

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Definitions of Celiac Disease and Normal Mucosa Using SNOMED Codes

Disease/Condition	Topographic code	SNOMED codes
Celiac disease	All T64, only T65, T65000, and T651	D6218, D62180, D62188, D6218X, D6218Y M58, M5800, M58000, M58001, M58005, M58006, M58007
Normal mucosa	Same as for Celiac disease	M00100, M00110

eTable 2. Definitions of Cause-Specific Mortality

Cause-specific mortality	ICD8 (1969-1986)	ICD9 (1987-1996)	ICD10 (1997-)
Cardiovascular disease	391-458	391-459	I00-I99
Cancer	140-209	140-209	C00-C99
Respiratory disease	460-519	460-519	J00-J99
Other	Remaining	Remaining	Remaining

eTable 3. Definitions of Baseline Comorbidities Ever Before Start of Follow-up

Comorbidity	ICD7 (1964-1968)	ICD8 (1969-1986)	ICD9 (1987-1996)	ICD10 (1997-)
Type 1 diabetes*	260	250	250	E10
Autoimmune thyroid disease	252,00; 252,01; 252,02; 253,10; 253,19; 253,20; 253,29; 254,00	242,00; 242,09; 244; 245,03	242A, 242X, 244X, 245C, 245W	E035, E039, E050, E055, E059, E063, E065
Rheumatoid arthritis		712,3; 714,93	714	M05, M06, M08, M123
Inflammatory bowel disease	572,09; 572,20; 572,21	572,00; 572,09; 563,00; 572,20; 572,21; 563,10	555, 556	K50, K51, K523

*Age <31 years at date of diagnosis

eTable 4. Comorbidity at Baseline, During Follow-up and at Baseline or Follow-up, by Index Year in Celiac Disease and Matched Comparators

Group	Celiac disease				Comparators			
	Overall	1969-1989	1990-2002	2003-2017	Overall	1969-1989	1990-2002	2003-2017
n	49 829	4 339	19 222	26 268	246 426	21 604	95 105	129 717
At baseline								
DM1	1 565 (3.1%)	53 (1.2%)	522 (2.7%)	990 (3.8%)	667 (0.3%)	21 (0.1%)	196 (0.2%)	450 (0.3%)
ATD	1 126 (2.3%)	34 (0.8%)	255 (1.3%)	837 (3.2%)	1 852 (0.8%)	39 (0.2%)	370 (0.4%)	1 443 (1.1%)
RA	423 (0.8%)	35 (0.8%)	127 (0.7%)	261 (1.0%)	1 096 (0.4%)	56 (0.3%)	322 (0.3%)	718 (0.6%)
IBD	1 401 (2.8%)	212 (4.9%)	554 (2.9%)	635 (2.4%)	365 (0.1%)	29 (0.1%)	146 (0.2%)	190 (0.1%)
During follow-up								
DM1	340 (0.7%)	47 (1.1%)	148 (0.8%)	145 (0.6%)	561 (0.2%)	68 (0.3%)	309 (0.3%)	184 (0.1%)
ATD	2 662 (5.3%)	331 (7.6%)	1 370 (7.1%)	961 (3.7%)	5 532 (2.2%)	795 (3.7%)	2 946 (3.1%)	1 791 (1.4%)
RA	573 (1.1%)	84 (1.9%)	316 (1.6%)	173 (0.7%)	1 850 (0.8%)	309 (1.4%)	1 053 (1.1%)	488 (0.4%)
IBD	1 098 (2.2%)	150 (3.5%)	526 (2.7%)	422 (1.6%)	1 550 (0.6%)	263 (1.2%)	811 (0.9%)	476 (0.4%)
At baseline or during follow-up								
DM1	1 907 (3.8%)	101 (2.3%)	670 (3.5%)	1 136 (4.3%)	1 228 (0.5%)	89 (0.4%)	505 (0.5%)	634 (0.5%)
ATD	3 796 (7.6%)	365 (8.4%)	1 628 (8.5%)	1 803 (6.9%)	7 386 (3.0%)	834 (3.9%)	3 316 (3.5%)	3 236 (2.5%)
RA	997 (2.0%)	120 (2.8%)	443 (2.3%)	434 (1.7%)	2 947 (1.2%)	365 (1.7%)	1 375 (1.4%)	1 207 (0.9%)
IBD	2 512 (5.0%)	362 (8.3%)	1 084 (5.6%)	1 066 (4.1%)	1 915 (0.8%)	292 (1.4%)	957 (1.0%)	666 (0.5%)

DM1: Type 1 diabetes, ATD: Autoimmune thyroid disease, RA: Rheumatoid arthritis, IBD: Inflammatory bowel disease

eTable 5. Narrowing the Definition of Celiac Disease

Analysis	N (%)		N events		Incidence rate (95% CI) per 1000 PY		HR* (95% CI)	HR** (95% CI)
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators		
Main analysis	49 829 (100%)	246 426 (100%)	6 596 (13.2%)	28 890 (11.7%)	9.7 (9.5-9.9)	8.6 (8.5-8.7)	1.21 (1.17-1.25)	1.14 (1.11-1.18)
Exclusion of GI-cancer and IBD	48 441 (97.2%)	239 580 (97.2%)	6 234 (12.9%)	27 730 (11.6%)	9.4 (9.2-9.7)	8.5 (8.4-8.6)	1.18 (1.15-1.22)	1.13 (1.09-1.16)
Including Celiac disease diagnosis# within 6 months of biopsy	22 115 (44.4%)	109 697 (44.5%)	1 428 (6.5%)	6 204 (5.7%)	5.7 (5.4-6.0)	5.0 (4.9-5.1)	1.24 (1.16-1.32)	1.17 (1.09-1.24)
*Conditioned on matching set (age, sex, county, and calendar period);								
**Conditioned on matching set and further adjusted for education, Nordic country of birth, and time dependent medical comorbidities (Type 1 diabetes, Autoimmune thyroid disease, Rheumatoid arthritis, and Inflammatory bowel disease)								

#Diagnosis from Swedish National Patient Register

GI, gastrointestinal. IBD, inflammatory bowel disease.

eTable 6. Celiac Disease With Positive Celiac Disease Serology vs Matched Comparators

Characteristic	Celiac disease (n=3 307)	Matched comparators (n=15 853)
Women, no. (%)	2 154 (65.1%)	10 399 (65.6%)
Men, no (%)	1 153 (34.9%)	5 454 (34.4%)
Age		
Mean (SD)	25.8 (24.3)	24.4 (23.4)
Median (IQR)	15.3 (3.7-46.6)	14.0 (3.5-43.6)
Range, min-max	0.6-89.8	0.0-89.9
Categories, no. (%)		
<18y	1 756 (53.1%)	8 738 (55.1%)
18y - <40y	557 (16.8%)	2 696 (17.0%)
40y - <60y	583 (17.6%)	2 740 (17.3%)
≥60y	411 (12.4%)	1 679 (10.6%)
Country of birth, no (%)		
Nordic country	3 252 (98.3%)	15 084 (95.1%)
Other	55 (1.7%)	769 (4.9%)
Missing	0	0
Level of education, no (%)		
≤9 years	417 (12.6%)	2 140 (13.5%)
10-12 years	651 (19.7%)	3 241 (20.4%)
>12 years	550 (16.6%)	2 023 (12.8%)
Missing	1 689 (51.1%)	8 449 (53.3%)
Level of education using highest level of education in parents when missing, n (%)		
≤9 years	449 (13.6%)	2 514 (15.9%)
10-12 years	1 372 (41.5%)	6 802 (42.9%)
>12 years	1 470 (44.5%)	6 431 (40.6%)
Missing	16 (0.5%)	106 (0.7%)
Start year of follow-up		
1969-1989	1 (0.0%)	5 (0.0%)
1990-1999	1 205 (36.4%)	5 803 (36.6%)
2000-2009	2 101 (63.5%)	10 045 (63.4%)
2010-2017	0	0
Disease history ever before start of follow-up, no. (%)		
Type 1 diabetes	134 (4.1%)	46 (0.3%)
Autoimmune thyroid disease	56 (1.7%)	72 (0.5%)
Rheumatoid arthritis	22 (0.7%)	65 (0.4%)
Inflammatory bowel disease	26 (0.8%)	51 (0.3%)
Deaths		
≤30 days after index date	0	4 (0.0%)
≤90 days after index date	2 (0.1%)	11 (0.1%)
≤365 days after index date	16 (0.5%)	47 (0.3%)
All follow-up time	289 (8.7%)	1 171 (7.4%)

eTable 7. Risk of All-Cause (Follow-up Until 31 Dec, 2017) and Cause-Specific (Follow-up Until 31 Dec, 2016) Mortality in Patients With Celiac Disease and Positive Celiac Disease Serology and Matched General Population Comparators

	All-cause mortality		Cardiovascular disease		Cancer		Respiratory disease		Other cause of death	
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators
N	3 307	15 853	3 307	15 853	3 307	15 853	3 307	15 853	3 307	15 853
Deaths, no (%)	289 (8.7%)	1 171 (7.4%)	92 (2.8%)	344 (2.2%)	72 (2.2%)	325 (2.1%)	18 (0.5%)	65 (0.4%)	85 (2.6%)	345 (2.2%)
Follow-up years										
Mean (SD)	16.0 (5.2)	15.9 (5.3)	15.1 (5.1)	15.0 (5.1)	15.1 (5.1)	15.0 (5.1)	15.1 (5.1)	15.0 (5.1)	15.1 (5.1)	15.0 (5.1)
Median (IQR)	15.5 (12.6-19.2)	15.4 (12.6-19.2)	14.6 (11.6-18.3)	14.5 (11.6-18.2)	14.6 (11.6-18.3)	14.5 (11.6-18.2)	14.6 (11.6-18.3)	14.5 (11.6-18.2)	14.6 (11.6-18.3)	14.5 (11.6-18.2)
Incidence rate per 1000 PY (95% CI)	5.5 (4.8-6.1)	4.7 (4.4-4.9)	1.8 (1.5-2.2)	1.4 (1.3-1.6)	1.4 (1.1-1.8)	1.4 (1.2-1.5)	0.4 (0.2-0.5)	0.3 (0.2-0.3)	1.7 (1.3-2.1)	1.5 (1.3-1.6)
Hazard ratio (95% CI)										
Conditioned	1.02 (0.89-1.17)		1.01 (0.78-1.30)		0.99 (0.76-1.29)		1.32 (0.74-2.36)		1.00 (0.77-1.29)	
Adjusted	0.98 (0.85-1.14)		0.99 (0.76-1.29)		0.95 (0.72-1.25)		1.63 (0.87-3.06)		0.98 (0.74-1.29)	

Conditioned: Conditioned on matching set (age, sex, county, and calendar period);

Adjusted: Conditioned on matching set and further adjusted for education, Nordic country of birth, and time dependent medical comorbidities (Type 1 diabetes, Autoimmune thyroid disease, Rheumatoid arthritis, and Inflammatory bowel disease)

eTable 8. Celiac Disease Compared to Siblings: Baseline Characteristics of Study Cohort

Characteristic	Celiac disease (n=32 558)	Siblings (n=56 442)
Women, no. (%)	20 608 (63.3%)	27 565 (48.8%)
Men, no (%)	11 950 (36.7%)	28 877 (51.2%)
Age		
Mean (SD)	27.1 (21.0)	30.6 (20.8)
Median (IQR)	22.6 (8.2-44.2)	28.6 (11.5-48.1)
Range, min-max	0.0-84.1	0.0-83.5
Categories, no. (%)		
<18y	14 241 (43.7%)	20 255 (35.9%)
18y - <40y	8 612 (26.5%)	15 850 (28.1%)
40y - <60y	6 881 (21.1%)	14 707 (26.1%)
≥60y	2 824 (8.7%)	5 630 (10.0%)
Country of birth, no (%)		
Nordic country	32 063 (98.5%)	55 061 (97.6%)
Other	494 (1.5%)	1 374 (2.4%)
Missing	1 (0.0%)	7 (0.0%)
Level of education, no (%)		
≤9 years	4 519 (13.9%)	9 377 (16.6%)
10-12 years	8 032 (24.7%)	16 019 (28.4%)
>12 years	5 794 (17.8%)	9 412 (16.7%)
Missing	14 213 (43.7%)	21 634 (38.3%)
Level of education using highest level of education in parents when missing, n (%)		
≤9 years	5 409 (16.6%)	12 017 (21.3%)
10-12 years	13 673 (42.0%)	24 289 (43.0%)
>12 years	13 118 (40.3%)	19 302 (34.2%)
Missing	358 (1.1%)	834 (1.5%)
Start year of follow-up		
1969-1989	2 261 (6.9%)	4 161 (7.4%)
1990-1999	7 874 (24.2%)	14 167 (25.1%)
2000-2009	13 598 (41.8%)	23 602 (41.8%)
2010-2017	8 825 (27.1%)	14 512 (25.7%)
Disease history ever before start of follow-up, no. (%)		
Type 1 diabetes	1 278 (3.9%)	431 (0.8%)
Autoimmune thyroid disease	629 (1.9%)	523 (0.9%)
Rheumatoid arthritis	221 (0.7%)	280 (0.5%)
Inflammatory bowel disease	963 (3.0%)	426 (0.8%)
Deaths		
≤30 days after index date	16 (0.0%)	14 (0.0%)
≤90 days after index date	49 (0.2%)	39 (0.1%)
≤365 days after index date	163 (0.5%)	133 (0.2%)
All follow-up time	1 580 (4.9%)	2 696 (4.8%)

eTable 9. Risk of All-Cause Mortality in Children (<18 Years) Diagnosed in 2010-2011 and in 2012-2014, Restricted to 3 Years of Follow-up

Group	N (%)		Time at risk (years)		N events		Mortality rate (95% CI)		HR* (95%CI)	HR** (95%CI)
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators		
Overall	3 682 (100%)	18 412 (100%)	11 011	54 829	3 (0.1%)	10 (0.1%)	0.3 (0.0-0.6)	0.2 (0.1-0.3)	1.67 (0.45-6.16)	2.92 (1.13-30.25)
Year										
2010-2011	1 770 (48.1%)	8 841 (48.0%)	5 294	26 316	2 (0.1%)	6 (0.1%)	0.4 (0.0-0.9)	0.2 (0.0-0.4)	1.67 (0.34-8.26)	2.23 (0.31-15.82)
2012-2014	1 912 (51.9%)	9 571 (52.0%)	5 716	28 513	1 (0.1%)	4 (0.0%)	0.2 (0.0-0.5)	0.1 (0.0-0.3)	1.67 (0.17-16.02)	NC

*Conditioned on matching set;

**Conditioned on matching set and adjusted for education and time dependent medical comorbidities (Type 1 diabetes [DM1], Autoimmune thyroid disease [ATD], Rheumatoid arthritis [RA], Inflammatory bowel disease [IBD])

NC, not calculated due to lack of convergence of the model

eTable 10. Baseline Characteristics of Study Cohort of Those With Mucosal Healing on Follow-up Biopsy Compared to Those With Persistent Villus Atrophy

Characteristic	Mucosal healing (n=6 924)	Persistent villus atrophy (n=2 919)
Women, no. (%)	4 494 (64.9%)	1 728 (59.2%)
Men, no (%)	2 430 (35.1%)	1 191 (40.8%)
Age		
Mean (SD)	32.8 (22.6)	44.0 (24.1)
Median (IQR)	30.7 (12.4-50.9)	47.7 (24.8-64.1)
Range, min-max	1.0-91.3	1.1-90.9
Categories, no. (%)		
<18y	2 150 (31.1%)	567 (19.4%)
18y - <40y	2 162 (31.2%)	576 (19.7%)
40y - <60y	1 584 (22.9%)	860 (29.5%)
≥60y	1 028 (14.8%)	916 (31.4%)
Duration since diagnosis, years		
Mean (SD)	1.7 (1.5)	1.6 (1.7)
Median (IQR)	1.3 (1.0-2.0)	1.2 (0.9-1.8)
Range, min-max	0.5-30.8	0.5-27.0
Country of birth, no (%)		
Nordic country	6 613 (95.5%)	2 786 (95.4%)
Other	311 (4.5%)	133 (4.6%)
Missing	0	0
Level of education, no (%)		
≤9 years	1 117 (16.1%)	696 (23.8%)
10-12 years	2 955 (42.7%)	1 233 (42.2%)
>12 years	2 725 (39.4%)	876 (30.0%)
Missing	127 (1.8%)	114 (3.9%)
Level of education using highest level of education in parents when missing, n (%)		
≤9 years	1 111 (16.0%)	695 (23.8%)
10-12 years	2 848 (41.1%)	1 211 (41.5%)
>12 years	2 570 (37.1%)	852 (29.2%)
Missing	395 (5.7%)	161 (5.5%)
Start year of follow-up		
1969-1989	240 (3.5%)	174 (6.0%)
1990-1999	1 549 (22.4%)	855 (29.3%)
2000-2009	3 093 (44.7%)	1 157 (39.6%)
2010-2017	2 042 (29.5%)	733 (25.1%)
Disease history ever before start of follow-up, no. (%)		
Type 1 diabetes	156 (2.3%)	49 (1.7%)
Autoimmune thyroid disease	227 (3.3%)	81 (2.8%)
Rheumatoid arthritis	57 (0.8%)	28 (1.0%)
Inflammatory bowel disease	336 (4.9%)	176 (6.0%)
Deaths		
≤30 days after index date	4 (0.1%)	1 (0.0%)
≤90 days after index date	14 (0.2%)	9 (0.3%)
≤365 days after index date	36 (0.5%)	35 (1.2%)
All follow-up time	497 (7.2%)	479 (16.4%)

eTable 11. Risk of All-Cause (Follow-up Until 31 Dec, 2017) and Cause-Specific (Follow-up Until 31 Dec, 2016) Mortality in Patients With Celiac Disease and Mucosal Healing vs Persistent Villus Atrophy

	All-cause mortality		Cardiovascular disease		Cancer		Respiratory disease		Other cause of death	
	Healing	Persistent VA	Healing	Persistent VA	Healing	Persistent VA	Healing	Persistent VA	Healing	Persistent VA
N	6 924	2 919	6 915	2 913	6 915	2 913	6 915	2 913	6 915	2 913
Deaths, no (%)	497 (7.2%)	479 (16.4%)	151 (2.2%)	137 (4.7%)	132 (1.9%)	141 (4.8%)	32 (0.5%)	32 (1.1%)	148 (2.1%)	134 (4.6%)
Follow-up years										
Mean (SD)	12.3 (7.4)	13.2 (8.1)	11.4 (7.3)	12.4 (8.0)	11.4 (7.3)	12.4 (8.0)	11.4 (7.3)	12.4 (8.0)	11.4 (7.3)	12.4 (8.0)
Median (IQR)	11.6 (6.1-17.1)	12.2 (6.5-18.9)	10.7 (5.3-16.2)	11.4 (5.7-18.1)	10.7 (5.3-16.2)	11.4 (5.7-18.1)	10.7 (5.3-16.2)	11.4 (5.7-18.1)	10.7 (5.3-16.2)	11.4 (5.7-18.1)
Incidence rate per 1000 PY (95% CI)	5.8 (5.3-6.3)	12.5 (11.3-13.6)	1.9 (1.6-2.2)	3.8 (3.2-4.4)	1.7 (1.4-2.0)	3.9 (3.3-4.6)	0.4 (0.3-0.5)	0.9 (0.6-1.2)	1.9 (1.6-2.2)	3.7 (3.1-4.3)
Hazard ratio (95% CI)										
Adjusted	0.99 (0.87-1.13)		1.18 (0.93-1.49)		0.82 (0.65-1.05)		1.03 (0.63-1.71)		1.00 (0.79-1.27)	

Adjusted: Adjusted for age, sex, start year of follow-up, duration since diagnosis, education, Nordic country of birth, and time dependent medical comorbidities (Type 1 diabetes, Autoimmune thyroid disease, Rheumatoid arthritis, and Inflammatory bowel disease)

VA, villus atrophy