Table 1: Evidence table – Godfrey et al. (2010)

Study type	Non-randomised comparative cross-sectional study
Country	USA
Number of patients	Cross-sectional: N=16 886 patients 50 years or older who were tested for CD Case control: N=127 patients with seropositivity, N=254 matched seronegative controls
quality	1. Did the study have a clearly focused aim? Yes 2. Was the cohort recruited in an acceptable way? Yes 3. Was the exposure accurately measured to minimise bias? No - not clearhow comorbidity was defined. 'List of 100' 4. Was the outcome accurately measured to minimise bias? Yes - CD serology 5. Have the authors identified all important confounding factors? Have they taken account of confounding factors in the design/analysis? Yes 6. Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough? Yes - median FU = 10 years

<table>
<tr><td></td><td>7. What are the results? Older adults with CD had limited comorbidity - except fir bone mineral health where people with undiagnosed CD had poorer bone health
8. How precise are the results? Precise - tight CI
9. Do you believe the results? Yes
10. Can the results be applied to the local population? Yes
11. Do the results fit with other available evidence? Yes
12. What are the implications of this study for practice? Undiagnosed CD can lead to reduced bone mineral density</td></tr>
<tr><td>Study population</td><td>Patients 50 years and older from Olmsted county who participated in a prior study of monoclonal gammopathy of undetermined significance and with serum samples obtained between the years of 1995 and 2001 and stored.
Exlusion criteria: known CD diagnosis, inconsistent serum volume for testing
(of 24 727 with serum samples saved, consent was gratned by 18 774 individuals but 34 with known CD and those without sufficient serum samples were excluded leaving 16 886 [90.1%] patients who were screened for CD)
<table>
<tr><td></td><td>Serologically negative (n=254)</td><td>Serologically positive (n=127)</td><td>OR (95% CI)[a]</td></tr>
<tr><td>Age at serum draw</td><td>62.9 (51.9, 87.7)</td><td>63.0 (51.7, 87.7)</td><td>1.19 (0.8, 1.78)</td></tr>
<tr><td>Proportion female</td><td>52% (132)</td><td>51.2% (62)</td><td>0.64 (0.13, 3.14)</td></tr>
<tr><td>Weight (kg) [b]</td><td>N=247 78 (38.9, 142)</td><td>N=125 (44, 120.6)</td><td>0.98 (0.97, 1.00)</td></tr>
<tr><td>Height (cm) [b]</td><td>N=242 166.4 (144.3, 189.7)</td><td>N=123 167.6 (124, 203.2)</td><td>1.01 (0.98, 1.04)</td></tr>
<tr><td>BMI</td><td>N=242 27.4 (17.5, 55.5)</td><td>N=123 26.4 (17.2, 42.9)</td><td>0.94 (0.90, 0.99)</td></tr>
</table>
[a] From conditioned logistic regression retaining matching, [b] recorded weight and height closest to date of serum draw</td></tr>
<tr><td>Control</td><td>2 sero-negative controls for every case and matched by age and gender; controls were taken from (appears that controls were selected from databases of patients at one of two major medical care providers in Olmsted county)</td></tr>
<tr><td>Length of follow-up</td><td>Median 10.3 years after serum samples collected</td></tr>
<tr><td>Details of coeliac testing</td><td>tTGA IgA ELISA (ThermoLab DSX ELISA automated system, INOVA Diagnostics, Inc, San Diego, CA; < 2.0 U/ml was considered negative)
Those with positive tests were tested with EMA an immunofluorescence assay (Beckman Coulter, Inc, Brea, CA)
Undiagnosed CD: presence of tTGA test > 2.0 U/ml with positive EMA test (samples were considered negative if tTGA was between 2 and 4 in addition to the EMA test being negative) (tests were considered indeterminate if the tTGA level was > 4.0 U/ml and the EMA was negative)</td></tr>
<tr><td>Results</td><td>Of 16, 886 serologically tested, 1% (163) tested positive for tTGA and 143 had borderline tTGA levels and were tested with EMA.
N=129 were considered serologically positive (0.8%, 95% CI 0.6, 0.9)
2 seropositives and 278 potential controls did not have authorisation for the emdical records so were excluded</td></tr>
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Of those with seropositivity, 20 were subsequently diagnosed clinically with CD after a median of 10.3 (range 0-12.9) years of follow-up but no seronegative controls were diagnosed with CD.

Associated conditions of undiagnosed coeliac disease (defined as serologically positive) compared to serologically negative controls

	Serologically negative (n=254)	Serologically positive (n=127)	OR (95% CI)*
Osteoporosis	Not reported	Not reported	2.59 (1.32, 5.09)
Cancer**	51 (20.1%)	31 (24.4%)	1.29 (0.77, 2.15)
CD-associated cancer	Not reported	Not reported	2.02 (0.29, 14.38)
Visceral cancer	Not reported	Not reported	1.36 (0.67, 2.77)

* conditional logistic regression retaining the matching
** two in each group had CD-associated malignancy (oesophageal cancer in serologically negative and small bowel lymphoma in serologically positive group)

Association between undiagnosed disease (defined as serologically positive) and mortality:

	HR (95% CI)*	p value
All-cause mortality	0.80 (0.45, 1.41)	0.44
Cancer-related mortality	0.63 (0.16, 2.48)	0.51
Visceral cancer-related mortality	0.79 (0.25, 2.50)	0.68
CD-associated cancer mortality	1.01 (0.14, 7.00)	0.99

* Risk in serologically positive cases compared to serologically negative controls (using Cox PH regression stratified on matched set)

Classic ceoalic disease symptoms in serology positive vs negative patients:

	Serologically negative (n=254)	Serologically positive (n=127)	OR (95% CI)**
Diarrhoea	65 (26.2%)	27 (21.4%)	0.77 (0.46, 1.31)
Weight loss	19 (1.8%)	14 (11.2%)	1.67 (0.79, 3.51)
Abdominal pain	92 (37.2%)	46 (36.2%)	0.96 (0.61, 1.51)
Dermatitis herpetiformis	0	5 (4.0%)	-
Irritable bowel syndrome	31 (12.6%)	13 (10.4%)	0.79 (0.40, 1.54)
Deficient haemoglobin	33 (13.1%)	23 (18.4%)	1.63 (0.86, 3.08)

* based on marginal distributions; does not take into account the matching

	**conditional logistic regression which retains the matching Of the 20 seropositive patients subsequently diagnosed clinically with coeliac disease:

	Serologically positive (n=20)
Iron deficiency	9 (45%)
Dermatitis herpetiformis	3 (15%)
Diarrhoea, weight loss	3 (15%)
Screened because of family history	3 (15%)
Small bowel lymphoma	1 (5%)
Nausea	1 (5%)

Source of funding	Research grants from the NIH (National Centre for Research Resources and NIH Roadmap for Medical Research)
Conflicts of interest	Paper states that there are none
Comments	OR for other associated conditions were reported but this was only extracted for those where they were possibley long-term complications of coeliac disease (known mechanisms) since this study did not perform biopsy to confirm coeliac disease (an inclusion characteristic for studies on conditions associated with coeliac disease)

Definitions of abbreviations are given at the end of this document.