
Article:
Duerksen, D.R., Lix, L.M., Johansson, H. et al. (4 more authors) (2021) Fracture risk assessment in celiac disease: a registry-based cohort study. Osteoporosis International, 32 (1). pp. 93-99. ISSN 0937-941X

https://doi.org/10.1007/s00198-020-05579-7

Published in final edited form as:
Osteoporos Int. 2021 January 01; 32(1): 93–99. doi:10.1007/s00198-020-05579-7.

Fracture Risk Assessment in Celiac Disease: A registry-based cohort study

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Abstract

Purpose—The fracture risk assessment tool (FRAX®) uses clinical factors and bone mineral density (BMD) measurement to predict 10-year major osteoporotic (MOF) fracture probability. The study aim was to determine whether celiac disease affects MOF risk independent of FRAX score.

Methods—The Manitoba BMD Registry includes clinical data, BMD measurements, 10-year probability of MOF calculated for each individual using the Canadian FRAX tool and diagnosed

Ethics approval: This study was approved by the University of Manitoba Research Ethics Board

Consent to Participate: This was a database study and therefore not applicable.

Consent for Publication: This was a database study and therefore not applicable.

Conflict of Interest
Donald Duerksen: Nothing to declare in the context of this paper but has served as a consultant for Takeda and Abbvie.
Lisa Lix: No conflicts of interest.
Helena Johansson: No conflicts of interest.
Eugene McCloskey: Nothing to declare for the context of this paper, but numerous ad hoc consultancies/ speaking honoraria and/or research funding from Amgen, Bayer, General Electric, GSK, Hologic, Lilly, Merck Research Labs, Novartis, Novo Nordisk, Nycomed, Ono, Pfizer, ProStrakan, Roche, Sanofi-Aventis, Servier, Tethys, UBS and Warner-Chilcott
Nicholas Harvey: Nothing to declare for the context of this paper, but has received consultancy/ lecture fees/ honoraria/ grant funding from Alliance for Better Bone Health, Amgen, MSD, Eli Lilly, Servier, Shire, Consilient Healthcare, Radius Health, UCB, Kyowa Kirin and Internis Pharma.
John A. Kanis: Nothing to declare in the context of this paper. Has received grants from Amgen, Lilly, Radius Health
William Leslie: No conflicts of interest.

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celiac disease. Using linkage to population-based healthcare databases, we identified incident MOF diagnoses over the next 10 years for celiac disease and general population cohorts.

Results—Celiac disease (N=693) was associated with increased fracture risk adjusted for FRAX score computed without secondary osteoporosis or BMD (adjusted hazard ratio [HR] 1.43, 95% confidence interval [CI] 1.11-1.86). Celiac disease was no longer a significant risk factor for fracture when secondary osteoporosis or BMD were included in the FRAX calculation (p>0.1). In subjects with celiac disease, each SD increase in FRAX score (calculated with and without secondary osteoporosis or BMD) was associated with higher risk of incident MOF (adjusted HR 1.66 to 1.80), similar to the general population (p-interaction > 0.2). Including celiac disease as secondary osteoporosis or including BMD in FRAX 10-year MOF probability calculations (10.1% and 8.6% respectively) approximated the observed cumulative 10-year MOF probability (10.8%, 95 % CI 7.8-13.9%).

Conclusions—Celiac disease is associated with an increased risk of major osteoporotic fractures. When celiac disease is considered as a secondary osteoporosis risk factor or BMD is included in FRAX assessment, FRAX accurately predicts fracture risk.

Keywords

FRAX score; Major osteoporotic fracture risk; Celiac disease; Osteoporosis; Epidemiology

Introduction

Celiac disease is an autoimmune disorder characterized by small intestinal inflammation and villous atrophy upon exposure to gluten in genetically susceptible individuals.[1] This clinical syndrome of varying manifestations can include gastrointestinal symptoms, extra-intestinal manifestations and malabsorption of nutrients including calcium and vitamin D. There is frequently a significant delay in the initial diagnosis of celiac disease and thus, malabsorption may be present for many years prior to definitive treatment.

Individuals with celiac disease (CD) are at increased risk of low bone mineral density (BMD) and osteoporosis-related fractures.[2] The mechanisms for these effects include calcium and vitamin D malabsorption, and chronic inflammation with the secretion of pro-inflammatory cytokines.[3] A gluten free diet is associated with an improvement in BMD as measured by dual-energy X-ray absorptiometry (DXA), although the reported magnitude of improvement has varied in the literature.[4] Fracture risk, including that for hip fracture, appears to be increased in patients with celiac disease although the effect size is uncertain.[5]

The most widely used approach to patient stratification for fracture risk is the FRAX® fracture risk assessment tool, which combines clinical factors that independently predict fracture risk as well as (optionally) BMD at the femoral neck to predict 10-year probability of major osteoporotic fracture (MOF; a composite of hip, clinical vertebral, forearm and humerus fractures) and 10-year probability of hip fracture.[6] The FRAX tool was initially developed for use in general practice. Since its initial development it has been included in over 100 clinical practice guidelines and is the most widely used fracture prediction tool worldwide. [7] CD is not a direct input to FRAX. An input for secondary osteoporosis

(including malabsorption) is included in the FRAX algorithm which affects the output when BMD is not available, but does not affect the risk calculation when BMD is included.

The aim of this study was to determine whether CD affects major osteoporotic fracture risk independent of FRAX probability.

Methods

Study Population

Manitoba is a central Canadian province with a population of approximately 1.3 million where health care is universal and publicly funded. The provincial healthcare databases include diagnoses from physician claims, hospitalizations, pharmacy-dispensed prescription medication use, and a provincial CD serology database; all databases can be linked using a unique, anonymized personal health identification number. The Manitoba Bone Mineral Density (BMD) Database includes all clinical DXA data for the province.[8] This database has been carefully validated and extensively used for clinical research, with completeness and accuracy in excess of 99%.[9] The Manitoba BMD Database was linked to the provincial databases listed previously.

Individuals were included in the study cohort if they were age 40 or older at the time of baseline DXA performed between 1 January 1996 and 30 March 2013 and were registered with Manitoba Health. The study protocol was approved by the Faculty of Medicine Research Ethics Board (REB) of the University of Manitoba.

Definition of CD

CD was defined as endomysial antibody (EMA) positivity (before 2003) or IgA tissue transglutaminase (tTG) and EMA positivity (after 2003) or from administrative healthcare data (2 physician claims or 1 hospitalization with a ICD-9-CM 579 or ICD-10-CA K90 diagnostic code for celiac disease). We have previously demonstrated that the administrative case definition for CD has a high sensitivity and specificity when assessed using the serologic diagnosis of CD as the reference standard.[10] Serologic testing with IgA tTG and IgA EMA antibodies has a high sensitivity and specificity for celiac disease for biopsy proven celiac disease.[1] While small bowel biopsy is recommended for a definitive diagnosis in adults, positive serologic testing with tTG and EMA antibodies has a positive predictive value of over 95% for biopsy confirmed celiac disease.[11] In Manitoba, all serologic testing for CD is performed by the Immunology Laboratory at St Boniface Hospital, Winnipeg, Canada. Since 1996, IgA endomysial antibody (EMA) testing has been performed using fluorescein-conjugated guinea pig IgA antibodies and fluorescence microscopy. Sera are considered positive if fluorescence is seen at dilutions of 1:5 or greater. IgA tissue transglutaminase (tTG) antibodies have been measured since 2003.

Individuals receiving BMD testing but who did not have positive serologic testing or did not meet the administrative case definition for celiac disease were considered the controls for this study and designated as members of the general population cohort.

Incident MOF

We defined incident MOF as fractures of the hip, wrist, spine, or humerus that occurred between the date of BMD screening and our study end date (March 31, 2013). Fractures were ascertained from diagnosis codes in physician claims and hospitalizations using previously validated case definitions.[12, 13] We excluded fractures associated with trauma diagnosis codes. We required a site-specific fracture fixation code and/or casting code for hip fracture or humerus fractures. To avoid double-counting health care interactions related to the same injury, we only counted a single fracture for a given site within a 180-day period. For individuals with more than one incident MOF, we used the first qualifying MOF.

Dual-energy X-ray Absorptiometry (DXA) and FRAX Calculation

DXA scans were performed and analyzed in accordance with manufacturer recommendations.[9] Hip T-scores were calculated from the NHANES III White female reference values. Age- and sex-matched Z-scores were also computed. Prior to 2000, DXA measurements were performed with a pencil-beam instrument (DPX, GE Lunar, Madison WI) and after this date a fan-beam instrument was used (Prodigy or iDXA, GE Lunar, Madison WI). Instruments were cross calibrated using anthropomorphic phantoms and volunteers. No clinically significant differences were identified (femoral neck T-score differences < 0.1). Therefore, all analyses are based upon the unadjusted numerical results provided by the instrument. Densitometers showed stable long-term performance (phantom coefficient of variation [CV] < 0.5%) and satisfactory in vivo precision (CV 2.3% for the femoral neck).[14]

Ten-year probability of an MOF was calculated for each subject using the Canadian FRAX tool (FRAX® Desktop Multi-Patient Entry, version 3.8). The Canadian FRAX tool was calibrated using nationwide hip fracture and mortality data (17). The Manitoba BMD Registry was not used in the creation or calibration of the FRAX tool. Weight and height were measured at the time of DXA, and body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Prior fracture and other FRAX input variables were assessed using administrative health data.[15] We defined prior fragility fracture as any non-traumatic MOF that occurred before the baseline DXA test examining medical records back to 1987. Prolonged oral glucocorticoid use (>90 days dispensed in the 1 year prior to DXA) was obtained from the provincial pharmacy system.[16] Parental hip fracture was by self-report from 2005 onwards. We adjusted for the effect of incomplete parental hip fracture information on FRAX probability estimates before 2005 using age- and sex-specific adjustment factors derived from 2005–2008 parental hip fracture responses as previously described. [15] Current smoking was by self-report from 2005 onwards and from a proxy variable in earlier years (chronic obstructive lung disease diagnosis codes in administrative data). High alcohol use from 2012 onwards and from a proxy variable in earlier years (alcohol substance abuse diagnosis codes in administrative data). For each subject we computed three FRAX MOF probability scores: from clinical predictors only (without secondary osteoporosis CD), from clinical predictors with secondary osteoporosis (for cohort members with CD), and from clinical predictors including BMD.

Statistical Analysis

Statistical analyses were performed with Statistica (Version 13.0, StatSoft Inc, Tulsa, OK). Descriptive statistics for demographic and baseline characteristics are presented as mean ± SD for continuous variables or frequency (%) for categorical variables. Analysis of variance and χ^2 tests of independence were used to test for differences between the CD and general population cohorts. Cox proportional hazards semi-parametric regression models were used to test the factors associate with time to first fracture, with cohort (CD vs. general population) as the covariate of interest. Model covariates included FRAX probability calculated from clinical predictors only without secondary osteoporosis for CD (Model 1), from clinical predictors with secondary osteoporosis for CD cohort members (Model 2), and from clinical predictors including BMD (Model 3). Risk gradients for the fracture probability measurements were also estimated for each cohort and are presented as hazard ratios (HRs) per SD decrease with 95% confidence intervals (CI). Two-way interaction terms (FRAX score * celiac disease) were included in models to test for differences between groups. FRAX scores were log-transformed due to a skewed distribution. Sensitivity analyses were performed after excluding individuals receiving anti-osteoporosis medication. The proportional hazards assumptions was tested and confirmed from the Schoenfeld residuals. We also compared cumulative observed fracture incidence to 10-years with FRAX score prediction in order to assess calibration (observed vs predicted fracture probability).

Results

The case definition of celiac disease was fulfilled by 693 individuals who were followed for a mean of 7.0 years and compared with 68,037 general population subjects followed for a mean of 7.1 years (duration of follow-up; p=0.458). Table 1 describes the baseline characteristics of the celiac cohort members compared with the general population members. The CD cohort tended to be younger, include more males and have lower BMI and femoral neck age/sex-adjusted Z-scores (all p<0.001). Despite being younger (p< 0.001) and more likely to be male (p<0.001), during follow up 58 (8.4%) members of the CD cohort sustained one or more MOF which was similar to the MOF rate experienced by members of the general population cohort 5692 (8.4%) (p=0.997).

Table 2 examines the independent effect of celiac disease on major osteoporotic fracture risk adjusted for baseline fracture risk using FRAX. FRAX was strongly predictive of incident fracture in all models, with an approximate doubling in risk per SD increase. Celiac disease was associated with increased fracture risk adjusted for FRAX score computed without secondary osteoporosis or BMD (adjusted HR 1.43, 95% CI 1.11-1.86). However, celiac disease was no longer a significant risk factor for fracture when secondary osteoporosis or bone mineral density inputs were included in the FRAX calculation (p>0.1). Anti-osteoporosis medication use did not significantly differ between the groups (12.4% in the CD cohort vs 14.8% in the general population cohort, p=0.074). Exclusion of treated individuals from the analysis did not affect our results (HR for CD 1.44, 95% CI 1.08-1.92 adjusted for FRAX score computed without secondary osteoporosis or BMD; p>0.1 when secondary osteoporosis or bone mineral density inputs were included in the FRAX calculation).

The performance of FRAX to stratify major osteoporotic fracture risk with and without secondary osteoporosis or bone mineral density in the CD cohort and in the general population cohort is demonstrated in Table 3. In individuals with CD, each SD increase in FRAX score (calculated with or without secondary osteoporosis or BMD) was associated with higher risk of incident MOF (adjusted HR 1.66 to 1.80). Similar HRs were noted in the general population and in models including two-way interaction terms between FRAX probability and cohort (celiac disease vs. general population), the interaction terms were not statistically significant (all P>0.2).

Figure 1 compares the observed 10-year major osteoporotic fracture probability with the FRAX predicted 10-year major osteoporotic fracture probability in celiac disease and in the general population. In the general population, there was good agreement between FRAX predicted (11.0% without and 10.6% with BMD) and observed (10.8%) 10-year major osteoporotic fracture probability. In celiac disease when secondary osteoporosis and BMD were not included in the risk assessment, the observed 10-year major osteoporotic fracture probability (10.8%, 95 % CI 7.8-13.9%) was greater than predicted by FRAX (7.4%). When celiac disease was considered as secondary osteoporosis, the FRAX major osteoporotic fracture probability (10.1%) approximated the observed major osteoporotic fracture probability. The predicted probability when BMD was included in the FRAX calculation (8.6%) also fell within the 95% CI of the observed probability).

Discussion

The association of celiac disease with abnormal bone mineral density and metabolic bone disease has been well established.[17] Our study demonstrates that celiac disease is associated with an increased risk of major osteoporotic fractures after controlling for multiple clinical risk factors. Despite being younger and including a greater proportion of men, the CD cohort had the same number of fractures as general population controls. There have been conflicting studies regarding the magnitude of increased fracture risk in celiac disease as well as the sites that are most at risk. A recent meta-analysis of 9 cross-sectional and case-control studies demonstrated an overall increased risk of any fracture of 1.91(95%CI 1.29, 2.84) compared with those without celiac disease and in 6 prospective studies an increased risk of any fracture of 1.30 (95% CI 1.14, 1.5).[5] For hip fractures, the 4 pooled cross sectional and case-control studies did not show an increase risk whereas the 4 prospective studies demonstrated an increased risk of 1.69 (95% CI 1.10, 2.59). Our study examined major osteoporotic fractures including hip fractures and demonstrated an increased risk of major osteoporotic fracture with an adjusted hazard ratio of 1.43 (95% CI 1.11, 1.86).

FRAX is a fracture risk assessment tool that has been validated in many patient populations. Our study has demonstrated that FRAX stratifies major osteoporotic fracture risk in the celiac disease population similar to the general population with no significant interaction, though it does underestimate fracture risk if the independent effect of celiac disease is not considered. When celiac disease is included in the FRAX calculation as a secondary condition that increases risk for major osteoporotic fractures, it accurately predicts this risk. Alternatively, including bone mineral density in the FRAX calculation also predicts that fracture risk. The secondary causes mentioned in FRAX are (conservatively) assumed to

confer a risk mediated by low BMD.[18] The present paper is the first formal demonstration that the assumption holds true for malabsorption due to celiac disease.

The Global Longitudinal Study of Osteoporosis in Women (GLOW) evaluated the effect of comorbidities on fracture risk in over 50000 women.[19] When looking at 2–year fracture rates, the age-adjusted hazard ratio for celiac disease was 1.4 (p=0.08). In this cohort, the prevalence of celiac disease in women with incident fractures, was 1.1 % in underweight women, 0.8% in non obese women and 0.4% in overweight women.[20] This cohort relied on patient self report for the diagnosis of celiac disease and therefore may have overestimated the true prevalence of celiac disease.

There have been several recent reports examining the ability of FRAX to predict osteoporotic fracture risk in celiac disease. In a study which utilized US National Health and Nutrition Examination (NHANES) data, Kamycheva et al demonstrated that celiac disease was an independent risk factor for osteoporotic fractures in men > 40 years of age but not in women.[21] This study was limited by the low number of tTG defined celiac patients; there were only sixteen male and nineteen female serologically positive cases amongst the cohort of 5031 patients. Therefore, it is difficult to draw major conclusions from this study and likely explains the negative findings in women. A second study applied FRAX scoring to 160 newly diagnosed patients with celiac disease who were greater than 40 years old.[22] While this study suggested that FRAX scoring could be useful to select patients who might benefit from a BMD test, it did not test the usefulness of the FRAX score in predicting fracture risk in established celiac disease. Similar to the Kamycheva study, this study was underpowered to detect a higher facture risk in celiac disease. Italian study that screened 7305 patients and looked at risk factors for osteoporosis, found that secondary conditions including hyperthyroidism, Crohn's disease, ulcerative colitis, hypercalciuria and celiac disease were osteoporosis risk factors in addition to FRAX, when pooled together.[23] There were only 22 patients with celiac disease in this cohort and therefore the role of celiac disease as an independent osteoporosis risk factor is unclear from this study.

Current guidelines on the management of celiac disease do not include the use of FRAX in their recommendations. The British Society of Gastroenterology[24] as well as the European Society for the Study of Celiac Disease[25] guidelines recommend routine testing of BMD at baseline while the American Society of Gastroenterology guidelines[26] have no recommendations for BMD testing at diagnosis or follow-up. Our study has validated the use of FRAX in celiac disease and future clinical practice guidelines should consider incorporation of FRAX estimation in their recommendations.

There are several limitations to this study. Males are underrepresented as the BMD database utilized in this study is a referral population with over 90% women. Therefore, the results may not apply to men with celiac disease. Dietary patterns including calcium and vitamin D intake cannot be assessed from administrative data sources. Similarly, this study could not evaluate gluten free diet adherence patterns in patients with celiac disease. Strict adherence to a gluten free diet has been associated with improved bone mineral density. Recent studies have emphasized that mucosal recovery at 2 years occurs in less than 50% of individuals on a gluten free diet,[27] an effect that is likely related to gluten ingestion. Therefore, there may

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be a subgroup of patients with higher MOF risk but this was not evaluated in this study. It is possible that including BMD in FRAX predicts MOF better than inclusion of celiac disease as a secondary osteoporosis risk factor in individuals who are adherent to a gluten free diet but this was not tested in our study. In addition, the celiac disease sample size was relatively small. It was of sufficient size to allow for evaluation of overall MOF risk but did not allow for analysis of fracture subtypes, most notably hip fractures.

In conclusion, this study demonstrated increased major osteoporotic fracture risk in individuals with celiac disease. FRAX is a useful tool to stratify fracture risk in individuals with celiac disease. When celiac disease is considered as a secondary osteoporosis risk factor or BMD is included in the FRAX assessment, FRAX accurately predicts fracture risk.

Acknowledgements

The authors acknowledge the Manitoba Centre for Health Policy (MCHP) for use of data contained in the Population Health Research Data Repository (HIPC Project Number (HIPC 2011/2012-31). The results and conclusions are those of the authors, and no official endorsement by the MCHP, Manitoba Health, or other data providers is intended or should be inferred. This article has been reviewed and approved by the members of the Manitoba Bone Density Program.

Funding

This study received no external funding. LML is supported by a Tier I Canada Research Chair.

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Mini Abstract

Celiac disease is associated with an increased fracture risk but is not a direct input to the FRAX®calculation. When celiac disease is considered as a secondary osteoporosis risk factor or BMD is included in the FRAX assessment, FRAX accurately predicts fracture risk.

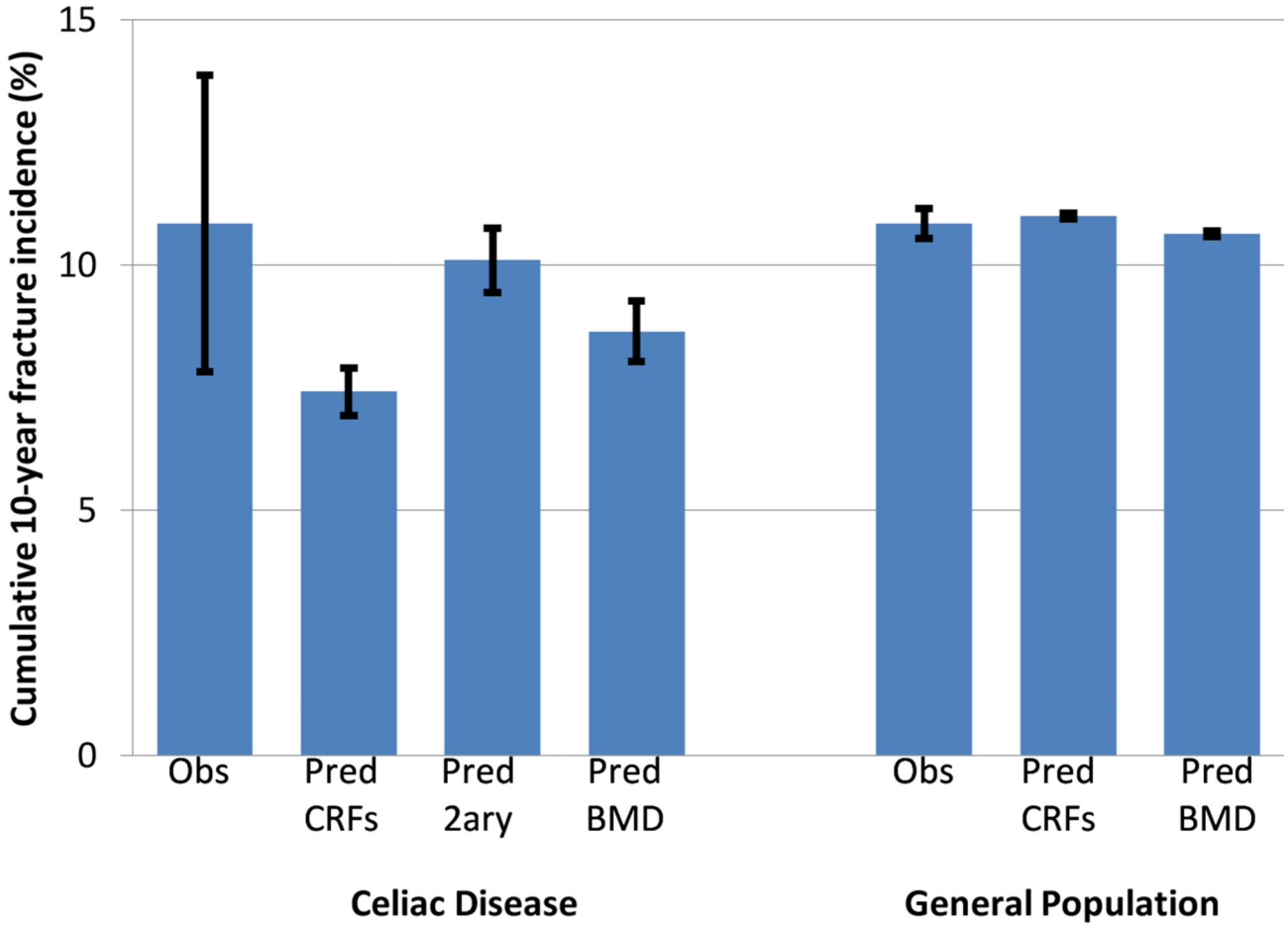

Figure 1.

Figure Legend Observed and predicted 10-year major osteoporotic fracture (MOF) probability in celiac disease cohort and general population cohort. Predicted MOF risk uses FRAX with clinical risk factors without secondary osteoporosis (CRFs), clinical risk factors with secondary osteoporosis (2ary), and with clinical risk factors and bone mineral density (BMD). Error bars are 95% confidence intervals.

Obs - Observed

Pred CRFs – predicted from clinical risk factors without secondary osteoporosis

Pred 2ary – predicted from clinical risk factors with celiac disease as secondary osteoporosis

Pred BMD – predicted with clinical risk factors and bone mineral density

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Table 1
Characteristics of General Population and Celiac Disease Cohorts

Characteristic	General population	Celiac disease	p-value
Frequency	68,037	693	
Age (years)	64.3 ± 11.2	58.1 ± 11.2	<0.001
Female	61,729 (90.7)	546 (78.8)	<0.001
BMI (kg/m^2)	27.1 ± 8.2	25.2 ± 5.3	<0.001
Prior fracture	9926 (14.6)	86 (12.4)	0.106
Femoral neck T-score	-1.4 ± 1.0	-1.3 ± 1.2	0.484
Femoral neck Z-score	0.0 ± 0.9	-0.3 ± 1.1	<0.001
Femoral neck osteoporotic	8018 (11.8)	99 (14.3)	0.042
FRAX MOF percent (clinical without secondary osteoporosis for celiac disease)	11.0 ± 8.3	7.4 ± 6.5	<0.001
FRAX MOF percent (clinical with secondary osteoporosis for celiac disease)	NA	10.1 ± 8.8	<0.001
FRAX MOF percent (with BMD)	10.6 ± 7.8	8.6 ± 8.3	<0.001
Observation time (years)	7.1 ± 4.2	7.0 ± 4.1	0.458
Incident MOF	5692 (8.4)	58 (8.4)	0.997

Data expressed as Mean ± SD or N (percent).
BMI – Body Mass Index
MOF – Major Osteoporotic Fracture
BMD – Bone Mineral Density
NA – Not Applicable

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Table 2
Predictors of Major Osteoporotic Fracture

		Hazard Ratio (95% CI)	P value
Model 1	Celiac disease (versus absent)	1.43 (1.11-1.86)	0.006
	FRAX (clinical without secondary osteoporosis) per SD increase	1.95 (1.89-2.00)	<0.001
Model 2	Celiac disease (versus absent)	1.08 (0.84-1.40)	0.542
	FRAX (clinical with secondary osteoporosis) per SD increase	1.94 (1.89-2.00)	<0.001
Model 3	Celiac disease (versus absent)	1.21 (0.93-1.57)	0.150
	FRAX (with BMD) per SD increase	2.09 (2.03-2.14)	<0.001

Note: CI = confidence interval

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Table 3

Hazard ratios (HR) with 95% confidence intervals (CI) for incident major osteoporotic fracture per standard deviation increase in FRAX probability.

Predictor	Celiac Disease HR 95% CI	General Population HR 95% CI	Interaction p-value*
FRAX probability from clinical predictors only	1.67 (1.29-2.17)	1.95 (1.89-2.00)	0.238
FRAX probability from clinical predictors with secondary osteoporosis for celiac disease	1.66 (1.28-2.16)	1.95 (1.89-2.00)	0.222
FRAX probability from clinical predictors with BMD	1.80 (1.43-2.27)	2.09 (2.03-2.15)	0.209

* FRAX score * celiac disease status.