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Gluten contamination in labelled gluten-free, naturally gluten-free and meals in food services in low-, middle- and high-income countries: a systematic review and meta-analysis

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Abstract

The gluten-free diet is based on the consumption of foods without gluten, which aims to manage celiac disease. The concern of celiac patients is that these foods should be safe. However, gluten contamination can affect these foods. The objectives of this review and meta-analysis were first, to identify articles that detected gluten contamination in gluten-free foods using validated methods. Second, to quantify the overall prevalence of gluten contamination of naturally gluten-free foods, labelled gluten-free products, and meals prepared in food services. Third, to highlight the influence of the country's income and the period of study on this prevalence. The studies were identified in Scopus, Science Direct, Web of Science, PubMed, and Google Scholar. Forty articles were included according to PRISMA guidelines. The statistical meta-analysis was performed using MedCalc 19 software. The results show that in the gluten-free foods analysed, the overall prevalence of gluten contamination was estimated at 15.12% (95% CI: 9.56%–21.70%), with more than 20 mg/kg of gluten. Naturally gluten-free foods were significantly more contaminated than labelled gluten-free products and than meals in food services (28.32%; 9.52%; 4.66% respectively; $p < 0.001$). Moreover, it was noticed that oats were the most contaminated food. In addition, the prevalence of gluten contamination has significantly decreased over time. The majority of the studies were carried out in upper-middle-income and high-income countries, while only one study was conducted in lower-middle income countries. Therefore, it is necessary to implement preventive actions to reduce gluten contamination, ensuring safe gluten-free foods for celiac patients, including low-income countries.

Key words: Coeliac disease: Gluten-free diet: Labelled gluten-free: Naturally gluten-free: Meals in food services: Gluten contamination.

Coeliac disease (CD) is an autoimmune disorder characterised by chronic enteropathy occurring after exposure to gluten in genetically predisposed individuals[1]. The main genetic risk factors for this disease are class II human leukocyte antigens DQ2 and DQ8[2]. CD affects between 0·7 % and 1·4 % of the world's population[3]. It is characterised by a villous atrophy of the small intestine, caused by the absorption of gluten proteins contained in wheat (gliadin), rye (secalin) and barley (hordein)[4]. The disease manifests by typical symptoms such as weight retardation in children, diarrhoea, abdominal bloating and symptoms of under nutrition[5], with a deterioration of nutritional status[6,7]. However, it can be asymptomatic, latent or silent[8] and may be revealed in all age groups even in elderly population[9]. Serological tests (anti-transglutaminase

Abbreviations: AOCA, Association of Official Analytical Collaboration; CD, coeliac disease; FDA, Food and Drug Administration; GFD, gluten-free diet; HIC, high-income countries; L-GF, labelled gluten-free; LIC, low-income countries; LMIC, lower-middle-income countries; N-GF, naturally gluten-free foods; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.

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antibodies, anti-deamidated gliadin peptide antibodies and anti-endomysium antibodies) and duodenal biopsy are used to confirm the diagnosis[10]. Once CD is confirmed, a lifelong gluten-free diet (GFD) is indicated[11]. This consists of excluding any food containing or suspected of containing gluten from wheat, rye and barley. This diet must be balanced; it combines naturally gluten-free (N-GF) foods and foods processed by manufacturers and labelled as gluten-free (L-GF)[12]. The increasing prevalence and incidence of CD over time have led producers to intensify the production of gluten-free foods[13]. As a result, the turnover of gluten-free food sales has increased considerably. The global market has been estimated at $14·94 trillion in 2016 and is expected to grow by 9·3 % annually between 2017 and 2025[14]. However, the low availability of gluten-free products on the market, their exorbitant price and sometimes the lack of labelling influences the adherence to GFD[15].

Labelling is a major concern for coeliac patients to differentiate so-called 'gluten-free' products, and the exact gluten content in such products remains essential for them. The Codex Alimentarius[16], the European Commission[17] and the Food and Drug Administration (FDA)[18] require a gluten content of <20 mg/kg for food to be labelled 'gluten-free'. Nevertheless, 'hidden gluten' may exist in N-GF foods and/or in industrial products labelled as 'gluten-free'. Accidental contamination may occur at any step, from field to shelf, due to the presence of these proteins during harvesting, transport, processing and storage[19,20]. This may happen particularly in the absence of a control system and an adequate allergen management plan integrated into Hazard Analysis and Critical Control Point. For this reason, there is a need for regular controls of gluten-free foods at the points of sale. In this sense, researchers have developed several methods whose objective was to qualitatively and/or quantitatively detect the gluten content. The main techniques used for this detection are subdivided into two: immunological techniques which include ELISA, Western blot, lateral flow devices and biosensors; and non-immunological techniques where gluten quantification is based on proteomic methods such as MS techniques and DNA amplification by PCR[21–24]. It is important to note that the Codex Alimentarius recommends the use of immunological techniques, with a quantification level below 10 mg/kg. In fact, Codex Alimentarius recommends the use of R5 ELISA, while FDA suggests the use of scientifically valid methods, like ELISA[25]. In fact, several other assays have been used, provided that they are validated and approved by certain organisations such as the Association of Official Analytical Collaboration (AOCA) and the American Association of Cereal Chemists International.

Thus, the objectives of this review and meta-analysis are first, to identify articles that have detected the gluten contamination in gluten-free foods using the methods required by FDA, Codex Alimentarius and/or those validated by the AOCA. Second, to quantify the overall prevalence of this contamination as well as that of N-GF foods, L-GF products and meals distributed in food services. Third, to highlight the influence of the country income and the study period on the prevalence of gluten contamination.

Methods

Protocol and registration

This meta-analysis focused on studies that assessed the gluten content in foods as the main subject of research. Therefore, the registration of this protocol in the International Prospective Register of Systematic Reviews 'PROSPERO' is not required.

Eligibility criteria

Review question. This review has been conducted according to the guidelines of 'Preferred Reporting Items for Systematic Reviews and Meta-analyses' (PRISMA)[26]. PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analysis[27]. Online supplementary material 1 shows a copy of the PRISMA checklist, indicating the corresponding sections in this article. The review question of this research aimed to answer the following main questions: 'Which studies have investigated gluten contamination of food stuffs?' and 'What was the reported gluten contamination prevalence in each study?' Other questions aimed to compare and highlight the potential impact of some factors on the prevalence of food contamination, like the country income and the time of food collection.

Inclusion criteria. To carry out this meta-analysis, the selected studies should meet the following criteria:

- studies conducted using a method adopted by Codex Alimentarius or FDA and/or other methods validated by AOCA;
- studies conducted on N-GF foods, L-GF products and/or meals in food services;
- studies published either in English or French, including those of which the abstract is available in English or in French;
- studies published between 1 January 2000 and 1 June 2020.

Exclusion criteria. Were excluded from this analysis:

- article reviews, book chapters, case reports;
- studies that did not indicate the prevalence of gluten contamination;
- qualitative studies that indicated only the presence or absence of gluten contamination without quantification according to Codex Alimentarius and FDA standards;
- clinical studies conducted in coeliac patients to determine the amount of gluten consumed.

Sources of information. The exploited studies were selected mainly through Scopus, Web of Science, Science Direct, PubMed and Google Scholar research databases. The research was conducted between April and June 2020. The research algorithm contained combinations of keywords in the following categories: topic (e.g. 'Gluten contamination', 'Gluten detection', 'Gluten quantification', 20 mg/kg, 20 ppm, secalin, hordein, gliadin); population (e.g. 'Gluten-free products', 'Meals in food services', 'Naturally gluten-free food'); outcome (e.g. 'prevalence of gluten contamination') and methods (e.g. ELISA, PCR, HPLC, Western blot, MS, Electrophoresis).

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Research strategy. Online supplementary material 2 details the algorithm strategy adopted during this research. It indicates the dates, the platform/interface, the databases, the terms used, the conjunctions used (search string) and the number of results obtained.

Study selection. First, two postgraduate students were appointed to conduct an advanced research on studies whose abstracts, titles or keywords are relevant to the topic of this research. These students independently identified duplicate studies by eliminating those that did not fit the inclusion criteria on basis of their abstracts. Second, the two postgraduate students read the full text of the articles in order to apply the inclusion and exclusion criteria. Then, two professors were notified in case of disagreement on the eligibility of an article. Finally, the list of included studies was sent to three professors in order to take into consideration their remarks and suggestions.

Data collection process. Using a designed data collection form, we collected the following information: reference, authors (years), country, methods of gluten analysis, categories of food analysed, sample size analysed, number of products L-GF, number of N-GF products, number of meals in food services, main categories of contaminated food, prevalence of gluten contamination and years of food collection.

Risk of bias. Each document included in this review is a multi-question whose objective was to assess the risk of bias using the Meta-analysis of Statistics Assessment and Review Instrument protocol[28]. Cochrane Collaboration's tool was used to assess the risk of bias[29]. Based on the answers to the questions (yes/no), the risk of bias was subdivided into three categories. Items are considered as 'Low' risk if the percentage of positive responses (yes) was >70 %. Items as 'Moderate' or 'High' risk if the percentage of positive responses (yes) were between 50 % and 70 % or <50 %, respectively.

The risk of bias was assessed through the following questions:

1- Were gluten-free products, N-GF foods and/or meals in food services indicated?
2- Was the method of analysis indicated?
3- Was the method used in the analysis required or validated by Codex Alimentarius, FDA, AOCA and/or American Association of Cereal Chemists International?
4- Was the method of gluten extraction well described in the Method section of the study ?
5- Was the prevalence of contaminated foods reported?
6- Was the prevalence of contaminated foods above 20 mg/kg reported?
7- Were the major types of contaminated foods reported?
8- Was the year of the study indicated in the full text?
9- Has the study received any funding source?

Studies included. Figure 1 shows an adapted PRISMA diagram of the research about identification, selection, eligibility and included items. The research identified 175 studies through Science Direct, 304 through Scopus, 1843 through a Web of Science, forty-eight through PubMed and ten through Google Scholar. The references of the reviewed articles were used to detect if there were any articles not included. This resulted in the identification of 2380 articles, and eighty of them were excluded after checking for duplicates. The application of the inclusion and exclusion criteria in the selection and eligibility of abstracts resulted in forty-five papers, and the eligibility on full-text articles allowed the inclusion of forty articles after excluding five others.

Synthesis and analysis. The use of a model type of meta-analysis (Random effects, Fixed effects or Mixed effects) depended primarily on the existence or absence of heterogeneity. The forest plots were based on the prevalence of gluten contamination with a 95 % CI on a logarithmic scale. Heterogeneity was measured using I^2 method[30,31]. I^2 represents the percentage of variability in results between studies due to heterogeneity rather than sampling error[32]. The value of I^2 indicates the strength of heterogeneity. Moderate heterogeneity corresponds to an I^2 value between 50 % and 75 %, and high heterogeneity corresponds to an I^2 value >75 %. While a value below 50 % indicates homogeneity between study results. Forest plots were also used to demonstrate clear heterogeneity. Meta-analysis was conducted using MedCalc statistical software version 19.4 (MedCalc Software bv; https://www.medcalc.org; 2019). The word frequency for estimating the main categories of analysed and contaminated food was carried out by the NVIVO software. This software makes it possible to know the most contaminated gluten-free foods. Therefore, this would be useful to suggest recommendations about precautions to consider during the manufacturing, distribution and consumption processes of these foods. ANOVA tests were used to investigate the significance between different factors such as the country incomes, the year of study and the type of gluten-free foods.

Results

Excluded and included studies

Some studies were excluded because they only indicated the presence or absence of gluten contamination of foods without determining the prevalence of food contamination levels[33–35]. Some other studies have been excluded for various reasons such as publication date[36] and the used methods[37]. Online supplementary material 3 (Excluded studies) gives more information about the excluded studies. The results presented by Bustamante *et al.*[38] covered two periods (1998–2002 and 2003–2016), and as our study included the data of the last two decades, we only considered those of the second period (2003–2016). The included studies cover the three categories of gluten-free foods. The first was N-GF foods (no wheat/barley/rye on ingredients), the second was about industrial foods labelled as 'gluten-free' by manufacturers and the third concerns certain gluten-free meals presented in food services. The majority of studies focused on L-GF and N-GF (34/40), and only six of them studied meals in food services.

Methods used to estimate the prevalence of gluten contamination

All studies included in this review used the ELISA method as recommended by the Codex Alimentarius. The Ridascreen Gliadin R5 Sandwich ELISA was the most used kit. Some other studies have used R5 Skerritt[38–40] or G12[41]. Western blot has generally

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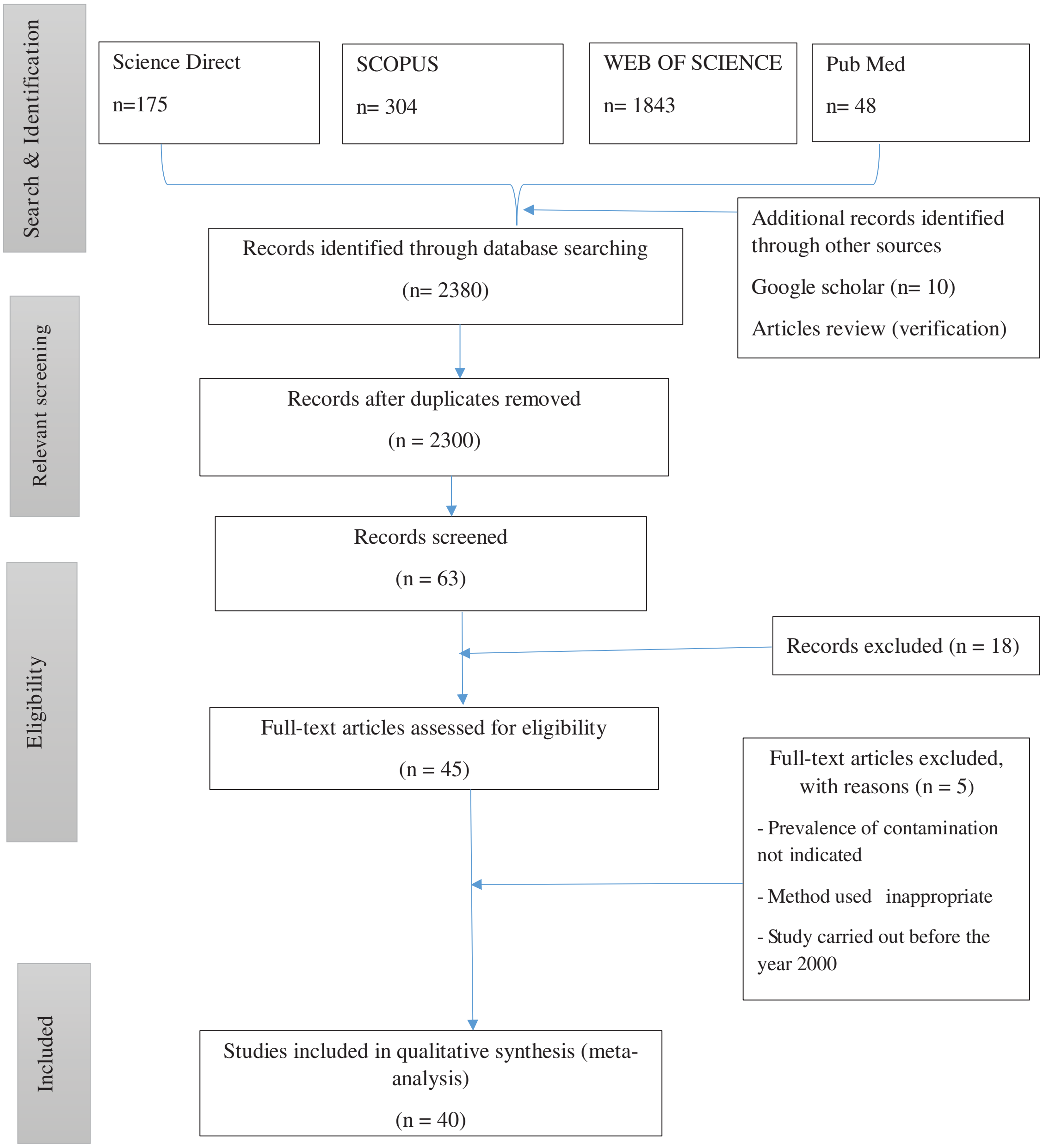

Fig. 1. Adapted version of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2009 flow diagram of literature search and selection criteria*.

been used as a complementary method to ELISA[42,43], and in parallel, some of the studies have used a PCR method[43–48] (Tables 1, 2 and 3).

Prevalence of gluten contamination according to food categories

The number of gluten-free foods analysed over the last two decades has reached 25 689. Gluten contamination of foods was absent in some studies[49–51], while it ranged from 0·5 % to 88 % in others[52,53]. This meta-analysis revealed an overall prevalence of gluten contamination estimated to 15·12 % (95 % CI 9·56 %, 21·70 %). The percentage of variability in outcomes across studies shows that I^2 was 99·28 % (95 % CI 99·20 %, 99·35 %). This suggests the existence of heterogeneity in the results. The number of analysed L-GF, N-GF and meals in food services was 20 938, 3586 and 798, respectively. Some studies did not specify the categories of food analysed[53,54]. A statistical comparison has shown that N-GF were significantly more contaminated than L-GF and meals in food services, respectively (28·32 % (95 % CI 18·60 %, 39·19 %); 9·52 % (95 % CI 4·76 %, 15·72 %); 4·66 % (95 % CI 1·39 %, 9·72 %); $P < 0·001$). Fig. 2(a), (b) and (c) (Forest plot) shows the prevalence of gluten contamination in each study in N-GF foods, gluten-free meals in food services and L-GF products, respectively.

Main categories of food analysed and contaminated

The articles included in this review show that the researchers analysed a wide variety of gluten-free foods. The frequency

Table 1. Description of characteristics, methods and results of studies about gluten contamination of 'Naturally gluten-free foods'

Authors, year (reference)	Country (income)*	Methods of gluten analysis	Main food categories analysed	Sample size	Main categories of contaminated food	% of contamination †
Raju *et al.*, 2020[55]	India (LMIC)	Ridascreen Gliadin R5 Competitive ELISA	Breakfast products, flours, batters, Oats	109	Oats, flour	36·7 %
Rysová *et al.*, 2019[44]	Czech (HIC)	Ridascreen Gliadin R5 Sandwich ELISA, PCR	Oats	35	Oats	83 %
Bustamante *et al.*, 2017[38]	Spain (HIC)	ELISA R5 Skerritt, R5 antibody Transia Plate Gluten, INGEZIM Gluten	Flours, breakfast cereals, bars, bakery, pasta, breads, dough, snacks and yeasts	962	Breakfast cereals, bars, bakery, pasta, breads, dough, snacks	8 %
Verma *et al.*, 2017[98]	Italy (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Oats, buckwheat, lentils, chickpeas, maize, mixed seeds, quinoa, chocolate	107	Oats, buckwheat, lentils	14·95 %
Mattioni *et al.*, 2016[99]	Brazil (UMIC)	ELISA R5 Antibody transia plate prolamne (AACC international method approved)	All food groups except fruits and meat	17	–	23·53 %
Thompson *et al.*, 2016[94]	USA (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Breakfast cereal, spices, snacks, seasoning mix, green tea leaves, oat cereal, legume, oat fibre	101	–	4·9 %
Sharma *et al.*, 2015[42]	USA (HIC)	Morinaga wheat protein sandwich ELISA, Ridascreen Gliadin R5 Sandwich ELISA; Western blotting	Grains, seeds, nuts, legumes, condiments, sauces, curry, soup, soup mixes, pasta products, breakfast cereals, snack foods, granola, bars, energy bars, beverages, ice creams, frozen desserts, meat, meat substitutes, refrigerated or frozen foods, oats	186	Grains, seeds, nuts, legumes, condiments, sauces, pasta, breakfast cereals, snack, meat, meat substitutes, refrigerated or frozen foods, oats	19·3 %
Koerner *et al.*, 2013[100]	Canada (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Flours starches, soya, millet, buckwheat	298	Soya, millet, buckwheat	10·1 %
Agakidis *et al.*, 2011[39]	Greece (HIC)	Skerritt: high sensitivity ω-gliadin (ELISA)	Flours, dairy products, sweets, miscellaneous	15	Flours, dairy products	13·3
Daniewski *et al.*, 2010[101]	Poland (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Variety of food groups such as pasta, bread, biscuits, bakery, flakes, flour	19	Pasta, bread, biscuits, bakery, flakes, flour	10·5 %
(Plazza-Silva, 2010)[97]	Brasil (UMIC)	Ridascreen Gliadin R5 Sandwich ELISA	Variety of food groups	86	–	9·3 %
Thompson *et al.*, 2010[102]	USA (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Grains, seeds, flours such as millet flour and grain, White rice flour, buckwheat flour, sorghum flour, soya flour	22	Millet flour and grain, white rice flour, buckwheat flour, sorghum flour, soya flour	32 %
Gélinas *et al.*, 2008[46]	Canada (HIC)	Ridascreen Gliadin R5 Sandwich ELISA, PCR	Variety of food groups such as breakfast cereals, cookies, pancake, flour, sauce	71	Breakfast cereals, cookies, pancake, flour, sauce	22·5 %
Hernando *et al.*, 2008[43]	Europe, the USA and Canada (HIC)	Ridascreen Gliadin R5 Sandwich ELISA, Western blot, PCR (Q-PCR)	Oats	134	Oats	57·5 %
Collin *et al.*, 2004[93]	Finland (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Cereals	24	–	45·83 %
Thompson, 2004[103]	USA (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Oats	12	Oats	75 %
Storsrud *et al.*, 2003[47]	Sweden (HIC)	ELISA, PCR	Oats, maize, rice, millet or buckwheat	22	Oats, rice, maize, buckwheat, millet	49·9 %
Valdés *et al.*, 2003[104]	Spain & other European counties (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Wheat starch, maize, oats, rice,	1366	Wheat starch, maize, oats, rice, gluten-free products	41·73 %

LMIC, lower-middle-income countries; UMIC, upper-middle-income countries; HIC, high-income countries; N-GF, naturally gluten-free food; AACC, American Association of Cereal Chemists; QC-PCR, quantitative competitive-PCR.
* Classification according to the World Bank[91].
† Gluten contamination above 20 mg/kg.

Table 2. Description of characteristics, methods and results of studies about gluten contamination of 'Labelled gluten-free products'

Authors, year (reference)	Country (income)*	Methods of gluten analysis	Main food categories analysed	Sample size	Main categories of contaminated food	% of contamination†
Raju *et al.*, 2020[55]	India (LMIC)	Ridascreen Gliadin R5 Competitive ELISA	Breakfast products, flours, batters, Oats	51	Oats, flour	9·8 %
Atasoy *et al.*, 2020[105]	Turkey (UMIC)	Ridascreen Gliadin R5 Sandwich ELISA	Pasta, bread, cookie, cracker, farina, buckwheat	200	Buckwheat	17·5 %
Rysová *et al.*, 2019[44]	Czech (HIC)	Ridascreen Gliadin R5 Sandwich ELISA, PCR	Oats	6	Oats	0 %
Halmos *et al.*, 2018 a[41]	Australia (HIC)	Ridascreen Gliadin Sandwich ELISA R5 & G12	Fruit, muesli bar, noodles, cracker, rice snacks, dry pasta	300	Fruit, muesli bar	0·66 %
Bustamante *et al.*, 2017[38]	Spain (HIC)	ELISA R5 Skerritt, R5 antibody Transia Plate Gluten, INGEZIM Gluten	Flours, breakfast cereals, bars, bakery, pasta, breads, dough, snacks and yeasts	1652	Breakfast cereals, bars, bakery, pasta, breads, dough, snacks	3·2 %
Hassan *et al.*, 2017[106]	Lebanon (UMIC)	Ridascreen Gliadin Sandwich ELISA R5	Grains, pasta products, soups, baking mixes, baked foods, breakfast cereals, snack foods, baby foods	173	Pasta products, baking mixes, baked foods, breakfast cereals, baby foods	6 %
Losio *et al.*, 2017[107]	Italy (HIC)	Ridascreen Gliadin Sandwich ELISA R5	Dry pasta, flours: maize, rice, quinoa, buckwheat and swabs	12 239	Dry pasta, flours: maize, rice, quinoa, buckwheat, swabs	0·8 %
Verma *et al.*, 2017[98]	Italy (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Oats, buckwheat and lentils as compared with chickpeas, maize, mixed seeds, quinoa, chocolate	93	Oats-, buckwheat-, and lentils-based items	2·15 %
Farage *et al.*, 2016[108]	Brasil (UMIC)	Ridascreen Gliadin R5 Sandwich ELISA	Bakery product	130	Bakery product	21·5 %
Forbes & Dods, 2016[50]	Australia (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Crackers, bread and biscuits, cereals, flour, grains , condiments and sauces, spices, pasta, drinks and soups, and confectionary and snacks	169	–	0 %
Fritz and Chen, 2016[109]	USA (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Oats	965	Oats	1·76 %
Mattioni *et al.*, 2016[99]	Brazil (UMIC)	ELISA R5 Antibody transia plate prolamne (AACC international method approved)	All food groups except fruits and meat	306	–	15·68 %
Sharma *et al.*, 2015[42]	USA (HIC)	Morinaga wheat protein sandwich ELISA, Ridascreen Gliadin R5 Sandwich ELISA; Western blotting	Grains, seeds, nuts, legumes, condiments, sauces, curry, soup, soup mixes, pasta, breakfast cereals, snack, granola, bars, beverages, ice creams, frozen desserts, meat, meat substitutes, refrigerated or frozen foods, oats	275	Grains, seeds, nuts, legumes, condiments, sauces, pasta, breakfast cereals, snack, meat, meat substitutes, refrigerated or frozen foods, oats	1·1 %
Thompson & Simpson, 2015[63]	USA (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Baking ingredients, beverages, bread, chilli, condiments, cookies, crackers, entrees, flour, grains, gravy, hot cereal, mixes, nuts and seeds, pasta, snack bars, snack food, soup, spices, tortillas	158	–	5·1 %
Lee *et al.*, 2014[110]	USA (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Breakfast cereals, pasta, bread, tortilla, snack food, baking mix, rice, maize	78	Rice, maize, mixed grains, maize-based foods	20·5 %
Gibert *et al.*, 2013[52]	Italy, Spain, Germany and Norway (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Bread, pasta, pastry, biscuits, pizza, breakfast cereals	205	Bread, pasta, pastry, biscuits, pizza, breakfast cereals	0·5 %

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Table 2. (*Continued*)

Authors, year (reference)	Country (income)*	Methods of gluten analysis	Main food categories analysed	Sample size	Main categories of contaminated food	% of contamination†
Koerner *et al.*, 2013[100]	Canada (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Flours starches, soya, millet, buckwheat	268	Soya, millet, buckwheat	1·11 %
Thompson & Grace, 2013[95]	USA (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Beans, beverages, breads, cookies, entrees, flours, grains, gravy, hot cereals, baking mixes, nut, pastas, snack bars, crackers, tortilla chips, soups, tortillas.	112	–	3·57 %
Agakidis *et al.*, 2011[39]	Greece (HIC)	Skerritt: high sensitivity ω-gliadin (ELISA)	Flours, dairy products, sweets, miscellaneous	26	Flours, dairy products	7·70 %
Cawthorn *et al.*, 2010[45]	South Africa (UMIC)	Ridascreen Gliadin R5 Sandwich ELISA, PCR	Buckwheat, rice, millet, maize, oats, porridges, rice- and maize-based cereals	8	–	50 %
Daniewski *et al.*, 2010[101]	Poland (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Variety of food groups such as pasta, bread, biscuits, bakery, flakes, flour	22	Pasta, bread, biscuits, bakery, flakes, flour	27·3 %
Laureano & Sliva, 2010[111]	Brasil (UMIC)	Immunological graphic test, Ridascreen Gliadin R5 Sandwich ELISA	Bread, flours, dough, sauce, cereal bars, snacks	70	Bread, flours, dough, sauce, cereal bars, snacks	12·9 %
Plazza-Silva, 2010[97]	Brasil (UMIC)	Ridascreen Gliadin R5 Sandwich ELISA	Variety of food groups	115	–	13 %
Gélinas *et al.*, 2008[46]	Canada (HIC)	Ridascreen Gliadin R5 Sandwich ELISA, PCR	Variety of food groups such as breakfast cereals, cookies, pancake, flour, sauce	77	Breakfast cereals, cookies, pancake, flour, sauce	9·09 %
Collin *et al.*, 2004[93]	Finland (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Cereals	59	–	22·03 %
Storsrud *et al.*, 2003[47]	Sweden (HIC)	ELISA, PCR	Oats, maize, rice, millet or buckwheat	78	Oats, rice, maize, buckwheat, millet	50 %
Valdés *et al.*, 2003[104]	Spain and other countries (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Wheat starch, maize, oats, rice, gluten-free products	3088	Wheat starch, maize, oats, rice, gluten-free products	34·1 %
Dahinden *et al.*, 2001[48]	Switzerland (HIC)	Ridascreen Gliadin R5 Sandwich ELISA, QC-PCR	Cereals, bread, industrialised baby food	15	Baby food	6 %

LMIC, lower-middle-income countries; UMIC, upper-middle-income; HIC, high-income countries; L-GF, labelled gluten-free food; N-GF, naturally gluten-free food; AACC, American Association of Cereal Chemists; QC-PCR, quantitative competitive-PCR.
* Classification according to the World Bank[91].
† Gluten contamination above 20 mg/kg.

Table 3 Description of characteristics, methods and results of studies about gluten contamination of 'Gluten-free Meals in food service'

Authors, year (reference)	Country (income)*	Methods of gluten analysis	Main food categories analysed	Sample size	Main categories of contaminated food	% of contamination †
Farage *et al.*, 2019[112]	Brazil (UMIC)	Ridascreen Gliadin R5 Sandwich ELISA	Dishes in food service	180	Dishes in food service	2·8 %
Bianchi *et al.*, 2018[49]	Brazil (UMIC)	Ridascreen Gliadin Sandwich ELISA R5	Gluten-free pizza restaurant	56	–	0 %
Halmos *et al.*, 2018 b[113]	Australia (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Chicken burger, banana bread, calamari	158	Chicken burger, banana bread, calamari	5·7 %
Vincentini *et al.*, 2016[51]	Italy (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	Pizza	84	Pizza	0 %
Oliveira *et al.*, 2014[40]	Brasil (UMIC)	ELISA R5 Skerritt	Beans	60	Beans	16·6 %
McIntosh *et al.*, 2011[96]	Ireland (HIC)	Ridascreen Gliadin R5 Sandwich ELISA	All food groups	260	–	10 %

UMIC, upper-middle-income; HIC, high-income countries.
* Classification according to the World Bank[91].
† Gluten contamination above 20 mg/kg.

analysis of contaminated foodstuffs carried out using the NVIVO software shows that the oat was the most contaminated food, followed by buckwheat, pasta, rice and maize.

Impact of the study period on the prevalence of gluten contamination

The number of studies has increased considerably over time; it was limited to eight between 2000 and 2008 and reached thirteen and seventeen during 2009–2014 and 2015–2020 periods, respectively. The overall prevalence of gluten contamination was significantly decreasing during these three periods (36·79 % (95 % CI 35·12 %, 38·58 %); 18·87 % (95 % CI 8·45 %, 32·24 %); 7·60 % (95 % CI 6·76 %, 8·50 %); $P = 0{\cdot}030$) (Fig. 3(a)). During these periods, the decrease of the prevalence of gluten contamination was significant for L-GF foods (33·55 % (95 % CI 31·61 %, 35·59 %); 6·64 % (95 % CI 5·06 %, 8·54 %); 5·60 % (95 % CI 4·47 %, 6·53 %); $P = 0{\cdot}045$) (Fig. 3(b)), while it was non-significant for N-GF foods (42·48 % (95 % CI 39·37 %, 1945·77 %); 13·02 % (95 % CI 7·96 %, 19·11 %); 23·42 % (95 % CI 19·57 %, 27·81 %); $P = 0{\cdot}95$) (Fig. 3(c)). Prior to 2009, the analysis process did not include meals in the food services, while between 2009–2014 and 2015–2020 periods, 320 and 478 meals were analysed, respectively. During these two periods, the gluten contamination prevalence of these meals has significantly decreased (11·25 % (95 % CI 7·88 %, 15·57 %); 2·93 % (95 % CI 1·60 %, 4·91 %); $P = 0{\cdot}049$) (Fig. 3(d)).

Prevalence of gluten contamination according to country income

The studies included in this review were carried out in only seventeen countries. Most of these studies were carried out in Europe (*n* 18) and South and North America (*n* 16), while Australia, Asia and Africa were represented by only six studies. The majority of studies were carried out in high-income (HIC) and upper-middle-income countries with twenty-nine and ten studies, respectively, and only one study was conducted in lower-middle-income countries (LMIC)[55], while no study was carried out in low-income countries (LIC) (Tables 1, 2 and 3). The number of foods analysed in HIC was important (23 985) compared with upper-middle-income countries and LMIC (1527 and 160, respectively). The difference in the prevalence of gluten contamination between upper-middle-income countries and HIC was not significant (20·39 % *v.* 13·11 %, $P = 0{\cdot}37$). The comparison between the prevalence of food contamination in the countries belonging to HIC in two different continents (North America and Europe) displayed no significant difference (10·16 % (95 % CI 9·76 %, 10·57 %); 11·66 % (95 % CI 10·02 %, 13·49 %); $P = 0{\cdot}374$).

Discussion

Quantitative detection of gluten in foods can be performed by several methods such as MALDI-TOF-MS, Aptamers, PCR, QC-PCR, RP-HPLC, LC-MS, gel and capillary electrophoresis, and immunological techniques. Each technique has its advantages as well as limitations[56–58]. The reliability of the results is impacted by several factors like the complexity of the food matrix, the type of antibodies applied, the gluten extraction procedures and the lack of reference material[59,60]. However, the FDA and the Codex Alimentarius consider ELISA as a reference technique[16,18]. Thus, all the studies included in this review have used the methods recommended by these committees. Using these techniques, the overall prevalence of gluten contamination was 15·12 % (95 % CI 9·56 %, 21·70 %). This shows that the food so-called 'gluten-free' intended for patients under GFD is exposed either to accidental gluten contamination or to non-conform gluten content threshold. In fact, even if the food is N-GF or L-GF, unintentional contamination can occur. Contamination is secondary to a direct contact with a source that contains gluten existing in wheat, rye or barley. This contamination may occur during the harvesting process, manufacturing, transportation and storage[61]. L-GF foods are less contaminated compared with N-GF foods. This can be explained by the fact that a maximum level of 20 mg/kg is required during the manufacturing process of 'so-labelled gluten-free' foods[16,18]. This underlines the need of implementing good hygiene and good manufacturing practices by manufacturers during the production chain. This system is reinforced by the implementation of a high-performance Hazard Analysis and Critical Control Point plan[62]. These steps make it possible to produce L-GF foods that comply with Codex Alimentarius and the FDA standards and requirements. However, non-compliance can occur especially during the production process and storage of these foods. Hence, there is a need to carry out regular controls even on gluten-free labelled foods. In this context, some associations related to gluten disease have introduced the concept of certification of L-GF foods. According to Thompson & Simpson[63], certified gluten-free foods are less contaminated compared with non-certified labelled foods and are more in line with the requirements of international committees. On the other hand, there are controversies about the amount of gluten to be tolerated by patients suffering from gluten-related pathologies. This varies according to individuals and pathologies[64,65]. It was shown that patients with CD may tolerate 10–36 mg[66], and even up to 50 mg/d[67]. Surprisingly, patients with non-coeliac gluten sensitivity may not tolerate even very low amounts of gluten[64]. Furthermore, it will be more interesting to add certain statements such as 'suitable for people with non-celiac wheat sensitivity', 'suitable for celiac', 'specifically formulated for people with non-celiac wheat sensitivity' or 'specifically formulated for celiac'[68]. This will allow a harmonisation of the rules concerning the information on gluten-free foods that coeliac patients can consume when following their GFD[69]. The current study showed that L-GF foods are more contaminated than N-GF food. Indeed, due to their low availability, the price of L-GF food is usually exorbitant[70]. This prompts coeliac patients to purchase more N-GF food than L-GF food, which puts them at a higher risk of contamination. In this context, several countries have facilitated access to L-GF food, such as monthly vouchers dedicated to gluten-free food for patients with CD in Italy[71], direct gluten-free food supply in Spain[72], reduction of taxes on gluten-free food in Ireland and in the USA[73,74] and reimbursement of gluten-free food consumers in France[75]. Therefore, these supportive strategies will allow patients to easily access less contaminated food. This will ensure good adherence to the

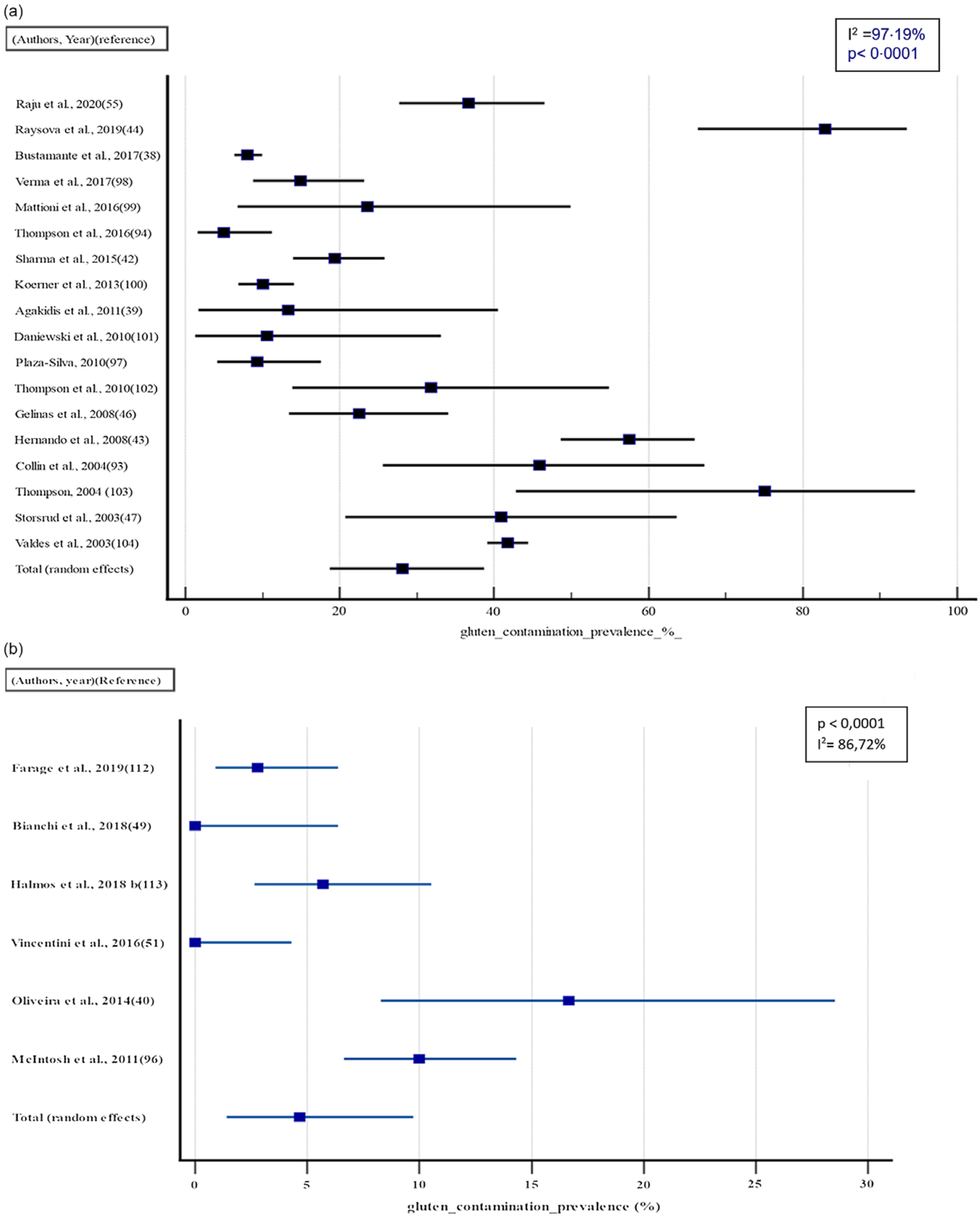

Fig. 2. (a) Forest plot of gluten contamination prevalence observed in naturally gluten-free foods. (b) Forest plot of gluten contamination prevalence observed in gluten-free meals in food services. (c) Forest plot of gluten contamination prevalence observed in labelled gluten-free.

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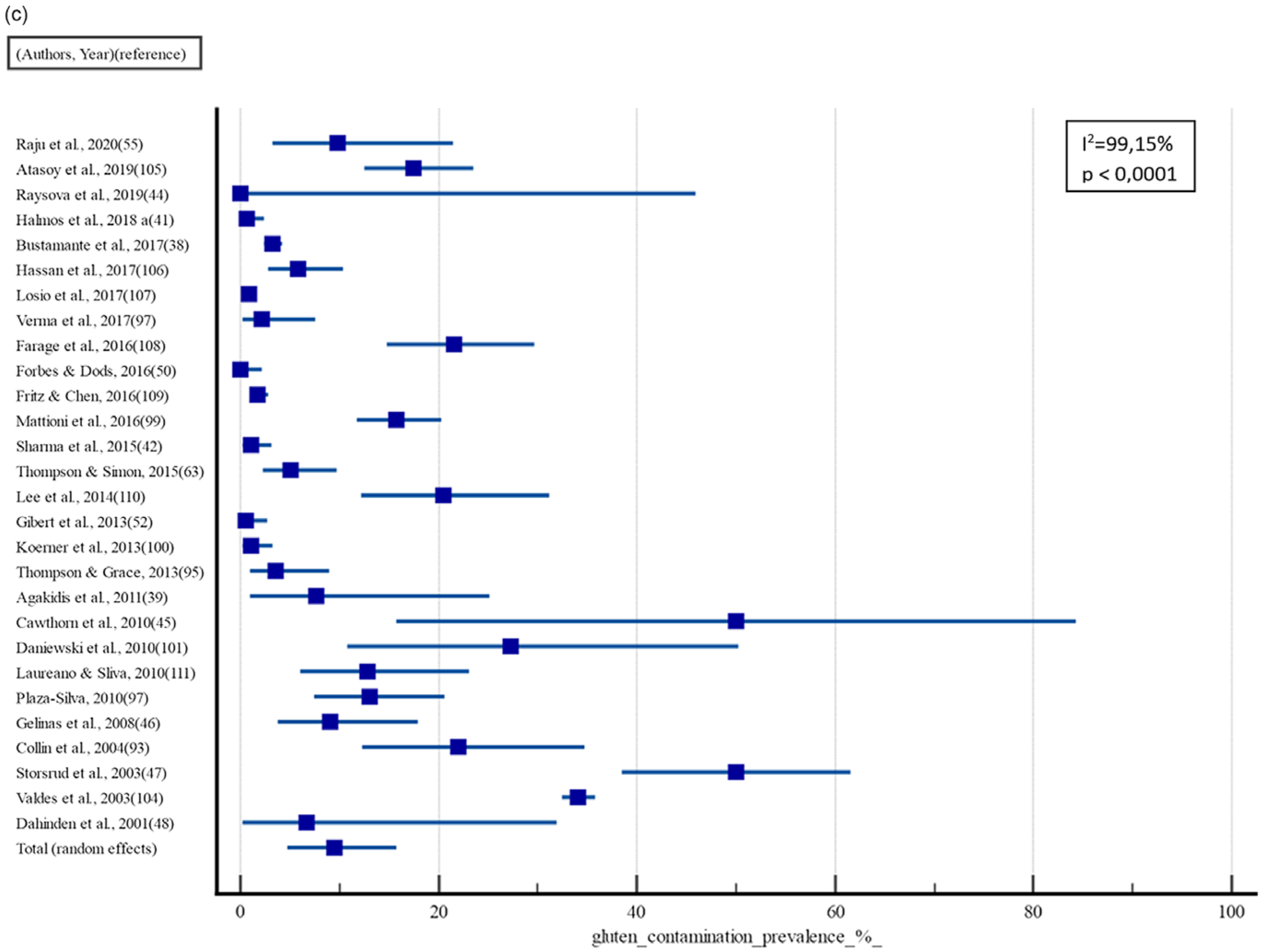

Fig. 2. (Continued).

GFD and therefore better recovery from CD and other gluten-related pathologies.

Meals in food services are the least contaminated in the included studies of this review. However, the number of foods analysed is so limited compared with the number of N-GF and L-GF foods. Unintentional contamination may occur when handling these meals in food services. In fact, the handler can be considered as a source of contamination more than the consumer. Other precautions should be taken into consideration when preparing gluten-free foods to prevent cross-contamination. Also, it is advisable to rigorously apply methods for cleaning kitchen equipment and utensils[76]. Furthermore, studies should be conducted in order to assess knowledge and practices related to safety of gluten-free foods in food services among handlers and consumers[77–79]. This will raise awareness and improve the level safe practices[80,81]. This can be provided through mass media (Newspapers, TV and Radio), social networks and on-site training.

Through the included studies, it was noticed that the oat was the most contaminated food. In fact, coeliac patients consume oat due to its beneficial effect on health[82]. In this context, the European Food Safety Authority and the FDA[83,84] have approved several claims about oat. In addition, the toxicity of avenin (oats prolamin) has not been proven for patients with CD[85] and oats are considered safe food for these patients[86,87]. According to a meta-analysis, no evidence has been shown about the effect of oats on the symptoms in coeliac patients. However, there is a need for a strict double-blind, systematic, randomised and placebo-controlled trials using oats that are commonly available in different regions[88]. In the EU (since 2009), the USA (since 2013) and Canada (since 2015), the oat products can be sold as gluten-free, provided that the level of gluten contamination is below 20 mg/kg[88]. However, contamination of oats by wheat, barley and rye is common. In conventional oat production, oat contamination is handled by conventional methods. This review shows that oats were frequently contaminated, especially when it comes to non-L-GF oats. According to Koerner *et al.*[54], 88 % of oats or oat-based products were contaminated with more than 20 mg/kg gluten. In the USA, the presence of oats in N-GF foods has been shown to correlate with a high level of gluten contamination[41]. This can happen during the harvesting, transportation and production chain process, alongside that of other cereals (wheat, barley and rye). Therefore, non-contamination of oats requires a separate system and regular monitoring of its effectiveness. Several researchers recommend eating only oats L-GF, while others recommend stopping

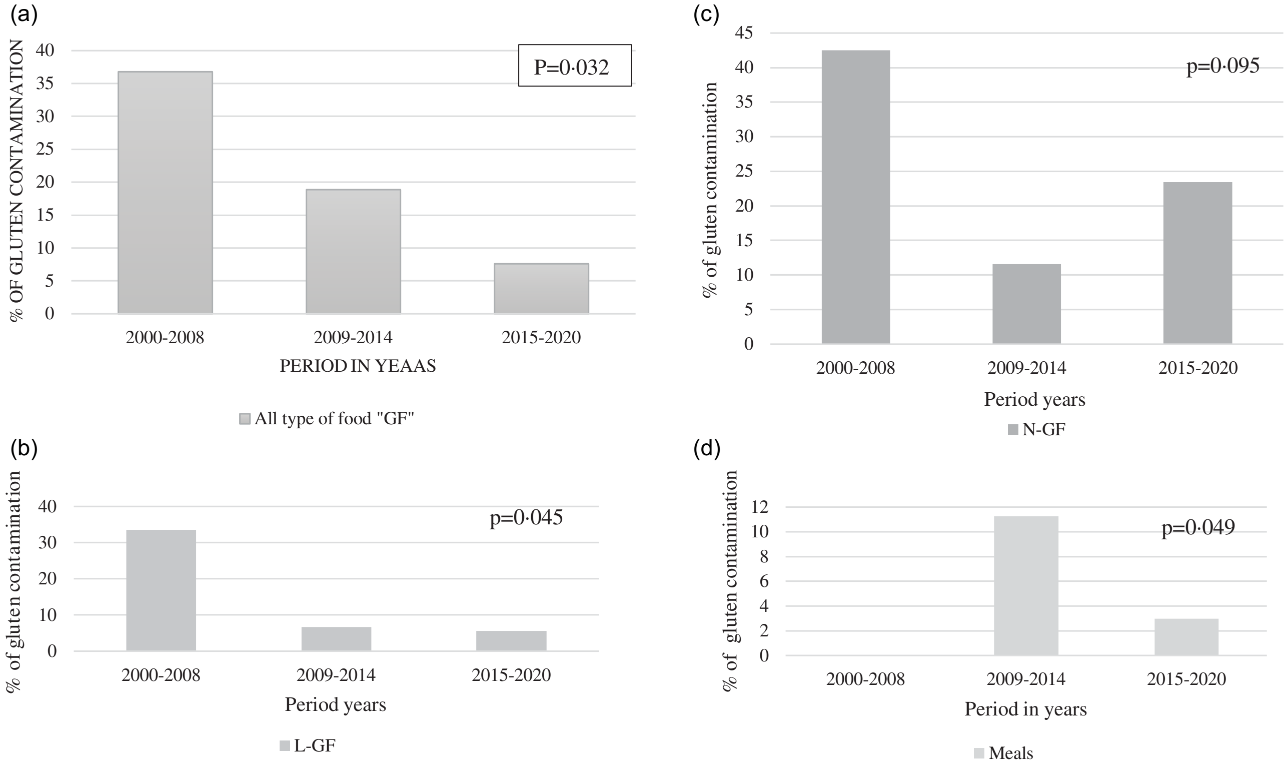

Fig. 3. Evolution of gluten contamination prevalence in all type of gluten-free foods, labelled-gluten-free (L-GF), naturally gluten-free (N-GF) and gluten-free meals over the years. (a) Evolution of gluten contamination prevalence in overall gluten-free foods over the years. (b) Evolution of gluten contamination prevalence in N-GF over the years. (c) Evolution of gluten contamination prevalence in L-GF over the years. (d) Evolution of gluten contamination prevalence in meals gluten-free in food services over the years.

oat consumption when symptoms develop[86]. Furthermore, some countries (e.g. the USA) have made efforts to address the problem of gluten contamination of oats by developing gluten-free oat production chains such as the progressive 'all-positive test' methodology, which consists of detecting kernel-based gluten contamination in oats at the serving-size level[89].

In this review, we focused on studies published based on current data during a period of 20 years (between 1 January 2000 and 1 June 2020), subdivided into three periods (2000–2008; 2009–2014; 2015–2020). The subdivision of these two decades depended mainly on the years in which legislators have highlighted regulatory laws concerning the gluten content in foods. In 2008, the Codex Alimentarius updated law 118-1978 by setting 20 mg/kg as the level of gluten below which the food is considered 'gluten-free"[16]. In 2014, the FDA also updated the law concerning so-called 'gluten-free' foods by setting the same level (20 mg/kg)[18]. In this context, the studies covering the period between 2000 and 2008 (year of the update of the Codex Alimentarius), between 2009 and 2014 (year of update of the law adopted by the FDA) and then between 2015 and 2020 (after the FDA update of the law) were set. The decrease of the average prevalence of gluten contamination over time may be explained by the fact that prior to 2008, foods were considered 'gluten-free foods' even if they contain up to 100 mg/kg of gluten. However, since 2008, the Codex Alimentarius required 20 mg/kg as a maximum level for a food to be 'gluten-free'. Moreover, during the period between 2009 and 2014, other similar regulations were set in place. In 2011, Regulation No. 1169/2011 of the European Parliament and of the Council on the provision of food information to consumers was issued with the main objective of ensuring a high level of consumer protection with regard to food information[90]. Three years after application, the FDA has established standard requiring manufacturers to comply with 20 mg/kg as a reference threshold in the USA for so-called 'gluten-free' products. Thus, these regulations made it possible to produce and market foods labelled 'gluten-free' with strict compliance to the standards required by these committees. However, there has been an increase of gluten contamination prevalence in N-GF foods during 2015–2020 period. This can be explained by the absence of standards that regulate the harvesting and marketing of these foods.

As previously mentioned, no studies were carried out in LIC and only one was recently conducted in LMIC. The classification of countries was done according to the income of countries according to the World Bank[91]. Actually, the limited research in LIC and LMIC can be explained on one hand by the limited budget for scientific research, and on the other hand, by the exorbitant prices of gluten extraction and detection kits. In addition, the extraction and analysis materials are produced in HIC and are subject to taxes imposed by the importing countries, which increases their prices even more. Furthermore, even if they are done, the number of foodstuffs analysed was limited and did not exceed 160 samples[55]. Therefore, precautions must be taken in food control in LIC or LMIC to ensure the safety of

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these gluten-free foods. This plays a key role in implementing a healthy and safe GFD when monitoring NCWS and CD patients. This latter is on the rise in LIC and LMIC, mainly African and Asian countries[3,92]. Thus, apart from the diagnostic difficulties, the failure to manage patients with CD will be very high in such context.

The availability of not conform gluten-free products (>20 mg/kg) in the markets is a factor in the failure to the GFD adherence. By consuming these foods considered within the limits of the standards, coeliac patients expose themselves to the risk of contamination by exceeding the threshold, estimated at 100 mg/kg according to Collin *et al.*[93]. Once this threshold is exceeded, the patient will enter into a vicious cycle during the GFD.

Risk of bias

Among forty studies included in this review, thirty-three of them show that the percentage of risk of bias was above 77 %, which corresponds to a low risk of bias. No risk of bias was observed regarding the indication of the foods analysed (L-GF, N-GF and/or meals), the method used, the validation of the method used by Codex Alimentarius, FDA and/or AOCA, and the indication contaminated foods prevalence. Only one study indicated a risk of bias about the 20 mg/kg contamination value[54]. The risk of bias concerning the indication of the extraction method and the indication of main categories of contaminated food was noted in seven and ten studies, respectively. Seven studies showed a moderate risk of bias (55·56 % or 66·67 %)[43,50,54,94–97]. Risk of bias about studies that received funding source was by eighteen studies. The financial support allowed an increasing of the sample size. The most remarkable risk of bias related to the indication of the year in which the analysed samples were collected. This was detected in twenty-four studies. Online supplementary material 4 (Risk of bias) shows the percentages of positive (yes) responses for each study included in this review and gives details about the answers related to the risk of bias assessment.

Limitations

The current review has some limitations: First, in some studies, the prevalence considered is that above 80 or 100 mg/kg; this does not show the exact prevalence of gluten contamination, and the real prevalence is higher than that indicated[54]. Second, the publication language. In fact, some studies published in Chinese, Russian or Spanish were excluded. Furthermore, the data related to Russian-, Chinese- and Spanish-speaking South American countries were not taken into consideration in this meta-analysis. In addition, several other studies were excluded because they only looked at the qualitative profile of the gluten contamination.

Conclusion

Gluten contamination of so-called ‘gluten-free’ foods is frequent, especially in N-GF foods. However, the overall prevalence of this contamination has declined over time. There have been very few studies conducted in LIC and LMIC. Therefore, it is necessary to promote such studies in these countries. It would be recommended to add some statements in gluten-free products such as ‘suitable for people with non-celiac wheat sensitivity’, ‘suitable for celiac’, ‘specifically formulated for people with non-celiac wheat sensitivity’ or ‘specifically formulated for celiac’. On the other hand, training of gluten-free food handlers in food safety knowledge and practices remains essential to avoid gluten contamination of meals in food services. In addition, it is necessary to implement preventive actions in order to reduce gluten contamination, ensuring safe GFD for coeliac patients.

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M. G.: First author, conceptualisation, investigation, data curation, visualisation, writing – original draft. Conduct an advanced research on studies whose are relevant to the topic of this research. Identified duplicate studies by eliminating those that did not fit the inclusion criteria. Read the full text of the articles in order to apply the inclusion and exclusion criteria. B. A.: writing – review and editing, validation, supervision, formal analysis. Intervene in case of disagreement on the eligibility of an article. N. E.: methodology, software, supervision, formal analysis. Intervene in case of disagreement on the eligibility of an article. L. G. Z.: investigation, data curation, visualisation. Conduct an advanced research on studies whose are relevant to the topic of this research. Identified duplicate studies by eliminating those that did not fit the inclusion criteria. Read the full text of the articles in order to apply the inclusion and exclusion criteria. A. B.: methodology, supervision, writing – review and editing. Intervene in case of disagreement on the eligibility of an article. L. E.: methodology, supervision, validation, formal analysis. Intervene in case of disagreement on the eligibility of an article. A. H.: conceptualisation, writing – review and editing, Gave his opinion on the articles included.

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Supplementary material

For supplementary material accompanying this paper visit https://doi.org/10.1017/S0007114521002488

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