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EARLY CHILDHOOD THYMECTOMY - IMPACT ON IMMUNE FUNCTION

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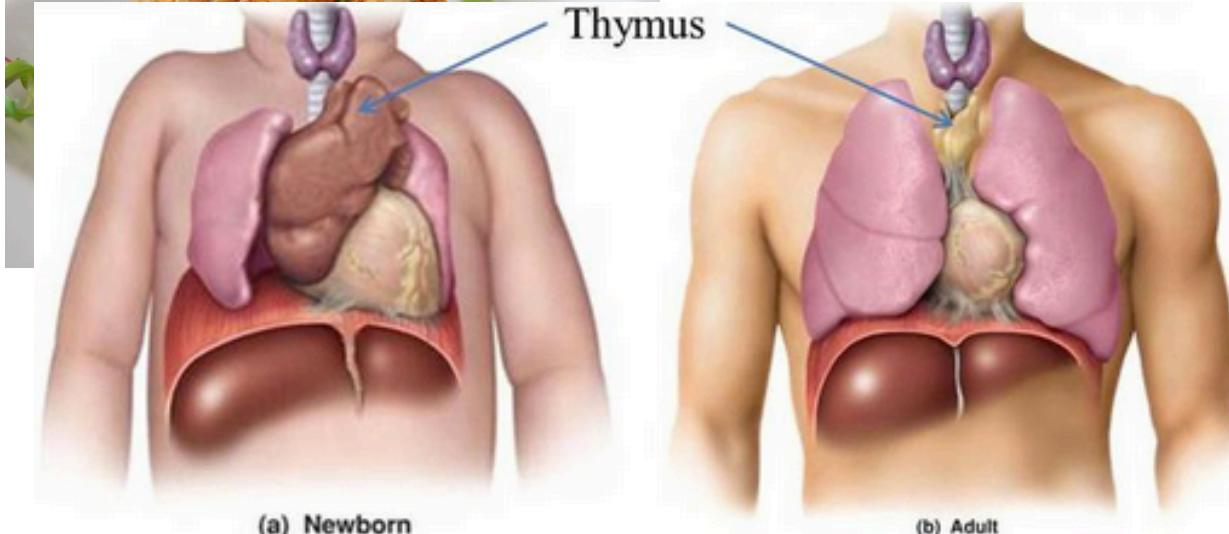
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Thymus



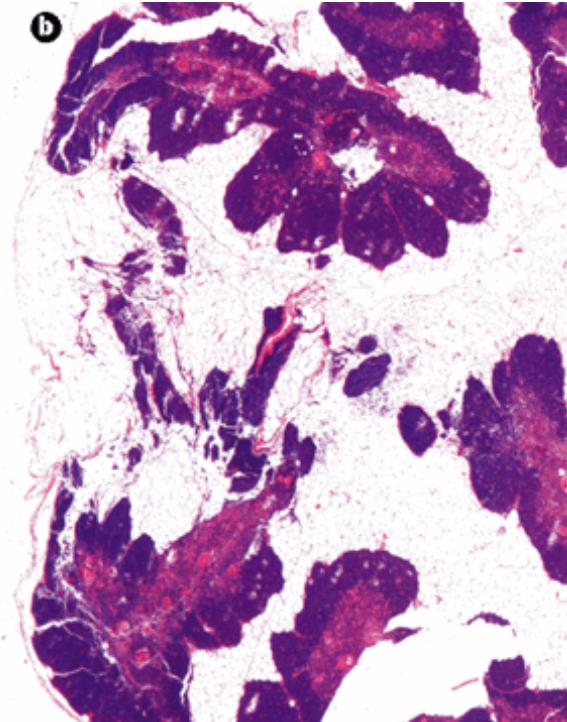
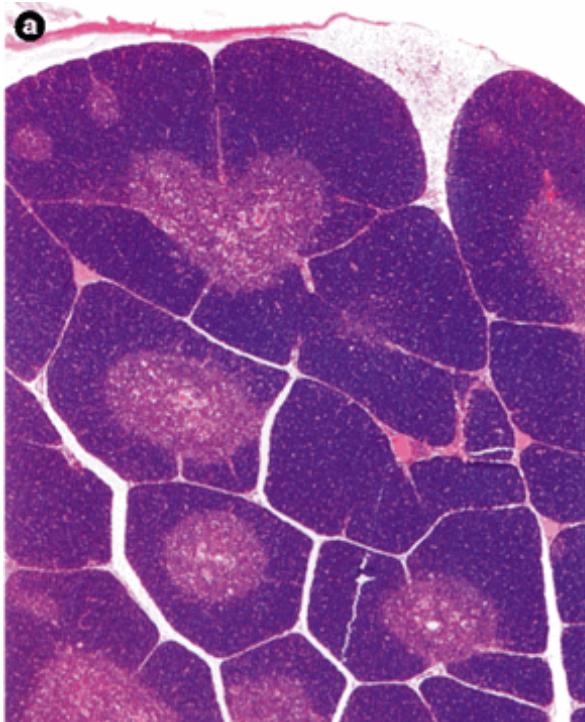
(a) Newborn

(b) Adult



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Thymic involution



©Geneser, F. *Color Atlas of Histology* 1985



Early thymectomy

- 1% of all children born with a congenital heart defect
 - 1/3 undergoes open heart surgery
- Thymus removed to facilitate surgical access
 - 250 each year
- Thymus central for T cell maturation
 - Impact of thymectomy on immune function?



What should we do with this extra part?



Aim: to investigate the immunologic and clinical long-term impact of early childhood thymectomy

- **Thymectomy (n=11)**
 - total thymectomy
 - before 6 months of age
 - analyses
 - before surgery
 - 18 months
 - 18 years
- **Controls (n=11)**
 - age and gender matched

Hjärt Lungfonden



”Barnen med hjärtfel
behöver forskning”

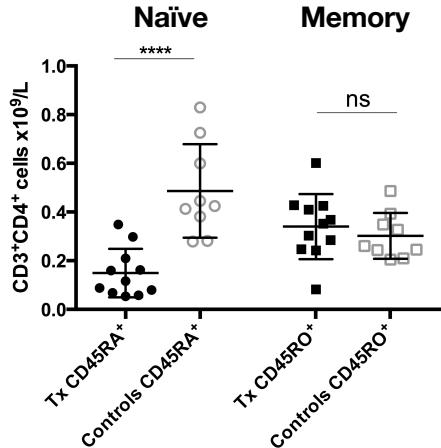
Ledande experter om värden av barn med hjärtfel
och vikten av forskning kring medfödda hjärtfel

Hjärt-Lungfonden, den 14 februari 2012

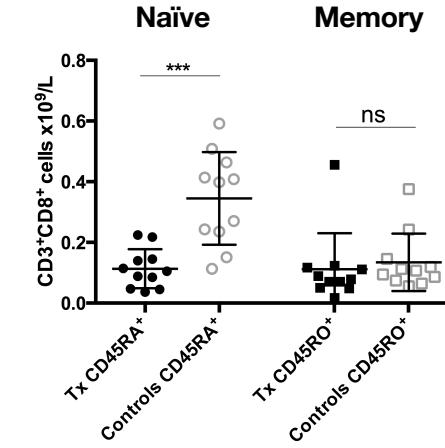
Thymectomy

- Analyses
 - Lymphocyte subpopulations

CD4⁺ T cell number



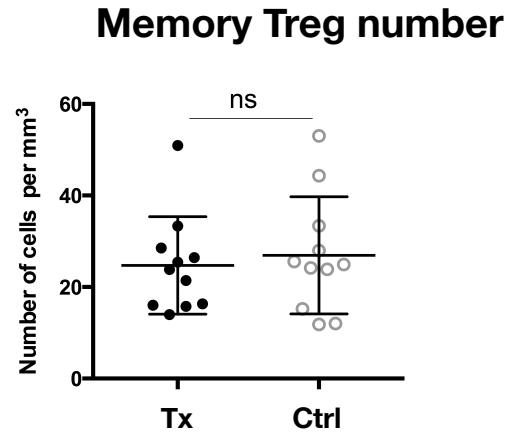
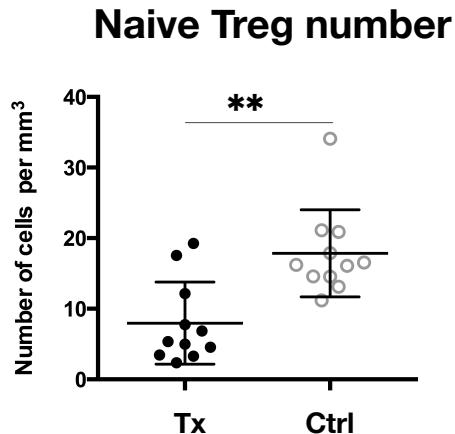
CD8⁺ T cell number



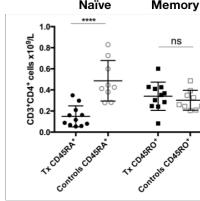


Thymectomy

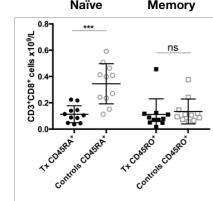
- Analyses
 - Lymphocyte subpopulations



CD4⁺ T cell number



CD8⁺ T cell number

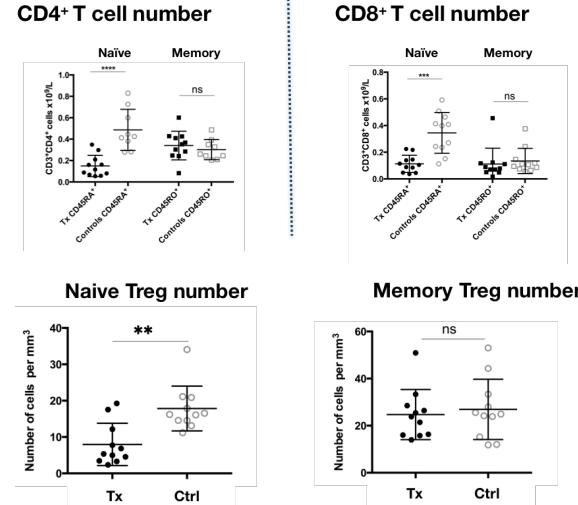
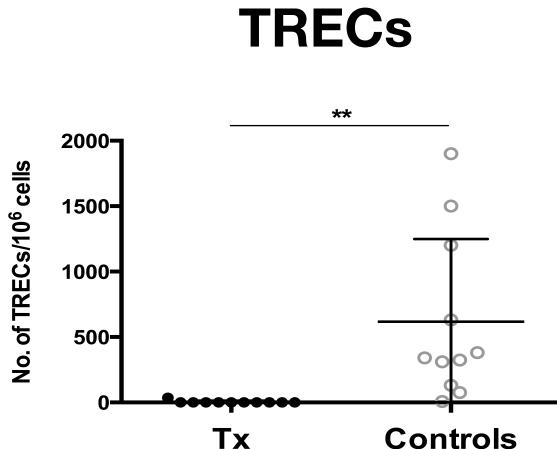
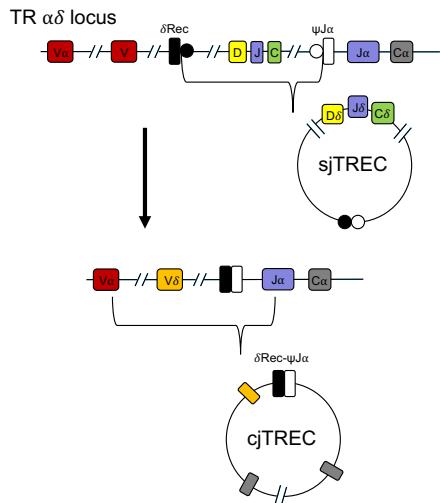




Thymectomy

- Analyses

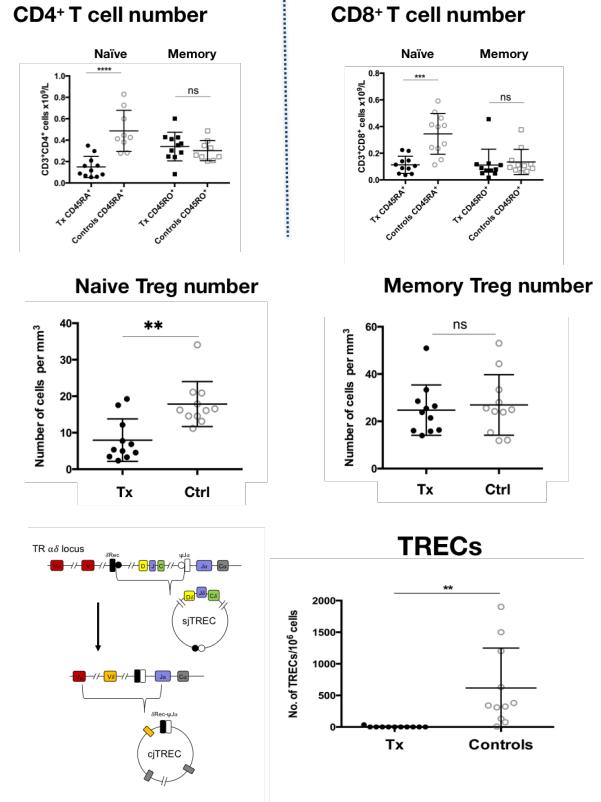
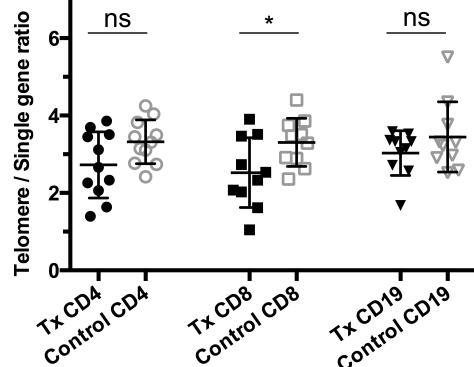
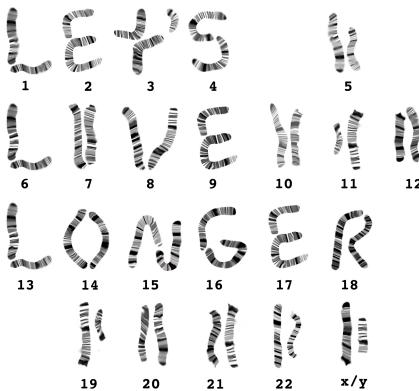
- Lymphocyte subpopulations
- TRECs





Thymectomy

- Analyses
 - Lymphocyte subpopulations
 - TRECs
 - Telomere length





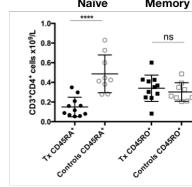
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Thymectomy

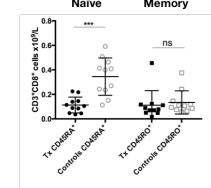
- Analyses

- Lymphocyte subpopulations
- TRECs
- Telomere length
- TCR V β analysis

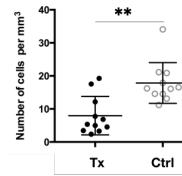
CD4 $^{+}$ T cell number



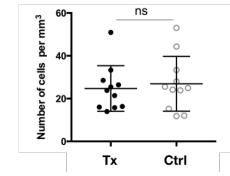
CD8 $^{+}$ T cell number



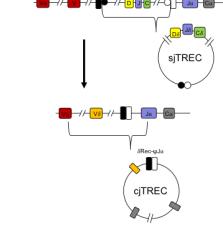
Naive Treg number



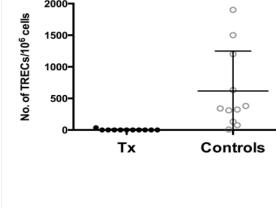
Memory Treg number



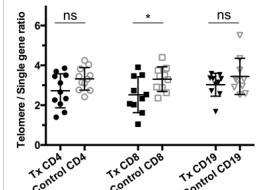
TR $\alpha\delta$ locus



TRECs



LET'S
LIVE
LONGER





TCR V β

Deviations ≥ 3 SD compared with mean of controls

Thymectomized	Oligoclonality CD8 $^{+}$	V β chain	Oligoclonality CD4 $^{+}$	V β chain
1	yes	V β 21.3	no	
2	yes	V β 2,3,5.1,5.3,12,14	yes	V β 7.2
3	yes	V β 3,5.1,12,14	no	
4	yes	V β 13.2	no	
5	no		no	
6	yes	V β 1,12,14,23	yes	V β 1
7	yes	V β 5.1	yes	V β 13.6
8	yes	V β 1,3,5.1,5.3,8,11,13.6,23	yes	V β 8
9	no		no	
10	yes	V β 1	yes	V β 22
11	n.a.		yes	V β 5.1,17
Controls	Oligoclonality CD8 $^{+}$	V β chain	Oligoclonality CD4 $^{+}$	V β chain
1	no		no	
2	n.a.		no	
3	no		no	
4	no		no	
5	no		no	
6	yes	13.2	no	
7	no		no	
8	no		no	
9	no		no	
10	no		no	
11	no		no	



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Thymectomy

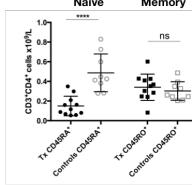
- Analyses

- Lymphocyte subpopulations
- TRECs
- Telomere length
- TCR V β analysis
- Next generation sequencing of TCR β chain

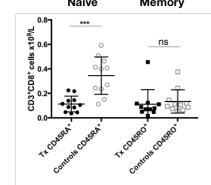
Numbered	Deviations ≥ 3 SD compared with mean of controls	
	Vβ chains	Vβ chains
1	+++	+++
2	+++	+++
3	+++	+++
4	+++	+++
5	+++	+++
6	+++	+++
7	+++	+++
8	+++	+++
9	+++	+++
10	+++	+++
11	+++	+++
12	+++	+++
13	+++	+++
14	+++	+++
15	+++	+++
16	+++	+++
17	+++	+++
18	+++	+++
19	+++	+++
20	+++	+++
21	+++	+++
22	+++	+++
x/y	+++	+++

Numbered	Deviations ≥ 3 SD compared with mean of controls	
	Vβ chains	Vβ chains
1	+++	+++
2	+++	+++
3	+++	+++
4	+++	+++
5	+++	+++
6	+++	+++
7	+++	+++
8	+++	+++
9	+++	+++
10	+++	+++
11	+++	+++
12	+++	+++
13	+++	+++
14	+++	+++
15	+++	+++
16	+++	+++
17	+++	+++
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19	+++	+++
20	+++	+++
21	+++	+++
22	+++	+++
x/y	+++	+++

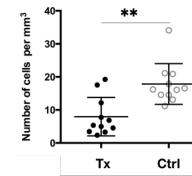
CD4+ T cell number



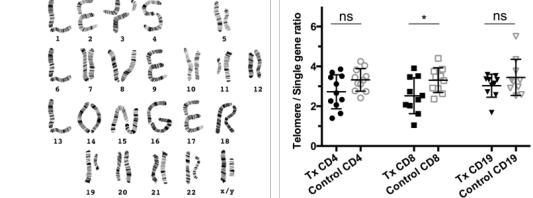
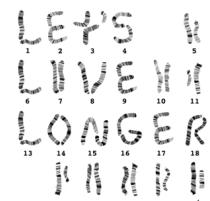
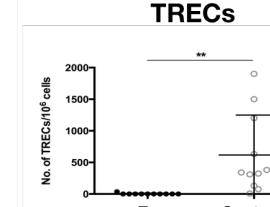
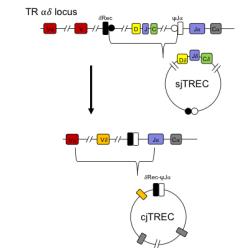
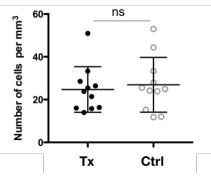
CD8+ T cell number



Naive Treg number



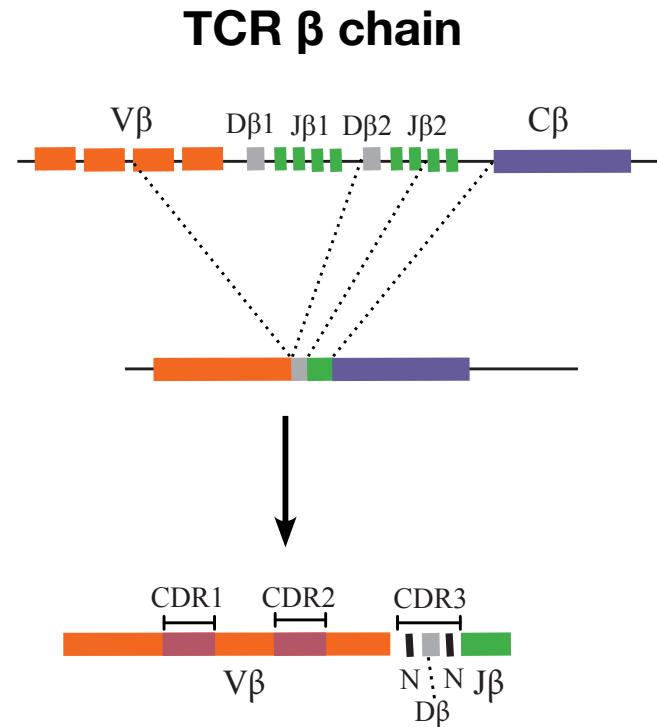
Memory Treg number





Next generation sequencing

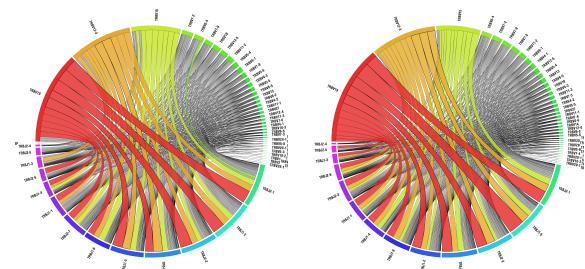
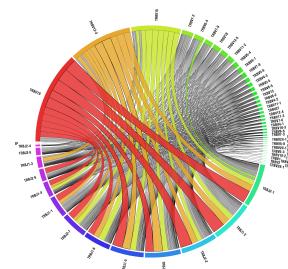
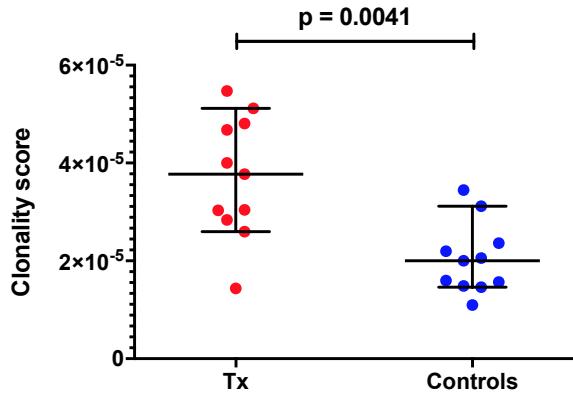
- TCR β chain and immunoglobulin heavy chain
 - number of distinct sequences
 - estimation of diversity
 - Insertions/deletions of non-template nucleotides
 - CDR3 length
 - amino acid usage
 - V, D and J usage



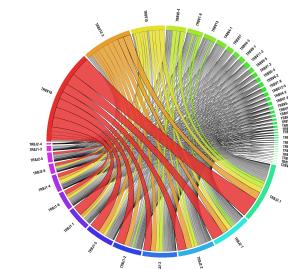
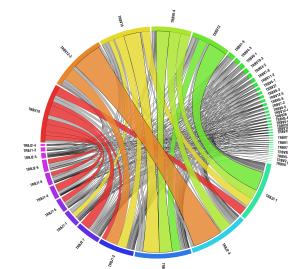
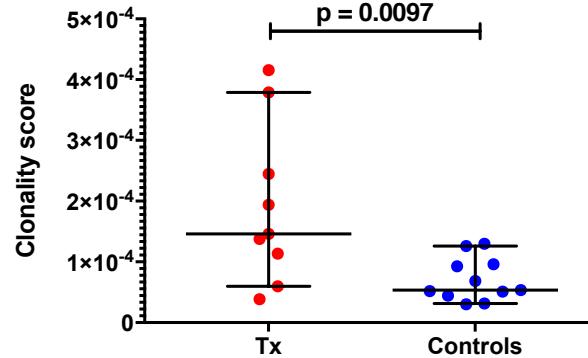


Repertoire diversity decreased

CD4



CD8

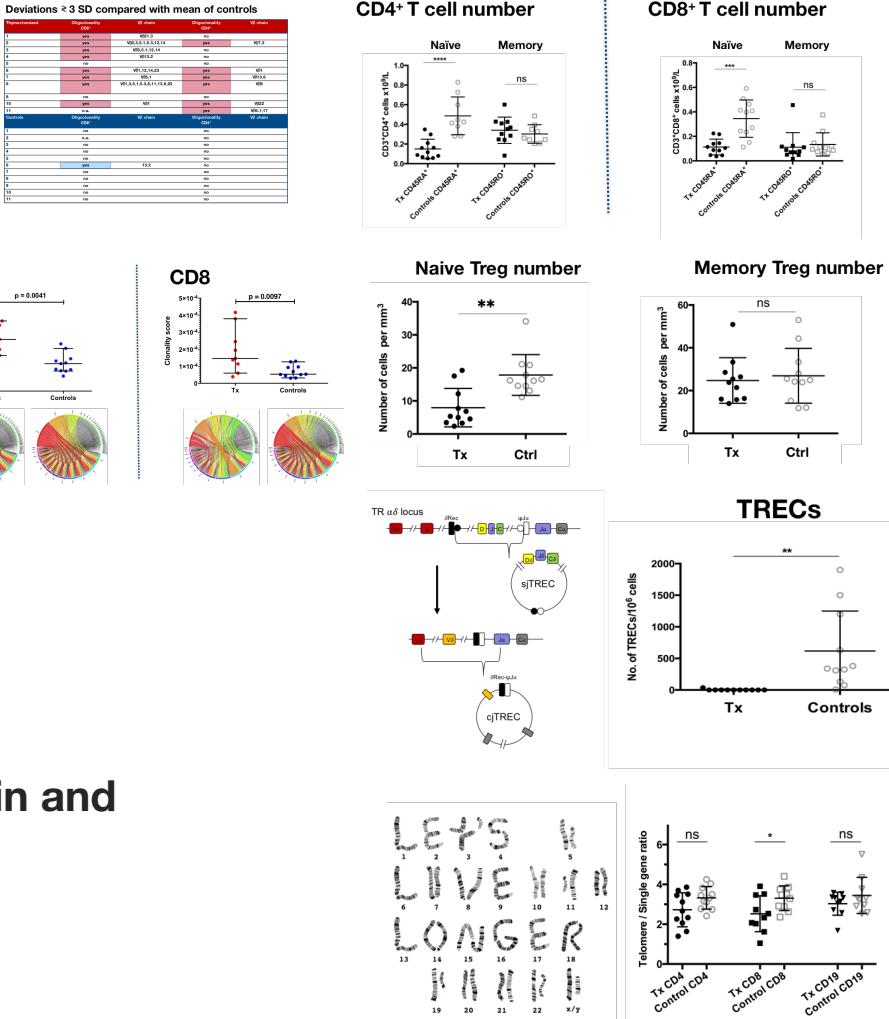




Thymectomy

- Analyses
 - Lymphocyte subpopulations
 - TRECs
 - Telomere length
 - TCR V β analysis
 - Next generation sequencing of TCR β chain and Ig heavy chain
 - Clinical data collection

Marker measured	Frequency (%)		Vβ chains	
	Vβ1	Vβ2	Vβ3	Vβ4
1	200	100	100	100
2	200	100	100	100
3	200	100	100	100
4	200	100	100	100
5	200	100	100	100
6	200	100	100	100
7	200	100	100	100
8	200	100	100	100
9	200	100	100	100
10	200	100	100	100
11	200	100	100	100
12	200	100	100	100
13	200	100	100	100
14	200	100	100	100
15	200	100	100	100
16	200	100	100	100
17	200	100	100	100
18	200	100	100	100
19	200	100	100	100
20	200	100	100	100
21	200	100	100	100
22	200	100	100	100
23	200	100	100	100
24	200	100	100	100
25	200	100	100	100
26	200	100	100	100
27	200	100	100	100
28	200	100	100	100
29	200	100	100	100
30	200	100	100	100
31	200	100	100	100
32	200	100	100	100
33	200	100	100	100
34	200	100	100	100
35	200	100	100	100
36	200	100	100	100
37	200	100	100	100
38	200	100	100	100
39	200	100	100	100
40	200	100	100	100
41	200	100	100	100
42	200	100	100	100
43	200	100	100	100
44	200	100	100	100
45	200	100	100	100
46	200	100	100	100
47	200	100	100	100
48	200	100	100	100
49	200	100	100	100
50	200	100	100	100
51	200	100	100	100
52	200	100	100	100
53	200	100	100	100
54	200	100	100	100
55	200	100	100	100
56	200	100	100	100
57	200	100	100	100
58	200	100	100	100
59	200	100	100	100
60	200	100	100	100
61	200	100	100	100
62	200	100	100	100
63	200	100	100	100
64	200	100	100	100
65	200	100	100	100
66	200	100	100	100
67	200	100	100	100
68	200	100	100	100
69	200	100	100	100
70	200	100	100	100
71	200	100	100	100
72	200	100	100	100
73	200	100	100	100
74	200	100	100	100
75	200	100	100	100
76	200	100	100	100
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78	200	100	100	100
79	200	100	100	100
80	200	100	100	100
81	200	100	100	100
82	200	100	100	100
83	200	100	100	100
84	200	100	100	100
85	200	100	100	100
86	200	100	100	100
87	200	100	100	100
88	200	100	100	100
89	200	100	100	100
90	200	100	100	100
91	200	100	100	100
92	200	100	100	100
93	200	100	100	100
94	200	100	100	100
95	200	100	100	100
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100	200	100	100	100



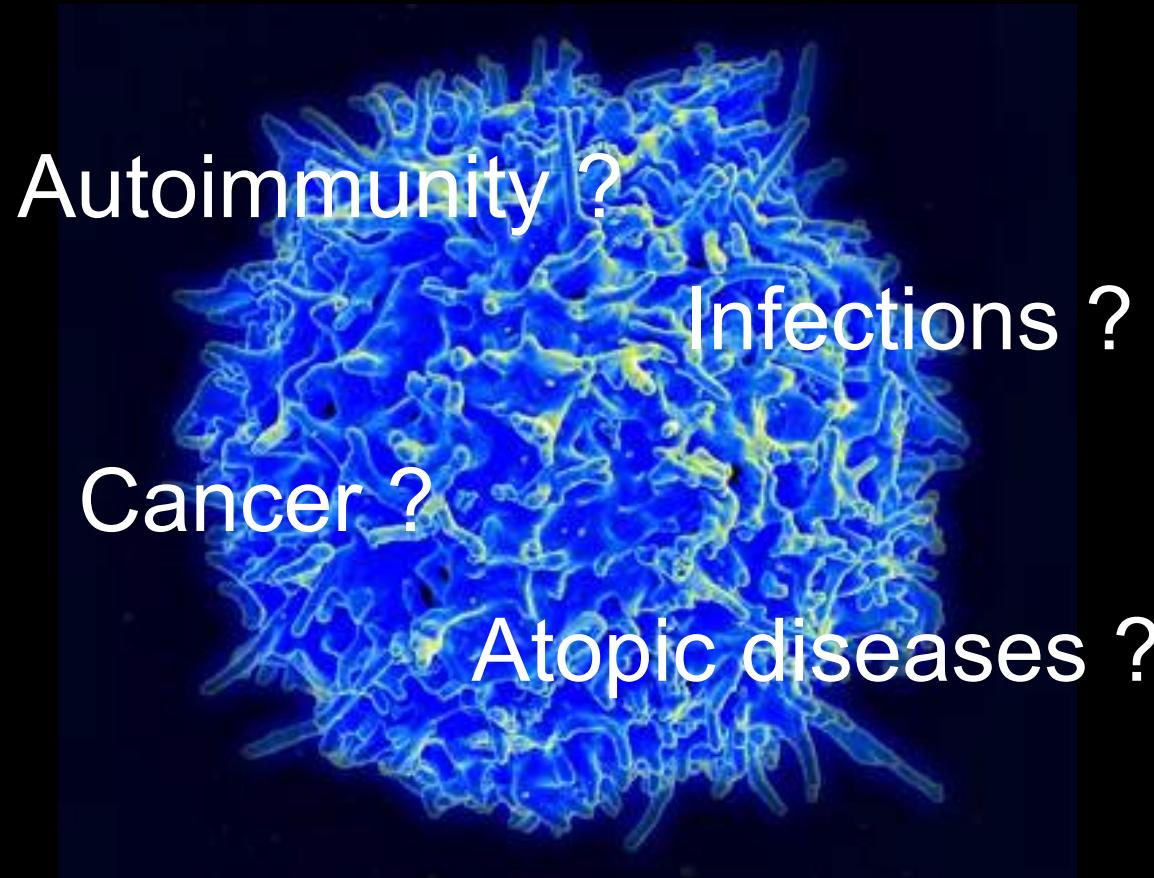


Clinical data

	Thymectomized (no. 11)	Controls (no. 10)
Acute otitis media:		
< 10 per individual in total	9	7
≥ 10 per individual in total	6	4
≥ 10 per individual in total	3	3
Surgery related to recurrent otitis media	1	3
Pneumonia	5	2
Frequent respiratory infections	7	1
Severe infection (Hospital admission)	6	1
Autoimmune disease (any)	1	1
Allergy (any)	5	2



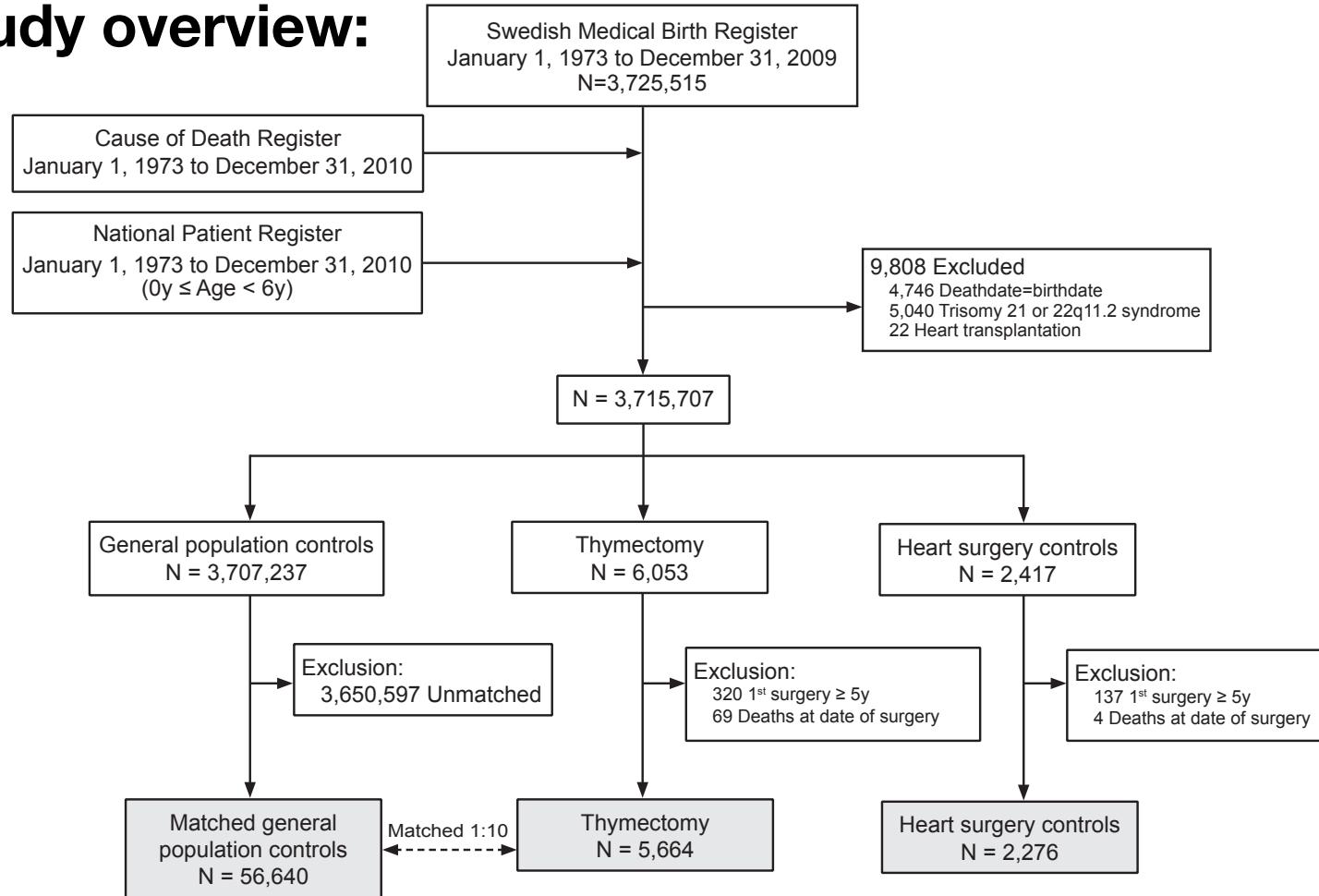
What about clinical consequences?





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Study overview:



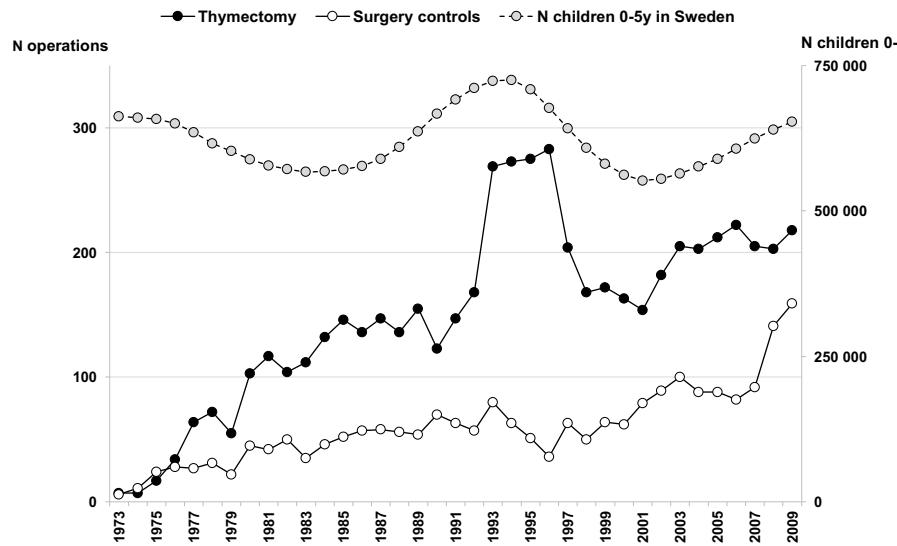


Outcomes:

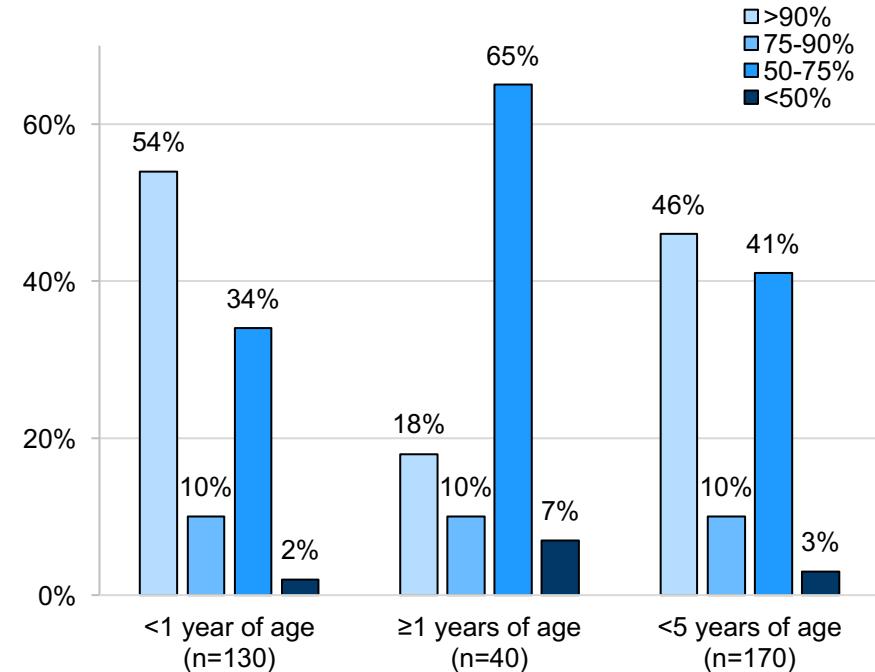
- **Autoimmune**
 - hypo- and hyperthyroidism, type 1 diabetes, rheumatoid arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus, Sjögren's disease, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease (Crohn's disease, ulcerative colitis), multiple sclerosis, psoriasis, and celiac disease
- **Cancer**
- **Infections**
 - Grouped according to etiology; bacterial, viral, and other (parasitic, fungal, protozoan)
- **Atopic**
 - asthma, rhinitis, eczema



Group Characteristics:



Time trend of cardiac surgery



Extent of thymectomy



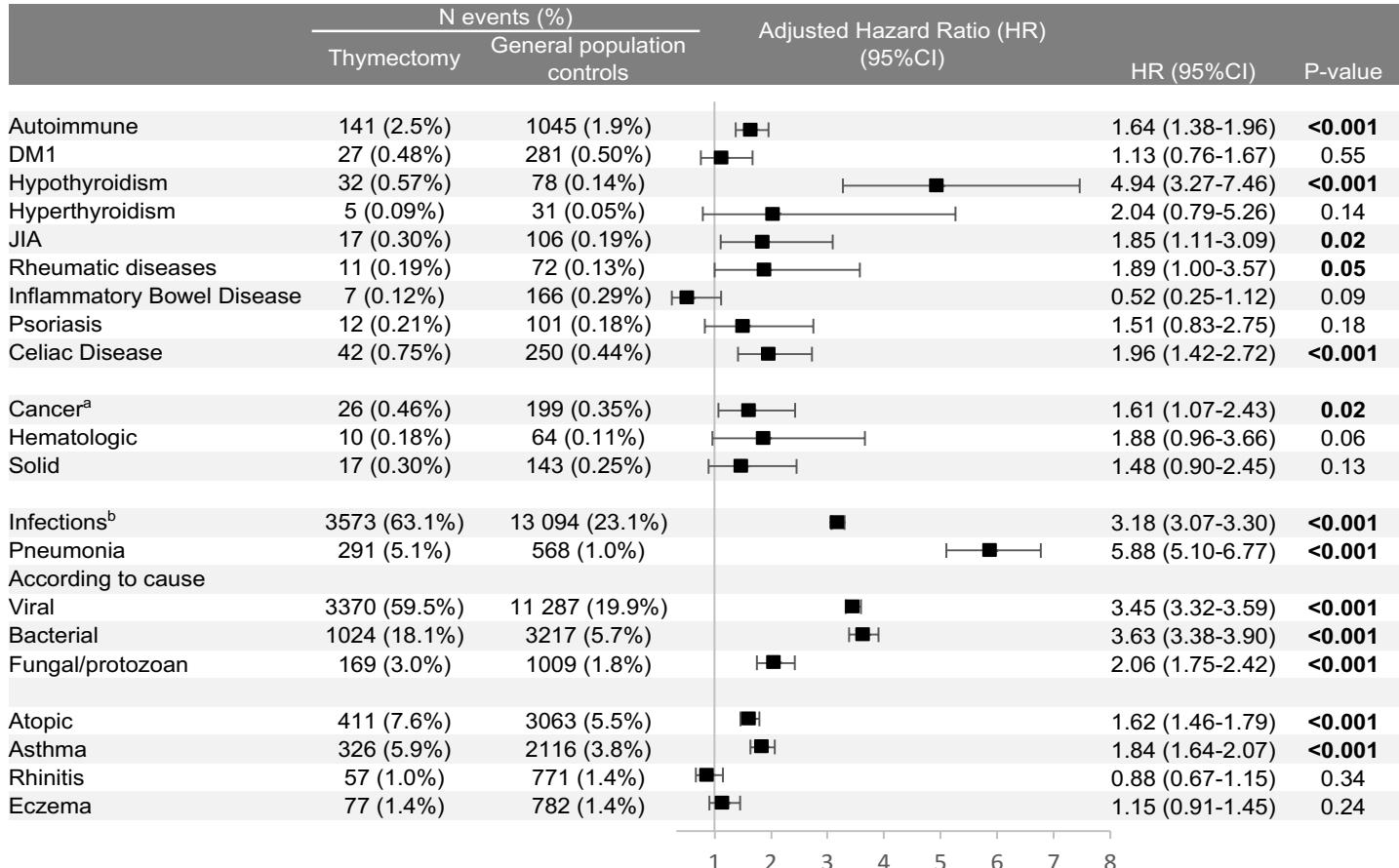
What did we end up with?

- 5,664 cases, 56,640 general population controls and 2,276 surgery controls
- Total follow-up time: 70,000 yrs
- Follow-up time of each individual: 1-38 years (mean 13 years)
- Mean age of thymectomized at end of study: 14 yrs
- Median age at thymectomy: 229 days
- Total thymectomy: 46%

Underestimation of long-term effects?

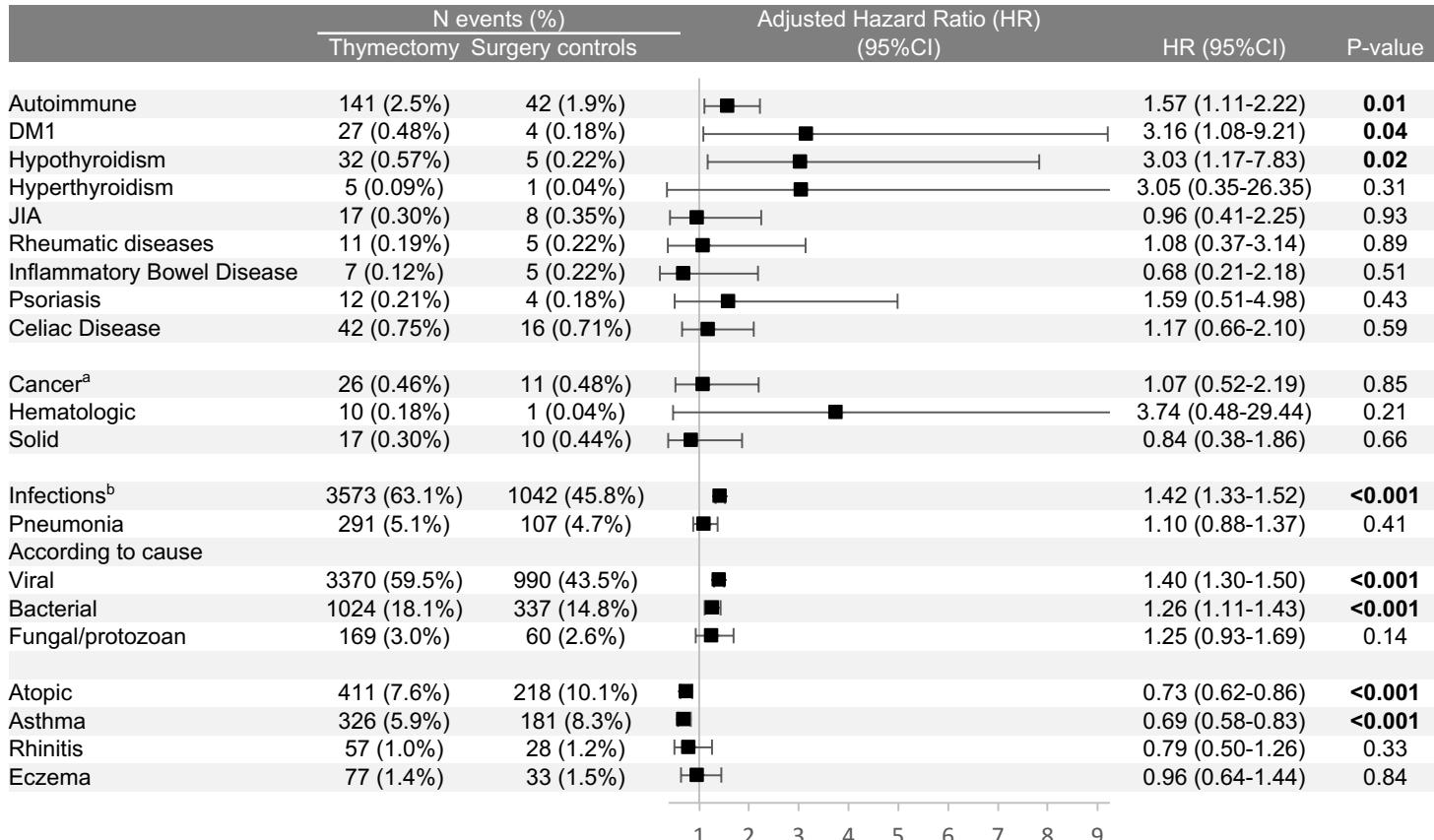
- ✓ 46% total thymectomy
- ✓ Relatively short follow-up time
- ✓ Long pre-clinical stage of diseases

Hazard ratios – general population





Hazard ratios – surgery controls





Conclusions

- Long lasting immunologic impact
- T cell lymphopenia
 - Especially naïve T cell subset
- Severely affected thymic output
- Decreased TCR repertoire diversity
- Association with increased risks of
 - Certain autoimmune diseases
 - Infections
 - Cancer
- Avoid total thymectomy if possible



Future research

- Continued follow-up
 - Growing group of individuals
 - Aging
 - Optimal clinical care
- Documentation of thymectomy
 - Degree of thymectomy





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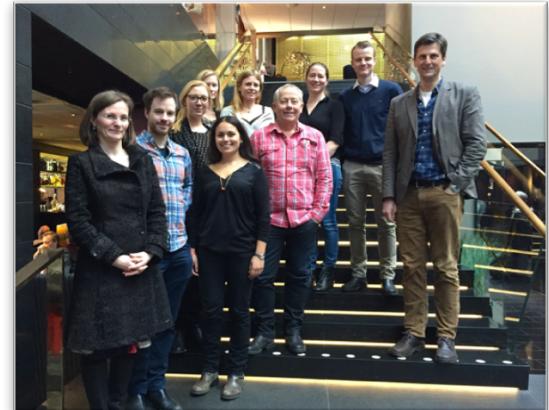
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- Martin Neovius

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- Hanna Ijspeert
- Eva van der Slik



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