**Supplemental Digital Content**

**Table 1.** Literature Review of comorbidities associated with celiac disease and the types of studies conducted.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Example Recent Study** | | | |
| **Comorbidities** | **Prevalence of Comorbidity in Patients with Celiac Disease (Adult and Pediatric populations)** | **Author (Year)** | **Type of Study** | **Size** | **Finding** |
| **Diabetes Mellitus Type 1** | Range: 2.2% -12.6%1,2 | Viljamaa (2005)1,3 | Adult + Pediatric Population, Retrospective Chart Review, Hypothesis Driven | 703 CD[[1]](#footnote-1) Cases, matched with 299 controls | Prevalence of Type I Diabetes in CD=12.6% (Significant) |
| **Autoimmune Thyroiditis** | Range: 5.95% - 17.6%1,4 | Cosnes (2008)5 | Adult + Pediatric Population, Retrospective Cross-sectional Study, Hypothesis Driven | 924 CD patients | Prevalence of Autoimmune Thyroiditis in CD=5.95% |
| **Autoimmune Thyroid Disorders** | Range: 4.8%- 10.2%6 | Canova (2016)7,8 | Pediatric population, Population-Based Cohort Study,  Hypothesis Driven | 1251 CD cases, 5:1 matching on age and gender | Prevalence of ATD[[2]](#footnote-2) in CD = 4.8% (not significant); Hazard Ratio = 4.64 (Significant) |
| **Systemic Lupus Erythematosus** | Range: 1.4% - 2.4%1 | Freeman (2008)9 | Adult Population, Cross-Sectional Study, Hypothesis Driven | 246 CD Cases | Prevalence of Systemic Lupus Erythematosus in CD=2.4% |
| **Juvenile Arthritis** | Range: 2.8% -6.6% (This is the range of CD found in patients with Juvenile Arthritis)10,11 | Stagi (2005)10 | Pediatric Population, Cohort Study, Hypothesis Driven | 151 Juvenile Idiopathic Arthritis Cases, matched with 158 controls | Prevalence of CD in Juvenile Arthritis cases=6.6% (Significant) |
| **Dermatologic Herpetiformis** | Range: 2.9% - 25%12,13 | Iqbal (2013)14 | Adult + Pediatric Population, Cross-Sectional Cohort Study | 360 CD Cases matched with 234 controls | Prevalence of Dermatologic Herpetiformis in CD=13.5% |
| **Alopecia Areata** | Range: 0.9% - 3.5%1 | Ventura (1999)12 | Adult + Pediatric Population, Retrospective Cohort Study, Hypothesis Driven | 909 CD Cases, matched with 1268 controls | Prevalence of Alopecia Areata in CD=1.1% in patients aged 2-10 years; =3.5% in patients aged 10+ (Significant) |
| **Psoriasis** | Range: 4.1% - 12.9%1,14 | Ludvigsson (2011)15 | Adult + Pediatric Population, Cohort Study, Hypothesis Driven | 28,958 CD Cases, matched with 143,910 controls | Hazard Ratio=1.72 |
| **Inflammatory Bowel Disease** | Range: 2.2% | Yang (2005)16 | Adult + Pediatric Population, Cross Sectional Study, Hypothesis Driven | 455 CD cases | Prevalence of IBD in CD=2.2% |
| **Autoimmune Hepatitis** | Range: 2.0%-12.5%17 | Najafi (2014)18 | Pediatric Population, Cross Sectional Study, Hypothesis Driven | 32 CD Patients | Prevalence of Autoimmune Hepatitis in CD= 12.5% |
| **Selective IgA Deficiency** | Range: 1.7% - 2.6%1,19,20 | Cataldo (1997)19 | Pediatric + Adult Population, Cross-Sectional Study, Hypothesis Driven | 688 CD Cases | Prevalence of IgA Deficiency in CD=1.7% |
| **Down Syndrome[[3]](#footnote-3)** | Range: 1.4% - 4.8%21 | Khatib (2016)22 | Pediatric Population, Cross-Sectional Study | 177 CD cases | Prevalence of Down Syndrome in CD=4.8% |
| **ADHD** | Range: 0.86% - 2.94%23 | Dazy (2013)24 | Pediatric + Adult Population, Case-Control Study, Hypothesis Driven | 281 CD cases matched with 301 controls | Prevalence of ADHD in CD-2.94%(Not significant) |
| **Turner**  **Syndrome[[4]](#footnote-4)** | Range: 0.26% - 0.3%25 | Marild (2016)26 | Pediatric + Adult Population, Case-Control Study, Hypothesis Driven | 7,548 CD cases matched with 34,492 controls | Prevalence of Turner’s Syndrome in CD=0.26% (Not significant) |

**Table 2**. Expansion of significant ICD-10 Level 1 Hierarchy Codes into their detailed subtypes.

**Expected Diseases**

|  |  |
| --- | --- |
| **ICD 10 Code** | **Frequency (Cases, Controls)** |
| **Other diseases of stomach and duodenum (K31)** | |
| Disease of stomach and duodenum, unspecified (K31.9) | 82,5 |
| Gastroparesis (K31.84) | 1,3 |
| Fistula of stomach and duodenum (K31.6) | 1,1 |
| **Gastritis and duodenitis (K29)** | |
| Acute gastritis without bleeding (K29.00) | 1,2 |
| Chronic atrophic gastritis without bleeding (K29.40) | 9,6 |
| Unspecified chronic gastritis without bleeding (K29.50) | 3,2 |
| Other gastritis without bleeding (K29.60) | 5,6 |
| Gastritis, unspecified, without bleeding (K29.70) | 11,14 |
| Duodenitis without bleeding (K29.80) | 36,1 |
| Gastroduodenitis, unspecified, without bleeding (K29.90) | 8,11 |
| **Other anemias (D64)** | |
| Anemia, unspecified (D64.9) | 35,62 |
| **Immunodeficiency with predominantly antibody defects (D80)** | |
| Selective deficiency of immunoglobulin A [IgA] (D80.2) | 8,2 |
| **Other hypothyroidism(E03)** | |
| Hypothyroidism, unspecified (E03.9) | 13,30 |
| Other specified hypothyroidism (E03.8) | 7,10 |
| Congenital hypothyroidism without goiter (E03.1) | 3,5 |
| Hypothyroidism due to meds and other exogenous substances (E03.2) | 1,0 |

**Expected Symptoms**

|  |  |
| --- | --- |
| **ICD 10 Code** | **Frequency (Cases, Controls)** |
| **Other symptoms and signs involving the digestive system and abdomen (R19)** | |
| Diarrhea, unspecified (R19.7) | 122,161 |
| Other fecal abnormalities (R19.5) | 12,11 |
| Other symptoms and signs involving the digestive sys and abdomen (R19.8) | 7,9 |
| Right lower quadrant abdominal swelling, mass and lump (R19.03) | 1,0 |
| **Other functional intestinal disorders (K59)** | |
| Constipation, unspecified (K59.00) | 120,357 |
| Other constipation (K59.09) | 20,21 |
| Slow transit constipation (K59.01) | 4,6 |

**Potential Novel Findings**

|  |  |
| --- | --- |
| **ICD 10 Code** | **Frequency (Cases, Controls)** |
| **Family history of other specific disorders (Z83)** | |
| Family history of other diseases of the digestive system (Z83.79) | 15,3 |
| Family history of endocrine, nutritional and metabolic diseases (Z83.49) | 6,8 |
| Family history of diabetes mellitus (Z83.3) | 9,24 |
| Family history of disorders of the blood/immune mechanism | 1,11 |
| **Abnormal serum enzyme levels (R74)** | |
| Nonspecific elevated of levels of transaminase & lactic acid dehydrogenase (R74.0) | 27,21 |
| Abnormal levels of other serum enzyme levels (R74.8) | 6,12 |
| **Persons encountering health services for counseling and medical advice, not elsewhere classified (Z71)** | |
| Dietary counseling and surveillance (Z71.3) | 82,9 |
| Other specified counseling (Z71.89) | 57,11 |
| Counseling, unspecified (Z71.9) | 1,0 |
| **Esophagitis (K20)** | |
| Eosinophilic esophagitis (K20.0) | 12,15 |
| Esophagitis unspecified (K20.9) | 6,5 |
| **Other joint disorder, not elsewhere classified (M25)** | |
| Pain in knee (M25.56) \*Includes (M25.561) (M25.562) (M25.569) | 26,110 |
| Pain in ankle and joints of foot (M25.57) \*Includes (M25.571) (M25.572) (M25.579) | 16,60 |
| Pain in unspecified joint (M25.50) | 20,34 |
| Pain in hip (M25.55) \*Includes (M25.551) (M25.552) (M25.559) | 9,50 |
| Pain in wrist (M25.53) \*Includes (M25.531) (M25.532) (M25.539) | 9,32 |
| Pain in shoulder (M25.51) \*Includes (M25.511) and (M25.519) | 7,39 |
| Pain in elbow (M25.529) | 6,17 |
| Effusion, ankle and foot (M25.47) \*Includes (M25.472) (M25.473) (M25.476) | 2,9 |
| Effusion, wrist (M25.432) | 2,0 |
| Effusion, unspecified joint (M25.40) | 3,0 |
| Effusion, elbow (M25.429) | 3,5 |
| Effusion, knee (M25.469) | 2,18 |
| **Other systemic involvement of connective tissue (M35)** | |
| Hypermobility syndrome (M35.7) | 6,6 |
| Systemic involvement of connective tissue, unspecified (M35.9) | 4,0 |
| Other specified systemic involvement of connective tissue (M35.8) | 1,0 |
| Other overlap syndromes (M35.1) | 1,0 |
| **Other diseases of anus and rectum (K62)** | |
| Hemorrhage of anus and rectum (K62.5) | 13,16 |
| Other specified diseases of anus and rectum (K62.89) | 3,3 |
| Rectal prolapse (K62.3) | 1,4 |
| Anal sphincter tear (healed) (non-traumatic) (old) (K62.81) | 1,0 |
| Disease of anus and rectum, unspecified (K62.9) | 1,0 |
| **Allergy status to drugs, medicaments and biological substances (Z88)** | |
| Allergy status to penicillin (Z88.0) | 12,64 |
| Allergy status to other anti-infective agent’s status (Z88.3) | 10,35 |
| Allergy status to other antibiotic agent’s status (Z88.1) | 8,25 |
| Allergy status to other drug/meds/biological substance status (Z88.8) | 6,34 |
| Allergy status to narcotic agent status (Z88.5) | 3,8 |
| Allergy status to sulfonamides status (Z88.2) | 2,15 |
| Allergy status to anesthetic agent status (Z88.4) | 2,1 |
| Allergy status to analgesic agent status (Z88.6) | 2,6 |

**Table 3**. Characteristics of comorbid celiac disease and eosinophilic esophagitis cases.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Eosinophilic Esophagitis Cases** | **Gender** | **Race** | **Age at Diagnosis of Celiac Disease (years)** | **Confirmed Eosinophilic Esophagitis (With Biopsy)** | **Other Comorbidities** |
| 1 | M | White | 11.3 | Yes | Sensorineural hearing loss, Congenital preauricular pit, Asthma, Hydronephrosis |
| 2 | F | Biracial/Multiracial | 9.6 | Yes | Calcaneal apophysitis, Instability of right shoulder joint, Asthma, Eczema, Food Allergies |
| 3 | M | White | 5.6 | Yes | Food Allergy, Feeding difficulties, Poor weight gain, Anxiety disorder of childhood, ADHD predominantly hyperactive impulsive type, Raynaud's Syndrome, Asthma, GERD, Constipation, Wheezing, Otitis Media |
| 4 | F | White | 17.4 | Yes | Pain in joint, multiple sites, High BMI |
| 5 | M | White | 13.3 | Yes | Periumbilical abdominal pain, Obesity, Acanthosis, Acne, Bloating, Fecal Urgency, Anxiety, Panic Attack, Concussion, Anemia |
| 6 | M | White | 11.0 | Yes | Allergic rhinitis, GERD |
| 7 | F | White | 10.4 | Yes | Abdominal Pain, Otitis Media |
| 8 | F | White | 14.8 | Yes | Peanut Allergy, Dysphagia, Depression, Asthma |
| 9 | M | White | 13.3 | Yes | Elevated IgA level |
| 10 | M | White | 9.6 | Yes | Dysphagia, Finger sprain |
| 11 | M | White | 8.2 | Yes | Congenital renal dysplasia, Hypospadias, RSV infection as an infant, Constipation |
| 12 | F | White | 5.4 | Yes | Dysphagia, Microcytosis, GERD |

**Table 4**. Investigation of “Overweight and obesity” (E66) finding via BMI analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Age Group (years)** | **Average BMI of Celiac Disease Cases** | **Number of Cases[[5]](#footnote-5)** | **Average BMI of Matched Controls** | **Number of Control Matched Entries[[6]](#footnote-6)** |
| 0 - 5 | 15.60 | 81 | 16.50 | 520 |
| 5 - 10 | 16.27 | 151 | 17.73 | 671 |
| 10 - 15 | 19.05 | 123 | 21.96 | 704 |
| 16 - Older | 22.90 | 77 | 25.24 | 406 |

**References**

1. Viljamaa M, Kaukinen K, Huhtala H, Kyrönpalo S, Rasmussen M, Collin P. Coeliac disease, autoimmune diseases and gluten exposure. Scand J Gastroenterol. 2005;40(4):437-443.

2. Iqbal T, Tariq I, Zaidi MA, Wells GA, Jacob K. Celiac disease arthropathy and autoimmunity study. J Gastroenterol Hepatol. 2012;28(1):99-105.

3. Viljamaa M, Kaukinen K, Huhtala H, Kyrönpalo S, Rasmussen M, Collin P. Coeliac disease, autoimmune diseases and gluten exposure. Scand J Gastroenterol. 2005;40(4):437-443.

4. Viljamaa M, Kaukinen K, Huhtala H, Kyrönpalo S, Rasmussen M, Collin P. Coeliac disease, autoimmune diseases and gluten exposure. Scand J Gastroenterol. 2005;40(4):437-443.

5. Cosnes J, Cellier C, Viola S, et al. Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet. Clin Gastroenterol Hepatol. 2008;6(7):753-758.

6. Elli L, Bonura A, Garavaglia D, et al. Immunological comorbity in coeliac disease: associations, risk factors and clinical implications. J Clin Immunol. 2012;32(5):984-990.

7. Canova C, Pitter G, Ludvigsson JF, et al. Celiac Disease and Risk of Autoimmune Disorders: A Population-Based Matched Birth Cohort Study. J Pediatr. 2016;174:146-152.e1.

8. Cosnes J, Cellier C, Viola S, et al. Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet. Clin Gastroenterol Hepatol. 2008;6(7):753-758.

9. Freeman HJ. Adult Celiac Disease Followed by Onset of Systemic Lupus Erythematosus. J Clin Gastroenterol. 2008;PAP. doi:10.1097/mcg.0b013e31802e70a1.

10. Stagi S, Giani T, Simonini G, Falcini F. Thyroid function, autoimmune thyroiditis and coeliac disease in juvenile idiopathic arthritis. Rheumatology . 2005;44(4):517-520.

11. Alpigiani MG, Haupt R, Parodi S, Calcagno A, Poggi E, Lorini R. Coeliac disease in 108 patients with juvenile idiopathic arthritis: a 13-year follow-up study. Clin Exp Rheumatol. 2008;26(1):162.

12. Ventura A, Magazzù G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. SIGEP Study Group for Autoimmune Disorders in Celiac Disease. Gastroenterology. 1999;117(2):297-303.

13. Lauret E, Rodrigo L. Celiac disease and autoimmune-associated conditions. Biomed Res Int. 2013;2013:127589.

14. Iqbal T, Tariq I, Zaidi MA, Wells GA, Jacob K. Celiac disease arthropathy and autoimmunity study. J Gastroenterol Hepatol. 2012;28(1):99-105.

15. Ludvigsson JF, Lindelöf B, Zingone F, Ciacci C. Psoriasis in a nationwide cohort study of patients with celiac disease. J Invest Dermatol. 2011;131(10):2010-2016.

16. Yang A, Chen Y, Scherl E, Neugut AI, Bhagat G, Green PHR. Inflammatory Bowel Disease in Patients with Celiac Disease. Inflamm Bowel Dis. 2005;11(6):528-532.

17. Di Biase AR, Colecchia A, Scaioli E, et al. Autoimmune liver diseases in a paediatric population with coeliac disease - a 10-year single-centre experience. Aliment Pharmacol Ther. 2010;31(2):253-260.

18. Najafi M, Sadjadei N, Eftekhari K, et al. Prevalence of Celiac Disease in Children with Autoimmune Hepatitis and vice versa. Iran J Pediatr. 2014;24(6):723-728.

19. Cataldo F, Marino V, Bottaro G, Greco P, Ventura A. Celiac disease and selective immunoglobulin A deficiency. J Pediatr. 1997;131(2):306-308.

20. Cataldo F, Marino V, Ventura A, Bottaro G, Corazza GR. Prevalence and clinical features of selective immunoglobulin A deficiency in coeliac disease: an Italian multicentre study. Italian Society of Paediatric Gastroenterology and Hepatology (SIGEP) and “Club del Tenue” Working Groups on Coeliac Disease. Gut. 1998;42(3):362-365.

21. Mårild K, Stephansson O, Grahnquist L, Cnattingius S, Söderman G, Ludvigsson JF. Down syndrome is associated with elevated risk of celiac disease: a nationwide case-control study. J Pediatr. 2013;163(1):237-242.

22. Khatib M, Baker RD, Ly EK, Kozielski R, Baker SS. Presenting Pattern of Pediatric Celiac Disease. J Pediatr Gastroenterol Nutr. 2016;62(1):60-63.

23. Ertürk E, Wouters S, Imeraj L, Lampo A. Association of ADHD and Celiac Disease: What Is the Evidence? A Systematic Review of the Literature. J Atten Disord. January 2016. doi:10.1177/1087054715611493.

24. Dazy KM, Rubenstein JH, Holevinski L, Kao JY. Sa1825 The Prevalence of ADHD in Adults and Children Previously Diagnosed with Celiac Disease: A Hospital-Based Study. Gastroenterology. 2013;144(5):S - 251 - S - 252.

25. Işikay S, Kocamaz H. The Neurological Face of Celiac Disease. Arq Gastroenterol. 2015;52(3):167-170.

26. Marild K, Stordal K, Hagman A, Ludvigsson JF. Turner Syndrome and Celiac Disease: A Case-Control Study. Pediatrics. 2016;137(2):e20152232-e20152232.

27. Lucendo AJ, Arias Á, Tenias JM. Systematic review: the association between eosinophilic oesophagitis and coeliac disease. Aliment Pharmacol Ther. 2014;40(5):422-434.

28. Ooi CY, Day AS, Jackson R, Bohane TD, Tobias V, Lemberg DA. Eosinophilic esophagitis in children with celiac disease. J Gastroenterol Hepatol. 2008;23(7 Pt 1):1144-1148

1. CD = Celiac Disease [↑](#footnote-ref-1)
2. ATD = Autoimmune Thyroid Disease [↑](#footnote-ref-2)
3. The prevalence of celiac disease in patients with Down syndrome has been better established than the inverse relationship [↑](#footnote-ref-3)
4. This study demonstrated an increased risk of developing CD in Turner Syndrome, but not the inverse relationship [↑](#footnote-ref-4)
5. Excluded one case of a missing BMI value [↑](#footnote-ref-5)
6. Excluded 2,022 controls of missing BMI values [↑](#footnote-ref-6)