Skin disorders in primary immunodeficiency diseases: highly prevalent and early presenting clinical features

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ABSTRACT

Background

Skin disorders are common clinical features in primary immunodeficiency diseases (PIDs) and may even precede diagnoses of PIDs for years. Most studies have focused on the prevalence of skin disorders in PIDs in Middle-Eastern countries.

Objective

To determine the prevalence and nature of skin disorders in Dutch children and adults with PIDs compared to partner-controls.

Methods

A partner-controlled questionnaire-based study was performed to evaluate skin disorders in PIDs. In a subsequent observational study in a subgroup of patients with possible *Staphylococcus* (*S.*) *aureus*-related skin disorders we determined the presence of skin disorders by physical examination and *S. aureus* on the lesional skin by culture.

Results

Forty-five children and 207 adults with PIDs, and 56 partner-controls completed the questionnaire. Thirty two (71.1%) children and 166 (80.2%) adults reported a history of skin disorders, compared with 23 (41.1%, $p<0.001$) partner-controls. (Atopic) dermatitis was the most common presenting manifestation in patients and partner-controls. Skin infections and nail disorders were reported more frequently in patients than in partner-controls. Skin disorders in adult patients developed at a mean age of 20.9 (SD 22.0) years; 20.3 (SD 20.5) years before diagnoses of PID, and in partner-controls at 33.7 (SD 26.6) years ($p=0.02$). Skin cultures were positive for *S. aureus* in 40.0% (12/30 cultures, 9/22 adult PID patients).

Conclusion

In PIDs, skin disorders are more prevalent and develop at an earlier age compared with partner-controls. Early recognition of skin disorders in combination with other warning signs could improve earlier diagnosis in PID.

INTRODUCTION

Primary immunodeficiency diseases (PIDs) encompass a heterogeneous group of more than 300 inheritable defects of immunity caused by variants in genes encoding functional proteins of human immune cells.[1,2] The worldwide prevalence of PIDs is estimated at 1 in 2000 live births of which the majority is due to highly consanguineous populations in the Middle-East region.[2,3] PIDs are typically characterized by recurrent and/or severe infections. Additionally, patients may suffer from autoimmunity, autoinflammation, malignancy and allergic disorders.[4-6] A systematic review showed that skin manifestations based on these pathological processes represent an important clinical feature in patients with PIDs.[7] *Staphylococcus* (*S.*) *aureus* induced skin infections were found to be the most common infectious skin disorders reported in PIDs.[8-10] Dermatitis turned out to be one of the most prominent non-infectious skin manifestations in PIDs, in which *S. aureus* has been suggested to play a role in its multifactorial pathogenesis.[11] However, most data originate from Middle-Eastern countries because of their high PID prevalence, and the prevalence and nature of PID-associated skin disorders in the western world remain largely unknown.

The quality of life (QoL) of patients with PIDs is lower for both mental and physical components compared with healthy controls and patients with other chronic diseases. This is mainly caused by the high number of hospitalizations, functional limitations and/or delayed diagnosis.[12-16] Delay in diagnoses and treatment of PIDs can lead to significant morbidity and even mortality.[17] The diagnostic delay of PIDs in the Netherlands ranges from 0 years for T-cell deficiencies, and autoimmune and immune dysregulation syndromes to 14.5 years for defects in innate immunity.[18] As a consequence, these inherited PIDs are diagnosed at a median age of 0 to 19.0 years, respectively.[18] Therefore, warning signs, including occurrence of repetitive (respiratory tract) infections or a family history of PID, have been developed to improve early recognition of an underlying PID.[19]

Skin disorders have been described as prominent clinical feature in PIDs and may even precede the diagnosis of PID. Studies on PID cohorts have demonstrated that skin manifestations preceded and were the basis for 31.8-78.9% of the PID diagnoses.[20,21] In this context, increased attention for skin manifestations as signal function of PIDs in combination with presence of the currently used warning signs of PIDs could improve earlier diagnoses of PIDs.

The aim of this study is to evaluate prevalence and nature of (presenting) skin disorders in a population of Dutch children and adults with a PID compared to partner-controls. Secondly, we assessed the influence of skin disorders on the health-related QoL (HR-QoL) and the prevalence of *S. aureus* on the skin and nose in patients with a skin disorder with possible *S. aureus*-related etiology.

METHODS

Study design

A retrospective adult partner-controlled questionnaire-based study on the prevalence of skin disorders in PIDs and the effect on HR-QoL was followed by a prospective observational clinical study in adult patients suspected of *S. aureus*-related skin disorders to confirm the patient-reported skin disorders by a dermatologist and determine the presence of *S. aureus* on the skin and in the nose. The study was designed and conducted by the department of Dermatology, department of Internal Medicine, division of Clinical Immunology, and department of Pediatrics, division of Infectious Diseases, of the Erasmus MC University Medical Center, Rotterdam, The Netherlands. The study procedures were approved by the institutional review board of the Erasmus MC University Medical Center (MEC-2018-1260 and MEC-2018-1425). All patients aged 16 years or older provided written informed consent themselves. For children below 12 years, both parents or guardians signed, and for children aged 12-16 years both the adolescent and both parents or caregivers signed, in accordance with the Dutch law.

Study population

The questionnaire-based study included patients of all ages with a PID diagnosis according to Picard *et al.*[1]. All patients diagnosed with a PID providing written informed consent are prospectively registered in an ongoing database from the end of 2013 (MEC-2013-026). We selected patients from the database until September 2018. Patients who underwent a curative hematopoietic stem cell transplantation were excluded from this study. Eligible patients or their parent/caregiver (patients <16 years) should have the ability to read and understand the Dutch language. The control group consisted of partners of adult patients who completed the questionnaire and were not deceased in order to correct for environmental factors regardless of genetic influences, which might be involved in development of atopic manifestations in PIDs. Adult patients (≥18 years) who reported to have an active skin disorder with possible *S. aureus*-related etiology, including (atopic) dermatitis, seborrheic dermatitis, nummular eczema, furuncles, impetigo, folliculitis, skin abscesses, erythroderma, cellulitis, perleche, paronychia, and a skin rash with unknown origin, in the questionnaire were eligible for the observational study.

Outcome measurements

The primary outcome of the questionnaire-based study was the self-reported prevalence of skin disorders in children (by parent/caregiver) and adults with PIDs compared to adult partner-controls. Skin disorders evaluated in our cohort included 70 specified skin manifestations, which are frequently reported in PIDs, based on a systematic literature search.[7] Secondary outcomes were the self-reported prevalence of skin disorders with possible *S. aureus*-related etiology, the delay between the first skin disorder and PID diagnosis, and

the influence of skin disorders on the HR-QoL (Appendix 1). In the observational clinical study, skin inspection was performed to confirm the patient-reported skin disorders by a dermatologist. Additionally, the prevalence of *S. aureus* on the lesional skin and nose of patients with an active skin disorder with possible *S. aureus*-related etiology was assessed by semi-quantitative culture.

Study procedures

A questionnaire was sent by mail to 79 pediatric and 360 adult patients with PIDs between October 2017 and September 2018. Adult patients who completed the questionnaire and reported a skin disorder with possible *S. aureus*-related etiology were contacted by telephone to verify the diagnosis. Patients with an active skin disorder at the moment of screening were invited to participate in the observational clinical study. During a subsequently scheduled study visit the skin was systematically inspected by the clinical study physician (JdW and SP) to diagnose and report specific skin disorders. Furthermore, swabs were collected of the lesional skin and nose. Patients with a positive *S. aureus* skin culture were cultured from the same lesional skin location at a second time point, at least two weeks after the first culture, to determine persistent colonization (Appendix 2).

Statistical analysis

The prevalence of skin disorders, diagnostic delay, QoL and presence of *S. aureus* on the skin and in the nose were presented as mean and standard deviation (SD) for normally distributed continuous data or otherwise as median and interquartile range (IQR). The difference in prevalence of skin disorders between adult patients and partner-controls was analyzed using a Chi-Square test or Fisher's Exact test. Basic descriptive statistics and tests were performed using SPSS version 25.0 for windows (IBM Corporation, Armonk, NY). The HR-QoL of pediatric (TAPQOL and Kidscreen-27) and adult (SF-36) patients and partner-controls were compared with adequate reference populations (Appendix 3).[22-24]

RESULTS

Patient characteristics

Questionnaires were completed and returned by 57.4% (45 pediatric and 207 adult) patients (Figure 1). Demographic and disease characteristics were comparable between responders and non-responders, but adult responders had a higher age compared with adult non-responders and more often had a history of skin disorders based on medical records (data not shown). Median age of the included patients was 46.3 (IQR 23.5-61.2) years; children had a median age of 11.2 (IQR 7.1-15.5) years and adults of 53.2 (IQR 37.1-64.6) years. One hundred and twenty (46.9%) patients were male and 248 (98.4%)

were of Caucasian race. The majority of patients (86.6%) had a predominant antibody deficiency (PAD) according to the 2017 international union of immunological societies (IUIS) phenotypic classification for primary immunodeficiencies (Table 1).[25] Mean age at time of diagnosis of the PID was 4.5 (SD 4.2) years in pediatric patients and 41.8 (SD 20.0) years in adult patients. The first classical PID symptom preceded the PID diagnosis 3.2 (SD 3.7) and 15.9 (SD 17.7) years, respectively. Classical symptoms were present at a mean age of 1.4 (SD 2.2) years in children and 25.3 (SD 22.8) years in adults and included mainly upper and lower respiratory tract infections (46.7% and 58.0%, respectively).

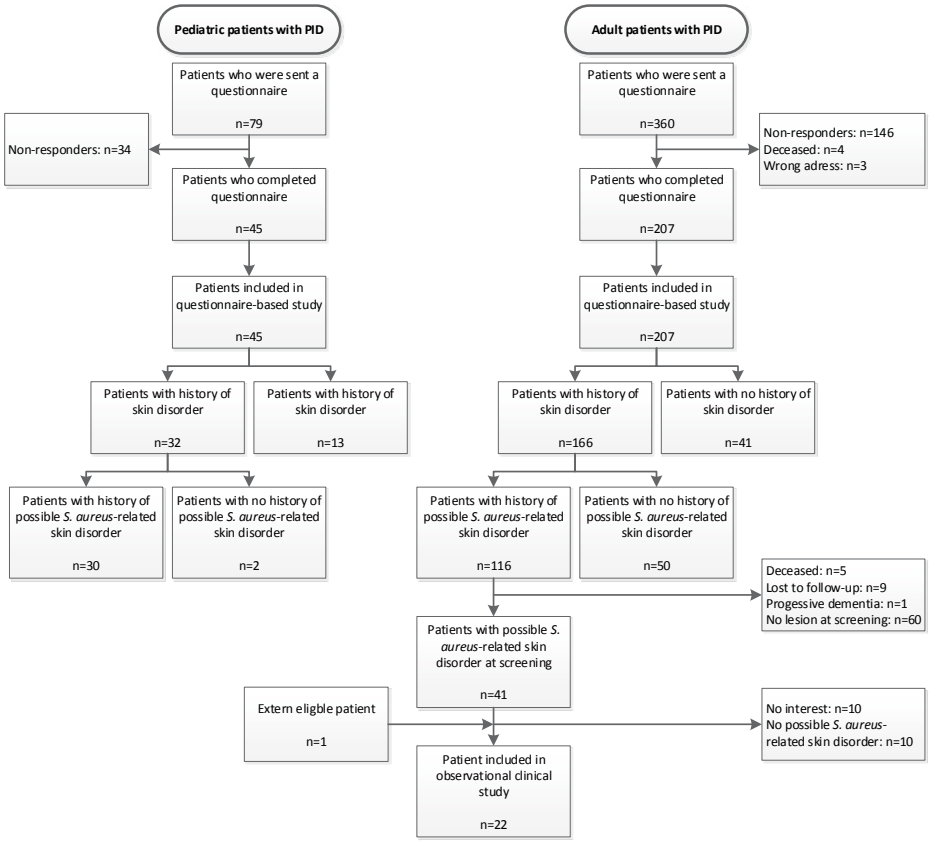

Figure 1. Flowchart of the study design

Partner-control characteristics

Five patients with PIDs died after completing the questionnaire. Therefore, 202 partners of adult patients were sent a questionnaire. A total of 56 (27.7%) questionnaires of partner-controls were completed and included in this study. Partner-controls had a median age of 59.3 (IQR 46.2-69.8) years and 34 (60.7%) were male.

Table 1. General patient demographics

	Questionnaire-based study			Observational clinical study
	Pediatric patients (n=45)	**Adult patients (n=207)**	**Adult partner-controls (n=56)**	**Adult patients (n=22)**
Age				
median (IQR)	11.2 (7.1-15.5)	53.2 (37.1-64.6)	59.3 (46.2-69.8)[1]	48.0 (43.5-56.8)
Sex, male				
n (%)	32 (71.1)	83 (40.1)	34 (60.7)	9 (40.9)
Race, n (%)			Not available	
White	44 (97.8)	204 (98.6)		22 (100)
Black or African American	0 (0)	0 (0)		0 (0)
Asian	1 (2.2)	0 (0)		0 (0)
American Indian or Alaska Native	0 (0)	3 (1.4)		0 (0)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)		0 (0)
Unknown	0 (0)	0 (0)		0 (0)
Age PID diagnosis, years			Not applicable	
mean (SD)	4.5 (4.2)[2]	41.8 (20.0)[3]		36.6 (17.0)[4]
IUIS phenotypic classification of PID, n (%)			Not applicable	
Immunodeficiencies affecting cellular and humoral immunity	2 (4.4)	1 (0.5)		0 (0)
CID with associated syndromic features	1 (2.2)	7 (3.4)		1 (4.5)
Predominantly antibody deficiencies	33 (73.3)	182 (87.9)		21 (95.5)
- Common variable immunodeficiency	7 (15.6)	74 (35.7)		8 (36.4)
- IgG subclass deficiency	2 (4.4)	34 (16.4)		7 (31.8)
- Selective IgA deficiency	1 (2.2)	5 (2.4)		0 (0)
- Selective antibody deficiency with normal immunoglobulins	0 (0)	27 (13.0)		2 (9.1)
- X-linked agammaglobulinemia	4 (8.9)	7 (3.4)		2 (9.1)
- Hypogammaglobulinemia	16 (35.6)	23 (11.1)		2 (9.1)
- Hyper IgM syndrome	0 (0)	3 (1.4)		0 (0)
- Combined antibody deficiency	0 (0)	7 (3.4)		0 (0)
- Other	4 (8.9)	2 (1.0)		0 (0)
Diseases of immune dysregulation	0 (0)	1 (0.5)		0 (0)
Congenital defects of phagocyte number, function or both	3 (6.7)	2 (1.0)		0 (0)
Defects in intrinsic and innate immunity	1 (2.2)	5 (2.4)		0 (0)
Auto-inflammatory disorders	2 (4.4)	4 (1.9)		0 (0)
Complement deficiencies	0 (0)	1 (0.5)		0 (0)
Phenocopies of PID	0 (0)	1 (0.5)		0 (0)
Unknown	3 (6.7)	3 (1.4)		0 (0)

Abbreviations: CID, combined immunodeficiency disease; IUIS, International Union of Immunological Societies; IQR, interquartile range; n, number; PID, primary immunodeficiency disease. Missings: [1]n=3 (5.4%), [2]n=1 (2.2%), [3]n=9 (4.3%), [4]n=1 (4.5%).

Skin disorders

Children with primary immunodeficiency disease

Thirty-two (71.1%) pediatric patients reported a history, i.e. lifetime prevalence, of one or more skin disorders, of which 96.9% comprised a history of at least one skin disorder with possible *S. aureus*-related etiology. In general, (atopic) dermatitis (48.9%), varicella zoster virus infection (46.7%) and oral ulcers (35.6%) were the most common skin manifestations (Table S1). Children reported their first skin disorder at a mean age of 1.5 (SD 3.0) years; 3.5 (SD 5.4) years before the PID diagnosis. (Atopic) dermatitis was the most prevalent presenting skin disorder in 17 (37.8%) patients reporting a history of skin disorders.

Adults with primary immunodeficiency disease and partner-controls

A history of one or more skin disorders was reported by 166 (80.2%) adult patients and 23 (41.1%, p <0.001) partner-controls, of which, respectively, 74.1% and 78.3% (p=0.67) included a history of at least one skin disorder with possible *S. aureus*-related etiology. In general, the most frequently noted skin disorders in patients were (atopic) dermatitis (29.5%), oral ulcers (22.7%) and warts (21.7%) (Table S1). (Atopic) dermatitis (25.0%) was most prevalent in partner-controls. Other skin disorders were reported in four or less (≤7.1%) partner-controls (Table S1). Skin infections and nail disorders, including paronychia and onychomycosis, were significantly more prevalent in adult patients compared with partner-controls (p=0.001 and p=0.005, respectively) (Table 2). Patients reported the first skin disorder at a mean age of 20.9 (SD 22.0) years; 20.3 (SD 20.5) years before the PID diagnosis. Partner-controls reported their first skin disorders at a mean age of 33.7 (SD 26.6) years (p=0.02). In adult participants reporting a history of skin disorders, (atopic) dermatitis was the most prevalent first developed skin disorder (15.0% patients and 52.2% partner-controls).

Quality of life

Children with primary immunodeficiency disease

Pediatric patients of all age categories reported a noticeably lower HR-QoL compared with norm data for the KIDSCREEN-27 dimension physical well-being (Table 3). On the other hand, the dimensions autonomy and parents, and social support and peers scored a noticeable better QoL based on the outcomes of the KIDSCREEN-27 proxy questionnaire for children 8-11 years. Children showed a good skin-related QoL (SR-QoL) with a median CDLQI of 1.5 (IQR 0.0-4.0) and IDQOL of 2.0 (Table 3). The influence of the skin disorder on the HR-QoL was limited (median NRS 1.0 (IQR 0.0-6.0)).

Table 2. Skin disorders in primary immunodeficiency diseases

	Pediatric patients (n=45)	Adult patients (n=207)[1]	Adult partner-controls (n=56)	*p*-value[†]
Dermatitis-like lesions, n (%)	24 (53.3)	97 (46.9)	17 (30.4)	0.155
(Atopic) dermatitis	22 (48.9)	61 (29.5)	14 (25.0)[2]	
Seborrheic dermatitis	7 (15.6)	27 (13.0)	1 (1.8)[2]	
Nummular eczema	8 (17.8)	22 (10.6)	1 (1.8)[2]	
Hair abnormalities, n (%)	5 (11.1)	55 (26.6)	5 (8.9)[2]	0.325
Hair loss disorders	3 (6.7)	45 (21.7)	4 (7.1)[2]	
Excessive hair growth disorders	1 (2.2)	15 (7.2)	2 (3.6)[2]	
Hair pigmentation disorders	0 (0.0)	13 (6.3)	0 (0.0)[2]	
Other hair abnormalities	0 (0.0)	1 (0.5)	0 (0.0)[2]	
Skin infections, n (%)	29 (64.4)	127 (61.4)	10 (17.9)	0.001**
Fungal skin infections	11 (24.4)	62 (30.0)	5 (8.9)	
Viral skin infections	24 (53.3)	84 (40.6)	3 (5.4)	
Bacterial skin infections	15 (33.3)	66 (31.9)	1 (1.8)	
Abscesses	4 (8.9)	25 (12.1)	0 (0.0)	
Impetigo	7 (15.6)	12 (5.8)	0 (0.0)	
Folliculitis	3 (6.7)	38 (18.4)	1 (1.8)	
Cellulitis	0 (0.0)	8 (3.9)	0 (0.0)	
Furuncle	3 (6.7)	28 (13.5)	0 (0.0)	
Other skin infections	8 (17.8)	38 (18.4)	1 (1.8)	
Perleche	8 (17.8)	38 (18.4)	1 (1.8)	
Ulcers, n (%)	16 (35.6)	53 (25.6)	2 (3.6)	0.022
Oral ulcers	16 (35.6)	47 (22.7)	2 (3.6)	
Nose ulcers	2 (4.4)	14 (6.8)	0 (0.0)	
Other ulcers	0 (0.0)	3 (1.4)	0 (0.0)	
Erythematous skin lesions, n (%)	5 (11.1)	45 (21.7)	2 (3.6)	0.056
Erythroderma	1 (2.2)	11 (5.3)	1 (1.8)	
Vascular disorders, n (%)	7 (15.6)	50 (24.2)	2 (3.6)	0.031
Telangiectasia	3 (6.7)	32 (15.5)	2 (3.6)	
Vasculitis	2 (4.4)	9 (4.3)	0 (0.0)	
Petechia/purpura	2 (4.4)	12 (5.8)	0 (0.0)	
Other vascular disorders	0 (0.0)	7 (3.4)	1 (1.8)	
Pigmentation disorders, n (%)	15 (33.3)	73 (35.3)	4 (7.1)	0.015
Hyperpigmentation disorders	13 (28.9)	45 (21.7)	3 (5.4)	
Hypopigmentation disorders	4 (8.9)	25 (12.1)	1 (1.8)	
Other pigmentation disorders	7 (15.6)	22 (10.6)	0 (0.0)	
Neoplastic disorders, n (%)	0 (0.0)	20 (9.7)	3 (5.4)	1.000
Rash, n (%)	24 (53.3)	57 (27.5)	4 (7.1)	0.103
Papulosquamous rash	3 (6.7)	9 (4.3)	1 (1.8)	

Table 2. Skin disorders in primary immunodeficiency diseases (continued)

	Pediatric patients (n=45)	Adult patients (n=207)[1]	Adult partner-controls (n=56)	*p*-value[†]
Maculopapular rash	11 (24.4)	15 (7.2)	0 (0.0)	
Papulopustular rash	6 (13.3)	15 (7.2)	1 (1.8)	
Eczematous rash	14 (31.1)	32 (15.5)	2 (3.6)	
Nail disorders, n (%)	12 (26.7)	80 (38.6)	4 (7.1)	0.005*
Non-infectious nail disorders	9 (20.0)	44 (21.3)	3 (5.4)	
Infectious nail disorders	5 (11.1)	61 (29.5)	2 (3.6)	
Paronychia	3 (6.7)	29 (14.0)	0 (0.0)	
Other nail disorders	0 (0.0)	1 (0.5)	0 (0.0)	
Psoriasis-like lesions, n (%)	1 (2.2)	20 (9.7)	1 (1.8)	0.479
Granulomatous disorders, n (%)	1 (2.2)	1 (0.5)	0 (0.0)	1.000
Acne-like lesions, n (%)	5 (11.1)	34 (16.4)	3 (5.4)	0.577
Urticaria, n (%)	6 (13.3)	29 (14.0)	0 (0.0)	0.028
Other skin disorders, n (%)	6 (13.3)	19 (9.2)	0 (0.0)	0.136

[†]Difference in prevalence of 14 main groups of skin disorders between adult patients and partner controls. *Significant after correction for multiple testing using the false discovery rate method (p=0.007). **Significant after correction for multiple testing using the Bonferroni method (p=0.003).

Table 3. Quality of life in pediatric patients with a primary immunodeficiency disease

	Pediatric patients	Range norm data[‡]
Health-related quality of life[†]		
KIDSCREEN-27 self report adolescents 12-18[a] (range 0-100), mean (SD), n=15		
Physical Well-being	41.47 (6.57)[1]*	43.84-53.30
Psychological	37.87 (2.76)*	43.94-53.72
Autonomy & Parents	52.07 (4.31)[2]	44.50-54.32
Social Support & Peers	49.02 (13.05)	44.64-54.60
School Environment	50.67 (7.72)[3]	43.73-53.15
KIDSCREEN-27 proxy children 8-11[b] (range 0-100), mean (SD), n=23		
Physical Well-being	44.57 (8.67)[4]*	47.90-57.40
Psychological	52.99 (10.90)[4]	46.93-56.51
Autonomy & Parents	59.21 (11.33)[5]**	45.93-55.59
Social Support & Peers	57.97 (9.39)[6]**	45.74-55.14
School Environment	54.42 (9.36)[6]	48.02-57.88
KIDSCREEN-27 proxy adolescents 12-18[c] (range 0-100), mean (SD), n=2		
Physical Well-being	25.22 (22.44)*	43.60-53.60
Psychological	42.08[7]*	44.05-54.15
Autonomy & Parents	45.47[7]	44.55-54.71
Social Support & Peers	49.14[7]	44.62-54.92
School Environment	35.35[7]*	43.60-53.34

Table 3. Quality of life in pediatric patients with a primary immunodeficiency disease (continued)

	Pediatric patients	Range norm data‡
TNO-AZL Preschool Children's Quality of Life (range 0-100), mean (SD), n=4		
Stomach problems	75.00 (35.36)[8]*	84.95-98.77
Skin problems	100 (0.00)[8]**	86.37-97.17
Lung problems	91.67 (16.67)	85.50-100
Sleeping problems	75.00 (19.76)	73.69-90.95
Appetite	75.00 (21.52)*	78.02-91.20
Liveliness	100 (0.00)	93.97-100
Positive mood	95.83 (8.33)	95.46-100
Problem behavior	58.93 (22.11)*	60.03-75.35
Anxiety	87.50 (25.00)**	69.33-87.33
TNO-AZL Preschool Children's Quality of Life extended version (range 0-100), mean (SD), n=3		
Social functioning	58.33 (58.93)[9]*	83.64-99.00
Motor function	75.00 (18.75)*	96.27-100
Communication	93.75 (8.49)[9]	86.72-96.60
Skin-related quality of life		
Children's Dermatology Life Quality Index (range 0-30), median (IQR), n=41	1.5 (0.0-4.0)[10]	Not available
Symptoms and feelings, median % (IQR)	16.7 (0.0-16.7)[11]	
Leisure, median % (IQR)	0.0 (0.0-0.0)[10]	
School or holidays, median % (IQR)	0.0 (0.0-33.3)[11]	
Personal relationships, median % (IQR)	0.0 (0.0-0.0)[12]	
Sleep, median % (IQR)	0.0 (0.0-0.0)[11]	
Treatment, median % (IQR)	0.0 (0.0-0.0)[10]	
Infant's Dermatitis Quality of Life Index (range 0-30), median (IQR), n=4	2.0[13]	Not available

Missing: [1]n=1 (6.7%), [2]n=3 (20.0%), [3]n=4 (26.7%), [4]n=3 (13.0%), [5]n=5 (21.7%), [6]n=1 (4.3%), [7]n=1 (50.0%), [8]n=2 (50.0%), [9]n=1 (33.3%), [10]n=3 (7.3%), [11]n=2 (4.9%), [12]n=4 (9.8%), [13]n=2 (50.0%). Note: 2 (4.9%) of the pediatric patients >3 years (n=41) did not completed the KIDSCREEN-27 questionnaire. †High scores indicate a good quality of life, low scores indicate a low quality of life. ‡Norm data thresholds for the TNO-AZL Preschool Children's Quality of Life questionnaires we were calculated using reference data of 340 Dutch children and for the KIDSCREEN-27 questionnaires using international T-values based on Rasch person parameter extracted from the KIDSCREEN questionnaires handbook, and fixed at a value of the mean minus half and plus half a standard deviation to mean.[22,24] A study population mean lower or higher than the norm data thresholds indicate a noticeable lower or better QoL, respectively, compared to the reference population. *Noticeable lower health-related quality of life compared to norm data. **Noticeable better health-related quality of life compared to the norm data. [a]Norm data based on "European Normdata KIDSCREEN females & males Adolescents 12-18".[22] [b]Norm data based on "European Normdata proxy KIDSCREEN females & males Children 8-11" .[22] [c]Norm data based on "European Normdata proxy KIDSCREEN females & males Adolescents 12-18".[22]

Adults with primary immunodeficiency disease and partner-controls

The HR-QoL of adult patients was significantly lower as compared with norm data for most of the SF-36 scales, except for emotional well-being (Table 4). The HR-QoL of partner-controls was comparable to norm data. Patients had a good SR-QoL with a median DLQI of 1.0 (IQR 0.0-3.0) (Table 4). Skin disorders had almost no influence on the HR-QoL (median NRS 1.0 (IQR 0.0-4.0)). All partner-controls had a good SR-QoL (median 0.0 (IQR 0.0-0.0)) and skin disorders had no influence on the HR-QoL (median NRS 0.0 (IQR 0.0-0.0)).

Table 4. Quality of life in adult patients with a primary immunodeficiency disease and partner-controls

	Adult patients n=207	Adult partner-controls n=56	Range norm data‡
Health-related quality of life			
Short Form 36 (range 0-100)†, mean (SD)			
Physical functioning	62.90 (30.57)[1]*	86.27 (21.09)[2]	70.30-93.50
Social functioning	59.70 (35.27)[1]*	94.58 (25.77)[3]	76.65-97.15
Role limitations due to physical health	42.08 (45.02)[4]*	79.63 (37.33)[2]	61.65-97.15
Role limitations due to emotional problems	65.82 (43.57)[5]*	88.68 (29.19)[3]	67.95-100
Emotional well-being	72.04 (18.89)[1]	76.07 (18.28)[6]	67.60-86.00
Energy/fatigue	49.88 (22.86)[1]*	71.39 (22.29)[6]	57.45-77.25
Pain	56.57 (44.53)[1]*	88.06 (21.32)[3]	66.70-92.30
General health	27.28 (18.58)[7]*	69.09 (20.69)[2]	61.35-84.05
Skin-related quality of life			
Dermatology Life Quality Index (range 0-30)†, median (IQR)	1.0 (0.0-3.0)[8]	0.0 (0.0-0.0)	Not available
Symptoms and feelings, median % (IQR)	0.0 (0.0-33.3)[8]	0.0 (0.0-0.0)	
Daily activities, median % (IQR)	0.0 (0.0-0.0)[1]	0.0 (0.0-0.0)	
Leisure, median % (IQR)	0.0 (0.0-0.0)[1]	0.0 (0.0-0.0)	
Work and school, median % (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	
Personal relationships, median % (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	
Treatment, median % (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	

Missing: [1]n=2 (1.0%), [2]n=1 (1.8%), [3]n=3 (5.4%), [4]n=5 (2.4%), [5]n=10 (4.8%), [6]n=3 (3.6%), [7]n=7 (3.4%), [8]n=3 (1.4%). †High scores indicate a good quality of life, low scores indicate a low quality of life. ‡Norm data thresholds for the Short Form 36 questionnaire were calculated using reference data of 1063 Dutch adults (mean age 44.1 years, age range 18-89 years, 65% female) and fixed at a value of the mean minus half and plus half a standard deviation.[23] A study population (adult patients or adult partner-controls) mean lower or higher than the norm data thresholds indicate a significantly lower or better QoL, respectively, compared to the reference population. *Significantly lower health-related quality of life compared to norm data.

Observational clinical study

Twenty-two adult patients were included in the observational clinical study (Figure 1 and Table 1). Most patients (95.5%) were diagnosed with a PAD. Dermatitis (57.1%), folliculitis (31.8%) and rosacea (22.7%) were the most prevalent skin disorders during physical examination (Table 5). Twenty-five (43.9%) of the 57 clinically observed skin disorders were also reported by the patients. Observed skin disorders were not specific to each of the PID diagnoses. Thirty skin lesions with possible *S. aureus*-related etiology were cultured, of which 40.0% (10 patients) were positive for *S. aureus*. Additionally, 50.0% of the 22 nose cultures were positive for *S. aureus.* After a median of 4.1 (IQR 3.1-6.0) weeks, 69.2% (7 patients) of the 12 skin cultures were still positive for *S. aureus* at the second time point.

Table 5. Case series of adult patients with a primary immunodeficiency disease and a *Staphylococcus aureus*-related skin disorder

Study number	Sex	Age, years	PID diagnosis	Reported history of skin disorders in questionnaire	Observed skin disorder	Semiquantitative *S. aureus* culture
01	Female	45	IgG_1 subclass deficiency	(Atopic) dermatitis*, seborrheic dermatitis*, hair loss scalp, papulosquamous rash*, maculopapular rash*, eczematous rash*, red spots	1. Seborrheic dermatitis scalp and face* 2. (Atypical) naevi back and mamma left 3. Xerosis cutis	Skin 1. Glabella – Nose –
02	Female	44	CVID	(Atopic) dermatitis*, seborrheic dermatitis*, oral herpes simplex infection, genital herpes simplex infection, oral ulcers, cafe au lait macula	1. Seborrheic dermatitis scalp and nasolabial* 2. Hyperpigmented macula flank left	Skin 1. Nasolabial left ++ Nose +
03	Female	58	IgG_1 and IgG_2 subclass deficiency	Dermatitis herpetiformis, hair loss scalp, eyelashes and eyebrows, hirsutism, oral candidiasis, genital candidiasis, abscesses*, folliculitis*, red spots, telangiectasia on the face, squamous cell carcinoma, maculopapular rash*, paronychia*	1. Erythrasma inguinal 2. Folliculitis upper leg left 3. Dermatitis lower arm left 4. Dermatitis/ intertrigo inframammary left	Skin 1. Inguinal right + 2. Upper leg left – 3. Lower arm left +++ Nose +
04	Male	46	SADNI	(Atopic) dermatitis*, hair loss eyelashes and eyebrows, oral candidiasis, genital candidiasis, dermal candidiasis, folliculitis*, furuncle*, perleche, nose ulcers, telangiectasia on shoulder, back or neck, cafe au lait macula, naevus > 5mm, freckles, neonatal skin rash, maculopapular rash*, papulopustular rash*, acne vulgaris	1. Erythrasma/ folliculitis inguinal left 2. Folliculitis chest, beard, pubis 3. Seborrheic dermatitis scalp 4. (Atypical) naevus back 5. Xerosis cutis	Skin 1. Inguinal left – 2. Chest left – Nose –
05	Male	50	Hyper IgE syndrome	Unknown	1. Dermatitis frontal 2. Dermatitis/ folliculitis coeur, abdominal, back, legs 3. Onychomycosis toe nails	Skin 1. Frontal – 2. Back - (*S. pin* +) Nose - (*S. pin* ++)

Table 5. Case series of adult patients with a primary immunodeficiency disease and a *Staphylococcus aureus*-related skin disorder (continued)

Study number	Sex	Age, years	PID diagnosis	Reported history of skin disorders in questionnaire	Observed skin disorder	Semiquantitative *S. aureus* culture
06	Male	42	CVID	Hypertrichosis, folliculitis*, cellulitis*, furuncle*, naevus flammeus, naevus >5mm, papulopustular rash*, onychomycosis, acne vulgaris	1. Psoriasis guttata/ dermatitis/ dermatomycosis flank left, back, arms, feet left 2. Rosacea papulopustulosa check 3. Folliculitis coeur, legs 4. (Atypical) naevi back 5. Naevi papillomatosus scalp	Skin 1. Flank right – (*S. cap* +) 2. Cheek left – Nose –
07	Female	64	IgG_2 and IgG_3 subclass deficiency	Seborrheic dermatitis*, nummular eczema*, dermatitis herpetiformis, hair loss scalp, hirsutism, bamboo hair, oral candidiasis, genital candidiasis, dermal candidiasis, varicella zoster virus infection, herpes zoster virus infection, warts, mollusca contagiosum, folliculitis*, oral ulcers, red spots, erythema nodosum, telangiectasia on eyes, cheek, nose, ears and chest, oral purpura/petechiae, hyperpigmented lesions, vitiligo, freckles, papulopustular rash*, maculopapular rash*, papulopustular rash*, eczematous rash*, onychomycosis, acute urticaria	1. Rosacea (telangiectasia/ papulopustulosa)/ folliculitis face	Skin 1. Temporal left – Nose +++
08	Female	57	CVID	Nummular eczema*, hair loss eyelashes, silver hair color, genital candidiasis, abscesses*, perleche*, telangiectasia on nose, hematomas, freckles, eczematous rash*, psoriasis, acne vulgaris, acute urticaria	1. Rosacea telangiectasia/ dermatitis periorbital 2. Furuncle	Skin 1. Periorbital left – 2. Back – Nose –
09	Female	46	Hypogamma-globulinemia	(Atopic) dermatitis*, seborrheic dermatitis*, nummular eczema*, dermatitis herpetiformis, oral candidiasis, genital candidiasis, dermal candidiasis, herpes zoster virus infection, oral herpes simplex virus infection, warts, oral ulcers, erythroderma, red spots, rosacea, telangiectasia on cheek or nose, brittle nails	1. Rosacea papulopustulosa face 2. Verruca vulgaris lower arm left 3. Dermatofibroma upper leg left	Skin 1. Cheek left + Nose –

Table 5. Case series of adult patients with a primary immunodeficiency disease and a *Staphylococcus aureus*-related skin disorder (continued)

Study number	Sex	Age, years	PID diagnosis	Reported history of skin disorders in questionnaire	Observed skin disorder	Semiquantitative *S. aureus* culture
10	Male	57	CVID	(Atopic) dermatitis*, hair loss scalp, perleche*, neonatal rash, eczematous rash*, acne vulgaris, acute urticaria	1. Dermatitis lower legs 2. Superficial basal cell carcinoma chest 3. Blue naevus hand right 4. Dermatofibroma upper arm and upper leg right	Skin 1. Tibia right – Nose –
11	Male	33	CVID	Folliculitis*, acne vulgaris	1. Folliculitis/ acne vulgaris scalp, neck, coeur, back, abdominal	Skin 1. Upper back – Nose ++
12	Female	35	IgG_4 subclass deficiency	Dermatitis herpetiformis, hair loss scalp, genital candidiasis, impetigo*, vitiligo, maculopapular rash*, papulopustular rash*	1. Ecthyma mamma right	Skin 1. Mamma right +++ Nose +
13	Female	58	IgG_1 and IgG_3 subclass deficiency	(Atopic) dermatitis*, seborrheic dermatitis*, nummular eczema*, dermatitis herpetiformis*, oral candidiasis, genital candidiasis, dermal candidiasis, varicella zoster virus infection, warts, abscesses*, folliculitis*, furuncle*, perleche*, oral ulcers, nasal ulcers, erythroderma*, red spots, erythema induratum, erythema nodosum, telangiectasia on legs, purpura/petechiae on arms and legs, naevus > 5mm, vitiligo, hypopigmented lesions, freckles, papulosquamous rash*, maculopapular rash*, papulopustular rash*, eczematous rash*, color change nails, paronychia*, onychomycosis, acne vulgaris, acute urticaria	1. Dermatitis of hands, feet and scalp	Skin 1. Palmar side hand right – Nose –
14	Female	36	SADNI	(Atopic) dermatitis*, hair loss scalp, eyelashes and eyebrows, dermal candidiasis, red spots, eczematous rash*, acute urticaria	1. Dermatitis ears 2. Alopecia areata of scalp	Skin 1. Ear right ++ 1. Ear left ++ Nose ++

Table 5. Case series of adult patients with a primary immunodeficiency disease and a *Staphylococcus aureus*-related skin disorder (continued)

Study number	Sex	Age, years	PID diagnosis	Reported history of skin disorders in questionnaire	Observed skin disorder	Semiquantitative *S. aureus* culture
15	Female	49	IgG_1 subclass deficiency	Folliculitis*, furuncle*, perleche*, oral ulcers, papulopustular rash*, onychomycosis, acne vulgaris	1. Dermatitis dorsal side hands and feet 2. Onychomycosis toe nails 3. Verruca vulgaris knee right	Skin 1. Dorsal side hand right ++ Nose –
16	Male	52	X-linked agamma-globulinemia	Warts, furuncle*, oral ulcers	1. Rosacea papulopustulosa face 2. Folliculitis abdominal 3. Orthostatic dermatitis legs	Skin 1. Nose – Nose –
17	Male	23	X-linked agamma-globulinemia	(Atopic) dermatitis*, seborrheic dermatitis*, hair loss scalp, oral candidiasis, genital candidiasis, dermal candidiasis, herpes zoster virus infection, impetigo*, folliculitis*, perleche*, erythroderma*, red spots, vitiligo, freckles, papulosquamous rash*, maculopapular rash*, papulopustular rash*, eczematous rash*, loss of toe nails, paronychia*	1. Erythroderma/ dermatitis 2. Folliculitis lower legs	Skin 1. Hand left ++++ 2. Lower leg right ++ 2. Lower leg left ++ Nose +++
18	Female	68	IgG_2 subclass deficiency	Seborrheic dermatitis*, nummular dermatitis*, red spots, eczematous rash*	1. Dermatitis face 2. Actinic keratosis frontal, lower arms, dorsal side of hands 3. Xerosis cutis	Skin 1. Frontal ++ Nose +++
19	Male	50	CVID	Skin infection tibia and inguinal*, hyperpigmented lesions, paronychia*	1. Dermatitis face 2. Postinflammatory hypo- and hyperpigmentation lower legs 3. Atrophy blanche ankles	Skin 1. Frontal – Nose ++++
20	Female	65	Hypogamma-globulinemia	(Atopic) dermatitis*, seborrheic dermatitis*, nummular eczema*, red spots, purpura/petechiae on feet, eczematous rash*, onychomycosis, loss of toe nails	1. Dermatitis scalp and face 2. Orthostatic changes legs	Skin 1. Frontal + Nose +++

Table 5. Case series of adult patients with a primary immunodeficiency disease and a *Staphylococcus aureus*-related skin disorder (continued)

Study number	Sex	Age, years	PID diagnosis	Reported history of skin disorders in questionnaire	Observed skin disorder	Semiquantitative *S. aureus* culture
21	Male	38	CVID	Abscesses*, impetigo*, telangiectasia chest, acne vulgaris	1. Folliculitis upper legs 2. Dermatitis neck and face	Skin 1. Upper leg right ++ 2. Neck left +++ Nose ++++
22	Female	29	CVID	Eczematous rash*	1. Seborrheic dermatitis scalp and face 2. Keratosis pilaris upper arms and legs	Skin 1. Frontal – Nose –

Abbreviations: CVID, common variable immunodeficiency disease; Ig, immunoglobulin; *S. cap*, *Staphylococcus capitis*; *S. pin*, *Staphylococcus pseudointermedius*; SADNI, selective antibody deficiency with normal immunoglobulins. * Skin disorders with possible *Staphylococcus aureus*-related etiology.

DISCUSSION

This study demonstrates that skin disorders, including skin infections and nail disorders, are more prevalent in children (71.1%) and adults (80.2%) with PIDs as compared with adult partner-controls (41.1%, $p<0.001$). The first skin disorder, of which (atopic) dermatitis was most commonly reported, developed 3.5 (SD 5.4) years in children and 20.3 (SD 20.5) years in adults before the PID diagnosis.

This is the first study evaluating the nature and prevalence of skin disorders in a mainly Caucasian population of both pediatric and adult patients with PIDs, of which the majority had a PAD. Our findings regarding the prevalence of skin disorders in PIDs are in accordance with a systematic review on skin manifestations in PIDs, which included mainly data from Middle-Eastern countries.[7] However, our population reported more often viral and bacterial skin infections, erythematous skin lesions and skin rashes.

Surprisingly, current literature appointed eczematous dermatitis as common finding and presenting clinical manifestation among PIDs.[26] Although a high frequency of (atopic) dermatitis was reported in PID patients included in this study, the prevalence in adult patients was not significantly different from the prevalence in partner-controls (29.5% vs. 25.0%, respectively) and even less adult patients reported (atopic) dermatitis as first developed skin disorder compared with partner-controls (15.0% vs. 52.2%, respectively). Moreover, the prevalence of a history of (atopic) dermatitis in both adult patients and partner-controls included in this study corresponds to the lifetime prevalence of atopic dermatitis in the Dutch population, which is up to 25% in children and 1-7% in adults.[27,28] Therefore, we feel that (atopic) dermatitis is not a specific skin condition related to PIDs and hypothesize that (a combination of) other skin disorders, like skin infections and nail disorders, are more useful in recognizing a possible underlying PID, additional to the presence of warning signs for PIDs.[19]

Recognition of PID-associated skin disorders might shorten the diagnostic delay of PIDs, which is 3.2 (SD 3.7) years in pediatric and 15.9 (SD 17.7) years in adult patients from the first classical PID symptom, such as respiratory tract infections, and even 3.5 (SD 5.4, $p=0.96$) and 20.3 (SD 20.5, $p=0.23$) years, respectively, from the first cutaneous manifestation. Although the first skin disorder did not precede the first classical PID symptom in pediatric patients for years, this was most likely due to the limited range of age in this population and because in particular PIDs with a long diagnostic delay are diagnosed in adulthood. Moreover, skin disorders might be a useful diagnostic feature in PIDs as patients with a PID appear to develop skin disorders at a younger age compared with people without a PID (adult patients reported their first skin disorder at the age of 20.9 (SD 22.0) years

and partner-controls at 33.7 (SD 26.6) years (p=0.02)). To further explore the usefulness of skin symptoms as warning signs of PIDs, registration of skin disorders on an international basis, for example in the PID database of The European Society for Immunodeficiencies registry, is recommended.

The influence of skin disorders on the HR-QoL was minimal; patients reported in general a lower HR-QoL than norm data and partner-controls, and a good SR-QoL. Other PID-related complaints and symptoms, like fatigue and infections, possibly have a greater influence on the HR-QoL than skin symptoms. Nonetheless, the HR-QoL could indirectly be positively influenced through reducing the diagnostic delay by early recognition of PID-associated skin disorders.[12]

The skin disorders diagnosed during physical examination of 22 adult patients were partly overlapping with those who were reported in the questionnaire. Skin cultures indicated 30.0% of the skin lesions that were persistent colonized with *S. aureus*; seven cultures from a dermatitis lesion, one from ecthyma, and one from folliculitis. The prevalence of lesional and nasal *S. aureus* carriage in patients with PIDs and skin disorders with possible *S. aureus*-related etiology was slightly lower than single culture data of patients with atopic dermatitis, but higher as compared with partner-controls.[11] In a recent study examining the skin microbiome in three rare monogenic PIDs colonization with *S. aureus* was found to be significantly correlated with skin disease severity.[29] Therefore, identification of PID-associated skin disorders with an increased risk of *S. aureus* colonization is necessary as patients with these PIDs could benefit from *S. aureus*-targeting treatments.[30,31]

This study has some limitations. Firstly, the majority of patients (86.6%) had a PAD according to the 2017 IUIS classification, which is in accordance with previous national and international studies.[18,25,32-35] Due to the skewed phenotype distribution and limited numbers of patients with rare PIDs we were not able to present data of skin disorders per specific PID (category) as shown in a systematic review.[7] Secondly, the responder population of adult patients was skewed with regard to age. This might have resulted in a self-selection bias and a subsequent overestimation of the prevalence of skin disorders in PIDs in this study as patients with a skin disorder were more likely to respond to the questionnaire. Lastly, in the observational clinical study we only cultured *S. aureus*, as most common skin pathogen in PIDs. However, an increased representation of the bacteria *Serratia macescens* and *Clostridium* species as well as the opportunistic fungi *Candida* and *Aspergillus* was also found in the skin microbiome of patients with PIDs, which indicates the need for more extensive study of the microbiome.[29] Nonetheless, these microorganisms were not correlated with skin disease severity and, therefore, antimicrobial treatment targeting these microorganisms may not be beneficial.

In conclusion, this questionnaire-based and observational clinical study shows that skin disorders are more prevalent and develop at an earlier age in patients with PIDs as compared with partner-controls. Reduction of the diagnostic delay could be achieved by recognition of non-dermatitis-like skin disorders, like skin infections and/or nail disorders, in combination with the warning signs for PIDs. Therefore, more awareness and detailed registration of skin disorders on an international basis is recommended in order to improve the diagnostic and therapeutic processes in patients with PIDs. Additionally, collection of large numbers of data within homogeneous groups of patients might result in identification of skin disorders specific per PID.

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SUPPLEMENTARY MATERIAL

Appendix 1. Quality of life outcome measurements

HR-QoL was assessed using the TNO-AZL Preschool Children's Quality of Life questionnaire (TAPQOL) for patients <4 years, KIDSCREEN-27 by parents for patients 4-11 years, KIDSCREEN-27 by child for patients 12-17 years, and Short Form 36 (SF-36) for adults. The skin-related QoL (SR-QoL) was measured using Infant's Dermatitis Quality of Life Index (IDQOL) for patients <4 years, Children's Dermatology Life Quality Index (CDLQI) for patients 4-17 years, and the Dermatology Life Quality Index (DLQI) for adults. The influence of the skin disorder on the HR-QoL was assessed using an 11-point Numeric Rating Scale (NRS).

Appendix 2. Detailed sample and laboratory procedures

Sampling procedures were based on the 'Manual of Procedures' for microbiome sampling of the Human Microbiome Project.[1] All samples were obtained by a clinical study physician wearing gloves. Sterile Copan 490CE.A swabs were used to sample the lesional skin and anterior nasal cavity. The skin surface was swabbed during 30 seconds. The mucosal surfaces of both the anterior nares were gently rubbed going round the area during 10 seconds. The swabs were sent to the laboratory at the day of collection using mail. Bacterial cultures were performed using routine diagnostic culture procedures, using blood agar plates and specific S. aureus culture plates (ChromID S. aureus Elite agar (SAIDE), Biomérieux, France) for overnight incubation at 37 °. Subsequently, species were determined by MALDI-TOF (Bruker Daltonics, Bremen, Germany).

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Appendix 3. Reference population KIDSCREEN-27

Norm data thresholds for all scales were based on the KIDSCREEN-27 instructions and fixed at a value of the mean minus half and plus half a standard deviation. A study population mean that was lower or higher than the norm data thresholds was considered as noticeable or significant (depending on study population sample size ≤50 or >50) lower or better QoL, respectively, compared to the reference population.[22]

Table S1. Skin disorders in primary immunodeficiency diseases

	Pediatric patients (n=45)	Adult patients (n=207)[1]	Adult partner-controls (n=56)
Dermatitis-like lesions, n (%)	24 (53.3)	97 (46.9)	17 (30.4)
(Atopic) dermatitis	22 (48.9)	61 (29.5)	14 (25.0)[2]
Seborrheic dermatitis	7 (15.6)	27 (13.0)	1 (1.8)[2]
Nummular eczema	8 (17.8)	22 (10.6)	1 (1.8)[2]
Dermatitis herpetiformis	9 (20.0)	24 (11.6)	2 (3.6)[2]
Other dermatitis-like lesions	0 (0.0)	17 (8.2)	4 (7.1)[2]
Hair abnormalities, n (%)	5 (11.1)	55 (26.6)	5 (8.9)[2]
Hair loss disorders	3 (6.7)	45 (21.7)	4 (7.1)[2]
Hair loss scalp	3 (6.7)	32 (15.5)[3]	4 (7.1)[2]
Hair loss eyelashes and eyebrows	2 (4.4)	11 (5.3)[3]	0 (0.0)[2]
Other	0 (0.0)	4 (1.9)[3]	0 (0.0)[2]
Excessive hair growth disorders	1 (2.2)	15 (7.2)	2 (3.6)[2]
Hypertrichosis	1 (2.2)	7 (3.4)[4]	1 (1.8)[2]
Hirsutism	1 (2.2)	11 (5.3)[4]	1 (1.8)[2]
Other	0 (0.0)	0 (0.0)[4]	0 (0.0)[2]
Hair pigmentation disorders	0 (0.0)	13 (6.3)	0 (0.0)[2]
Local depigmentation	0 (0.0)	5 (2.4)	0 (0.0)[2]
Silvery hair	0 (0.0)	6 (2.9)	0 (0.0)[2]
Other	0 (0.0)	2 (1.0)	0 (0.0)[2]
Other hair abnormalities	0 (0.0)	1 (0.5)	0 (0.0)[2]
Bamboo hair	0 (0.0)	1 (0.5)	0 (0.0)[2]
Skin infections, n (%)	29 (64.4)	127 (61.4)	10 (17.9)
Fungal skin infections	11 (24.4)	62 (30.0)	5 (8.9)
Oral fungal infection	8 (17.8)	38 (18.4)[4]	2 (3.6)
Genital fungal infection	3 (6.7)	37 (17.9)[4]	3 (5.4)
Cutaneous fungal infection	4 (8.9)	40 (19.3)[4]	4 (7.1)
Other	1 (2.2)	1 (0.5)[4]	0 (0.0)
Viral skin infections	24 (53.3)	84 (40.6)	3 (5.4)
Varicella zoster virus infection	21 (46.7)	21 (10.1)	1 (1.8)
Herpes zoster virus infection	3 (6.7)	32 (15.5)	2 (3.6)
Oral herpes simplex infection	4 (8.9)	32 (15.5)	0 (0.0)
Genital herpes simplex infection	0 (0.0)	16 (7.7)	0 (0.0)
Warts	11 (24.4)	45 (21.7)	0 (0.0)
Molluscum contagiosum	13 (28.9)	15 (7.2)	0 (0.0)
Other	0 (0.0)	1 (0.5)	0 (0.0)
Bacterial skin infections	15 (33.3)	66 (31.9)	1 (1.8)
Abscesses	4 (8.9)	25 (12.1)	0 (0.0)
Impetigo	7 (15.6)	12 (5.8)	0 (0.0)

Table S1. Skin disorders in primary immunodeficiency diseases (continued)

	Pediatric patients (n=45)	Adult patients (n=207)[1]	Adult partner-controls (n=56)
Folliculitis	3 (6.7)	38 (18.4)	1 (1.8)
Cellulitis	0 (0.0)	8 (3.9)	0 (0.0)
Furuncle	3 (6.7)	28 (13.5)	0 (0.0)
Other	1 (2.2)	4 (1.9)	0 (0.0)
Other skin infections	8 (17.8)	38 (18.4)	1 (1.8)
Perleche	8 (17.8)	38 (18.4)	1 (1.8)
Other	1 (2.2)	5 (2.4)	0 (0.0)
Ulcers, n (%)	16 (35.6)	53 (25.6)	2 (3.6)
Oral ulcers	16 (35.6)	47 (22.7)	2 (3.6)
Nasal ulcers	2 (4.4)	14 (6.8)	0 (0.0)
Other ulcers	0 (0.0)	3 (1.4)	0 (0.0)
Ecthyma	0 (0.0)	0 (0.0)	0 (0.0)
Erythematous skin lesions, n (%)	5 (11.1)	45 (21.7)	2 (3.6)
Erythroderma	1 (2.2)	11 (5.3)	1 (1.8)
Red spots	3 (6.7)	28 (13.5)	2 (3.6)
Erythema induratum	1 (2.2)	3 (1.4)	1 (1.8)
Erythema nodosum	0 (0.0)	3 (1.4)	1 (1.8)
Other	1 (2.2)	12 (5.8)	0 (0.0)
Vascular disorders, n (%)	7 (15.6)	50 (24.2)	2 (3.6)
Telangiectasia	3 (6.7)	32 (15.5)	2 (3.6)
Telangiectasia on eyes	2 (4.4)	4 (1.9)	0 (0.0)
Telangiectasia on cheeks and/or nose	1 (2.2)	21 (10.1)	0 (0.0)
Telangiectasia on ears	0 (0.0)	0 (0.0)	0 (0.0)
Telangiectasia on shoulders, back and/or neck	0 (0.0)	4 (1.9)	0 (0.0)
Telangiectasia on total body	0 (0.0)	2 (1.0)	0 (0.0)
Other	1 (2.2)	10 (4.8)	1 (1.8)
Vasculitis	2 (4.4)	9 (4.3)	0 (0.0)
Allergic vasculitis	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (2.2)[4]	9 (4.3)	0 (0.0)
Petechia/purpura	2 (4.4)	12 (5.8)	0 (0.0)
Oral petechia/purpura	0 (0.0)	2 (1.0)	0 (0.0)
Other	2 (4.4)	10 (4.8)	0 (0.0)
Other vascular disorders	0 (0.0)	7 (3.4)	1 (1.8)
Pigmentation disorders, n (%)	15 (33.3)	73 (35.3)	4 (7.1)
Hyperpigmentation disorders	13 (28.9)	45 (21.7)	3 (5.4)
Cafe au lait maculae	6 (13.3)	18 (8.7)	1 (1.8)
Naevus >5mm	8 (17.8)	23 (11.1)	2 (3.6)
Acanthosis nigricans	0 (0.0)	4 (1.9)	0 (0.0)

Table S1. Skin disorders in primary immunodeficiency diseases (continued)

	Pediatric patients (n=45)	Adult patients (n=207)[1]	Adult partner-controls (n=56)
Other	1 (2.2)	11 (5.3)	0 (0.0)
Hypopigmentation disorders	4 (8.9)	25 (12.1)	1 (1.8)
Vitiligo	0 (0.0)	21 (10.1)	0 (0.0)
Albinism	0 (0.0)	0 (0.0)	0 (0.0)
Halo naevus	0 (0.0)	2 (1.0)	0 (0.0)
Hypopigmented spots	4 (8.9)	3 (1.4)	0 (0.0)
Other	0 (0.0)	0 (0.0)	1 (1.8)
Other pigmentation disorders	7 (15.6)	22 (10.6)	0 (0.0)
Blue naevus	0 (0.0)	1 (0.5)	0 (0.0)
Freckles	7 (15.6)	22 (10.6)	0 (0.0)
Other	0 (0.0)	2 (1.0)	0 (0.0)
Neoplastic disorders, n (%)	0 (0.0)	20 (9.7)	3 (5.4)
Cutaneous lymphoma	0 (0.0)	1 (0.5)	0 (0.0)
Basal cell carcinoma	0 (0.0)	10 (4.8)	1 (1.8)
Squamous cell carcinoma	0 (0.0)	4 (1.9)	0 (0.0)
Melanoma	0 (0.0)	2 (1.0)	1 (1.8)
Other neoplastic disorders	0 (0.0)	6 (2.9)	1 (1.8)
Rash, n (%)	24 (53.3)	57 (27.5)	4 (7.1)
Newborn rash	6 (13.3)	6 (2.9)	0 (0.0)
Papulosquamous rash	3 (6.7)	9 (4.3)	1 (1.8)
Maculopapular rash	11 (24.4)	15 (7.2)	0 (0.0)
Papulopustular rash	6 (13.3)	15 (7.2)	1 (1.8)
Eczematous rash	14 (31.1)	32 (15.5)	2 (3.6)
Other	2 (4.4)	10 (4.8)	0 (0.0)
Nail disorders, n (%)	12 (26.7)	80 (38.6)	4 (7.1)
Non-infectious nail disorders	9 (20.0)	44 (21.3)	3 (5.4)
Congenital nail disorders	2 (4.4)	2 (1.0)	0 (0.0)
Acquired nail disorders	2 (4.4)	11 (5.3)	2 (3.6)
Thickening	3 (6.7)	24 (11.6)	1 (1.8)
Other	5 (11.1)	20 (9.7)	1 (1.8)
Infectious nail disorders	5 (11.1)	61 (29.5)	2 (3.6)
Paronychia	3 (6.7)	29 (14.0)	0 (0.0)
Onychomycosis	3 (6.7)	39 (18.8)	2 (3.6)
Other	0 (0.0)	3 (1.4)	0 (0.0)
Other nail disorders	0 (0.0)	1 (0.5)	0 (0.0)
Psoriasis-like lesions, n (%)	1 (2.2)	20 (9.7)	1 (1.8)
Psoriasis	0 (0.0)[5]	17 (8.2)	1 (1.8)
Other psoriasis like-lesions	0 (0.0)[5]	2 (1.0)	0 (0.0)

Table S1. Skin disorders in primary immunodeficiency diseases (continued)

	Pediatric patients (n=45)	Adult patients (n=207)[1]	Adult partner-controls (n=56)
Granulomatous disorders, n (%)	1 (2.2)	1 (0.5)	0 (0.0)
Acne-like lesions, n (%)	5 (11.1)	34 (16.4)	3 (5.4)
Neonatal acne	2 (4.4)	1 (0.5)	0 (0.0)
Acne	4 (8.9)	34 (16.4)	3 (5.4)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Urticaria, n (%)	6 (13.3)	29 (14.0)	0 (0.0)
Acute urticaria	4 (8.9)	16 (7.7)[4]	0 (0.0)
Chronic urticaria	1 (2.2)	6 (2.9)[4]	0 (0.0)
Cold induced urticaria	0 (0.0)	3 (1.4)[4]	0 (0.0)
Other	2 (4.4)	7 (3.4)	0 (0.0)
Other skin disorders, n (%)	6 (13.3)	19 (9.2)	0 (0.0)

Missing: [1]n=3 (1.4%), [2]n=1 (1.8%), [3]n=8 (3.9%), [4]n=4 (1.9%), [5]n=1 (4.5%).