AGA and SSCD Clinical Practice Guideline on Management of Asymptomatic Celiac Disease

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Manuscript Information *(To be added prior to publication)*

- **Word Count**:
- **Number of References:**
- **Number of Tables/Figures**:
- **Number of Supplemental Tables/Figures**:

Acknowledgements

The authors would like to thank Caitlin Bakker for expertise in designing and conducting the literature searches. The Guideline Panel also acknowledges the support of AGA staff, Melanie Stephens-Lyman, director guideline development and senior director patient engagement, Aimee M. Fischer. The Guideline Panel also would like to thank the patient representatives for their contributions, time and commitment.

ABSTRACT

(To be added prior to publication)

INTRODUCTION

Scope

Celiac disease (CeD) is an immune-mediated enteropathy triggered by dietary gluten in genetically susceptible individuals, with a pooled global seroprevalence of 1.4% and biopsy-confirmed prevalence of 0.7%.[1] While prevalence varies by population, overall diagnosis rates are rising, attributed to a true increase in incidence rather than improved detection alone.[2, 3] A substantial and growing share of cases are identified through serologic screening programs and such patients may lack symptoms or observed manifestations,[4, 5] meeting the Oslo definition of asymptomatic CeD.[6] Treatment even in this scenario has intuitive benefits given the risks associated with CeD, including metabolic bone disease, nutritional deficiencies, hepatic abnormalities, impaired growth in children, and excess morbidity.[7, 8] However, a competing risk is imposing a burden of lifelong dietary management when it is uncertain whether individuals with asymptomatic CeD are similarly affected by these complications. This guideline addresses a single recurring clinical conundrum, i.e., whether a gluten-free diet (GFD), versus a gluten-containing or unrestricted diet (GCD), benefits adults and children with asymptomatic CeD. The Panel prioritized eight populations: (1) purely asymptomatic CeD; asymptomatic CeD with (2) iron deficiency, (3) metabolic bone disease, (4) abnormal liver enzymes, or (5) impaired growth and short stature; and asymptomatic CeD with associated (6) type 1 diabetes mellitus (T1DM), (7) autoimmune thyroid disease, or (8) Down syndrome. Each subgroup represents a common screen-detected presentation in which the balance of benefits and harms of dietary treatment may be uncertain, though the decision of whether to screen was outside the scope of this guideline. The Panel took confirmed, asymptomatic CeD as its base case and these recommendations are intended for use in primary care, pediatric, and gastroenterology specialty settings.

Guideline Development Procedures

The guideline development process and methods are presented after the recommendations section.

Supplementary Material

This guideline should be read in conjunction with the Supplemental Material, which contains additional tables and other supporting material. Clinicians may also find the clinical decision support tool (Figure 1) helpful to guide clinical decision-making and inform patient management.

Summary of Recommendations

Table 1: Guideline Recommendations

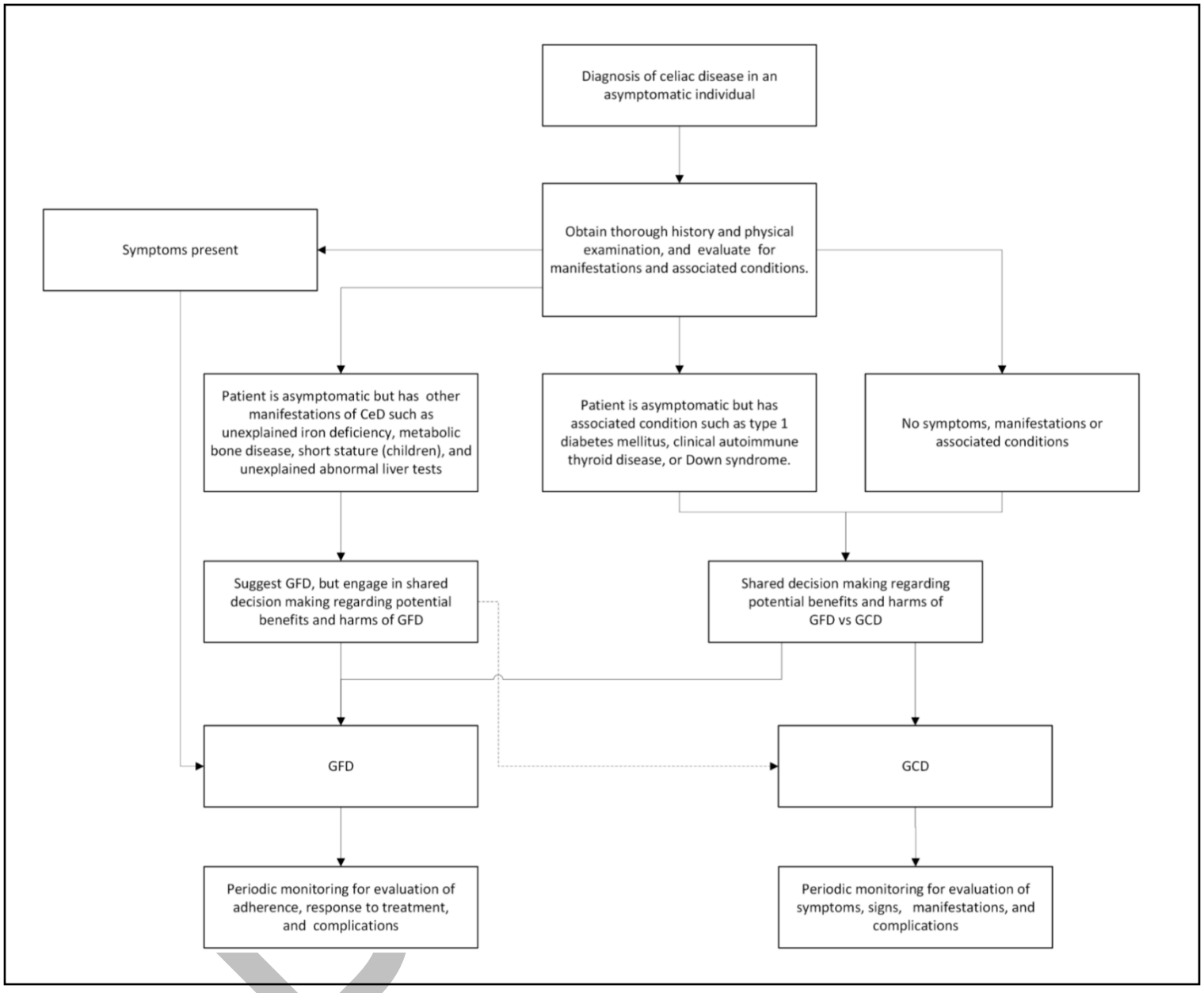
	RECOMMENDATION	STRENGTH	COE
1	**In individuals with asymptomatic celiac disease, the AGA/SSCD make no recommendation on the use of a gluten-free diet.** *Implementation Considerations:* • *In the absence of symptoms or clinical manifestation, the decision to initiate a GFD versus continuing a GCD should be based on shared decision making.*	No recommendation	Very Low
2	**In individuals with asymptomatic celiac disease with unexplained iron deficiency, the AGA/SSCD suggest the use of a gluten-free diet.** *Implementation Considerations:* • *Additional reasons to consider a GFD in this population include avoiding the risk of iron deficiency, avoiding the side effects of iron replacement therapy (e.g., nausea and constipation), and obviating the need for iron replacement.* • *The management strategy for individuals with iron deficiency with anemia versus those without anemia may reasonably vary, and a context-specific individualized discussion between patients and/or caregivers and their clinician is warranted.*	Conditional	Very Low
3	**In individuals with asymptomatic celiac disease and metabolic bone disease, the AGA/SSCD suggest the use of a gluten-free diet.** *Implementation Considerations:* • *Additional reasons to consider a GFD in this population include the potential reduction in the risk of osteoporotic fractures. However, given the uncertain relationship between imaging assessment of bone mineral density and pathologic fracture risk in this population and the uncertain skeletal benefit, implementation should be individualized with focus on patient values and preferences, baseline bone*	Conditional	Very Low

	RECOMMENDATION	STRENGTH	COE
	health, fracture risk, role of antiresorptive therapy, and tolerance for treatment burden.		
4	**In individuals with asymptomatic celiac disease with otherwise unexplained liver enzyme abnormalities, the AGA/SSCD suggest the use of a gluten-free diet.** *Implementation Considerations:* • *Persistent celiac-associated hepatitis may have the potential to progress to liver dysfunction. Thus, additional reasons to consider a GFD in this population include the potential to reduce the risk of advanced liver disease.* • *In order to assess improvement or persistent inflammation, periodic assessments may be needed because liver enzyme levels may fluctuate.* • *Adopting a GFD may be associated with an increased risk of weight gain and metabolic dysfunction-associated steatotic liver disease.* • *The lack of improvement may indicate alternative causes for the persistent liver enzyme abnormalities warranting further evaluation.*	Conditional	Very Low
5	**In prepubertal children or adolescents with asymptomatic celiac disease with short stature, the AGA/SSCD suggest the use of a gluten-free diet.** *Implementation Considerations:* • *The impacts of even strict adherence to a GFD on catch-up growth are variable, and earlier intervention relative to puberty onset and bone age is suspected to improve the chances of greater catch-up.* • *The decision to forgo treatment with a GFD may be reasonable in asymptomatic individuals, particularly when balanced against a patient's age as well as the potential negative impacts on quality of life and costs associated with dietary adherence.* • *Failing to achieve improvement in growth or height velocity in children may indicate a coexisting alternative etiology for short stature such as GH deficiency.*	Conditional	Very Low

	RECOMMENDATION	STRENGTH	COE
6	**In individuals with asymptomatic celiac disease with type 1 diabetes mellitus, the AGA/SSCD make no recommendation on the use of a gluten-free diet.** *Implementation Considerations:* • *Additional reasons to consider a GFD in this population include the associated risk of macrovascular and microvascular complications with a dual diagnosis of CeD and T1D.* • *Potential additional adverse effects of a GFD in this patient population, including the costs and potential implications for quality of life (particularly social functioning) due to the lifestyle restrictions in addition to considering foods with a low glycemic index, should also be discussed. These potential impacts may vary based on the age of the patient.*	No recommendation	Very Low
7	**In individuals with asymptomatic celiac disease and autoimmune thyroid disease, the AGA/SSCD make no recommendation on the use of a gluten-free diet.** *Implementation Considerations:* • *Patients with hypothyroidism and CeD may require higher doses of thyroid replacement therapy to achieve euthyroid status in the setting of untreated CeD.* • *The use of a GFD does not eliminate the need for thyroid replacement therapy. Experts in the panel observed in their practice that patients who are having difficulty in achieving euthyroid status may particularly benefit from a GFD.* • *If a patient on thyroid hormone replacement therapy initiates a GFD, more frequent dose monitoring may be needed to achieve euthyroid status.*	No recommendation	Very Low
8	**In individuals with asymptomatic celiac disease and Down syndrome, the AGA/SSCD make no recommendation on the use of a gluten-free diet.** *Implementation Considerations:* • *The presentation of celiac disease can vary, and individuals with Down syndrome may have difficulty recognizing or reporting symptoms beyond those in*	No recommendation	Knowledge gap

	RECOMMENDATION	STRENGTH	COE
	other populations, which can be mitigated by use of a Down syndrome-specific checklist (e.g., Global Down Syndrome Foundation checklist). Thus, additional reasons to consider a GFD in this patient population include the potential improvement in under-recognized symptoms. • *Other challenges such as difficulty with adherence and oral aversion may present further barriers for following a GFD in patients with Down syndrome.*		

Figure 1: Clinical Decision Support Tool



--------- Indicates an option that many patients would reasonably choose.
- - - - - Indicates an option that a smaller number of patients may choose based on their values and references.
CeD, celiac disease; GCD, gluten-containing diet; GFD, gluten-free diet

1. RECOMMENDATIONS

1.1 General Implementation Considerations

Given that the primary motivation for treating asymptomatic patients with CeD is avoiding potential complications, to help guideline users contextualize these risks, the panel evaluated evidence on the potential long-term complications of CeD, namely mortality, development of intestinal malignancies, and osteoporotic fractures. As the panel could not identify studies that evaluated those outcomes in patients with asymptomatic CeD specifically, studies of patients with CeD regardless of symptom status were included.

Compared with individuals without CeD, those with CeD had a small increase in mortality with pooled hazard ratio 1.06 (95% CI 0.92 to 1.21; N/n = 4/64,193; I^2 = 80%).[9-12] The pooled mortality rate among patients with CeD was 10.1 per 1,000 person-years (95% CI 8.8 to 11.6; N/n = 6/67,872; I^2 = 85%),[9-11, 13-15] while the pooled rate of small bowel adenocarcinoma was 0.41 per 1,000 person-years (95% CI 0.15 to 1.10; N/n = 2/1,246; I^2 = 78%)[16, 17] and the pooled rate of enteropathy-associated T-cell lymphoma was 0.92 per 1,000 person-years (95% CI 0.59 to 1.42; N/n = 3/2,366; I^2 = 69%).[16, 18, 19] Critically, those studies included all individuals with CeD regardless of symptoms, treatment status, possible delays in diagnosis, clinical presentation, or the presence of comorbidities. Therefore, how adherence to a GFD affects these outcomes is unclear.

As for risk of fractures, one study that included patients with biopsy-confirmed CeD across the clinical spectrum (n=265) estimated the overall peripheral fracture (upper and lower extremities) incidence rate at 8.7 per 1,000 person-years before diagnosis and 7.5 per 1,000 person-years after GFD initiation. The pre-diagnosis fracture risk varied between classically symptomatic patients (10.14 per 1,000 person-years) and those with atypical and silent presentations (5.44 per 1,000 person-years).[20] However, the study outcome was not specific to osteoporotic fractures only.

The guideline panel offers the following implementation considerations to guide clinicians' treatment decisions for patients with asymptomatic celiac disease:

- A diagnosis of celiac disease (CeD) does not necessarily require initiation of a gluten-free diet (GFD) in all scenarios. However, knowledge of a diagnosis may nonetheless make it

difficult for a patient or caregiver to choose not to treat. Ideally, the decision to test an asymptomatic individual should account for treatment implications before testing is undertaken.

- When deciding to treat asymptomatic individuals with CeD, regardless of associated conditions and extra-intestinal manifestations, patients and/or caregivers should weigh the potential risks of untreated disease against the burdens of treatment. Patients and/or caregivers who place a higher value on avoiding potential risks such as growth implications (for children), osteoporosis, and/or small intestinal malignancy may reasonably choose to adhere to a GFD. Conversely, those who place a higher value on avoiding the drawbacks of a GFD, such as cost and potential worsening quality of life, may reasonably choose a gluten-containing diet (GCD).
- Prior to choosing a GCD, a thorough clinical history and evaluation is needed to confirm asymptomatic status and the absence of complications.
- Individuals who elect not to follow a GFD warrant periodic monitoring to assess for the development of symptoms and disease complications.
  - The strategy of deferring treatment until or unless symptoms develop may nonetheless lead to morbidity given that some outcomes (e.g., advanced osteoporosis with fracture, malignancy) may not become apparent until advanced.
  - Panel members have observed in their practice that some individuals with CeD who were asymptomatic prior to adopting a GFD may develop new symptoms upon subsequent gluten exposure.

Regardless of the treatment decision, patients and/or caregivers need adequate medical follow-up and nutritional and mental health support. The decision to treat is ongoing and dynamic with patients choosing to resume a GCD if a GFD results in negative impacts on quality of life.

1.2 Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease?

Recommendation 1: In individuals with asymptomatic celiac disease, the AGA/SSCD make no recommendation on the use of a gluten-free diet (no recommendation; very low certainty of evidence)

Implementation considerations:

- In the absence of symptoms or clinical manifestation, the decision to initiate a GFD versus continuing a GCD should be based on shared decision making.

1.2.1 Summary of the Evidence

Evidence informing the recommendation was derived from two randomized controlled trials (RCTs) examining outcomes of health-related quality of life (QoL), development of symptoms, laboratory values, and growth; these studies included 91 individuals. One RCT, by Kurppa *et al*, consisted of asymptomatic adults with CeD (n=40) in Finland who were diagnosed after screening due to family history. After the diagnosis was confirmed with intestinal biopsy, subjects were randomized 1:1 to a GFD vs. a GCD. Outcomes included gastrointestinal symptoms, QoL, bone mineral density (BMD), body mass index (BMI), and nutrient levels.[21] The second trial, by Mahmud *et al*, consisted of 51 asymptomatic children and adults with CeD ranging in age from 8-45 with T1DM, with outcomes including QoL (generic and diabetes-specific), height, weight, BMI, glycemic control, and laboratory values.[22, 23] Evidence from observational studies was also reviewed which included (1) comparative studies of outcomes in patients who were adherent to a vs those who were not adherent to a GFD, and (2) uncontrolled single-arm studies that reported change in outcomes before and after implementing a GFD.[24-29]

Both RCTs reported follow-up at one year; this is an important limitation given the life-long nature of the GFD, and the concern that untreated CeD may lead to complications in the long-term. The details of the studies baseline characteristics and risk of bias (RoB) assessment are reported in Supplemental Table 1 and Supplemental Figures 1 to 15.

1.2.2 Benefits and Harms

The effect of the GFD on QoL utilized data from the two RCTs.[21-23] Compared with continuing a GCD, initiating a GFD led to a trivial improvement in quality of life with a pooled mean difference of 3.24 points (95% CI 0.42 to 6.07; N/n = 2/91; I^2 = 0%), on a scale of 0 to 100.[30, 31] The pooled change in quality of life was trivial in the uncontrolled studies (2.03; 95% CI –1.62 to 5.68; N/n= 2/69; I^2 = 94.1%).[24, 28]

The effect of the GFD on symptoms was derived from the trial by Kurppa *et al*.[21] Compared with continuing a GCD, starting a GFD led to a trivial decrease in overall GI symptom burden [mean difference in Gastrointestinal Symptom Rating scale (GSRS) -0.40, 95% CI -0.69 to -0.11], even though all the included patients reported to be asymptomatic at the time of recruitment. The decrease was most evident for diarrhea (-0.6, 95% CI -1.13 to -0.07), indigestion (-0.70, 95% CI -1.14 to -0.26), and reflux (-0.50, 95% CI -0.89 to -0.11), with little to no change for constipation (-0.10, 95% CI -0.49 to 0.29) or abdominal pain (-0.20, 95% CI -0.54 to 0.14).

Compared with continuing a GCD, initiating a GFD resulted in no clinically important differences in most laboratory outcomes, including hemoglobin, ferritin, vitamin D, and glycemic control (HbA1c), with pooled mean differences close to zero and confidence intervals spanning no effect. A GFD was associated with a trivial reduction in alanine aminotransferase (ALT) with a pooled mean difference of -5.20 U/L (95% CI –11.37 to -0.97), although the clinical significance is uncertain given the effect size and the potential lack of similar normal ranges across labs.[21-23]

There was little to no effect of a GFD on bone mineral density, BMI or growth parameters (height Z-score and weight Z-score) compared with a GCD in the RCTs.[21-23] One comparative observational study by Rami *et al* (n=58) reported that children with CeD and T1DM who were adherent with the GFD, based on becoming and remaining EMA-negative, had a lower BMI Z-score compared to non-adherent children (0.08 ± 0.25 vs 0.70 ± 0.25, p = 0.08).[26] Uncontrolled single arm studies that evaluated outcomes before and 2 years after a GFD showed no to trivial impact on height Z-score (-0.09; 95% CI –0.18 to -0.01; N/n= 5/177; I^2 = 94%), weight Z-score (-0.14; 95% CI –0.38 to 0.09; N/n= 3/80; I^2 = 80%), and BMI Z-score (0.03; 95% CI -0.07 to 0.03; N/n= 5/177; I^2 = 94.7%).[22, 25-27, 29]

1.2.3 Certainty in Evidence of Effects

The overall certainty of evidence was very low. This was based on the suspected serious risk of bias, serious to very serious imprecision, and the need to rely on observational studies for some of the critical outcomes (impact on growth and, risk of malignancy and mortality). The evidence profile is presented in Supplemental Table 2.

1.2.4 Discussion

In making the decision regarding the recommendation, the panel considered the very low certainty regarding the balance of the potential desirable and undesirable effects of implementing a GFD in an individual with asymptomatic CeD. Additionally, input from patient representatives highlighted the meaningful uncertainty and variability in patients' values and preferences as well as potential impacts on health equity due to the financial burden of a GFD and its impact on daily activities. Accordingly, the panel elected to emphasize this uncertainty of patients' values and preferences by making no recommendation and prioritizing the importance of shared decision-making between healthcare providers, patients, and caregivers. The panel acknowledges that the limited duration of follow-up in the available RCTs and their small sample sizes contributed to the very low certainty of evidence. From an implementation perspective, prescribing a GFD currently implies life-long behavioral modification that is associated with financial, social, and quality-of-life burdens. Thus, acceptability may be lower in asymptomatic patients in whom there is unclear benefit. These issues may be compounded by limited access to gluten-free foods and specialized nutritional counseling, which may disproportionately affect individuals with lower socioeconomic status, potentially exacerbating health inequities. The evidence-to-decision framework (EtD) assessment is presented in Supplemental Table 3.

The GFD is the cornerstone of the treatment of CeD. Indeed, prior to the discovery of gluten as the antigen driving immune activation and enteropathy, the prognosis of children with CeD was poor and treatment was unsatisfactory.[32, 33] Adherence to a GFD in symptomatic individuals with CeD leads to rapid improvement, often within days when diarrhea is present.[34] As a result, there is no meaningful conundrum regarding the decision to prescribe a GFD in symptomatic patients with CeD and controlled trials of the intervention in that context are unnecessary.

In asymptomatic CeD individuals, however, the value of the GFD is less immediately apparent. Whereas in other asymptomatic conditions such as hypertension the benefit of treatment to mitigate long-term risk is clear, the rationale for recommending a GFD in the context of asymptomatic CeD depends on several factors. Specifically, it is important to contextualize the risk reduction for outcomes often associated with untreated CeD such as osteoporosis, or intestinal malignancy. While there is evidence of long-term morbidity (and, in some studies, mortality) risk associated with CeD,[35] in many cases the risk ratios for these outcomes decline over the time after diagnosis, suggesting that the institution of the GFD decreases this risk. Though mechanistically plausible, it is impossible to separate out the beneficial effect of the GFD from surveillance and ascertainment bias that leads to increased risks documented in the years immediately surrounding a CeD diagnosis. Likewise, observational studies linking mucosal healing to decreased risks of intestinal lymphoma and fracture may be confounded by health-seeking behaviors that are associated with both villous healing and protection against these outcomes.[10, 36]

Treatment with a GFD for asymptomatic patients with CeD may also mitigate the risks for other outcomes, namely related to growth potential or infertility. These outcomes are associated with significant morbidity and might only occur when severe or irreversible inflammatory changes from CeD happen. It is unknown, and likely unknowable, when an asymptomatic individual has accumulated a threshold of celiac-related damage to trigger these events as is the counterfactual, i.e., to what extent these outcomes might have been prevented by adoption of the GFD let alone how many patients would need to be treated with the diet to prevent one such outcome.

Asymptomatic CeD presumably has a variable natural history, and there are no data that allow extrapolation to calculate how many such people go on to develop morbidity versus how many remain asymptomatic in the long-term. Indeed, there may be “subclinical” asymptomatic CeD in which patients do not recognize their symptoms as pathologic. Therefore, in addition to emphasizing a thorough history and evaluation to confirm the patient is asymptomatic, it is also necessary to acknowledge the potential drawbacks of prescribing the GFD, including its higher cost and its association with food insecurity, which may also undermine adherence.[37-43] Additional social challenges[44] may be experienced, particularly in younger patients, and based

on observations of the Panel member in their practice many may experience the development of a sensitivity to inadvertent gluten exposure (sometimes entailing acute symptoms such as vomiting and diarrhea) after otherwise eliminating it from the diet.

1.3 Should gluten-free diet vs. gluten-containing diet be used for individuals with unexplained iron deficiency diagnosed with asymptomatic celiac disease?

Recommendation 2: In individuals with asymptomatic celiac disease with unexplained iron deficiency, the AGA/SSCD suggest the use of a gluten-free diet (conditional recommendation; very low certainty of evidence)

Implementation considerations:

- Additional reasons to consider a GFD in this population include avoiding the risk of iron deficiency, avoiding the side effects of iron replacement therapy (e.g. nausea and constipation), and obviating the need for iron replacement.
- The management strategy for individuals with iron deficiency with anemia versus those without anemia may reasonably vary and a context-specific individualized discussion between patients and/or caregivers and their clinician is warranted.

1.3.1 Summary of the Evidence

Evidence informing the recommendation was derived from two studies that explored the impact of a GFD on adult[45] and pediatric patients[46] with newly diagnosed CeD. There were no RCTs that addressed this question. In a study by Ben Ami *et al*, patients under 18 years old were diagnosed with or without a duodenal biopsy. Among a cohort of 304 patients, 60 were found to be iron deficient without anemia and included in their analysis. The study did not report the symptom status of the included patients, and none of the included patients had anemia. All patients in the study were placed on a GFD and those with iron replacement (n=29) were compared to those without iron replacement (n=31). Adherence was assessed but not reported for either the use of iron replacement or dietary compliance. The outcomes for this study included a biochemical response at 6 and 12 months.

In a separate study by Annibale *et al*, adult patients with iron deficiency anemia (IDA) were referred from hematology to gastroenterology clinics and evaluated for the presence of CeD. Among 190 patients evaluated, CeD was diagnosed and confirmed by small bowel biopsy in 26 individuals. All the patients were invited to follow a GFD but adherence was not assessed. All patients had evidence of IDA that was symptomatic, including for fatigue and pallor, though 10 patients were reported to have no CeD-associated symptoms. There were 8 patients with concomitant *H. pylori* infection at the time of CeD diagnosis. Patients were followed at 6, 12, and 24 months. The details of the studies' characteristics and risk of bias assessment are reported in Supplemental Tables 4 and Supplemental Figures 16 and 17.

1.3.2 Benefits and Harms

In the study by Ben Ami et al., no participants were anemic at baseline; therefore, no changes in hemoglobin levels were observed following the intervention. Ferritin concentrations increased from baseline in both groups. In the iron-supplementation group, ferritin levels increased from 9.0 ± 4.7 ng/mL at baseline to 25.2 ± 20.8 ng/mL at 12 months, whereas in the non-treated group, ferritin levels increased from 8.9 ± 3.8 ng/mL to 18.6 ± 9.5 ng/mL. However, there was no clinically meaningful difference in ferritin levels between the groups at the 12-month follow-up..

In the study by Annibale *et al*, all patients had previously been on iron supplementation, which reported resolved anemia in the majority (80%) of these patients. Among the 26 total patients, 20 were ultimately followed up to 2 years, including 18 women and 2 men. Among the female CeD patients, at 12 months 17 out of 18 had resolution of anemia and 9 out of 18 had resolution of iron deficiency. At 12 months, both male CeD patients had resolution of iron deficiency and anemia. The iron deficiency anemia resolved in those patients without the need for iron replacement therapy.

1.3.3 Certainty in Evidence of Effects

The overall certainty of evidence was very low. This was mainly due to reliance on observational studies in addition to the serious imprecision and concerns about serious indirectness. The evidence profile is presented in Supplemental Table 5.

1.3.4 Discussion

The presence of iron deficiency, with or without anemia, is a common sign prompting evaluation for CeD. Among teenagers and adults, IDA that persists despite oral iron supplementation is the most frequent presentation for CeD.[47] The overall prevalence of CeD among patients with IDA is estimated to be 5.5% based on a recent systematic review and meta-analysis[48] whereas the prevalence of IDA among patients with CD varies widely, with estimates at least as high as 23%.[49] The age of presentation and other clinical factors can influence these prevalence estimates,[50] as well as whether patients present with IDA or iron deficiency without anemia.[51]

Given their frequent coexistence, the AGA Guidelines on the management of IDA outline the importance of considering CeD as part of the differential diagnosis even among asymptomatic patients. Current guideline suggests serologic testing for CeD even in asymptomatic adult patients with IDA, though the optimal approach in those without anemia is less clear.[52] In the presence of IDA or iron deficiency without anemia, oral iron supplementation even when combined with a GFD may be less successful at normalizing this deficiency or resolving the anemia in patients with more severe CeD due to a combination of factors such as genetics, more severe enteropathy, coexisting anemia of chronic disease.[53]

In making the decision regarding the recommendation, the panel noted that the moderate desirable effect of resolution of iron deficiency with GFD outweighs the potential undesirable effects of GFD. Also, patient representatives highlighted that there was no important uncertainty or variability in how they valued the noted desirable effect. Thus, the panel made a conditional recommendation for the use of a GFD. The current recommendation is based exclusively on observational studies with very low certainty of evidence. In the included studies, resolution of anemia and/or iron deficiency occurred after one year of therapy. This was weighed against the use of iron supplementation, which has acknowledged gastrointestinal side effects such as nausea and constipation, and may not be sufficient to treat iron deficiency or anemia. Similarly, the panel also considered scenarios in which parenteral iron might be needed as well as whether patients with anemia could be entirely asymptomatic. The panel also strongly considered the potential to normalize anemia following a GFD as justification for suggesting this approach, as it may preclude the need for additional therapy. The EtD framework assessment is presented in Supplemental Table 6.

1.4 Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease with metabolic bone disease?

Recommendation 3: In individuals with asymptomatic celiac disease and metabolic bone disease, the AGA/SSCD suggest the use of a gluten-free diet (conditional recommendation; very low certainty of evidence)

Implementation considerations:

- Additional reasons to consider a GFD in this population include the potential reduction in the risk of osteoporotic fractures. However, given the uncertain relationship between imaging assessment of bone mineral density and pathologic fracture risk in this population and the uncertain skeletal benefit, implementation should be individualized with focus on patient values and preferences, baseline bone health, fracture risk, role of antiresorptive therapy, and tolerance for treatment burden.

1.4.1 Summary of the Evidence

Evidence informing the recommendation was derived from the RCT by Kurppa *et* al which evaluated the effect of a GFD compared to GCD among asymptomatic adults in Finland with screen-detected CeD confirmed by duodenal biopsies. The trial reported the change in bone mineral density (BMD) in lumbar spine and femur neck after 1 year of a GFD vs GCD.[21] We also relied on data from observational studies. Valdimarsson *et al* conducted an uncontrolled single-arm study in newly diagnosed CeD (n = 63) including those with no symptoms of malabsorption (54%; n = 34). They reported the change in BMD and presence of severe osteopenia defined as Z-score less than -2. While the authors reported that 13 patients received calcium and/or vitamin D supplementation, it is unclear whether any of them received other bone-active medications (e.g., bisphosphonates, calcitonin, or hormonal replacement therapy).[54] In another study, Lebwohl *et al* conducted an observational study using Swedish pathology registries of biopsy-confirmed CeD who underwent a follow-up intestinal biopsies within 6 months to 5 years of diagnosis. They reported the association between persistent villous atrophy, as a surrogate

for ongoing gluten intake, and risk of fractures. The study lacked data on BMD measurements, GFD adherence, or use of bone-active medications.[36] The details of the studies characteristics and risk of bias assessment are reported in Supplemental Tables 7 and Supplemental Figures 18 to 20.

1.4.2 Benefits and Harms

In the study by Kurppa *et al*, the patients in the GCD and GFD groups had similar lumbar spine BMD and femoral neck BMD at baseline. After 1 year of dietary interventions, there was no to trivial change in BMD (Lumbar spine BMD difference of 0.01 g/cm² ;95% CI −0.01 to 0.02 and femoral neck BMD difference of 0.01 g/cm²; 95% CI −0.01 to 0.03).[21]

In the study by Valdimarsson *et al*, after one year of a GFD, the percentage of CeD with severe osteopenia decreased from 22% to 17% in the forearm, from 15% to 8% in the lumbar spine, from 9% to 2% in the femoral neck, and from 18% to 5% in the trochanter.[54]

In the study by Lebwohl *et al*, persistent villous atrophy was associated with increased risk of hip fractures (hazard ratios 1.67; 95% CI 1.06 to 2.66) but no associated risk of overall fractures (HR 0.93; 95% CI 0.82 to 1.06) or likely osteoporotic fractures (HR 1.11; 95% CI 0.84 to 1.46).[36]

1.4.3 Certainty in Evidence of Effects

The overall certainty of evidence was very low. This was due to reliance on observational studies with serious risk of bias, serious indirectness, and serious imprecision. The evidence profile is presented in Supplemental Table 8.

1.4.4 Discussion

In making the decision regarding the recommendation, the panel noted that the small to moderate desirable effect of improvement on BMD with a GFD combined the small increased risk of hip fractures with uncontrolled CeD probably outweigh the potential undesirable effects of a GFD. Also, patient representatives valued the potential benefit of improved bone health, even if uncertain, over the potential impacts of a GFD. While a GFD may increase bone mass over longer durations or in selected patients, this potential benefit has not been clearly demonstrated in asymptomatic populations within the timeframe studied. For this PICO question, the panel emphasized the absence of evidence regarding the association between a GFD and fracture

risk in this patient population as key reasons for not issuing a stronger recommendation based solely on bone health. The EtD framework assessment is presented in Supplemental Table 9.

Improvements in BMD following a GFD have been reported in adults and children with CeD, including older individuals, although recovery may be incomplete and influenced by age at diagnosis and duration of untreated CeD.[36, 54-57] In a study that stratified fracture risk in CeD by clinical phenotype, bone disease and fractures were observed across the clinical spectrum, including those without classical symptoms.[58]

However, there are no studies that evaluated the effect of a GFD, compared with a GCD, on the risk of bone disease-related fractures in asymptomatic CeD. As a result, the effect of dietary treatment on fracture outcomes in this population is unknown and the relative value of monitoring surrogate outcomes, e.g., change in BMD, is unclear. Nonetheless, there is a plausible mechanistic rationale for treating underlying small bowel inflammation, which can result in vitamin D and calcium malabsorption.[36] There are no RCTs that evaluated the effect of a GFD compared with no treatment in individuals with CeD and established osteopenia or osteoporosis. The role of bone-active medications in CeD with osteopenia or osteoporosis is unclear. However, a pilot study that included 28 patients with CeD and osteopenia suggested no additional gain from adding zoledronic acid to a GFD.[59]

Recent observational studies continue to report increases in vitamin D levels and modest improvements in BMD following initiation of a GFD; however, these studies are limited by heterogeneity in study populations, lack of control groups, and variable follow-up duration.[60]

1.5 Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease and unexplained abnormal liver function tests and enzymes?

Recommendation 4: In individuals with asymptomatic celiac disease with otherwise unexplained liver enzyme abnormalities, the AGA/SSCD suggest the use of a gluten-free diet (conditional recommendation; very low certainty of evidence)

Implementation considerations:

- Persistent celiac-associated hepatitis may have the potential to progress to liver dysfunction. Thus, additional reasons to consider a GFD in this population include the potential to reduce the risk of advanced liver disease.
- In order to assess improvement or persistent inflammation, periodic assessments may be needed because liver enzyme levels may fluctuate.
- Adopting a GFD may be associated with an increased risk of weight gain and metabolic dysfunction-associated steatotic liver disease
- The lack of improvement may indicate alternative causes for the persistent liver enzyme abnormalities warranting further evaluation.

1.5.1 Summary of the Evidence

Evidence informing the recommendation was derived from one study evaluating the prevalence of liver-associated enzyme abnormalities and the effect of a GFD among adult patients with CeD.[61] Bardella *et al* evaluated 158 consecutive patients with newly diagnosed CeD based on intestinal biopsy who were started on a GFD and followed for 1 to 10 years (median 4 years); 21 of these individuals were asymptomatic. The study included 67 individuals with elevated liver enzymes (47 with elevated AST/ALT, 6 elevated AST, 14 elevated ALT, and 3 with concomitant increase in alkaline phosphatase) who were started on a GFD. Daily alcohol intake was absent or low (<20 g/day) in all participants. There was no evidence of hepatotoxic medication use or exposure to hepatotoxins. Three patients with abnormal liver enzymes tested positive for hepatitis B surface antigen, and one patient tested positive for hepatitis C antibody. Reported outcomes were measured at 3 months, 6 months, and 1 year. [61] The details of the study

characteristics and risk of bias assessment are reported in Supplemental Tables 10 and Supplemental Figure 21.

1.5.2 Benefits and Harms

In the study by Bardella *et al*, after 3 months of a strict GFD, transaminase levels normalized in 22 patients (33%) with hepatitis. After 6 months, normalization occurred in 60 patients (89%). Mean AST decreased from 47 U/L (range 30–190) at diagnosis to 27 U/L (range 19–275) after 1 year of a GFD. Mean ALT decreased from 61 U/L (range 25–470) to 29 U/L (range 19–390) over the same period. Among the seven patients whose liver enzymes did not normalize, liver biopsy revealed hepatic steatosis in two and autoimmune hepatitis in five.[61]

1.5.3 Certainty in Evidence of Effects

The overall certainty of evidence was very low. This was due to reliance on observational studies with serious risk of bias and serious imprecision. The evidence profile is presented in Supplemental Table 11.

1.5.4 Discussion

In making the decision regarding the recommendation, the panel noted that the moderate desirable effect of resolution of liver enzyme abnormalities with a GFD probably outweighs the potential undesirable effects of a GFD. Also, patient representatives valued the resolution of the liver abnormalities and potential risk reduction of advanced liver disease, even if uncertain, over the potential undesirable effects of a GFD. The current recommendation is based exclusively on observational uncontrolled studies with very low certainty of evidence. The EtD framework assessment is presented in Supplemental Table 12.

CeD is associated with a number of disparate hepatic disorders including cryptogenic hypertransaminasemia, hepatic steatosis, autoimmune liver disease, and vascular liver disease.[62] Bardella et al reported 41% of patients with CeD have elevated liver enzymes. Among these individuals, 31% were asymptomatic. Nearly all subjects who started treatment with a GFD had biochemical improvement in their liver enzyme profile and those who failed to improve had additional sources of hepatic dysfunction.[61] Thus, starting a GFD in individuals with CeD without an alternative etiology will likely lead to biochemical improvement. At present, there

are no reliable clinical, serological, or histological predictors to identify which individuals with CeD will develop hypertransaminasemia.

Additionally, minimal and indirect evidence suggests that patients with cirrhosis and concomitant CeD may improve on a strict GFD. While there are no overall differences in mortality, one study found that 4.6% (11/232) of individuals with cryptogenic cirrhosis have concomitant CeD and when these 11 patients were prospectively followed after starting a strict GFD, they had fewer decompensations and improved Model for End-Stage Liver Disease–Sodium (MELD-Na) compared to matched controls.[62]

Predicting which patients with CeD will have liver involvement is challenging, let alone identifying within that group which patients will progress to clinically important outcomes such as cirrhosis if they do not adhere to a GFD. Limited evidence suggests that some individuals with persistent celiac-associated hepatitis may progress to cirrhosis; however, whether adherence to a GFD can modify this trajectory remains unclear. Notably, the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) appears to be higher among patients with CeD on a GFD than among treatment-naïve patients.[63] This association may be related to dietary changes following GFD initiation, including increased consumption of energy-dense gluten-free foods. These findings underscore the importance of nutritional counseling when implementing a GFD.

1.6. Should gluten-free diet vs. gluten-containing diet be used for children with asymptomatic celiac disease with short stature?

Recommendation 5: In prepubertal children or adolescents with asymptomatic celiac disease with short stature, the AGA/SSCD suggest the use of a gluten-free diet (conditional recommendation; very low certainty of evidence)

Implementation considerations:

- The impacts of even strict adherence to a GFD on catch up growth are variable and earlier intervention relative to puberty onset and bone age is suspected to improve the chances of greater catch-up.
- Failing to achieve improvement in growth or height velocity in children may indicate a coexisting alternative etiology for short stature such as GH deficiency.

1.6.1 Summary of the Evidence

Evidence informing the recommendation was derived from observational studies which evaluated the effect of a GFD on growth in children with short stature and CeD. The follow-up in the included studies was no longer than three years. The studies were published between 1980 and 1992 and involved 81 total individuals across 5 studies.[64-68] These studies all included patients who had serology and small bowel biopsy to confirm CeD diagnosis, and the population included both those with and without symptoms. All the patients included had growth assessments performed and were evaluated for various endocrinopathies which could also result in short stature. Nutritional parameters were assessed along with bone age. Follow-up biopsies, serologic studies, and nutritional parameters confirmed GFD adherence. All studies performed growth assessments at the initiation of the GFD and at various time intervals after treatment. The details of the studies characteristics and risk of bias assessment are reported in Supplemental Tables 13 and Supplemental Figure 22.

1.6.2 Benefits and Harms

Four of the identified studies reported the change in height velocity after initiation of a GFD in patients with CeD. Groll *et al* reported mean acceleration in height velocity of 4.1 ± 1.6 cm/year after implementing a GFD in 7 children found to have CeD with no gastrointestinal symptoms; however, one of them had no change in height velocity after starting a GFD.[68] Bonamico *et al*

reported a change in growth velocity from -2.3 standard deviation score (SDS) to 3.7 SDS after one year of a GFD in 29 children with short stature and CeD. Importantly, six children who had growth hormone (GH) deficiency along with CeD showed no growth even with GH therapy until the GFD was started, after which they had growth acceleration.[64] Cacciari *et al* reported change in growth velocity for 11 children with short stature and CeD without GI symptoms. After around 1 year of a GFD, mean growth velocity increased from -1.56 SDS (range -2.44 to 0) to +1.1 SDS (range -6.1 to 6.69).[67] Similarly, Rosenbach *et al* reported change in height velocity in 11 children with CeD, including eight children with diarrhea, six children with growth retardation in the first two years of life, and two children with recurrent abdominal pain and distention. After 6 to 50 months of a GFD, the mean height velocity increased from -2.9 SDS (range -4.8 to 0) to +1.9 SDS (range 0 to +6); and from 3.1 cm/year (range 0 to 6) to 9.2 cm/year (range 6 to 12).[66]

One additional study by Bosio *et al* included 24 children with CeD, poor weight gain and delayed height velocity and 15 of them had GI symptoms. There were 23 patients (10 males and 13 females) followed for 9 to 15 months. The mean height SDS in the male patients went up from of -2.46 ± 0.96 (range -1.63 to -4.83) to -1.99 ± 0.78 (range -0.87 to -3.53), and in the female patients from -2.58 ± 0.64 (range -1.65 to -3.65) to -2.28 ± 0.70 (range -1.05 to -3.67). In 12 patients (4 males and 9 females) followed for three years, the mean height SDS went up from -2.52 ± 0.67 (range -1.65 to -3.5) to -1.77 ± 0.61 (range -0.64 to -2.55).[65]

1.6.3 Certainty in Evidence of Effects

The overall certainty of evidence was very low. This was due to reliance on observational studies with serious risk of bias, and serious imprecision due to the small number of included patients. The evidence profile is presented in Supplemental Table 14.

1.6.4 Discussion

The panel noted that the moderate desirable effect of catch-up growth with a GFD outweighs its potential disadvantages. Also, patient representatives highlighted that they valued the potential catch-up growth, even if uncertain, over the potential impact of a GFD. Thus, the panel made a conditional recommendation for the use of a GFD, acknowledging that the recommendation is based exclusively on observational uncontrolled studies with very low certainty of evidence. The EtD framework assessment is presented in Supplemental Table 15.

Short stature, defined by a height less than or equal to 2 standard deviations below the mean for the age and sex or height below the 3rd percentile, is often observed in patients with CeD due to a combination of factors including poor nutrient absorption in the setting of small bowel inflammation. Addressing short stature is broadly relevant for children due to social burdens and isolation, stigmatization, and lower self-esteem and QOL,[69] which could be further affected by a diagnosis of CeD. Children with shorter stature are often perceived as younger and subsequently have lower expectations from teachers and peers.[70] Some studies have reported a lower mean IQ score in children with heights less than the 5th percentile.[71] Speculatively, these factors may have psychological impact on both parents and children that can persist and influence future expectations though cultural background and gender are relevant cofactors.

It is possible that short stature may be the only clinical feature present in patients with CeD and may be more common than GH deficiency as an etiology.[64] The reported benefits of a GFD to significantly accelerate growth velocity in prepubertal and adolescent children is a benefit observed even among those with coexisting GH deficiency on replacement therapy. While catch-up growth may be variable, the majority of studies indicate that when CeD is diagnosed early, catch-up growth is rapid and normal height can be achieved in approximately 12 months.[65] However, some children with CeD had no observed change in height velocity after starting a GFD and post-pubertal children did not see the same benefit for catch-up growth after starting a GFD.[68] The rate of catch up growth differs according to age at the time of CeD diagnosis, with patients diagnosed later and closer to puberty showing slower and possibly incomplete catch-up. Growth velocity also appears to slow down, suggesting a threshold effect for the benefit of a GFD. Additionally, childrens' growth is dictated by their midparental height which provides realistic growth expectations. Despite the observed variable effects of a GFD on growth after initiating a GFD, failing to achieve improved growth or height velocity in children may indicate a coexisting alternative etiology for short stature such as GH deficiency.

1.7 Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease and type 1 diabetes mellitus?

Recommendation 6: In individuals with asymptomatic celiac disease with type 1 diabetes mellitus, the AGA/SSCD make no recommendation on the use of a gluten-free diet (no recommendation; very low certainty of evidence)

Implementation considerations:

- Additional reasons to consider a GFD in this population include the associated risk of macrovascular and microvascular complications with a dual diagnosis of CeD and T1D.
- Potential additional adverse effects of a GFD in this patient population including the costs and potential implications for quality of life (particularly social functioning) due to the lifestyle restrictions in addition to considering foods with a low glycemic index should also be discussed. These potential impacts may vary based on the age of the patient.

1.7.1 Summary of the Evidence

Evidence informing the recommendation was derived from one RCT, Mahmud *et al*, which compared outcomes between individuals (n= 51) with established CeD and T1DM were randomized to a GFD or GCD.[22, 23] Additionally, four observational studies that compared outcomes before and after treatment with a GFD were assessed. The four observational studies combined included 169 individuals.[25-27, 29] All studies included patients with established T1DM and a subsequent CeD diagnosis as determined by histologic confirmation. All studies primarily assessed hemoglobin A1c as the outcome measurement for glycemic control and follow-up was limited to two years or less. We did not identify any study that evaluated the impact of treatment of CeD on microvascular or macrovascular outcomes. The details of the studies characteristics and risk of bias assessment are reported in Supplemental Tables 16 and Supplemental Figures 23 to 25.

1.7.2 Benefits and Harms

Compared to remaining on a GCD, adherence to a GFD led to a clinically non meaningful change in glycemic control (defined by hemoglobin A1c) of 0.14% (95%CI -0.77 to 1.05%). In

this RCT, greater post-prandial hyperglycemia was observed with continuous glucose monitor data. In the observational studies, compared to baseline, two-year adherence to a GFD led to a similarly trivial change in glycemic control with a mean increase in HgbA1c of 0.25% (95% CI 0.09% to 0.42%). None of these studies observed an improvement in anthropometrics for up to two years of follow up on a GFD. Importantly, there was also no increase in hypoglycemia or associated adverse events with initiation of a GFD, indicating no increased risk with respect to glycemic control after treatment.

The RCT also reported a trivial change in health-related quality of life score with a mean increase of 1.8 points (95% CI -6.1 to 9.7) on a scale from 0 to 100.[23]

1.7.3 Certainty in Evidence of Effects

The overall certainty of evidence was very low. This was due to reliance on observational studies with serious risk of bias, and serious to very serious imprecision due to the small number of included patients. The evidence profile is presented in Supplemental Table 17.

1.7.4 Discussion

The panel considered the very low certainty regarding the balance of the potential desirable and undesirable effects of implementing a GFD in individuals with T1DM and asymptomatic CeD. The input from the patient representatives highlighted the possibility of the presence of important uncertainty and variability in patients' values and preferences, and variable impact on health equity. Thus, the panel prioritized patients' values and preferences by making no recommendation and emphasizing the importance of shared decision-making between healthcare provider, patients, and caregivers. The EtD framework assessment is presented in Supplemental Table 18.

The prevalence of CeD among those with T1DM is high. The increased risk of vascular complications such as retinopathy and nephropathy in the setting of a dual CeD and T1DM diagnosis have also been reported based on registry data.[72, 73] One study also suggests more severe subclinical atherosclerosis in patients with a dual diagnosis.[74] Earlier identification of patients with overlapping conditions may provide an opportunity to initiate a GFD among those who are asymptomatic, to mitigate these potential risks and supports consideration of treatment with a GFD even in the absence of recognizable symptoms.

However, there are also challenges unique to a dual diagnosis of CeD and T1DM that are important, especially the restrictive diets and food costs. While many studies do not show a difference in quality of life with initiation of a GFD in patients with a dual diagnosis,[23, 75, 76] others have shown decreased QoL particularly related to social functioning.[77, 78]

It is important to highlight again that the currently available comparative studies do not demonstrate a clinically important difference in benefit. Acknowledging that some of these were limited in follow-up to two years, they do not provide insight on long-term complications such as osteopenia and osteoporosis, micro and macrovascular diabetes-associated complications, and intestinal lymphoma. Whereas studies that report long-term outcomes included both symptomatic and asymptomatic patients and did not stratify findings by GFD adherence, limiting their applicability to our question of interest.

1.8. Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease and autoimmune thyroid disease?

Recommendation 7: In individuals with asymptomatic celiac disease and autoimmune thyroid disease, the AGA/SSCD make no recommendation on the use of a gluten-free diet (no recommendation; very low certainty of evidence)

Implementation considerations:

- Patients with hypothyroidism and CeD may require higher doses of thyroid replacement therapy to achieve euthyroid status in the setting of untreated CeD.
- The use of a GFD does not eliminate the need for thyroid replacement therapy. Experts in the panel observed in their practice that patients who are having difficulty in achieving euthyroid status may particularly benefit from a GFD.
- If a patient on thyroid hormone replacement therapy initiates a GFD, more frequent dose monitoring may be needed to achieve euthyroid status.

1.8.1 Summary of the Evidence

Evidence informing this recommendation is limited to a small number of observational studies evaluating the effect of a GFD on thyroid outcomes in patients with asymptomatic CeD and autoimmune thyroid disease. Virili et al. identified 35 patients with CeD and hypothyroidism secondary to Hashimoto's thyroiditis through screening of individuals with unexplained iron deficiency anemia, short stature, or low body weight and compared them with 68 matched patients with isolated Hashimoto's thyroiditis.[79] All patients received levothyroxine, although only 21 patients with CeD adhered to a GFD. Collins et al. identified seven patients with concurrent CeD and hypothyroidism from a pathology database and compared their levothyroxine requirements with those of 200 controls with hypothyroidism alone.[80] Levothyroxine requirements before and after GFD initiation were assessed in the CeD cohort. Finally, Krysiak et al. evaluated 34 euthyroid women with autoimmune thyroiditis and positive anti-tTG antibodies but no clinical symptoms of CeD.[81] Sixteen participants followed a GFD and 18 continued a GCD diet for 6 months, with outcomes including changes in thyroid function, anti-TPO and anti-tTG antibody levels, and the development of CeD-related symptoms. We did not identify any study that compared the effect of using a GFD versus GCD in patients with CeD and concurrent clinical autoimmune thyroid disease, and none of the studies reported the impact of a GFD on hypothyroidism-related symptoms. The details of the studies characteristics and risk of bias assessment are reported in Supplemental Tables 19 and Supplemental figures 26 and 27.

1.8.2 Benefits and Harms

In the study by Virili et al, target serum TSH was reached after treatment with mean dose of levothyroxine of 1.31 µg/kg/day for 5 months in all patients with isolated hypothyroidism while a comparable mean dose of 1.47 µg/kg/day for 6 months led at achieving target TSH in only one out of 35 patients with CeD and hypothyroidism. Those who were compliant with a GFD (n = 21) achieved target TSH on a comparable dose of levothyroxine (mean 1.32 µg/kg/day) within 11 months of starting the diet. However, those who were noncompliant with a GFD (n =14) required a higher dose of levothyroxine (mean 1.96 µg/kg/day) to achieve target TSH which they achieved within 4 months of increasing the dose.[79]

In the study by Collins et al, those with concomitant untreated CeD required a mean dose 2.6 µg/kg/day to achieve euthyroid status, compared to 1.3 µg/kg/day for those with isolated

hypothyroidism. After starting a GFD, the mean dose required to achieve euthyroid status for those with concomitant CeD decreased to 1.9 µg/kg/day.[80]

The study by Krysiak et al did not include any patient with clinical thyroid disease. There was no clinically important difference between patients who followed a GFD versus GCD in terms of change in thyroid functions or development of symptoms. The study reported no adverse events or need to discontinue the diet in any of the included participants.[81]

1.8.3 Certainty in Evidence of Effects

The overall certainty of evidence was very low. This was due to reliance on observational studies with serious risk of bias, serious indirectness, and very serious imprecision due to the small number of included patients. The evidence profile is presented in Supplemental Table 20.

1.8.4 Discussion

Prior large observational studies have estimated that CeD may affect around 1.6% of patients with autoimmune thyroid disease, and autoimmune thyroid diseases have been reported in up to 15% of patients with CeD.[82, 83] The impact of having CeD on the management of autoimmune thyroid diseases was evaluated by the two observational studies, which suggested that patients with CeD may require higher doses of thyroid replacement therapy to achieve euthyroid status, and that treatment of CeD may lead to a reduction in the required doses.[79, 80] None of the studies reported the impact of treatment of CeD on the resolution of symptoms of autoimmune thyroid diseases. Additionally, the presence or absence of symptoms attributable to CeD was not clear in the studies.

The panel considered the very low certainty regarding the balance of the potential desirable and undesirable effects of implementing a GFD in individuals with autoimmune thyroid disease and asymptomatic CeD. Combined with the possible uncertainty and variability in patients' values and preferences, this led the panel to prioritize patients' values and preferences by making no recommendation and emphasizing the importance of shared decision-making between healthcare provider, patients, and caregivers. The EtD framework assessment is presented in Supplemental Table 21.

1.9 Should gluten-free diet vs. gluten-containing diet be used for individuals with Down syndrome and asymptomatic celiac disease?

Recommendation 8: In individuals with asymptomatic celiac disease and Down syndrome, the AGA/SSCD make no recommendation on the use of a gluten-free diet (no recommendation; knowledge gap)

Implementation considerations:

- The presentation of celiac disease can vary and individuals with Down syndrome may have difficulty recognizing or reporting symptoms beyond those in other populations, which can be mitigated by use of Down syndrome-specific checklist (*e.g. Global Down Syndrome Foundation* checklist). Thus, additional reasons to consider a GFD in this patient population include the potential improvement in under recognized symptoms.
- Other challenges such as difficulty with adherence and oral aversion may present further barriers for following a GFD in patients with Down syndrome.

1.9.1 Summary of the Evidence

The search strategy did not identify any study that compared the effect of using a GFD versus GCD in patients with CeD and Down syndrome. Due to the lack of evidence, this is considered a knowledge gap. The panel elected to include a discussion of this question nonetheless given it is frequently encountered. The evidence profile is presented in Supplemental Table 22.

Individuals with Down syndrome are at higher risk of many of the complications of untreated CeD including osteoporosis,[84] poor growth early in life,[85] neuropsychiatric manifestations,[84] nutritional deficiencies,[86] certain malignancies,[85] and overall mortality.[87] Little is known about the combined effects of both diseases on these outcomes in symptomatic individuals, let alone asymptomatic individuals, but it is hypothesized that individuals with Down syndrome may experience a higher risk of these outcomes with concurrent CeD. However, it should be noted that one study found no excess mortality risk from having concurrent Down syndrome and CeD.[87] Another study found that screening for CeD in individuals with Down syndrome was not a cost-effective strategy for preventing intestinal lymphoma.[88]

1.9.2 Discussion

The rate of CeD among those with Down syndrome is high[89] and assessing symptoms in such patients is challenging. Individuals with Down syndrome may have difficulties with self-reporting of symptoms and the symptoms of CeD may be difficult for caregivers to recognize. One study that compared screening-identified individuals to clinically-identified individuals with Down syndrome demonstrated a longer lag from the onset of symptoms to diagnosis in individuals that were clinically-identified.[90] A majority of individuals in this study were screening-identified and 45.5% had unrecognized symptoms at the time of positive screening or subclinical presentations. There was not follow up in this study to determine whether symptoms improved on a GFD. Symptom check lists have been developed (https://www.ncdsalliance.org/wp-content/uploads/2022/11/GLOBAL-Guideline-Celiac-Disease-Toolkit.pdf), but these symptoms may be difficult for caregivers to identify and are common in Down syndrome, so discerning CeD based on these symptoms may also be challenging.

Ultimately, it is also acknowledged that adherence to a GFD has unique challenges in individuals with Down syndrome. Individuals with Down syndrome may have barriers to self-advocacy for gluten-free items when not with an educated caregiver or peers. One recent study found that individuals with Down syndrome take longer to achieve serologic normalization compared to controls without Down syndrome and this was in part attributed to potential inadequate GFD adherence,[91] highlighting this knowledge gap.

1.10 Evidence Gaps and Future Research

There are no currently available pharmaceutical interventions for patients with CeD, and the availability of such a therapy would likely have substantial impact on the treatment calculus for patients with asymptomatic CeD. For now, we have relied on the evidence that undiagnosed CeD may be deleterious for both children and adults,[92-94] but there is not currently sufficient certainty evidence to demonstrate that a GFD will alter the course of outcomes in asymptomatic individuals.

To help clarify the optimal management, data from RCTs would mitigate the biases from uncontrolled studies. While RCTs may be impractical to answer all questions, such as those with a protracted time horizon in the case of intestinal malignancies, they could be leveraged to

explore other outcomes, including growth, abnormal liver enzymes, and fracture risk. A notable limitation was that throughout evaluated studies there was a short duration of follow-up. Future non-randomized observational studies may be well-suited to help inform whether to treat asymptomatic CeD, or this could be in the form of leveraging pragmatic trial design nested in the increasing population-level screening programs. Prospective screening programs are already yielding valuable insights regarding the outcomes of children who are screened for CeD,[95] and these results will be critical to extending our understanding of the longer-term impact of dietary choices.

Furthermore, many studies used various definitions of asymptomatic CeD. For example, some patients were classified as “atypical” CeD whereas others were explicitly noted to have no symptoms as part of the larger study. Future work focusing on this truly asymptomatic and complication-free group will provide more robust understanding of the potential risks of untreated CeD among those following a GCD. Other specific comparison groups that may be helpful include differentiating the efficacy of a GFD compared to iron supplementation alone in populations with iron deficiency with or without anemia. Another important comparison is GFD versus anti-resorptive therapies for patients with metabolic bone disease.

Nearly every recommendation to suggest a GFD rests on a surrogate outcome (e.g. ferritin, bone mineral density, liver-enzyme normalization, height velocity, hemoglobin A1c, and biochemical euthyroid status) rather than on a demonstrated effect on a patient-important endpoint. Thus, future work should measure patient-important outcomes directly (e.g. symptomatic anemia and its sequelae, incident osteoporotic fractures, progression of liver disease, final adult height, micro- and macrovascular complications, malignancy, and validated quality-of-life and psychological outcomes). Another goal should be to formally validate, in asymptomatic CeD specifically, whether and how strongly each surrogate predicts its corresponding patient-important outcome. Without that validation, the inferential chain from surrogate improvement to patient benefits remains a logical leap.

Persistent villous atrophy is associated with downstream risk (e.g., fractures)[36] and is a plausible, modifiable treatment target, yet it was inconsistently measured in the available studies. Future research should incorporate longitudinal histologic and serologic outcomes and clarify the relationship between mucosal healing and patient-important endpoints in asymptomatic CeD. This work is increasingly complicated by the advocacy for and growth of no-

biopsy (serology-only) diagnosis. As more patients are diagnosed without baseline histology, studies must determine how the recommendations apply when no histologic anchor exists, and whether serologic normalization is an adequate predictor of patient-important outcomes in this setting.

Lastly, a deeper understanding of the potential drawbacks of adherence to a GFD is critical, as well as an assessment of its social impact, on patients with asymptomatic CeD. This could be especially important for specific populations such as those with co-existing CeD and T1DM as well as those patients with Down's syndrome and CeD.

2. GUIDELINE DEVELOPMENT PROCEDURES

2.1 Aims and Objectives of the Guideline

The purpose of these guidelines is to provide evidence-based recommendations for *patients with asymptomatic celiac disease with or without the presence of extra-intestinal manifestations (e.g. iron deficiency, metabolic bone disease, elevated liver enzymes, and short stature) or associated conditions (e.g. type 1 diabetes mellitus, autoimmune thyroid disease, and Down syndrome)* based on a comprehensive assessment of the literature and a thorough and robust analysis of available data.

This document represents the official recommendations of the AGA and SSCD. It was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework and adheres to best practices in guideline development as outlined by the National Academy of Medicine (formerly Institute of Medicine), using a process outlined previously.[96]

2.2 Target Audience

While the Guideline Panel is aware that this guideline will be read by a wide audience, including policymakers and industry, that is not the guideline's intended primary audience. This guideline, like all AGA guidelines, is primarily targeted towards healthcare providers in the fields of gastroenterology, primary care, internal medicine, and pediatrics who depend on our expert, evidence-based recommendations to inform their clinical practice and shared decision-making with patients. Rather than represent a specific standard to adhere to, we intend these recommendations to be used by clinicians to guide their patient management decisions and to inform considerations of benefits and harms of treatments in each individual case. If used in this way, this guideline's recommendations will contribute to improved, personalized health care for all gastroenterology patients.

2.3 Conflict of Interest

Each nominee to this Guideline Panel underwent a vetting process that required them to report all commercially funded and other relevant activities within the previous 24 months. All reported financial or intellectual conflicts were reviewed by the Chair of the AGA Institute Clinical

Guidelines Committee (CGC) and adjudicated against rules and criteria in the CGC Conflict of Interest (COI) Policy. Only nominees whose COI status complied with this policy were appointed as Guideline Panel members (Supplemental Table 23).

2.4 Guideline Funding

AGA and SSCD provided all financial support for the development of this guideline. No funding from industry was offered or accepted to support the writing effort.

2.5 Organization and Panel Composition

The Guideline Panel was comprised of 8 members (Supplemental **Table 24**), all selected based on their specific expertise. There were 4 clinical content experts with clinical and/or research expertise in the clinical topic, a guideline clinical co-chair, a senior methodologist (guideline methodology co-chair) with specialized GRADE guideline development skills, and two junior methodologists. A librarian assisted the Panel members with designing and executing the required literature searches. All Panel members participated in evidence review and the Senior Methodologist oversaw data synthesis and analysis. All members of the Guideline Panel then reviewed the results of the analysis, contributed to consensus development, and constructed the final recommendations.

2.6 Document Review

(To be added prior to publication)

2.7 Guideline Updates

Guidelines should be “living” products. To remain useful, they need to be updated as new information accumulates. This document will be updated when major new research is published. The need for update will be determined by the Guideline Panel members and the CGC.

2.8 Methods

2.8.1 Formulation of Clinical Questions

The clinical research questions which underpin this guideline were developed by the Guideline Panel, with methodologists and clinical content experts working together to develop specific questions which address current knowledge gaps in this area. The PICO format was used to outline the specific patient population (P), intervention (I), comparator (C), and outcome(s) for each clinical question. The list of PICO question is presented in Supplemental Table 25.

When addressing extra-intestinal manifestation of CeD, in addition to iron deficiency, metabolic bone diseases, LFTs abnormalities, and short stature, the panel also considered headaches, impaired cognition, and infertility as well but ended not prioritizing the for the purpose of the development of this guideline as they may be considered symptoms of celiac disease. When addressing conditions associated with CeD, in addition to T1DM, autoimmune thyroid disorders, and Down syndrome, the panel also considered Turner syndrome, Williams syndrome, autoimmune arthropathies, autoimmune skin disease (other than dermatitis herpetiformis), multiple sclerosis, alopecia, idiopathic neuropathy, autism, eosinophilic esophagitis, autoimmune and collagenous gastritis, inflammatory bowel diseases, and microscopic colitis. However, for the purpose of developing this guideline, the committee discussed prioritizing the three listed conditions only.

The panel selected desirable and undesirable patient-important outcomes (benefits and harms). Critical and important outcomes for decision making for all interventions are summarized in the evidence profiles which were presented under the Certainty of Evidence sections. A group of patient representatives provided feedback on selected outcomes, priorities, balance between desirable and undesirable outcomes and, where applicable, how patients' values and preferences may affect the strength of recommendations.

The panel defined the thresholds for minimally important differences (MID) *a priori* for each outcome to guide the interpretation of continuous outcome measures like symptom scores and quality of life scores. For example, for the health-related quality of life (QOL) scores on a scale of 0 to 100, the MID was determined to be 5, and for the symptoms score like GSRS it was determined to be 0.5 on a scale of 0 to 7.

2.8.2 Search Strategy

The systematic review process was guided by a search protocol developed a priori by the Guideline Panel members in collaboration with the medical librarian. The librarian conducted a comprehensive search of the following databases from MEDLINE, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews from inception to April 8, 2025 using a combination of controlled vocabulary terms supplemented with keywords. A total of three rounds of literature searches were conducted. In the first round, we performed a systematic search for RCTs comparing a GFD versus no GFD in individuals with asymptomatic CeD, across all predefined outcomes. In the second round, we conducted an umbrella review of systemic reviews of studies of any design involving individuals with asymptomatic CeD, focusing on clinically relevant outcomes, including growth, diabetes, bone health, mortality, lymphoma, and quality of life. In the third round, we performed an additional umbrella review of the broader CeD literature to identify evidence specifically addressing the outcomes of mortality and malignancy. The search was limited not limited by language or age. The final strategy is available in Supplemental Table 26. The bibliography and included references of prior guidelines on this topic were searched to identify relevant studies that may have been missed. Additionally, content experts helped identify any ongoing studies with results expected soon.

2.8.3 Study Selection, Data Collection, and Analysis

The inclusion and exclusion criteria were based on the clinical research questions developed by the Guideline Panel. Searches from all databases were combined in *Covidence*. As outlined above, the Guideline Panel sought to identify RCTs; however, where these were not available or were sparse, observational studies were also considered, giving preference to observational studies with control arms then uncontrolled observational studies. For uncontrolled observational studies, we only included studies that included 20 or more patients. We also included studies that had a highly specific inclusion criteria for CeD by requiring histologic and serologic evidence of CeD. Thus, studies that relied on diagnostic codes were excluded. A consensus was reached on study inclusion (Supplemental Figure 28). Any disagreements were resolved with adjudication by consensus.

Data were extracted from each study, including study characteristics such as year of publication, study site, study population, intervention, comparison group, outcomes, and methods for risk-of bias (RoB) assessment. For the RCTs, RoB was assessed using the Cochrane Risk-of-Bias tool 2.0.[97] For the comparative observational studies and studies that reported the incidence rate, we used modified versions of the Newcastle Ottawa scale.[98] For the uncontrolled observational pre-post studies, we used the National Heart, Lung, and Blood Institute tool.[99]

Meta-analyses were conducted when more than one study contributed data for the same intervention and outcome. For continuous outcomes, the mean difference (MD) was pooled unless the scales were substantially different, then then the standardized mean difference (SMD) was pooled. The relative risk (RR) was pooled for dichotomous outcomes, and the hazard ratio (HR) for time-to-event outcomes. For uncontrolled observational studies, the mean change and incidence rate were pooled depending on the outcome. For the meta-analyses, the generic inverse-variance method of weighting was used and the random-effects model applied using the restricted maximum-likelihood estimator to estimate between study variance. However, if three or fewer studies were present, a fixed-effects model was used due to the instability of between-study variance. The statistical heterogeneity was assed using the I^2 index. All the analyses were conducted using R version 4.5.3 with the packages meta version 8.3-0 and metafor version 4.8-0.[100-102]

2.8.4 Certainty of the Evidence

The Guideline Panel used the GRADE approach to assess the certainty of evidence for the effect of the intervention on each outcome using the GradePro Guideline Development Tool software (https://gradepro.org). The GRADE approach considers factors such as study design, population studied, risk of bias, inconsistency, indirectness, imprecision, and risk of publication bias to rate the certainty of evidence as high, moderate, low, or very low (Supplemental Table 27). The results of certainty assessment are reported with each recommendation.

2.8.5 Development of Recommendations

The process of translation of evidence into guideline recommendations followed the GRADE Evidence to Decision framework and was achieved by means of discussion during virtual meetings of the Guideline Panel. The Evidence-to-Decision (EtD) framework considers the certainty of evidence, balance of benefits and harms, patient values and preferences, feasibility,

acceptability, equity, and resource use. EtD tables are presented in the Supplemental Tables. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications.

To inform the EtD framework judgments, we conducted a focus group with three external representatives, one adult patient with asymptomatic CeD and two parents of pediatric patients with asymptomatic CeD, who were identified by the AGA Patient Engagement staff. Representatives participated in a discussion to elicit outcome priorities, evaluate dietary burden ratings, and cancer risk thresholds. Discussion was organized around the PICO questions and targeted EtD domains including values and preferences, cost, acceptability, feasibility, and equity. The group discussion was qualitative and not intended to estimate or quantify population preferences.

The interpretation of strength of recommendations is summarized in Supplemental Table 28. The certainty of evidence and the strength of recommendation are provided for each clinical question. As per GRADE methodology, recommendations are labeled as “strong” or “conditional”. The words “we recommend” indicate strong recommendations and “we suggest” indicate conditional recommendations. In situations when the recommendation is only supported with very low certainty for the benefits and very low certainty for the harm outcomes, the guideline panel put a higher value on risk avoidance.

A systematic search for studies on health equity and disparities was performed using the MEDLINE/PubMed Health Disparities and Minority Health Search Strategy filter, and the identified references were reviewed and summarized in the discussion sections.

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AGA/SSCD Clinical Practice Guideline on the Management of Asymptomatic Celiac Disease Supplemental Materials

Table of Contents:

PICO 1: Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease?

Supplemental Table 1. PICO 1 Study Characteristics

Study	Patient population	Baseline characteristics	Outcome(s)
Studies of patients with asymptomatic celiac disease			
Kurppa 2014[1] RCT Finland Follow-up: 1 year Funding: Academy of Finland Research Council for Health, the Competitive Research Funding of the Pirkanmaa Hospital District, the Sigrid Juselius Foundation, the Finnish Foundation for Gastroenterological Research, the Yrjö Jahnsson Foundation, the Finnish Medical Foundation, the	**Inclusion**: Asymptomatic* adults >18yr, at-risk relatives of celiac patients, and with EmA positive **Exclusion**:<18 yr of age, evident clinical symptoms, dietary gluten restriction, severe contemporary illness or immunosuppressive medication, ongoing or planned pregnancy **Diagnosis of celiac disease**: EmA + gluten-dependent enteropathy **Definition of asymptomatic**: absence of abdominal	**GFD** (*n* randomized = 20) *Age Median (range)*: 42 (21-74) *Sex Female, n (%)*: 9 (45) *Comorbidities (Asthma, endometriosis, diverticulosis, allergies)*:7 (35) *Loss to follow-up*: 0 **GCD** (*n* randomized = 20) *Age*: *Median (range)*: 42 (23-62) *Sex: Female, n (%)*:5(25) *Comorbidities (Asthma, endometriosis, diverticulosis, allergies.)*: 7(25) *Loss to follow-up*: 0 **Method of implementing dietary instructions**: visits with a dietitian at baseline and 1 yr FU	**<u>GI symptoms</u>** *Definition*: Gastrointestinal symptoms subdimensions: diarrhea, indigestion, constipation, abdominal pain, and reflux *Scale*: GSRS; 7-point Likert scale from no symptoms (grade 1) to severe symptoms (grade 7). Values in each sub-dimension are calculated as a mean of the relevant items and the total score is calculated as a mean of all items *n*: 20 vs 20 *Events*: NA *Change*: Baseline total Mean ± SD; GFD: 1.8 ± 0.6 GCD: 1.7 ± 0.6 1 yr mean difference (95% confidence interval) GFD vs GCD: -0.4 (-0.7 to -0.1) (Figure 2) Diarrhea: -0.6 (-1.1 to -0.0) Indigestion: -0.7 (-1.1 to –0.2) Constipation: -0.1 (-0.5 to 0.3) Abd. Pain: -0.2 (-0.5 to 0.2) Reflux: -0.5 (-0.9 to -0.1)

Foundation for Pediatric Research and the Finnish Celiac Society.	pain (>3 pain episodes over 3 months interfering with function), constipation (<3 BMs per week or difficulty during defecation), and diarrhea (3 loose stools/day) or extraintestinal (joint pain, rash, neurologic) **Age group(s)**: no **High risk group**: no **Extra-intestinal manifestations**: None **Other**: All subjects had HLA DQ2 or 8	**Method to ascertain adherence to dietary instructions**: Information not provided.	**<u>Health-related Quality of Life assessed by 2 measurements/scales</u>** *Definition*: The Psychological General Well-Being (PGWB) *Scale*: subdimensions: anxiety, depression, wellbeing, self-control, general health, and vitality 6 grade Lickert scale; higher score= better QoL *N*:20 vs 20 *Events*: NA *Change*: Baseline total Mean ± SD: GFD 112.2 ± 12; GCD 111.3 ± 11 1 yr mean difference (95% CI) GFD vs GCD: (Figure 2) Anxiety: 1.6 (0.4 to 2.8) Depression :0.3 (-0.5 to 1.2) Well-being: 0.5 (-1.0 to 2.0) Self-control: 0.3 (-0.7 to 1.4) General Health: 0.7 (-1.0 to 2.4) Vitality: 0.4 (-1.5 to 2.2) *Definition*: Short-Form 36 (SF-36) *Scale*:8 subdimensions: physical functioning, role limitations owing to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. The scores range from 0 to 100, with higher scores indicating better health and quality of life *n*: 20 vs 20 *Events*: N/A *Change*: Baseline total Mean ± SD: Not provided 1 yr mean difference (95% CI) GFD vs GCD: (Figure 2) Physical functioning: -2.8 (-8.2 to 2.6) Role limitation due to PP: 2.3 (-12.4 to 17)

			Role limitation due to EP: 7.2 (-12.6 to 27) Vitality: 6.0 (-4.3 to 16.4) Mental health: 2.6 (-3.8 to 8.9) Social functioning: -8.3 (-15.8 to -0.8) Bodily pain: 0.8 (-9.8 to 11.4) General Health: 2.8 (-7.1 to 12.7) **<u>Bone Mineral Density</u>** Assessed with Dual-energy X-ray Absorptiometry (Lunar Prodigy Advance, GE Healthcare, Waukesha, WI). BMD values were expressed as T-scores and as age- and sex-matched Z-scores. *Scale*: g/m2 *n*: 20 vs 20 *Events*: N/A *Change*: Mean ± SD except differences in the changes between the groups, expressed as means (95% CI) All comparison GCD vs GFD Lumbar spine BMD, g/cm^2 Baseline: 1.17 ± 0.21 vs 1.17 ± 0.19 Change: -0.01 ± 0.03 vs 0.00 ± 0.02 Difference: 0.01 (-0.01 to 0.02) Femur neck BMD, g/cm^2 Baseline: 1.00 ± 0.12 vs 0.97 ± 0.14 Change: -0.01 ± 0.03 vs 0.00 ± 0.02 Difference: 0.01 (-0.01 to 0.03) **<u>Body Mass Index</u>** Definition: BMI was determined as weight (kg)/height $(m)^2$; a value less than 18.5 was considered underweight, 18.5–24.9 was considered normal, 25.0–29.9 was considered overweight, and 30.0 or higher was considered obese Scale: kg/m^2

			n: 20 vs 20 Events: N/A Change: Mean ± SD except differences in the changes between the groups, expressed as means (95% CI) Comparison GCD vs GFD Baseline: 26.4 ± 3.7 vs 27.0 ± 6.8 Change: -0.3 ± 1.0 vs 0.0 ± 1.2 Difference: 0.3 (-0.5 to 1.0) **Body composition (Total body fat %)** Assessed with Dual-energy X-ray Absorptiometry (Lunar Prodigy Advance, GE Healthcare, Waukesha, WI). Scale: % *n*: 20 vs 20 Events: N/A Change: Mean ± SD except differences in the changes between the groups, expressed as means (95% CI) All comparison GCD vs GFD Baseline: 28.9 ± 8.2 vs 34.0 ± 8.9 Change: -0.6 ± 2.4 vs -1.2 ± 3.4 Difference: -0.5 (-2.4 to 1.4) **Nutrients** *Definition*: laboratory: Hb, plasma albumin, serum ionized calcium, plasma PTH, serum total iron, blood cell folate, B12 serum, ALT serum *Scale*: g/dl; mmol/L, umol/L, nmol/L U/L *n*: 20 vs 20 *Events*: N/A *Change*: Mean ± SD except differences in the changes between the groups, expressed as means (95% CI) All nutrients comparison GCD vs GFD Blood hemoglobin level, g/dL • Baseline: 14.3 ± 1.4 vs 14.4 ± 1.6 • Change: -0.2 ± 0.6 vs -0.2 ± 0.7

			• Difference: 0.0 (-0.4 to 0.4) Plasma albumin level, g/dL • Baseline: 4.1 ± 0.3 vs 4.0 ± 0.4 • Change: 0.2 ± 0.3 vs 0.2 ± 0.4 • Difference: 0.0 (-0.2 to 0.2) Serum ionized calcium level, mmol/L • Baseline: 1.28 ± 0.03 vs 1.26 ± 0.03 • Change: -0.01 ± 0.03 vs 0.00 ± 0.04 • Difference: 0.00 (-0.02 to 0.03) Plasma intact parathormone level, pmol/L • Baseline: 5.4 ± 2.0 vs 4.7 ± 1.8 • Change: -0.3 ± 1.1vs -0.3 ± 0.9 • Difference: 0.0 (-0.7 to 0.6) Serum total iron level, mmol/L • Baseline: 17.3 ± 5.7 vs 20.0 ± 8.6 • Change: 2.8 ± 6.8vs 0.3 ± 7.2 • Difference: -2.5 (-7.0 to 2.1) Red blood cell folate level, nmol/L • Baseline: 497 ± 193 vs 477 ± 187 • Change: 183 ± 215 vs 300 ± 260 • Difference: 117 (-39 to 272) Serum vitamin B12 level, pmol/L • Baseline: 366 ± 108 vs 316 ± 72 • Change: 18 ± 63 vs 45 ± 54 • Difference: 27 (-11 to 65) Serum alanine aminotransferase level, U/L

			• Baseline: 28.8 ± 11.6v s 32.2 ± 20.0 • Change: 0.2 ± 10.4 vs -5.1 ± 13.9 • Difference: -5.2 (-13.2 to 2.8) **GFD Adherence:** Maintaining the GFD was considered "easy" by 5%, "goes by itself" by 67%, and "difficult" by 13%; 15% could not say. Finally, 58% experienced their celiac disease screening and diagnosis as positive or very positive, 42% were indifferent, and none were negative.
CD-DIET (Mahmud 2020, Weiman 2021)[2, 3] RCT Canada Follow-up: 1 year Funding: JDRF Canadian Clinical Trial Network	**Inclusion**: 8-45 years with DM1 for at least 1 year; tTG-IgA positive (≥30 chemiluminescent units [CU]); duodenal biopsy confirmation (Marsh score ≥2); **Exclusion**: CD symptoms (gastrointestinal symptomatology or evidence of growth impairment, anemia, or osteoporosis); a previous CD diagnosis; on GFD; menopause; aphthous ulcers; dermatitis herpetiformis; and pregnancy. **Diagnosis of celiac disease**: TG IgA positive (≥30 chemiluminescent units [CU]); duodenal biopsy	**GFD** (*n* randomized = 27) *Age*: 27 ± 10.9 *Sex*: 63% M vs 37% F *Comorbidities*: DM1 *Dietary adherence*: tTG-IgA became undetectable *Loss to follow-up*: 2 **GCD** (*n* randomized = 24) *Age*: 26.6 ± 11.3 *Sex*: 45.8% M vs 54.2% F *Comorbidities*: DM1 *Dietary adherence*: tTG-IgA continued to be elevated *Loss to follow-up*: 2 **Method of implementing dietary instructions**:visits with a dietitian occurred every 3 months using a standardized educational curriculum **Method to ascertain adherence to dietary instructions**:	**<u>Quality of Life</u>** Generic HRQoL *Definition*: Pediatric Quality of Life Inventory Generic Core Scales 4.0. Assesses HRQoL in 4 domains: 1) physical functioning, 2) emotional functioning, 3) social functioning, and 4) school functioning. *Scale*: Questions are answered on a 5-point Likert-like scale and standardized scores out of 100 are calculated overall and for subscales, with higher scores indicating better HRQoL *n*: 27 vs 24 *Events*: N/A *Change (95% CI)*: Baseline: 79.7 (75.0 - 84.4) vs 79.5 (73.9-84.9) 6 months: 80.6 (75.5-85.9) vs 76.5 (69.6-83.4) 12 months: 80 (75.4-84.9) vs 78.0 (73.1-82.9) Diabetes Specific HRQoL *Definition*: Pediatric Quality of LIfe Inventory Diabetes Module 3.2. Evaluates diabetes-specific HRQoL in 5 areas: 1) diabetes symptoms, 2) treatment barriers, 3) treatment adherence, 4) worries, and 5) communication. *Scale*: Questions are answered on a 5-point Likert-like scale and standardized scores out of 100 are calculated overall and for subscales, with higher scores indicating better HRQoL

	confirmation (Marsh score ≥2) **Definition of asymptomatic**: No gastrointestinal symptomatology or evidence of growth impairment, anemia, or osteoporosis **Age group(s)**: Adults and children **High risk group**: DM1 **Extra-intestinal manifestations**: None **Other**: NA	- dietary interviews and the assessment of 3-day food records and 24-hour recalls to quantify gluten intake. - assessment of TTG-IgA titers at baseline, and at 6 and 12 months. - a 50% or greater decrease in their TTG-IgA from baseline were considered adherent and vice versa.	*N*: 27 vs 24 *Events*: NA *Change*: Baseline: 63 (58.4 - 67.4) vs 64.3 (57.7 - 71.1) 6 months: 66.8 (60.9 - 72.5) vs 63.0 (56.0 - 70.0) 12 months: 67.1 (61.6 - 72.5) vs 64.3 (57.8 - 70.9) Self-perceived wellness *Definition*: NR. *Scale*: rated self-perceived health status on a 5-point Likert scale ranging from “poor” to “excellent.” They also rated how concerned they were about their health on a 4-point Likert scale ranging from “extremely” to “not at all.” Participants were asked to provide their SPW score by rating their overall health from 0 to 100, with higher SPW scores indicating better perceived health. *Events*: Not reported *Change*: Not reported **<u>Height</u>** *Scale*: Z-score *n*: 8 vs 8 *Change (mean ± SD)*: Baseline: 0.27 ± 1.27 vs 0.63 ± 1.22 12 months: 0.25 ± 1.38 vs 0.35 ± 0.84 **<u>Weight</u>** *Scale*: Z-score *n*: 8 vs 8 *Change (mean ± SD)*: Baseline: 0.76 ± 1.36 vs 0.80 ± 0.96 12 months: 0.59 ± 1.51 vs 0.61 ± 1.07 **<u>Body Mass Index</u>** *Scale*: Z-score *n*: 8 vs 8 *Change (mean ± SD)*: Baseline: 0.88 ± 1.14 vs 0.76 ± 0.77

			12 months: 0.67 ± 1.17 vs 0.66 ± 0.94 **Hemoglobin** *Scale*: g/dL *n*: 27 vs 24 *Change (mean ± SD)*: Baseline: 14.3 ± 1.6 vs 13.6 ± 1.4 12 months: 14.5 ± 1.4 vs 13.3 ± 1.9 **Ferritin** *Scale*: MR *n*: 27 vs 24 *Change (mean ± SD)*: Baseline: 73.9 ± 67.8 vs 58.8 ± 52.1 12 months: 80.9 ± 73.4 vs 62.4 ± 59.6 **ALT** *Scale*: NR *n*: 27 vs 24 *Change (mean ± SD)*: Baseline: 24.1 ± 24.4 vs 22.1 ± 11.3 12 months: 18.8 ± 9.5 vs 22.0 ± 10.4 **25-OH vitamin D** *Scale*: NR *n*: 27 vs 24 *Change (mean ± SD)*: Baseline: 61.2 ± 16.3 vs 60.9 ± 28.1 12 months: 70.1 ± 19.5 vs 68.7 ± 32.0 **Hemoglobin A1c** *Scale*: NR *n*: 27 vs 24 *Change*: at 12 months +0.14% (95%CI: -0.79 - 1.08; *p* = 0.76) **Hypoglycemia** *Definition*: non-severe *n*: 27 vs 24

			Events: 0 vs 3
Rami 2005[4] Pre-post study Multicenter (10 pediatric diabetic centers in their clinic cohort of diabetic children since 1995 (Kosice), 1996 (Vienna, Prague, Ljubiljana, Budapest), 1997 (Groningen), 1998 (Lisbon) and 2000 (Szedged, Pecs). Follow-up: every 6 months for at least 1 yr (Mean observation period 3.3 ± 1.9 years) Funding: not reported	**Inclusion**: T1DBT and screen-detected CeD with EmA+ and biopsy positive **Exclusion**: data not provided **Diagnosis of celiac disease**: EmA+ in 2 occasions (repeated after 3 months) and confirmed by duodenal biopsies (performed only if EmA was positive) **Definition of asymptomatic**: silent CD, not much information on definition. **Age group(s)**: pediatric (6.5 ± 4.1 yrs) **High risk group**: T1DBT **Extra-intestinal manifestations**: No	**GFD definition**: Patients who became EMA-negative on GFD and remained EMA-negative during the study period were thought to be compliant to GFD (compliance category 1) and patients who refused to maintain GFD or did not become EMA-negative on the suggested GFD were considered as noncompliant (compliance category 2) **CeD=** 74/98 **GFD** (*n* = 33) *Age*: not provided *Sex* Girls = 19/33 *Comorbidities*: not provided *Loss to follow-up*: not provided **GCD** (*n* = 25) *Age*: not provided *Sex*: Girls 19/25 *Comorbidities*: not provided *Loss to follow-up*: not provided **Method of implementing dietary instructions**: not provided	**Outcomes provided for CeD vs controls:** Hemoglobin A1c; BMI; Height, but not for GFD vs GCD. Only BMI provided for GFD vs GCD **<u>Body Mass Index</u>** *Scale*: kg/m^2 *N*: 33 vs 25 *Events*: N/A *Change*: "Trend to lower BMI-SDS" GCD vs GFD: (0.70 ± 0.25 vs 0.08 ± 0.25; *p* = 0.089). **<u>Height</u>** Reported not different, but data not provided.

		Method to ascertain adherence to dietary instructions: not provided	
Valletta 2007[5] Pre-post study Verona, Italy Follow-up: 4 years Funding: Not reported	**Inclusion:** Patients with DM1 screened for CeD annually with AGA, EMA and tTG IgA/IgG. Histologic diagnosis confirmed. **Exclusion:** CeD diagnosed before DM. Incomplete records.	*n* = 23 Mean age at DM1 diagnosis: 8 ± 3.3 yr Mean time interval between DM1 and CeD diagnosis: 1.8 yr (range: 0.1- 23.9 yr)	**Height SDS:** At CeD diagnosis: -0.04 ± 0.96 After 2 yr GFD: -0.17 ± 1.01 After 4 yr GFD: -0.06 ± 1.25 **Height SDS:** At CeD diagnosis: 7.5 ± 8.5 After 2 yr GFD: 7.6 ± 8.6 After 4 yr GFD: 7.7 ± 8.7 **Height SDS:** At CeD diagnosis: 7.48 ± 8.5 At 2 yr: 7.58 ± 8.62 At 4 yr: 7.70 ± 8.73
Sun 2009[6] Pre-post study Northwest England Follow-up: 2 years Funding: Diabetes UK	**Inclusion:** Children aged < 16 years with DM1 who had positive IgA EMA, anti-gliadin, and tTG on local routine annual screening. Endoscopic biopsies obtained from the jejunum. **Exclusion:** Refused small bowel biopsy or GFD; positive antibodies while on GFD **Symptoms:** Asymptomatic	*n* = 49 Mean age at DM1 diagnosis: 5.9 ± 4.1 yr Mean age at CeD diagnosis: 9.1 ± 3.7 yr Mean current age: 11.9 ± 3.5 yr	**Height SDS** Prior to CD: -0.1 ± 0.8 At CD diagnosis: -0.2 ± 0.8 After 1 yr GFD: -0.2 ± 1.0 After 2 yr GFD: -0.3 ± 0.8 **Glycemic control assessed with HbA1c** Prior to CD: 8.3 ± 1.1 At CD diagnosis: 8.4 ± 1.3 After 1 yr GFD: 8.9 ± 1.5 After 2 yr GFD: 8.7 ± 1.4

Ukkola 2011[7] Pre-post study Finland Follow-up: 1 year Funding: Academy of Finland Research Council for Health, the Competitive Research Funding of the Pirkanmaa Hospital District, the Sigrid Juselius Foundation, the Foundation for Paediatric Research, the EU Commission Marie Curie Excellence grant (FP6 contract MEXT-CT-2005-025270), Marie Curie mobility grant (MRTNCT-2006-036032; TRACKS), the National Graduate School of Clinical Investigation, the Ehrnrooth Foundation, and the Finnish Celiac Society.	Patients aged >16 years with "biopsy-proven" asymptomatic CeD	*n* = 23 91% female Median age: 44 yr (range: 19-82)	**Quality of life assessed with Psychological General Well-Being Index** Baseline: 103.0 (95% CI: 95.9 - 110.1) After 1 yr GFD: 103.1 (95% CI: 94.0 - 112.2) Subscores provided in manuscript but not included in analysis.
Mackinder 2014[8]	**Inclusion**: Children with DM1, CeD or dual	*n* = 23 with dual diagnosis	**Height SDS:** Prior to CeD: -0.36 ± 1.26

Pre-post study United Kingdom Follow-up: 2 years Funding: EU Charity Nutricia Research Foundation	diagnosis. Serologic screening with EMA and tTG IgA. Positive serologies underwent endoscopy. DM1 diagnosed at least 2 years prior to CeD. No other chronic conditions. Anthropometric data available for 2 years before and after CeD diagnosis.	52% female Mean age at DM1 diagnosis: 5.3 ± 3.4 yr Mean age at CeD diagnosis: 10.7 ± 2.8	At CeD diagnosis: -0.26 ± 1.21 After 1 yr GFD: -0.32 ± 1.10 After 2 yr GFD: -0.38 ± 1.61 **<u>Glycemic control assessed with hemoglobin A1c</u>** At CeD diagnosis: 8.1 ± 1.1 After 2 yr GFD: 8.5 ± 1.1
Studies of patients with all celiac disease, including symptomatic			
Cottone 1999[9] Observational rate study Italy Follow-up: mean 73 months (range: 1 – 204) Funding: not reported	Patients with CeD confirmed with duodenal and jejunal biopsy	*n* = 216 with complete follow-up information *n* = 228 for entire population (described below) 76% female Symptoms: Anemia: 60% Diarrhea, weight loss: 20% Other: 10% Asymptomatic: 10%	Of 216 individuals with complete follow-up, there were 12 deaths in 1348.53 person-years or 8.9 per 1,000 person years. Expected: 3.12. Standardized mortality ratio: 3.8 (95% CI: 1.9 - 6.7). Four deaths due to enteropathy-associated T-cell lymphoma were reported.
Corrao 2001[10] Observational rate study Italy Follow-up: mean	Adults with biopsy-proven CeD and histological improvement after gluten-free diet	*n* = 1,072 76% women Mean age at diagnosis: 35.7 ± 14.1 years 50 patients lost during	There were 53 deaths per 6444 person-years (8.2 per 1,000 person-years). Expected: 25.9; standardized mortality ratio: 2.0 (95% CI: 1.5 - 2.7) There were 5 deaths out of 627 GFD-adherent patients vs 26 out of 155 in likely non-adherent; standardized mortality ratio in those who were likely adherent: 0.5 (0.2 - 1.1); in not likely: 6.0 (4.0 - 8.8)

6.0 ± 4.9 years Funding: Associazione Italiana Celiachia, the Istituto Superiore di Sanità and the Ministero dell'Università e della Ricerca Scientifica e Tecnologica		follow-up Symptoms: Severe: 55% Mild: 39% Asymptomatic: 6% Adherence to GFD: Likely: 59% Not likely: 15% Uncertain: 27%	
Green 2003[11] Observational rate study USA Follow-up: mean 6 ± 11 years Funding: Not reported	Adults with CeD established by accepted criteria	*n* = 381 64% female Mean age at diagnosis: 44 ± 18 years Mean age at follow-up: 52 ± 18 years	3 cases of small bowel cancer reported versus 0.1 expected. Age-adjusted incidence rate: 40 per 100,000 person-years (expected: 1.2). Standardized mortality ratio: 34 (95% CI: 24 - 32)
Card 2004[12] Observational rate study United Kingdom Follow-up: median 6.6 years (interquartile range: 2.2 - 14.5)	Patients with CeD diagnosed with small intestinal biopsy	*n* = 865 total population *n* = 637 with >2 years follow-up, described below 70% female Age at diagnosis: Under 2 yr: 5% 2-20 yr: 9% 20-40 yr: 30% 40-60 yr: 33%	1 case of small bowel carcinoma or 62 / 100,000 crude risk; 0.02 expected. Standardized incidence ratio: 59.97 (95% CI: 1.52 - 334.12). 3 cases of small intestinal lymphoma or 187 / 100,000 crude risk; 0.01 expected. Standardized incidence ratio: 358.8 (95% CI: 74.01 - 1048.34)

Funding: authors supported by Wellcome Training Fellowships in Clinical Epidemiology (numbers 060529 and 063800)		Over 60 yr: 22%	
Leslie 2012[13] Observational rate study USA Follow-up: 10.6 ± 8.2 years in CeD only; 6.6 ± 7.5 in CeD and lympho-proliferative disorder (LPD) Funding: Not reported	Patients aged ≥18 years with "biopsy-proven" CeD	*n* = 1285 70.4% female Mean age at diagnosis: 40.3 ± 17.5 years	12 cases of enteropathy-associated T-cell lymphoma in 12,693 person-years, or 0.95 per 1000 person-years. Unable to calculate standardized incidence ratio due to expected rate of 0.
Holmes 2018[14] Observational rate study United Kingdom Follow-up: median 9.3 years (interquartile range: 5.6 - 14.5)	Patients with CeD determined with small-bowel biopsy or serological testing alone	*n* = 2515 total population *n* = 2174 with ≥ 2 years follow-up, described below 66.8% female Mean age at baseline: 45.5 ± 18.9 years	284 deaths reported out of 23,955 person-years; 180.4 expected. Standardized mortality ratio: 1.57 (95% CI: 1.40 - 1.77)

Funding: None declared			
Quarpong 2019[15] Observational rate study United Kingdom Follow-up: mean 31.7 ± 15.5 years Funding: Scottish Home and Health Department	Patients with at least one small bowel biopsy showing abnormalities typical of CeD, some of which were confirmed by a second small bowel biopsy following a gluten withdrawal or gluten challenge (i.e. confirmed CeD; 73%) and some of which were not (i.e. probable CeD; 27%)	*n* = 602 61.1% female Mean age at diagnosis: 25.2 ± 23.9 years	237 deaths reported out of 19,071.74 person-years; 166.2 expected. Standardized mortality ratio: 1.43 (95% CI: 1.25 - 1.62)
Kårhus 2020[16] Comparative study Denmark Follow-up: Funding: Tryg Foundation (7-11-0213), Dansk Cøliaki Forening (the Danish Celiac Disease Patient Organization), The Novo Nordisk Foundation	Patients with CeD diagnosed through serology (IgG-DGP-positive only [35%], IgA-TTG-positive only [39%], both [21%], or IgG-TTG-positive only [5%])	*n* = 169 50.3% female Mean age at examination: 49.0 years (95% CI: 47.3 - 50.7)	All-cause mortality hazard ratio: 1.19 (95% CI: 0.87 - 1.61) All-cause mortality hazard ratio adjusted for sex, body mass index, smoking, alcohol, consumption and study: 1.17 (95% CI: 0.85 - 1.61)

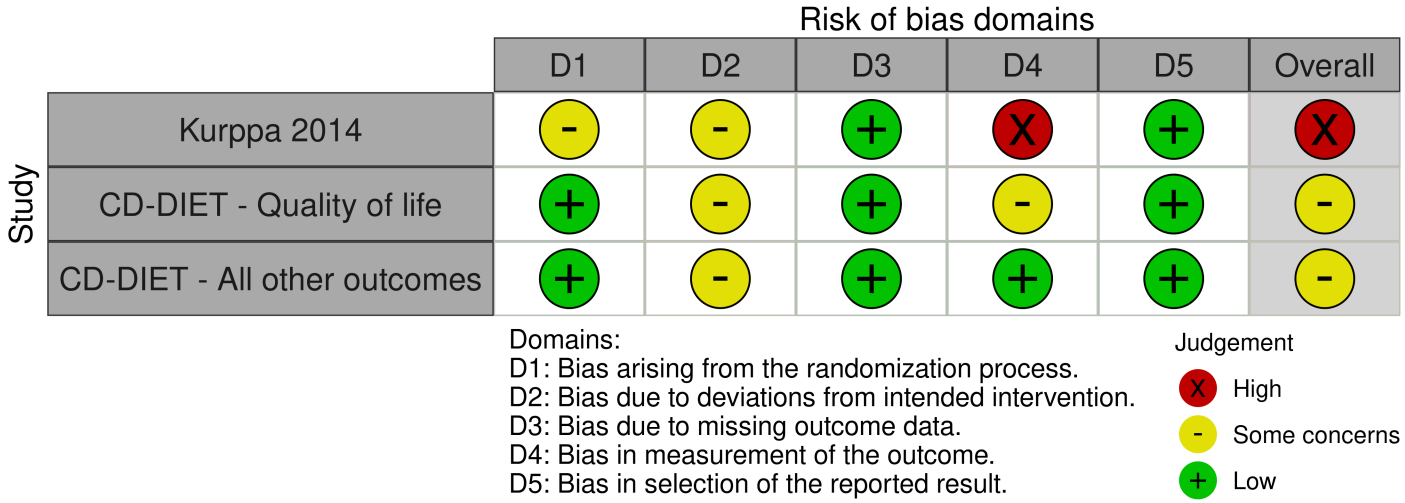
(NNF160C0022464), and Independent Research Fund Denmark (7016-00122B)			
Koskinen 2020[17] Comparative study Finland Follow-up: mean 7.7 ± 3.0 years Funding: Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (Grant 9P060)	Patients with CeD diagnosed with duodenal biopsy showing villous atrophy	*n* = 12,803 62% female Age at diagnosis: 20-29 yr: 12.7% 30-39 yr: 16.2% 40-49 yr: 20.2% 50-59 yr: 22.4% 60-69 yr: 17.9% 70-79 yr: 10.6%	All-cause mortality hazard ratio: 1.01 (95% CI: 0.94 - 1.09)
Lebwohl 2020[18] Comparative study Sweden Follow-up: median 12.5 years Funding: Celiac Disease Foundation Young Investigator Research Grant Award, grant from the Louis	Patients with CeD diagnosed with small intestinal biopsy	*n* = 49,892 62.4% female Mean age at diagnosis: 32.2 ± 25.2 years	All-cause mortality hazard ratio: 1.21 (95% CI: 1.17 - 1.25) All-cause mortality hazard ratio adjusted for educational attainment, region of birth, and the presence of type 1 diabetes, autoimmune thyroid disease, rheumatoid arthritis, and inflammatory bowel disease: 1.14 (95% CI: 1.11 - 1.18)

and Gloria Flanzer Philanthropic Trust, and support from the Swedish Research Council			
Koskinen 2022[19] Comparative study Finland Follow-up: mean 41 years; median 26.5 years Funding: Sigrid Juselius Foundation, the Emil Aaltonen Foundation, the Academy of Finland, the Research Fund of the Finnish Coeliac Society, the Finnish Cultural Foundation and the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital	Patients with biopsy-proven CeD	*n* = 1,392 63.2% female Age at diagnosis: < 20 yr: 19.0% 20-39 yr: 32.3% 40-59 yr: 35.3% ≥60 yr: 13.4%	All-cause mortality hazard ratio: 0.96 (95% CI: 0.85 - 1.08)
Sanchez 2011[20]	Patients with CeD diagnosed based on combination of clinical	*N* = 265 (7,028 person-year before diagnosis and	Total number of fractures 89 Total number of cases with at least once fracture 61 Total number of cases with at least once fracture

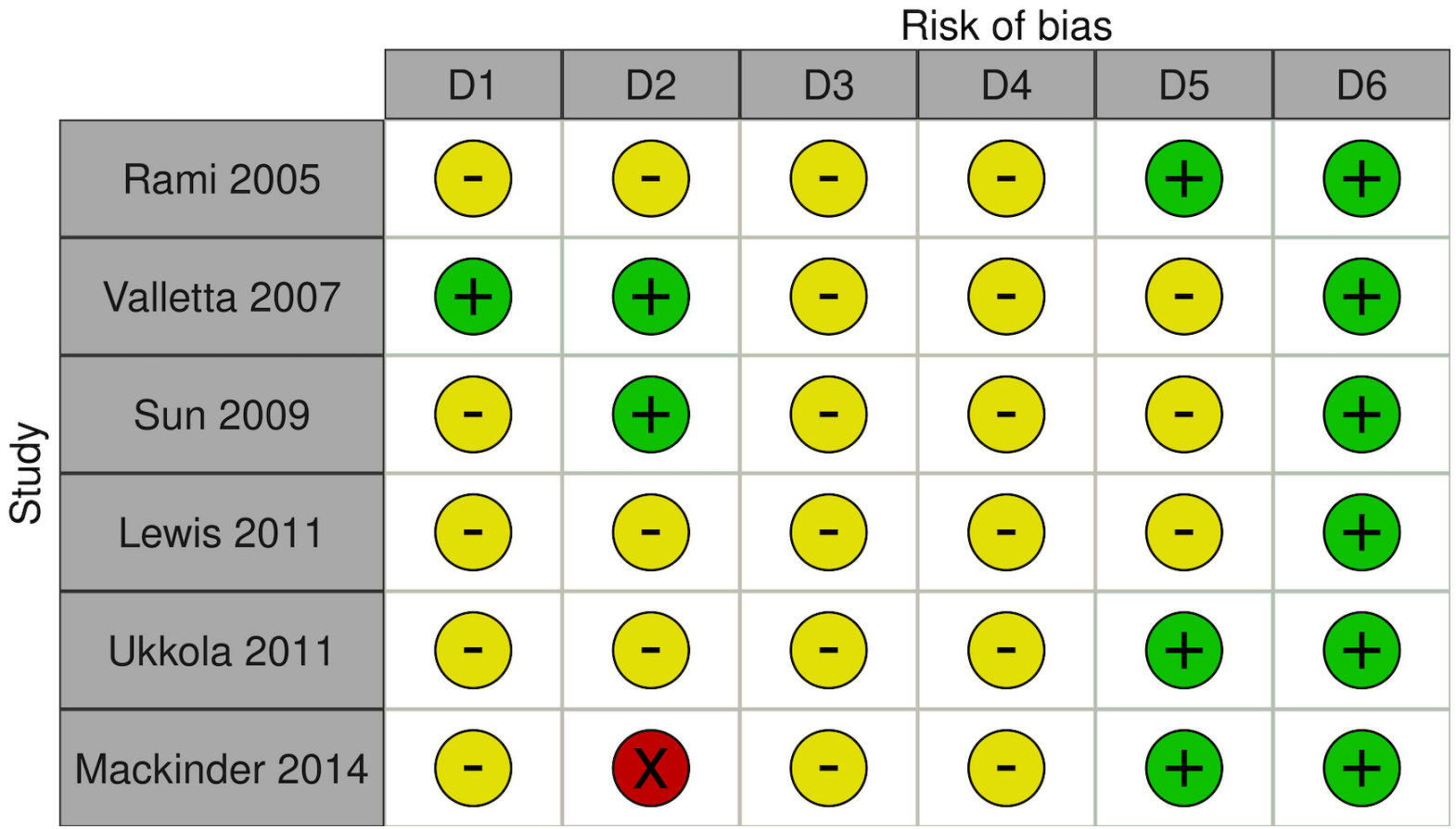
Buenos Aires, Argentina Follow-up	findings, duodenal biopsies, positive CeD-specific serology, and a positive clinical and/or histologic response to GFD. Diagnosed at least 5 years prior to the entry to the study. Exclusion criteria: disorders that could independently reduce bone health, patient took medication that may affect bone metabolism, and complicated CeD.	2,815 person-year after diagnosis) 83.2% females Median age 42 GFD adherence: 40% poor, 21% partial, and 40% strict	before diagnosis 40 Total number of cases with at least once fracture afte diagnosis 21 Incidence rate of peripheral fractures before diagnosis: - Classic CeD 10.1/1,000 person-year - Atypical/silent CeD 5.4/1,000 person/year

Risk of bias assessments

Supplemental Figure 1. PICO 1 Risk of Bias Assessment for RCTs

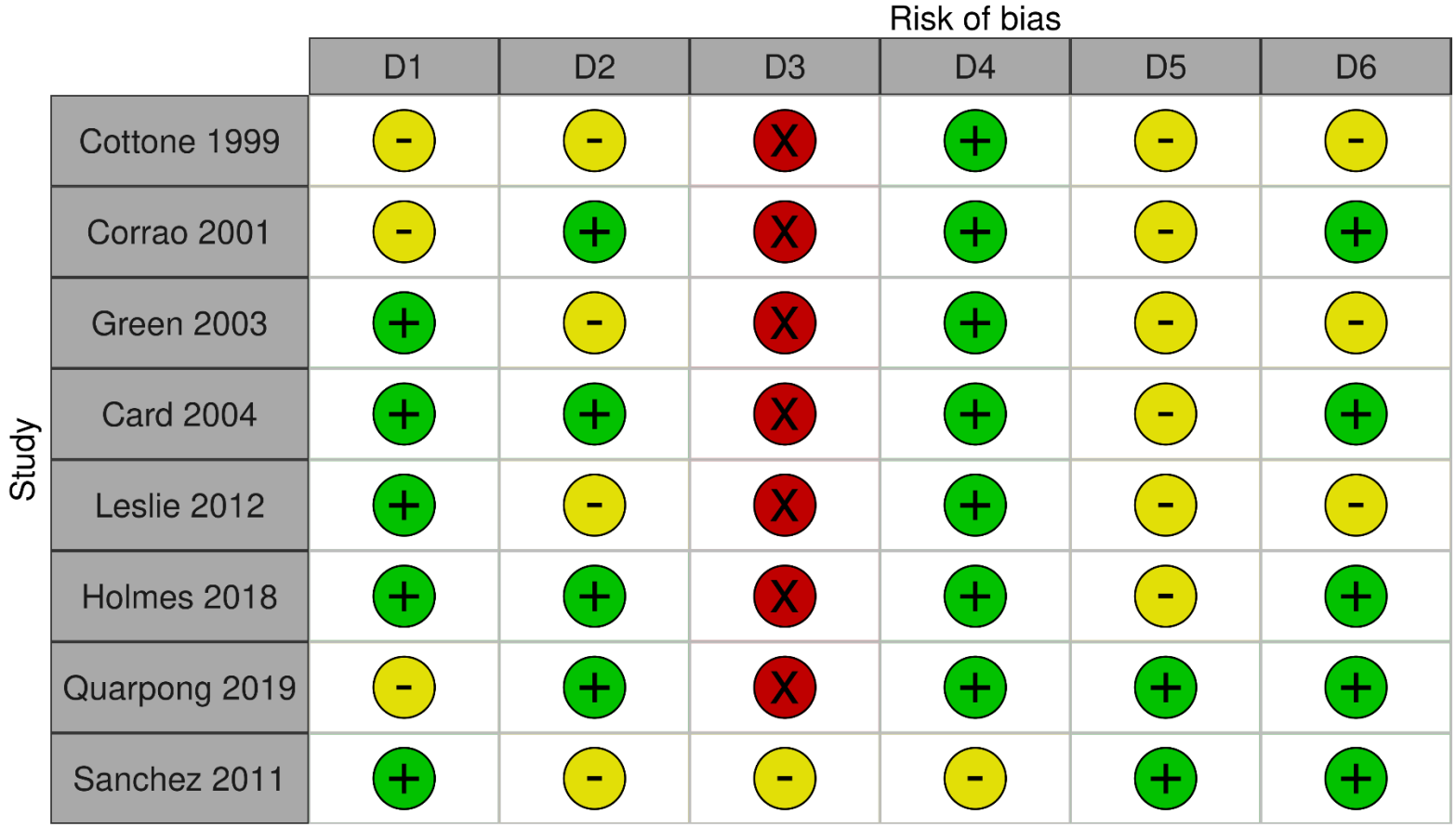


Supplemental Figure 2. PICO 1 Risk of Bias Assessment for Pre-post Studies



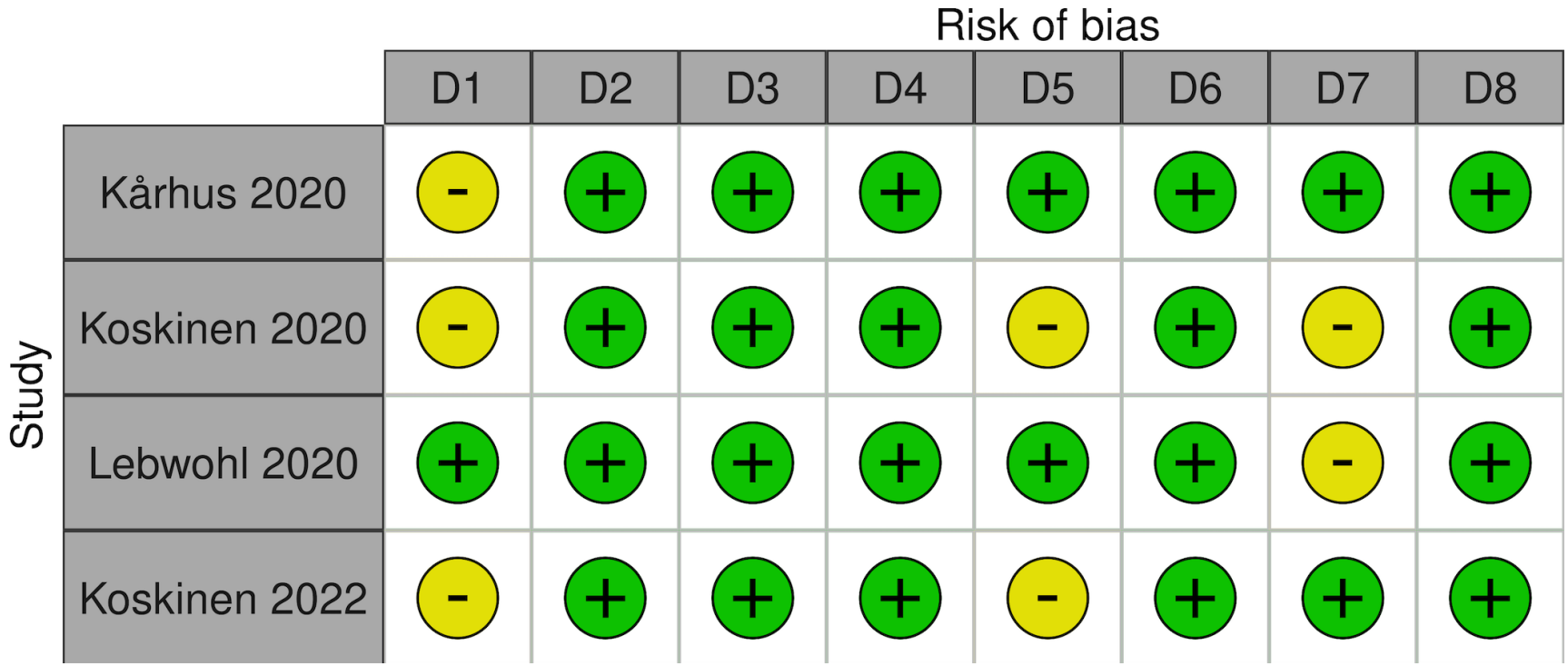
D1: Were all eligible participants that met the prespecified entry criteria enrolled?
D2: Was the intervention clearly described and delivered consistently across the study population?
D3: Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
D4: Were the people assessing the outcomes blinded to the participants' exposures/interventions?
D5: Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
D6: Was follow-up long enough for outcomes to occur?

Supplemental Figure 3. PICO 1 Risk of Bias Assessment for Rate Studies



D1: Valid methods for ascertainment of exposure
D2: Demonstration that outcome of interest was not present at start of study
D3: Adjustment for confounders
D4: Assessment of outcome
D5: Was follow-up long enough for outcomes to occur
D6: Adequacy of follow up of cohorts (attrition)

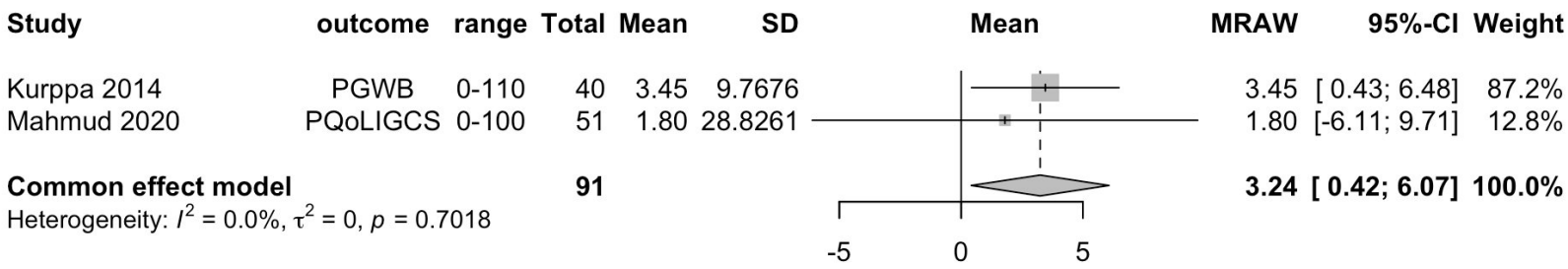
Supplemental Figure 4. PICO 1 Risk of Bias Assessment for Comparative Cohort Studies



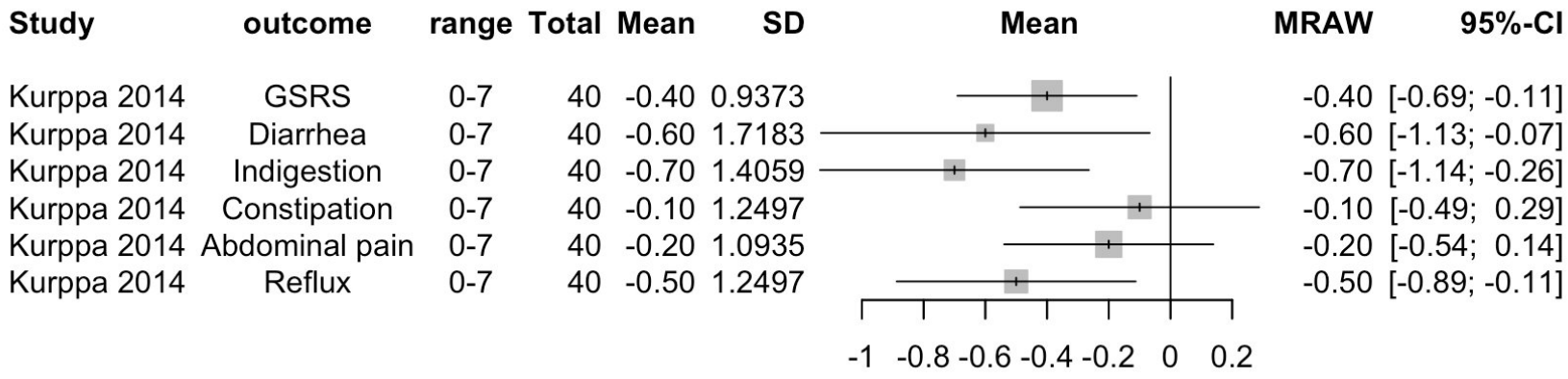
D1: Representativeness of the exposed cohort
D2: Selection of the non-exposed cohort
D3: Ascertainment of exposure
D4: Demonstration that outcome of interest was not present at start of study
D5: Comparability of cohorts on the basis of the design or analysis
D6: Assessment of outcome
D7: Follow-up long enough for outcomes to occur
D8: Adequacy of follow-up of cohorts

Meta-Analyses

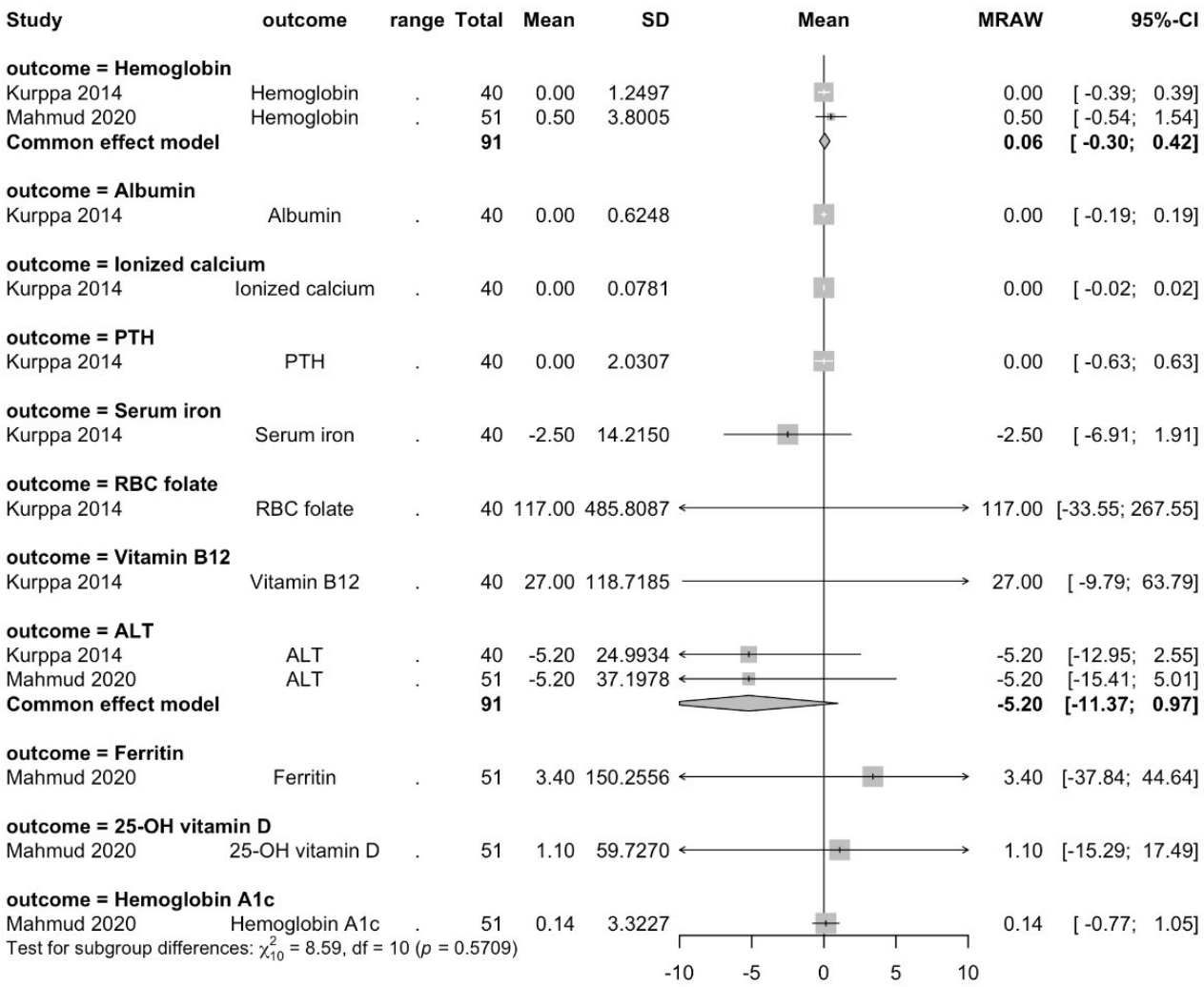
Supplemental Figure 5: Quality of Life from RCT Data



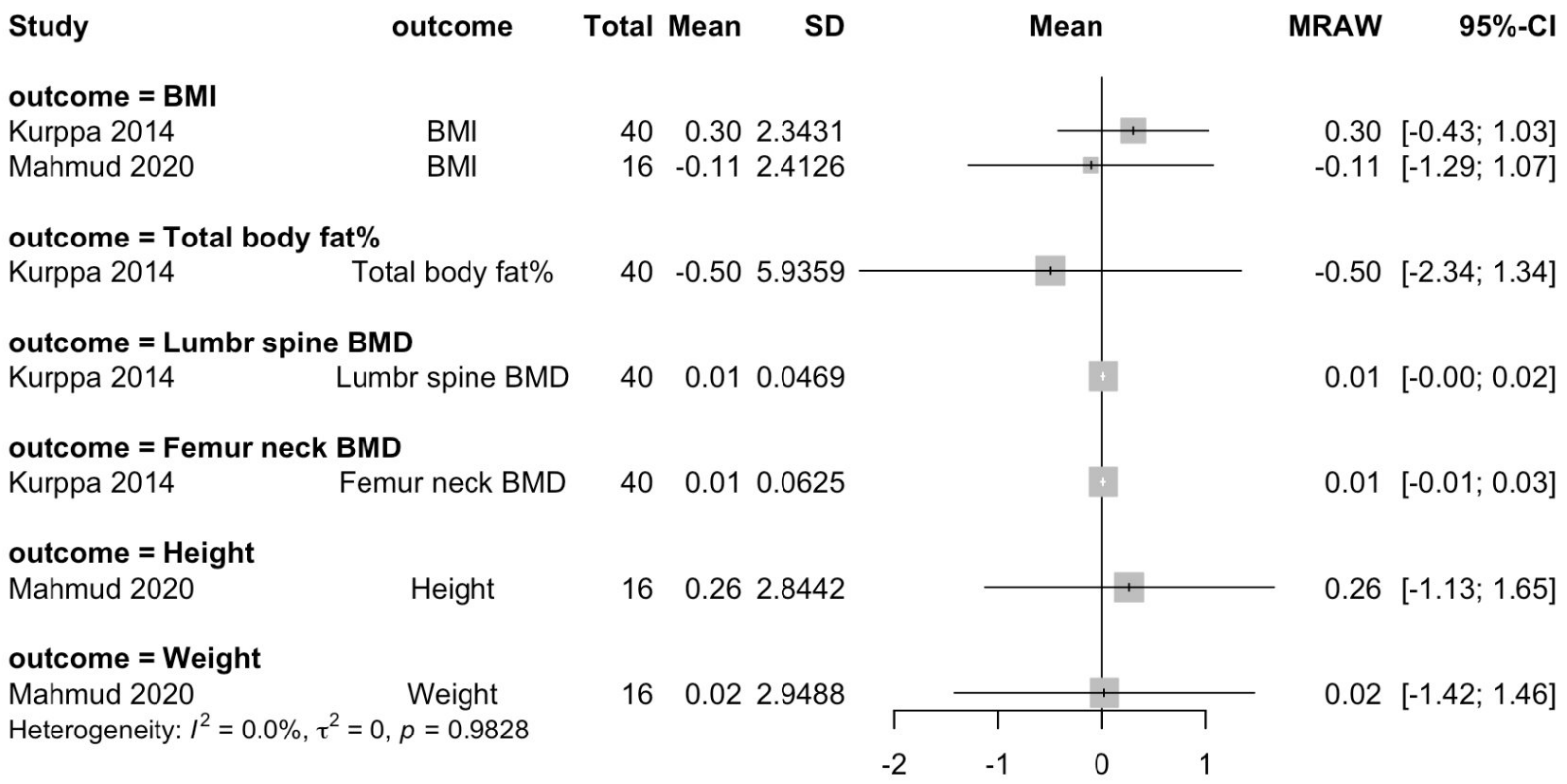
Supplemental Figure 6: Symptoms



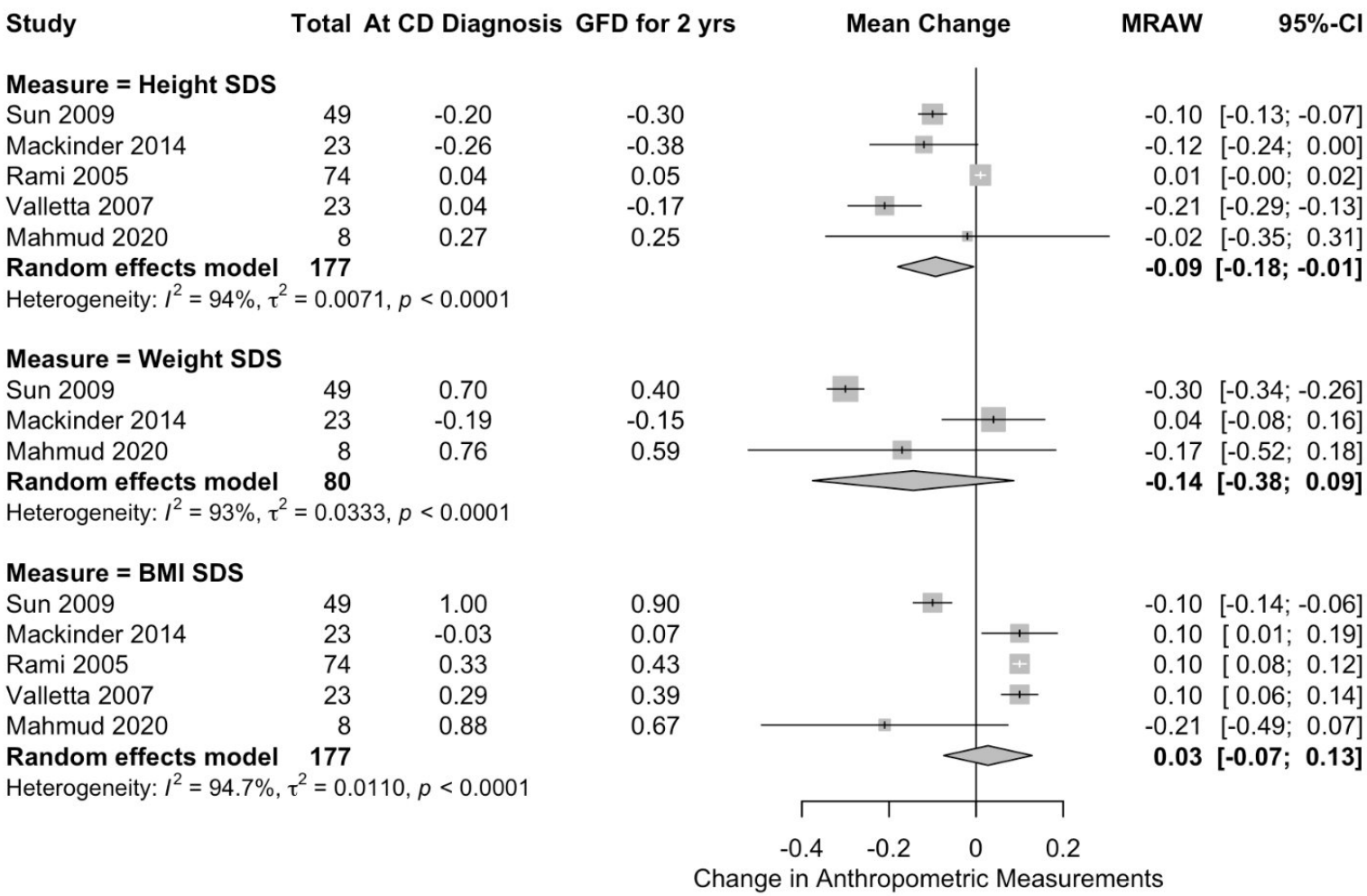
Supplemental Figure 7: Laboratory Values



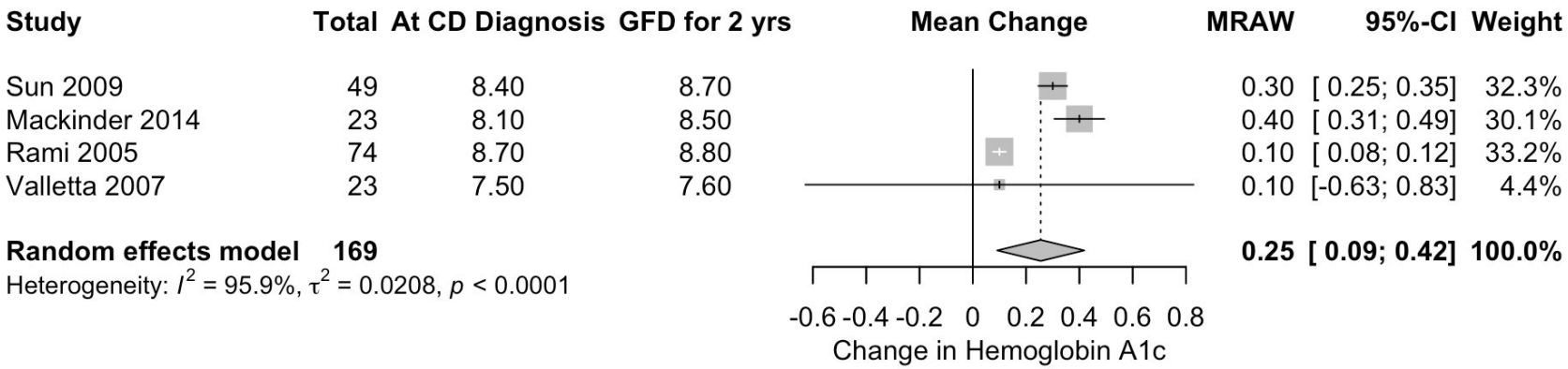
Supplemental Figure 8: Anthropometrics from RCT Data



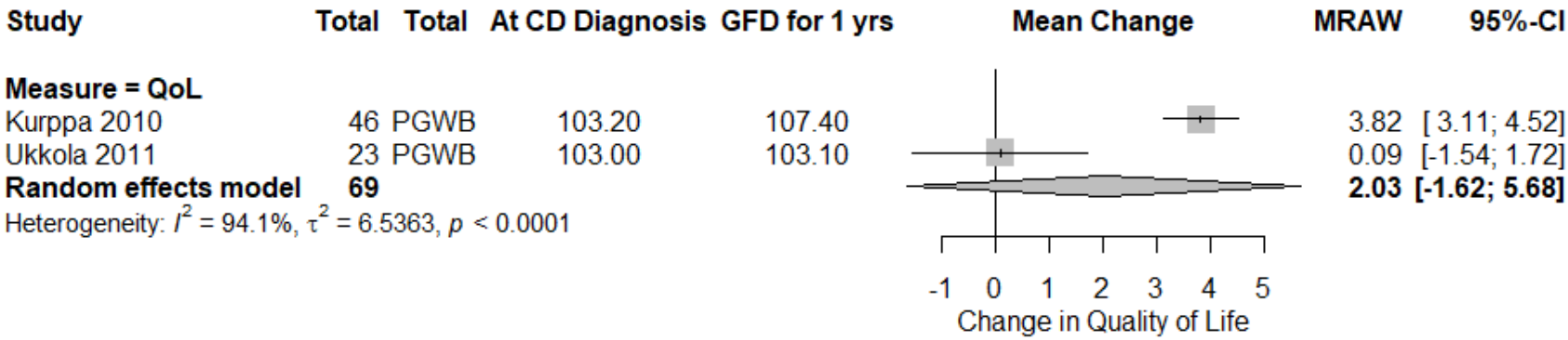
Supplemental Figure 9: Anthropometrics from Pre-post Study Data



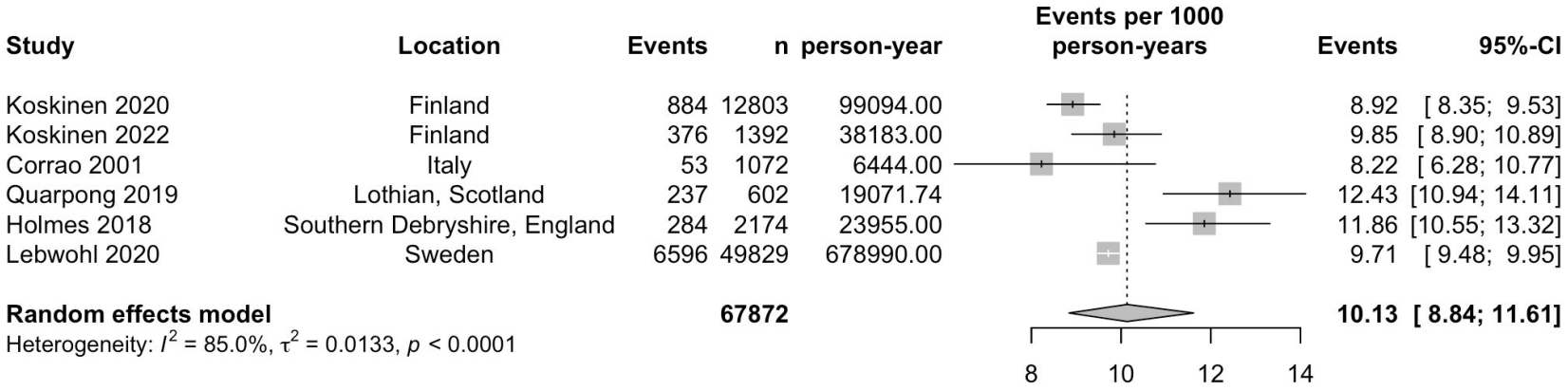
Supplemental Figure 10: Hemoglobin A1c



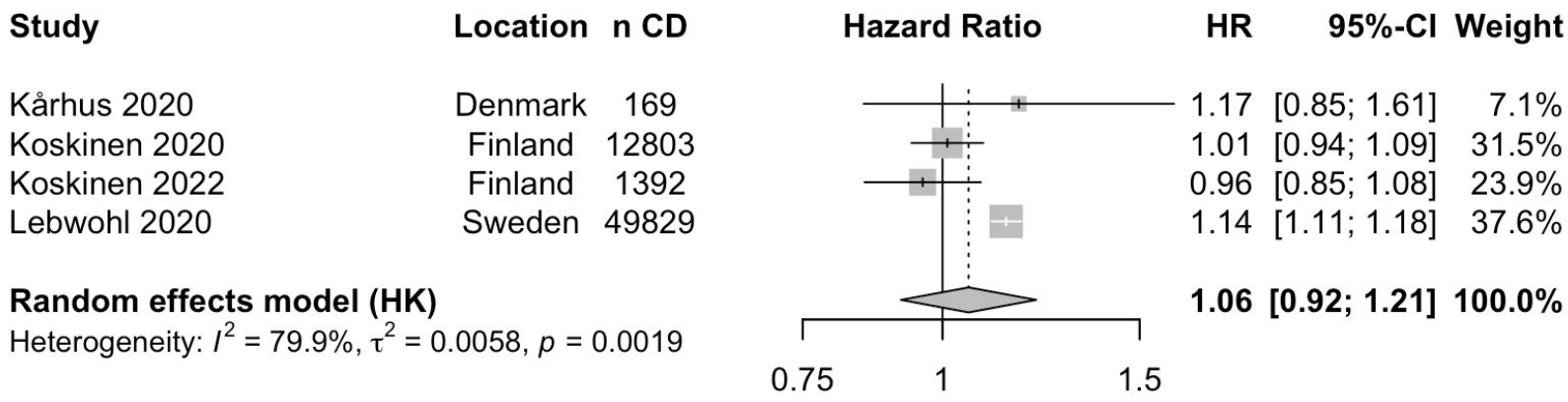
Supplemental Figure 11: Quality of Life from Pre-post Study Data



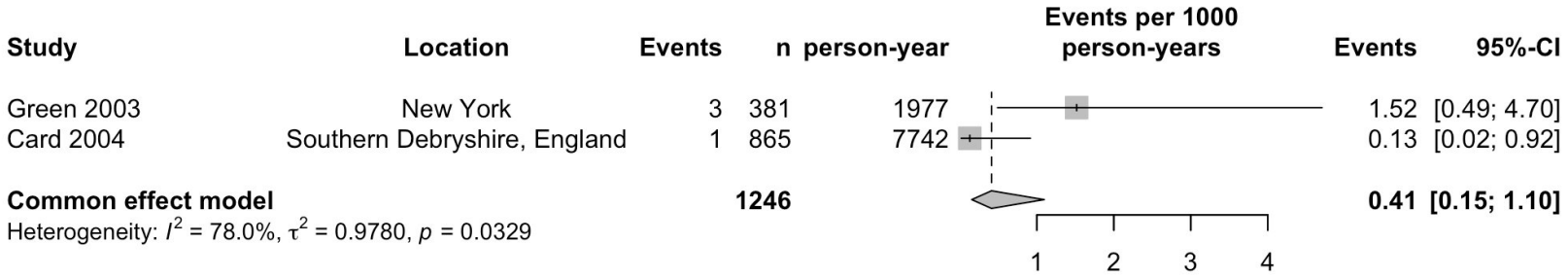
Supplemental Figure 12: Mortality Rate



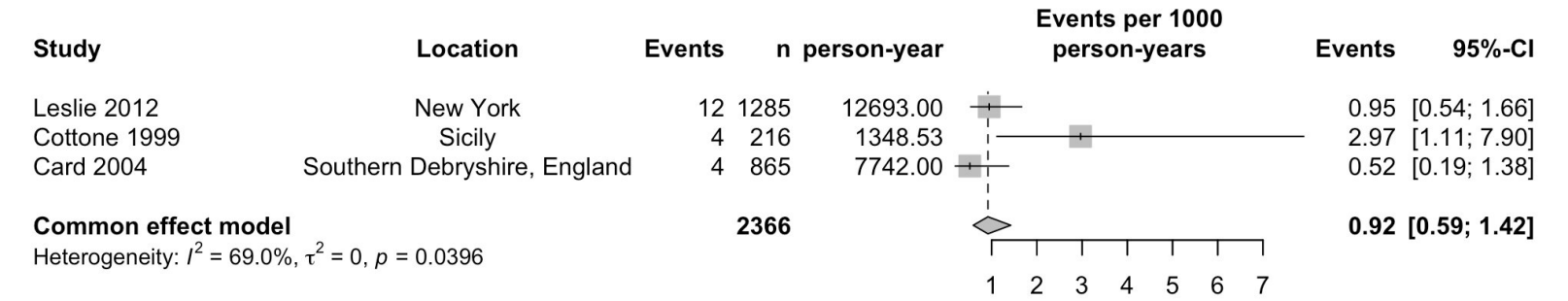
Supplemental Figure 13: Mortality Hazard Ratio



Supplemental Figure 14: Small-bowel Adenocarcinoma



Supplemental Figure 15: Enteropathy-associated T-cell Lymphoma



Supplemental Table 2: PICO 1 Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gluten-free diet**	**Gluten-containing diet**	**Relative (95% CI)**	**Absolute (95% CI)**		
Quality of life (follow-up: 1 years; assessed with: PedsQLI and PGWB; Scale from: 0 to 100)												
2	RCTs	serious[a]	not serious	not serious	serious[b]	none	47	44	-	MD **3.24 points higher** (0.42 higher to 6.07 higher)	⨁⨁◯◯ Low[a,b]	CRITICAL
New onset GI symptoms (follow-up: 1 years; assessed with: GSRS; Scale from: 0 to 7)												
1	RCT	serious[a]	not serious	not serious	serious[c]	none	20	20	-	MD **0.4 points lower** (0.69 lower to 0.11 lower)	⨁⨁◯◯ Low[a,c]	CRITICAL
Change in height (growth in children) (follow-up: 1 years; assessed with: height-for-age Z-score)												
1[d]	RCT	not serious[e]	not serious	not serious	very serious[f]	none	8	8	-	MD **0.26 points higher** (1.13 lower to 1.65 higher)	⨁⨁◯◯ Low[e,f]	IMPORTANT
Change in height (growth in children) (follow-up: range 1 years to 2 years; assessed with: height-for-age Z-score)												
5	non-randomized studies	serious[g]	not serious[h]	not serious	not serious	none	177	0	-	mean **0.09 lower** (0.18 lower to 0.01 lower)	⨁◯◯◯ Very low[g,h]	IMPORTANT
Fractures due to metabolic bone disease - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Change in bone mineral density (follow-up: 1 years; assessed with: Lumbar spine BMD)												
1[i]	RCT	not serious[e]	not serious	serious[j]	serious[c]	none	20	20	-	MD **0.01 g/cm2 more** (0.01 fewer to 0.02 more)	⨁⨁◯◯ Low[c,e,j]	IMPORTANT
Development of small bowel malignancy - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Development of small bowel adenocarcinoma (follow-up: median 6 years)												

2	non-randomized studies	serious[k]	serious[l]	serious[m]	not serious[n]	none	Two observational studies that included 1,246 individuals with celiac disease were identified. The pooled rate of developing small bowel adenocarcionma in patients with celiac disease was 0.41/1000 person-years (95% CI 0.15-1.10).	⨁◯◯◯ Very low[k,l,m,n]	IMPORTANT
Development of enteropathy-associated T-cell lymphoma (follow-up: median 6 years)									
3	non-randomized studies	serious[k]	serious[o]	serious[m]	not serious[n]	none	Three observational studies that included 2,366 individuals with celiac disease were identified. The pooled rate of developing EATL in patients with celiac disease was 0.92/1000 person-years (95% CI 0.59-1.42).	⨁◯◯◯ Very low[k,m,n,o]	IMPORTANT

CI: confidence interval; **MD:** mean difference

Explanations

a. Risk of bias related to deviation from intended intervention (lack of blinding) and measurement of outcome (outcome assessors not blinded).
b. The confidence interval includes no-to-trivial benefit and small benefit based on MID of 4.5 for PedsQL 4.0 (PMID: 14616041; DOI: 10.1367/1539-4409(2003)003<0329:tpaapp>2.0.co;2).
c. Small sample size.
d. The trial patients were stratified based on age during randomization.
e. We did not rate down for lack of blinding as the outcome is unlikely to be affected by blinding.
f. Very wide confidence interval that includes moderate benefit and moderate harm based on MID of 0.5 points.
g. Rated down due to concerns regarding selection of included patients and uncertainty about adherence to the diet.
h. Although the i2 of 94% suggests statistical heterogeneity, based on MID of 0.5 the results were consistent in showing no-to-trivial worsening in Z-score.
i. Study also reported results for femur neck BMD which were similar.
j. Bone mineral density is a surrogate outcome for fracture reduction.
k. Serious risk of bias due to lack of adjustment for confounders and unclear adequacy of follow-up.
l. One study showed an incidence rate of 0.13/1000 person-years and the other showed a rate of 1.52/1000 person-years.
m. The studies included all patients with celiac disease regardless of symptoms status.
n. We did not rate down because the wide confidence interval was probably due to the statistical heterogeneity.
o. Studies reported variable incidence rates 0.52 per 1000, 0.95 per 1000, and 2.97 per 1000 person-years.

Supplemental Table 3: PICO 1 Evidence-to-Decision Framework

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

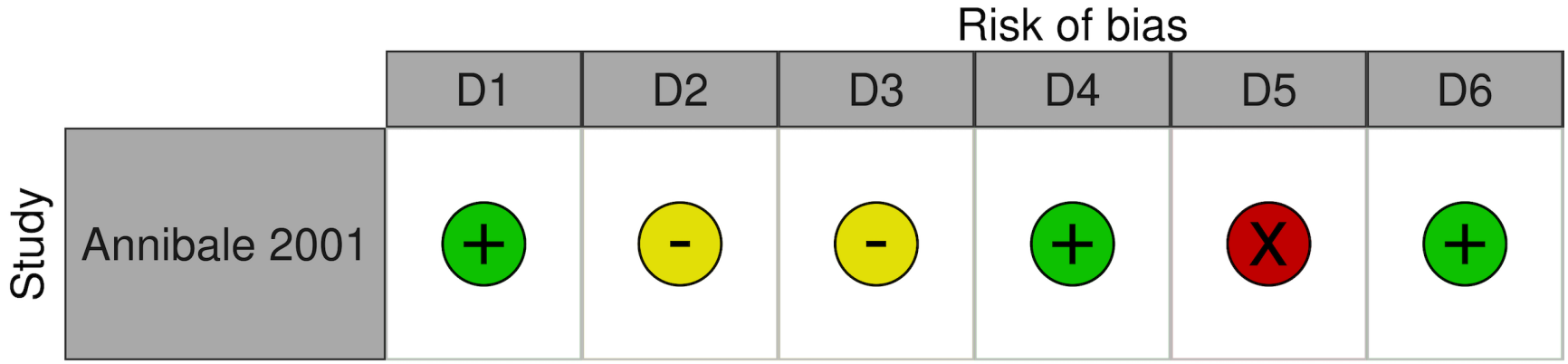
PICO 2: Should gluten-free diet vs. gluten-containing diet be used for individuals with unexplained iron deficiency diagnosed with asymptomatic celiac disease?

Supplemental Table 4: PICO 2 Study Characteristics

Study	Patient population	Baseline characteristics	Outcome(s)
Annibale 2001[21] Pre-post study Italy Follow-up: 2 years Funding: grant 02/12/01/10, 1995-97 from the Italian Ministry for the University (MURST) and by a grant from FIMAD	**Inclusion:** Adults referred from hematology for IDA (80% were iron dependent), screened for celiac disease by duodenal biopsies and EMA IgA antibodies **Exclusion:** obvious causes of blood loss (heavy menstrual loss, active GI hemorrhage) and other conditions that could justify microcytic anemia (positive fecal occult blood tests, liver cirrhosis, hemolytic disease, renal failure, thalassemia, malignancies)	*n* = 26 (out of 190 with IDA) 92% female Median age: 31.3 yr (range: 20-72) Histological score of duodenitis: A3: 76.9% A2: 23.1% 11 with GI symptoms either loose stool or constipation Only 20 were followed as 5 were lost to follow-up and 1 was not compliant with GFD	**Hemoglobin (without iron supplementation):** At baseline: 10.7 (range: 6.1 - 11.9) After 6 months: 12.5 (range: 8.3 - 14.4) After 12 months: 13.3 (range: 9.7 - 15.3) After 24 months: 13.8 (range: 10.4 - 14.7) **Ferritin:** At baseline: 4 (range: 1 - 10) After 6 months: 11.5 (range: 3 - 82) After 12 months: 19 (range: 5.1 - 63) After 24 months: 21 (range: 4 - 58)
Ben-Ami 2024[22] Comparative study Israel Follow-up: 1 year Funding: Open access	Children diagnosed with celiac disease (with or without biopsies) with iron deficiency without anemia (ferritin ≤ 10) started on a GFD.	*n* = 60 Half of participants (*n* = 29) were recommended to take iron supplementation by their pediatricians 49% female Mean age: 7.3 ± 3.9 yr	**Ferritin (on iron supplementation vs no supplementation)**: At baseline: 9.4 ± 5.1 (*n* = 29) vs 9.9 ± 5.4 (*n* = 31) At 6 months: 18.9 ± 15.9 (*n* = 22) vs 17.3 ± 13.6 (*n* = 22) At 12 months: 23.5 ± 19.1 (*n* = 20) vs 16.1 ± 8.9 (*n* = 18)

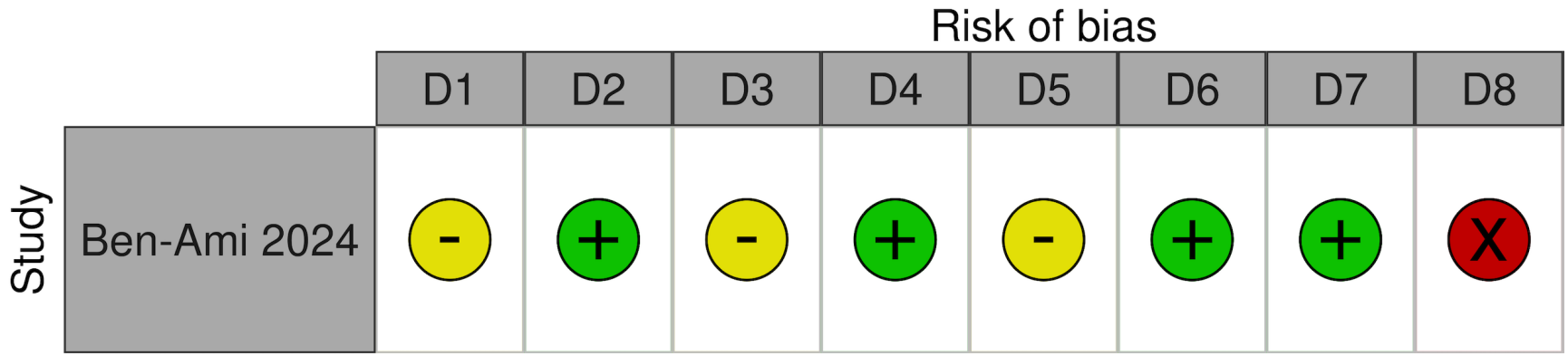
funding provided by Hebrew University of Jerusalem		10 diagnosed with biopsy	

Supplemental Figure 16: PICO 2 Risk of Bias Assessment for Pre-post Studies



D1: Were all eligible participants that met the prespecified entry criteria enrolled?
D2: Was the intervention clearly described and delivered consistently across the study population?
D3: Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
D4: Were the people assessing the outcomes blinded to the participants' exposures/interventions?
D5: Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
D6: Was follow-up long enough for outcomes to occur?

Supplemental Figure 17: PICO 2 Risk of Bias Assessment for Comparative Cohort Studies



D1: Representativeness of the exposed cohort
D2: Selection of the non-exposed cohort
D3: Ascertainment of exposure
D4: Demonstration that outcome of interest was not present at start of study
D5: Comparability of cohorts on the basis of the design or analysis
D6: Assessment of outcome
D7: Follow-up long enough for outcomes to occur
D8: Adequacy of follow-up of cohorts

Supplemental Table 5: PICO 2 Evidence Profile

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Resolution of anemia									
1	non-randomized study	not serious	not serious	serious[a]	serious[b]	none	**Annibale et al (2001)** reported on 20 patients with iron defiency anemia and celiac disease treated with gluten-free diet followed for 24 months. Anemia resolved in 14/18 patients by 6 months, 17/18 by 12 months, and 17/18 by 24 months without iron replacement therapy. The patient had no to mild GI symptoms.	⨁◯◯◯ Very low[a,b]	Critical
Resolution of iron deficiency									
1	non-randomized study	not serious	not serious	serious[a]	serious[b]	none	**Ben-Ami et al (2024)** reported on 60 children with newly diagnosed celiac disease with evidence of iron deficiency. 29 received iron replacement with GFD while 31 only did GFD without iron replacement. Ferritin levels increased from 9.0 to 25.2 in the iron replacement group, and from 8.9 to 18.6 in the GFD only group.	⨁◯◯◯ Very low[a,b]	Important

CI: confidence interval

Explanations

a. Not all the included patients were asymptomatic.

b. Very small to small sample size.

Supplemental Table 6: PICO 2 Evidence-to-Decision Framework

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

PICO 3: Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease with metabolic bone disease?

Supplemental Table 7: PICO 3 Study Characteristics

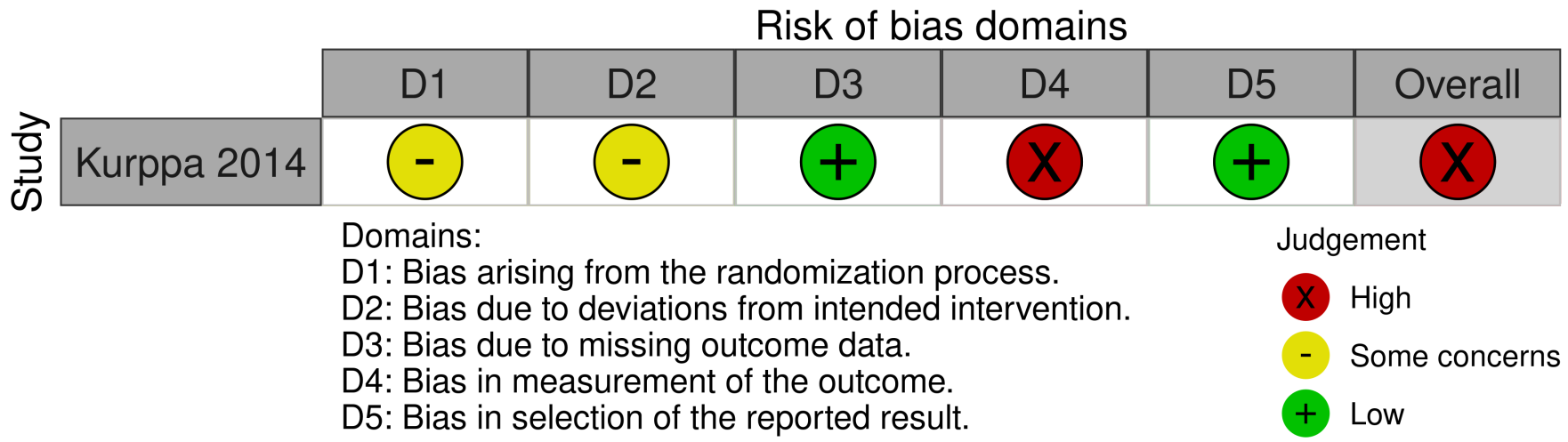
Study	Patient population	Baseline characteristics	Outcome(s)
Kurppa 2014[1] RCT Finland Follow-up: 1 year Funding: Academy of Finland Research Council for Health, the Competitive Research Funding of the Pirkanmaa Hospital District, the Sigrid Juselius Foundation, the Finnish Foundation for Gastroenterological Research, the Yrjö Jahnsson Foundation, the Finnish Medical Foundation, the Foundation for Pediatric Research and the Finnish Celiac Society.	**Inclusion**: Asymptomatic* adults >18yr, at-risk relatives of celiac patients, and with EmA positive **Exclusion**:<18 yr of age, evident clinical symptoms, dietary gluten restriction, severe contemporary illness or immunosuppressive medication, ongoing or planned pregnancy **Diagnosis of celiac disease**: EmA-positive gluten-dependent enteropathy **Definition of asymptomatic**: absence of abdominal pain (>3 pain episodes over 3 months interfering with function), constipation (<3 BMs per week or difficulty during defecation), and diarrhea (3 loose stools/day) or extraintestinal (joint pain, rash, neurologic) **Age group(s)**: no	**GFD** (*n* randomized = 20) *Age Median (range)*: 42 (21-74) *Sex Female, n (%)*: 9 (45) *Comorbidities (Asthma, endometriosis, diverticulosis, allergies)*:7 (35) *Loss to follow-up*: 0 **GCD** (*n* randomized = 20) *Age*: *Median (range)*: 42 (23-62) *Sex: Female, n (%)*:5(25) *Comorbidities (Asthma, endometriosis, diverticulosis, allergies.)*: 7(25) *Loss to follow-up*: 0 **Method of implementing dietary instructions**: visits with a dietitian at baseline and 1 yr FU **Method to ascertain adherence to dietary instructions**: Information not provided.	**Bone Mineral Density** Assessed with Dual-energy X-ray Absorptiometry (Lunar Prodigy Advance, GE Healthcare, Waukesha, WI). BMD values were expressed as T-scores and as age- and sex-matched Z-scores. *Scale*: g/m2 *n*: 20 vs 20 *Events*: N/A *Change*: Mean ± SD except differences in the changes between the groups, expressed as means (95% CI) All comparison GCD vs GFD Lumbar spine BMD, g/cm^2 Baseline: 1.17 ± 0.21 vs 1.17 ± 0.19 Change: -0.01 ± 0.03 vs 0.00 ± 0.02 Difference: 0.01 (-0.01 to 0.02) Femur neck BMD, g/cm^2 Baseline: 1.00 ± 0.12 vs 0.97 ± 0.14 Change: -0.01 ± 0.03 vs 0.00 ± 0.02 Difference: 0.01 (-0.01 to 0.03)

	High-risk group: no **Extra-intestinal manifestations**: None **Other**: All subjects had HLA DQ2 or 8		
Valdimarsson 1996[23] Prospective cohort study Sweden Follow-up: 1 year **Funding:** Not reported	**Inclusion:** Adults with newly diagnosed CeD based on clinical suspicion (diarrhea, weight loss, dyspepsia, or biochemical abnormalities) with villous atrophy grade III or IV (Alexander's classification) in the proximal small bowel **Exclusion:** Presence of other disease(s) known to affect bone mineral density (e.g., hypercalcemic hyperparathyroidism)	n = 63 (35 women, 28 men) Median age: 53.5 years (range 17–79) 7 patients had co-existing dermatitis herpetiformis 34 patients (54%) had no symptoms of malabsorption (no weight loss or diarrhea) at diagnosis **Prevalence of severe osteopenia (Z score < −2) at baseline:** Forearm: 22% Lumbar spine: 15% Femoral neck: 9% Trochanter: 18% Biochemical abnormalities at baseline: 25-OH-D3 <35 nmol/l: 8% PTH >65 ng/l: 27% ALP >4.6 µkat/l: 23% ionized calcium <1.18 mmol/l: 18% 13 patients with low ionized calcium or low dietary calcium intake received calcium supplementation; 5 also received vitamin D supplementation	<u>Severe osteopenia (Z score < −2) — before vs. after 1 year of GFD:</u> Forearm: 22% → 17% Lumbar spine: 15% → 8% Femoral neck: 9% → 2% Trochanter: 18% → 5% <u>Bone Mineral Density (BMD) — change during 1 year of GFD:</u> BMD increased significantly at all sites during the first year of GFD (p<0.01 for all): Forearm (SPA): median +1% (IQR −1/+4), p<0.01 Lumbar spine (DXA): median +3% (IQR +1/+7), p<0.001 Femoral neck (DXA): median +2% (IQR −1/+10), p<0.001 <u>Notable subgroup findings:</u> Patients without malabsorption symptoms had similar osteopenia at baseline and similar BMD improvement as those with symptoms Patients ≥65 years showed BMD improvement comparable to younger patients Patients with dermatitis herpetiformis did not show BMD improvement

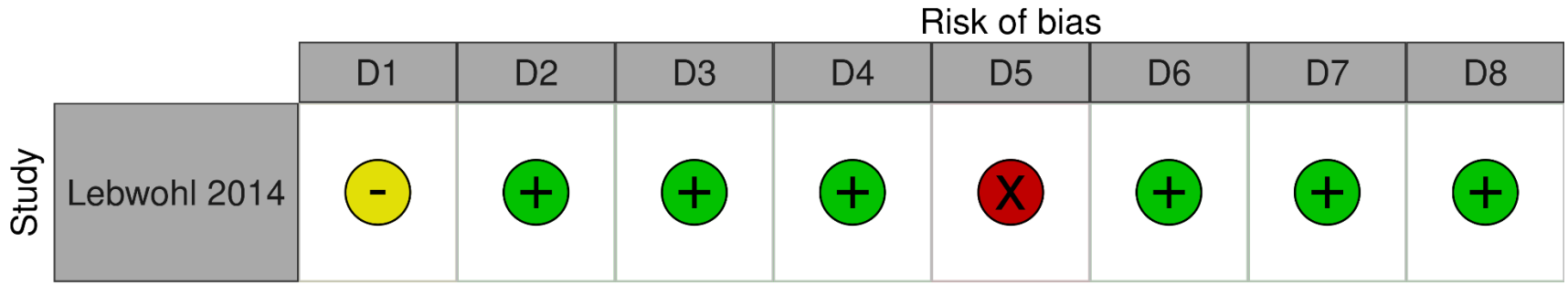
			<u>Biochemical markers after 1 year:</u> 25-OH-D3 <35 nmol/l: 8% → 0% PTH >65 ng/l: 27% → 12% ALP >4.6 µkat/l: 23% → 11% Ionized calcium <1.18 mmol/l: 18% → 0% BMD remained reduced at all sites after 1 year ($p<0.05$), but was normalized in patients who had adhered strictly to GFD for ≥4 years in prior cross-sectional data
Lebwohl 2014[24] Retrospective cohort study Sweden (nationwide) Follow-up: median 8.6 years after follow-up biopsy (IQR 5.2–13.8) **Funding:** American Scandinavian Foundation; Celiac Sprue Association; NIH (KL2 TR000081); Örebro University Hospital; Karolinska Institutet; Swedish Society of Medicine; Swedish Research Council	Patients in Sweden with histologically confirmed CeD (Marsh stage 3 / villous atrophy) who underwent a follow-up small intestinal biopsy between 6 months and 5 years after initial CD diagnosis **Comparator:** Persistent villous atrophy (VA) on follow-up biopsy (Marsh stage 3) vs. mucosal healing (Marsh stages 1–2 or normal mucosa) **Exclusion:** History of fracture prior to the date of the follow-up biopsy (for hip fracture analysis: prior hip fracture excluded)	n = 7,146 (after excluding 502 with prior fracture) Median age at diagnosis: 23 years (IQR 2–49) Median age at follow-up biopsy: 25 years (IQR 5–51) 64% female 46% were <20 years at follow-up biopsy 43% had persistent VA on follow-up biopsy (3,105/7,146) Interval to follow-up biopsy: 6–12 months: 26% 1–2 years: 45% 2–5 years: 29% 51% had follow-up biopsy after 2000 Overall fracture incidence during follow-up: Any fracture: 975/7,146 (14%)	<u>Primary outcomes — effect of persistent VA vs. mucosal healing on fracture risk:</u> **Any fracture:** HR 0.93 (95% CI 0.82–1.06) — no significant association Rate: 1,376 per 100,000 person-years overall **Likely osteoporotic fracture** (hip, distal forearm, thoracic/lumbar spine, proximal humerus): HR 1.11 (95% CI 0.84–1.46) — no significant association overall Rate: 676 per 100,000 person-years In the first year after follow-up biopsy: HR 2.54 (95% CI 1.15–5.61), $p<0.05$ **Hip fracture:** HR 1.67 (95% CI 1.05–2.66) — significantly increased risk

		Hip fracture: 89/7,146 (1.2%)	Absolute excess risk: 63 events per 100,000 person-years Rate: 158 vs. 69 per 100,000 person-years (persistent VA vs. healing) Risk confined to >5 years after follow-up biopsy: HR 2.18 (95% CI 1.17–4.05) <u>Dose-response by degree of VA (hip fracture):</u> Partial VA: HR 1.70 (95% CI 0.82–3.49) Subtotal/total VA: HR 2.16 (95% CI 1.06–4.41) <u>Gender-stratified analyses:</u> Hip fracture risk was similar in men (HR 1.63, 95% CI 0.76–3.53) and women (HR 1.67, 95% CI 0.93–2.99) Likely osteoporotic fractures showed a significant interaction by gender (p=0.01), with a trend in women (HR 1.39, 95% CI 0.98–1.95) but not men (HR 0.75, 95% CI 0.47–1.22) <u>Age-stratified analyses:</u> Any fracture risk was null in both <25 years (HR 0.90) and ≥25 years (HR 0.99) Likely osteoporotic fracture risk was nonsignificantly increased only in patients ≥25 years (HR 1.23, 95% CI 0.87–1.75)

Supplemental Figure 18: PICO 3 Risk of Bias Assessment for RCTs

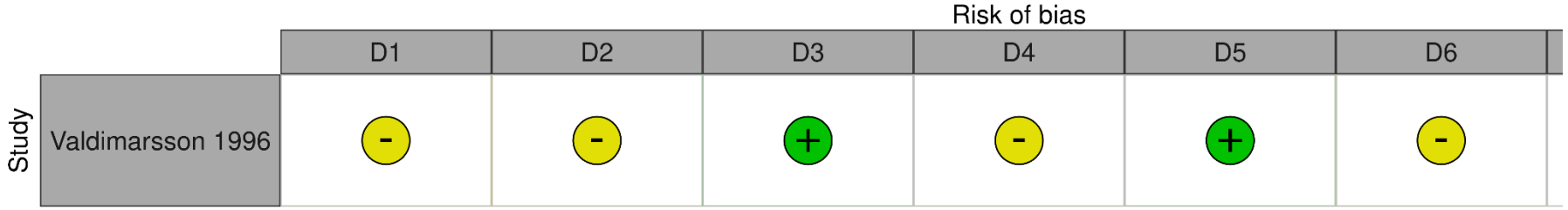


Supplemental Figure 19: PICO 3 Risk of Bias Assessment for Comparative Observational Study



D1: Representativeness of the Exposed Cohort
D2: Selection of the Non-Exposed Cohort
D3: Ascertainment of Exposure
D4: Demonstration That Outcome of Interest Was Not Present at Start of Study
D5: Comparability of Cohorts on the Basis of the Design or Analysis
D6: Assessment of Outcome
D7: Was Follow-Up Long Enough for Outcomes to Occur
D8: Adequacy of Follow Up of Cohorts

Supplemental Figure 20: PICO 3 Risk of Bias Assessment for Pre-Post Study



D1: Were all eligible participants that met the prespecified entry criteria enrolled?
D2: Was the intervention clearly described and delivered consistently across the study population?
D3: Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
D4: Were the people assessing the outcomes blinded to the participants exposures/interventions?
D5: Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
D6: Was Follow-Up Long Enough for Outcomes to Occur

Supplemental Table 8: PICO 3 Evidence Profile

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in bone disease related fractures									
1	non-randomized study	serious[a]	not serious	serious[b]	serious[c]		There are no studies evaluating the effect of GFD on risk of fractures in asymptomatic CeD. However, Lebwohl et al reported that in all patients with CeD persistent villous atrophy was associated with increased risk of hip fractures (hazard ratios 1.67; 95% CI 1.06 to 2.66) but no associated risk of overall fractures (HR 0.93; 95% CI 0.82 to 1.06) or likely osteoporotic fractures (HR 1.11; 95% CI 0.84 to 1.46)	⨁◯◯◯ Very low[a,b,c]	CRITICAL
Change in bone mineral density; follow-up: 1 year									
1	RCT	not serious	not serious	not serious	serious[d]		Based on one RCT (Kurppa 2014) with 40 patients; 20 in each arm. No differences in lumbar spine and femur neck BMD in participants with asymptomatic CeD on GFD compared to GCD. Lumbar spine BMD, g/cm2 Difference: 0.01 (-0.01 to 0.02); Femur neck BMD, g/cm2 Difference: 0.01 (-0.01 to 0.03)	⨁◯◯◯ Very low[d]	IMPORTANT

Change in bone mineral density; follow-up: 1 year									
1	non-randomized study	serious*	not serious	serious[b]	serious[e]		Valdimarsson et al reported that in all patients with celiac disease after one year of a GFD, the percentage of CeD with severe osteopenia decreased from 22% to 17% in the forearm, from 15% to 8% in the lumbar spine, from 9% to 2% in the femoral neck, and from 18% to 5% in the trochanter	⨁◯◯◯ Very low[b,e]	IMPORTANT

BMD: bone mineral density; **CeD:** celiac disease; **CI:** confidence interval; **GCD:** gluten-containing diet; **GFD:** gluten-free diet

Explanations

a. Concern regarding selection bias and comparability

b. Study included both all disease spectrum (classic presentation, asymptomatic, etc)

c. Wide confidence interval including trivial increased risk to at least moderate increase in risk

d. Downgraded one level for imprecision due to the small sample size (1 RCT, n=40) and confidence intervals crossing the line of no effect for both lumbar spine and femoral neck BMD.

e. Small sample size with only 63 included patients

Supplemental Table 9: PICO 3 Evidence-to-Decision Framework

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	Favors the intervention	Varies	Don't know

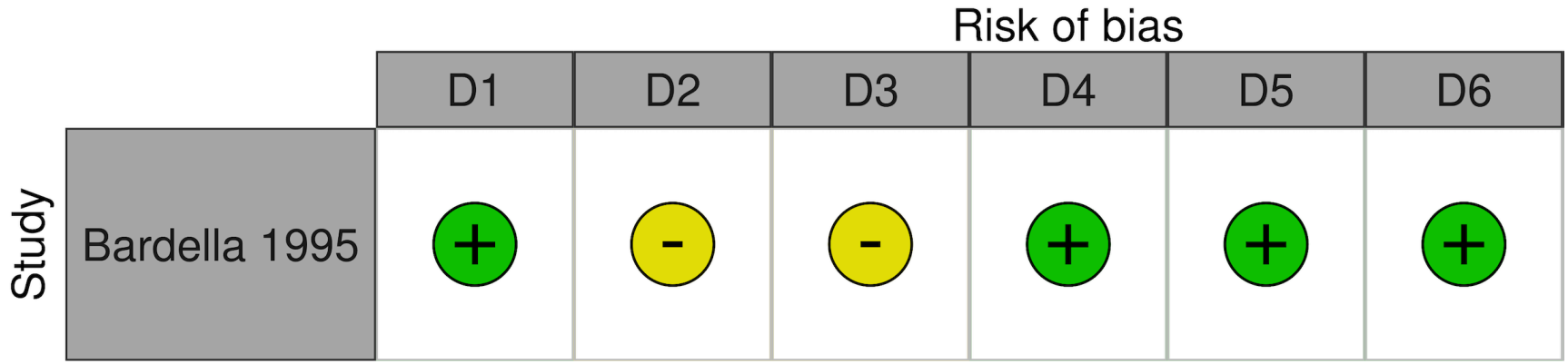
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

PICO 4: Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease with unexplained abnormal liver function tests and enzymes?

Supplemental Table 10: PICO 4 Study Characteristics

Study	Patient population	Baseline characteristics	Outcome(s)
Bardella 1995[25] Pre-post study Italy Follow-up: median 4 years (range: 1 – 10) Funding: Not reported	Patients with CeD diagnosed with duodenal biopsy	*n* = 158 total population *n* = 67 with altered LFTs (elevated ALT and AST in 47; elevated AST only in six; elevated ALT only in 14). Concomitant increase in alkaline phosphatase in three patients. Of the 67, 40 had chronic symptoms; 18 classical malabsorption symptoms; 9 asymptomatic/DH 80.5% women Mean age: 31.5 years (range: 18 – 61)	After 6 months of GFD, transaminase levels normalized in 60 patients (89%). Mean AST decreased from 47 (range 30-190) at diagnosis to 27 (range 19-275) after 1 year of GFD, and mean ALT decreased from 61 (range 25-470) to 29 (range 19-390).

Supplemental Figure 21: PICO 4 Risk of Bias Assessment for Pre-post Studies



D1: Were all eligible participants that met the prespecified entry criteria enrolled?
D2: Was the intervention clearly described and delivered consistently across the study population?
D3: Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
D4: Were the people assessing the outcomes blinded to the participants' exposures/interventions?
D5: Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
D6: Was follow-up long enough for outcomes to occur?

Supplemental Table 11: PICO 4 Evidence Profile

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Normalization of LFTs									
1	non-randomized study	not serious	not serious	serious[a]	serious[b]	none	**Bardella et al (1995)** reported on 67 patients with celiac disease and altered LFTs (47 with elevated AST/ALT, 6 elevated AST, 14 elevated ALT, and 3 with concomitant increase in alkaline phosphatase). After 6 months of gluten-free diet, transaminase levels normalized in 60 patients (89%). Mean AST decreased from 47 (range 30-190) at diagnosis to 27 (range 19-275) after 1 year of GFD, and mean ALT decreased from 61 (range 25-470) to 29 (range 19-390).	⨁◯◯◯ Very low[a,b]	CRITICAL

CI: confidence interval

Explanations

a. Not all patients were asymptomatic.

b. Small sample size.

Supplemental Table 12: PICO 4 Evidence-to-Decision Framework

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

PICO 5: Should gluten-free diet vs. gluten-containing diet be used for children with asymptomatic celiac disease with short stature?

Supplemental Table 13: PICO 5 Study Characteristics

Study	Patient population	Baseline characteristics	Outcome(s)
Groll 1980[26] Pre-post study United Kingdom Follow-up: Not reported Funding: Not reported	Children with short stature, no GI symptoms, and CeD diagnosed with jejunal biopsy	*n* = 6 37.5% female	**Growth Velocity** The mean acceleration in height velocity was 4.1 ± 1.6 cm/year after implementing gluten-free diet.
Cacciari 1985[27] Pre-post study Italy Follow-up: range 6 – 33 months Funding: Consiglio Nazionale Ricerche contracts 82.02114.56 and 83.02561.56	Children with short stature, no GI symptoms, and CeD diagnosed with duodenal biopsy	*n* = 11 (9 with total villous atrophy, 2 with mild partial villous atrophy) 36% female Age: range 2 – 15 years	**Growth Velocity** After around 1 year of gluten-free diet, mean growth velocity increased from -1.56 SD (range: -2.44 to 0) to +1.1 SD (range: -6.1 to 6.69).
Rosenbach 1986[28] Pre-post study	Children with short stature and CeD diagnosed withs small-bowel biopsy	*n* = 11 (8 with history of diarrhea, 6 with growth retardation in the first two years of life, and 2 with	**Growth Velocity** After 6-50 months of GFD, the mean height velocity increased from -2.9 SD (range -4.8 to 0) to +1.9 SD (range 0 to +6); and from 3.1

Israel Follow-up: range 6 – 50 months Funding: Not reported		recurrent abdominal pain and distention) 73% female Age: range 5 – 14 years	cm/year (range 0 to 6) to 9.2 cm/year (range 6 to 12).
Bosio 1990[29] Pre-post study Italy Follow-up: range 9 – 15 months Funding: Not reported	Children with poor weight gain, retarded height velocity, and CeD diagnosed with small-bowel biopsy	*n* = 24 (15 with history of GI symptoms) 58% female Mean age: 11.9 years in males, 8.7 years in females	**Change in Height Assessed with Z-Score** 23 patients (10 males and 13 females) were followed for 9 to 15 months. The mean height Z-score in the male patients went up from of -2.46 ± 0.96 (range -1.63 to -4.83) to -1.99 ± 0.78 (range -0.87 to -3.53), and in the female patients from -2.58 ± 0.64 range (-1.65 to -3.65) to -2.28 ± 0.70 (range -1.05 to -3.67). In 12 patients (4 males and 9 females) followed for three years, the mean height Z-score went up from -2.52 ± 0.67 (range -1.65 to -3.5) to -1.77 ± 0.61 (range -0.64 to -2.55).
Bonamico 1992[30] Pre-post-study Italy Follow-up: 1 year Funding: Not reported	Children with short stature, no GI symptoms, and CeD diagnosed with intestinal biopsy	*n* = 29 Demographics not reported	**Growth Velocity** Growth hormone measurement in 14 patients showed partial deficiency in 5 (36%), total deficiency in 1 (7%), and normal in 8 (57%). GH therapy did not lead to an increase in growth velocity in patients with GH deficiency. Mean height Z-score at diagnosis was -2.7 (range -2 to -3.7). After one year of GFD, the mean growth velocity increased from -2.3 SD to +3.7 SD. GH normalized in patients that had GH deficiency.

Supplemental Figure 22: PICO 5 Risk of Bias Assessment for Pre-post Studies

D1: Were all eligible participants that met the prespecified entry criteria enrolled?
D2: Was the intervention clearly described and delivered consistently across the study population?
D3: Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
D4: Were the people assessing the outcomes blinded to the participants' exposures/interventions?
D5: Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
D6: Was follow-up long enough for outcomes to occur?

Supplemental Table 14: PICO 5 Evidence Profile

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Growth Velocity									
4	non-randomized studies	serious[a]	not serious	not serious	serious[b]	none	**Groll et al (1980)** reported change in growth velocity in 6 children with celiac disease without GI symptoms. The mean acceleration in height velocity was 4.1 ± 1.6 cm/year after implementing gluten-free diet. **Cacciari et al (1985)** reported change in growth velocity for 11 children with short stature and celiac disease without GI symptoms. After around 1 year of gluten-free diet, mean growth velocity increased from -1.56 SD (range -2.44 to 0) to +1.1 SD (range -6.1 to 6.69). **Rosenbach et al (1986)** reported change in height velocity in 11 children with celiac disease. 8 of them had diarrhea, 6 had growth retardation in the first two years of life, and 2 had recurrent abdominal pain and distention. After 6-50 months of GFD, the mean height velocity increased from -2.9 SD (range -4.8 to 0) to +1.9 SD (range 0 to +6); and from 3.1 cm/year (range 0 to 6) to 9.2 cm/year (range 6 to 12). **Bonamico et al (1992)** reported on 29 children with short stature with celiac disease without GI symptoms. Growth hormone measurement in 14 patients showed partial deficiency in 5 (36%), total deficiency in 1 (7%), and normal in 8 (57%). GH therapy did not lead to an increase in growth velocity in patients with GH deficiency. Mean height Z-score at diagnosis was -2.700(range -2 to -3.7). After one year of GFD, the mean growth velocity increased from -2.3 SD to +3.7 SD. GH normalized in patients that had GH deficiency.	⨁◯◯◯ Very low[a,b]	Critical
Change in Height (assessed with: Height Z-score)									
1	non-randomized study	serious[a]	not serious	serious[c]	serious[b]	none	**Bosio et al (1990)** reported on 24 children with celiac disease, poor weight gain and retarded height velocity. 15 of them had GI symptoms, and the remaining had history of having symptoms previously. 23 patients (10 males and 13 females) were followed for 9 to 15 months. The mean height Z-score in the male patients went up from of -2.46 ± 0.96 (range -1.63 to -4.83) to -1.99 ± 0.78 (range -0.87 to -3.53), and in the female patients from -2.58 ± 0.64 range (-1.65 to -3.65) to -2.28 ± 0.70 (range -1.05 to -3.67). In 12 patients (4 males and 9 females) followed for three years, the mean height Z-score went up from -2.52 ± 0.67 (range -1.65 to -3.5) to -1.77 ± 0.61 (range -0.64 to -2.55).	⨁◯◯◯ Very low[a,b,c]	Critical

CI: confidence interval

Explanations

a. Duration of follow-up varied, and some of the studies had missing outcome data.

b. Small sample size overall.

c. Study included patients with symptomatic celiac disease.

Supplemental Table 15: PICO 5 Evidence-to-Decision Framework

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

PICO 6: Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease and type 1 diabetes mellitus?

Supplemental Table 16: PICO 6 Study Characteristics

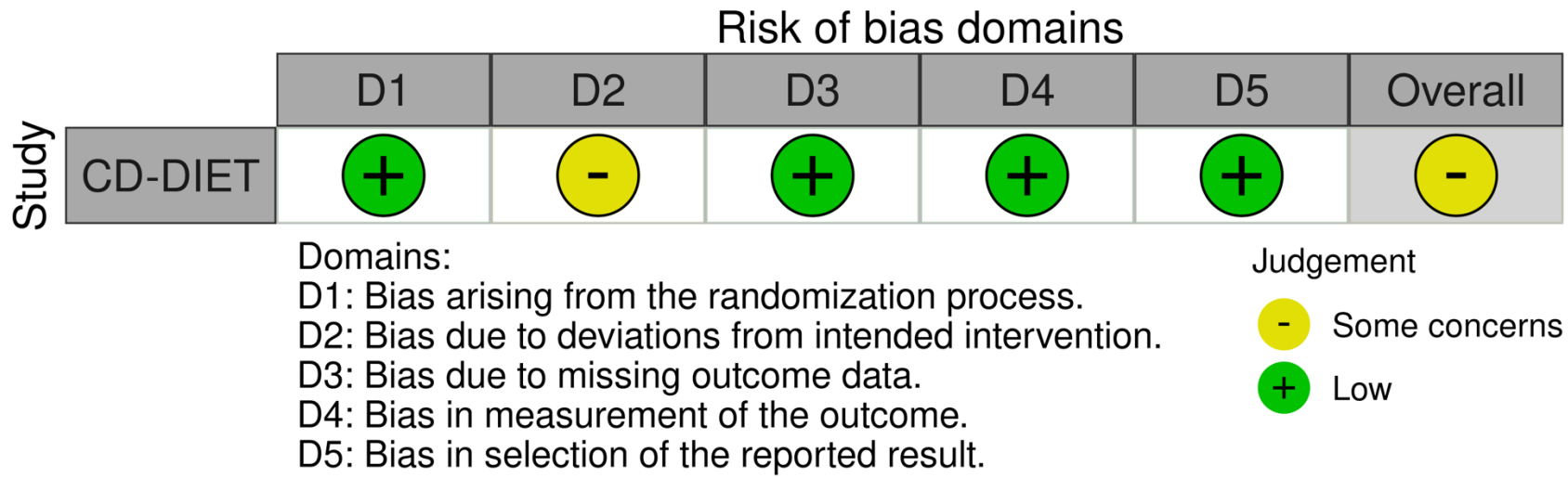
Study	Patient population	Baseline characteristics	Outcome(s)
CD-DIET (Mahmud 2020, Weiman 2021) [2, 3] RCT Canada Follow-up: 1 year Funding: JDRF Canadian Clinical Trial Network	**Inclusion**: 8-45 years with DM1 for at least 1 year; tTG-IgA positive (≥30 chemiluminescent units [CU]); duodenal biopsy confirmation (Marsh score ≥2); **Exclusion**: CD symptoms (gastrointestinal symptomatology or evidence of growth impairment, anemia, or osteoporosis); a previous CD diagnosis; on GFD; menopause; aphthous ulcers; dermatitis herpetiformis; and pregnancy. **Diagnosis of celiac disease**: TG IgA positive (≥30 chemiluminescent units [CU]); duodenal biopsy confirmation (Marsh score ≥2) **Definition of asymptomatic**: No gastrointestinal symptomatology or evidence of growth impairment, anemia, or osteoporosis **Age group(s)**: Adults and children **High risk group**: DM1 **Extra-intestinal manifestations**: None	**GFD group** (*n* randomized = 27) *Mean Age*: 27 ± 10.9 y *Sex*: 63% M vs 37% F *Comorbidities*: DM1 *Dietary adherence*: tTG-IgA became undetectable *Loss to follow-up*: 2 **GCD group** (*n* randomized = 24) *Mean Age*: 26.6 ± 11.3 y *Sex*: 45.8% M vs 54.2% F *Comorbidities*: DM1 *Dietary adherence*: tTG-IgA continued to be elevated *Loss to follow-up*: 2 **Method of implementing dietary instructions**: visits with a dietitian occurred every 3 months using a standardized educational curriculum	**Hemoglobin A1c** *n*: 27 vs 24 *Mean difference*: +0.14% (95% CI: -0.79 to 1.08; *p* = 0.76) at 12 months **Hypoglycemia** *Definition*: non-severe *n*: 27 vs 24 *Events:* 0 vs 3

	Other: NA	**Method to ascertain adherence to dietary instructions**: - dietary interviews and the assessment of 3-day food records and 24-hour recalls to quantify gluten intake - assessment of TTG-IgA titers at baseline, and at 6 and 12 months. - a 50% or greater decrease in their TTG-IgA from baseline were considered adherent and the vice versa.	
Rami 2005 [4] Pre-post study Multicenter (10 pediatric diabetic centers in their clinic cohort of diabetic children since 1995 (Kosice), 1996 (Vienna, Prague, Ljubiljana, Budapest), 1997 (Groningen), 1998 (Lisbon) and 2000 (Szedged, Pecs).	**Inclusion**: T1DBT and screen-detected CeD with EmA+ and biopsy positive **Exclusion**: data not provided **Diagnosis of celiac disease**: EmA+ in 2 occasions (repeated after 3 months) and confirmed by duodenal biopsies (performed only if EmA was positive) **Definition of asymptomatic**: "silent CeD"; definition not provided **Age group(s)**: pediatric (6.5 ± 4.1 yrs) **High risk group**: T1DBT **Extra-intestinal manifestations**:	**GFD definition**: Patients who became EMA-negative on GFD and remained EMA-negative during the study period were thought to be compliant to GFD (compliance category 1) and patients who refused to maintain GFD or did not become EMA-negative on the suggested GFD were considered as noncompliant (compliance category 2). **CeD =** 74/98 **GFD** (*n* =33) *Age*: not provided *Sex* Girls=19/33	**<u>Hemoglobin A1c</u>** At DM diagnosis: 8.8 ± 1.3 At CeD diagnosis: 8.7 ± 0.9 At follow-up (mean 3 years): 8.8 ± 0.9

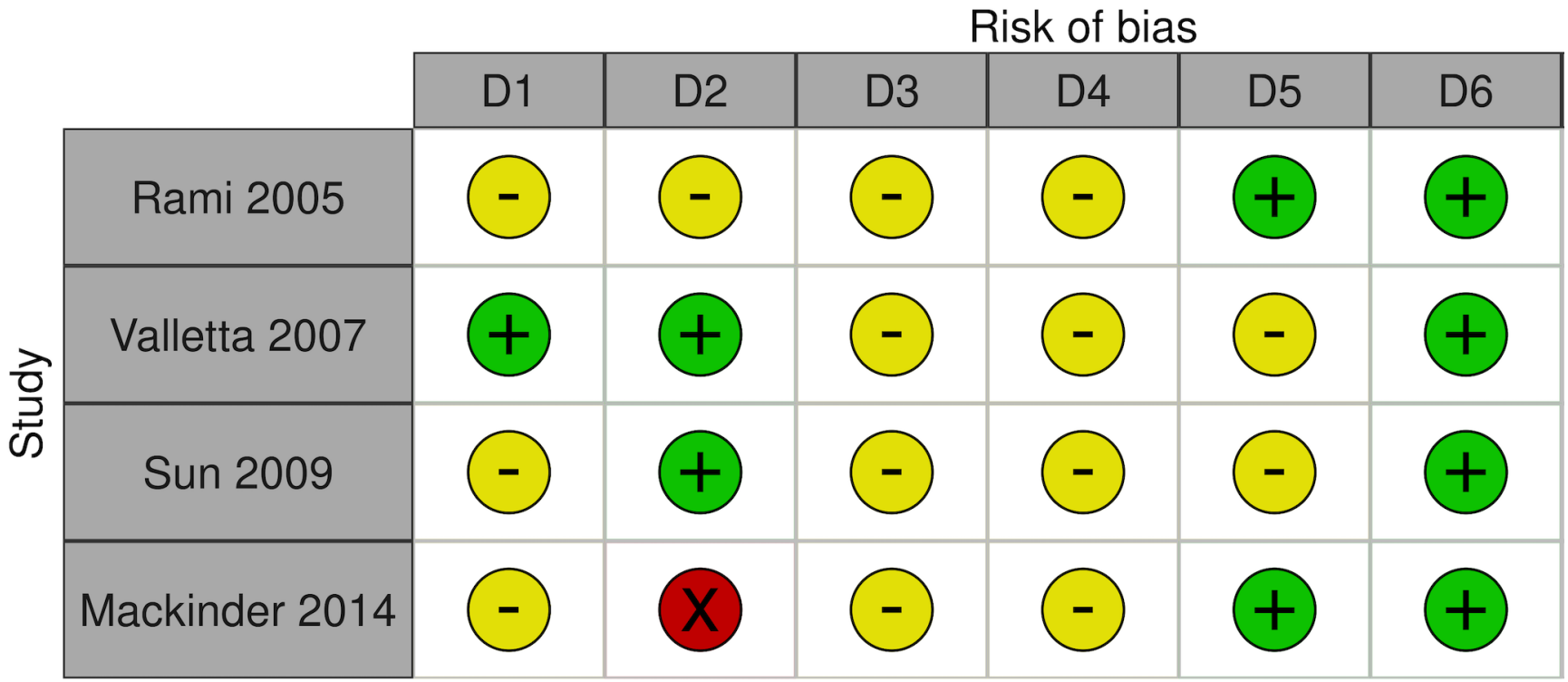
Follow-up: every 6 months for at least 1 yr (Mean observation period 3.3± 1.9 years) Funding: not reported	No	*Comorbidities*: not provided *Loss to follow-up*: not provided **GCD** (*n* = 25) *Age*: not provided *Sex*: Girls 19/25 *Comorbidities*: not provided *Loss to follow-up*: not provided **Method of implementing dietary instructions**: not provided **Method to ascertain adherence to dietary instructions**: not provided	
Valletta 2007 [5] Pre-post study Verona, Italy Follow-up: 4 years Funding: Not reported	Inclusion: Patients with DM1 screened for CeD annually with AGA, EMA and tTG IgA/IgG. Histologic diagnosis confirmed. Exclusion: CeD diagnosed before DM. Incomplete records.	*n* = 23 Mean age at DM1 diagnosis: 8 ± 3.3 yr Mean time interval between DM1 and CeD diagnosis: 1.8 yr (range: 0.1- 23.9 yr)	**<u>Hemoglobin A1c</u>** At CeD diagnosis: 7.48 ± 8.5 At 2 years: 7.58 ± 8.62 At 4 years: 7.70 ± 8.73

Sun 2009 [6] Pre-post study Northwest England Follow-up: 2 years Funding: Diabetes UK	Inclusion: Children aged < 16 years with DM1 who had positive IgA EMA, anti-gliadin, and tTG on local routine annual screening. Endoscopic biopsies obtained from the jejunum. Exclusion: refused small bowel biopsy or GFD; positive antibodies while on GFD Symptoms: Asymptomatic	*n* = 49 Mean age at DM1 diagnosis: 5.9 ± 4.1 yr Mean age at CeD diagnosis: 9.1 ± 3.7 years Mean current age: 11.9 ± 3.5 years	**Hemoglobin A1c** Prior to CeD: 8.3 ± 1.1 At CeD diagnosis: 8.4 ± 1.3 After 1 year GFD: 8.9 ± 1.5 After 2 years GFD: 8.7 ± 1.4
Mackinder 2014[8] Pre-post study United Kingdom Follow-up: 2 years Funding: EU Charity Nutricia Research Foundation	Inclusion: Children with DM1, CD or dual diagnosis. Serologic screening with EMA and tTG IgA. Positive serologies underwent endoscopy. DM1 diagnosed at least 2 years prior to CD. No other chronic conditions. Anthropometric data available for 2 years before and after CD diagnosis.	*n* = 23 with dual diagnosis 52% female Mean age at DM1 diagnosis: 5.3 ± 3.4 years Mean age at CD diagnosis: 10.7 ± 2.8 years	**Hemoglobin A1c** At CeD diagnosis: 8.1 ± 1.1 After 2 years GFD: 8.5 ± 1.1

Supplemental Figure 23: PICO 6 Risk of Bias Assessment for RCTs



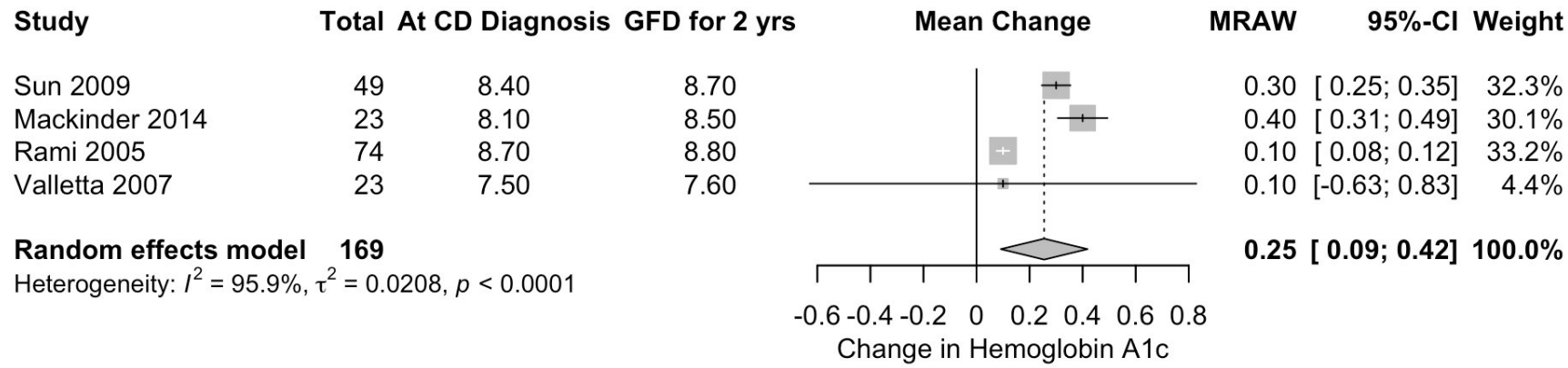
Supplemental Figure 24: PICO 6 Risk of Bias Assessment for Pre-post Studies



D1: Were all eligible participants that met the prespecified entry criteria enrolled?
D2: Was the intervention clearly described and delivered consistently across the study population?
D3: Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
D4: Were the people assessing the outcomes blinded to the participants' exposures/interventions?
D5: Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
D6: Was follow-up long enough for outcomes to occur?

Meta-analyses

Supplemental Figure 25: Hemoglobin A1c



Supplemental Table 17: PICO 6 Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**gluten-free diet**	**gluten-containing diet**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mirco- and Macrovascular complications												
No studies												Critical
Glycemic control (follow-up: 1 years; assessed with: Hemoglobin A1c)												
1	RCT	not serious[a]	not serious	not serious	very serious[b]	none	27	24	-	MD **0.14 % higher** (0.79 lower to 1.08 higher)	⨁⨁◯◯ Low[a,b]	Important
Glycemic control (follow-up: 2 years; assessed with: Hemoglobin A1c)												
4	Non-randomized studies	serious[c]	not serious	not serious	serious[d]	none	169	0	-	mean **0.25 % higher** (0.09 higher to 0.42 higher)	⨁◯◯◯ Very low[c,d]	Important

CI: confidence interval; **MD:** mean difference

Explanations

a. We did not rate down for lack of blinding as the outcome is unlikely to be affected by blinding.

b. Confidence interval includes both moderate benefits and moderate harms; based on FDA non-inferiority margin (MID) of 0.3%.

c. Rated down due to concerns regarding selection of included patients and uncertainty about adherence to the diet.

d. Confidence interval included no-to-trivial to small harm based on on MID of 0.3%.

Supplemental Table 18: PICO 6 Evidence-to-Decision Framework

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

PICO 7: Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease and autoimmune thyroid disease?

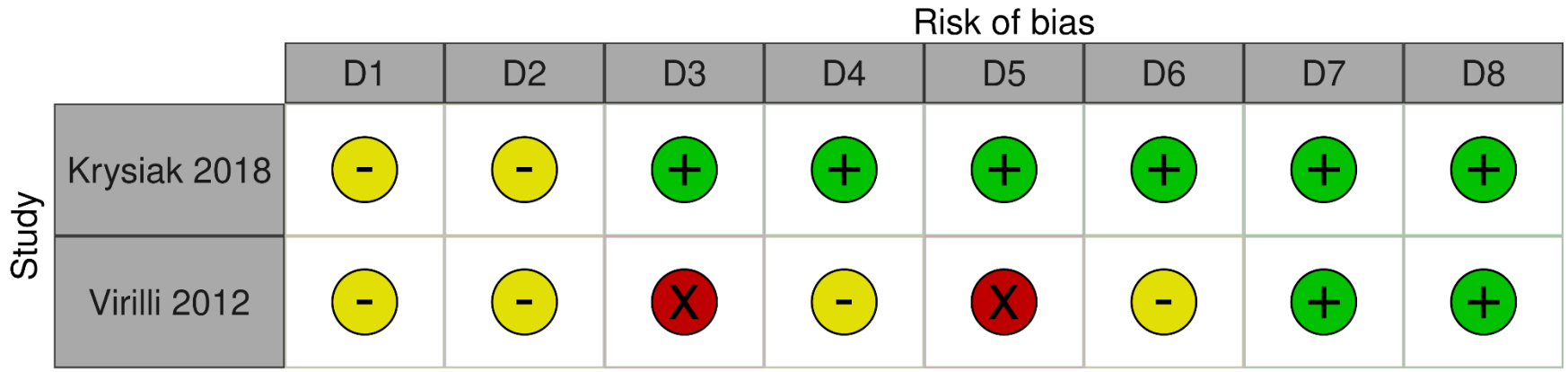
Supplemental Table 19: PICO 7 Study Characteristics

Study	Patient population	Baseline characteristics	Outcome(s)
Krysiak 2018[31] Comparative study Poland Follow-up: 6 months Funding: statutory grant of the Medical University of Silesia (KNW-1-062/N/7/0)	Women aged 20 – 45 with recently diagnosed and previously untreated autoimmune thyroiditis **Inclusion criteria** - positive TPOAb (>100U/mL), - reduced echogenicity of the thyroid parenchyma on thyroid ultrasonography - normal thyroid function (thyrotropin levels in the range between 0.4 and 4.5 mU/L, free thyroxine in the range between 10.0 and 21.0 pmol/L and free triiodothyronine in the range between 2.6 and 6.5pmol/L) - incidentally found positive anti-tissue transglutaminase antibodies without clinical symptoms of CeD	**GFD group** *n* = 16 Mean age: 30 ± 5 years 25% smokers Mean BMI: 22.9 ± 2.3 kg/m^2 **GCD group** *n* = 18 Mean age: 31 ± 6 years 22% smokers Mean BMI: 23.1 ± 2.1 kg/m^^{2} The diet choice was based on patient preference.	**Thyroid status** After 6 months, the GFD group demonstrated a reduction in TPO (-200 ± 105 U/mL) and thyroglobulin antibodies (-203 ± 120 U/mL), and an increase in SPINA-GT index (0.34 ± 0.12 pmol/s). There was no change in TSH or free thyroid hormones.
Virili 2012[32] Comparative study Italy Follow-up: variable (5–11 months)	**Inclusion (CeD + HT group):** Adults with Hashimoto's thyroiditis (HT) requiring levothyroxine (LT4) treatment in whom atypical CeD was suspected due to unexplained iron-deficiency anemia, short stature, or low/recent weight loss (per AGA criteria), confirmed by positive anti-tTG and/or anti-EMA antibodies and duodenal/jejunal biopsy (Marsh class II–IIIb)	**CeD + HT group:** n = 35 (31 female, 4 male) Median age: 39 years (IQR 33–50) Median weight: 60 kg (IQR 53.5–69.5) Median BMI: 22.5 kg/m² (IQR 19.7–24.8) TPOAb: 730 U/ml (IQR 288–1882)	LT4 dose to achieve target TSH: **Isolated HT (n=68):** Target TSH (median 1.02 mU/L; IQR 0.82–1.46) achieved in all patients Time to target: 5 ± 2 months Median LT4 dose: 1.31 µg/kg/day (IQR 1.22–1.42)

Funding: "Sapienza" University of Rome (University Grants prot.0006345)	**Comparator (isolated HT):** 68 patients with hypothyroid HT without evidence of CeD or other conditions interfering with LT4 absorption, comparable in age and sex **Exclusion:** Pregnancy; recent use of iodine-containing substances or drugs interfering with LT4 absorption; known CeD or other relevant GI disease; already on GFD	Subclinical hypothyroidism: n=21 (TSH median 7.26 mU/L) Overt hypothyroidism: n=14 (TSH median 21.15 mU/L) CD biopsy: mostly class II–IIIb **Isolated HT (comparator):** n = 68 (61 female, 7 male) Median age: 41 years (IQR 33–51) Median weight: 66 kg (IQR 60–77) Subclinical hypothyroidism: n=55 (TSH median 5.7 mU/L) Overt hypothyroidism: n=13 (TSH median 5.5 mU/L) Starting LT4 dose for all patients: ~1.3 µg/kg/day under fasting conditions (taken ≥1 h before eating)	**CeD + HT at similar dose (1.47 µg/kg/day; p=0.53 vs isolated HT):** Target TSH achieved in only 1 of 35 patients after 6 ± 2 months (Fisher's exact test p<0.0001) Median TSH at that timepoint: 4.20 mU/L (IQR 3.69–5.87) — significantly higher than isolated HT (p<0.0001) <u>Subgroup: GFD-compliant CeD patients (n=21):</u> Remained on same LT4 dose (median 1.32 µg/kg/day) Target TSH (median 1.25 mU/L; IQR 1.03–2.00) achieved after 11 ± 3 months of GFD No dose increase required <u>Subgroup: GFD non-compliant CeD patients (n=14):</u> LT4 dose increased by 25 µg after further hormone testing (median TSH 3.78 mU/L) Target TSH (median 1.54 mU/L; IQR 0.98–2.60) achieved after 4 additional months Median LT4 dose required: 1.96 µg/kg/day (+49% vs isolated HT; p=0.0002) Multivariate analysis: higher LT4 requirement did not correlate with age, BMI, baseline free T4, or TSH
Collins 2012[33]	**Cases:**	**Cases (CeD + hypothyroidism):**	<u>Levothyroxine dose to maintain euthyroid state</u>

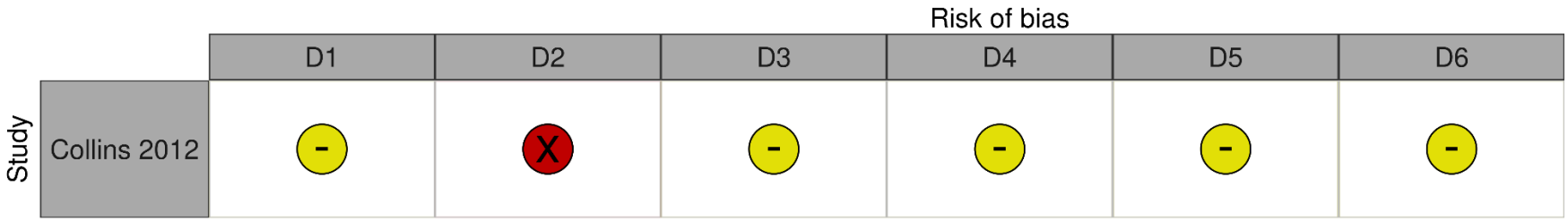
Pre-post study (Case control study) USA (University of Vermont / Fletcher Allen Health Care) Follow-up: variable (June 2000–June 2010) **Funding:** None	Patients with hypothyroidism diagnosed before (or at time of) CeD diagnosis. CeD defined as villous blunting or atrophy on biopsy plus positive tTG or EMA serology **Controls:** 200 patients with hypothyroidism alone, randomly selected from the endocrinology clinic (June 2005–June 2010). ICD-9 codes: 244.9 (unspecified hypothyroidism) and 245.2 (chronic lymphocytic thyroiditis / Hashimoto disease) **Exclusion:** Prior surgical resection of the upper intestinal tract	n = 7 (met inclusion criteria out of 22 identified) Mean age: 56 ± 20 years 71% female Mean weight: 139 ± 30 pounds (significantly lower than controls, p=0.04) Mean TSH: 2.3 ± 2.2 mU/mL All required ≥125 µg total LT4 and ≥1.5 µg/kg pre-GFD **Controls (hypothyroidism alone):** n = 200 Mean age: 51 ± 15 years 82% female Mean weight: 178 ± 50 pounds Mean TSH: 1.9 ± 1.4 mU/mL No significant difference between groups in age, sex, TSH, or creatinine	**Pre-GFD (cases) vs. controls:** Total dose: 154 ± 65 µg vs 106 ± 46 µg (p=0.007; 95% CI 13–83 µg) Weight-based dose: 2.6 ± 1.3 µg/kg vs 1.3 ± 0.5 µg/kg (p<0.001; 95% CI 0.9–1.7 µg/kg) All 7 cases required ≥125 µg total and ≥1.5 µg/kg to maintain euthyroid state pre-GFD (31% of controls required ≥125 µg; 40% of controls required ≥1.5 µg/kg) **Post-GFD (cases, n=6 with available data):** A reduction in LT4 dose was required in all 6 cases after dietary treatment Total dose: decreased from 154 µg to 111 µg (p=0.03; 95% CI 6.8–88.9 µg) Weight-based dose: decreased from 2.64 µg/kg to 1.89 µg/kg (p=0.04; 95% CI 0.5–1.5 µg/kg) **Post-GFD cases vs. controls:** Total dose: 111 µg vs 106 µg — not significantly different (p=0.79) Weight-based dose: 1.9 µg/kg vs 1.3 µg/kg — remained significantly higher than controls (p=0.01; 95% CI 0.1–0.9 µg/kg) Dietary compliance assessed indirectly via post-therapy serology (5 patients — normalization in 4, significant decrease in 1) and direct patient contact (1 patient)

Supplemental Figure 26: PICO 7 Risk of Bias Assessment for Comparative Cohort Studies



D1: Representativeness of the exposed cohort
D2: Selection of the non-exposed cohort
D3: Ascertainment of exposure
D4: Demonstration that outcome of interest was not present at start of study
D5: Comparability of cohorts on the basis of the design or analysis
D6: Assessment of outcome
D7: Follow-up long enough for outcomes to occur
D8: Adequacy of Follow-up of cohorts

Supplemental Figure 27: PICO 7 Risk of Bias Assessment for Pre-post Studies



D1: Were all eligible participants that met the prespecified entry criteria enrolled?
D2: Was the intervention clearly described and delivered consistently across the study population?
D3: Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
D4: Were the people assessing the outcomes blinded to the participants exposures/interventions?
D5: Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
D6: Was Follow-Up Long Enough for Outcomes to Occur

Supplemental Table 20: PICO 7 Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**gluten-free diet**	**gluten-containing diet**	**Relative (95% CI)**	**Absolute (95% CI)**		
Achieving euthyroid status												
3	non-randomized study	serious[a]	not serious	serious[b]	very serious[c]	none	Krysiak et al reported on 34 patients with untreated autoimmune thryoiditis with positive TPO antibodies, reduced thyroid parenchymal echogenicity, normal thyroid function, and incidentally-found positive tTG antibodies. 16 received GFD and 18 continued regular diet. After 6 months, GFD was associated with reduction in TPO and thyroglobulin antibodies, and an increase in SPINA-GT index. There was no change in TSH or free thyroid hormones. Virili et al reported that the target serum TSH was reached after treatment with mean dose of levothyroxine of 1.31 µg/kg/day for 5 months in all patients with isolated hypothyroidism while a comparable mean dose of 1.47 µg/kg/day for 6 months led at achieving target TSH in only one out of 35 patients with CeD and hypothyroidism. Those who were compliant with a GFD (n = 21) achieved target TSH on a comparable dose of levothyroxine (mean 1.32 µg/kg/day) within 11 months of starting the diet. However, those who were noncompliant with a GFD (n =14) required a higher dose of levothyroxine (mean 1.96 µg/kg/day) to achieve target TSH which they achieved within 4 months of increasing the dose. Collins et al reported that those with concomitant untreated CeD (n = 7) required a mean dose 2.6 µg/kg/day to achieve euthyroid status, compared to 1.3 µg/kg/day for those with isolated hypothyroidism. After starting a GFD, the mean dose required to achieve euthyroid status for those with concomitant CeD decreased to 1.9 µg/kg/day				⨁◯◯◯ Very low[a,b,c]	CRITICAL

CI: confidence interval

Explanations

a. Unclear how patients were assigned to each treatment group.

b. For Krysiak et al, [atient did not have dysregulated thyroid functions at baseline to allow assessment of clinical impact of the diet. Also, patients were diagnosed with celiac disease based on positive antibodies with unknown levels with no biopsies done. For Virilli et al and Collins et al, the studies included anyone with CeD and not necessarily asymptomatic. Also, no reporting of impact on symptoms.

c. Very small sample sizes.

Supplemental Table 21: PICO 7 Evidence-to-Decision Framework

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	**Small**	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

PICO 8: Should gluten-free diet vs. gluten-containing diet be used for individuals with Down syndrome and asymptomatic celiac disease?

Supplemental Table 22: PICO 8 Evidence Profile

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Quality of life - not reported									
-	-	-	-	-	-	-		-	CRITICAL
Behavioral changes - not reported									
-	-	-	-	-	-	-		-	CRITICAL

CI: confidence interval

Supplemental Table 23. Conflict of Interest Disclosures

Name	Conflict of interest
David A. Leiman, MD, MS	None
Maria Ines Pinto-Sanchez, MD, MS	Provention Bio, research funding; Taked, research funding; Celiac Disease Foundation, travel grant
Marisa G. Stahl, MD, MS	Celiac Disease Foundation, research grang; Takeda, consulting
Ritu Verma, MD	None
Madeline R. Siedler, PhD	None
Joshua E. Rubin, MD	None
Benjamin Lebwohl, MD, MS	None
Osama Altayar, MD, MS	None

Supplemental Table 24. Guideline Panel Members

Name	Role	Institution
David A. Leiman, MD, MS	Clinical Co-Chair	Division of Gastroenterology and Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA
Maria Ines Pinto-Sanchez, MD, MS	Junior Methodologist	Department of Medicine, Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, ON, Canada
Marisa G. Stahl, MD, MS	Clinical Expert	Department of Pediatrics, Colorado Center for Celiac Disease, Digestive Health Institute, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA
Ritu Verma, MD	Clinical Expert	Department of Pediatrics, University Of Chicago Celiac Disease Center, Comer Children's Hospital, Chicago, IL, USA
Madeline R. Siedler, PhD	Trainee Methodologist	College of Saint Benedict and Saint John's University, Saint John, MN, USA
Joshua E. Rubin, MD	Clinical Expert	Division of Gastroenterology, University of California San Diego School of Medicine, La Jolla
Benjamin Lebwohl, MD, MS	Clinical Expert	Celiac Disease Center, College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, NY, USA;
Osama Altayar, MD, MS	Methodology Co-Chair	Division of Gastroenterology, Washington University School of Medicine, St. Louis, Missouri, USA

Supplemental Table 25. PICO Questions

Informal Question	Population	Intervention	Comparison	Outcomes	Study Designs
1. Should a gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease?	Individuals with asymptomatic celiac disease	Gluten-free diet (GFD)	Gluten-containing diet	Quality of life Symptoms Nutritional status Anthropometrics and growth Glycemic control Bone disease-related fracture Bone mineral density Malignancy Mortality	RCTs Non-randomized studies
2. Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease with unexplained iron deficiency?	Individuals with asymptomatic celiac disease and unexplained iron deficiency	Gluten-free diet (GFD)	Gluten-containing diet	Resolution of anemia Resolution of iron deficiency	RCTs Non-randomized studies

3. Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease with metabolic bone disease?	Individuals with asymptomatic celiac disease and metabolic bone disease	Gluten-free diet (GFD)	Gluten-containing diet	Bone disease-related fracture Bone mineral density	RCTs Non-randomized studies
4. Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease with abnormal liver function tests (LFTs)?	Individuals with asymptomatic celiac disease and abnormal LFTs	Gluten-free diet (GFD)	Gluten-containing diet	Normalization of LFTs	RCTs Non-randomized studies
5. Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease with short stature?	Individuals with asymptomatic celiac disease and short stature	Gluten-free diet (GFD)	Gluten-containing diet	Adult height Growth velocity Change in height assessed with Z-score	RCTs Non-randomized studies

6. Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease with type 1 diabetes (T1D)?	Individuals with asymptomatic celiac disease and T1D	Gluten-free diet (GFD)	Gluten-containing diet	Glycemic control assessed with hemoglobin A1c	RCTs Non-randomized studies
7. Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease and autoimmune thyroid disease?	Individuals with asymptomatic celiac disease and autoimmune thyroid disease	Gluten-free diet (GFD)	Gluten-containing diet	Achievement of euthyroid status	RCTs Non-randomized studies
8. Should gluten-free diet vs. gluten-containing diet be used for individuals with asymptomatic celiac disease and Down syndrome?	Individuals with asymptomatic celiac disease and Down syndrome	Gluten-free diet (GFD)	Gluten-containing diet	Quality of life Behavioral changes	RCTs Non-randomized studies

Supplemental Table 26. Search Strategy

Database	Search strategy
Medline via Ovid	1. exp Celiac Disease/ 2. (((celiac or coeliac) adj2 disease) or (gluten adj2 enteropath*) or ((nontropical or endemic) adj2 sprue)).ti,ab,kw. 3. 1 or 2 4. exp Asymptomatic Diseases/ 5. (asymptomatic or presymptomatic or "pre-symptomatic" or silent or atypical or non-traditional or nontraditional).ti,ab,kw. 6. 4 or 5 7. 3 and 6 8. review.pt. 9. (medline or medlars or embase or pubmed or cochrane or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or (hand adj2 search$) or (manual$ adj2 search$) or "electronic database$" or "bibliographic database$" or "computeri?ed database$" or "online database$ pooling" or pooled or "mantel haenszel" or peto or dersimonian or "der simonian" or "fixed effect").tw,sh. 10. 8 and 9 11. ("Meta-Analysis" or "Systematic Review").pt. 12. (meta-analys$ or "meta analys$" or metaanalys$ or ((systematic$ or quantitativ* or methodologic*) adj5 (review$ or overview$ or synthes?s))).tw,sh. 13. (integrative research review$ or research integration).tw. 14. or/10-13 15. 7 and 14 16. exp randomized controlled trial/ 17. controlled clinical trial.pt. 18. (randomi#ed or placebo or randomly or trial or groups).ab. 19. drug therapy.fs. 20. or/16-19 21. 7 and 20 22. exp cohort studies/ 23. cohort$.tw. 24. controlled clinical trial.pt.

	25. epidemiologic methods/ 26. limit 25 to yr=1966-1989 27. exp case control studies/ 28. (case$ and control$).tw. 29. or/22-24,26-28 30. 7 and 29 31. 15 or 21 or 30 32. exp Animals/ not humans.sh. 33. 31 not 32 34. ("Case Reports" or Editorial or "Retracted Publication" or "Retraction of Publication").pt. 35. 33 not 34 36. remove duplicates from 35
Embase	1. exp celiac disease/ 2. (((celiac or coeliac) adj2 disease) or (gluten adj2 enteropath*) or ((nontropical or endemic) adj2 sprue)).ti,ab,kw 3. 1 or 2 4. exp asymptomatic disease/ 5. (asymptomatic or presymptomatic or "pre-symptomatic" or silent or atypical or non-traditional or nontraditional).ti,ab,kw. 6. 4 or 5 7. 3 and 6 8. exp review/ or (literature adj3 review$).ti,ab. 9. (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab. 10. 8 and 9 11. exp meta analysis/ or exp "Systematic Review"/ 12. (systematic$ adj2 (review$ or overview)).ti,ab. 13. (meta?anal$ or “meta anal$” or meta-anal$ or metaanal$ or metanal$).ti,ab. 14. OR/10-13 15. 7 and 14 16. exp randomized controlled trial/ or controlled clinical trial/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/

	17. (random$ or placebo or compare or compared or comparison or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or crossover or "cross over" or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)) or assigned or allocated or (controlled adj7 (study or design or trial)) or volunteer or volunteers).ti,ab. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. or trial.ti. 18. ((random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)) or (cross-sectional study/ not (exp randomized controlled trial/ or controlled clinical trial/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)) or (((case adj control$) and random$) not "randomi#ed controlled").ti,ab. or ("systematic review".ti,ab. not (trial or study).ti.) or (non random$ not random$).ti,ab. or "random field$".ti,ab. or ("random cluster" adj3 sample$).ti,ab. or ((review.ab. and review.pt.) not trial.ti.) or ("we searched".ab. and (review.ti. or review.pt.)) or ("update review" or (databases adj4 searched)).ab. 19. (16 or 17) not 18 20. 7 and 19 21. exp cohort analysis/ or exp longitudinal study/ or exp prospective study/ or exp follow up/ or cohort$.tw. or exp case control study/ or (case$ and control$).tw. 22. 7 and 21 23. 15 or 20 or 22 24. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ 25. animal experiment/ not (human experiment/ or human/) 26. 24 or 25 27. 23 not 26 28. "Case Report".ti,ab. or "Case Description".ab or "Editorial".pt. or "Retracted Publication".pt. or "Retraction of Publication".pt. 29. 27 not 28 30. remove duplicates from 29
Cochrane Library	1. MeSH descriptor: [Celiac Disease] explode all trees 2. ((((celiac OR coeliac) NEAR/2 disease) OR (gluten NEAR/2 enteropath*) OR ((nontropical OR endemic) NEAR/2 sprue))):ti,ab,kw 3. #1 OR #2

	4. MeSH descriptor: [Asymptomatic Diseases] explode all trees 5. (asymptomatic OR presymptomatic OR "pre-symptomatic" OR silent OR atypical OR non-traditional OR nontraditional):ti,ab,kw 6. #4 OR #5 7. #3 AND #6 8. MeSH descriptor: [Animals] explode all trees 9. MeSH descriptor: [Humans] explode all trees 10. #8 NOT #9 11. #7 NOT #10
Scopus	(INDEXTERMS("Celiac Disease") OR TITLE-ABS-KEY(((celiac or coeliac) W/2 disease) or (gluten W/2 enteropath*) or ((nontropical or endemic) W/2 sprue))) AND (INDEXTERMS("Asymptomatic Disease") OR TITLE-ABS-KEY(asymptomatic or presymptomatic or "pre-symptomatic" or silent or atypical or non-traditional or nontraditional)) AND ((DOCTYPE("Re") AND TITLE-ABS-KEY(medline or medlars or embase or pubmed or cochrane or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or (hand W/2 search*) or (manual* W/2 search*) or "electronic database*" or "bibliographic database*" or "computerized database*" or "online database* pooling" or pooled or "mantel haenszel" or peto or dersimonian or "der simonian" or "fixed effect")) OR TITLE-ABS-KEY(meta-analys* or "meta analys*" or metaanalys* or ((systematic* or quantitativ* or methodologic*) W/5 (review* or overview* or synthes*))) OR TITLE-ABS-KEY("integrative research review*" or "research integration") OR TITLE-ABS-KEY(randomized OR randomised OR randomly OR trial OR groups) OR INDEXTERMS("Randomized Controlled Trial" OR "Randomization" OR "Intermethod Comparison" OR "Double Blind Procedure" OR "Human Experiment") OR TITLE-ABS-KEY(cohort* OR (case* AND control*)) OR INDEXTERMS("Cohort Stuides" OR "Controlled Clinical Trial" OR "Case Control Studies" OR "Longitudinal Study" OR "Cohort Analysis" OR "Prospective Study" OR "Follow Up")) AND NOT (INDEXTERMS("Animals") AND NOT INDEXTERMS("Humans")) AND NOT (DOCTYPE("Ed") OR DOCTYPE("Er") OR DOCTYPE("Tb"))
Web of Science	1. TS=(((celiac or coeliac) NEAR/2 disease) or (gluten NEAR/2 enteropath*) or ((nontropical or endemic) NEAR/2 sprue)) 2. TS=(asymptomatic or presymptomatic or "pre-symptomatic" or silent or atypical or non-traditional or nontraditional) 3. #1 AND #2 4. TS=("integrative research review*" OR "research integration" OR meta-analys* or "meta analys*" or metaanalys* or ((systematic* or quantitativ* or methodologic*) NEAR/5 (review* or overview* or synthes*)))

	5. TS=(randomised OR randomized OR randomisation OR randomization OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple))) 6. TS=(cohort* OR (case* AND control*)) 7. #4 OR #5 OR #6 8. #3 AND #7 9. #8 NOT DT=(Editorial Material OR Retracted Publication OR Retraction) 10. #9 NOT TI=("Case Report") 11. #10 NOT AB=("Case Description") 12. #11 NOT TS=(animal or animals or pisces or fish or fishes or catfish or catfishes or sheatfish or silurus or arius or heteropneustes or clarias or gariepinus or fathead minnow or fathead minnows or pimephales or promelas or cichlidae or trout or trouts or char or chars or salvelinus or salmo or oncorhynchus or guppy or guppies or millionfish or poecilia or goldfish or goldfishes or carassius or auratus or mullet or mullets or mugil or curema or shark or sharks or cod or cods or gadus or morhua or carp or carps or cyprinus or carpio or killifish or eel or eels or anguilla or zander or sander or lucioperca or stizostedion or turbot or turbots or psetta or flatfish or flatfishes or plaice or pleuronectes or platessa or tilapia or tilapias or oreochromis or sarotherodon or common sole or dover sole or solea or zebrafish or zebrafishes or danio or rerio or seabass or dicentrarchus or labrax or morone or lamprey or lampreys or petromyzon or pumpkinseed or pumpkinseeds or lepomis or gibbosus or herring or clupea or harengus or amphibia or amphibian or amphibians or anura or salientia or frog or frogs or rana or toad or toads or bufo or xenopus or laevis or bombina or epidalea or calamita or salamander or salamanders or newt or newts or triturus or reptilia or reptile or reptiles or bearded dragon or pogona or vitticeps or iguana or iguanas or lizard or lizards or anguis fragilis or turtle or turtles or snakes or snake or aves or bird or birds or quail or quails or coturnix or bobwhite or colinus or virginianus or poultry or poultries or fowl or fowls or chicken or chickens or gallus or zebra finch or taeniopygia or guttata or canary or canaries or serinus or canaria or parakeet or parakeets or grasskeet or parrot or parrots or psittacine or psittacines or shelduck or tadorna or goose or geese or branta or leucopsis or woodlark or lullula or flycatcher or ficedula or hypoleuca or dove or doves or geopelia or cuneata or duck or ducks or greylag or graylag or anser or harrier or circus pygargus or red knot or great knot or calidris or canutus or godwit or limosa or lapponica or meleagris or gallopavo or jackdaw or corvus or monedula or ruff or philomachus or pugnax or lapwing or peewit or plover or vanellus or swan or cygnus or columbianus or bewickii or gull or chroicocephalus or ridibundus or albifrons or great tit or parus or aythya or fuligula or streptopelia or risoria or spoonbill or platalea or leucorodia or blackbird or turdus or merula or blue tit or cyanistes or pigeon or pigeons or columba or pintail or anas or starling or sturnus or owl or athene noctua or pochard or ferina or cockatiel or nymphicus or hollandicus or skylark or alauda or tern or sterna or teal or crecca or oystercatcher or haematopus or ostralegus or shrew or shrews or sorex or araneus or crocidura or russula or european mole or talpa or chiroptera or bat or bats or

	eptesicus or serotinus or myotis or dasycneme or daubentonii or pipistrelle or pipistrellus or cat or cats or felis or catus or feline or dog or dogs or canis or canine or canines or otter or otters or lutra or badger or badgers or meles or fitchew or fitch or foumart or foulmart or ferrets or ferret or polecat or polecats or mustela or putorius or weasel or weasels or fox or foxes or vulpes or common seal or phoca or vitulina or grey seal or halichoerus or horse or horses or equus or equine or equidae or donkey or donkeys or mule or mules or pig or pigs or swine or swines or hog or hogs or boar or boars or porcine or piglet or piglets or sus or scrofa or llama or llamas or lama or glama or deer or deers or cervus or elaphus or cow or cows or bos taurus or bos indicus or bovine or bull or bulls or cattle or bison or bisons or sheep or sheeps or ovis aries or ovine or lamb or lambs or mouflon or mouflons or goat or goats or capra or caprine or chamois or rupicapra or leporidae or lagomorpha or lagomorph or rabbit or rabbits or oryctolagus or cuniculus or laprine or hares or lepus or rodentia or rodent or rodents or murinae or mouse or mice or mus or musculus or murine or woodmouse or apodemus or rat or rats or rattus or norvegicus or guinea pig or guinea pigs or cavia or porcellus or hamster or hamsters or mesocricetus or cricetulus or cricetus or gerbil or gerbils or jird or jirds or meriones or unguiculatus or jerboa or jerboas or jaculus or chinchilla or chinchillas or beaver or beavers or castor fiber or castor canadensis or sciuridae or squirrel or squirrels or sciurus or chipmunk or chipmunks or marmot or marmots or marmota or suslik or susliks or spermophilus or cynomys or cottonrat or cottonrats or sigmodon or vole or voles or microtus or myodes or glareolus or primate or primates or prosimian or prosimians or lemur or lemurs or lemuridae or loris or bush baby or bush babies or bushbaby or bushbabies or galago or galagos or anthropoidea or anthropoids or simian or simians or monkey or monkeys or marmoset or marmosets or callithrix or cebuella or tamarin or tamarins or saguinus or leontopithecus or squirrel monkey or squirrel monkeys or saimiri or night monkey or night monkeys or owl monkey or owl monkeys or douroucoulis or aotus or spider monkey or spider monkeys or ateles or baboon or baboons or papio or rhesus monkey or macaque or macaca or mulatta or cynomolgus or fascicularis or green monkey or green monkeys or chlorocebus or vervet or vervets or pygerythrus or hominoidea or ape or apes or hylobatidae or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or hominidae or orangutan or orangutans or pongo or chimpanzee or chimpanzees or pan troglodytes or bonobo or bonobos or pan paniscus or gorilla or gorillas or troglodytes)
Health Disparities and Minority Health Search using Pubmed	1. ("health status disparities"[MeSH Terms] OR "health disparities"[All Fields] OR "healthcare disparities"[MeSH Terms] OR "healthcare disparities"[All Fields] OR "health inequality"[All Fields] OR "health inequities"[All Fields] OR "health inequity"[All Fields] OR "health inequalities"[All Fields] OR "health status inequality"[All Fields] OR "minority health"[MeSH Terms] OR "minority health"[All Fields] OR "vulnerable populations"[MeSH Terms] OR "vulnerable populations"[All Fields] OR "health services accessibility"[MeSH Terms] OR "health services accessibility"[All Fields] OR "underserved"[All Fields] OR "rural health"[MeSH Terms] OR "urban

	health"[MeSH Terms] OR "social determinants of health"[MeSH Terms] OR "social determinants of health"[All Fields]) 2. "Celiac Disease"[MeSH Terms] OR ("Celiac Disease"[Title/Abstract] OR "coeliac disease"[Title/Abstract] OR ("gluten"[Title/Abstract] AND "enteropathy*"[Title/Abstract]) OR "nontropical sprue"[Title/Abstract] OR "endemic sprue"[Title/Abstract]) 3. #1 and #2

Supplemental Figure 28. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram

Step	N of records	Qualify	Outcomes
Step 1- RCT asymptomatic GFD vs no GFD for all outcomes	1616	5	GI symptoms =1 QoL=2 BMD=1 BMI=2 Body comp=1 Nutrients=2 Diabetes=1 Height/wt=1 HbA1c=1 Glycemia=1 Mortality=0 Cancer=0
Step 2- Umbrella review for most relevant outcomes (growth, diabetes, bones, mortality, lymphoma, QoL) in asymptomatic any design	970 (May)	14 studies from 4 SR (3 may be excluded) 6 individual studies	DBT=9 Glycemic=7 Mortality=0 Bones=5 AdenoCa=0 Lymphoma=0 QoL=8 Growth=7 Down =0

Step 3- Umbrella for mortality and cancer in any celiac – individual studies	537	25 studies from 6 SR Treated vs untreated=3 Celiac vs GP or other population= 24	Mortality=2 AdenoCa=0 Lymphoma=0 Mortality =16 AdenoCa=5 Lymphoma=9

Supplemental Table 27. Interpretation of the Certainty in Evidence (CoE) of Effects Using the GRADE Framework

CoE	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

Supplemental Table 28. Interpretation of Strong and Conditional Recommendations Using the GRADE Framework

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared-decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations	Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.
* Strong recommendations are indicated by statements that lead with “we recommend”, while conditional recommendations are indicated by statements that lead with “we suggest”		

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