



ICDS2022SORRENTO

19th INTERNATIONAL CELIAC DISEASE SYMPOSIUM

Association between IBD and celiac disease: Should IBD patients be screened for celiac disease?

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Agenda

- ✓ Similarities/differences between IBD and celiac disease
- ✓ Evidence on the association between IBD and celiac disease
- ✓ Areas for research
- ✓ Recommendations for screening of IBD in CeD and viceversa





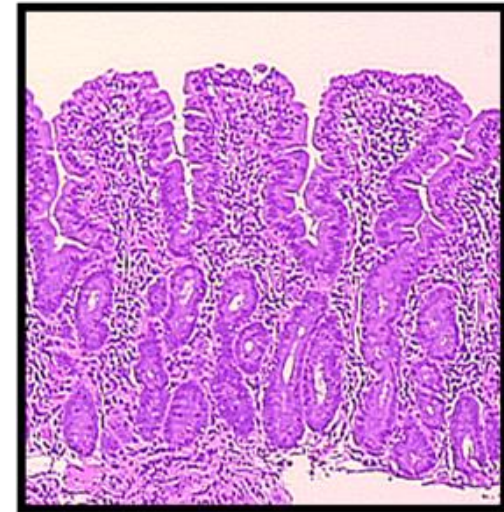
Celiac disease



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HLA DQ2-8

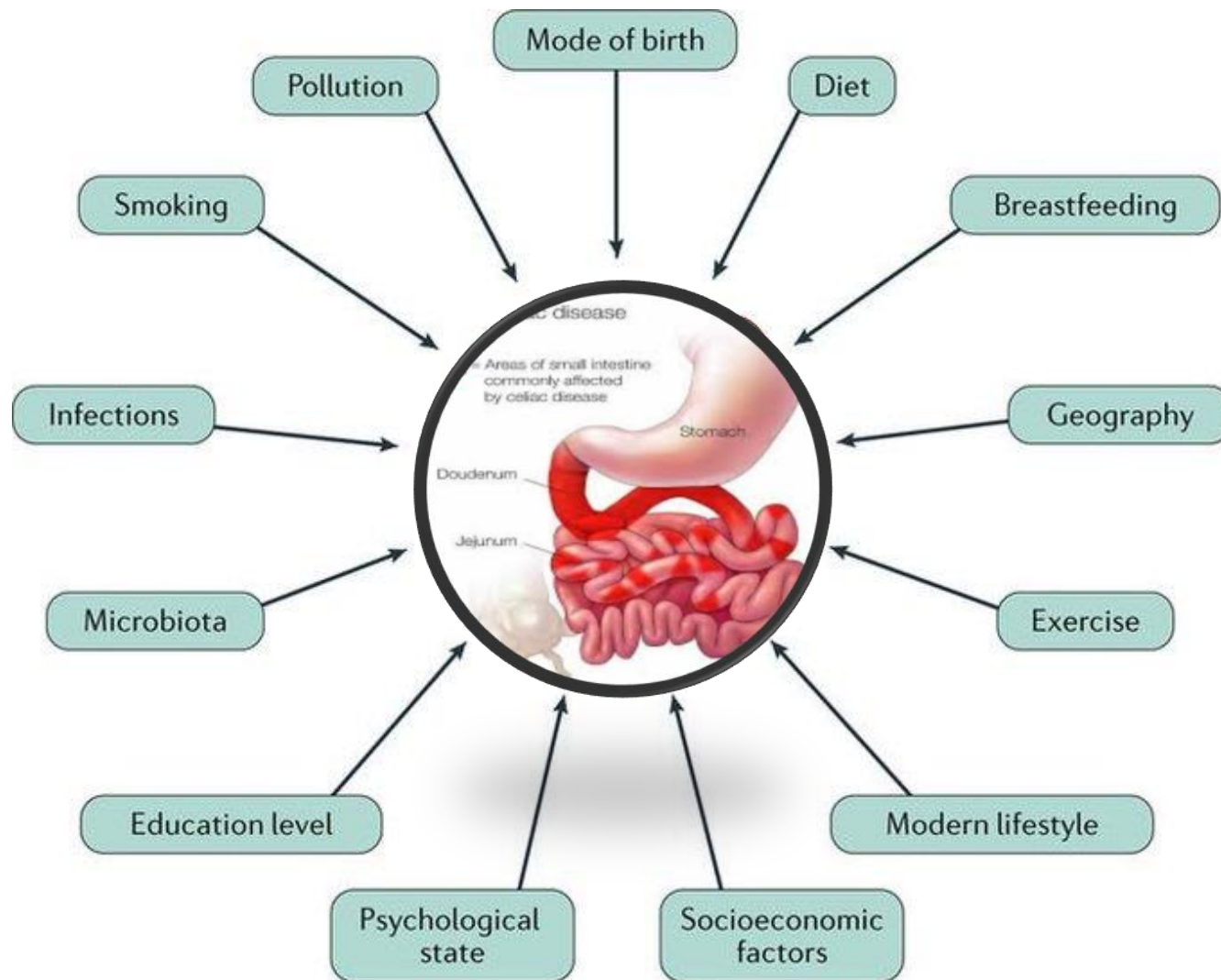
Gluten

Enteropathy

Genetic is required but insufficient to explain the mechanisms of immune reaction in celiac disease

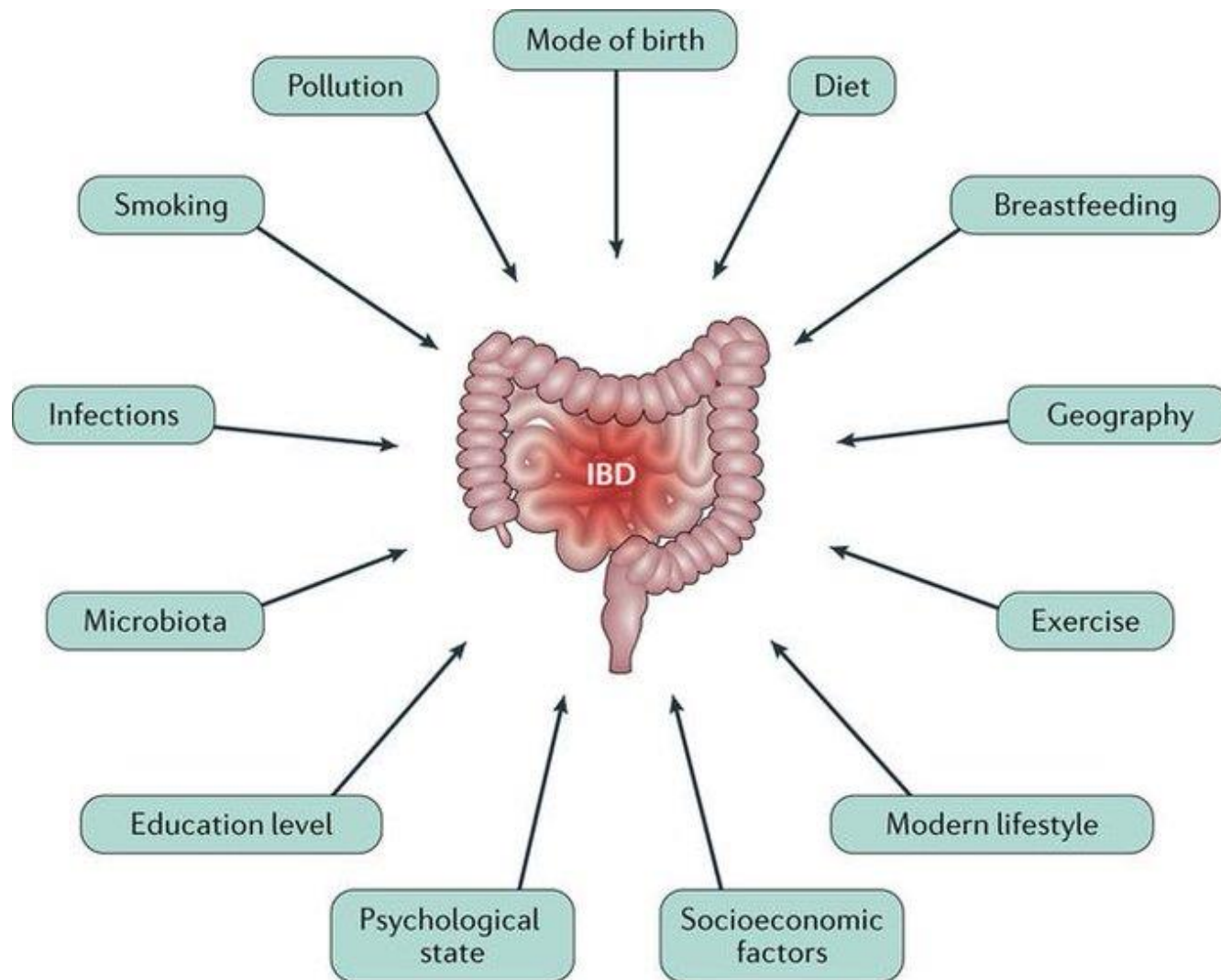


Pathophysiology of CeD





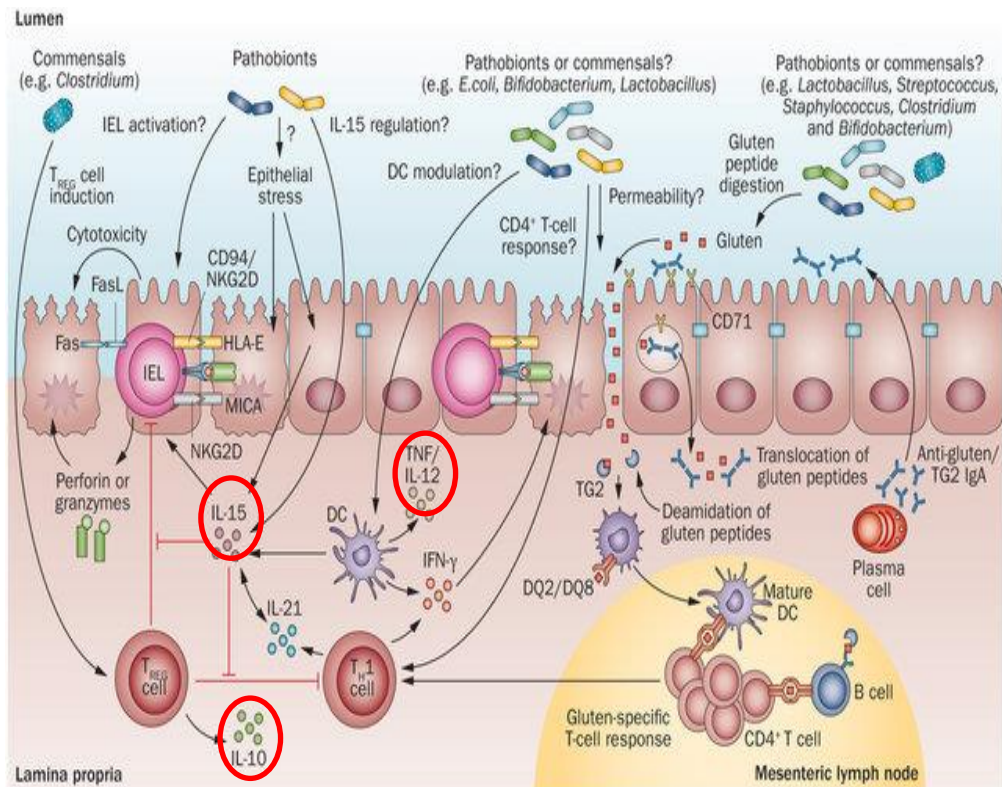
Pathophysiology of IBD





Mechanisms Celiac disease and IBD

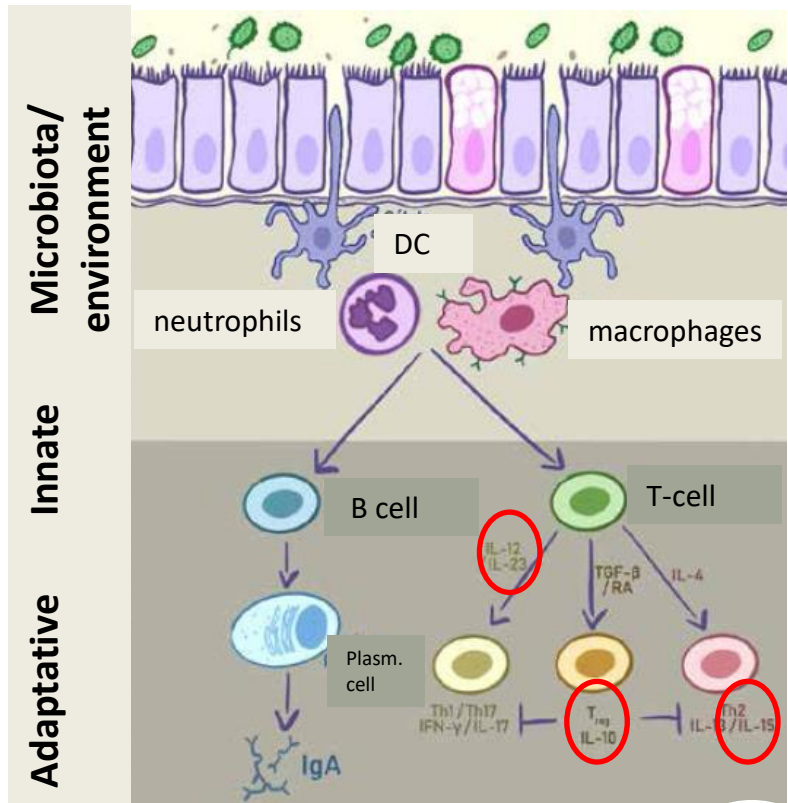
Celiac Disease



Nature Reviews | Gastroenterology & Hepatology

Trigger: Gluten

IBD



Trigger: Unknown

Verdu E et al, Nature Rev Gastro Hep 2015; Silva et al, Rev Clin LC 2019





Mechanisms Celiac disease and IBD

- Tryptophan can be metabolized by the gut microbiota into ligands of the aryl hydrocarbon receptor (AhR)
- AhR has an important role in modulating immunity; IELS, T cells, and innate lymphoid cells that produce interleukin-17 (IL-17) and IL-22

Celiac Disease

IBD

- Production of AhR ligands by the gut microbiota is decreased in celiac disease and IBD leading to intestinal inflammation.
- Modulation of gut microbiota leads to increase AhR ligands and reducing inflammation



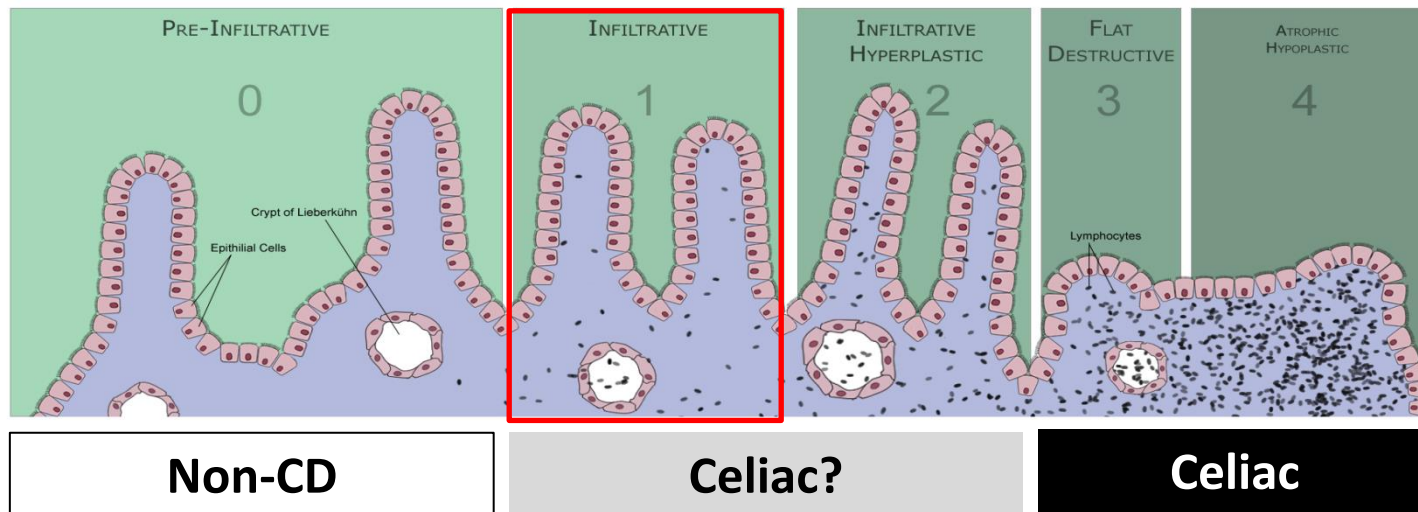
Celiac disease specific antibodies

		Sensitivity (%)	Specificity (%)
<i>Anti-gliadin</i>	IgA AGA *	<70–91	80–95
	IgG AGA *	17–100	80–95
<i>Anti-endomysium</i>	IgA EMA *	75–100	98–100
<i>Anti-tissue transglutaminase</i>	IgA tTG *†	75–95	91–99
<i>Anti-deaminated gliadin peptide</i>	IgA DGP *†	82–96	93–96
	IgG DGP †	70–95	99–100
	IgA + IgG DGP †	76–97	96–99
	IgA e IgG DGP y tTG †	83–100	98–99

Antibodies ~10-15% false positive: IBD differential Dx!



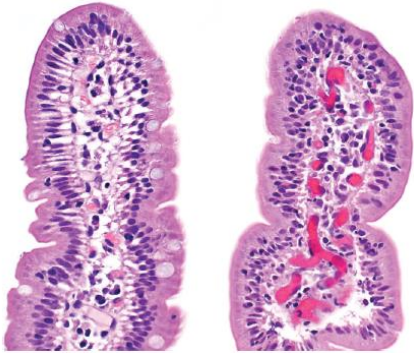
Celiac disease histology





Celiac disease histology: differential dx.

Lymphocytosis



Villous atrophy

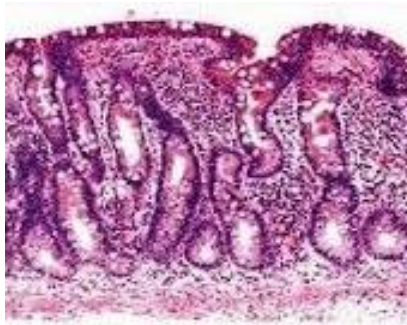
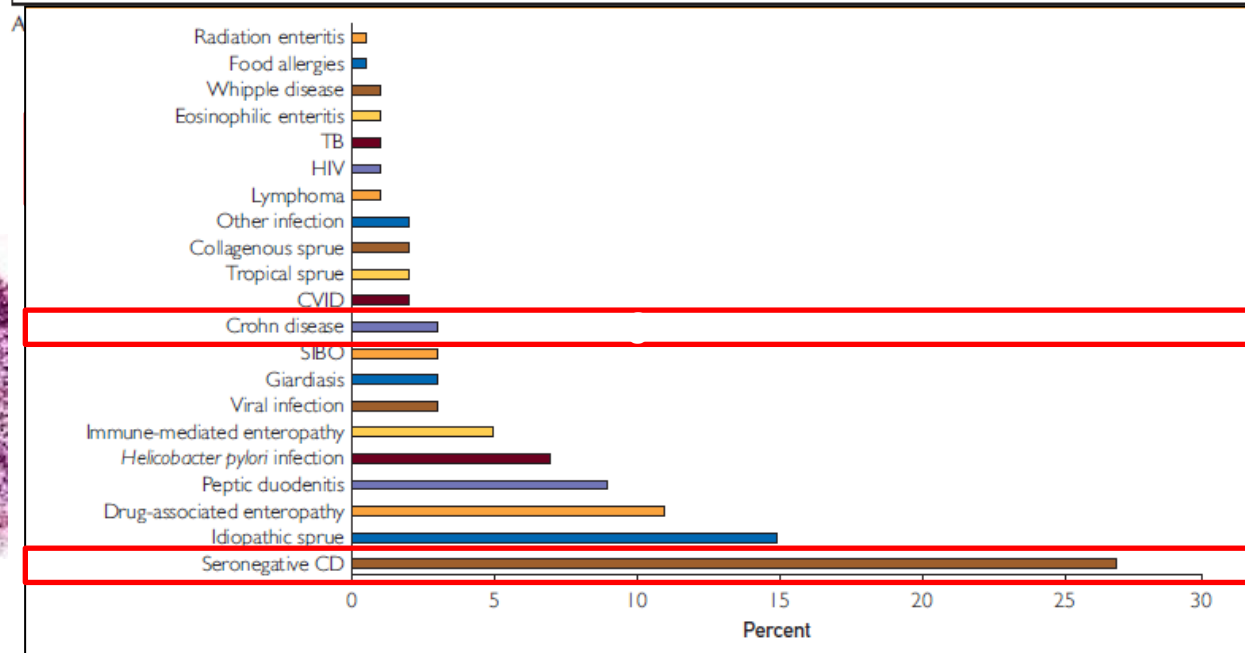


Table 1. Disease Associations

Disease Associations	Kakar et al, ² 2003, No. (%), n = 43	Mahadeva et al, ⁴ 2002, No. (%), n = 14	Hammer et al, ¹¹ 2010, No. (%), n = 100
Celiac disease	4 (9)	3 (21)	18 (18)
Tropical sprue	1 (2)	0 (0)	1 (1)
<i>Helicobacter pylori</i>	0 (0)	0 (0)	6 (6)
Bacterial overgrowth	2 (5)	0 (0)	3 (3)
NSAID use	6 (14)	0 (0)	8 (8)
Inflammatory bowel disease	5 (12)	0 (0)	8 (8)
Autoimmune conditions	6 (14)	0 (0)	6 (6)
Infection	0 (0)	0 (0)	0 (0)
Unexplained	3 (7)	3 (21)	26 (26)
Irritable bowel syndrome	4 (9)	2 (14)	20 (20)
Other	12 (28)	6 (43)	4 (4)



Hammer et al, Arch Lab pathol 2013; Jansson Knodel, Mayo clinic 2018





Celiac disease and IBD: similarities

- 1- Mechanisms pathophysiology
- 2- Celiac antibodies may be present in IBD
- 3- Enteropathy may be present in Crohn's disease
- 4- Clinical presentation

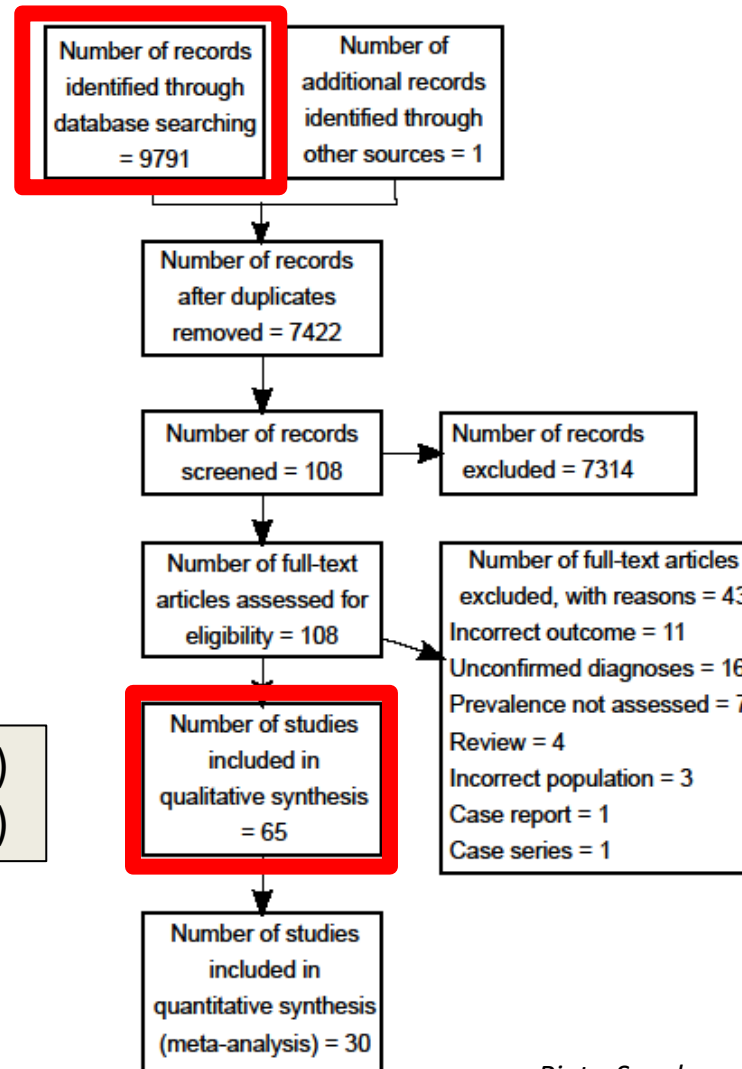


Are CeD and IBD associated? What is the risk of developing CeD in IBD and visversa?

Research for over 30 yrs; controversial results



Celiac disease and IBD SR and meta-analysis



Risk of IBD in CeD (n=37)
Risk of CeD in IBD (n=29)



Risk of Celiac disease in IBD:SR and meta-analysis



High risk



Low risk

			# celiac per group				
Study, year	Country	Age Category	IBD	Crohn's	UC	IC	Controls
Cohort Studies n=22							
Aletaha 2019	US	Adults	2.9/1000*	-	-	-	0.2/1000*
Alper 2018	US	Children	1/130	0/75	1/55	-	12/257
Bierdermann 2018	Switzerland	Adults	9/2019	-	-	-	-
Casella 2010	Italy	Adults	9/1711	3/860	6/791	0/60	-
Cucco 2014	Italy	Adults	0/179	0/71	0/108	-	-
Dhalwal 2009	Canada	Adults	0/150	0/150	-	-	-
El-Matary 2012	Canada	Children	1/164	0/85	1/79	-	1/164
Giorgetti 2006	Italy	Adults	8/48	8/48	-	-	-
Jandaghi 2015	Iran	Adults	1/406	0/206	1/200	-	1/166
Klincewicz 2007	Poland	Children	6/136	4/49	2/87	-	-
Lakatos 2003	Hungary	Both	2/873	1/254	1/619	-	-
Malmborg 2017	Sweden	Children	12/256	9/190	3/60	0/6	-
Mantzaris 2005	Greece	Adults	6/639	1/281	5/358	-	-
Merrick 2015	UK, Scotland, Canada	Children	4/809	4/533	0/204	0/72	-
Perez 2017	UK	Children	8/578	-	-	-	-
Ronnblom 2015	Sweden	Both	17/790	4/264	13/526	-	-
Szafarska-Poplawska 2016	Poland	Both	0/71	0/71	-	-	-
Tursi 2005	Italy	Adults	5/27	5/27	-	-	-
Virta 2013	Finland	Children	13/595	4/233	9/362	-	14/2380
Watanabe 2014	Japan	Adults	0/172	0/62	0/110	-	0/190
Yehuda 2019	Israel	Adults	141/12625	96/6364	45/6261	0/342	51/12625
Zwolinska-Wcislo 2009	Poland	Adults	4/80	-	4/80	-	-
Case-control Studies n=4							
Bizzaro 2003	Italy	Adults	1/170	0/70	1/100	-	0/120
Kull 1999	Estonia	Adults	0/50	-	0/50	-	0/53
Leeds 2007	UK	Adults	3/354	1/173	2/154	0/18	5/601
Ribeiro-Cabral 2014	Brazil	Adults	0/33	0/33	-	-	4/45
Cross-sectional Studies n=11							
Akkelle 2019	Turkey	Children	0/125	0/57	0/66	0/2	-
Casellas 2016	Spain	Adults	5/407	-	-	-	0.47% **
de Carvalho 2018	Brazil	Adults	0/83	0/36	0/47	-	-
Halling 2017	Denmark	Adults	280/47325	133/13343	132/31066	15/2916	92/92839
Korponay-Szabó 1993	Hungary	Children	1/38	-	-	-	11/718
Limketkai 2018	US	Adults	5/102	-	-	-	-
Lu 2015	Canada	-	10/780	-	-	-	-
Oxford 2013	US	Adults	393/33963	220/17288	173/16675	-	42/17503
Sjoberg 2002	Sweden	Adults	0/57	0/34	0/23	-	0/44
Taghvai 2014	Iran	Adults	0/84	-	0/84	-	-
Tavakkoli 2012	Iran	Adults	9/100	3/30	6/70	-	-

Pinto-Sanchez et al, Gastroenterology 2020





Risk of IBD in CeD



High risk



Low risk

			# IBD		# Crohn's		# UC	
Study, year	Country	Age	Celiac	Control	Celiac	Control	Celiac	Control
Cohort Studies n=19								
Akin 2012	Turkey	Adults	1/22	-	1/22	-	0/22	-
Aletaha 2019	Turkey	Adults	10/1000*	0.5/1000*	-	-	-	-
Basaranoglu 2015	Turkey	-	5/198	-	1/198	-	4/198	-
Breen 1987	Ireland	Adults	3/42	-	0/42	-	3/42	-
Canova 2017	Italy	Children	29/1294	6/6470	11/1294	3/6470	10/1294	2/6470
Collin 1994	Finland	Adults	1/335	7/335	-	-	-	-
Cooper 1978	UK	Adults	4/314	-	1/314	-	3/314	-
Cuoco 2014	Italy	Adults	0/744	-	0/744	-	0/744	-
Damoiseaux 2002	Netherlands	Both	0/37	0/35	0/37	0/35	0/37	0/35
Dominguez Castro 2017	Ireland	Adults	14/749	-	6/749	-	8/749	-
Jansson-Knodell 2018	US	Adults	4/282	-	4/282	-	0/282	-
Juhász 2012	Hungary	Adults	6/132	-	6/132	-	0/132	-
Kocsis 2015	Hungary	Adults	8/245	-	6/245	-	2/245	-
Mantzaris 2005	Greece	Adults	6/53	-	1/53	-	5/53	-
Nijhawan 2013	India	Both	2/363	-	0/363	-	2/363	-
Sood 2003	India	Adults	3/96	-	0/96	-	3/96	-
Spijkerman 2016	Netherlands	Adults	6/412	-	-	-	-	-
Ventura 1999	Italy	Both	2/909	3/1268	0/909	0/1268	2/909	3/1268
Yang 2005	US	Adults	10/455	362/ 100,000	5/455	133/ 100,000	5/455	229/100,000
Case-control Studies n=4								
Bibbò 2017	Italy	Adults	6/255	-	3/255	-	3/255	-
Delcò 1999	US	Adults	13/458	18/2692	8/458	6/2692	5/458	12/2692
Leeds 2007	UK	Adults	5/305	2/601	0/305	1/601	5/305	1/601
Paoletta 2014	Italy	Children	0/350	0/350	0/350	0/350	0/350	0/350
Cross-sectional Studies n=6								
Assa 2017	Israel	Teens	27/7145	1483/ 1580896	-	-	-	-
Conti 2018	Italy	Adults	1/341	-	-	-	-	-
Grode 2018	Denmark	Both	462/ 10285	1105/ 104928	140/ 10285	238/ 104928	322/ 10285	867/ 104928
Hernandez Camba 2013	Spain	Adults	4/91	-	3/91	-	1/91	-
Inserra 2011	Italy	Adults	80/1268	1.61%**	-	-	-	-
Prinzbach 2018	US	Children	10/433	11/4330	10/433	8/4330	0/433	3/4330



Risk of IBD in CeD and viseversa

Outcomes	Anticipated absolute effects* (95% CI)		Relative risk (95% CI)	No pts (studies)	Certainty of evidence (GRADE)	Comments
	Risk in controls	Risk in cases				
CeD in IBD	1 per 1,000	5 per 1,000 (3 to 10)	RR 3.96 (2.23 to 7.02)	189,344 (5)	⊕⊕⊕○ MODERATE a,b,c	The risk of CeD is likely much higher in IBD than in controls.
CeD in CD	2 per 1,000	10 per 1,000 (5 to 20)	RR 4.43 (2.15 to 9.14)	60,443 (4)	⊕⊕⊕○ MODERATE a,b,c	The risk of CeD is likely much higher in Crohn's than in controls.
CeD in UC	2 per 1,000	5 per 1,000 (3 to 8)	RR 2.81 (1.82 to 4.36)	148,890 (10)	⊕⊕⊕○ MODERATE b,c,d	The risk of CeD is likely much higher in UC than in controls.
IBD in CeD	9 per 1,000	88 per 1,000 (36 to 216)	RR 9.88 (4.03 to 24.21)	148,646 (5)	⊕⊕⊕○ MODERATE a,b	The risk of IBD is likely much higher in CeD than in controls.
CD in CeD	2 per 1,000	14 per 1,000 (9 to 21)	RR 7.73 (5.09 to 11.73)	232,323 (7)	⊕⊕⊕⊕ HIGH d,f	The risk of Crohn's disease is much higher in CeD than in controls.
UC in CeD	5 per 1,000	21 per 1,000 (12 to 35)	RR 4.08 (2.40 to 6.95)	234,500 (8)	⊕⊕⊕○ MODERATE b,d	The risk of UC is likely much higher in CeD than in controls.

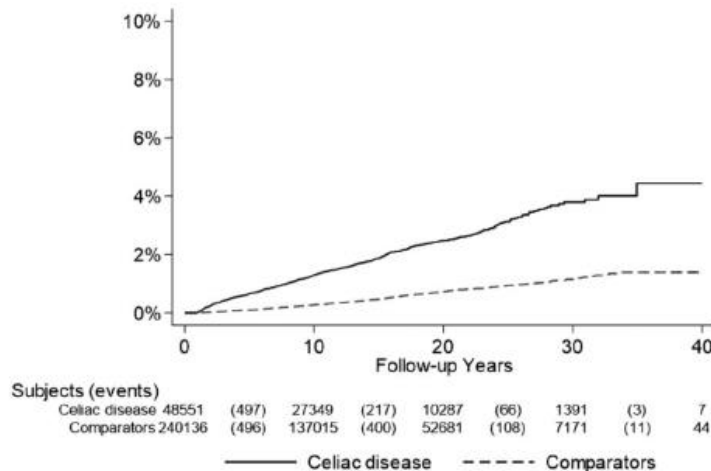


Association of IBD in CeD

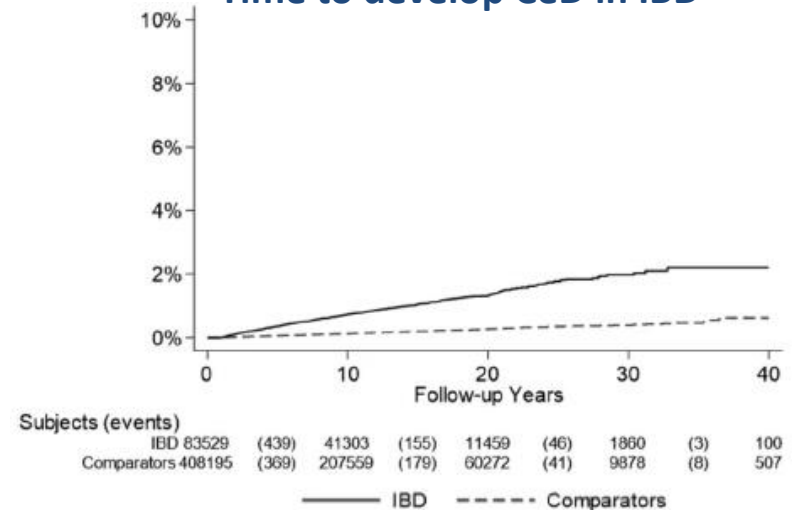
Risks vs matched general population comparators (1969-2017)

Cases	Matched comparators
48,551 CeD	240,136
85,529 IBD	408,195

Time to develop IBD in CeD



Time to develop CeD in IBD



2.5% of CeD developed IBD, and 1.3% with IBD developed CeD; higher than GP



Summary: Association of IBD in CeD

- The bidirectional association between CeD diagnosis and IBD warrants attention in the initial assessment and follow-up of these conditions.
- Their co-occurrence, independent of temporal sequence, suggests shared etiology

Should IBD patients
be screened for IBD?





Unknown areas that need research

- ✓ Association IBD and CeD in different countries
- ✓ False positive CeD serology in IBD- how impact on risk
- ✓ Cost effectiveness of detecting CeD in IBD and vise versa
- ✓ Clinical benefit of detecting CeD in IBD and vise versa

