

Supplementary Table 4. Subgroup analyses of clinical manifestations at presentation vs overall clinical manifestations during the disease course compared to population lifetime prevalence.

	At or before diagnosis		Overall		General population prevalence
Manifestation	Pooled proportion (95% CI)	I ²	Pooled proportion (95% CI)	I ²	Lifetime prevalence percentage estimates from various sources
Clinical phenotype^a					
Infections only	93 (78-100)	74	48 (39-58)	93	n/a
Autoimmunity	19 (11-28)	81	27 (22-32)	91	3.9% (1)
Polyclonal lymphocytic infiltration	n/a	n/a	29 (22-37)	92	<<1%
Enteropathy	n/a	n/a	9 (6-13)	86	<<1%
Lymphoid malignancy	2 (0-4)	0	5 (3-7)	81	2.1 + 0.2 = 2.3% (2)
Malignancy	4 (1-8)	0	10 (7-14)	87	39.5 (2)
Respiratory involvement					
Otitis	39 (28-49)	88	43 (35-51)	86	n/a ^b
Sinusitis	59 (47-71)	93	67 (57-77)	95	11.2% (3)
Upper respiratory tract infections	73 (53-89)	96	84 (75-92)	89	n/a ^b
Pneumonia	57 (43-69) ^c	94	62 (54-70) ^d	92	n/a ^b
Bronchitis	57 (42-72)	92	62 (44-78)	97	n/a ^b
Lower respiratory tract infections	73 (56-86)	85	78 (64-90)	84	n/a
Bronchiectasis	28 (18-40)	91	32 (26-38)	93	0.27% (4)
Lymphocytic interstitial pneumonia	n/a	n/a	3 (1-5)	40	n/a
GLILD	n/a	n/a	15 (7-25)	96	n/a
Lymphoid hyperplasia ^e	n/a	n/a	10 (5-17)	91	n/a
Asthma	31 (3-69)	92	25 (17-35)	94	13.6% (3)
Allergic rhinitis	36 (9-68)	82	18 (8-31)	95	6.6% (5)
Idiopathic lung fibrosis	n/a	n/a	12 (1-30)	92	0.01% (6)
Emphysema	4 (1-10)	0	4 (1-10)	0	1.3% (3)
Pulmonary lobe resection	5 (3-8)	0	5 (3-8)	0	n/a
Respiratory tract infections	86 (62-99)	94	92 (78-99)	93	n/a
Lung cancer	n/a	n/a	1 (0-1)	44	6.3% (2)
Allergy	16 (0-63)	96	33 (13-56)	94	4.6 (7)
Mastoiditis	8 (3-16)	0	3 (1-7)	64	<0.1% (1.2/10,000 child years) (8)
Interstitial lung disease	n/a	n/a	13 (6-23)	88	n/a
Lung nodules	n/a	n/a	3 (1-6)	53	n/a
Pharyngitis/tonsillitis	n/a	n/a	18 (12-24)	68	n/a ^b
Conjunctivitis	14 (6-25)	73	10 (5-16)	87	n/a ^b
COPD	n/a	n/a	34 (14-58)	61	1.7% (9)
Gastrointestinal involvement					
Chronic diarrhea of unknown origin	21 (11-34)	92	27 (21-34)	88	4-5% (10)
Gastrointestinal tract infection	29 (15-44) ^f	72	29 (21-38) ^g	92	n/a ^b
Intestinal granulomatosis	n/a	n/a	1 (0-4)	81	<<0.01%
Inflammatory bowel disease	11 (3-23)	59	10 (6-16)	90	0.71% (1)
Crohn's disease	n/a	n/a	3 (2-4)	0	0.23% (1)
Ulcerative colitis	n/a	n/a	2 (1-3)	0	0.48% (1)
Lymphocytic colitis	n/a	n/a	9 (4-16)	0	n/a

Eosinophilic inflammation	n/a	n/a	5 (2-10)	0	<<1% (11)
Celiac disease	1 (0-4)	23	3 (2-4)	25	0.06% (1)
Villous atrophy ^h	n/a	n/a	11 (1-28)	83	n/a
Atrophic gastritis	n/a	n/a	5 (3-9)	62	n/a (12)
Protein losing enteropathy	n/a	n/a	1 (0-3)	0	<<1% (13)
Stomach cancer	n/a	n/a	2 (1-4)	61	0.8% (2)
Colorectal cancer	n/a	n/a	1 (0-2)	40	4.2% (2)
Gastro-esophageal reflux disease	n/a	n/a	16 (8-25)	84	22.2% (14)
Gastritis	n/a	n/a	28 (22-35)	17	n/a
Peritonitis	3 (1-8)	0	4 (1-8)	0	<<1%
Malabsorption	n/a	n/a	13 (4-26)	96	n/a
Glandular tissue					
Sjogren's syndrome	13 (2-25)	67	3 (1-6)	86	0.06% (1)
Breast cancer	n/a	n/a	1 (1-2)	39	12.9% (2)
Cervix cancer	n/a	n/a	1 (1-2)	0	0.6% (2)
Uterine cancer	n/a	n/a	1 (0-2)	28	3.1% (2)
Hepatic involvement					
Autoimmune hepatitis	n/a	n/a	4 (0-10)	89	0.045% (1)
Primary biliary cirrhosis	n/a	n/a	2 (1-3)	39	<<1%
Unexplained hepatomegaly	n/a	n/a	14 (8-72)	93	<<1%
Viral hepatitis	n/a	n/a	4 (2-6)	64	n/a
Liver granuloma	n/a	n/a	3 (1-6)	68	n/a
Liver cirrhosis	n/a	n/a	4 (1-9)	0	n/a
Liver cancer	n/a	n/a	1 (0-1)	44	1% (2)
Hepatitis (not further specified)	n/a	n/a	4 (0-12)	94	n/a
Urinary tract involvement					
Urinary tract infection	14 (5-25)	83	14 (11-18)	66	30% (female 50%, male 12%) (15)
Pyelonephritis	n/a	n/a	8 (0-22)	77	2% (15)
Hematologic involvement					
Idiopathic thrombocytopenia	6 (4-9)	20	10 (7-14)	84	0.045% (1)
Autoimmune cytopenia	10 (7-14)	0	13 (10-17)	86	n/a
Autoimmune hemolytic anemia	3 (2-5)	0	6 (4-8)	77	0.013% (1)
Autoimmune neutropenia	3 (0-9)	48	4 (2-6)	68	<<0.1% (16)
Unknown/other neutropenia	n/a	n/a	6 (3-10)	86	<<0.1% (16)
Evans syndrome	n/a	n/a	2 (1-2)	0	<<0.1% (17)
Iron deficiency anemia	n/a	n/a	10 (2-22)	97	12.2% (18) ⁱ
Pernicious anemia	n/a	n/a	3 (1-5)	84	0.05% (1)
Bloodstream infection	8 (4-13)	77	9 (5-13)	85	1.2% (19)
Neurological involvement					
Headache/migraine	n/a	n/a	17 (n/a)	n/a	15.9% (20)
Infectious meningitis	5 (3-9) ^j	76	7 (5-9) ^k	62	0.3% (21)
Myasthenia gravis	n/a	n/a	0 (0-1)	47	0.018% (1)
Multiple sclerosis	n/a	n/a	0 (0-1)	22	0.19% (1)
Bell's palsy	n/a	n/a	1 (0-2)	52	0.6% (22)
Polyneuropathy	n/a	n/a	3 (1-6)	64	1% (23)
Epilepsy	n/a	n/a	6 (2-11)	71	10% (24)
Bone and joint involvement					

Septic arthritis	2 (1-4)	0	4 (1-8)	72	0.15% (25)
Rheumatoid arthritis	4 (1-10)	70	3 (2-4)	42	0.5% (1)
Seronegative arthritis	6 (2-12)	21	4 (2-7)	74	21.4% (26)
Juvenile idiopathic arthritis	n/a	n/a	1 (0-4)	82	0.073% (1)
Psoriatic arthritis	n/a	n/a	0 (0-1)	47	n/a
Osteomyelitis	4 (1-9)	16	4 (1-8)	83	1.7% (27)
Multiple myeloma	n/a	n/a	0 (0-1)	0	n/a
Kaposi's sarcoma	n/a	n/a	0 (0-1)	0	n/a
Osteoporosis/osteopenia	n/a	n/a	10 (1-25)	92	27% (28)
Lymph node and spleen involvement					
Lymphadenopathy	27 (0-90)	96	30 (20-42)	96	64% (29)
Non-malignant lymphoproliferation	n/a	n/a	28 (16-40)	94	n/a
Splenomegaly	13 (5-23)	90	29 (22-37)	94	2% (30)
Non-hodgkin's lymphoma	n/a	n/a	4 (3-5)	56	2.1% (2)
Splenectomy	3 (1-6)	0	6 (3-8)	57	n/a
Pancreatic cancer	n/a	n/a	2 (0-7)	57	1.6% (2)
Leukemia	n/a	n/a	1 (1-2)	22	1.5% (2)
Granuloma in lymph node	n/a	n/a	2 (0-5)	80	n/a
Granuloma in spleen	n/a	n/a	1 (0-2)	24	n/a
Granuloma in bone marrow	n/a	n/a	0 (0-1)	0	n/a
Endocrinological involvement					
Thyroid disease (all)	16 (0-43)	92	9 (4-16)	95	12% (31)
Autoimmune thyroiditis	3 (0-8)	68	4 (2-6)	80	0.058% (1)
Diabetes mellitus	2 (0-7)	0	2 (1-3)	18	0.9% (type 1) (1)
Thyroid cancer	n/a	n/a	1 (0-3)	68	1.3% (2)
Muco/cutaneous involvement					
Psoriasis	n/a	n/a	3 (2-5)	38	0.32% (1)
Atopic dermatitis	12 (4-24)	0	12 (7-18)	86	2.1-4.9% (32)
Alopecia	n/a	n/a	3 (2-4)	0	0.031% (1)
Vitiligo	2 (1-5)	0	5 (3-8)	81	0.022% (1)
Warts	n/a	n/a	5 (4-7)	0	n/a
Skin cancer	n/a	n/a	3 (1-5)	70	20% (33)
Skin infections	10 (6-15)	43	13 (10-17)	59	n/a
Cutaneous abscesses	3 (1-6)	17	5 (2-10)	79	n/a
(Recurrent) herpes zoster	n/a	n/a	9 (5-14)	84	23.8% (34)
(Recurrent) herpes simplex	n/a	n/a	9 (2-10)	89	38.3% (35)
Oral candidiasis	3 (1-5)	0	6 (2-11)	91	n/a
Genital candidiasis	n/a	n/a	6 (3-12)	0	30-50% (36)
Urticaria	n/a	n/a	5 (3-8)	71	11.5% (37)
Oral/dental infections	10 (3-21)	0	4 (3-6)	5	n/a
Skin granuloma	n/a	n/a	1 (0-2)	41	n/a
Severe varicella	n/a	n/a	4 (2-7)	0	n/a
Recurrent parotitis	n/a	n/a	6 (0-3)	93	n/a
Clubbing	n/a	n/a	19 (0-73)	97	n/a
Aphthous lesions	n/a	n/a	16 (5-31)	77	0.1-1.2% (38)
Other clinical manifestations					
Growth retardation/weight loss	8 (1-22)	82	13 (7-22)	87	n/a
Unexplained granuloma	5 (4-7)	0	12 (9-16)	79	n/a
Vasculitis	n/a	n/a	2 (1-3)	44	n/a

Systemic lupus erythematosus	2 (0-6)	28	1 (1-2)	48	0.048% (1)
Asymptomatic	6 (2-11)	74	n/a	n/a	n/a

^aAccording to Chapel et al. (39)

^bThe lifetime prevalence of respiratory and gastrointestinal tract infections is also high in the general population and may lack any discriminating value, unless their unusually recurrent and persistent nature is recognized. Because of the absence of data on the number of infectious episodes in the included studies, population lifetime prevalence percentages are not shown.

^c*Streptococcus pneumoniae* 11% (6-19), *Haemophilus influenzae* 17% (0-49), mycobacterial infection 5% (2-8).

^d*Streptococcus pneumoniae* 15% (8-23), *Haemophilus influenzae* 19% (8-33), *Moraxella Catharalis* 7% (0-19), *Staphylococcus aureus* 7% (3-12), Mycobacterial infection 1% (0-2), *Pneumocystis Jiroveci* 1% (0-2), *Pseudomonas* 6% (2-10), *Aspergillus* 3% (1-5), Enterobacteriaceae 6% (2-13), *Mycoplasma* 2% (0-4).

^eNot only pulmonary.

^f*Giardia intestinalis* 11% (3-22), *Salmonella* species 6% (3-11).

^g*Giardia intestinalis* 13% (7-21), *Salmonella* species 6% (2-12), *Campylobacter* species 4% (1-8), *Clostridium difficile* 2% (1-3), cytomegalovirus 2% (0-7), *Cryptosporidium* species 1% (0-2), *Helicobacter pylori* 9% (3-18), *Escherichia coli* 8% (4-13), *Candida* species 10% (4-19), Strongyloidiasis 7% (3-13).

^hHistologic findings of villous atrophy are similar to those found in patients with celiac disease, but with some differences; in CVID plasma cells are absent from the intestinal lamina propria, and the crypt epithelium is not hyperplastic.

ⁱPrevalence, not lifetime prevalence.

^j*Streptococcus pneumoniae* 3% (2-6), *Haemophilus influenzae* 1% (0-3).

^k*Streptococcus pneumoniae* 3% (2-6), *Haemophilus influenzae* 1% (0-3).

Abbreviations: COPD, chronic obstructive pulmonary disease; GLILD, Granulomatous-lymphocytic interstitial lung disease; n/a, not applicable.

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