė	4,0 ± 0,7	4,01 (3,6–4,4)	0,057
DTL (mmol/l)	AD	1,6 ± 0,3	1,55 (1,39–1,78)	0,972
	Kontrolinė	1,6 ± 0,3	1,58 (1,4–1,8)	0,972
MTL (nmol/l)	AD	2,4 ± 0,5	2,4 (2,1–2,8)	0,097
	Kontrolinė	2,3 ± 0,6	2,24 (1,8–2,6)	0,097

Charakteristika	Grupė	Vidurkis ± SD	Mediana (Q1–Q3)	p reikšmė
Trigliceridai (mmol/l)	AD	1,0 ± 0,6	0,79 (0,6–1,1)	0,104
	Kontrolinė	0,8 ± 0,4	0,66 (0,5–0,9)	0,104
Kortizolis (nmol/l)	AD	252,9 ± 304,3	200,1 (135,7–302,6)	0,047
	Kontrolinė	351,6 ± 126,1	279,7 (209–373)	0,047
Prolaktinas (mU/l)	AD	206,8 ± 200,3	155,4 (123,5–246,7)	0,198
	Kontrolinė	237,9 ± 125,7	200,6 (152–263,2)	0,198
Anti-TPO (IU/ml)	AD	28,6 ± 80,7	14,22 (11,4–17,4)	0,430
	Kontrolinė	15,2 ± 9,6	13,7 (11,6–16,2)	0,430
TTH (mkU/ml)	AD	2,3 ± 1,5	1,98 (1,5–2,5)	0,757
	Kontrolinė	2,4 ± 1,3	2,02 (1,5–2,9)	0,757
25(OH)D3 (nmol/l)	AD	71,6 ± 22	68 (56,98–81,1)	0,112
	Kontrolinė	65,6 ± 27,4	62,22 (48,8–79,2)	0,112

Paaiškinimai: *anti-TPO, skydliaukės peroksidazės antikūnai; DTL, didelio tankio lipoproteinai; EOS, eozinofilai; MTL, mažo tankio lipoproteinai; SD, standartinis nuokrypis; TTH, skydliaukę stimuliuojantis hormonas; 25(OH)D3, 25-hidroksivitaminas D3; Q, kvartilis.*

3.3.1. 25(OH)D3 kiekis sergančiųjų AD ir kontrolinės grupės vaikų organizme

Normalus 25(OH)D3 kiekis nustatytas 18 iš 52 (34,6 proc.) AD grupės pacientų ir 17 iš 55 (30,9 proc.) kontrolinės grupės vaikų; nepakankamas – atitinkamai 27 (51,9 proc.) ir 21 (38,2 proc.); trūkumas – 7 (13,5 proc.) ir 17 (30,9 proc.). Tik 1 (1,8 proc.) priklausančiam kontrolinei grupei vaikui nustatyta vitamino D hipervitaminozė. 52 AD sergančių vaikų vidutinė 25(OH)D3 koncentracija serume (71,6 ± 2 nmol/l) statistiškai nesiskyrė ($p = 0,112$) nuo 55 kontrolinės grupės tiriamųjų (65,6 ± 27 nmol/l). AD sergančių vaikų, kurie buvo tirti saulėtojo sezono metu (balandžio–rugsėjo mėnesiais) ($n = 34$), vidutinė 25(OH)D3 koncentracija serume buvo reikšmingai didesnė ($p = 0,0244$) (66,2 ± 27,6 nmol/l) nei tirtų mažo saulės aktyvumo sezono metu (spalio–kovo mėnesiais) ($n = 18$) (71,8 ± 23 nmol/l) AD grupės pacientų. Tačiau lyginant tuos pačius vidurkius kontrolinėje grupėje ($n = 53$, 66,2 ± 27,7 nmol/l ir $n = 2$, 49,7 ± 11,3 nmol/l) reikšmingo skirtumo nenustatyta ($p = 0,197$).

Statistiškai reikšmingo skirtumo ($p = 0,148$) tarp vidutinių 25(OH)D3 balų SCORAD sunkumo grupėse nebuvo.

Apibendrinant galima teigti, kad statistiškai reikšmingo 25(OH)D3 verčių skirtumo tarp sergančiųjų AD ir kontrolinės grupės vaikų nenustatyta, tačiau AD grupėje vitamino D kiekis mažo saulės aktyvumo sezono metu buvo mažesnis. Nenustatyta sąsajos tarp AD sunkumo laipsnio ir 25(OH)D3 kiekio.

3.3.2. Kortizolio kiekis sergančiųjų AD ir kontrolinės grupės vaikų organizme

Rytinės kortizolio kiekio serume vertės viršijo viršutinę pamatinio intervalo ribą (171–536 nmol/l 7–10 val. ryto) 2 (4 proc.) pacientams AD grupėje ($n = 52$) ir 1 (2 proc.) kontrolinėje grupėje ($n = 55$). Mažesnės vertės pagal pamatinį intervalą buvo nustatytos 14 (27 proc.) AD grupės pacientų ir 4 (7 proc.) kontrolinės grupės tiriamiesiems. Lyginant sergančiųjų AD (252,9 ± 304,3 nmol/l) ir kontrolinės grupės vaikų (351,6 ± 126,1 nmol/l) rytinės kortizolio koncentracijos serume vidutines vertes, tarp šių dviejų grupių nustatytas statistinis skirtumas ($p = 0,047$). Lygintas kortizolio kiekis tų AD grupės pacientų, kurie per pastarąsias dvi savaites buvo gydomi vietinio poveikio kortikosteroidais, ir tų, kurie šių vaistų negavo. Statistiškai reikšmingo kortizolio koncentracijos skirtumo tarp abiejų grupių nebuvo. Taip

pat nenustatyta kortizolio lygio vidutinių verčių skirtumo tarp SCORAD sunkumo grupių.

Apibendrinant galima teigti, kad sergančiųjų AD kortizolio koncentracija serume buvo mažesnė, palyginti su sveikais vaikais, tačiau AD sunkumo laipsnis nedarė poveikio kortizolio kiekio serume vertėms.

3.3.3. Skydliaukę stimuliuojančio hormono ir skydliaukės peroksidazės antikūnų kiekis sergančiųjų AD ir kontrolinės grupės vaikų organizme

Skydliaukės peroksidazės antikūnų (anti-TPO) vidutinės vertės tarp AD ir kontrolinės grupių nesiskyrė. Anti-TPO vidutinė vertė AD grupėje buvo 28,6 ± 80,7 TV/ml, o kontrolinėje grupėje 15,2 ± 96 IU/ml ($p = 0,430$). Tokie pat rezultatai gauti, lyginant skydliaukę stimuliuojančio hormono (TSH) vertes: AD grupėje vidutinė TSH vertė buvo 2,3 ± 1,5 mkU/ml, o kontrolinėje grupėje 2,4 ± 1,3 mkU/ml ($p = 0,757$). Analizuojant anti-TPO vertes nustatyta, kad 2 AD grupės pacientų ir 1 kontrolinės grupės tiriamojo anti-TPO vertė buvo didesnė už normą ($p = 0,757$), tačiau visų jų TSH vertės buvo normalios. Anti-TPO ir TSH lygių vidutinių verčių skirtumo tarp SCORAD sunkumo grupių nenustatyta.

Apibendrinant galima teigti, kad statistiškai reikšmingų TSH ir anti-TPO verčių skirtumų tarp sergančiųjų AD ir kontrolinės grupės vaikų nenustatyta.

3.3.4. Prolaktino kiekis sergančiųjų AD ir kontrolinės grupės vaikų organizme

1 sergančiajam AD ir 2 kontrolinės grupės tiriamiesiems nustatyta hiperprolaktinemija, o 1 AD grupės pacientui – hipoprolaktinemija. Vidutinė prolaktino koncentracija serume buvo 206,8 ± 200,3 mU/l, mediana 155,4 (123,5–246,7) AD grupėje ir 237,9 ± 125,7 mU/l, mediana 200,6 (152–263,2) kontrolinėje grupėje ($p = 0,198$). Reikšmingo prolaktino kiekio skirtumo tarp AD sunkumo grupių nenustatyta ($p = 0,168$) (3 lentelė). Prolaktino kiekio skirtumų tarp sergančiųjų AD ir kontrolinės grupės vaikų taip pat nenustatyta. Negalima daryti išvados, kad prolaktino kiekis svarbus AD patogenezei, nes sergančiųjų prolaktino kiekis serume yra panašus kaip AD nesergančios populiacijos.

3.4. Sergančiųjų AD ir kontrolinės grupės vaikų gyvenimo kokybė

247 AD grupės pacientai ir 50 kontrolinės grupės tiriamųjų tinkamai užpildė gyvenimo kokybės klausimynus. Nustatytas reikšmingas gyvenimo kokybės indekso (GKI) skirtumas tarp AD grupės (GKI: 6,3 ± 5,56 balo) ir kontrolinės grupės (GKI 0,54 ± 1,05 balo) ($p < 0,001$). Sergančiųjų GKI klausimynai rodo vidutinį ligos poveikį gyvenimo kokybei.

Analizuojant GKI klausimynų detales nustatyta, kad AD sergantiems vaikams labai svarbūs visi gyvenimo aspektai, ypač simptomai, jausmai (Q1, Q2) ir gydymas (Q10). AD daro reikšmingą poveikį vaikų draugystei (Q3) ir veiklai (Q4, Q5, Q6, Q7), palyginti su kontroline grupe.

3.5. Sergančiųjų AD ir kontrolinės grupės vaikų šeimos gyvenimo kokybė

Sergančiųjų AD šeimos gyvenimo kokybės indekso (FDLQI) vidurkis buvo 7,1 ± 6,9, tai yra vidutinis poveikis šeimos gyvenimo kokybei, o kontrolinės grupės vaikų FDLQI vidurkis buvo 2,1 ± 5,9, tai yra mažas poveikis šeimos gyvenimo kokybei ($p < 0,001$). Daugiausia balų surinkę AD grupės pacientų FDLQI punktai buvo atsakymai į klausimus apie emocinį stresą (Q1), gydymui ir namų ruošos darbams skiriamą laiką (Q7, Q8), padidėjusias namų ūkio išlaidas (Q10).

3.6. Gyvenimo kokybės palyginimas tarp POEM sunkumo grupių

Buvo išanalizuoti AD grupės užpildyti 186 DLQI ir POEM klausimynai. Pagal POEM 24 pacientai sirgo sunkaus, 59 – vidutinio, 103 – lengvo laipsnio AD. Tyrimas atskleidė, kad ligos sunkumas neigiamai veikia pacientų gyvenimo kokybę. Nustatyta, kad sunkaus laipsnio AD atveju vidutinis GKI buvo 14,3 ± 6,2 (labai didelis poveikis), vidutinio laipsnio – 6,9 ± 4,4 (vidutinis poveikis), lengvo laipsnio – 4,4 ± 4,2 (nedidelis poveikis) ($p < 0,001$), o tarp grupių nustatyta statistiškai reikšmingų skirtumų ($p < 0,001$). Sunkaus laipsnio AD sergančių vaikų gyvenimo kokybė beveik visais aspektais buvo labiau paveikta, palyginti su tų, kurie sirgo lengvo ar vidutinio laipsnio AD. Lyginant atskirus atsakymus į klausimus lengvos ir vidutinio sunkumo ligos grupėse reikšmingas poveikis nustatytas simptomų ir jausmų (Q1, Q2), asmeninių santykių (Q8) atžvilgiu.

Analizuojant POEM ir FDLQI duomenis taip pat nustatytas reikšmingas neigiamas poveikis šeimų gyvenimo kokybei: sunkaus laipsnio AD poveikis

buvo labai stiprus (16,3 ± 7,6, $p < 0,001$), o vidutinio ir lengvo laipsnio – vidutinis (7,6 ± 5,4 ir 5 ± 5,9).

3.7. Atopinio dermatito ir elgesio sunkumų sąsajos

101 iš 107 CBCL 6/18 klausimynų buvo užpildytas tinkamai: į klausimus atsakė 48 (48 proc.) AD grupės pacientai ir 53 (52 proc.) kontrolinės grupės tiriamieji. AD sergančių vaikų amžiaus vidurkis buvo 10 ± 2,7, o sveikų – 10,5 ± 3,1 metų. 20 (42 proc.) AD grupės ir 26 (49 proc.) kontrolinės grupės tiriamųjų buvo berniukai. Iš suaugusiųjų, užpildžiusių klausimynus, 93 (92 proc.) buvo motinos ir 8 (8 proc.) tėvai.

4 lentelėje pateikiami AD ir kontrolinės grupių vidutiniai CBCL 6/18 ir T balai. Bendro elgesio problemų vertinimo rezultatai parodė, kad tik 1 (2 proc.) AD grupės paciento ir 2 (4 proc.) kontrolinės grupės tiriamųjų balai viršijo 70, o tai atitinka klinikinį sindromą. Ribinį sutrikimą galima nustatyti 1 (2 proc.) kontrolinės grupės vaikui. Kitų 47 (98 proc.) AD grupės pacientų ir 50 (97 proc.) kontrolinės grupės tiriamųjų bendras rezultatas nesiekė 64 balų.

Nustatyta, kad AD ir kontrolinės grupių bendras trijų skalių balų skaičius skiriasi. Sergančiųjų AD vidinės elgsenos skalės balai ir T balas buvo 6,6 ± 6,4 su 9,6 ± 6,9 ir 47,9 ± 9,5 su 52,3 ± 10,2 ($p = 0,01$), nerimo ir depresijos skalės balai ir T balas buvo 2,8 ± 2,7 su 4,3 ± 3,5 ir 47,7 ± 8,4 su 52,3 ± 10,2 ($p = 0,01$), somatinių problemų skalės balai ir T balas buvo 2,1 ± 2,3 su 3,5 ± 3 ir 47,6 ± 8,5 su 52,7 ± 10,9 ($p = 0,005$).

Vidutinis bendras elgesio sunkumų balas ir vidutinis T balas AD grupėje buvo didesnis nei kontrolinėje (26,1 ± 16,3 prieš 22,2 ± 17,3 ir 51,2 ± 9,7 prieš 48,9 ± 10,2), bet šis skirtumas nebuvo statistiškai reikšmingas ($p = 0,134$). Tačiau duomenis stratifikavus pagal lytį ir amžių (6–11 metų ir 12–18 metų) tarp 6–11 metų mergaičių grupių nustatytas statistiškai reikšmingas skirtumas. AD sergančių mergaičių bendras elgesio sunkumų skalės balas buvo aukštesnis nei kontrolinės grupės mergaičių (31,8 ± 19,37 prieš 22,4 ± 7,3, $p = 0,036$). Taip pat nustatyta, kad šioje amžiaus (6–11 metų) imtyje AD sergančių mergaičių socialinių sunkumų ir mąstymo sunkumų skalės balai buvo aukštesni nei kontrolinės grupės mergaičių. Socialinių sunkumų skalės vidurkis AD grupėse buvo 3,1 ± 2,8, palyginti su kontroline grupe 1,4 ± 1,2 ($p = 0,014$), o mąstymo sunkumų skalės vidurkis – atitinkamai 2,8 ± 2,3, palyginti su 1,4 ± 1 ($p = 0,013$).

6–11 metų ir 12–18 metų amžiaus berniukų grupėse skirtumai nustatyti tik pagal somatinių sunkumų skalės balus. AD sergančių berniukų rezultatai buvo

aukštesni nei kontrolinės grupės berniukų. Rezultatai suskirstyti taip: 6–11 metų amžiaus grupėse – 2,8 ± 2,3 prieš 1,35 ± 1 (p = 0,013), o 12–18 metų amžiaus grupėse – 5,2 ± 4,5 prieš 2 ± 2,7 (p = 0,03). Kitos klinikinės CBCL 6/18 balų diapazono reikšmės tarp grupių nesiskyrė.

Buvo lyginami CBCL ir T skalių balai tarp skirtingo sunkumo AD grupių. 19 (40 proc.) vaikų sirgo sunkaus laipsnio AD, o 29 (60 proc.) – lengvo arba vidutinio sunkumo. Sunkiu AD sergantys vaikai patyrė daugiau miego sutrikimų ir intensyvesnį niežulį. Jų miego sutrikimų ir niežėjimo rodikliai buvo aukštesni nei sergančių lengvu arba vidutinio sunkumo AD (5,4 ± 2,6 prieš 2,4 ± 2,2, p < 0,001 ir 6,6 ± 2,4 prieš 4 ± 2,8, p = 0,001). Tačiau bendras elgesio problemų balas ir kiti klinikiniai CBCL balų intervalai reikšmingai nesiskyrė tarp sunkaus ir lengvo arbavidutinio sunkumo AD grupių.

Siekiant patikrinti, kurių veiksnių poveikis yra didžiausias, buvo modeliuojamos elgesio skalės pagal veiksnius: pagal SCORAD sunkumą, amžių, lytį, rytinį kortizolio kiekį, ligos trukmę, niežėjimo intensyvumą, miego sutrikimo intensyvumą. Nė vieno iš šių veiksnių poveikis nebuvo statistiškai reikšmingas.

4 lentelė. Sergančiųjų AD ir kontrolinės grupės vaikų CBCL 6/18 balų ir T balų rezultatai.

Sindromas	**Grupė**	**Vidurkis ± SD [Mediana (Q1–Q3)]**	**T balas Vidurkis ± SD [Mediana (Q1–Q3)]**	**p reikšmė**
Internalių sunkumų skalė	K	6,6 ± 6,4 [5,0 (3–8)]	47,9 ± 9,5 [45,6 (42,7–50,5)]	0,010
Internalių sunkumų skalė	AD	9,6 ± 6,9 [8,5 (4–13)]	52,3 ± 10,2 [50,7 (44,1–57,3)]	0,010
Nerimastingumo /depresiškumo	K	2,8 ± 2,7 [2,0 (1–4,1)]	47,7 ± 8,4 [45,3 (42,1–51,6)]	0,020
Nerimastingumo / depresiškumo	AD	4,3 ± 3,5 [3 (2–6,3)]	52,5 ± 11 [48,4 (45,3–58,6)]	0,020
Užsisklendimo / depresiškumo	K	1,7 ± 2,5 [1 (0–3)]	49,9 ± 10,9 [46,8 (42,4–55,5)]	0,564
Užsisklendimo / depresiškumo	AD	1,8 ± 2,1 [1 (0–3)]	50,1 ± 9 [46,8 (42,4–55,5)]	0,564
Somatinių skundų	K	2,1 ± 2,3 [2 (0–3)]	47,6 ± 8,5 [47,3 (40–50,9)]	0,005
Somatinių skundų	AD	3,5 ± 3 [3 (1,8–5)]	52,7 ± 10,9 [50,9 (46,4–58,2)]	0,005
Eksternalių sunkumų skalė	K	5,8 ± 4,6 [5 (2–9)]	49,6 ± 9,3 [48,1 (42–56,2)]	0,819
Eksternalių sunkumų skalė	AD	6,1 ± 5,3 [5,0 (2,0–9,3)]	50,4 ± 10,8 [48,1 (42,0–56,7)]	0,819
Taisyklių laužymo	K	1,9 ± 2,0 [1 (0–3)]	50,9 ± 10,7 [46,0 (40,6–56,7)]	0,433
Taisyklių laužymo	AD	1,6 ± 1,7	49,0 ± 9,2	0,433

Sindromas	Grupė	Vidurkis ± SD [Mediana (Q1–Q3)]	T balas Vidurkis ± SD [Mediana (Q1–Q3)]	p reikšmė
		[1 (0–2,3)]	[46,0 (40,6–52,7)]	
Agresyvaus elgesio	K	3,8 ± 3,3 [3 (1–6)]	49,0 ± 8,7 [46,8 (41,5–54,8)]	0,520
Agresyvaus elgesio	AD	4,6 ± 4,2 [3,5 (1–7)]	51 ± 11,2 [48,2 (41,5–57,5)]	0,520
Socialinių sunkumų	K	1,9 ± 2,2 [1 (0–3)]	48,8 ± 10,1 [44,7 (40,2–53,8)]	0,104
Socialinių sunkumų	AD	2,5 ± 2,2 [2 (1–4)]	51,3 ± 9,8 [49,2 (44,7–58,3)]	0,104
Mąstymo sunkumų	K	1,9 ± 2,4 [1 (0–3)]	49,2 ± 10,1 [45,3 (41–53,9)]	0,279
Mąstymo sunkumų	AD	2,3 ± 2,3 [2 (0–3,3)]	50,9 ± 9,9 [49,6 (41,0–54,9)]	0,279
Dėmesio sunkumų	K	3,5 ± 3,4 [3 (1–5)]	50,2 ± 11,1 [48,7 (42,2–55,2)]	0,856
Dėmesio sunkumų	AD	3,3 ± 2,7 [3 (1,0–4,3)]	49,7 ± 8,7 [48,7 (42,2–52,8)]	0,856
Bendra elgesio sunkumų skalė	K	22,2 ± 17,3 [22 (11–26)]	48,9 ± 10,2 [48,8 (42,3–51,2)]	0,134
Bendra elgesio sunkumų skalė	AD	26,1 ± 16,3 [25,5 (12,5–37,5)]	51,2 ± 9,7 [50,9 (43,2–58)]	0,134

Paaiškinimai: *CBCL 6/18 – 2001 m. vaikų elgesio sunkumų klausimynas, skirtas 6–18 metų amžiaus vaikams; K, kontrolinė; SD – standartinis nuokrypis; Q, kvartilis.*

3.8. Sergančiųjų AD kortikofobijos vertinimas

Išanalizuoti 296 TOPICOP klausimynai. 244 (82 proc.) anketas užpildė AD sergančių vaikų tėvai (globėjai), o 52 (18 proc.) – kontrolinės grupės vaikų tėvai (globėjai). Kontrolinėje grupėje buvo 25 (48 proc.), o AD grupėje 119 (49 proc.) mergaičių. Pacientų amžiaus vidurkis AD grupėje buvo 6,84 ± 4,43 metų, o kontrolinėje grupėje 10,5 ± 3,1 metų. Kortikofobijos paplitimas tiriamoje populiacijoje buvo 55 proc. (pagal teigiamus atsakymus į klausimą, ar jaučia nerimą arba dvejoja, prieš tepdami kortikosteroidiniu kremu).

TOPICOP klausimyno rezultatai parodė, kad 76 (32 proc.) AD grupės ir 5 (14 proc.) kontrolinės grupės pacientai turi didelę kortikofobijos riziką, 109 (46 proc.) AD grupės ir 18 (50 proc.) kontrolinės grupės pacientų turi vidutinę kortikofobijos riziką. Kitų 53 (22 proc.) AD grupės ir 13 (36 proc.) kontrolinės grupės pacientų kortikofobijos rizika yra maža.

Siekta išsiaiškinti, kokie veiksniai lemia didesnę kortikofobijos riziką. Nustatyta, kad kortikofobija nebuvo susijusi su respondentų išsilavinimu, AD sunkumo laipsniu pagal POEM, tėvų lytimi (motina ar tėvas), ankstesniu vietinių arba sisteminių steroidų vartojimu, steroidų vartojimu per pastarąsias

dvi savaites, dalyvavimu specialiose AD sergantiems pacientams ir jų artimiesiems skirtose edukacinėse programose ir (arba) paskaitose. TOPICOP balų vidurkiai tarp šių grupių statistiškai nesiskyrė. Nustatyta, kad TOPICOP balų vidurkis skyrėsi tik tarp AD ir kontrolinės grupių (atitinkamai 42,7 ± 44,5 ir 30,1 ± 19,3, p = 0,0481), todėl daroma išvada, kad AD diagnozė gali didinti kortikofobijos riziką.

4. IŠVADOS

1. Vaikų AD yra susijęs su alergija maistui, rinokonjunktyvitu, didesniu bendru IgE, mažesniu kortizolio ir vitamino D kiekiu serume mažo saulės aktyvumo sezono metu, palyginti su neatopiškais kontroliniais vaikais. AD sergančių pacientų odą labiau veikia išoriniai veiksniai.
2. AD daro vidutinį neigiamą poveikį sergančių vaikų ir jų šeimų gyvenimo kokybei, be to, nustatyta tiesioginė šio poveikio priklausomybė nuo ligos sunkumo laipsnio.
3. AD sergančių vaikų (nuo 6 iki 18 metų) elgesio sunkumų skalių rodikliai aukštesni, palyginti su sveikų vaikų, o sunkaus laipsnio AD sergantys vaikai patiria daugiau miego sutrikimų ir intensyvesnį niežulį. Tirtoje populiacijoje nenustatėme veiksnių turinčių poveikį elgesio problemoms atsirasti
4. AD sergančių vaikų tėvai turi vidutinę kortikofobijos riziką. Ji yra susijusi su pačia ligos diagnoze, bet nėra susijusi su respondentų išsilavinimu, lytimi, AD sunkumo laipsniu, ankstesniu steroidų vartojimu ir dalyvavimu specialiose mokymo programose arba paskaitose.

PASIŪLYMAI IR TĘSTINUMAS

1. Esant indikacijoms, sergantiems AD rekomenduojama patikrinti kortizolio, bendrojo IgE ir vitamino D kiekį serume (ypač mažo saulės poveikio laikotarpiais).
2. Gyvenimo kokybės klausimynai turėtų būti įtraukti į įprastinį paciento būklės vertinimą konsultacijos metu, o sudarant gydymo planą rekomenduojama atsižvelgti į paciento ir šeimos gyvenimo kokybės gerinimo aspektą
3. Psichologinės paramos terapija turėtų būti įtraukta į individualų gydymo planą ir nacionalines atopinio dermatito gydymo gaires.
4. Siekiant sumažinti kortikofobijos paplitimą, pagerinti paskirto gydymo plano laikymąsi, pagerinti imunizacijos rodiklius rekomenduojama toliau plėtoti pacientams (interneto svetainės, “egzemos mokyklos”) ir gydytojams, skirtas informacines sistemas (paskaitos konferencijose, profesiniai mokymai).

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TRUMPOS ŽINIOS APIE DISERTANTĘ

Inga Kisielienė 2006 m. baigė vientisąsias medicinos studijas Kauno medicinos universitete Medicinos fakultete (VU MF), 2011 m. užbaigė VU MF dermatovenerologijos rezidentūros programą. Nuo 2007 m. dirbo gydytoja asistente, nuo 2011 m. - gydytoja dermatovenerologe Vilniaus universiteto ligoninės Santaros klinikose. Nuo 2015 metų dirba jaunesniąja asistente Vilniaus universitete Medicinos fakultete. Stažavosi Karolinska ligoninėje (Stokholmas, Švedija) ir Skane universitetinėje ligoninėje (Malme, Švedija). Nuo 2005 metų yra Lietuvos Dermatovenerologijos draugijos narė, nuo 2011 m. Europos pediatrinės dermatologijos asociacijos narė. Disertantė yra Lietuvos ir tarptautinių kongresų lektorė, 8 mokslinių tezių ir publikacijų autorė ir bendraautorė.

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NOTES

Vilniaus universiteto leidykla
Saulėtekio al. 9, III rūmai, LT-10222 Vilnius
El. p. info@leidykla.vu.lt, www.leidykla.vu.lt
bookshop.vu.lt, journals.vu.lt
Tiražas 20 egz.