



# **Gluten Causes Gastrointestinal Symptoms in Subjects Without Celiac Disease**

A Double – Blind Randomized Placebo – Controlled Trial

## A Double – Blind Randomized Placebo – Controlled Trial

Despite the increased prescription of a gluten-free diet for gastrointestinal symptoms in individuals who do not have celiac disease, there is minimal evidence that suggests that gluten is a trigger.

This study was performed by Biesiekierski *et al.*, in 2010 at Monash University, Australia.

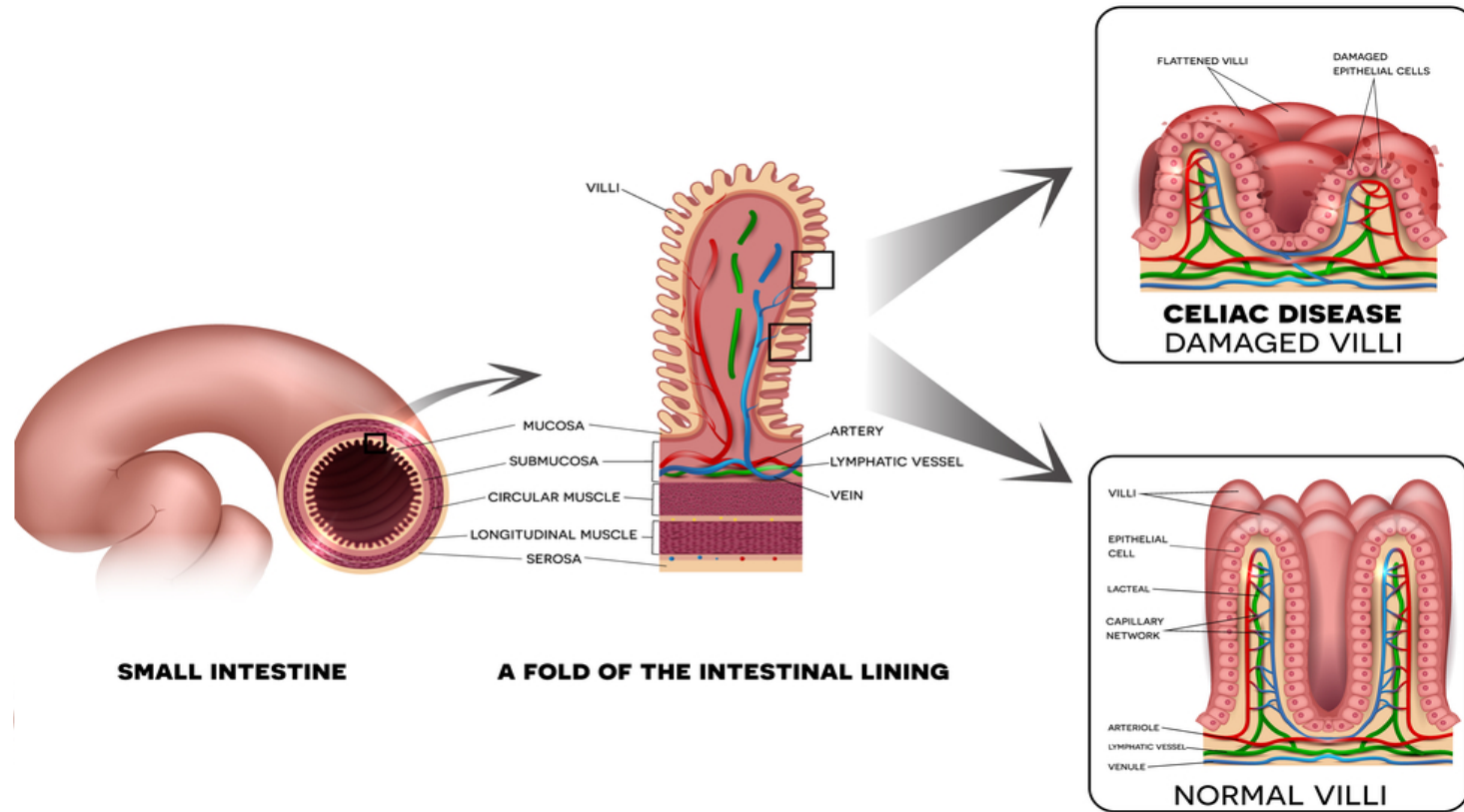
The aims of this study were to determine whether gluten consumption can induce symptoms in non-celiac individuals.



## What is Celiac Disease?

- A serious genetic autoimmune disease that damages the small intestine and interferes with the absorption of nutrients from food when gluten, is ingested.
- Celiac disease affects 1% of the general population, or 1 in 133 Americans. Onset can occur at any age.
- Multiple systems in our bodies are affected by undiagnosed celiac disease, resulting in a number of symptoms including gastrointestinal distress, chronic fatigue, osteoporosis, anemia, and nutritional deficiencies. Symptoms vary from person to person, and some may experience no symptoms at all. A small intestine biopsy is needed to confirm the diagnosis.
- Left undiagnosed and untreated, celiac disease can lead to further complications, such as osteoporosis, infertility, and the onset of other autoimmune diseases and some cancers.

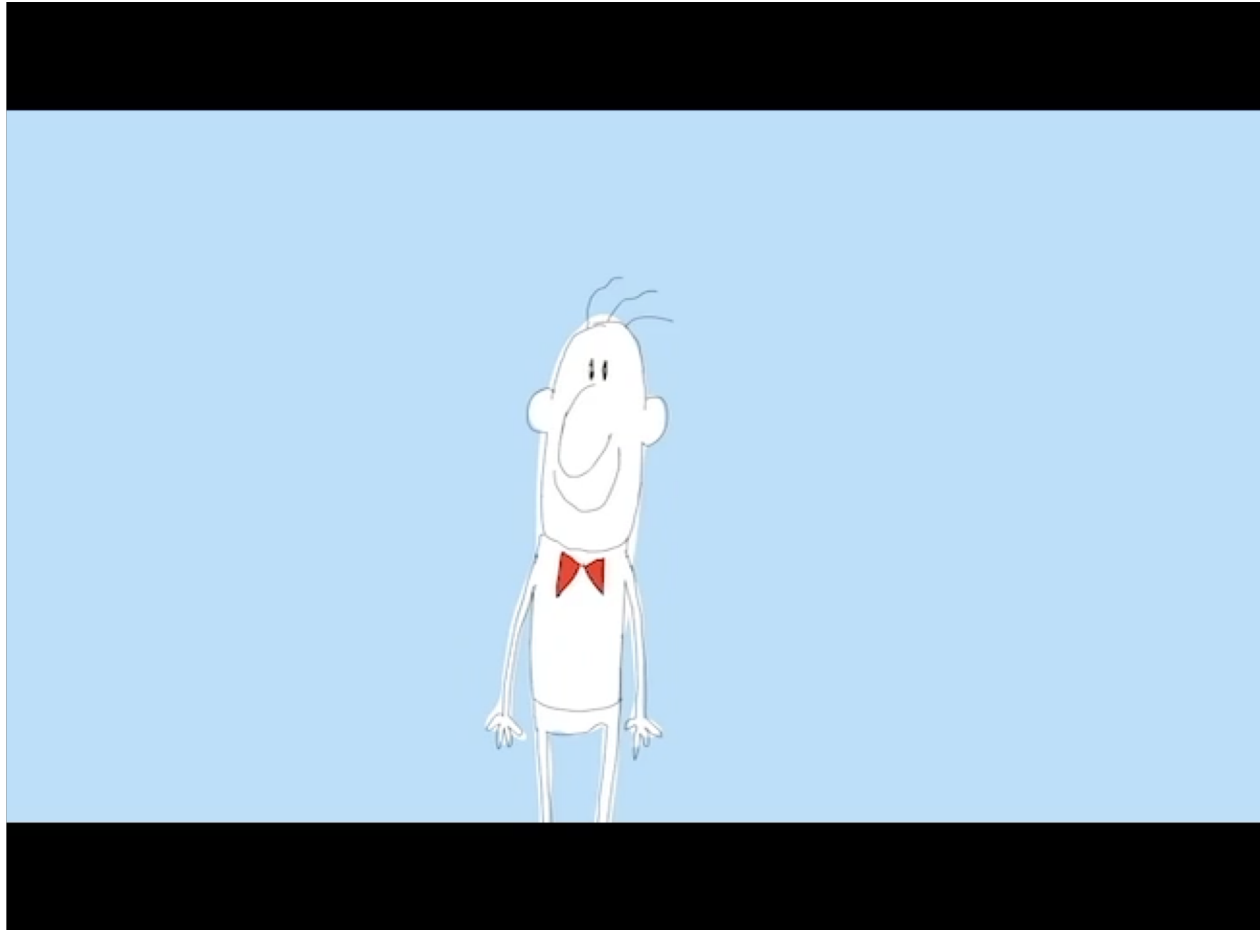
# What does Celiac Disease looks like?



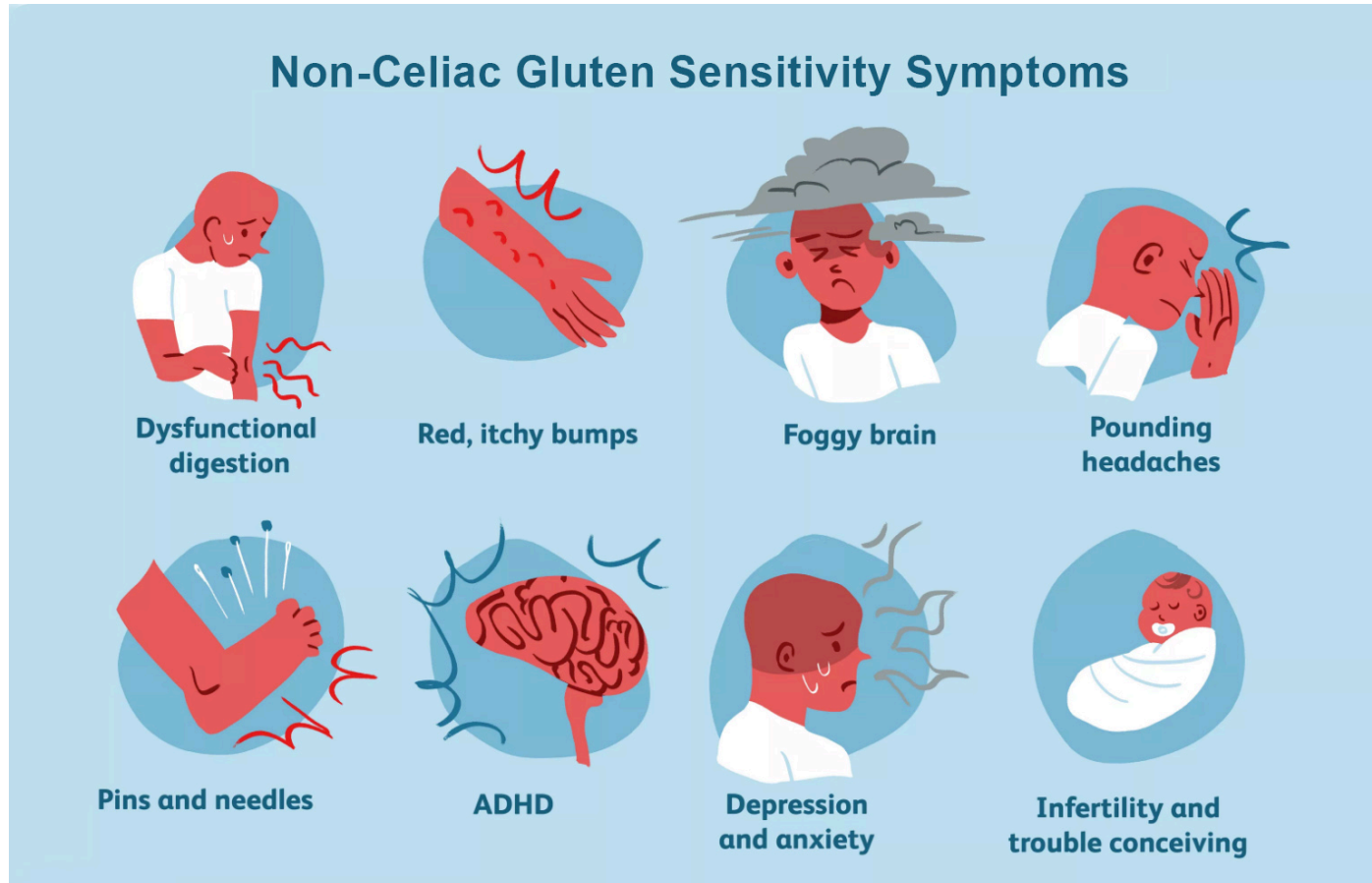
## What is Non-Celiac Gluten Sensitivity?

- A non-specific immune response that has been clinically recognized as less severe than celiac disease.
- It is a gastrointestinal disorder that is not easy to diagnose due to the lack of biomarkers (measurable indicators).
- Some people experience symptoms found in celiac disease, such as brain fog, depression, ADHD, abdominal pain, bloating, diarrhea, constipation, headaches, bone or joint pain, and chronic fatigue when they have gluten in their diet, yet do not test positive for celiac disease.
- No laboratory tests can currently diagnose NCGS, making the diagnosis a process of exclusion. Celiac disease must be ruled out through testing before proceeding to an elimination diet, followed by a monitored gluten challenge.

## What does Non-Celiac Gluten Sensitivity look like?



# What are the Symptoms of Non-Celiac Gluten Sensitivity?



# METHODS



# Patients

Participants were recruited between July 2007 and December 2008 through advertisements, e-newsletters, and community newspapers

## Inclusion Criteria

- Age 16 and over
- Symptoms of IBS fulling Rome III criteria\* that have improved on a gluten free diet
- Adherence to diet for six weeks prior to screening

## Exclusion Criteria

- Celiac disease
- Cirrhosis
- Inflammatory bowel disease
- Excessive alcohol intake
- Intake of non-steroidal inflammatory agents

\*Rome III criteria recurrent abdominal pain or discomfort at least three days a month over the duration of a three month period associated with two or more of the following: improvement with defecation, onset associated with change in frequency of stool, onset associated with change in stool appearance

# Study Design

Participants were asked to consume a gluten free diet and to eat a muffin and two slices of bread per day, provided by the researchers. The study was a randomized, double-blind design.

Gluten group: muffin and bread slices contained gluten

Non-gluten group: muffin and bread slices gluten free

- Both breads were baked in gluten free ovens and conditions with the same gluten free base
- Commercially available, carbohydrate depleted wheat gluten was added to the mix for the gluten group
- 8g gluten per muffin
- 4g gluten per slice of bread
- Breads were tested for taste/texture differences

# Patients

## Weeks 1 - 3

At the end of each week participants were asked to complete a symptoms questionnaire on overall symptoms of bloating, abdominal pain, stool consistency, nausea and fatigue.

## Weeks 0 and 6

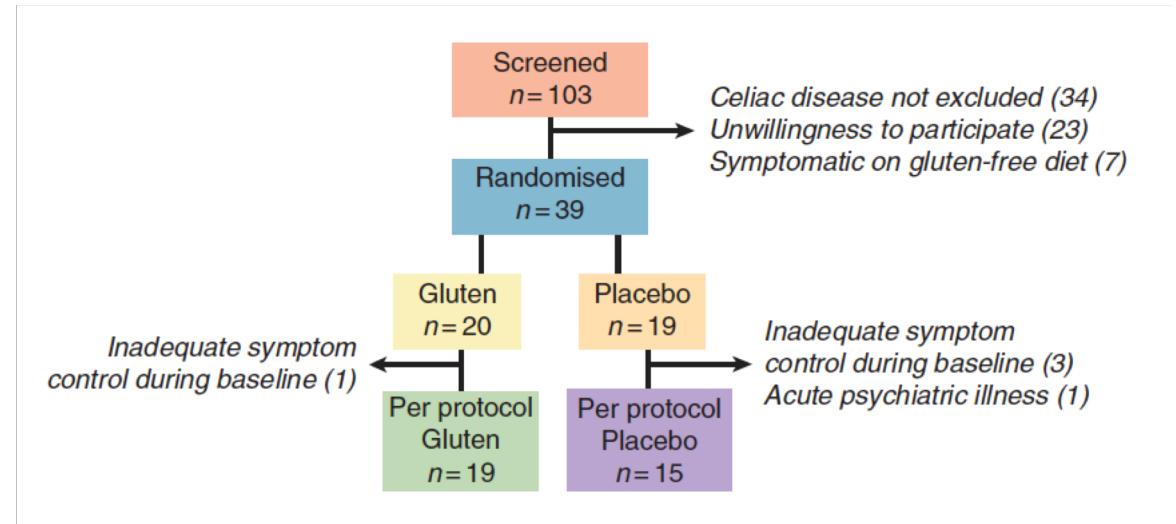
Serum, urine, and stool samples were collected for analysis and intestinal permeability was measured (biomarkers)

## Weeks 3 and 6

- Participants were asked to report food diaries

## Compliance

- Returned bread/muffins at weeks 3 and 6
- Food diaries



## Biomarkers Assessments



- Serum analyzed for antibodies to tissue transglutaminase (IgA and IgG) using INOVA diagnostics
- Intestinal permeability measured using a dual sugar test
- Urine analysis completed through calculating lactulose to rhamnose ratio
- Fecal lactoferrin measured by ELISA using an IBD scan

# Statistical Analysis

- Relationship between tolerable symptoms for the duration of the study was determined by a generalized estimating question “Over the last week were your symptoms adequately controlled?”
- Change in symptom severity was calculated as the scored difference between the first and sixth week, and the results were tested by the independent samples t-test for within group comparisons. ANOVA was used for between group comparisons
- Changes in biomarker levels after therapy were assessed by paired t-test using log-transformed data and ANOVA for between group comparisons

# RESULTS

# Results

- Of the 103 participants screened, 39 were randomized into control and placebo groups where 5 more participants were withdrawn
- All remaining participants adhered to the diet during the study
- 9 more patients withdrew due to intolerances due to the diet
- 6 from the gluten group
- 3 from the placebo group

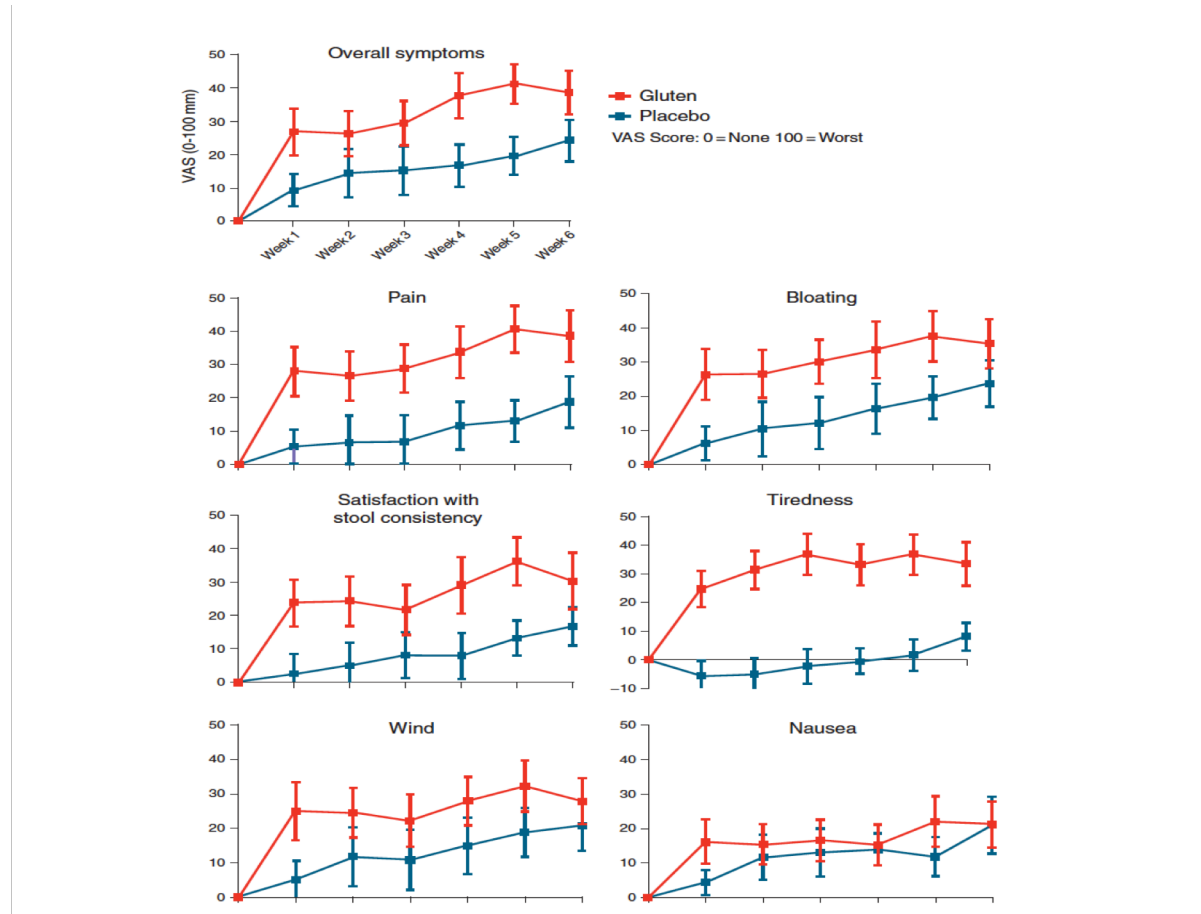
# Results

- Based on the primary outcome of the study, the proportion of participant answering “no” on more than half of the symptom assessments to the question, “Over the last week were your symptoms adequately controlled?”
- 68% from the gluten group said no
- 40% from the placebo group said no





# Results



# Results

**Table 2.** Celiac serology, intestinal permeability, and C-reactive protein results before and during therapy with gluten or placebo, shown as median (range), and changes in those indices, shown as mean (s.e.m.)

Biomarker	Gluten (n=19)			Placebo (n=15)		
	Baseline	With therapy	Change	Baseline	With therapy	Change
<i>Celiac serology (Units/ml)</i>						
Tissue transglutaminase (IgA)	3.0 (2.0–7.0)	4.5 (2.0–7.0)	0.6 (0.3)	3.0 (2.0–10.0)	3.5 (2.0–10.0)	0.4 (0.5)
Whole gliadin (IgA)	10.8 (3.5–241.5)	4.6 (0.1–51.3)	–29.7 (19.2)	6.6 (0.1–36.6)	5.9 (0.1–36.6)	–4.3 (2.5)
Whole gliadin (IgG)	14.6 (12.1–31.5)	15.5 (11.4–50.6)	2.5 (2.0)	11.9 (10.9–14.6)	11.9 (10.6–15.7)	0.2 (0.3)
Intestinal permeability (L:R ratio)	0.02 (0.01–0.6)	0.01 (0.01–2.4)	0.09 (0.1)	0.04 (0.01–0.15)	0.02 (0.01–0.18)	–0.01 (0.02)
Highly sensitive C-reactive protein (mg/l)	1.4 (0.3–5.3)	0.3 (0.4–19.8)	2.1 (1.4)	1.1 (0.2–8.2)	1.2 (0.3–13.1)	0.5 (0.9)

ANCOVA, analysis of covariance; L:R ratio, lactulose-to-rhamnose ratio

There were no statistically significant differences within each dietary group (paired t-test on log-transformed data) or between treatment groups whether evaluated using baseline and treatment data (ANCOVA) or the changes in indices (independent samples t-test; all  $P \geq 0.1$ ).

# Discussion

- Gluten intolerance without having celiac has been a controversial topic
  - “no man’s land of gluten sensitivity”
- Gluten specifically has been proved to trigger symptoms including bloating, dissatisfaction with stool consistency, abdominal pain and tiredness



THANK YOU!!!

# References

- Gluten Causes Gastrointestinal Symptoms in Subjects Without Celiac Disease: A Double-Blind Randomized Placebo-Controlled Trial - Jessica R. Biesiekierski, et al.
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- Gluten Freedom / Alessio Fasano, MD with Susie Flaherty