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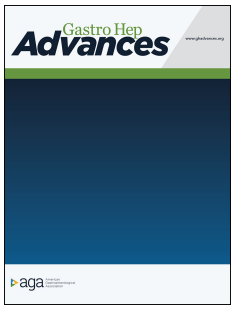

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Authors' contributions

- NAF- conceptualization, methodology, validation, data curation, writing- original draft, writing- review & editing, project administration, prepared figures, supervision
- FD- methodology, software, validation, formal analysis, data curation, writing- review & editing, prepared figures
- RO- conceptualization, methodology, validation, writing- review & editing, project administration, supervision
- All authors have approved the final version for submission.

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Ethics Statement: This study was reviewed and deemed exempt from human subjects research regulations by the Institutional Review Board of the University of California, San Diego (IRB #809009).

Availability of data and materials: Data available in the All of Us database website v7.

Reporting Guidelines: STROBE

List of abbreviations:

1. CD – Celiac disease
2. CTD – Connective tissue disorders
3. EDS – Ehlers-Danlos syndrome
4. cEDS – Classical EDS
5. vEDS – Vascular EDS
6. hEDS – Hypermobile EDS

7. AoU- All of Us
8. OR – Odds ratios
9. SNOMED - Systematized Nomenclature of Medicine
10. SD – Standard deviation
11. AI – Autoimmune
12. JHS – Joint hypermobility syndrome

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Celiac disease (CD) is an auto-immune condition triggered in genetically susceptible individuals when consuming gluten. The relationship between CD and connective tissue disorders (CTD) has been studied to varying degrees. Ehlers-Danlos syndrome (EDS) encompasses a heterogeneous group of CTD resulting from abnormal collagen, the primary structural component of connective tissue.[1]

The 2017 international classification of EDS identifies 13 subtypes, each associated with specific genetic variants affecting collagen structure and function. Notably, classical EDS (cEDS) is commonly linked to mutations in the COL5A1 and COL5A2 genes, which encode type V collagen, while vascular EDS (vEDS) is linked to mutations in the COL3A1 gene, affecting type III collagen. Hypermobile EDS (hEDS), the most prevalent subtype, has an unknown genetic cause, though suspected to have an autosomal dominant inheritance pattern. This genetic heterogeneity may lead to joint hypermobility, skin hyperextensibility, and tissue fragility, varying considerably among the different subtypes.[2]

Few studies have examined the CD-EDS association and findings have been inconsistent. To our records, only one population-based study has been done investigating the EDS-CD association, with only two smaller studies examining this link, all in Europe.[1] To assess the risk of a clinical diagnosis of EDS in CD patients in the United States (US), we used the All of Us (AoU) database, a National Institutes of Health (NIH) initiative designed to advance research in underrepresented populations in the US.[2] Our study is the first to highlight this association in this nationwide, US cohort of over 400,000 participants.

We conducted a case-control study with US adults, enrolled in the the AoU program from May 6, 2018 to February 2, 2025. We followed the STROBE reporting guidelines. Fisher's exact tests

or Chi-square tests were used to analyze categorical variables such as sex, race, and ethnicity. Unpaired t test was used for continuous variables, such as age and body mass index (BMI). We applied logistic regression to estimate odds ratios (OR).

EDS ad CD were identified using electronic health record (EHR) data within AoU, utilizing Systematized Nomenclature of Medicine (SNOMED) codes (detailed in the supplement). Each CD case was matched by age, sex, race, ethnicity, and BMI to four controls. Two-sided P-value of less than 0.05 was determined statistically significant. Analyses were performed in Python using Pandas, NumPy, SciPy, Statsmodels, and Seaborn libraries.

We identified 1,866 CD cases (mean [SD] age: 57.8 [17.0] years) and 7,290 matched controls (mean [SD] age: 57.8 [16.8] years). CD cases were matched 4:1 with controls by age, sex, race and ethnicity, and BMI. CD participants had higher EDS diagnoses than controls (51 [2.7%] vs 29 [0.3%]; p<0.001 (Table 1).

Our univariable and multivariable models were as follows, EDS (OR, 9.73; 95% CI, 5.84-16.21) and (OR, 8.93; 95% CI, 5.31-15.01; p<.001), respectively. We found a significant association between EDS and CD before and after adjusting for autoimmune disease (AI) (Sjogren's syndrome, rheumatoid arthritis, and systemic lupus erythematosus). Out of over 400,000 AoU participants, 721 had EDS, yielding a prevalence of ~0.18%.

This is the first large-scale, US investigation linking CD and EDS. We found an 8.93- fold increase in odds of CD individuals being diagnosed with EDS compared to controls. Prior studies have been limited to European populations and yielded mixed results. Laszkowska et al reported a 49% increased risk of EDS or joint hypermobility syndrome (JHS) in CD patients, though this was not seen when compared to biopsy-negative controls, suggesting possible surveillance bias.[1] They also found an increased risk in CD patients diagnosed with EDS, though to a lesser degree. Fikree et al found 31% of CD patients had JHS, compared to 25% of individuals with other gastrointestinal diseases, though the odds were not statistically significant.[3] Danese et al screened 31 patients with confirmed EDS/JHS and reported a significantly higher prevalence of CD compared to the general population.[4] These findings suggest CTD may predispose individuals to autoimmunity and systemic inflammation, increasing the risk of developing CD.

We adjusted for AI, which are independently associated with both CD and EDS and were not considered in prior studies. These conditions share common immunological and genetic underpinnings that may contribute to the increased prevalence of EDS among CD patients, and vice versa. Of note, we found a link of hypothyroidism and diabetes mellitus type 1 with CD during our literature review, but not with EDS so we refrained from adjusting for these conditions. This may also help clarify why our observed association is stronger than in prior studies, which did not account for these potential confounders and often relied on smaller or more homogenous populations.

One potential explanation causing a higher prevalence of AI in EDS cases is increased intestinal permeability (leaky gut), a phenomenon implicated in autoimmunity. Paray et al, suggests that

defects in the intestinal barrier allow luminal antigens to enter the bloodstream, initiating immune activation and contributing to disease.[8] It is plausible that connective tissue dysfunction contributes to barrier instability, facilitating heightened immune responses. This mechanism has been associated with CD, suggesting that CTD may predispose individuals to autoimmunity via impaired gut integrity. We present this as a hypothesis that warrants further investigation.

Our limitations include the lack of data on disease severity, potential misclassification of diagnoses, and observational study. Prospective research should focus on examining the temporal relationship between CD and EDS. Genetic studies investigating shared genetic markers between CD and EDS could explain potential common pathways. Biochemical and nutritional assessments evaluating the role of nutrient deficiencies in contributing to CTD in CD patients may provide further insight. Mechanistic studies exploring inflammatory pathways and immune-mediated mechanisms underlying the EDS-CD association would also be beneficial.

This study highlights a robust association between CD and EDS, suggesting that EDS-related connective tissue dysfunction may contribute to autoimmune susceptibility, including CD. Clinicians should perform a review of systems to evaluate for the development of inflammatory bowel disease in EDS patients. Further research is needed to elucidate shared genetic and immunological pathways.

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Table 1 Clinical Characteristics of celiac disease (CD) Cases and Matched Controls, and odds ratios (OR) of Ehlers-Danlos syndrome (EDS) in CD Patients vs Controls

	Participants, No. (%)[a]			OR (95% CI)[e]			
Characteristic	**Patients with CU, (n = 1,866)**	**Matched controls, (n = 7,290)**	***P*-value[d]**	**Univariable Analysis**	***P*-value**	**Multivariable Analysis**	***P*-value**
Age, mean (SD), y	57.8 (17.0)	57.8 (16.8)	0.92				
Sex			1.00				
Female	1453 (77.9)	5685 (78.0)	0.91				
Male	382 (20.5)	1501 (20.6)	1.00				
Other [b]	31 (1.7)	104 (1.4)	0.52				
Race and ethnicity							
Not Hispanic or Latino			>0.99				
Asian	<20	49 (0.7)					
Black	74 (4.0)	292 (4.0)					
White	1510 (80.9)	5924 (81.3)					
Hispanic or Latino							
Asian	<20	<20					
Black	<20	<20					
White	29 (1.6)	112 (1.5)					
Other [c]	238 (12.8)	905 (12.4)					
BMI, mean (SD)	27.1 (7.9)	27.1 (7.7)	0.9				
Autoimmune Disease [f]	324 (17.4)	369 (5.1)	<0.001				
EDS	51 (2.7)	21 (0.3)	<0.001	9.73 (5.84-16.21)	<0.001	8.93 (5.31-15.01)	<0.001

[a] In line with the data and statistics dissemination policy of the NIH All of Us Research Program, any values involving fewer than 20 individuals are presented in this manner to ensure participant privacy.

[b] Includes participants who either had no matching concept or who did not identify as male or female, preferred not to answer, or skipped the question.

[c] Includes participants who did not indicate Hispanic or Latino, skipped, did not identify with any of the races, identified with more than one Hispanic or Latino population, identified with more than one non-Hispanic or non-Latino origin, or belonged to single population not Hispanic or Latino.

[d] Statistical p-values highlighting prevalence variations between CU cases and controls.

[e] Statistical p-values assessing the significance of the OR.

[f] Sjogren's syndrome, rheumatoid arthritis, and systemic lupus erythematosus.