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Biomarkers of gluten sensitivity in patients with non-affective psychosis: A meta-analysis

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ABSTRACT

Background: Dohan first proposed that there may be an association between gluten sensitivity and schizophrenia in the 1950s. Since then, this association has been measured using several different serum biomarkers of gluten sensitivity. At this point, it is unclear which serum biomarkers of gluten sensitivity are elevated in patients with schizophrenia. However, evidence suggests that the immune response in this group is different from the immune response to gluten found in patients with Celiac disease.

Methods: A systematic literature review was performed to identify all original articles that measured biomarkers of gluten sensitivity in patients with schizophrenia and non-affective psychoses compared to a control group. Three databases were used: Ovid MEDLINE, Psych INFO, and Embase, dating back to 1946. Forward tracking and backward tracking were undertaken on retrieved papers. A meta-analysis was performed of specific biomarkers and reported according to MOOSE guidelines.

Results: 17 relevant original articles were identified, and 12 met criteria for the meta-analysis. Five biomarkers of gluten sensitivity were found to be significantly elevated in patients with non-affective psychoses compared to controls. The pooled odds ratio and 95% confidence intervals were Anti-Gliadin IgG OR = 2.31 [1.16, 4.58], Anti-Gliadin IgA OR = 2.57 [1.13, 5.82], Anti-TTG2 IgA OR = 5.86 [2.88, 11.95], Anti-Gliadin (unspecified isotype) OR = 7.68 [2.07, 28.42], and Anti-Wheat OR = 2.74 [1.06, 7.08]. Four biomarkers for gluten sensitivity, Anti-EMA IgA, Anti-TTG2 IgG, Anti-DGP IgG, and Anti-Gluten were not found to be associated with schizophrenia. **Conclusions:** Not all serum biomarkers of gluten sensitivity are elevated in patients with schizophrenia. However, the specific immune response to gluten in this population differs from that found in patients with Celiac disease.

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1. Introduction

An association between gluten sensitivity and schizophrenia has been reported (Dohan, 1966; Reichelt and Landmark, 1995; Kalaydjian et al., 2006). Gluten is a protein that usually stays in the digestive tract. If the lining of the gut is compromised, it enters the bloodstream and can trigger an immune reaction. In neuropsychiatric disorders, gluten breakdown products are also important as they can act as ligands at opioid receptors in the central nervous system (Ziodrou et al., 1979; Severance et al., 2012).

The immune response to gluten has been investigated in a number of non-affective psychoses and there are reports that this immune response is different from that seen in Celiac disease (Samaroo et al., 2010). However, there is inconsistency with regard to which serum antibodies are studied. There are several different serum biomarkers

of gluten sensitivity that can be measured, and some antibodies exist in both the IgG and IgA isotype. IgG antibodies represent 75% of human immunoglobulins found in serum. Alternatively, IgA antibodies are primarily involved in the mucosal immune system, which protects epithelial surfaces in the body from pathogens. However, IgA antibodies can also exist in the serum where they serve to initiate the inflammatory response to pathogens (Janeway et al., 2001).

Further difficulty in identifying a specific reaction to gluten in patients with schizophrenia comes from the fact that there are general immune alterations in schizophrenia that are also common to patients with Celiac disease and other autoimmune disorders (Smith, 1991; Kalaydjian et al., 2006; Saetre et al., 2007). In addition, adults with psychiatric disorders, exhibit increased immune reactivity to foodstuffs (Mascord et al., 1978; Dickerson et al., 2011; Severance et al., 2012). It may be that gluten sensitivity can be a surrogate marker for increased gastrointestinal permeability or inflammation (Severance et al., 2012).

It is worth clarifying here that gluten sensitivity is a separate condition from Celiac disease. Nevertheless, patients who are gluten-sensitive experience symptoms when they consume gluten. It is postulated that only the innate immune response is involved in gluten sensitivity whereas both the innate and adaptive immune responses are involved in Celiac disease (Volta and De Giorgo, 2012). Volta et al. (2012) sought

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to characterize the immune response to gluten in gluten sensitivity. They found that 56.4% of individuals with gluten sensitivity had elevations in AGA IgG, 7.7% had elevations in AGA IgA, and elevations in anti-TTG2, anti-EMA, and anti-DGP were rare (Volta et al., 2012).

This study aims to address the following questions: Do individuals with non-affective psychoses have higher levels of serum biomarkers of gluten sensitivity compared to the general population? If so, which biomarkers of gluten sensitivity are elevated in non-affective psychoses and at what rate? Lastly, is the specific immune response to gluten, as indicated by the pattern of elevated biomarkers of gluten sensitivity, in non-affective psychoses different from that seen in Celiac disease?

A review of this kind has never been performed. Our results will help inform research design of future studies and to increase our understanding of gluten sensitivity in patients with non-affective psychosis. Specifically, we hope to help inform researchers which biomarkers of gluten sensitivity are worth measuring in patients with non-affective psychoses in various research designs exploring this area including epidemiological studies or clinical trials.

2. Materials and methods

2.1. Selection of articles for inclusion

To identify studies relevant for the current literature review and meta-analysis, a computerized OVID search of Medline, PsychINFO,

and Embase was performed. All abstracts from 1946 to October Week 1 2011 were retrieved using the following MeSH terms: Glutens, Gliadin, Triticum, food hypersensitivity, and wheat hypersensitivity, along with their associated keywords. These results were combined with the MeSH terms “schizophrenia” and “psychotic disorders” and their corresponding keywords. The above search was completed a second time in order to retrieve articles published from October Week 1 2011 to November Week 1 2013. Searches were performed by a resident physician, and a librarian at the Centre for Addiction and Mental Health (CAMH) was consulted to help design the above search strategy.

We included only English language articles that had been published in peer-reviewed journals or books, with independent data. All abstracts were read, and full papers were read by two raters for all articles, which met the criteria for the review. The inclusion criteria for the review were: original research article, measurement of serum or blood markers indicating increased immune reactivity to gluten/wheat/gliadin, and studies of groups with a diagnosis of schizophrenia or psychotic disorder (non-affective psychosis). In order to be included in the meta-analysis, additional inclusion criteria had to be met: Inclusion of a defined control group without evidence of Celiac disease, psychiatric illness, or increased risk of schizophrenia (i.e. first degree relative). The presence of a control group was necessary in order to allow for a comparison in the rates of immune reactivity to gluten between the two groups. In addition, given the heterogeneity of the study and control samples, we attempted to restrict our quantitative analysis to

Flow Chart of Literature Search and Meta-Analysis

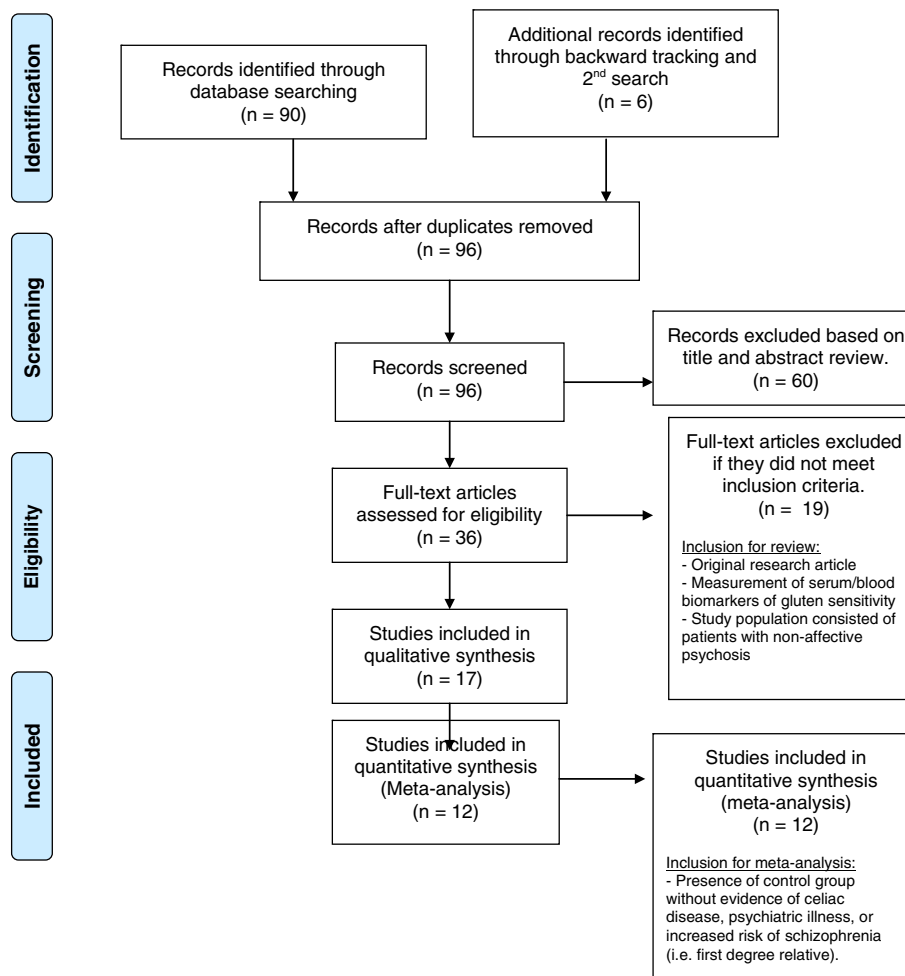


Fig. 1. Flow chart of literature search and meta-analysis.

studies that included control groups that were more representative of the general population as defined by the inclusion criteria above.

For papers that met the inclusion criteria for the review, all references were hand searched. Any additional citations that were of interest were retrieved. All relevant articles were also forward tracked to search for additional articles to include. Study authors were contacted to obtain original data when it was not included in the articles. This meta-analysis was performed and reported according to MOOSE guidelines.

A quality assessment was conducted for the papers included in the review and meta-analysis. We designed our own quality assessment tool as no standardized and validated tool was available for cross-sectional studies. It is included in Appendix A. Specifically, our tool assessed how participants and controls were recruited, and if the control and patient groups were matched with respect to socio-demographic variables. We also considered whether the control group was representative of the general population. We examined how the diagnosis was confirmed in the patient group, and whether comorbidities were measured. We also verified if control groups were screened for absence of a psychiatric disorder. Lastly, our tool included an assessment of the relevance of the particular biomarkers measured, as well as a score for the laboratory methods and quality of data analysis. The quality assessment yielded a score out of 30.

2.2. Statistical methods

Studies were analyzed using Review Manager 5.1 software. For dichotomous outcomes, odds ratios and 95% confidence intervals were calculated using a random effects model. This model assumes that the

underlying true effect varies from one study to another. If there is significant heterogeneity, a random effects model will give wider confidence intervals than a fixed effect model. Therefore, when significant heterogeneity is anticipated, a random effects model is more conservative (Higgins and Thompson, 2002). The presence or absence of an elevated level of a particular serum biomarker of gluten sensitivity was analyzed as a dichotomous outcome. Where studies had more than one population, separate odds ratios for each specific biomarker in each patient population compared to the control group were calculated (Hekkens et al., 1980; Rix et al., 1985; Dickerson et al., 2010). Pooled odds ratios for each serum biomarker of gluten sensitivity were calculated (with 95% confidence intervals) and results were compiled into Forest Plots using the Mantel–Haenszel statistical method. A chi square test was performed to measure heterogeneity. Statistical power calculations were performed using a web-based power calculator (13).

3. Results

3.1. Literature review and meta-analysis

A flow chart outlining the literature search and meta-analysis is shown as Fig. 1. From the initial OVID search, 90 papers were retrieved after duplications were excluded. All titles and abstracts were read, and 60 papers were excluded as not relevant to the current topic at this level. The remaining 30 articles were read completely and 19 were excluded because they did not meet the inclusion criteria. Specifically, they were not original research articles, they did not include measurements of serum biomarkers of gluten sensitivity, or the study

Table 1
Characteristics of studies included in the literature review and meta-analysis.

First author	Year	Biomarkers	Method of measurement	Patient group	Control group
Okusaga O	2013	AGA IgG	ELISA	SCZ inpatients and outpatients	Healthy controls screened to confirm absence of psychiatric disorder
Jin SZ	2012	AGA IgG, AGA IgA, Anti-TTG2 IgA, Anti Deamidated Gliadin IgG	ELISA	SCZ illness duration of minimum one year, taking anti-psychotic medication	Healthy controls, screened for absence of history of autoimmune condition
Sidhom O	2012	AGA IgG, AGA IgA, Anti-TTG2 IgA, Anti-EMA IgA	ELISA	SCZ inpatients, screened to confirm absence of history of autoimmune disorder	Age and sex matched blood donors, screened for absence of psychiatric history
Casella NG	2011	AGA IgG, AGA IgA, Anti-TTG2 IgA	ELISA	SCZ participants in CATIE trial	Outpatients from primary health care unit who answered a questionnaire indicating elevated risk for CD.
Dickerson F	2010	AGA IgG, AGA IgA, Anti-TTG2 IgG, Anti-TTG2 IgA, Anti-Deamidated Gliadin IgG	ELISA	Recent-onset SCZ (within 24 months), and multi-episode SCZ	Healthy controls screened to confirm absence of psychiatric disorder
Samaroo D	2010	AGA IgG, AGA IgA, Anti-TTG2 IgA, Anti-Deamidated Gliadin IgG	ELISA	SCZ (known history of gluten sensitivity)	Celiac Disease
Peleg R	2004	Anti-EMA IgA	Indirect immunofluorescence	SCZ outpatients, excluded if previous diagnosis of CD	Healthy controls from primary care clinic for visits unrelated to GI complaints, excluded if diagnosis of CD
Reichelt KL	1995	AGA IgA, Anti-Gluten	ELISA	SCZ	Healthy hospital staff
Rybakowski JK	1990	Anti-EMA IgA	Not available	SCZ	Celiac Disease
Rix KJB	1985	Anti-Wheat	Indirect immunofluorescence, RAST	SCZ Inpatients	Surgical Inpatients
Kinnell HG	1982	Anti-gluten	Microprecipitin test for food antibodies	SCZ inpatients and outpatients	First degree relatives
Sugerman AA	1982	Anti-Wheat	RAST IgE	SCZ Inpatients, excluded if allergic symptoms or elevated levels of total IgE	Healthy hospital staff
McGuffin P	1981	Anti-gluten	Tanned red cell agglutination	SCZ Inpatients	Healthy hospital staff
Hekkens WTJM	1980	Anti-Wheat, AGA unspecified immunoglobulin type	Indirect immunofluorescence, ELISA	SCZ Inpatients	Healthy hospital staff
Hekkens WTJM	1978	AGA unspecified immunoglobulin type	ELISA	SCZ Inpatients	Healthy hospital staff
Mascord D	1978	Anti-Wheat	Indirect immunofluorescence	SCZ Inpatients	General hospital inpatients
Dohan FC	1972	AGA unspecified immunoglobulin type	Tanned red cell agglutination	SCZ Inpatients	Healthy controls

Legend: AGA = anti-gliadin antibody, SCZ = patients with a diagnosis of schizophrenia, CD = Celiac disease.

population did not consist of patients with non-affective psychoses. The references of all 11 remaining articles to be included in the review were hand searched. Three additional articles published in books were identified and retrieved. When the above search was completed a second time in November of 2013, 3 additional relevant articles were found, resulting in a total of 17 articles.

All together, 12 studies met criteria for the meta-analysis. Five studies were removed from those included in the review because they did not meet the additional inclusion criteria for the meta-analysis. Inclusion in the meta-analysis required the presence of a control group that was relatively representative of the general population. We achieved this by ensuring that the participants in the control group did not have evidence of a psychiatric disorder or Celiac disease, and they were not at increased risk of non-affective psychoses (i.e. first degree relative). The 12 studies included 3704 patients with schizophrenia and 2898 controls.

The participants included both inpatients and outpatients with a diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder as diagnosed according to DSM III, III-R, IV or IV-TR depending on the time period of the study. The vast majority of participants were taking anti-psychotic medication.

The results of the literature review can be found in Tables 1 and 2. Table 1 lists all 17 relevant studies as described in Section 2.1, including

those analyzed in the meta-analysis. In total, 9 different serum biomarkers of gluten sensitivity were measured, using a variety of laboratory methods. These included: Anti-Gliadin (AGA) IgG, AGA IgA, Anti-TTG2 IgG, Anti-TTG2 IgA, Anti-EMA, Anti-Gliadin (unspecified immunoglobulin isotype), Anti-Wheat, Anti-Gluten, Anti-Deamidated Gliadin (DGP) IgG. The specific laboratory tests used, as well as features of the control and study participant groups are described in the table.

There was significant variation in the types of biomarkers studied, the specific bioassay used, as well as the methods used to confirm the clinical diagnosis of schizophrenia or other psychotic disorders.

Table 2 reports the odds ratios comparing rates of gluten sensitivity between the patient group and the control group (with 95% confidence intervals) for the studies included in the meta-analysis. Table 3 shows the pooled odds ratios for each serum biomarker of gluten sensitivity based on the Forest Plot analysis. Anti-gluten, anti-gliadin (unspecified immunoglobulin isotype), and anti-wheat were analyzed together as a pooled odds ratio. This was done because these biomarkers are likely indistinguishable by our current assays and represent gluten fractions in various stages of digestion (Sharma, 2012).

Four individual serum biomarkers of gluten sensitivity did not show a statistically significant increased rate in patients with schizophrenia: Anti-TTG2 IgG, Anti-Gluten, Anti-EMA IgA, and Anti-DGP IgG. We attempted to calculate the post-hoc statistical power of the studies

Table 2
Rate of gluten sensitivity in patients with non-affective psychosis compared to controls.

Biomarker	First author	Year	Patient group			Control group			Odds ratio
			# Positive	n	% Positive	# Positive	n	% Positive	
Anti-gliadin IgG	Okusaga O	2013	208	950	21.90%	100	1000	10.00%	2.13 (1.57–2.91)
	Sidhom O	2012	28	47	59.00%	10	41	23.90%	4.57 (1.82–11.47)
	Cascella NG	2011	20	1401	1.43%	30	900	3.33%	0.42 (0.24–0.74)
	Jin SZ	2012	75	419	17.90%	68	478	14.23%	1.32 (0.92–1.88)
	Dickerson F	2010			N/A			N/A	5.50 (2.65–11.42)
	Dickerson F	2010			N/A			N/A	6.19 (2.70–14.16)
	Samaroo D	2010	17	17	100%	25	25	100%	0.67 (0.01–36.25)
Anti-gliadin IgA	Jin SZ	2012	128	473	27.06%	85	478	17.80%	1.72 (1.25–2.35)
	Sidhom O	2012	2	47	4.47%	4	41	10.49%	0.41 (0.07–2.37)
	Cascella NG	2011	323	1401	23.05%	28	900	3.11%	9.33 (6.28–13.87)
	Dickerson F	2010			N/A			N/A	2.75 (1.31–5.75)
	Dickerson F	2010			N/A			N/A	2.00 (1.00–3.00)
	Samaroo D	2010	17	17	100%	25	25	100%	0.67 (0.01–36.25)
	Reichelt KL	1995	9	48	18.75%	0	13	0.00%	6.33 (0.34–116.53)
Anti-gliadin (unspecified immunoglobulin isotype)	Hekkens WTJM	1980	13	75	17.33%	24	121	19.83%	0.85 (0.40–1.79)
	Hekkens WTJM	1978	2	20	10.00%	0	26	0.00%	7.22 (0.33–159.57)
	Dohan FC	1972	46	229	20.09%	2	64	3.13%	7.80 (1.84–33.05)
Anti-TTG2 IgG	Dickerson F	2010	2	102	1.96%	7	173	4.05%	2.29 (1.15–4.55)
	Dickerson F	2010			N/A			N/A	1.00 (0.50–1.50)
Anti-TTG2 IgA	Jin SZ	2012	1	473	0.00%	1	478	0.00%	1.01 (0.06–16.20)
	Sidhom O	2012	0	47	0.00%	0	41	0.00%	1.06 (0.02–54.66)
	Cascella NG	2011	76	1401	5.42%	7	900	0.78%	7.32 (3.36–15.94)
	Dickerson F	2010	1	129	0.78%	0	151	0.00%	3.54 (0.14–87.64)
	Dickerson F	2010	1	191	0.52%	0	151	0.00%	2.38 (0.10–58.95)
	Samaroo D	2010	1	17	5.88%	22	25	88.00%	0.01 (0.00–0.09)
	Anti-DGP IgG	Jin SZ	2012	8	473	1.69%	10	478	2.09%
Dickerson F		2010	0	129	0.00%	1	151	0.66%	0.39 (0.02–9.60)
Dickerson F		2010	0	191	0.00%	1	151	0.66%	0.26 (0.01–6.47)
Samaroo D		2010	1	17	5.88%	22	25	88.00%	0.01 (0.00–0.09)
Anti-EMA IgA	Sidhom O	2012	0	47	0.00%	0	41	0.00%	1.06 (0.02–54.66)
	Peleg R	2004	0	50	0.00%	0	50	0.00%	1.0 (0.02–51.40)
	Rybakowski JK	1990	0	33	0.00%	99	99	100%	0.02 (0.00–0.25)
Anti-gluten	Reichelt KL	1995	5	48	10.42%	1	13	7.69%	1.40 (0.15–13.11)
	McGuffin P	1981	16	31	51.61%	12	30	40.00%	1.6 (0.58–4.41)
Anti-wheat	Rix KJB	1985	26	100	26.00%	24	100	24.00%	1.11 (0.59–2.11)
	Rix KJB	1985	5	86	5.81%	0	83	0.00%	11.27 (0.61–207.17)
	Sugerman AA	1982	2	10	20.00%	1	11	9.09%	2.50 (0.19–32.80)
	Mascord D	1978	5	31	16.13%	1	57	1.75%	10.77 (1.20–96.89)
	Hekkens WTJM	1980	19	44	43.18%	5	27	18.52%	3.34 (1.07–10.45)

Table 3
Pooled odds ratios for each serum biomarker of gluten sensitivity.

Biomarker	Study	Year	Pooled odds ratio with 95% confidence interval
Anti-gliadin IgG	Okusaga O	2013	2.31 [1.16, 4.58]
	Jin SZ	2012	
	Sidhom O	2012	
	Cascella NG (14)	2011	
	Dickerson F (10)	2010	
Anti-gliadin IgA	Jin SZ	2012	2.57 [1.13, 5.82]
	Sidhom O	2012	
	Cascella NG (14)	2011	
	Dickerson F (10)	2010	
	Reichelt KL (2)	1995	
Anti-DGP IgG	Jin SZ	2012	0.70 [0.30, 1.67]
	Dickerson F (10)	2010	
Other wheat protein antibodies			
Anti-gluten	Reichelt KL (2)	1995	1.93 [1.21, 3.08]
	McGuffin P (19)	1981	
Anti-wheat	Rix KJB (11)	1985	1.93 [1.21, 3.08]
	Sugerman AA (21)	1982	
	Mascord D (8)	1978	
	Hekkens WTJM (12)	1980	
Anti-gliadin (unspecified immunoglobulin isotype)	Hekkens WTJM (15)	1978	1.93 [1.21, 3.08]
	Dohan FC (16)	1972	
Anti-TTG2 IgA	Jin SZ	2012	5.86 [2.88, 11.95]
	Sidhom O	2012	
	Cascella NG (14)	2011	
	Dickerson F (10)	2010	
Anti-TTG2 IgG	Dickerson F (10)	2010	1.47 [0.65, 3.33]

that reported no association between gluten sensitivity and non-affective psychoses since no power calculations were included in the studies. Only one study measured anti-TTG2 IgG, and only odds ratios were available (no raw data provided). Therefore, a power calculation could not be performed. Power calculations were not performed for anti-deamidated gliadin or anti-EMA because no patients with schizophrenia demonstrated elevations in these antibodies. Two studies measured anti-gluten, their total sample size was 79 patients and 43 controls. The power to detect a difference between the two groups was 12.2% at a significance level of $p < 0.05$.

Fig. 2 depicts selected forest plots from the meta-analysis: Anti-Gliadin IgG, Anti-Gliadin IgA, and Anti-TTG2 IgA. The results of the chi-square test for heterogeneity are displayed below each forest plot in Fig. 2.

3.2. Quality assessment

Several observations can be made from the quality assessment depicted in Table 4. First, the majority of the studies were determined to be of average quality. Based on our quality assessment criteria, there was a trend toward the newer studies (published after 1995) being of higher quality compared to the older studies.

Overall weaknesses of the current research included the following: In terms of sampling, only 9 of 17 studies made an attempt to demonstrate that their sample was representative of the larger population of patients with non-affective psychoses. Therefore, there may have been significant biases in sampling. With regard to statistical analysis, it is worth mentioning that no studies included a power calculation, and only 7 out of 17 studies used a regression type analysis to ensure that covariates between the patients and controls did not account for the observed differences in gluten sensitivity.

Three recent larger studies stood out as being of higher quality than most. These were the studies published by Dickerson et al. (2010), Cascella et al. (2011), and Okusaga et al. (2013). All three of these groups demonstrated that their study samples were representative of the general population with non-affective psychoses, and included a regression analysis to examine whether differences in gluten sensitivity between the control and study samples could be accounted for by other demographic variables. One important feature of the control group in the Cascella study has not been addressed thus far. The control group in this study was recruited from a primary health care population who responded to a questionnaire indicating that they had an elevated risk for Celiac disease. We have specifically mentioned this detail here because this study contributed a substantive amount of data to the current meta-analysis because it was so large. It is possible that the control group had a higher rate of gluten sensitivity compared to the general population, and this may have decreased the odds ratios for the various biomarkers studied.

On the other hand, it is also worth taking a closer look at the findings from the studies that were determined to be of poorer quality. Three out of four studies with a quality assessment score of less than ten had either non statistically significant odds ratios for the particular serum biomarker of gluten sensitivity studied, or the odds ratios were less than one.

4. Discussion

4.1. Summary

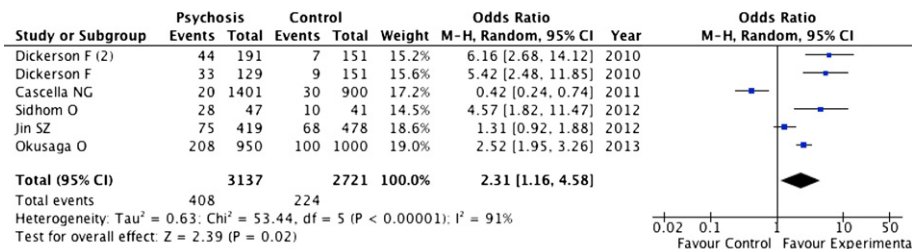
We found that five serum biomarkers of gluten sensitivity are elevated in patients with non-affective psychosis compared to controls. When analyzed together, anti-gluten antibodies (anti-gluten, AGA unspecified immunoglobulin isotype, and anti-wheat) were also significantly elevated in the patient group compared to controls. This difference was found in studies carried out over 4 decades. As demonstrated by our data, the following 5 serum biomarkers of gluten sensitivity were elevated in patients with non-affective psychoses compared to a control group: Anti-Gliadin IgG, Anti-Gliadin IgA, Anti-TTG2 IgA, Anti-Gliadin (unspecified isotype) and Anti-Wheat. This is consistent with the findings by Samaroo et al. (2010), that individuals with schizophrenia exhibit a novel immune response to gluten. Samaroo et al. (2010) sought to characterize the molecular specificity and mechanism of the immune response to gluten in a subset of patients with schizophrenia with an elevated anti-gliadin antibody titre. In contrast to individuals with Celiac disease, this group found that the majority of gluten sensitive patients with schizophrenia did not show elevated levels of anti-DGP or anti-TTG2 IgA. This is consistent with the immune response to gluten found in individuals with gluten sensitivity (Volta et al., 2012). In addition, specimens from representative subjects in the Samaroo study were further characterized using immunoblotting. This technique revealed that antibodies from the individuals with schizophrenia bound to a limited repertoire of fractionated gluten proteins compared to antibodies from individuals with Celiac disease (Samaroo et al., 2010). Taken together, the findings from this paper suggest a shared and distinct immune response to gluten in a subset of individuals with schizophrenia.

4.2. Limitations

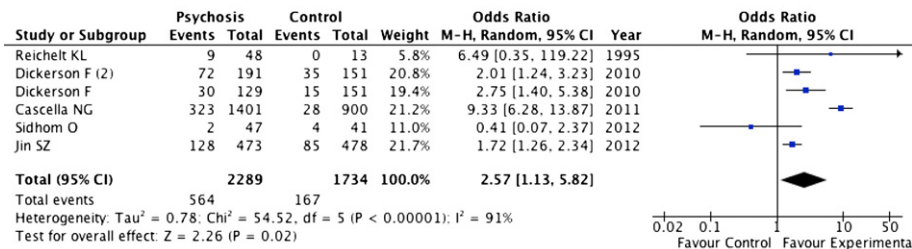
The heterogeneity of the data collected for the current paper precluded the ability to perform a meta-analysis of the results of all relevant studies. For instance, there was significant variation in the laboratory tests with regard to both the specific biomarker measured, and the bio-assay used. In addition, there was variation in the patient populations studied. For example, duration of illness, duration of anti-psychotic treatment, diet, and presence of gastrointestinal symptoms varied

Selected Forest Plot Analysis

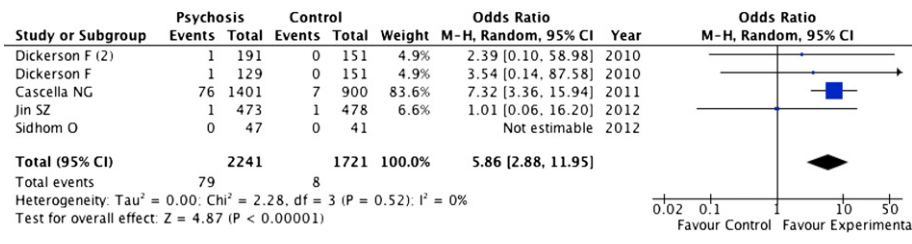
2.1 Anti-Gliadin IgG



2.2 Anti-Gliadin IgA



2.3 Anti-TTG2 IgA



Legend: (2) refers to the population with multi-episode schizophrenia in the Dickerson study.

Fig. 2. Selected forest plot analyses.

among patient populations. Furthermore, some control groups were screened for the absence of psychiatric disorder while others were not.

A historical perspective is warranted when considering the variety of laboratory methods and biomarkers included in this review. For instance, antibodies to gluten were discovered in 1964 however, anti-EMA was only identified in 1973. What is more, anti-TTG2 and anti-DGP were not identified until the late 1990s. This explains why these biomarkers could not have been studied in some of the earlier papers. Similarly, as a laboratory method, ELISA was first invented in 1971 (Tommasini et al., 2011).

Among studies included in the meta-analysis, statistical heterogeneity was demonstrated using the chi-square test.

Lastly, the current paper is not without bias. Mostly English language articles published in peer-reviewed journals and indexed in online databases were used. Two books were identified via hand searching the references of key review articles. This may have resulted in selection bias. In addition, sampling bias was likely present. This occurred primarily because the articles used in the current study were published over four decades. For example, older research studies were based almost exclusively on inpatients, while newer research tended to include a mix of inpatients and outpatients. Also, the diagnostic criteria for schizophrenia have evolved over the time period that this research was conducted.

4.3. Conclusion

Certain serum biomarkers of gluten sensitivity are elevated in patients with non-affective psychoses. Moreover, the specific immune response to gluten in this population differs from that found in patients with Celiac disease.

4.4. Future questions/directions

Based on the current literature, it appears that patients with non-affective psychoses demonstrate a different immune response to gluten than individuals with Celiac disease. A finding such as this may help us to uncover the pathogenesis of this immune response and may provide further insight into the etiology of non-affective psychoses in a subset of patients.

***The patient group in the study by Dickerson et al. (2010) was separated into recent onset psychosis and multi-episode schizophrenia. Both groups showed elevations in certain biomarkers of gluten sensitivity, which demonstrates that these abnormalities are present both early and late in the disease process. Of note, anti-gliadin IgA was more strongly elevated in the recent onset group—the significance of this is unknown (Dickerson et al., 2010). In addition, the vast majority of

Table 4
Quality assessment scores for each study.

First author, year	Total score/30	Sample of patients	Method of diagnosis	Assessment of comorbidity	Control sample	Control sample diagnosis	Power	Biomarkers/ antibodies	Methods	Analysis
Dickerson, 2010	25	2	4	2	1	4	0	4	4	4
Okusaga, 2013	23	2	4	2	1	4	0	2	4	4
Sidhom et al., 2012	19	1	4	1	1	4	0	2	4	2
Cascella, 2011	19	2	4	0	1	0	0	4	4	4
Rix 1985	19	1	4	1	2	2	0	2	4	4
Samaroo 2005	18	0	4	2	0	0	0	4	4	4
Peleg et al., 2004	17	2	1	0	2	2	0	2	4	4
Sugerman et al., 1982	15	1	4	1	1	2	0	2	4	0
Reichelt 1995	14	0	4	1	1	2	0	2	4	0
Jin et al., 2012	13	1	4	1	1	0	0	2	4	0
McGuffin et al., 1981	13	0	4	1	1	2	0	1	4	0
Mascord 1978	10	0	1	0	2	2	0	1	4	0
Rybakowski et al., 1990	8	0	1	0	1	0	0	2	4	0
Hekkens 1980	7	0	0	0	2	0	0	1	4	0
Kinnell et al., 1982	7	2	1	0	1	0	0	1	2	0
Dohan et al., 1972	6	0	1	0	1	0	0	0	4	0
Hekkens, 1978	5	0	0	0	0	0	0	1	4	0

patients included in the meta-analysis were taking anti-psychotic medication. In a recent paper, Severance EG et al. found that anti-psychotic naïve individuals with schizophrenia exhibited higher levels of ASCA (Anti *Saccharomyces Cerevisiae* Antibody), a marker of gastrointestinal inflammation used as a diagnostic aid in Crohn's disease, compared to those who had been treated with anti-psychotic medications (Severance et al., 2012). Therefore, it may be possible that treatment with anti-psychotic medications could alter the rate of gluten sensitivity in individuals with schizophrenia. Future research is required in order to appreciate the implications of these findings.

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Laura R. Lachance was provided with office space, printing, and software resources to conduct the current research project.

Contributors

LRL - first author, designed and conducted search, performed data analysis, wrote the paper, developed the research question. KM - verified data extraction and acted as second rater for search results, provided feedback to first author for editing, helped develop quality assessment.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.schres.2013.12.001>.

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