# Supplementary Online Content

Achler T, Patalon T, Gazit S, Cohen S, Shaoul R, Ben-Tov A. Early-life exposure to acid-suppressive therapy and the development of celiac disease autoimmunity. *JAMA Netw Open.* 2025;8(4):e253376. doi:10.1001/jamanetworkopen.2025.3376



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

**eTable 1.** Variables Stratified in Cox Models to Address Non-Proportional Hazards Assumption

| Exposure | Outcome | Non-stratified covariates | Stratified covariates | Comment |
|---|---|---|---|---|
| AST | CDA | Sex, SES | Birth year | |
| AST level (1,2+) | CDA | | | |
| AST type | CDA | | | |
| AST | CDA test | | Sex, birth year, SES | Schoenfeld residuals were significant (<0.001) for the exposure variable |
| AST level (1,2+) | CDA test | | | |
| AST type | CDA test | | | |

Abbreviations: AST, acid-suppressive therapy; CDA, celiac disease autoimmunity; SES, socioeconomic status.

**eTable 2.** Baseline Characteristics Per Maximal CDA Test ULN in the Case-Control Analysis, Post Matching

| | Maximal ULN ≤ 10 | Maximal ULN > 10 | p |
|---|---|---|---|
| n | 2,761 | 3,415 | |
| Male[a] (%) | 1,085 (39.3) | 1,252 (36.7) | 0.04 |
| Female (%) | 1,676 (60.7) | 2,163 (63.3) | 0.04 |
| Birth year[a], median (IQR) | 2013 (2009-2016) | 2012 (2009-2016) | 0.33 |
| SES[a,b], median (IQR) | 7.0 (5.0-9.0) | 7.0 (4.0-9.0) | <0.001 |
| AST usage (%) | 151 (5.5) | 158 (4.6) | 0.15 |

Abbreviations: AST, acid-suppressive therapy; CD, Celiac disease; IQR, interquartile range; SD, standard deviation; SES, socioeconomic status.
[a] Covariates used for propensity score matching
[b] Residential area SES by the central bureau of statistics census data. Range 1-10 (10 indicates high status).
[d] The number of positive test for tested positive and the number of latest test for tested negative.

**eTable 3.** Cox Proportional Hazard Model of Acid-Suppressive Therapy for Celiac Disease Autoimmunity Using Unmatched Data

| | aHR for CD-positive (95% CI) |
|---|---|
| AST Usage | 1.47 (1.31-1.65) |
| Male | 0.58 (0.55-0.61) |

Abbreviations: aHR, adjusted hazard-ratio; AST, acid-suppressive therapy; CD, celiac disease.

* Covariates that showed dependency between Schoenfeld residuals and time were used to stratify the model.

**eTable 4.** Cox Proportional Hazard Model of Acid-Suppressive Therapy for 10 Times Upper Limit Normal Celiac Disease Autoimmunity Using Unmatched Data

| | aHR for ten-time ULN CD-positive (95% CI) |
|---|---|
| AST Usage | 1.37 (1.17-1.61) |
| Male | 0.55 (0.51-0.59) |
| SES[a] | 1.06 (1.05-1.08) |

Abbreviations: aHR, adjusted hazard-ratio; AST, acid-suppressive therapy; CD, celiac disease; SES, socioeconomic status; ULN, upper limit normal.

* Covariates that showed dependency between Schoenfeld residuals and time were used to stratify the model.

[a] Residential area SES by the central bureau of statistics census data. Range 1-10 (10 indicates high status).

**eFigure.** Directed Acyclic Graph Showing the Association Between AST and CDA in the Test-Negative Design. The model was adjusted for the baseline covariates (C) and was restricted for tested population (T)

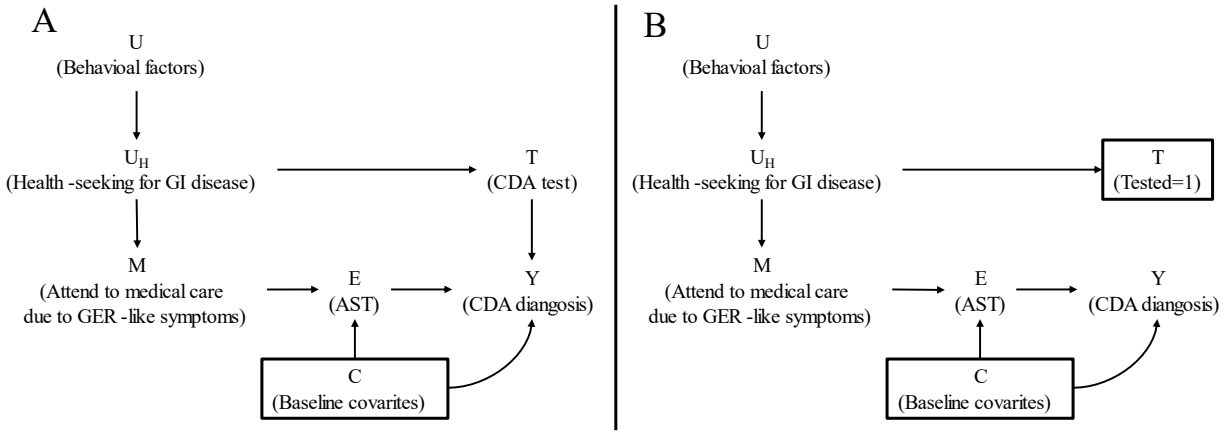


Figure S1. Directed acyclic graph showing the relationship between AST and CDA prior and after applying the test-negative design. U – behavioral factors such as child temperament and mother health-seeking behavior. E – using AST; Y – positive CDA serology test; $U_H$ – health seeking behavior specific for GI diseases; M – attending to doctor due to GER-like symptoms;T – perform a serology test for CDA; C – baseline confounders (sex, birth year, birth order, preterm level, gestational age, and socioeconomic status). Abbreviations: AST – acid-suppressive therapy; CDA – celiac disease autoimmunity; GER – gastroesophageal reflux; GI – gastrointestinal.(A) Before applying the test negative design, a possible backdoor pathway linking E to Y through the common ancestor $U_H$ (B) Conditioning the analysis on the tested population eliminates the backdoor pathway between E and Y.