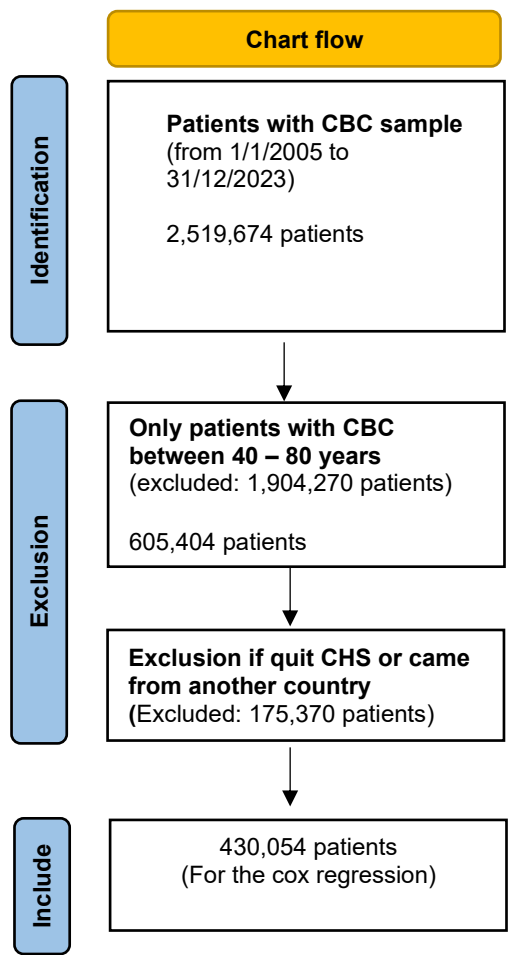


Supplement File (1)

Diagram of eligibility for the cox regression

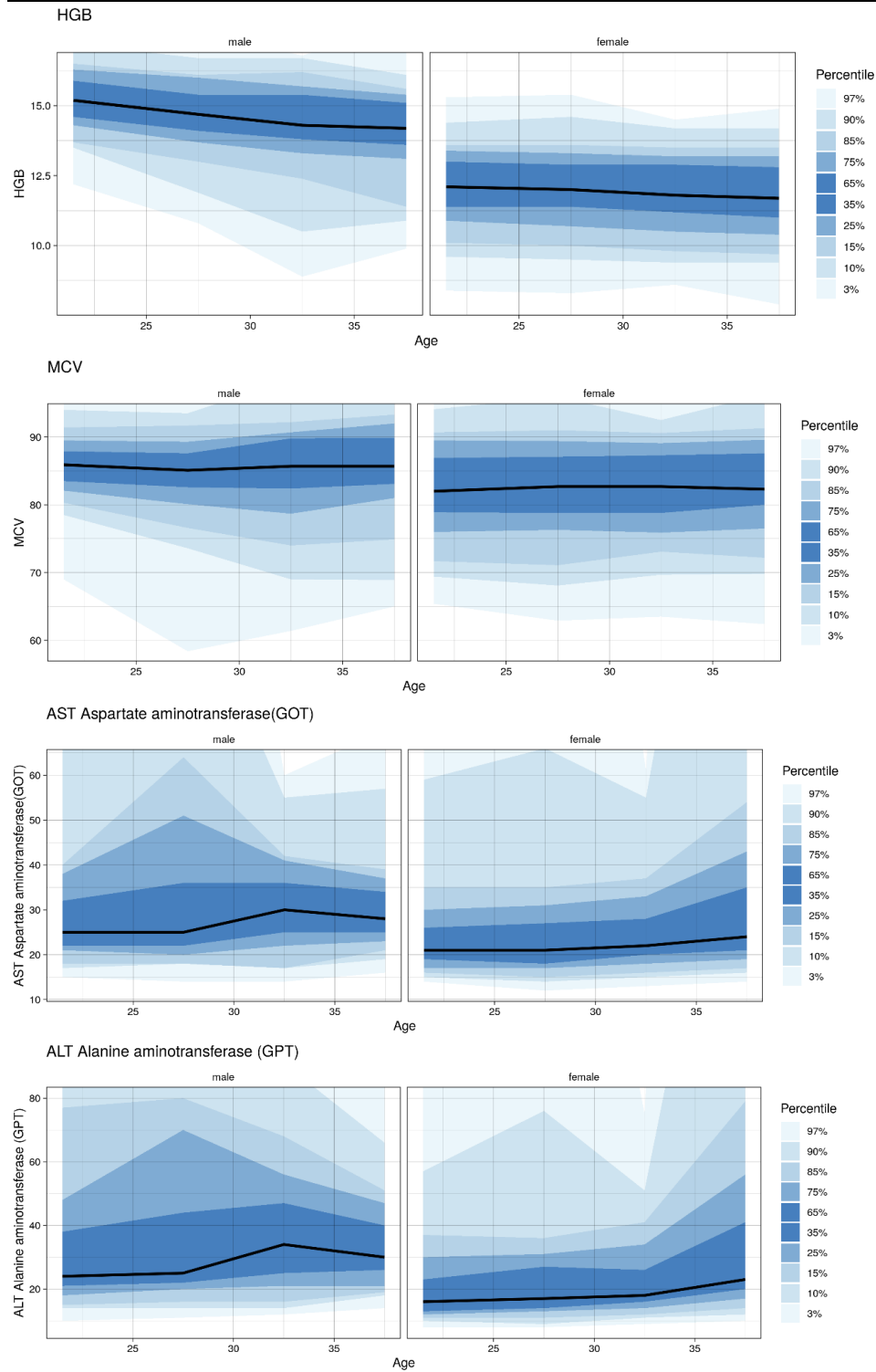


Median laboratories used in the cox regression

Laboratory	Sex	Value (with units)
Hemoglobin (Hg)	Female	11.9 g/dL
Hemoglobin (Hg)	Male	14.6 g/dL
Mean Corpuscular Volume (MCV)	Female	82.0 fL
Mean Corpuscular Volume (MCV)	Male	85.7 fL
Alanine Aminotransferase (ALT)	Female	18 U/L
Alanine Aminotransferase (ALT)	Male	27 U/L
Aspartate Aminotransferase (AST)	Female	22 U/L
Aspartate Aminotransferase (AST)	Male	26 U/L
Body Mass Index (BMI)	Female	21.6 kg/m ²
Body Mass Index (BMI)	Male	22.5 kg/m ²

Table – median laboratories used in the cox regression

Trends of Hg, MCV, AST, ALT by age at diagnosis (male, female)



**Table Multivariable Cox Proportional Hazards Models for Celiac Disease
(by time window)**

Feature	<u>0–4 years HR (95% CI)</u>	<u>4–7 years HR (95% CI)</u>	<u>7–10 years HR (95% CI)</u>
Age	0.99 (0.97–1.02)	1.02 (0.98–1.05)	0.98 (0.94–1.02)
Male sex	0.60 (0.38–0.96)	0.46 (0.23–0.92)	0.43 (0.21–0.89)
Type 1 diabetes	1.36 (0.19–9.81)	NE	NE
Chromosomal abnormality	15.64 (2.18–112.24)	NE	NE
Autoimmune disease	0.90 (0.13–6.39)	2.55 (0.35–18.34)	NE
Overweight/obesity	0.71 (0.46–1.12)	0.72 (0.34–1.52)	1.10 (0.55–2.21)
Neurological disorder	0.86 (0.48–1.54)	1.90 (0.95–3.82)	1.25 (0.54–2.90)
Fatigue/weakness	1.26 (0.52–3.07)	NE	0.88 (0.12–6.32)
Psychiatric disorder	0.72 (0.18–2.91)	0.94 (0.13–6.81)	1.14 (0.16–8.21)
Infertility (male + female)	1.04 (0.43–2.54)	1.02 (0.25–4.17)	0.58 (0.08–4.22)
Repeated GI symptoms	6.01 (1.91–18.91)	NE	NE
Relative low hemoglobin (men)	2.15 (1.33–3.49)	1.62 (0.69–3.79)	1.75 (0.74–4.13)
Relative low hemoglobin (women)	5.66 (3.88–8.24)	4.79 (2.60–8.84)	4.37 (2.28–8.37)
Relative elevated liver enzymes (men)	2.37 (1.52–3.68)	1.69 (0.79–3.59)	1.97 (0.91–4.28)
Relative elevated liver enzymes (women)	3.28 (2.26–4.76)	1.64 (0.83–3.25)	1.35 (0.62–2.94)
Relative low BMI (men)	2.81 (1.57–5.03)	3.38 (1.36–8.38)	2.28 (0.78–6.67)
Relative low BMI (women)	1.98 (1.24–3.16)	1.89 (0.88–4.08)	1.07 (0.38–3.01)

NE : Not Estimable

Over the 10-year follow-up, several clinical and laboratory features showed time-dependent associations with subsequent celiac disease. Sex differences were consistent and striking. Women with relatively low hemoglobin had markedly increased hazards across all intervals (HR 5.66, 95% CI 3.88–8.24 in years 0–4; HR 4.79, 2.60–8.84 in years 4–7; HR 4.37, 2.28–8.37 in years 7–10). The corresponding association in men was weaker but remained elevated (HRs 2.15, 1.33–3.49 in the first 4 years).

Anthropometric and biochemical predictors also emerged. Low BMI in men conferred a two- to three-fold higher risk throughout follow-up, with the strongest effect at 4–7 years (HR 3.38, 1.36–8.38). In women, low BMI was most evident early (HR 1.98, 1.24–3.16 in years 0–4). Elevated liver enzymes were associated with diagnosis primarily within the first 4 years (men: HR 2.37, 1.52–3.68; women: HR 3.28, 2.26–4.76), with attenuation over time.

Symptomatic predictors were more limited. Recurrent gastrointestinal symptoms strongly predicted near-term diagnosis (HR 6.01, 1.91–18.91 within 4 years), but sparse data precluded estimation at later intervals. Fatigue, psychiatric disorders, and infertility showed no consistent associations.

Rare but high-risk conditions included chromosomal abnormalities, which carried a >15-fold hazard (HR 15.64, 2.18–112.24) in early follow-up, and type 1 diabetes, which showed elevated risk but was too infrequent for stable estimates.

Overall, most associations were strongest in the first 4 years and diminished thereafter, suggesting that patients with overt hematologic, anthropometric, or hepatic abnormalities are diagnosed earlier, while more indolent presentations accumulate later in follow-up.

Multivariable Cox Regression for Celiac Disease (2–10 Years Follow-up)

Feature	HR (95% CI)
Age	1.00 (0.97–1.02)
Male sex	0.38 (0.24–0.58)
Type 1 diabetes	NE
Chromosomal abnormality	15.00 (2.09–107.46)
Autoimmune disease	0.89 (0.13–6.38)
Overweight/obesity	0.79 (0.51–1.22)
Neurological disorder	1.57 (1.01–2.44)
Fatigue/weakness	0.50 (0.12–2.02)
Psychiatric disorder	1.03 (0.33–3.24)
Infertility (male + female)	0.72 (0.27–1.95)
Repeated GI symptoms	1.60 (0.22–11.49)
Relative low hemoglobin (men)	1.44 (0.83–2.51)
Relative low hemoglobin (women)	5.33 (3.77–7.54)
Relative elevated liver enzymes (men)	2.06 (1.29–3.29)
Relative elevated liver enzymes (women)	1.48 (0.99–2.23)
Relative low BMI (men)	3.09 (1.72–5.57)
Relative low BMI (women)	1.39 (0.84–2.28)
NE : Not Estimable	

Multivariable Cox Regression for Celiac Disease : complete case analysis (0–10 Years Follow-up).

Feature	Hazard Ratio (95% CI)
Relative anemia (male)	0.89 (0.49–1.59)
Relative anemia (women)	3.69 (2.18–6.26)
Relative elevated liver enzymes (male)	4.36 (2.23–8.52)
Relative elevated liver enzymes (women)	3.66 (2.14–6.26)
Relative low BMI (male)	3.72 (2.03–6.81)
Relative low BMI (women)	1.83 (1.07–3.11)

Laboratory (6 months prior diagnosis) – Effect size

age	Lab & Sex	Test Chosen	Effect Size Method & Value	P-value
18-40 years	Hg male	Paired t-test	Hedges' g = -0.557	< 0.001
18-40 years	Hg female	Paired t-test	Hedges' g = -0.708	< 0.001
18-40 years	MCV female	Paired t-test	Hedges' g = -0.737	< 0.001

There was no large effect size, we report here only the medium effect size.

Hazard ratio of symptoms within 7 years before the index date

Feature	Ratio - 2.5%	Hazard Ratio	Ratio - 97.5%
Overweight or obesity	0.529773	0.730237	1.006556
Neurological problem	0.728615	1.041557	1.48891
Fatigue or weakness	0.388362	0.872302	1.95928
Infertility (male + female)	0.47854	0.930407	1.808955
Constipation	0.025853	0.184263	1.313285
Psychological problem	0.376021	0.911651	2.210273

HR of Repeated GI symptoms (1.5 year)

Feature	Ratio - 2.5%	Hazard Ratio	Ratio - 97.5%
Repeated GI symptoms	0.774241	1.878145	4.555982

Potential link between ventricular septal defect and celiac disease in young adult

Ventricular septal defect (VSD) is one of the most prevalent congenital heart malformations. Its etiology is multifactorial, with genetic, environmental, and immunological contributors, and it is frequently observed in association with chromosomal abnormalities such as Down syndrome. Although celiac disease (CD) and VSD arise from distinct mechanisms, both involve immune-mediated processes, and CD has been linked to congenital anomalies, including cardiac defects. Despite these observations, a direct association between VSD and CD has yet to be formally elucidated.

Feature	Ratio - 2.5%	Hazard Ratio	Ratio - 97.5%
VSD	0.85	6.04	43.00

In this analysis, the presence of celiac disease was not statistically associated with an increased risk of ventricular septal defect, with a hazard ratio of 6.04 (95% CI: 0.85–43.00). Although the wide confidence interval indicates limited precision, likely reflecting the rarity of VSD events. The magnitude of association suggests a potential biological link warranting further exploration. These findings lend preliminary support to the hypothesis of shared immune-mediated or developmental pathways between celiac disease and congenital cardiac defects, underscoring the need for replication in larger, prospectively designed cohorts

Groups (definition of variables)

Celiac group (1587 patients)

1. Have ANY of the following conditions:

CELIAC SCREEN positif or
TRANSGLUTAMINASE SCREEN positif or
TRANSGLUTAMINASE_IgA SCREEN positif or
GLIADIN IgA Ab > 15 or
GLIADIN IgG Ab > 19 or

2. Have ALL of the following conditions:

579.0* CELIAC DISEASE [-365,365 Days]

3. Do NOT have ANY of the following conditions:

Date of Alia (Emigrate)
Patients left clalit for good

Study Group

Include all patients that:

1. Have ANY of the following conditions:

HGB

2. Have ALL of the following conditions:

Age [18,40]

3. Do NOT have ANY of the following conditions:

Date of Alia (Emigrate)
Patient left Clalit for good

Relative anemia male

1. Have ANY of the following conditions:

HGB <= 14.6 and MCV <= 85.9

2. Have ALL of the following conditions:

Male and Age [18,40]

Relative anemia female

1. Have ANY of the following conditions:

HGB <= 11.8 and MCV <= 82.1

2. Have ALL of the following conditions:

Female and Age [18,40]

Relative elevated liver enzymes female

1. Have ANY of the following conditions:
AST > 22 or ALT > 18
2. Have ALL of the following conditions:
female and Age [18,40]

Relative elevated liver enzymes male

1. Have ANY of the following conditions:
AST > 26 or ALT > 27
2. Have ALL of the following conditions:
Male and Age [18,40]

Diabetes Miletus type 1

1. Have ANY of the following conditions:
250.03* or 250.01* or HEMOGLOBIN A1C CALCULATED > 6.4
2. Adjust disease onset according to first appearance of ANY of the following criteria:
HEMOGLOBIN A FOR A1C >= 6.4

Chromosomal abnormality

1. Have ANY of the following conditions:
758.8*, 758.39*, 758.3, 758.0*, 758

Autoimmune disease

1. Have ANY of the following conditions:
576.1*, 571.42*, 370.33*, 255.41, 255.41*, SSB/A positive, 64200, 695.4*, 714*, 244.8*, 242.0*, 696.1*, 696.0*

Immunodeficiency

1. Have ANY of the following conditions:
279.06*, 279.01*, 279.1*, 279.0*

Neurological problem

1. Add time point at **ANY** of the following conditions:
784.0*, 356.9*, 337.0*

Overweight or obesity

1. Add time point at **ANY** of the following conditions:
278.02*, 278.0*, BMI > 25

Fatigue or weakness

1. Add time point at **ANY** of the following conditions:
A04*, 780.79*, 780.71*, 780.7, 780.7*

Repeated GI symptoms

1. Add time point at **ANY** of the following conditions:
Gastro-enteritis or GI symptoms
2. Requiring ALL of the following conditions:
Gastro-enteritis or GI symptoms [-180,0 Days]
and
Gastro-enteritis or GI symptoms [-360,-181 Days]
and
Gastro-enteritis or GI symptoms [-540,-361 Days]

GI symptoms

1. Add time point at **ANY** of the following conditions:
789.0*, 787.91*, 787.0*, 536.2*, 536.8*

Gastro-enteritis

1. Add time point at **ANY** of the following conditions:

009.2*, 009.0*, 009*, 008.62*, 008.61*, 008.6, 008.6*, 008.5*, 004*, 003*, 008*

Infertility (male + female)

1.Add time point at **ANY** of the following conditions:

628*, 606*

Psychological problem

1.Add time point at **ANY** of the following conditions:

F34*, 799.2*, 311*, 296.3*, 296.2*, F32*, 300.0*

VSD

1.Add time point at **ANY** of the following conditions:

745.4*

2.Do NOT have ANY of the following conditions:

Z35.9*, Z35.72*, Z35.7, Z35.7*, Z35.62*, Z35.6, Z35.6*, Z35.55*, Z35.53*, Z35.5, Z35.5*,
Z35*, 745.5*, 745.3*, 745.2*, 747.0*, 746.02*

Date of Alia (Emigrate), patient left clalit for good.

Number of patients with diagnosis of CD and immunodeficiency: 1