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# Investigation into complementary and integrative medicine practitioners' clinical experience of intestinal permeability: A cross-sectional survey

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ABSTRACT

*Background:* This study aims to explore the conditions complementary and integrative medicine (CIM) practitioners associate with increased intestinal permeability (IP) and the methods they employ to assess IP.

*Methods:* A cross-sectional survey of naturopaths, nutritionists and Western herbal medicine practitioners was undertaken (n = 227) through the Practitioner Research and Collaboration Initiative (PRACI) network.

*Results:* CIM practitioners (n = 36, response rate 15.9%) associate IP with gastrointestinal (100.0%), autoimmune (91.7%), skin (91.7%), neurological (80.6%), respiratory (55.6%) and liver-related conditions (44.4%). CIM practitioners frequently treat IP (72.7%); observing a minimum 3 months of treatment is required to resolve IP. Patient's signs and symptoms were the main reasons CIM practitioners suspected IP (94.1%).

*Conclusion:* CIM practitioners observe a clinical link between IP and a wide range of conditions, including those not yet recognised within the literature. The clinical experience of CIM practitioners holds substantial value to the advancement of research and the clinical management of IP.



## 1. Introduction

Complementary and integrative medicine (CIM) practitioners use the “best” available methods from conventional and complementary medicine for optimal patient care [1]. CIM practitioners such as naturopaths, nutritionists and Western herbal medicine practitioners see a large variety of health conditions in clinical practice, with over 72% reporting a clinical interest in woman's health, general health and well-being and digestive disorders [2]. CIM practitioners may view disease aetiology through a different perspective in accordance with naturopathic philosophies underpinning their clinical practice [3]. Through this clinical experience and deductive reasoning, CIM practitioners may provide insights into the understanding of disease aetiology, pathogenesis and methods to assess digestive health not yet published in the literature [4].

One aspect of digestive health is increased intestinal permeability (IP) which involves the loss of tight junction integrity between epithelium cells of the small intestine [5]. The consequence of IP in health and disease is not fully understood, however, IP has been suggested to play a role in the aetiology or pathogenesis of Crohn's disease [6], coeliac disease [7] and type 1 diabetes [7,8], and to exacerbate the pathogenesis of primary liver disease [9]. Furthermore, IP is suggested to be associated with a wide range of gastrointestinal conditions, autoimmune conditions, liver-related conditions, metabolic conditions and neurological conditions [10–14].

There is limited published literature on the clinical presentation of IP as symptoms can vary and are often non-specific [15,16]. Although the list of conditions associated with IP appears to be diverse, common symptomatology may be shared between individuals with IP. Unverified non-specific symptoms of IP may include bloating, flatulence, diarrhoea, depression and dermatitis

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[15,16]. Current evidence suggests that ameliorating IP corresponds with a reduction in symptoms such as abdominal pain, headaches and tiredness [17] and inducing IP may increase disease severity [18–20]. IP may contribute to disease exacerbation through mechanisms driven by both inflammation and dysbiosis [21–25]. The correlation between IP and disease severity may suggest that treating IP may consequently alter the presentation and progression of associated diseases.

However, the ideal treatment time to resolve IP and any corresponding symptoms remains unknown. The development and thereby the treatment of IP is suggested to be multifactorial, inflecting the time required to resolve IP [26,27]. Gene expression of tight junction proteins involved in IP is suggested to be influenced in a time-dependent manner [28]. There is no set time frame for clinical trial's investigating a treatment intervention for IP, with variation generally ranging from 4-12 weeks [29,30]. Insufficient treatment time may pose a limitation on clinical trials, as the modulation of IP appears to be time-dependent, suggesting that appropriate treatment length may coincide with a greater improvement of IP [31].

Drawing on the clinical experience of CIM practitioners who provide clinical care to individuals with IP, may offer insights to address some of the research knowledge gaps previously mentioned. Therefore, the aim of this study is to explore and describe the conditions CIM practitioners associate with IP and the methods they employ to assess IP in clinical practice.

## 2. Methods

### 2.1. Design

The study consisted of a cross-sectional electronic, self-administrated survey and was conducted with approval from the Human Research Ethics Committees (HREC) of Endeavour College of Natural Health (#20170762).

### 2.2. Setting

The Practitioner Research and Collaboration Initiative (PRACI) is a practice-based research network (PBRN) for CIM practitioners and is designed to facilitate collaboration between researchers and practitioners [32]. The PRACI membership provides researcher access to a national CIM practitioner population with preliminary analysis suggesting representativeness of some CIM professions [2]. The PRACI Steering Committee approved the study following the review of a formal Expression of Interest application (#201700614).

### 2.3. Participants

The source population approached to participate in this study were members of PRACI who identified as holding a diploma qualification or above in naturopathy, nutrition or Western herbal medicine (n = 227). Eligibility to participate in the study also required participants to be currently working within the clinical practice in Australia.

### 2.4. Recruitment

The survey invitation was emailed, on behalf of the research team, by PRACI administration to all PRACI members complying with the eligibility criteria. The survey was open for six weeks between August and September 2017. Two follow-up invitations were emailed to the sample population: the first was two weeks after the initial invitation and the second one-week before data collection was concluded.

### 2.5. Survey

The survey was piloted with six qualified CIM practitioners not associated with PRACI for validity to assess language clarity, the time required and relevance, with corrections made accordingly. The survey included three main domains: *demographics, qualifications and clinical experience, conditions associated with IP and clinical improvement* and *testing methods and frequency of treatment.*

#### 2.5.1. Demographics, qualifications and clinical experience

Basic demographic attributes such as gender, state/territory, level of professional qualification, average hours spent in clinical practice each week and years of clinical experience was included. Participant response to this section was used to determine respondents' eligibility to participate in the survey.

#### 2.5.2. Conditions associated with IP and clinical improvement

A list of 61 different conditions was selected from published epidemiological research. Participants were asked, '*In your clinical experience as a CIM practitioner, which of the following (*corresponding disease category*) have you observed to have ANY association with IP? Select ALL that apply.*' From the categories participants select, a list of corresponding conditions became available with a five-point Likert scale to explore the degree of observed association with IP. These same conditions were used to explore the level of improvement participants observe from treating IP. A five-point Likert scale ranging from "major improvement" to "no improvement" was used to gauge the level of improvement participants observe from treating IP.

#### 2.5.3. Testing methods and frequency of treatment

A five-point Likert scale was used to explore the frequency with which participants test and treat patients for IP. A number of questions explored the factors that influenced participants' decision to test IP.

### 2.6. Data collection

Data collection was undertaken by an online survey administered through *SurveyGizmo*. Once data collection period concluded, data both complete and incomplete were transferred to a spreadsheet before analysis. To limit bias, authors were restricted from participating in the survey. Consent was obtained electronically from participants before the commencement of the survey.

### 2.7. Data analysis

Data were reported as frequencies and percentages. Chi-square tests were also used to examine associations between basic demographics and observed time to resolve IP. Statistical analysis was undertaken using STATA® 14.

## 3. Results

### 3.1. Participant characteristics

A total of 37 applicants responded to the survey with 36 meeting the eligibility criteria and completing the survey (response rate 15.9%). The majority of participants were female (n = 29, 80.6%) and worked in clinical practice in either Victoria (n = 16, 44.4%) or New South Wales (n = 11, 30.6%). Participants held a vocational (diploma/advanced diploma) (n = 15, 41.7%) or university (bachelor degree and above) (n = 21, 58.3%) qualification in naturopathy (n = 32) and/or nutrition (n = 20) and/or Western herbal medicine (n = 12), many of which held dual qualifications. Years of clinical

experience ranged from 1-20 years (mean = 11.5) and hours spent in clinical practice were evenly distributed between 1 hour to over 30 hours per week.

### 3.2. Clinical observed association between IP and disease

Almost all respondents (93.4%) 'often' or 'always' observed an association between IP and at least one of the conditions listed. In particular, they reported observing an association between IP and gastrointestinal (n = 36, 100.0%), autoimmune (n = 33, 91.7%), skin (n = 33, 91.7%), neurological (n = 29, 80.6%), metabolic (n = 23, 63.9%), respiratory (n = 20, 55.6%) and liver-related conditions (n = 16, 44.4%). After treating IP in these conditions, the majority of CIM practitioners observed a clinical improvement in their patients (good: n = 37, 60.6%; major: n = 20, 32.8%; slight: n = 4, 6.6%). Furthermore, as the frequency of the observed association between disease and IP reduced so did the degree of clinical improvement after treating IP.

### 3.3. Autoimmune conditions

The majority of CIM practitioners observed some association between IP and the incidence of Crohn's disease (n = 30, 83.3%), coeliac disease (n = 28, 77.8%), rheumatoid arthritis (n = 27, 75.0%), ulcerative colitis (n = 24, 66.7%), Hashimoto's thyroiditis (n = 23, 63.9%), psoriasis (n = 23, 63.9%), systemic lupus erythematosus (n = 20, 55.6%), multiple sclerosis (n = 17, 47.2%) and dermatitis herpetiformis (n = 12, 33.3%) (see Table 1). The association between IP and autoimmune hepatitis (n = 5, 13.9%), type 1 diabetes (n = 6, 16.7%), systemic sclerosis (n = 6, 16.7%) and ankylosing spondylitis (n = 8, 22.2%) was less commonly reported. From this list of possible conditions, the CIM practitioners identified coeliac disease (n = 26, 92.9%), dermatitis herpetiformis (n = 10, 90.9%), Crohn's disease (n = 26, 89.7%) and ulcerative colitis (n = 20, 87.0%) as the conditions observed to be 'often' or 'always' associated with IP. The respondents also indicated that there was a 'major' improvement in Crohn's disease (n = 10, 41.7%) and ulcerative colitis (n = 8, 40.0%)

**Table 1**
Association between autoimmune conditions and intestinal permeability: degree of association and clinical improvement.

| Condition | Observed association with IP (n = 36) | | Degree of association observed[a] | | | Degree of improvement after treating IP[a] | | |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | Scale | *n* | % | Scale | *n* | % |
| Crohn's disease | 30 | 83.3 | Unsure/Rarely | 1 | 3.5 | Slight/Some | 6 | 25.0 |
| | | | Sometimes | 2 | 6.9 | Good | 8 | 33.3 |
| | | | Often/Always | 26 | 89.7 | Major | 10 | 41.7 |
| Coeliac disease | 28 | 77.8 | Unsure/Rarely | – | – | Slight/Some | 7 | 26.9 |
| | | | Sometimes | 2 | 7.1 | Good | 10 | 38.5 |
| | | | Often/Always | 26 | 92.9 | Major | 9 | 34.6 |
| Rheumatoid arthritis | 27 | 75.0 | Unsure/Rarely | – | – | Slight/Some | 8 | 38.1 |
| | | | Sometimes | 4 | 15.4 | Good | 8 | 38.1 |
| | | | Often/Always | 22 | 84.6 | Major | 5 | 23.8 |
| Ulcerative colitis | 24 | 66.7 | Unsure/Rarely | – | – | Slight/Some | 6 | 30.0 |
| | | | Sometimes | 3 | 13.0 | Good | 6 | 30.0 |
| | | | Often/Always | 20 | 87.0 | Major | 8 | 40.0 |
| Hashimoto's thyroiditis | 23 | 63.9 | Unsure/Rarely | – | – | Slight/Some | 5 | 26.3 |
| | | | Sometimes | 5 | 22.7 | Good | 9 | 47.4 |
| | | | Often/Always | 17 | 77.3 | Major | 5 | 26.3 |
| Psoriasis | 23 | 63.9 | Unsure/Rarely | 1 | 4.6 | Slight/Some | 7 | 36.8 |
| | | | Sometimes | 4 | 18.2 | Good | 6 | 31.6 |
| | | | Often/Always | 17 | 77.3 | Major | 6 | 31.6 |
| Systemic lupus erythematosus | 20 | 55.6 | Unsure/Rarely | 1 | 5.3 | Slight/Some | 5 | 29.4 |
| | | | Sometimes | 3 | 15.8 | Good | 8 | 47.1 |
| | | | Often/Always | 15 | 80.0 | Major | 4 | 23.5 |
| Multiple sclerosis | 17 | 47.2 | Unsure/Rarely | 1 | 6.3 | Slight/Some | 4 | 30.8 |
| | | | Sometimes | 5 | 31.3 | Good | 7 | 53.9 |
| | | | Often/Always | 10 | 62.5 | Major | 2 | 15.4 |
| Dermatitis herpetiformis | 12 | 33.3 | Unsure/Rarely | 1 | 9.1 | Slight/Some | 1 | 11.1 |
| | | | Sometimes | – | – | Good | 4 | 44.4 |
| | | | Often/Always | 10 | 90.9 | Major | 4 | 44.4 |
| Ankylosing spondylitis | 8 | 22.2 | Unsure/Rarely | – | – | Slight/Some | 2 | 33.3 |
| | | | Sometimes | 1 | 14.3 | Good | 2 | 33.3 |
| | | | Often/Always | 6 | 85.7 | Major | 2 | 33.3 |
| Systemic sclerosis | 6 | 16.7 | Unsure/Rarely | – | – | Slight/Some | 1 | 16.7 |
| | | | Sometimes | 1 | 16.7 | Good | 5 | 83.3 |
| | | | Often/Always | 5 | 83.3 | Major | – | – |
| Type 1 diabetes | 6 | 16.7 | Unsure/Rarely | – | – | Slight/Some | 2 | 33.3 |
| | | | Sometimes | 1 | 16.7 | Good | 2 | 33.3 |
| | | | Often/Always | 5 | 83.3 | Major | 2 | 33.3 |
| Autoimmune hepatitis | 5 | 13.9 | Unsure/Rarely | 1 | 20.0 | Slight/Some | 1 | 25.0 |
| | | | Sometimes | 2 | 40.0 | Good | 2 | 50.0 |
| | | | Often/Always | 2 | 40.0 | Major | 1 | 25.0 |
| Primary biliary cirrhosis | 3 | 8.6 | Unsure/Rarely | – | – | Slight/Some | 1 | 33.3 |
| | | | Sometimes | 1 | 33.3 | Good | 1 | 33.3 |
| | | | Often/Always | 2 | 66.7 | Major | 1 | 33.3 |
| Behçet's disease | 2 | 5.6 | Unsure/Rarely | 1 | 50.0 | Slight/Some | 1 | 50.0 |
| | | | Sometimes | – | – | Good | – | – |
| | | | Often/Always | 1 | 50.0 | Major | 1 | 50.0 |

-, Not selected by any participants.
[a] Frequencies based on answers from respondents who reported observing an association in the condition.

after treating IP. All other autoimmune conditions were observed to have a 'good' improvement apart from psoriasis, which was observed to have a 'slight' or 'some' improvement after treating IP (n = 7, 36.8%).

### 3.4. Gastrointestinal conditions

As seen in Table 2, the CIM practitioners observed some association between IP and the occurrence of irritable bowel syndrome (IBS) (n = 33, 91.7%), non-coeliac gluten sensitivity (n = 33, 91.7%), food allergies (n = 30, 83.3%), small intestinal bacteria overgrowth (SIBO) (n = 30, 83.3%), constipation (n = 29, 80.6%), diarrhoea (n = 28, 77.8%), reflux (n = 19, 52.8%) and functional dyspepsia (n = 18, 50.0%). From these conditions, the CIM practitioners observed IBS (n = 26, 83.9%), non-coeliac gluten sensitivity (n = 27, 87.1%), food allergies (n = 25, 89.3%) and SIBO (n = 22, 78.6%) to be associated with IP 'often' or 'always'. The CIM practitioners reported that there was a 'major' clinical improvement after treating IP in constipation (n = 13, 54.2%), diarrhoea (n = 13, 54.2%), reflux (n = 9, 60.0%), non-coeliac gluten sensitivity (n = 12, 44.4%) and functional dyspepsia (n = 8, 53.3%).

### 3.5. Other health conditions

As seen in Table 3, CIM practitioners observed some association between IP and the occurrence of eczema (n = 31, 88.6%), acne (n = 26, 74.3%), dermatitis (n = 26, 74.3%), anxiety (n = 25, 71.4%), depression (n = 24, 68.6%), chronic fatigue syndrome (n = 24, 66.7%), fibromyalgia (n = 21, 58.3%), attention deficit hyperactive disorder (ADHD) (n = 20, 57.1%) and asthma (n = 18, 51.4%). An association between IP and liver cirrhosis (n = 2, 5.7%), gestational diabetes (n = 2, 5.7%) and Parkinson's disease (n = 6, 17.1%) was observed less frequently. The CIM practitioners further observed non-alcoholic fatty liver disease (NAFLD) (n = 11, 91.7%), eczema (n = 26, 86.7%), chronic fatigue syndrome (n = 19, 82.6%), type 2 diabetes (n = 10, 76.9%), dermatitis (n = 19, 76.0%) and acne (n = 19, 76.0%) to have an association with IP 'often' or 'always' of the time. The CIM practitioners indicated that there was a 'major' clinical improvement in polycystic ovarian syndrome (n = 6, 66.7%), type 2 diabetes (n = 6, 54.6%), asthma (n = 8, 53.3%), metabolic syndrome (n = 6, 46.2%) and acne (n = 9, 45.0%) after treating IP. Whereas migraine headaches (n = 7, 50.0%) and depression (n = 8, 42.1%) was perceived to have only 'slight' or 'some' clinical improvement after treating IP.

### 3.6. Signs and symptoms observed to be associated with IP

CIM practitioners observed some association between IP and food sensitivities (n = 35, 97.2%), intestinal dysbiosis (n = 33, 91.7%), abdominal pain (n = 31, 86.1%), bloating (n = 30, 83.3%), candida overgrowth (n = 28, 77.8%), parasitic infection (n = 25, 69.4%), brain fog (n = 23, 65.7%), flatulence (n = 23, 63.9%), inflammation (n = 22, 62.9%), stress (n = 22, 62.9%), obesity (n = 19, 54.3%), over-weight (n = 18, 51.4%) and insulin resistance (n = 14, 40.0%). From this list of possible signs and symptoms, the CIM practitioners reported food sensitivities (n = 31, 93.9%), intestinal dysbiosis (n = 29, 93.6%), inflammation (n = 18, 85.7%) and over-weight (n = 14, 82.4%) to be 'often' or 'always' associated with IP (see Table 4). The CIM practitioners reported 'major' clinical improvement in flatulence (n = 11, 57.9%), candida and yeast overgrowth (n = 12, 52.2%), bloating (n = 13, 52.0%), intestinal dysbiosis (n = 14, 51.9%), food sensitivities (n = 14, 48.3%) and abdominal pain (n = 13, 48.2%) after treating IP, whereas, only 'slight' or 'some' clinical improvement was observed in stress (n = 7, 38.9%).

### 3.7. CIM practitioners' practices and attitude towards testing IP

The CIM practitioners treat IP 'often' or 'always' within their clinical practice (n = 24, 72.7%) however; 'never' or 'rarely' test for

**Table 2**
Association between gastrointestinal conditions and intestinal permeability: degree of association and clinical improvement.

| Condition | Observed association with IP (n = 36) | | Degree of association observed[a] | | | Degree of improvement after treating IP[a] | | |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | Scale | *n* | % | Scale | *n* | % |
| Irritable bowel syndrome | 33 | 91.7 | Unsure/Rarely | – | – | Slight/Some | 2 | 7.4 |
| | | | Sometimes | 5 | 16.1 | Good | 14 | 51.9 |
| | | | Often/Always | 26 | 83.9 | Major | 11 | 40.7 |
| Non-coeliac gluten sensitivity | 33 | 91.7 | Unsure/Rarely | – | – | Slight/Some | 4 | 14.8 |
| | | | Sometimes | 4 | 12.9 | Good | 11 | 40.7 |
| | | | Often/Always | 27 | 87.1 | Major | 12 | 44.4 |
| Food allergies | 30 | 83.3 | Unsure/Rarely | 1 | 3.6 | Slight/Some | 4 | 17.4 |
| | | | Sometimes | 2 | 7.1 | Good | 9 | 39.1 |
| | | | Often/Always | 25 | 89.3 | Major | 10 | 43.5 |
| Small intestinal bacteria overgrowth | 30 | 83.3 | Unsure/Rarely | – | – | Slight/Some | 7 | 28.0 |
| | | | Sometimes | 6 | 21.4 | Good | 9 | 36.0 |
| | | | Often/Always | 22 | 78.6 | Major | 9 | 36.0 |
| Constipation | 29 | 80.6 | Unsure/Rarely | – | – | Slight/Some | 4 | 16.7 |
| | | | Sometimes | 9 | 33.3 | Good | 7 | 29.2 |
| | | | Often/Always | 18 | 66.7 | Major | 13 | 54.2 |
| Diarrhoea | 28 | 77.8 | Unsure/Rarely | – | – | Slight/Some | 4 | 16.7 |
| | | | Sometimes | 9 | 34.6 | Good | 7 | 29.2 |
| | | | Often/Always | 17 | 65.4 | Major | 13 | 54.2 |
| Reflux | 19 | 52.8 | Unsure/Rarely | – | – | Slight/Some | 3 | 20.0 |
| | | | Sometimes | 5 | 29.4 | Good | 3 | 20.0 |
| | | | Often/Always | 12 | 70.6 | Major | 9 | 60.0 |
| Functional dyspepsia | 18 | 50.0 | Unsure/Rarely | – | – | Slight/Some | 2 | 13.3 |
| | | | Sometimes | 5 | 31.3 | Good | 5 | 33.3 |
| | | | Often/Always | 11 | 68.8 | Major | 8 | 53.3 |

-, Not selected by any participants.
[a] Frequencies based on answers from respondents who reported observing an association in the condition.

**Table 3**
Association between other health conditions and intestinal permeability: degree of association and clinical improvement.

| Condition | Observed association with IP (n = 36) | | Degree of association observed[a] | | | Degree of improvement after treating IP[a] | | |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | Scale | *n* | % | Scale | *n* | % |
| Eczema | 31 | 88.6 | Unsure/Rarely | – | – | Slight/Some | 5 | 20.0 |
| | | | Sometimes | 4 | 13.3 | Good | 11 | 44.0 |
| | | | Often/Always | 26 | 86.7 | Major | 9 | 36.0 |
| Acne | 26 | 74.3 | Unsure/Rarely | – | – | Slight/Some | 7 | 35.0 |
| | | | Sometimes | 6 | 24.0 | Good | 4 | 20.0 |
| | | | Often/Always | 19 | 76.0 | Major | 9 | 45.0 |
| Dermatitis | 26 | 74.3 | Unsure/Rarely | – | – | Slight/Some | 4 | 20.0 |
| | | | Sometimes | 6 | 24.0 | Good | 8 | 40.0 |
| | | | Often/Always | 19 | 76.0 | Major | 8 | 40.0 |
| Anxiety | 25 | 71.4 | Unsure/Rarely | – | – | Slight/Some | 7 | 36.8 |
| | | | Sometimes | 10 | 41.7 | Good | 7 | 36.8 |
| | | | Often/Always | 14 | 58.3 | Major | 5 | 26.3 |
| Depression | 24 | 68.6 | Unsure/Rarely | 1 | 4.2 | Slight/Some | 8 | 42.1 |
| | | | Sometimes | 10 | 41.7 | Good | 7 | 36.8 |
| | | | Often/Always | 13 | 54.2 | Major | 4 | 21.1 |
| Chronic fatigue syndrome | 24 | 66.7 | Unsure/Rarely | – | – | Slight/Some | 4 | 20.0 |
| | | | Sometimes | 4 | 17.4 | Good | 11 | 55.0 |
| | | | Often/Always | 19 | 82.6 | Major | 5 | 25.0 |
| Fibromyalgia | 21 | 58.3 | Unsure/Rarely | – | – | Slight/Some | 3 | 17.7 |
| | | | Sometimes | 5 | 25.5 | Good | 9 | 52.9 |
| | | | Often/Always | 15 | 75.0 | Major | 5 | 29.4 |
| Attention deficit hyperactivity disorder | 20 | 57.1 | Unsure/Rarely | 1 | 5.6 | Slight/Some | 5 | 35.7 |
| | | | Sometimes | 6 | 31.6 | Good | 5 | 35.7 |
| | | | Often/Always | 12 | 63.1 | Major | 4 | 28.6 |
| Asthma | 18 | 51.4 | Unsure/Rarely | – | – | Slight/Some | 1 | 6.7 |
| | | | Sometimes | 6 | 33.3 | Good | 6 | 40.0 |
| | | | Often/Always | 12 | 66.7 | Major | 8 | 53.3 |
| Migraine headaches | 18 | 51.4 | Unsure/Rarely | 1 | 5.6 | Slight/Some | 7 | 50.0 |
| | | | Sometimes | 8 | 44.4 | Good | 3 | 21.4 |
| | | | Often/Always | 9 | 50.0 | Major | 4 | 28.6 |
| Metabolic syndrome | 15 | 42.9 | Unsure/Rarely | – | – | Slight/Some | 2 | 15.4 |
| | | | Sometimes | 4 | 26.7 | Good | 5 | 38.5 |
| | | | Often/Always | 11 | 73.3 | Major | 6 | 46.2 |
| Autism spectrum disorder | 14 | 40.0 | Unsure/Rarely | 1 | 7.1 | Slight/Some | 3 | 30.0 |
| | | | Sometimes | 3 | 21.4 | Good | 4 | 40.0 |
| | | | Often/Always | 10 | 71.4 | Major | 3 | 30.0 |
| Type 2-diabetes | 14 | 40.0 | Unsure/Rarely | 1 | 7.7 | Slight/Some | 1 | 9.1 |
| | | | Sometimes | 2 | 15.4 | Good | 4 | 36.4 |
| | | | Often/Always | 10 | 76.9 | Major | 6 | 54.6 |
| Nonalcoholic fatty liver disease | 12 | 34.3 | Unsure/Rarely | – | – | Slight/Some | 1 | 10.0 |
| | | | Sometimes | 1 | 8.3 | Good | 6 | 60.0 |
| | | | Often/Always | 11 | 91.7 | Major | 3 | 30.0 |
| Polycystic ovarian syndrome | 11 | 31.4 | Unsure/Rarely | – | – | Slight/Some | 2 | 22.2 |
| | | | Sometimes | 4 | 36.4 | Good | 1 | 11.1 |
| | | | Often/Always | 7 | 63.6 | Major | 6 | 66.7 |
| Chronic liver disease | 9 | 25.7 | Unsure/Rarely | 1 | 11.1 | Slight/Some | 1 | 14.3 |
| | | | Sometimes | 2 | 22.2 | Good | 5 | 71.4 |
| | | | Often/Always | 6 | 66.7 | Major | 1 | 14.3 |
| Hyperlipidaemia | 9 | 25.7 | Unsure/Rarely | – | – | Slight/Some | 1 | 11.1 |
| | | | Sometimes | 2 | 22.2 | Good | 5 | 55.6 |
| | | | Often/Always | 7 | 77.8 | Major | 3 | 33.3 |
| Hypertension | 9 | 25.7 | Unsure/Rarely | – | – | Slight/Some | 1 | 12.5 |
| | | | Sometimes | 2 | 22.2 | Good | 4 | 50.0 |
| | | | Often/Always | 7 | 77.8 | Major | 3 | 37.5 |
| Alzheimer's disease | 8 | 22.9 | Unsure/Rarely | 1 | 12.5 | Slight/Some | 1 | 25.0 |
| | | | Sometimes | 3 | 37.5 | Good | 2 | 50.0 |
| | | | Often/Always | 4 | 50.0 | Major | 2 | 25.0 |
| Parkinson's disease | 6 | 17.1 | Unsure/Rarely | – | – | Slight/Some | 1 | 20.0 |
| | | | Sometimes | 3 | 50.0 | Good | 2 | 40.0 |
| | | | Often/Always | 3 | 50.0 | Major | 3 | 40.0 |
| Schizophrenia | 5 | 14.3 | Unsure/Rarely | – | – | Slight/Some | – | – |
| | | | Sometimes | 1 | 20.0 | Good | 2 | 66.7 |
| | | | Often/Always | 4 | 80.0 | Major | 1 | 33.3 |
| Chronic obstructive pulmonary disease | 3 | 8.6 | Unsure/Rarely | 1 | 33.3 | Slight/Some | 1 | 50.0 |
| | | | Sometimes | – | – | Good | 1 | 50.0 |
| | | | Often/Always | 2 | 66.7 | Major | – | – |
| Portal hypertension | 3 | 8.6 | Unsure/Rarely | 1 | 33.3 | Slight/Some | 1 | 50.0 |
| | | | Sometimes | 1 | 33.3 | Good | 1 | 50.0 |
| | | | Often/Always | 1 | 33.3 | Major | – | – |
| Gestational diabetes | 2 | 5.7 | Unsure/Rarely | – | – | Slight/Some | – | – |

**Table 3** (*continued*)

| Condition | Observed association with IP (n = 36) | | Degree of association observed[a] | | | Degree of improvement after treating IP[a] | | |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | Scale | *n* | % | Scale | *n* | % |
| | | | Sometimes | 1 | 50.0 | Good | 2 | 100.0 |
| | | | Often/Always | 1 | 50.0 | Major | – | – |
| Liver cirrhosis | 2 | 5.7 | Unsure/Rarely | – | – | Slight/Some | 1 | 50.0 |
| | | | Sometimes | – | – | Good | 1 | 50.0 |
| | | | Often/Always | 2 | 100.0 | Major | – | – |

-, Not selected by any participants.
[a] Frequencies based on answers from respondents who reported observing an association in the condition.

**Table 4**
Association between signs and symptoms and intestinal permeability: degree of association and clinical improvement.

| Condition | Observed association with IP (n = 36) | | Degree of association observed[a] | | | Degree of improvement after treating IP[a] | | |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | Scale | *n* | % | Scale | *n* | % |
| Food sensitivities | 35 | 97.2 | Unsure/Rarely | – | – | Slight/Some | 2 | 6.9 |
| | | | Sometimes | 2 | 2.8 | Good | 13 | 44.8 |
| | | | Often/Always | 31 | 93.9 | Major | 14 | 48.3 |
| Intestinal dysbiosis | 33 | 91.7 | Unsure/Rarely | – | – | Slight/Some | 1 | 3.7 |
| | | | Sometimes | 2 | 6.5 | Good | 12 | 44.4 |
| | | | Often/Always | 29 | 93.6 | Major | 14 | 51.9 |
| Abdominal pain | 31 | 86.1 | Unsure/Rarely | – | – | Slight/Some | 3 | 11.1 |
| | | | Sometimes | 12 | 40.0 | Good | 11 | 40.7 |
| | | | Often/Always | 18 | 60.0 | Major | 13 | 48.2 |
| Bloating | 30 | 83.3 | Unsure/Rarely | – | – | Slight/Some | 2 | 8.0 |
| | | | Sometimes | 7 | 25.0 | Good | 10 | 40.0 |
| | | | Often/Always | 21 | 75.0 | Major | 13 | 52.0 |
| Candida and yeast overgrowth | 28 | 77.8 | Unsure/Rarely | 1 | 3.9 | Slight/Some | 3 | 13.0 |
| | | | Sometimes | 6 | 23.1 | Good | 8 | 34.8 |
| | | | Often/Always | 19 | 73.1 | Major | 12 | 52.2 |
| Parasitic infection | 25 | 69.4 | Unsure/Rarely | – | – | Slight/Some | 4 | 21.1 |
| | | | Sometimes | 5 | 21.7 | Good | 8 | 42.1 |
| | | | Often/Always | 18 | 78.3 | Major | 7 | 36.8 |
| Brain fog | 23 | 65.7 | Unsure/Rarely | – | – | Slight/Some | 3 | 17.7 |
| | | | Sometimes | 8 | 36.4 | Good | 8 | 47.1 |
| | | | Often/Always | 14 | 63.6 | Major | 6 | 35.3 |
| Flatulence | 23 | 63.9 | Unsure/Rarely | – | – | Slight/Some | 2 | 10.5 |
| | | | Sometimes | 5 | 23.8 | Good | 6 | 31.6 |
| | | | Often/Always | 16 | 76.2 | Major | 11 | 57.9 |
| Inflammation | 22 | 62.9 | Unsure/Rarely | – | – | Slight/Some | 3 | 17.7 |
| | | | Sometimes | 3 | 14.3 | Good | 7 | 41.2 |
| | | | Often/Always | 18 | 85.7 | Major | 7 | 41.2 |
| Stress | 22 | 62.9 | Unsure/Rarely | 1 | 4.6 | Slight/Some | 7 | 38.9 |
| | | | Sometimes | 7 | 31.8 | Good | 6 | 33.3 |
| | | | Often/Always | 14 | 63.6 | Major | 5 | 27.8 |
| Obesity | 19 | 54.3 | Unsure/Rarely | – | – | Slight/Some | 4 | 28.6 |
| | | | Sometimes | 5 | 27.8 | Good | 6 | 42.9 |
| | | | Often/Always | 13 | 72.2 | Major | 4 | 28.6 |
| Over-weight | 18 | 51.4 | Unsure/Rarely | – | – | Slight/Some | 3 | 23.1 |
| | | | Sometimes | 3 | 17.7 | Good | 5 | 38.5 |
| | | | Often/Always | 14 | 82.4 | Major | 5 | 38.5 |
| Insulin resistance | 14 | 40.0 | Unsure/Rarely | – | – | Slight/Some | 1 | 10.0 |
| | | | Sometimes | 6 | 46.2 | Good | 4 | 40.0 |
| | | | Often/Always | 7 | 53.9 | Major | 5 | 50.0 |

-, Not selected by any participants.
[a] Frequencies based on answers from respondents who reported observing an association in the condition.

IP (n = 20, 58.8%) (see Table 5). The most frequent method to evaluate IP was the lactulose/mannitol urine test (n = 16, 47.1%) followed by the comprehensive digestive stool analysis (n = 6, 17.7%), serum zonulin (n = 4, 11.8%), hemaview – live blood analysis (n = 3, 8.8%) and iridology (n = 2, 5.9%). The reasons that CIM practitioners suspect IP are their patient's signs and symptoms (n = 32, 94.1%) and medical history (n = 28, 82.4%) followed by patient's disease diagnosis (n = 21, 61.8%), medication use (n = 18, 52.9%), dietary intake (n = 17, 50.0%), lactulose/mannitol urine test (n = 12, 35.3%) and comprehensive digestive stool analysis (n = 10, 29.4%). The CIM practitioners acknowledged that the factor influencing their decision not to test for IP is the price associated with testing (n = 28, 82.4%). Whereas the decision to test is primarily based on an individual basis (n = 24, 70.6%), with many CIM practitioners recognising the importance for patient's compliance (n = 22, 64.7%). CIM practitioners monitor the treatment of IP

**Table 5**
Complementary and integrative medicine practitioners' clinical attitude towards testing for increased intestinal permeability.

| Subject | Scale/Response | (*n* = 34) | % |
|---|---|---|---|
| Frequency of treating IP | Never/Rarely | – | – |
| | Sometimes | 9 | 27.3 |
| | Often/Always | 24 | **72.7** |
| Frequency of testing for IP | Never/Rarely | 20 | **58.8** |
| | Sometimes | 8 | 23.5 |
| | Often/Always | 6 | 17.7 |
| Method used to evaluate IP | Lactulose/Mannitol urine test | 16 | **47.1** |
| | Comprehensive digestive stool analysis | 6 | 17.7 |
| | Serum zonulin | 4 | 11.8 |
| | Hemaview – live blood analysis | 3 | 8.8 |
| | Iridology | 2 | 5.9 |
| Clinical reasons to suspect IP | Patient's signs and symptoms | 32 | **94.1** |
| | Patient's medical history | 28 | 82.4 |
| | Patient's disease diagnosis | 21 | 61.8 |
| | Patient's medication use | 18 | 52.9 |
| | Patient's dietary intake | 17 | 50.0 |
| | Lactulose/Mannitol urine test | 12 | 35.3 |
| | Comprehensive digestive stool analysis | 10 | 29.4 |
| Factors that influence decision not to test for IP | Expensiveness of the test | 28 | **82.4** |
| | Would treat regardless | 18 | 52.9 |
| | Insufficient value to treatment protocol | 11 | 32.4 |
| | Unreliable test results | 9 | 26.5 |
| Factors that influence decision to test for IP | Different for each patient | 24 | **70.6** |
| | Supports patient's compliance | 22 | 64.7 |
| | Patient's signs and symptoms | 9 | 26.5 |
| | Method of monitoring treatment | 9 | 26.5 |
| | Evaluate the presence of IP | 9 | 26.5 |
| | Baseline for patient's with suspected IP | 2 | 5.9 |
| Methods of monitoring the treatment of IP | Change in patient's signs and symptoms | 6 | **17.7** |
| | Patient's verbal opinion | 5 | 14.7 |
| | Grading questions | 4 | 11.8 |
| Observed time to resolve IP | 3 months | 10 | 29.4 |
| | 4-5 months | 10 | 29.4 |
| | Over 6 months | 14 | **41.2** |
| Treatment time before retesting is considered | 3 months | 6 | 21.4 |
| | 4-5 months | 5 | 17.9 |
| | 6 months | 13 | **46.4** |
| | Over 6 months | 4 | 14.3 |

**Bold** values are highest frequency.
IP, increased intestinal permeability; -, not selected by any participants.

through the change in patient's signs and symptoms (n = 6, 17.7%), patient's verbal opinion (n = 5, 14.7%) and grading questions (n = 4, 11.8%). The majority of CIM practitioners report retesting IP at 6 months post-treatment (n = 13, 46.4%), although some practitioners did report retesting at 3 months (n = 6, 21.4%), 4-5 months (n = 5, 17.9%). Very few practitioners waited for more than 6 months to retest (n = 4, 14.3%).

### 3.8. Treatment time required to resolve IP

CIM practitioners reported that the treatment length required to resolve IP was 3 months (n = 10, 29.4%), 4-5 months (n = 10, 29.4%) and over 6 months (n = 14, 41.2%). No significant difference was seen between observed time to resolve IP and level of qualification ($p = 0.18$), years in clinical practice ($p = 0.11$) or hours in clinical practice ($p = 0.43$) (see Table 5).

## 4. Discussion

This is the first study to explore and describe the conditions CIM practitioners associate with IP and the methods they employ to assess IP within clinical practice. Our analysis highlights a number of key findings. Firstly, the CIM practitioners observe a clinical link between IP and a wide range of conditions. The relationship between IP and some of these conditions aligns with existing epidemiological research while others have not yet been investigated at a population level (see Table 6). Only in the instances of reflux, functional dyspepsia and ankylosing spondylitis did CIM practitioner's observations conflict with the available epidemiological evidence in conditions not associated with IP. Epidemiological research is inconclusive regarding the association between IP and Parkinson's disease [33–35]. However, CIM practitioners did not observe an association.

Previous research may justify the closer examination of the conditions that have been overlooked in the epidemiological research yet are reported to be associated with IP by CIM practitioners. For example, chronic fatigue syndrome has been postulated to be associated with IP however, lack conclusive evidence [64]. There is also limited published literature correlating acne with IP, despite an observed link with other skin conditions [15,42,65]. These conditions warrant further investigation to explore the potential role of IP.

In contrast, an association between IP and a number of other conditions supported by epidemiological data [10,11,36,38,41,43,45,49–51,53,57,61] was observed infrequently by CIM practitioners. The difference between current evidence and clinical experience may reflect the lower prevalence of a number of these conditions [66,67], thereby impacting on the frequency that individuals with these conditions present in CIM clinical practice. However, the *strength* of association between IP and conditions rather than the observed *frequency* were more consistent with the published literature, especially in NAFLD and dermatitis

**Table 6**
Conditions associated with increased intestinal permeability as reported in published literature and observed by complementary and integrative medicine practitioners.

| Published literature only | Published literature and CIM practitioners' observation | CIM practitioners' observation only[a] |
|---|---|---|
| Positive correlation | | |
| Autoimmune Disease | | |
| Autoimmune hepatitis [36] | Coeliac disease [12,37] | Hashimoto's thyroiditis |
| Behcet's disease [38] | Crohn's Disease [39,40] | Multiple sclerosis |
| Primary biliary cirrhosis [41] | Dermatitis herpetiformis [42] | Psoriasis |
| Systemic sclerosis [43] | Ulcerative colitis [44] | Rheumatoid arthritis |
| Type 1 diabetes [11,45] | | Systemic lupus erythematosus |
| Gastrointestinal Conditions | | |
| Nil | Food allergies/food sensitivities [46] | Functional dyspepsia≠ |
| | Irritable bowel syndrome [47] | Non-coeliac gluten sensitivity |
| | Small intestinal bacteria overgrowth [48] | Reflux≠ |
| Liver Related Conditions | | |
| Liver cirrhosis [49–51] | Chronic liver diseases [52] | Nil |
| Portal hypertension [53] | Non-alcoholic fatty liver disease [13,54] | |
| Metabolic Conditions | | |
| Gestational diabetes [10] | Polycystic ovary syndrome [55,56] | Metabolic syndrome |
| Intrahepatic cholestasis of pregnancy [57] | Type 2 diabetes [58,59] | |
| Neurological Conditions | | |
| Parkinson's disease [34,35] | Autism spectrum disorder [14,60] | Anxiety |
| | | Attention deficit hyperactivity disorder |
| | | Depression |
| Skin Conditions | | |
| Nil | Nil | Acne |
| | | Dermatitis |
| | | Eczema |
| Respiratory Conditions | | |
| Chronic obstructive pulmonary disease [61] | Nil | Asthma |
| Other Health Conditions | | |
| Nil | Nil | Chronic fatigue syndrome |
| | | Fibromyalgia |
| Negative correlation | | |
| Functional dyspepsia [62] [b] | Parkinson's disease [33] | Ankylosing spondylitis |
| Reflux [63] [b] | | |

[a] Conditions observed to be associated with IP by more than 25% of participants.
[b] A positive correlation between functional dyspepsia and reflux was observed by CIM practitioners whilst a negative correlation was reported in epidemiological literature.
CIM, complementary and integrative medicine; IP, increased intestinal permeability.

herpetiformis [13,42,54]. This may suggest that the CIM practitioners who see a particular condition more frequently within clinical practice may provide a more accurate observed association to IP. However, as there is no comprehensive list of conditions CIM practitioners treat within clinical practice further research is needed to confirm this explanation [3].

Based on our findings, CIM practitioners utilise clinical signs and symptoms as the preferred method to evaluate and indicate IP over validated diagnostic instruments. Some of the signs and symptoms observed by CIM practitioners correspond with previous research [15,16]. These include bloating, flatulence, food sensitivities and diarrhoea [15,16,46]. There is potential value in drawing upon the clinical experience of CIM practitioners to develop a validated diagnostic instrument to identify IP, after a robust diagnostic criteria is developed. A validated diagnostic instrument for IP may then provide CIM practitioners with a cost-effective method to identify IP within clinical practice, addressing the major factor reported to influence their decision not to test for IP. Furthermore, a patient-reported outcome measure surrounding the symptoms of IP when utilised concurrently with a verified testing method in research may supply additional information regarding the application of the intervention [68].

Our study suggests a stronger observed association with IP correlates with a greater observed clinical improvement after treating IP. Moreover, as the observed association to IP reduces, so does the degree of clinical improvement experienced after treating IP. These findings are supported by previous research, which suggests that ameliorating IP through pharmacological methods corresponds with a reduction in clinical symptoms of the disease [17]. In addition, the severity of IP is speculated to influence the seriousness of clinical symptoms of the diagnosed condition [46]. Treating IP in conditions associated with IP, especially those with a stronger association may improve clinical symptoms of the associated condition. Alternatively, the responsiveness to treatment of IP may influence CIM practitioners' perception of the strength of the association.

CIM practitioners reported that a minimum 3 months of treatment is required to resolve IP, with over 6 months in some circumstances. The treatment of IP is multifactorial with both environmental and genetic factors involved in the development and as such resolving IP may entail a lengthy treatment process [26,27]. Clinical trials investigating a treatment intervention for IP vary in length and are generally between 4 and 12 weeks [29,30]. Considering there is no current research stating the treatment length required to resolve IP, clinical trials evaluating treatment options may not be conducting a long enough trial to ascertain adequate results. Therefore, further research is required to explore whether 3 months is the optimal length required for clinical trials to sufficiently evaluate interventions use in resolving IP.

As this was the first study to explore and describe the conditions CIM practitioners associated with IP and the methods they employ to assess IP, results are preliminary. The findings may be affected by response bias, as data was not collected on the non-respondents and therefore not included in final analysis. The low response rate may have occurred due to the saturation of PRACI members with other surveys being conducted at a similar time frame. Due to the small sample size more advanced statistical analysis was not possible. Furthermore, the sample size may prevent the

generalizability of the results to the wider CIM practitioner community in Australia. Despite, these limitations the findings of this study presents novel insights for CIM and mainstream medical practice and research.

## 5. Conclusion

CIM practitioners observed a clinical association between IP and a wide range of conditions, including conditions not yet recognised within the published literature. This highlights the importance of continuing to explore the conditions that may involve IP as part of their presentation. The emphasis CIM practitioners place on patient's signs and symptoms lays the foundations for the development of a validated diagnostic instrument to assess IP. The experience that CIM practitioners have obtained through deductive reasoning holds potential value to the advancement of research and the clinical management of IP.

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## Conflicts of interest

All authors declare no conflict of interest.

## Contributors

BL lead the development of the study, conducted the study and drafted the manuscript. JS and AS provided expertise on all stages of the study and revised the manuscript.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ctcp.2018.02.014.

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