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Systematic Review

# Association between increased intestinal permeability and disease: A systematic review

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ABSTRACT

*Objective:* Increased intestinal permeability (IP) may play an important role in health and disease. The purpose of this review is to explore the association between IP and diseases frequently found within clinical practice.
*Design and methods:* A systematic literature search was conducted up until July 2018 in MEDLINE, PubMed, EMBASE and AMED. A total of 48 articles met the inclusion/exclusion criteria.
*Results:* IP is strongly associated with autoimmune disease and liver conditions, with the estimated prevalence of 25–87.5% and 17–65% respectively. IP also correlates with diabetes (30–65%), food allergies/hypersensitivity, irritable bowel syndrome (35.6%), polycystic ovary syndrome and autism (36.7%). Disease severity in addition to clinical symptoms of menstrual disorders, food allergy or hypersensitivity directly correlates with IP. Finally, the severity of IP appears to be exacerbated by the presence of dysbiosis, inflammation and glucose metabolism disorders.
*Conclusions:* IP is a potentially influential factor that coincides with a variety of health conditions and diseases. IP should be considered as a factor in the pathophysiology and differential diagnosis for patient's presenting with autoimmune diseases, non-alcoholic fatty liver disease, liver cirrhosis, polycystic ovary syndrome, irritable bowel syndrome, diabetes, autism, food allergies and food hypersensitivity. Further research is required to determine if IP plays a pathogenic role in the progression and development of disease or whether the disease causes IP. While the clinical significance between IP and these diseases is unclear, the findings of the review suggest the treatment of IP in patients presenting with these conditions may warrant the consideration of clinicians.


**What is already known about the topic?**

- Increased intestinal permeability compromises the integrity of the intestinal barrier.
- The clinical significance of increased intestinal permeability in diagnosed health conditions is under-examined.
- The degree to which disease severity and clinical symptoms correlate with increased intestinal permeability remains unknown.

**What this paper adds?**

- Increased intestinal permeability is associated with a number of health conditions important to integrative medicine practice.
- Dysbiosis, inflammation and glucose metabolism disorders appear to exacerbate the severity of increased intestinal permeability.

*Abbreviations:* AAD, autoimmune autistic disorder; IBS, irritable bowel syndrome; IP, increased intestinal permeability; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome; T1D, type-1 diabetes; T2D, type- 2 diabetes.

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**How did you gather, select and analyse the info you considered in your review?**

- Systematic search of MEDLINE, PubMed, EMBASE and AMED up until July 2018.
- Included articles were original peer-reviewed observational studies, assessing increased intestinal permeability in humans with a health condition or disease.
- Articles were critically appraised using the STROBE guidelines.
- Data was independently and collectively examined to form the results.

**What is the take-home message for the clinician?**

- Increased intestinal permeability should be considered as a differential diagnosis for patient's presenting with autoimmune diseases, non-alcoholic fatty liver disease, liver cirrhosis, polycystic ovary syndrome, irritable bowel syndrome, diabetes, autism, food allergies and food hypersensitivity.
- Disease severity and clinical symptoms directly correlate with increased intestinal permeability.
- The severity of increased intestinal permeability appears to be exacerbated by dysbiosis, inflammation and glucose metabolism disorders.
- There is a substantial increase in the likelihood of increased intestinal permeability in individuals with some diagnosed health conditions.

## 1. Introduction

A major challenge for integrative practitioners is the management of chronic disease, particularly where the aetiology and pathophysiology is complex or unclear [1]. For such conditions, addressing factors that may contribute to the progression or severity of the disease is an important aspect of clinical management [2]. One such factor that is attracting attention from researchers is increased intestinal permeability (IP). In particular, it has been suggested that IP contributes to the development and progression of Crohn's disease [3], coeliac disease and type 1 diabetes (T1D) with IP preceding the clinical onset of T1D [4,5]. Furthermore, IP is speculated to be a strong enhancer of primary liver disease [6]. Ameliorating IP appears to reduce clinical signs and symptoms associated with disease [2], whereas inducing IP has been shown to increase disease severity [7–9]. The prevalence of IP among healthy individuals is unconfirmed, however, preliminary evidence estimates it to be between 4.8–6.1% [10,11].

IP affects the paracellular pathway between the small intestinal epithelium, resulting in compromised integrity of the intestinal barrier [12,13]. The intestinal paracellular pathway forms the interconnection between enterocytes and is composed of tight junctions, adherens junctions and desmosomes [14]. Of these, tight junctions strongly regulate paracellular permeability and are modulated by a protein called zonulin [13]. Zonulin is the only physiological mediator known to regulate IP [15]. The production of inflammatory cytokines is exacerbated in individuals with IP and corresponds with disease severity and activity [16–18]. This inflammation is thought to occur in response to host exposure to endotoxins [18,19]. IP may lead to increased absorption of dietary antigens and lipopolysaccharides from gram-negative bacteria, also known as endotoxins [20]. Elevated serum endotoxins can be used as a marker of IP and also correspond with disease severity and activity [21,22]. Exposure to endotoxins can interfere with the host's immune system, stimulate inflammation, and lead to dysbiosis [23].

It has been postulated that IP may promote translocation of bacteria, endotoxins and dietary antigens into the portal vein which may stimulate inflammation [24]. Factors that may increase IP include, dysbiosis [12], alcohol consumption [25], strenuous exercise [26], systemic inflammation [17], exposure to glyphosate [27], loss of redox homeostasis [28,29], nutrient deficiencies [30] and medications such as non-steroidal anti-inflammatory drugs [9] and antibiotics [31]. Larazotide acetate is a locally acting drug that acts as a tight junction regulator [2] and has been proposed as a possible pharmaceutical solution to the management of IP. Larazotide acetate is now in phase III clinical trials after establishing its safety in phase II clinical trials. A pitfall of larazotide acetate is the short acting time, lasting only 2–3 h, therefore continuous dosing is required [32].

Dual sugar probes are the most common test used to diagnose IP, and the most widely used of these is lactulose/mannitol urinary collection. This is due to its high diagnostic value for assessing IP [33]. There is no accepted standard for urine collection time for this test, however, emerging evidence suggests <5 h from the time of oral consumption of lactulose/mannitol is most accurate for measuring IP [34,35]. In individuals with Crohn's disease, specificity and sensitivity of lactulose/mannitol for measuring IP has been shown to be 100% and 89.5% respectively [33]. Serum zonulin, another available test that appears to correlate with lactulose/mannitol as a marker of IP [36], has a 100% specificity and sensitivity diagnostic value for non-alcoholic steatohepatitis [14]. Other tests that have been used with in clinical trials to measure IP include different dual sugars, stool zonulin, oral polyethylene glycol 3350/400 and duodenal biopsy [13].

A number of narrative reviews have reported on the association between IP and disease [37,38]. However, no known systematic review has been conducted investigating the correlation between IP and the incidence and severity of diagnosed health conditions collectively. In response, this systematic review aims to explore the association between IP and diseases frequently found within clinical practice.

## 2. Methods

The protocol was developed and implemented according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement [39].

### 2.1. Search strategy

The following databases were searched up until July 2018: MEDLINE, PubMed, EMBASE and AMED. Medical subject heading (MeSH) was used to help formulate the search terms. The search terms were grouped and then used in combination: ("permeability" OR "integrity") AND ("intestine*" OR "bowel" OR "gut" OR "mucosal") AND ("observational" OR "cohort" OR "case control" OR "cross sectional" OR "epidemiologic" OR "longitudinal" OR "retrospective").

### 2.2. Eligibility criteria

Articles included were original peer-reviewed observational studies, assessing increased small intestinal permeability in humans with a health condition or disease. There were no time limits or language restrictions applied. Articles were excluded if the subjects involved in the study were critically ill i.e. palliative care or in intensive care; or reported an experimental design. Critically ill subjects were excluded as this review is focused on health conditions or diseases frequently found within community-based primary care practice. Articles were also excluded if they used a method of measuring IP that also measured gastric or colonic permeability. Examples of these include sucrose urine collection less than 5 h or polyethylene glycol 3350/400 collected over 8 h.

### 2.3. Study selection

The search strategy was applied to MEDLINE, PubMed, EMBASE and AMED databases and all identified citations were downloaded to Endnote referencing software. After removal of duplicates, the remaining citations were screened by title and abstract against the inclusion/exclusion criteria by one researcher (B.L.). Any uncertainties regarding the inclusion criteria were reviewed by a second researcher (J.S.). This process is summarised using the PRISMA flow diagram in Fig. 1 [40].

### 2.4. Data extraction and quality assessment

Data was independently extracted by one researcher (B.L.) and reviewed by two other researchers (J.S. and A.S.). The extracted information was composed of authors, publishing date, health condition/disease, study design, sample size, demographics, pathology test utilised and final results. Each paper was critically appraised by the lead researcher (B.L.) using the criteria outlined in the *Strengthening the Reporting of Observational studies in Epidemiology* (STROBE) guidelines [41] and reviewed by two other researchers (J.S. and A.S.). Low-quality articles with a high risk of bias were given less weighting within the results.

## 3. Results

### 3.1. Study characteristics

Within the 48 articles included in this review (Table 1), 34 different health conditions or diseases were identified. The sample size varied from 20 to 1196 [42,43] (mean = 127) with demographics also varying from, children (n = 13), adult (n = 23), elderly (n = 3), children/adults (n = 3) and adult/elderly (n = 6). The gender ratios of included participants were 54% female and 46% male. These studies were conducted across 17 countries with the majority in the continents Europe (n = 23), Asia (n = 11), and North America (n = 9).

### 3.2. Critical appraisal

The outcomes of the critical appraisal process are reported in Table 2. Many identified articles failed to describe study design [10,11,44–50,52–59,64–67,70,72,74,78–84,86,87], report potential bias [10,11,42–44,46–64,67,68,70,72,74,75,77,79–84,86], present a flow diagram [10,11,42–46,49–68,70–86] or discuss potential limitations [10,11,44–50,52,54–58,60,64–67,69,72,75,79,81,83–85]. A few articles reported incomplete or inadequate information suggesting a potential risk of bias [49,64,67,82]. These lower quality articles were given less weighting within the results of this review [49,64,67,82].

### 3.3. Prevalence of increased intestinal permeability

Twelve studies reported the prevalence of IP in a variety of diseases with a range of 10.5–87.5% (Table 3). The prevalence of IP may be influenced by medication (5.6–34.3%) [10], disease location/severity (10.5–42.9%) [10], dietary intake [56] and coexisting diseases (15–65%) [56].

### 3.4. Autoimmune disease

Sixteen studies included in this review evaluated a variety of autoimmune diseases [10,42–55,66], of these, fifteen found a direct correlation between IP and the autoimmune disease studied [10,42,44,43–55,66]. Two studies evaluating IP in healthy first-degree relatives of individuals with Crohn's disease found conflicting results, with one study reporting association [51] and the other study reporting no association [43]. The autoimmune diseases reported to be associated with IP include ankylosing spondylitis [44], autoimmune hepatitis [45], Behcet's disease [46], coeliac disease [47,48], Crohn's disease (36%) [49,50,53] compared to first-degree relatives (11–30%) [43,51], dermatitis herpetiformis (87.5%) [52], primary biliary cirrhosis (25%) [66], systemic sclerosis (34.3%) [54], T1D (30%) [42,55] and ulcerative colitis (28.1%) compared to their first-degree relatives (20%) and healthy control (6.1%) [10]. Two studies reported a direct correlation with disease severity and IP [49,52]. IP appears to involve genetic factors in coeliac disease [47], ulcerative colitis [10] and T1D [55], with conflicting results in Crohn's disease [43,51]. The studies that measured the microbiota reported the degree of IP correlates with the level of dysbiosis [42,44,45]. In studies where inflammation was measured, mucosal inflammation and systemic inflammation directly correlates with the degree of IP and may precede the onset of IP [10,46,48,53].

### 3.5. Liver-related conditions

Twelve studies evaluated a variety of liver-related conditions; eleven studies found a direct correlation to IP [45,56–63,65,66]. These liver-related conditions and the known prevalence of IP include autoimmune hepatitis [45], chronic liver disease as a primary presentation (17%) and in individuals with type 2 diabetes (T2D) (65%) [56], intrahepatic cholestasis of pregnancy [57], liver cirrhosis (35%) [58–61], primary biliary cirrhosis (25%) [66], portal hypertension [65] and non-alcoholic fatty liver disease (NAFLD) (31%) [62,63]. Four studies reported the correlation between IP and severity of steatosis ($P < .05$) [62,63], portal hypertension ($P < .01$) [56,66] portal inflammation ($P = .02$), fibrosis ($P = .0002$) and ballooning ($P = .003$) [63]. Whereas, the prognosis of liver disease found no association between Child B to Child C cirrhosis score [56,58,60]. Collectively, the underlying factor influencing the association between IP and disease severity is inflammation [45,56,63].

### 3.6. Autism

Five studies reported on populations with autism of which three studies [11,67,70] found a direct correlation between autism and IP and two studies [68,69] found no correlation. Two studies reported the prevalence of IP in subjects with autism (43%) [67] and (36.7%) [11] and one compared this to relatives (21.2%) [11] and healthy controls (4.8%) [11]. The severity of autism was reported to have a positive correlation with IP [70].

### 3.7. Diabetes and obesity

A cluster of identified studies examined T2D [78,79], gestational diabetes [73], obesity [75] and impaired fasting glucose [74] in relation to IP. All studies investigating diabetes found an association with IP. IP was reported to correlate with higher odds of developing gestational diabetes in overweight or obese pregnant women with a prevalence of 37.5% [73]. Furthermore, independent factors such as insulin resistance [78], inflammation [78,79] and dyslipidaemia [78] were found to be associated with IP in subjects with T2D. A small pilot study of 13 obese subjects found no correlation between obesity and IP [75]. However, collectively, obesity in combination with glucose

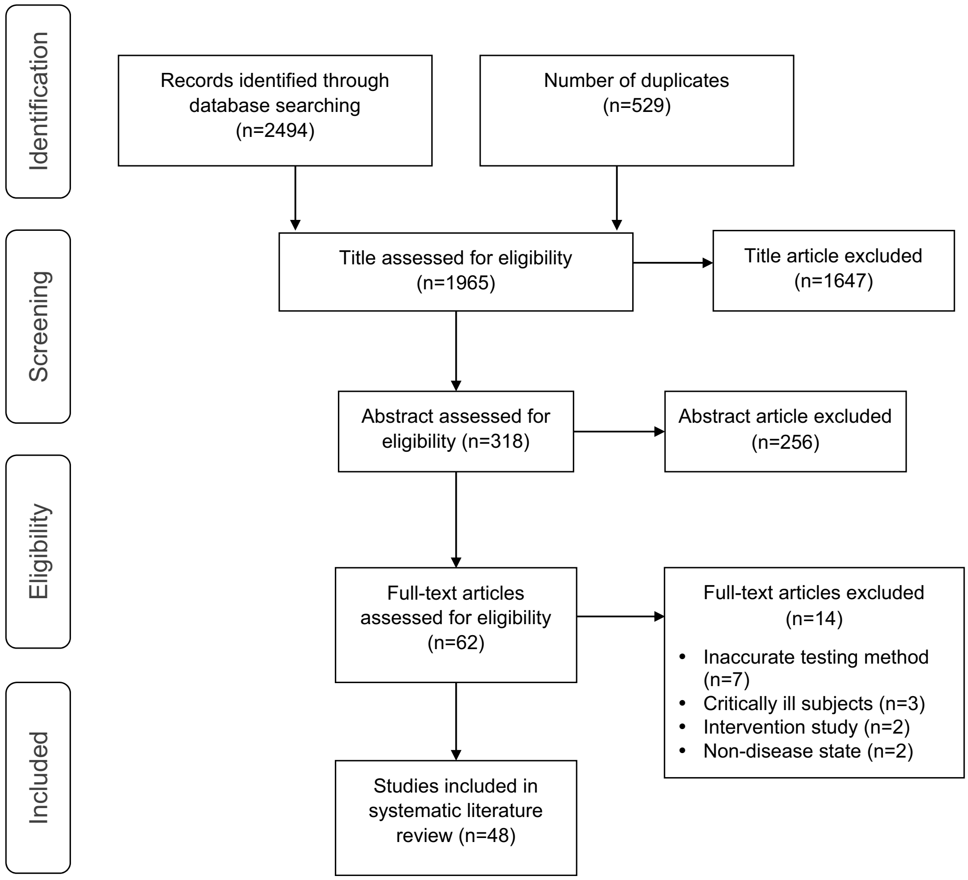


**Fig. 1.** Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. Starting with 2494 citations identified in the database, 48 articles were included in the final systematic literature review.

metabolism disorders is associated with a greater degree of IP than obesity alone [73–75,78,79].

### 3.8. Gastrointestinal conditions

Seven studies evaluated IP in conditions related to the gastrointestinal tract. Three studies found a direct correlation between IP and food allergy ($P = .003$), food hypersensitivity ($P = .0008$) [81], irritable bowel syndrome (IBS) (18.4% vs. 8.3% in healthy control) ($P < .05$) [85] and IBS in subjects with a history of gastroenteritis (35.6% vs. 18.6% in healthy control) ($P = .007$) [83]. Whereas, four studies reported no correlation between IP and eosinophilic and reflux esophagitis [80], functional abdominal pain in subjects with IBS [86], constipation predominant IBS (IBS-C) [84], and functional dyspepsia [82]. Upon dividing conditions into upper and lower gastrointestinal related conditions, the conditions within the lower gastrointestinal system were found to be associated with IP but not conditions within the upper gastrointestinal system. Furthermore, a higher prevalence of IP can be seen in IBS patients when another condition such as gastroenteritis or small intestinal bacteria overgrowth affects the microbiome [83,85,86]. IP correlates with the seriousness of clinical symptoms of food allergy and food hypersensitivity [81].

### 3.9. Polycystic ovary syndrome

Two studies found a direct correlation between IP and polycystic ovary syndrome (PCOS) [76,77]. Within one study, IP was associated with insulin resistance, as was the severity of menstrual disorders, in subjects with PCOS [76].

### 3.10. Possible influential factors

A number of studies reported data on confounding variables which may influence the incidence of IP including gender [50,83], age [43], alcohol [56] and smoking status [43,53]. A number of included studies indicate male gender to be an independent factor associated with a higher prevalence of IP [50,83]. No consistency between age and IP were found, with IP being associated with younger subjects (<19) in Crohn's disease ($P = .008$) [43] and older subjects (>50 years) in liver conditions ($P < .001$) [56] or not associated with other conditions. Conflicting results were reported in smoking status, with one study reporting both inflammatory bowel disease and healthy control smokers experience higher rate of IP compared to non-smokers ($P < .001$) [53], whereas another study reported non-smokers to have a higher rate of IP compared to smokers ($P = .033$) [43].

### 3.11. Measuring intestinal permeability

The methods used to measure IP varied across the included studies. Thirteen studies used oral lactulose/mannitol with 5-h collection time [10,11,42,43,50,55–57,60,65,75,81,82], three with 6 to 8 h collection time [63,66,68], four with unknown collection time [47,67,69,83], one with 3-h collection time [86], one with 2-h collection time [84], and three that included

**Table 1**
Summary of observational studies included in the systematic review.

| Author | Year | Disease | Study Design | Subjects | Country | Test Used | Results |
|---|---|---|---|---|---|---|---|
| **Autoimmune Disease** | | | | | | | |
| Ciccia et al. [44] | 2017 | Ankylosing spondylitis | Case-control study | n = 70<br>c = 20 | Italy | Serum zonulin | IP is associated with HLA-B27 positive patients with ankylosing spondylitis. (*P*<.0001). |
| Lin et al. [45] | 2015 | Autoimmune hepatitis | Case-control study | n = 32<br>c = 8 | China | ZO-1 and occludin expression in duodenal biopsy | IP is associated with autoimmune hepatitis and correlates with the disease severity (*P*<.05). |
| Koc et al. [46] | 2003 | Behcet's disease | Case-control study | n = 47<br>c = 21 | Turkey | Sucrose, 5 h urine collection | IP is associated with active Behcet's disease (*P*<.0001). |
| Smecuol et al. [47] | 1999 | Coeliac disease (First degree relatives) | Cross-sectional study | n = 66<br>c = 0 | Argentina | L/M, overnight urine collection | IP is associated with newly diagnosed Coeliac disease (*P*<.00003). |
| Rauhavirta et al. [48] | 2014 | Coeliac disease | Cohort study | n = 67<br>c = 20 | Finland | ZO-1 and occludin claudin expression in duodenal biopsy | IP is associated with early stage Coeliac disease (*P*<.05). |
| Murphy et al. [49] | 1989 | Crohn's disease | Cross-sectional study | n = 48<br>c = 31 | England | C/M, 5 h urine collection | IP is associated with Crohn's disease (*P*<.002). The severity of Crohn's disease is correlated with IP (r = .59, *P*<.01). |
| Benjamin et al. [50] | 2008 | Crohn's disease | Case-control study | n = 147<br>c = 22 | India | L/M, 5 h urine collection | IP is associated with Crohn's disease (*P* = .0044). |
| Kevans et al. [43] | 2013 | Crohn's disease (First degree relatives) | Cohort study | n = 1196<br>c = 0 | Canada & America | L/M, 5 h urine collection | IP is not significantly heritable in Crohn's disease (*P* = .13). |
| Teshima et al. [51] | 2017 | Crohn's disease (First degree relatives) | Cross-sectional study | n = 223<br>c = 0 | Canada | L/M, overnight urine collection | IP is increased in 30% of asymptomatic first-degree relatives of patients with Crohn's disease. |
| Smecuol et al. [52] | 2005 | Dermatitis herpetiformis | Case-control study | n = 82<br>c = 64 | Argentina | L/M, 5 h urine collection including first void and serum zonulin | IP is associated dermatitis herpetiformis (*P*<.05) and it correlates with disease severity. |
| Malickova et al. [53] | 2017 | Inflammatory bowel disease | Case-control study | n = 80<br>c = 40 | Czech Republic | Serum and stool zonulin | The severity of IP is greater in Crohn's disease compared to ulcerative colitis (*P* = .038). |
| Caserta et al. [54] | 2003 | Systemic sclerosis | Case-control study | n = 65<br>c = 33 | Italy | C/M, 5 h urine collection | IP is possibly associated with systemic sclerosis with higher mean value compared to control however still within normal range (*P*<.05). |
| Kuitunen et al. [55] | 2002 | Type 1 diabetes | Case-control study | n = 50<br>c = 24 | Finland | L/M, 5 h urine collection | IP is associated in subjects with type 1 diabetes that also have HLA-DQB1*02 allele (*P* = .02). |
| Maffeis et al. [42] | 2016 | Type 1 diabetes | Case-control study | n = 20<br>c = 10 | Italy | L/M, 5 h urine collection | IP in children with beta cell autoimmunity IP is associated with a higher risk of type 1 diabetes than healthy control (*P* = .019). |
| Buning et al. [10] | 2012 | Ulcerative colitis | Cross-sectional study | n = 247<br>c = 99 | Germany | L/M, 5 h urine collection | IP is associated with ulcerative colitis (28.1%) (*P*<.001). IP was increased in relatives (20%) more so than spouses (12.5%) suggesting a possible genetic association. |
| **Liver Related Conditions** | | | | | | | |
| Cariello et al. [56] | 2010 | Chronic liver diseases | Cohort study | n = 217<br>c = 134 | Italy | L/M, 5 h urine collection | IP is associated with chronic liver disease (*P* = .01). |
| Reyes et al. [57] | 2006 | Gestational intrahepatic cholestasis | Case-control study | n = 70<br>c = 51 | Chile | L/M, 5 h urine collection | IP is associated with intrahepatic cholestasis of pregnancy (*P*<.01). |
| Zuckerman et al. [58] | 2004 | Liver cirrhosis | Case-control study | n = 140<br>c = 74 | America | L/R, 5 h urine collection | IP is increased in liver cirrhosis subjects with ascites (*P*<.001) however, not in subjects without ascites. |
| Lee et al. [59] | 2008 | Liver cirrhosis | Case-control study | n = 79<br>c = 26 | Korea | PEG, 8 h urine collection | IP is associated with liver cirrhosis in subjects that had ascites (*P*<.05) however, not associated in subjects without ascites. |
| Benjamin et al. [60] | 2013 | Liver cirrhosis | Prospective cohort study | n = 80<br>c = 0 | India | L/M, 5 h urine collection | IP is associated with liver cirrhosis (*P* = .007). |
| Raparelli et al. [61] | 2017 | Liver cirrhosis | Cross-sectional study | n = 99<br>c = 30 | Italy | Serum zonulin | IP is associated with liver cirrhosis (*P*<.006). |
| Pacifico et al. [62] | 2014 | | | | Italy | Serum zonulin | |

**Table 1** (*Continued*)
Summary of observational studies included in the systematic review.

| Author | Year | Disease | Study Design | Subjects | Country | Test Used | Results |
|---|---|---|---|---|---|---|---|
| | | Non-alcoholic fatty liver disease | Case-control study | n = 80<br>c = 40 | | | IP is associated with non-alcoholic fatty liver disease ($P<.01$). The severity of steatosis is correlated with higher serum zonulin levels (r = 0.372, $P<.05$). |
| Giorgio et al. [63] | 2014 | Non-alcoholic fatty liver disease | Case-control study | n = 60<br>c = 21 | Italy | L/M, 6 h urine collection | IP is associated with non-alcoholic fatty liver disease ($P<.05$). The severity of non-alcoholic fatty liver disease correlates with higher IP (95% CI: 1.78-47.19; $P<.007$). |
| Wigg et al. [64] | 2001 | Non-alcoholic steatohepatitis | Case-control study | n = 45<br>c = 23 | Australia | L/R, 5 h urine collection | IP does not appear to be associated with non-alcoholic steatohepatitis. |
| Borkar et al. [65] | 2015 | Portal hypertension | Case-control pilot study | n = 46<br>c = 15 | India | L/M, >5 h urine collection | IP is associated with portal hypertension ($P<.01$). |
| Feld et al. [66] | 2006 | Primary biliary cirrhosis | Case-control study | n = 254<br>c = 101 | Canada | L/M, 8 h urine collection | IP is associated with primary biliary cirrhosis and hepatitis C ($P = .01$). |
| **Neurological Conditions** | | | | | | | |
| D'Eufemia et al. [67] | 1996 | Autism | Case-control study | n = 61<br>c = 40 | Italy | L/M, unknown urine collection | IP is associated with autism ($P<.001$). |
| de Magistris et al. [11] | 2010 | Autism | Cohort study | n = 446<br>c = 210 | Italy | L/M, 5 h urine collection | The prevalence of IP in autism (36.7%), their relatives (21.2%), controls (4.8%) ($P<.0001$). |
| Dalton et al. [68] | 2014 | Autism | Cohort study | n = 133<br>c = 0 | England | L/M, 6 h urine collection | There is no difference in IP between autism and subjects with special educational needs. |
| Pusponegoro et al. [69] | 2015 | Autism | Cross-sectional study | n = 209<br>c = 62 | Indonesia | L/M, unknown collection time | There is no difference in IP between controls, and subjects with mild and severe maladaptive behaviour in children with autism ($P = .45$). |
| Esnafoglu et al. [70] | 2017 | Autism | Case-control study | n = 65<br>c = 33 | Turkey | Serum zonulin | IP is associated with autism ($P<.001$). The severity of autism has a positive correlation with IP ($P<.001$). |
| Schwiertz et al. [71] | 2018 | Parkinson's disease | Case-control study | n = 62<br>c = 28 | Germany | Stool zonulin | IP is associated with Parkinson's disease (P.004). |
| Davies et al. [72] | 1996 | Parkinson's disease | Case-control study | n = 30<br>c = 15 | England | C/M, 5 h urine collection | IP does not appear to be associated with Parkinson's disease. |
| **Metabolic Conditions** | | | | | | | |
| Mokkala et al. [73] | 2017 | Gestational diabetes | Observational cohort study | n = 88<br>c = 0 | Finland | Serum zonulin | IP is associated with higher odds of developing gestational diabetes (OR 1.08, 95% CI: 1.02-1.15; $P = .009$). |
| Carnevale et al. [74] | 2017 | Impaired fasting glucose | Cross-sectional study | n = 70<br>c = 35 | Italy | Serum zonulin | IP is associated with impaired fasting glucose ($P<.001$). |
| Brignardello et al. [75] | 2010 | Obesity | Case-control pilot study | n = 24<br>c = 11 | Chile | L/M, 5 h urine collection | IP does not appear to be associated with obesity compared to healthy controls. |
| Zhang et al. [76] | 2015 | Polycystic ovarian syndrome | Case-control study | n = 141<br>c = 63 | China | Serum zonulin | IP is higher in women with polycystic ovarian syndrome than healthy control ($P = .022$). The severity of menstrual disorders is correlated with higher serum zonulin levels (r= -0.398, $P<.001$). |
| Lindheim et al. [77] | 2017 | Polycystic ovarian syndrome | Cross-sectional pilot study | n = 43<br>c = 19 | Austria | Serum and stool zonulin | IP is possibly associated with polycystic ovarian syndrome serum zonulin ($P = .006$) however not stool zonulin ($P = .063$). |
| Zhang et al. [78] | 2014 | Type 2 diabetes | Cross-sectional study | n = 388<br>c = 121 | China | Serum zonulin | IP is associated with type 2 diabetes (OR = 1.080, 95% CI: 1.005-1.161; p = 0.037). IP correlates with dyslipidaemia, inflammation and insulin resistance. Zonulin may be an independent predictor of type 2 diabetes. |

**Table 1** (*Continued*)
Summary of observational studies included in the systematic review.

| Author | Year | Disease | Study Design | Subjects | Country | Test Used | Results |
|---|---|---|---|---|---|---|---|
| Jayashree et al. [79] | 2014 | Type 2 diabetes | Case-control study | n = 90 c = 45 | India | Serum zonulin | IP is associated with type 2 diabetes (OR 13.43, 95% CI; 1.998-18.9; *P* = .003). Zonulin is correlated with inflammatory markers, glycemic and lipid control. |
| **Gastrointestinal Conditions** | | | | | | | |
| Leung et al. [80] | 2015 | Eosinophilic esophagitis and reflux esophagitis | Case-control study | n = 83 c = 26 | Canada | L/M, 5 h urine collection including overnight and first morning void. | IP does not appear to be associated with eosinophilic esophagitis and reflux esophagitis. |
| Ventura et al. [81] | 2006 | Food allergy and hypersensitivity | Case-control study | n = 82 c = 41 | Italy | L/M, 5 h urine collection | IP is associated with both food allergy (*P*=.003) and hypersensitivity (*P* = .0008). IP correlates with the seriousness of clinical symptoms (*P* = .005). |
| Neilan et al. [82] | 2014 | Functional dyspepsia | Case-control pilot study | n = 39 c = 19 | America | L/M, 5 h urine collection | IP does not appear to be associated with functional dyspepsia. |
| Marshall et al. [83] | 2004 | Irritable bowel syndrome (after acute gastroenteritis) | Case-control study | n = 218 c = 86 | Canada | L/M, urine collected overnight. | IP is associated with acute gastroenteritis 2 years after the event in subjects with irritable bowel syndrome (OR 2.99, 95% CI: 1.46-6.11; *P* = .003). |
| Peters et al. [84] | 2017 | Irritable bowel syndrome (constipation) | Case-control study | n = 37 c = 18 | America | L/M, 2 h urine collection | IP does not appear to be associated with irritable bowel syndrome (constipation). |
| Jung et al. [85] | 2009 | Irritable bowel syndrome (Small intestinal bowel overgrowth) | Cohort study | n = 50 c = 12 | Korea | PEG, 8 h urine collection | IP is associated with irritable bowel syndrome (*P*<.05) however, no correlation was found in subjects with small intestinal bowel overgrowth (*P*>.05). |
| Shulman et al. [86] | 2008 | Irritable bowel syndrome and Functional abdominal pain | Case-control study | n = 122 c = 46 | America | L/M, 3 h urine collection | IP does not appear to be associated with functional abdominal pain and irritable bowel syndrome. |
| **Respiratory Conditions** | | | | | | | |
| Rutten et al. [87] | 2014 | Chronic obstructive pulmonary disease | Case-control study | n = 32 c = 14 | Netherlands | L/R, >3 h urine collection | IP is associated with chronic obstructive pulmonary disease (*P* = .01). |

overnight and first morning void [51,52,80]. Seven studies used different sugar probes including two oral lactulose/rhamnose 5-h collection time [58,64] and one 3-h collection [87], three oral cellobiose/mannitol with 5-h collection [49,54,72] and one oral sucrose with 5-h collection [46]. Twelve studies used serum zonulin [44,52,53,61,62,70,73,74,76–79] and three stool zonulin [53,71,77]. Two studies use oral polyethylene glycol 3350/400 8-h collection time [59,85] and one study used duodenal biopsy [45] to measure IP. Two studies included in this review used unreliable testing methods and also produced a negative result regarding IP association. One failed to report the urine collection time [69] and the other collected urine from first morning void [80].

## 4. Discussion

Based on this first systematic review examining the correlation between IP and disease there is a range of diseases that are associated with IP and others which are not associated. When the prevalence of IP are collated, IP can be seen in 25–87.5% of patients with an autoimmune diseases [10,50,52,66], 17–65% of patients with liver-related conditions [56,60,63,66] 30–65% of patients with diabetes [42,56,73], 35.6% is IBS patients [83] and 36.7% of patients with autism [11,67]. This is compared to approximately 4.8–6.1% in healthy individuals [10,11]. The majority of diseases discussed with a known prevalence suggest that approximately 1 in 3 individuals experience IP during their disease. Autoimmune diseases had the strongest correlation to IP with the largest body of research collected to date. Other experimental studies investigating autoimmunity and IP including, multiple sclerosis [88] supports the trend seen in the epidemiological research included in this review that IP is strongly associated with autoimmune diseases. It has been suggested that the higher correlation of autoimmune disease to IP is due to a combination of genetics [89], dysbiosis [90] and inflammation [91]. Although the cause of autoimmune disease remains unknown, IP is reported to play a pathogenic role in the development and progression of Crohn's disease [3], coeliac disease and T1D [5]. However, further research is necessary to confirm the suggested link between IP and autoimmunity and to understand the risk factors predisposing a susceptible individual to the development of IP.

This review identified conflicting findings related to the relationship between IP and autism possibly due to the low overall quality of the studies including the absence of sub-analyses to account for subsets of autism. For example, it has been postulated that a major subset of autism is autoimmune autistic disorder (AAD), which is understood to develop as a result of cross-reactions with the measles virus in susceptible individuals [92]. A

**Table 2**
Results from critical appraisal according to STROBE guidelines for included articles.

| STROBE critical appraisal tool. | Title, abstract & Introduction | | | | Methods | | | | | | | | | | | | | | | Results | | | | | | | | | | | Discussion & other information | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | Title & Abstract | | Background | Objectives | Study design | Setting | Participants | | Variables | Data sources | Bias | Study size | Quantitative variables | Statistical methods | | | | | Participants | | | Descriptive data | | | Outcome data | Main results | | | Other analyses | Key results | Limitations | Interpretation | Generalizability | Funding |
| | 1a | 1b | 2 | 3 | 4 | 5 | 6a | 6b | 7 | 8 | 9 | 10 | 11 | 12a | 12b | 12c | 12d | 12e | 13a | 13b | 13c | 14a | 14b | 14c | 15 | 16a | 16b | 16c | 17 | 18 | 19 | 20 | 21 | 22 |
| Schwiertz et al. [71] | x | x | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | - | x | x | - | x | x | x | x | x | x | x | x | x | x |
| Teshima et al. [51] | x | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | - | x | x | x | x | x | x | x | x | - | x |
| Raparelli et al. [61] | x | x | x | x | x | x | x | x | x | x | - | - | x | x | x | x | x | x | x | x | - | x | x | - | x | x | x | x | x | x | x | x | - | x |
| Peters et al. [84] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | - | x | x | x | x | x | x | - | x | - | x |
| Malickova et al. [53] | - | x | x | x | x | x | x | x | x | x | - | - | x | x | x | x | x | x | x | x | - | x | x | - | x | x | x | x | x | x | x | x | x | x |
| Esnafoglu et al. [70] | - | x | x | x | x | x | x | x | x | x | - | - | x | x | x | - | x | x | x | x | - | x | x | x | x | x | x | x | x | x | x | x | - | x |
| Ciccia et al. [44] | - | x | x | x | x | x | x | x | x | x | - | - | x | x | x | x | x | x | x | x | - | x | x | - | x | x | x | x | x | x | - | x | - | x |
| Carnevale et al. [74] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | - | - | x | x | - | x | x | x | x | x | x | x | x | x | x |
| Mokkala et al. [73] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | - | - | x | x | x | x | - | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Lindheim et al. [77] | x | x | x | x | x | x | x | x | x | x | - | x | x | x | - | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Maffeis et al. [42] | x | x | x | x | x | x | x | x | x | x | - | x | x | x | x | - | x | x | x | x | - | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Zhang et al. [76] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Pusponegoro et al. [69] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | - | x | x | x | - | x | x | - | x | x | - | - | - | x | x | - | x | x | x |
| Lin et al. [45] | - | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | - | - | x | x | x | x | x | x | x | x | - | x | x | x |
| Leung et al. [80] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | - | x | x | x | x | x | x | - |
| Borkar et al. [65] | - | x | x | x | x | x | x | x | x | x | x | x | x | x | - | - | x | x | x | x | - | - | x | x | x | x | x | x | x | x | - | x | x | - |
| Zhang et al. [78] | - | x | x | x | x | x | x | x | x | x | - | - | x | x | x | - | x | x | x | x | - | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Rutten et al. [87] | - | x | x | x | x | x | x | x | x | x | x | x | x | x | - | - | - | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Rauhavirta et al. [48] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | - | - | x | x | - | x | x | x | x | x | x | x | - | x | x | x |
| Pacifico et al. [62] | x | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Neilan et al. [82] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | - | - | - | - | - | - | x | x | x | x | x | x | x | x | x | - |
| Jayashree et al. [79] | - | x | x | x | x | x | x | x | x | x | - | - | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | - |
| Giorgio et al. [63] | x | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Dalton et al. [68] | x | x | x | x | x | x | x | x | x | x | - | x | x | x | x | - | x | x | x | x | - | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Kevans et al. [43] | x | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | x | - | x | x |
| Benjamin et al. [60] | x | x | x | x | x | x | x | x | x | x | - | x | x | x | x | - | - | x | x | - | - | x | x | x | x | x | x | x | x | x | - | x | x | x |
| Buning et al. [10] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x |
| de Magistris et al. [11] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x |
| Cariello et al. [56] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x |
| Brignardello et al. [75] | x | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x |
| Jung et al. [85] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x |
| Shulman et al. [86] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Lee et al. [59] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | - | x | x | x | x | x | x | x | x | x | x | x |
| Benjamin et al. [50] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | - | x | x | x | - | x | x | x |
| Ventura et al. [81] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | - |
| Reyes et al. [57] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | - | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x |
| Feld et al. [66] | - | x | x | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | - |
| Smecuol et al. [52] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | - |
| Zuckerman et al. [58] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | - |
| Marshall et al. [83] | - | x | x | x | x | x | x | x | x | x | - | x | - | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | - |
| Koc et al. [46] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | - |
| Caserta et al. [54] | - | x | x | x | x | x | x | x | x | x | - | x | - | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | - | x | x | - |
| | - | x | x | x | x | x | x | x | x | x | - | - | x | x | x | x | x | x | x | x | - | - | x | x | x | x | x | x | x | x | - | x | x | x |

**Table 2** (*Continued*)
Results from critical appraisal according to STROBE guidelines for included articles.

| STROBE critical appraisal tool. | Title, abstract & Introduction | | | | Methods | | | | | | | | | | | | | | | Results | | | | | | | | | | | | Discussion & other information | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | Title & Abstract | | Background | Objectives | Study design | Setting | Participants | | Variables | Data sources | Bias | Study size | Quantitative variables | Statistical methods | | | | | Participants | | | Descriptive data | | | Outcome data | Main results | | | Other analyses | Key results | Limitations | Interpretation | Generalizability | Funding |
| | 1a | 1b | 2 | 3 | 4 | 5 | 6a | 6b | 7 | 8 | 9 | 10 | 11 | 12a | 12b | 12c | 12d | 12e | 13a | 13b | 13c | 14a | 14b | 14c | 15 | 16a | 16b | 16c | 17 | 18 | 19 | 20 | 21 | 22 |
| Kuitunen et al. [55] | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Wigg et al. [64] | - | x | x | x | x | x | x | x | x | x | - | x | - | x | x | x | x | x | x | x | - | x | x | x | x | x | - | - | - | x | - | x | x | - |
| Smecuol et al. [47] | - | x | x | x | x | x | x | x | x | x | - | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | - | x | x | - |
| Davies et al. [72] | - | x | x | - | x | x | x | x | x | x | - | - | x | x | x | x | x | x | x | x | - | - | x | x | x | x | x | x | x | x | - | x | x | - |
| D'Eufemia et al. [67] | - | x | - | x | x | - | x | - | - | - | - | - | x | - | x | x | x | x | x | x | - | - | - | x | x | x | - | x | - | x | - | - | x | - |
| Murphy et al. [49] | x | x | x | - | x | - | x | x | x | x | - | - | - | x | - | x | x | x | x | x | - | - | x | x | x | x | x | x | - | x | - | x | x | - |

'X': Found within study, '-': Not found within study.

**Table 3**
The prevalence of increased intestinal permeability.

| Disease | Increased Intestinal Permeability | Reference |
|---|---|---|
| **Autoimmune Disease** | | |
| Dermatitis herpetiformis | 87.5% | [52] |
| Ulcerative colitis | 10.5-42.9% | [10] |
| Crohn's disease | 36% | [50] |
| Systemic sclerosis | 34.3% | [54] |
| Type 1 diabetes | 30% | [42] |
| Primary biliary cirrhosis | 25% | [66] |
| **Liver Related Conditions** | | |
| Chronic liver disease with type 2 diabetes | 65% | [56] |
| Liver cirrhosis | 35% | [60] |
| Chronic liver disease | 15-35% | [56] |
| Non-alcoholic fatty liver disease | 31% | [63] |
| **Diabetes** | | |
| Chronic liver disease with type 2 diabetes | 65% | [56] |
| Gestational diabetes | 37.5% | [73] |
| Type 1 diabetes | 30% | [42] |
| **Neurological** | | |
| Autism | 36.7% | [11] |
| **Gastrointestinal** | | |
| Irritable bowel syndrome | 35.6% | [83] |

family history of any autoimmune disease has been associated with a 28% higher risk of developing autism in children [93]. The studies on autism in this review [11,67–70] failed to control for a family history of autoimmune disease, anti-myelin basic protein and anti-bodies to measles virus, in their analysis despite the potential for these factor to be markers of AAD [93,94]. Future research should ensure these factors are accounted for in the final analysis.

### *4.1. Increased intestinal permeability and disease severity*

Disease severity and clinical symptoms rather than disease prognosis appear to directly correlate with the severity of IP. Furthermore, disease severity corresponds with conditions where inflammation is considered part of the aetiology or pathogenesis [17,95]. Inflammation along with dysbiosis and glucose metabolism disorders were found to exacerbate the severity of IP [10,42,45,46,48,53,78,79,83,85]. Considering inflammation can affect both IP and disease severity, it is possible that this correlation seen between IP and disease severity is influenced by inflammation rather than IP. In regards to the clinical treatment of IP an improvement in disease symptoms and disease severity has been reported after correcting IP which may also coincide with reduced inflammation from the treatment [96]. The degree of IP in susceptible individuals can be influenced or exacerbated by stressors and corresponds with disease severity [7–9]. Amending dysbiosis, inflammation and glucose metabolism may reduce IP and thereby disease severity. Preliminary studies support amending dysbiosis [96], inflammation [97] and glucose metabolism [97] for correcting IP. However, amending dysbiosis, glucose metabolism and especially inflammation may improve disease severity through other mechanisms not related to IP and thereby may influence the interpretation of the results [98]. Further research is required to understand the connection between dysbiosis, inflammation and glucose metabolism for the treatment of IP, particularly as it relates to the clinical significance of ameliorating these factors in the management and treatment of IP.

### *4.2. Testing methods for increased intestinal permeability*

There are issues with the consistency of IP testing methods used in the studies included in this review. Using dual sugar probes prevents confounding factors such as gastric emptying, intestinal transit time and renal function affecting the results [91]. Furthermore, longer urine collection period, liquid intake and urine volume may negatively influence results and cause a false negative [99]. Urine volume <500 ml during collection may cause a lower lactulose/mannitol ratio compared to urine volume >500 ml [99]. Early research did suggest that urine collection <5 h is the most accurate collection time [34,35] however, more recent research indicates 2 $^{1}/_{2}$ to 4 h is the most accurate collection time to measure IP [100]. The rationale for collecting urine for <5 h has logic as 50% of lactulose/mannitol is excreted in the first 2 h after dual sugar consumption [34,35]. Inconsistencies in applying this standard may have significant impact on the results of IP research, for example one study [69] which reported no relationship between autism and IP may largely be affected by lactulose/mannitol measurement, whereas another study that used serum zonulin to identify IP, reported a direct association between the two conditions [70]. Recent research suggests that serum zonulin is associated with the risk of obesity and hyperlipidaemia [101], however, serum zonulin is considered an accurate marker of IP [36].

### *4.3. Limitations*

Given the review consisted of a heterogeneous mix of studies, no cumulative statistical meta-analysis was conducted. This was due to the combination of a large diversity of diseases along with insufficient consistency among tests used to measure IP. The major limitation of the included studies was, the variety of methods used to assess IP. There was the possibility of false negatives using lactulose/mannitol and false positives using serum zonulin as discussed above. Finally, IP is not universally accepted as a health condition and as such the clinical significance of the findings of this review need to be cautiously considered.

## 5. Conclusion

IP should be considered as a differential diagnosis for patient's presenting with the conditions identified in this review, especially in autoimmune diseases. Factors that exacerbate IP such as inflammation, dysbiosis and glucose metabolism disorders should be addressed during the treatment of IP. Further research is required to determine if IP plays a pathogenic role in the progression and development of disease or whether the disease causes IP. Likewise, future research should explore the degree to which treating IP ameliorates the symptoms of these health conditions.

## Declaration of interests

None.

## Acknowledgment

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