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Gluten Restriction and Dietary Replacement in Adults without Gluten Related Disorders

—A Critical Narrative Review

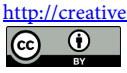
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Abstract

Objectives: To distinguish gluten-specific effects from dietary replacement effects in adults without gluten-related disorders. Background: Gluten restriction changes cereal sources, fermentable substrates, fortification, and processing, complicating interpretation of biological and clinical findings. Methods: This critical narrative synthesis expanded an initial reference set through targeted searches updated on 15 October 2026. Retrieved records, article text, and tables informed interpretation. Adult interventions, higher-risk populations, mixed-age context, cohorts, and product surveys were distinguished. Full-text access was incomplete for two reports (Campagna and Henriques), which were appraised from indexed abstracts and, where available, secondary extraction. No meta-analysis or formal certainty grading was performed. Results: Interventions show selected microbial changes without consistent clinical consequences. Product surveys frequently identify lower protein or micronutrient content, with category-specific exceptions. A randomized oat-versus-rice low-gluten trial demonstrates replacement-related differences without isolating gluten removal. Inflammatory, weight, and well-being findings remain mixed or imprecise. Cohorts do not establish cardiovascular benefit from restriction. Microbial and compositional differences alone do not establish disease risk. Conclusion: Evidence does not support routine restriction for general health improvement without a medical indication or establish universal harm from a nutritionally adequate gluten-free diet. Future trials should distinguish gluten from food substitution and connect mechanistic endpoints with clinical outcomes.

Keywords

Gluten-Free Diet, Low-Gluten Diet, Dietary Replacement, Gut Microbiome, Diet Quality, Cardiometabolic Health

1. Introduction

Gluten is a collective term for storage proteins in wheat, barley, and rye. Wheat gluten includes gliadins and glutenins, while related proteins include hordeins in barley and secalins in rye [1]. A gluten-free diet is an established treatment for celiac disease, where dietary advice serves a disease-specific therapeutic purpose [2]. This clinical setting differs from elective avoidance by people without a diagnosed gluten-related disorder.

Public discussion often treats gluten absence as a marker of nutritional quality. Reviews have questioned this assumption, identifying possible nutritional disadvantages and uncertainty concerning benefits outside medical indications [3]. Yet reversing the assumption is equally problematic. A gluten-free label does not establish either health benefit or harm. The relevant comparison is between defined dietary patterns, including the foods removed, the foods introduced, and the resulting nutrient intake.

Three evidence streams are often brought together without sufficient separation. Microbiome experiments measure microbial responses over weeks. Food surveys compare products rather than diets or individuals. Cohort studies relate estimated habitual gluten intake to later disease. Their conclusions concern different exposures and outcomes. A microbial change, a label-based nutrient difference, and a clinical event cannot be treated as interchangeable evidence of the same causal effect.

This review therefore asks whether gluten restriction itself, or the dietary changes accompanying it, best explains the available findings in adults without gluten-related disorders. Its contribution is an explicit distinction between gluten exposure, food substitution, intermediate biological measures, and health outcomes. It integrates selected evidence on the gut microbiome, packaged-food composition, inflammatory and metabolic measures, body weight, cardiovascular outcomes, and trace-element exposure, while maintaining the boundary between healthy populations and disease-specific evidence.

2. Methods

2.1. Scope and Evidence Identification

This critical narrative review examines whether studies distinguish gluten-specific effects from the consequences of food substitution. The initial 16-reference set was the working scoping corpus available at the start of the review rather than the product of a formal systematic search. It comprised core background sources and previously identified studies addressing gluten-free or low-gluten diets, healthy or

non-celiac populations, microbiome outcomes, nutritional composition, and cardiometabolic questions. This corpus was then expanded through targeted searches updated on 15 October 2026 using web-based retrieval of PubMed-indexed records, publisher-hosted articles, and accessible full-text material. Searches combined gluten-free or low-gluten diets with healthy adults, randomized trials, microbiome, cardiovascular outcomes, inflammatory biomarkers, nutritional composition, and trace elements. Searches for 2024-2026 publications updated the evidence. Selected executed search strings appear in **Supplementary material S1**. The approach was selective, rather than an exhaustive search of multiple bibliographic databases.

Priority was given to original human interventions in adults without known gluten-related disorders and to prospective cohorts without known celiac disease. Selection required relevance to the review question, an identifiable dietary exposure or comparator, and interpretable human outcomes; higher cardiometabolic risk was distinguished from absence of disease or symptoms. Mixed-age cohorts, disease-population reviews, and product surveys were retained only as explicitly indirect context. Systematic reviews contextualized primary reports rather than being counted as independent replications. Disease-specific treatment studies, isolated recipe-development studies, and retracted intervention evidence did not support conclusions about healthy adults. Reports sharing a trial registration or cohort were linked to avoid duplicate counting. Ascertainment of gluten-related disorders varied across the included interventions. Most reports defined eligibility through absence of known or diagnosed celiac disease or gluten-related disorders, clinical history, self-report, or study-specific exclusion criteria rather than uniform diagnostic screening with celiac serology and/or biopsy. Accordingly, this review refers to adults without known gluten-related disorders and does not assume that every participant had diagnostically confirmed absence of such disorders.

2.2. Extraction and Interpretation

The synthesis recorded population, diet definition, duration, comparator, sample size, principal outcomes, and design limitations. Numerical results were checked against retrieved article text, tables, or indexed abstracts. Inaccessible full texts were not treated as fully assessed reports. For Campagna and Henriques, interpretation remained limited to the indexed abstract and, for Campagna, the trial extraction in the Cochrane review. Detailed estimates unsupported by retrieved material were omitted. This access limitation is part of the review's appraisal.

ChatGPT (OpenAI) assisted targeted source retrieval, synthesis drafting, and language editing. Numerical statements were checked against retrieved sources. This assistance did not provide independent human duplicate screening or constitute formal risk-of-bias assessment.

Evidence was organized by the question each design answers. Randomized dietary comparisons address an assigned dietary strategy. Uncontrolled before-after

studies establish temporal changes but do not isolate intervention effects. Habitual-intake cohorts provide associations rather than tests of adopting a strict gluten-free diet. Product comparisons characterize availability and formulation. Differences across populations, exposures, and outcome methods precluded a meaningful pooled estimate in this narrative synthesis. No independent duplicate screening, formal risk-of-bias instrument, or GRADE assessment was undertaken. Appraisal below is design-based and qualitative. Table 1 summarizes selected interventions, Table 2 compares product surveys, and Table 3 defines the interpretive boundaries of each evidence stream.

Table 1. Selected human interventions and their applicability.

Study	Design and population	Diet and duration	Findings and interpretive limits
De Palma *et al.* (2009) [5]	Uncontrolled before-after study. 10 healthy adults	Gluten-free diet. 1 month	Selected qPCR counts changed. Polysaccharides also decreased. Ex vivo cytokine responses are not systemic inflammation.
Bonder *et al.* (2016) [6]	Longitudinal dietary switch. 21 volunteers aged 16 - 61 years. Mixed-age context.	Gluten-free diet for 4 weeks. Five-week washout before habitual-diet assessment.	Eight taxa differed. No alpha-diversity or measured biomarker differences. No randomized parallel control.
Hansen *et al.* (2018) [4]	Randomized crossover. 60 randomized adults with elevated BMI and/or waist criteria	2 vs 18 g gluten/day. 8 weeks each. Washout ≥6 weeks	Selected microbial shifts, less hydrogen exhalation and bloating. Fiber types differed. Not complete gluten exclusion.
Campagna *et al.* (2020) [19]	Randomized comparison. 60 healthy adults	Gluten-free vs control diet. 6 months	Selected favorable outcomes reported. Cochrane found no clear between-group effects on LDL, blood pressure, or BMI.
Henriques *et al.* (2022) [17]	Single-blind, non-randomized crossover. 23 healthy women	Gluten-containing vs gluten-free muffins. 3 weeks per period	No clear body-composition or symptom differences. Diet-quality comparison was against habitual baseline.
Lange *et al.* (2024) [18]	Uncontrolled before-after study. 27 completers, 22 women	Gluten-free diet. 4 weeks	Leukocytes decreased. CRP $p = 0.0689$ and FMD $p = 0.0897$. No control group.
Delmas *et al.* (2025) [7]	Microbiome report within a registered trial. 40 at baseline and week 8; a protocol-planned subgroup of 20 continued to week 16.	Low-gluten diet. 8 - 16 weeks	Microbial and metabolite changes. Week-16 n = 20 reflected a planned duration subgroup, not attrition. Smaller sequencing subset. Time-point comparisons do not isolate gluten.
Mannila *et al.* (2025, 2026) [9] [10]	Randomized parallel comparison. 72 randomized and 69 analyzed. Adults with cardiometabolic risk.	Oat-rich vs rice-rich low-gluten diets for 6 weeks. NCT05526092.	Different lipid, bowel, and microbial/metabolic responses. The 2025 clinical report tested multiple outcomes with nominal $p < 0.05$; the 2026 report used FDR correction for metagenomic and inflammatory-marker analyses. No significant inflammatory-marker changes after correction. Two reports from one trial.

Selected reports are shown, not an exhaustive trial inventory. Adult, higher-risk, and mixed-age populations are distinguished. Sample sizes vary by assay. The Mannila reports describe one trial. BMI, body mass index. CRP, C-reactive protein. FMD, flow-mediated dilation. LDL, low-density lipoprotein cholesterol. qPCR, quantitative polymerase chain reaction.

Table 2. Selected comparisons of packaged gluten free and gluten containing products.

Study and scope	Quantitative findings	Interpretation
Jamieson *et al*. (2018). [11] Canada. 398 GF and 445 GC products	Staples, medians per 100 g. Energy 357 vs 353 kcal, p = 0.1976. Protein 7.0 vs 10.9 g, p < 0.0001. Sugars 3.4 vs 3.5 g, p = 0.1464	Lower protein did not coincide with higher energy or sugar at conventional significance thresholds in this category.
Myhrstad *et al*. (2021). [13] Norway. 423 GF and 337 GC products	All products, medians per 100 g. Energy 359 vs 350 kcal. Protein 5.8 vs 9.5 g. Fiber 4.4 vs 6.0 g. All three p < 0.01	Comparators preferentially met nutrition guidance. In bread, fiber was 6.3 vs 6.0 g/100 g, p = 0.71.
Missbach *et al*. (2015). [14] Austria. 63 GF and 126 GC products	Across seven categories. Protein less than half in 57% of categories. Price premiums of 205% - 267% in specified categories	Nutrient and price differences depend on product category.
Lavriša *et al*. (2020). [15] Slovenia. Food-supply database	Category-dependent differences. GF-labelled foods often lower in protein and sugar	GF labelling was not limited to cereal substitutes. Comparisons do not measure consumer diets.
Jamieson and Blewett (2025). [12] Canada. 581 GF and 581 GC products	2024 iron fortification. 5% of GF vs 46% of GC staples	Updated evidence of fortification differences. Product data do not establish consumer deficiency.
Wu *et al*. (2015). [16] Australia. 3213 products across ten categories.	Health Star Ratings did not differ significantly for breads or breakfast cereals. Gluten-free pasta scored lower.	Lower protein across core groups coexisted with similar composite ratings in some categories.

Values are reported in GF versus GC order. GF, gluten-free. GC, gluten-containing. Comparisons are within each study. Categories, summary measures, comparator selection, and countries differ, so values must not be pooled or interpreted as a global average. Historical product composition does not describe every current brand.

Table 3. Evidence streams and the conclusions they support.

Evidence stream	Supported inference	Inference not established
Healthy-adult interventions	Defined dietary changes alter selected measured outcomes under the study conditions.	A gluten-specific effect when fiber, food sources, and energy also change.
Microbiome measures	Taxa, richness, counts, or metabolites respond to the exposure.	Clinical disease, impaired immunity, or toxicity from taxonomic direction alone.
Product surveys	Certain replacements differ in composition, fortification, or price.	Nutrient deficiency, habitual intake, or net health effect in an individual.
Habitual-intake cohorts	Estimated gluten intake is associated or not associated with later outcomes.	The causal effect of adopting a strict gluten-free diet.
Disease-population reviews	Diet and outcomes are linked within a disease and treatment context.	An effect size directly applicable to healthy adults.

This interpretive framework is developed for the present narrative synthesis. It is not a formal risk-of-bias instrument or certainty grading system.

2.3. Defining the Exposure and the Comparison

A strict gluten-free diet, a low-gluten diet, and a low estimated intake within an otherwise unrestricted population are different exposures. For example, the Hansen trial compared approximately 2 with 18 g/day, rather than complete exclusion with usual intake [4]. It is inappropriate to relabel such a contrast as evidence for

a strictly gluten-free diet.

Food replacement introduces a second distinction. Replacing wheat bread with refined rice-starch bread changes more than gluten. Replacing it with a combination of legumes, buckwheat, nuts, and other foods produces a different nutritional comparison again. Total fiber matching also does not ensure matching of fiber type or fermentability. The analytical question is therefore not simply whether gluten was removed, but which components changed alongside it and which remained comparable.

For this review, evidence is considered directly relevant when participants lack a known gluten-related disorder and the intervention tests dietary restriction. Evidence is considered indirect when it comes from disease populations, product labels, or habitual-intake categories. These categories describe applicability, not a numerical quality score. Even an internally valid result from a disease population does not automatically answer a prevention question in healthy adults.

2.4. Gut Microbiome Responses

Gluten free interventions

De Palma *et al*. [5] studied ten healthy adults before and after one month of a gluten-free diet. Quantitative polymerase chain reaction (qPCR) indicated lower *Bifidobacterium*, *Lactobacillus*, and *B. longum* counts, with higher Enterobacteriaceae and *Escherichia coli* counts. Polysaccharide intake also decreased. Fecal samples stimulated less cytokine production in an ex vivo peripheral-blood-mononuclear-cell assay. This assay measured the immune-stimulatory properties of samples, not circulating inflammation or immune failure in participants. The small, uncontrolled design prevents attribution of these changes specifically to gluten removal.

Bonder *et al*. [6] analyzed 21 volunteers aged 16 - 61 years during a four-week gluten-free period and a later habitual-diet period, with a five-week washout. This is mixed-age contextual evidence, not an adult-only estimate. Eight taxonomic groups differed, including lower Veillonellaceae abundance, but alpha-diversity indices and measured gut-health biomarkers did not differ between diets. Inter-individual variation exceeded diet-associated variation. Functional pathways were inferred computationally from marker-gene data rather than measured as metabolic flux. The findings support a microbial response to dietary change without establishing clinical harm.

Low gluten interventions

Hansen *et al*. [4] randomized 60 Danish adults to two eight-week dietary periods separated by a washout of at least six weeks. Participants had no known chronic disorders but met criteria involving elevated body mass index (BMI) and/or waist circumference, which narrows applicability to lean young adults. Compared with the high-gluten period, the low-gluten period altered selected taxa, reduced hydrogen exhalation, and improved reported bloating. The authors proposed qualitative differences in dietary fiber as an explanation. Because wheat-

containing foods also provide fermentable fructans, reducing wheat intake can lower fermentable substrate delivery to the colon; this offers a plausible explanation for lower hydrogen exhalation and bloating that is not specific to the gluten protein [4]. Because dietary components changed together, the study does not quantify the independent contribution of fructans, other fiber fractions, or gluten.

Delmas *et al*. [7] reported microbiome outcomes within a registered trial. Forty adults provided samples at baseline and after eight weeks of low-gluten intake, and the protocol prospectively assigned a subgroup of 20 participants to continue the low-gluten diet for a further eight weeks. The 20 participants assessed at week 16 therefore represent a planned intervention-duration subgroup rather than loss to follow-up from an intended 40-person week-16 assessment. The microbiome report principally compares time points after a dietary switch, rather than a sustained gluten-containing parallel control. It reported lower richness and changes in Bifidobacterium, Akkermansia, cultured Enterobacteriaceae, and fecal metabolites. These endpoints were not accompanied by evidence of incident disease. Sequencing analyses used a smaller subset than the qPCR analyses, so the total enrolled sample should not be assigned to every assay.

Clinical meaning and consistency

Across these studies, the most defensible common finding is alteration of selected microbial features after changing cereal intake. A consistent clinical syndrome has not been demonstrated. The decrease in *Lactobacillus* in the earliest study is not an established universal response. Similarly, a change in Enterobacteriaceae does not identify pathogenic strains or establish infection. Richness, relative abundance, absolute counts, and culture-based enumeration answer different questions and should remain distinct when comparing studies [5]-[7].

Kaliciak *et al*. [8] found that a gluten-free diet did not fully normalize microbial patterns in celiac disease. This provides disease-management context, not a direct harm estimate for healthy adults. Disease activity, mucosal injury, treatment response, and dietary restriction coexist in that setting. Microbial findings require linkage to validated measures of intestinal function or symptoms before taxonomic direction is treated as a health outcome.

Replacement cereals and the OAT GUT BRAIN trial

Mannila *et al*. [9] compared oat-rich with rice-rich low-gluten diets for six weeks in adults with cardiometabolic risk. The full report describes 72 randomized participants and 69 analyzed participants, despite the abstract's shorthand description of n = 69. The study was powered using serum total cholesterol as the endpoint, while multiple dietary, clinical, gastrointestinal, and biochemical variables were analyzed. LDL cholesterol fell by 0.41 versus 0.17 mmol/L in the oat and rice groups, respectively (group-by-time $p = 0.047$). The report used a two-sided $p < 0.05$ threshold for these analyses and did not report a multiplicity adjustment across the broad set of clinical and dietary outcomes; the LDL result should therefore be interpreted as a nominal secondary/exploratory finding rather than as a single confirmatory endpoint. Constipation favored oats, whereas waist reduction

favored rice. Both groups restricted gluten, so the contrast tests replacement strategies, not the effect of gluten removal. The per-protocol analysis and higher-risk population further constrain generalization.

The 2026 secondary report from the same registered trial (NCT05526092) examined prespecified study domains including fecal microbiome, plasma short-chain fatty acids (SCFAs), and inflammatory markers [10]. A greater rise in plasma butyrate was reported with oats (interaction $p = 0.033$); SCFA analyses used the nominal $p < 0.05$ threshold. For metagenomic and inflammatory-marker analyses, the report applied Benjamini-Hochberg false-discovery-rate correction. The Shannon-diversity diet-by-time interaction remained significant after this correction ($q = 0.025$), whereas no significant inflammatory-marker changes remained after correction. These linked reports arise from one experiment and contain multiple endpoints, so nominal lipid and SCFA findings should not be interpreted as equivalent in evidential status to multiplicity-corrected microbiome or inflammatory results. They show why microbial, metabolic, inflammatory, and clinical endpoints require separate interpretation.

Nutritional quality and affordability of replacement foods

Product surveys show recurring disadvantages in some gluten-free categories, particularly protein and fortification, but also demonstrate category-specific exceptions. In the Canadian survey of 398 gluten-free and 445 gluten-containing products, staple foods contained median protein values of 7.0 versus 10.9 g/100g. Energy and sugar differences in the staple category were not statistically significant [11]. A 2025 Canadian update compared 581 products in each group and reported iron fortification in 5% of gluten-free versus 46% of comparator staples in 2024 [12]. These findings concern food availability, not measured deficiency in consumers.

The Norwegian survey included 423 gluten-free and 337 comparator products. Overall protein and fiber were lower, but bread fiber was similar between groups. Importantly, investigators preferentially selected gluten-containing comparators meeting dietary guidance or carrying a Nordic nutrition label, and often selected whole-grain breads. This choice informs the nutritional comparison but limits a simple attribution to gluten status. The comparator was not an unrestricted sample of all conventional foods [13].

The Austrian study found lower protein in several categories and substantial price premiums [14]. In Slovenia, gluten-free-labelled foods often contained less protein and sugar, with differences depending on category [15]. These results challenge blanket statements that gluten-free foods always contain more sugar or less fiber. Median differences across mixed product groups also depend on the composition of the sampled market.

An Australian survey of 3213 products adds an important qualification. Gluten-free breads and breakfast cereals did not have significantly different mean Health Star Ratings from comparators, while gluten-free pasta scored lower. Protein was lower across the core categories [16]. Similar composite scores alongside nutrient-

specific differences show why the selected outcome changes the nutritional interpretation. A survey does not establish clinical benefit or harm from eating those products.

The practical inference is to evaluate replacement foods by their complete composition, portion size, cost, and contribution to the total diet. Label-based surveys cannot establish habitual intake, bioavailability, or nutritional status. Their strongest role is to identify potential substitution problems and priorities for reformulation. Affordability is also relevant to adherence when the diet is medically necessary, rather than an argument against treatment [12].

2.5. Inflammatory Metabolic and Clinical Outcomes

Diet quality and circulating biomarkers

Henriques *et al*. [17] studied 23 women in a single-blind, non-randomized crossover experiment, using gluten-containing or gluten-free muffins against a gluten-free dietary background over six weeks. Body composition, resting energy expenditure, and gastrointestinal symptoms did not differ between the three-week periods. The gluten-free period, compared with the habitual baseline diet, involved lower fiber and several B-vitamin intakes and a higher Dietary Inflammatory Index. That index summarizes dietary composition. It is not a direct measure of systemic inflammation, and the baseline comparison differs from the within-experiment gluten comparison.

Lange *et al*. [18] followed 27 healthy adults, predominantly women, through four weeks of gluten avoidance without a parallel control. Leukocyte counts decreased from 5.24 to 5.00/nL ($p = 0.0135$). C-reactive protein (CRP) fell numerically from 0.89 to 0.62 mg/L, but the reported p value was 0.0689. Flow-mediated dilation also did not reach statistical significance ($p = 0.0897$), and quality of life did not improve. Despite the abstract's anti-inflammatory framing, these data do not establish a CRP benefit. The absence of a control and multiple biomarker measurements further constrain inference.

These studies are not direct contradictions. One evaluates dietary composition and a calculated index, while another measures blood variables after an uncontrolled intervention. They support neither a general pro-inflammatory claim nor a general anti-inflammatory claim for gluten restriction in healthy adults. A controlled effect on a prespecified circulating endpoint would be more informative than an isolated within-group change.

Body weight and cardiometabolic risk factors

Campagna *et al*. [19] enrolled 60 healthy adults in a six-month dietary comparison. The abstract reported favorable changes in selected hematological, lipid, and psychological measures. In contrast, the Cochrane synthesis found no clear between-group differences for the trial's blood pressure, low-density lipoprotein (LDL) cholesterol, or BMI outcomes, with considerable imprecision [20]. The reports concern different endpoints and comparisons. Within-group improvement should not be substituted for a treatment effect relative to the control group.

Xin *et al*. [21] pooled 27 articles involving participants with and without celiac disease. The overall weight estimate was 1.20 kg (95% confidence interval [CI] −1.16 to 3.55), which does not establish either a weight-loss benefit or equivalence. Because populations were mixed, it is not a healthy-adult effect estimate. Barone *et al*. [22] examined weight outcomes in celiac disease specifically. Changes after treatment in that population occur in a setting of altered disease activity and absorption, and should not be used to predict weight change after elective restriction in healthy adults.

Cardiovascular disease and diabetes

Lebwohl *et al*. [23] followed 110,017 adults without known celiac disease in two US cohorts. The reported hazard ratio of 0.95 (95% CI 0.88 - 1.02) compared participants in the highest fifth of estimated gluten intake with those in the lowest fifth. Cox models were conditioned on age and follow-up cycle and, in the pooled analysis, stratified by cohort. The multivariable model adjusted for demographic, anthropometric, clinical, medication, lifestyle, and reproductive covariates, including race, BMI, height, diabetes, aspirin/non-steroidal anti-inflammatory drug use, statin and multivitamin use, alcohol, smoking, parental coronary-heart-disease history, hypertension, hypercholesterolemia, physical activity, and menopausal status/hormone use, with additional dietary covariates in the fully adjusted estimate. The association remained null. Further adjustment for whole grains produced a hazard ratio of 1.00 (95% CI 0.92 - 1.09), whereas adjustment for refined grains produced 0.85 (95% CI 0.77 - 0.93), illustrating the dependence of interpretation on grain-source covariation. This was a study of habitual intake, not random assignment to a strict gluten-free diet.

Zong *et al*. [24] analyzed three US cohorts and reported an inverse association between gluten intake and type 2 diabetes. After additional cereal-fiber adjustment, the highest versus lowest quintile hazard ratio was 0.87 (95% CI 0.81 - 0.93). Gluten intake was strongly correlated with other carbohydrate components. The result does not establish a protective effect of gluten, and these cohorts overlap with those used in the coronary analysis. Their participant totals should therefore not be added as independent populations.

The Cochrane review identified one randomized trial and three observational studies for primary cardiovascular prevention and judged important results to have low or very low certainty [20]. This supports restraint in clinical recommendations. It does not justify asserting either proven cardiovascular benefit or proven cardiovascular harm from elective gluten avoidance.

Trace element exposure

Bulka *et al*. [25] analyzed National Health and Nutrition Examination Survey data from 7471 participants, including 73 reporting a gluten-free diet. Adjusted geometric mean ratios were 1.5 (95% CI 1.2 - 2.0) for total urinary arsenic and 1.7 (1.1 - 2.4) for total blood mercury. The mixed-age sample was not restricted to healthy adults, although an adult-only sensitivity analysis was reported as similar. The paper also examined arsenic estimates excluding selected organic species, so

describing it as measuring total arsenic alone would be inaccurate. Cross-sectional exposure biomarkers did not establish dietary causation or clinical toxicity.

Punshon and Jackson [26] measured essential and potentially toxic elements in gluten-containing and gluten-free foods and identified differences related in part to rice-based ingredients. Together, these studies provide a rationale for examining replacement grain sources. They do not demonstrate that removing gluten directly increases metal exposure. Arsenic speciation, serving size, consumption frequency, seafood intake, and other sources are necessary for interpreting an individual's exposure. Product concentrations and biomarker measurements should not be translated directly into clinical risk without an exposure assessment.

3. Discussion

3.1. Dietary Replacement as an Explanatory Framework

The evidence is more coherent when three linked processes are separated: restriction of gluten-containing foods, substitution with other foods, and downstream biological or clinical responses. Current whole-diet experiments often modify the first two processes together. An effect of the assigned diet therefore does not automatically identify an effect of the gluten protein. This distinction applies equally to apparently favorable and unfavorable findings.

For example, microbial substrate availability and reported bloating may change together while the clinical meaning of the microbial shift remains uncertain. A nutrient-poor substitute may lower dietary quality, while an alternative pattern built around nutrient-dense foods produces a different comparison. These possibilities are not evidence that outcomes depend entirely on replacement. They explain why isolating gluten requires controls beyond a gluten-free label.

The proposed framework organizes what each comparison identifies. The oat-versus-rice trial supplies an empirical example of outcome differences between two low-gluten strategies [9] [10]. It does not establish that replacement explains every reported effect or quantify an independent gluten effect. A complementary design would reintroduce purified gluten against a matched dietary background. Comparing that estimate with a whole-food substitution trial would help distinguish the protein-specific question from the practical consequences of changing a diet.

3.2. Implications for Practice

Routine gluten restriction for general health improvement is not supported by the selected evidence in adults without a medical indication. This conclusion does not apply to patients requiring treatment for celiac disease, and it does not exclude individualized dietary assessment for symptoms. Diagnostic evaluation should precede self-directed elimination when a gluten-related disorder is suspected, because assessment and management depend on the clinical context [2].

For people already following the diet, nutritional assessment should focus on the replacement pattern: fiber sources, protein, fortification, food variety, and af-

fordability. A gluten-free pattern does not inherently require dependence on refined starch substitutes. Recommendations should address demonstrated dietary gaps rather than presume deficiency or toxicity from the label alone [3] [11].

3.3. Priorities for Research

A useful next generation of trials would compare at least two questions separately: a matched gluten challenge assessing a protein-specific effect, and a whole-diet substitution strategy assessing real-world effectiveness. Energy, macronutrients, total fiber, fiber type, whole-grain exposure, and processing should be measured rather than assumed equivalent. A factorial design would help separate gluten from replacement quality when feasible.

Primary outcomes should be prespecified and selected for the hypothesis, with sample-size calculations based on the between-group contrast. Inflammation studies should distinguish dietary indices from blood markers. Microbiome studies should report assay-specific sample sizes, repeated-measures analyses, multiple-testing control, and absolute abundance where feasible, alongside functional or clinical outcomes. Demonstrating a taxonomic change alone is insufficient.

Short-term mechanistic trials and longer-term clinical studies serve complementary purposes. The former require adherence monitoring and dietary characterization. The latter require sufficient duration, retention, and endpoint assessment to evaluate sustained benefit or harm. Future studies should also report nutrient adequacy, cost, symptoms, and adverse events, while specifying whether effects differ by baseline diet, sex, age, or metabolic status. These are research priorities, not findings established by the present review.

4. Limitations

This review is selective and narrative. Targeted retrieval, English-language sources, incomplete full-text access, and absence of independent duplicate screening introduce risks of omission and interpretation bias. Campagna and Henriques were appraised within the limits of retrieved abstracts and relevant secondary extraction, rather than as fully assessed original articles. The search update is not equivalent to a comprehensive multi-database search. No formal pooled effect, risk-of-bias score, or new certainty rating is claimed.

The evidence itself is heterogeneous. Samples in intervention studies are often small, follow-up is generally short, and populations described as healthy differ in age, sex distribution, and adiposity. Some reports analyze subsets for particular assays. Gluten-free and low-gluten exposures are not interchangeable. Food surveys differ by country, product category, comparator selection, and fortification practices. Observational estimates retain residual confounding, and reviews frequently overlap in their primary studies. These constraints limit causal claims and prevent a universal verdict on all gluten-free dietary patterns.

5. Conclusion

In adults without a gluten-related disorder, current selected evidence does not es-

tablish a general health benefit from routine gluten restriction. It also does not demonstrate universal clinical harm from a nutritionally adequate gluten-free diet. The clearest observations concern changes in selected microbial features and compositional disadvantages in some replacement products. Clinical implications remain less certain. Interpretation and future trial design should center on the foods replacing gluten-containing staples, with explicit separation of intermediate biological measures from health outcomes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplementary Material S1

Search update and source verification

Search update date: 15 October 2026. The initial 16-reference working corpus was assembled during preliminary scoping of the review and was not generated from a formal systematic screening denominator. It contained core background sources and previously identified human dietary studies, product-composition studies, and contextual reviews relevant to gluten restriction or replacement. Targeted searches then added ten references, producing a final bibliography of 26 references. This is not a count of independent adult intervention studies. Retrieval used targeted web searches of PubMed-indexed records, publisher pages, and accessible original-article material.

Selected executed search strings are reproduced below. These are web-retrieval queries, not a claimed reproducible PubMed or MEDLINE database strategy. Additional author, title, DOI, and endpoint searches verified individual records. Search ranking and indexing affect retrieval, and no exhaustive screening denominator is available.

gluten free diet healthy adults randomized trial 2024 2025 2026 cardiometabolic systematic review

gluten intake type 2 diabetes three prospective cohort 2018 Zong

gluten free diet non celiac cardiovascular prevention Cochrane 2022

“gluten-free” “healthy adults” trial 2025 2026 -diabetes -celiac -coeliac

“gluten-free” “healthy” “2024” randomized trial diet

“The Price of Canadian Gluten-Free Staple Foods”

“A Low-Gluten Diet Reduces” “random” “group”

“Lange” “2265” “CRP” “0.0689”

“Oat-rich low-gluten diet modulates” “Results”

Source access: original article text or tables informed verification of Bonder, Hansen, Delmas, Lange, the 2025 Mannila trial, the 2026 Mannila secondary report, Bulka, Punshon, the Austrian product survey, the Australian survey, and the Norwegian product survey. Other sources were checked using accessible primary-record text or abstracts. Campagna and Henriques remained abstract-limited, with the Cochrane review supplying additional trial extraction for Campagna. No inaccessible article was classified as fully assessed.

Interpretive checks: Bonder included ages 16 - 61 and is retained as mixed-age context. In Delmas, 40 participants were assessed at baseline/eight weeks and a protocol-planned subgroup of 20 continued to week 16; this was not treated as attrition from an intended 40-person week-16 sample. Lange’s CRP decrease did not reach conventional statistical significance. Bulka used additional arsenic estimates beyond total arsenic. The Norwegian comparison preferentially used nutritionally favorable conventional products. The Mannila 2025 and 2026 reports share NCT05526092 and are not independent replications; the 2025 clinical report used nominal p values across multiple outcomes, whereas the 2026 report applied false-discovery-rate correction to metagenomic and inflammatory-marker analyses. Retracted Croall 2019 evidence was not used.