Systematic Review

Metabolic benefits of dietary prebiotics in human subjects: a systematic review of randomised controlled trials

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Abstract

Complex relationships exist between the gut microflora and their human hosts. Emerging evidence suggests that bacterial dysbiosis within the colon may be involved in the pathogenesis of the metabolic syndrome, type 2 diabetes and CVD. The use of dietary prebiotic supplements to restore an optimal balance of intestinal flora may positively affect host metabolism, representing a potential treatment strategy for individuals with cardiometabolic disorders. The present review aimed to examine the current evidence supporting that dietary prebiotic supplementation in adults has beneficial effects on biochemical parameters associated with the development of metabolic abnormalities including obesity, glucose intolerance, dyslipidaemia, hepatic steatosis and low-grade chronic inflammation. Between January 2000 and September 2013, eight computer databases were searched for randomised controlled trials published in English. Human trials were included if at least one group received a dietary prebiotic intervention. In the present review, twenty-six randomised controlled trials involving 831 participants were included. Evidence indicated that dietary prebiotic supplementation increased self-reported feelings of satiety in healthy adults (standardised mean difference $20.57$, $95\%$ CI $21.13$, $20.01$). Prebiotic supplementation also significantly reduced postprandial glucose ($20.76$, $95\%$ CI $21.41$, $20.12$) and insulin ($20.77$, $95\%$ CI $21.50$, $20.04$) concentrations. The effects of dietary prebiotics on total energy intake, body weight, peptide YY and glucagon-like peptide-1 concentrations, gastric emptying times, insulin sensitivity, lipids, inflammatory markers and immune function were contradictory. Dietary prebiotic consumption was found to be associated with subjective improvements in satiety and reductions in postprandial glucose and insulin concentrations. Additional evidence is required before recommending prebiotic supplements to individuals with metabolic abnormalities. Large-scale trials of longer duration evaluating gut microbial growth and activity are required.

Key words: Prebiotics: Gut microflora: Human subjects: Metabolic disorders

The composition and possible health effects of human gut micro-organisms have been the focus of renewed interest since the development of metagenomic techniques enabling the identification and characterisation of intestinal bacteria that cannot be cultured. In addition, the discovery of differences in gut microbial composition between lean and obese individuals(1) and people with and without type 2 diabetes(2,3) has highlighted the potential role played by the colonic microflora and their fermentation products in the pathogenesis of host metabolic health and disease.

Although the number and diversity of bacterial species within an individual’s gastrointestinal tract remain relatively constant throughout life, it is possible to stimulate the proliferation of specific micro-organisms known to have beneficial health effects by manipulating the host diet. Prebiotics are defined as non-digestible plant-derived carbohydrates that

Abbreviations: GLP, glucagon-like peptide; GPR, G protein-coupled receptor; HOMA-IR, homeostasis model assessment for insulin resistance; LPS, lipopolysaccharide; NASH, non-alcoholic steatohepatitis; SMD, standardised mean difference.

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act as a fermentation substrate within the colon, stimulating the preferential growth and activity of a limited number of microbial species that confer health benefits on the host(4). Carbohydrates with an established prebiotic effect include inulin-type fructans (inulin, oligofructose and fructo-oligosaccharides) and galactans (galacto-oligosaccharides)(5), known to promote the proliferation of beneficial lactic acid-producing species such as bifidobacteria and lactobacilli(6).

Gut bacteria play an important role in the development of the host immune system(7) and modulation of inflammatory processes(8), extraction of energy from the host diet(9), fermentation of dietary fibres to produce SCFA(10), alteration of human mineral absorption by the host(14). They may also be involved in the modification of the secretion of gut hormones to enhance satiety and improve gastrointestinal function(15). Dietary prebiotic supplements capable of favourably altering the composition of the intestinal microflora might represent a potential therapeutic strategy for the prevention and treatment of metabolic abnormalities widespread in modern society.

The present review aimed to examine the current evidence supporting dietary prebiotic supplementation in adults on biochemical parameters associated with the development of metabolic abnormalities such as obesity, glucose intolerance, dyslipidaemia, non-alcoholic fatty liver disease and low-grade chronic inflammation.

Methods

A computer search of databases such as MEDLINE, CINAHL, Embase, Current Contents, PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and AMED was undertaken for the period between 1 January 2000 and 30 September 2013. Databases were not searched before 2000, to exclude studies utilising non-molecular, culture-dependent techniques for the characterisation of intestinal bacteria. Reference lists of all identified studies were hand-searched for relevant trials. The following search terms were used: (1) (prebiotic* OR fructan* OR oligofructose OR inulin OR fructooligosaccharide* OR galactooligosaccharide*) and (gut OR obes* OR diabet* OR lipid* OR hepat* OR immune* OR metaboli*); (2) limit 1 to year = '2000–2003'; (3) limit 2 to humans. Trials were included if they were published in English and involved human participants aged ≥18 years and at least one group of participants were randomised to receive a dietary prebiotic intervention. For the purposes of the present review, a prebiotic intervention was defined as one that contained inulin, oligofructose, fructo-oligosaccharides or galacto-oligosaccharides. Additional plant-derived carbohydrates such as arabinoxylan and β-glucan were excluded from the search, as, although demonstrated to have prebiotic effects(16,17), these compounds require further research before being formally classified as prebiotics.

Dietary prebiotic intervention studies of less than 24 h duration were excluded from the present review, as the growth of colonic microflora is unlikely to be affected in this brief time period(18). Nutritional intervention studies involving the administration of probiotics (beneficial live micro-organisms) or synbiotics (a combination of pre- and probiotics) were also excluded. Trials involving prebiotic supplementation in people with disease conditions such as HIV and inflammatory bowel disease were considered to be outside the scope of the present review and were therefore excluded. The methodological quality of all the included trials was assessed by two authors independently using the Heyland Methodological Quality Score(19) (Table 1). This checklist rates primary research based on the use of allocation concealment during randomisation, intention-to-treat analysis, double-blinding, patient selection with minimal risk of bias, comparability of intervention and control groups at baseline, 100 % participant follow-up, clearly described treatment protocol and well-defined outcome measurements. Trials scoring ≥8 out of a possible 14 points were considered to be of high methodological quality. Disagreements between authors in assigning methodological quality scores were resolved by discussion until consensus was reached.

Trials measuring similar outcomes were subjected to a random-effects model meta-analysis using RevMan 5.1 (The Cochrane Collaboration, Copenhagen 2011). Treatment effects and 95 % CI were calculated using the Hedges (adjusted-g) standardised mean difference (SMD), to enable the comparison of effect sizes between trials using different

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The Heyland Methodological Quality Score for individual studies is based on nine quality criteria. The maximum possible score is 14 with studies scoring ≥8 considered to be of high methodological quality.
outcome measures. SMD values of 0·2, 0·5 and 0·8 were considered to represent small, moderate and large effect sizes, respectively.\(^{20}\) Limited numbers of studies investigating comparable outcomes, small sample sizes and heterogeneity among trial subjects, disease conditions, prebiotic supplements, intervention duration and outcome measures limited the majority of data synthesis to a narrative analysis.

**Results**

**Description of the selected trials**

A total of 1130 citations were originally identified at the time of the initial database search and were selected to be included in the review based on the predefined inclusion criteria (Fig. 1). In the present review, twenty-nine articles reporting on twenty-six randomised controlled trials involving 831 participants were ultimately included\(^{21–49}\). The characteristics of the included trials are outlined in Table 2. Of the twenty-six trials included in the present review, thirteen trials included only healthy participants, five trials included only overweight or obese participants, one trial included only overweight participants with the metabolic syndrome, two trials included only participants with type 2 diabetes, two trials included only participants with hypercholesterolaemia, one trial included only participants with non-alcoholic steatohepatitis (NASH), one trial included only participants with gastro-oesophageal reflux disease and one trial included only elderly participants diagnosed with mild malnutrition or at risk of becoming malnourished. The duration of intervention ranged from 2 d to 28 weeks and the participants were aged 19–99 years. A variety of post-intervention outcome measures were reported including self-reported hunger and satiety ratings, total body weight, BMI, waist circumference, energy intake, gastric emptying times, concentrations of appetite-regulating hormones (ghrelin, cholecystokinin, peptide YY and glucagon-like peptide (GLP)-1), concentrations of lipids (total cholesterol, LDL, HDL, TAG, Lp(a) and NEFA), indicators of glucose homeostasis (glucose, insulin, glucagon, homeostasis model assessment for insulin resistance (HOMA-IR), HbA1c and fructosamine), inflammatory markers (TNF-α, C-reactive protein and IL), indices of immune function (natural killer cell activity and T-cell activation), and parameters associated with oxidative stress (total radical-trapping antioxidant parameter (TRAP), photosensitive chemiluminescence, total antioxidant capacity, superoxide dismutase and malondialdehyde) and liver function (aspartate aminotransferase). All the trials were of high methodological quality as assessed by the Heyland Methodological Quality Score. Methodological strengths of the trials included double-blinding utilised in the majority of the studies and random allocation of participants to intervention and control groups or treatment sequence. Methodological limitations of most of the trials included small sample sizes and short study duration. Some cross-over studies did not have a washout period or did not stipulate the duration of their washout period.

**Outcomes associated with body weight**

Of the five trials investigating the effect of dietary prebiotic supplementation on self-reported quantitative ratings of satiety, three demonstrated improvements in subjective satiety measurements in healthy participants consuming prebiotics in comparison with controls\(^{22,23,49}\). After the meta-analysis (\(n = 52\)), the pooled SMD for satiety was $-0.57 \pm 1.13$, $-0.01$; $P = 0.05$, indicating a statistically significant effect favouring prebiotic supplementation over placebo (Fig. 2). Inclusion of two trials finding no change in satiety

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**Fig. 1.** Flow chart showing the progression of trials through each stage of the selection process. RCT, randomised controlled trial. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).
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<td>Bunout et al. (2002)</td>
<td>Chile, n 43 normal-weight and overweight elderly adults: sex not stated (mean age 75-5 years; mean BMI 27 kg/m²)</td>
<td>Parallel RCT double-blinded HMQS: 11</td>
<td>Random assignment to either a 28-week prebiotic-supplemented diet (6 g FOS/d) or a 28-week placebo-supplemented diet (6 g maltodextrin/d)</td>
<td>IL-4 and interferon-gamma, Secretory IgA</td>
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<td>Cani et al. (2006)</td>
<td>Belgium, n 10 healthy adults: five males and five females (mean age 27 years; mean BMI 22-3 kg/m²)</td>
<td>Cross-over RCT subjects blinded HMQS: 9</td>
<td>Random assignment to either a 2-week prebiotic-supplemented diet (16 g oligofructose/d) or a 2-week placebo-supplemented diet (16 g maltodextrin/d) before cross-over. Washout period: 2 weeks</td>
<td>Satiety after breakfast and dinner, Energy intake after dinner, Total energy intake, Plasma GLP-1, Plasma peptide YY, Postprandial plasma glucose</td>
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<tr>
<td>Cani et al. (2009)</td>
<td>Belgium, n 10 healthy adults: five males and five females (mean age 26 years; mean BMI 21-6 kg/m²)</td>
<td>Parallel RCT double-blinded HMQS: 10</td>
<td>Random assignment to either a 2-week prebiotic-supplemented diet (16 g chicyory-derived fructan/d) or a 2-week placebo-supplemented diet (16 g maltodextrin/d)</td>
<td>Hunger, Satiety</td>
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<td>Causey et al. (2000)</td>
<td>USA, n 12 adult males with mild hypercholesterolaemia (age range 27–49 years)</td>
<td>Cross-over RCT double-blinded HMQS: 8</td>
<td>Random assignment to either a 3-week prebiotic-supplemented diet (20 g inulin/d in low-fat ice cream) or a 3-week placebo-supplemented diet (regular low-fat ice cream containing sucrose). Washout period: nil</td>
<td>Serum AST, Serum insulin, Serum TAG, Fasting glucose, Energy intake and HbA1c, CRP and TNF-α, Lipopolysaccharide, Malondialdehyde, TAG and SOD activity, Fasting insulin and HOMA-IR, Glutathione peroxidase activity, Total cholesterol, LDL and CRP (only males), Total body weight, HOMA, TAG and HDL, Glucose after OGTT, Insulin after OGTT, Fasting glucose and fasting insulin, HbA1c and HOMA, Lipid levels, CRP, Total body weight, BMI, Waist circumference, Fasting serum insulin, HOMA and serum LDL, Satiety (only qualitative), Fasting serum glucose, Serum total cholesterol, HDL and TAG</td>
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<tr>
<td>Daubioul et al. (2005)</td>
<td>Belgium, n 7 adult males with NASH (mean age 55 years; mean BMI 29-1 kg/m²)</td>
<td>Cross-over RCT double-blinded HMQS: 8</td>
<td>Random assignment to either an 8-week prebiotic-supplemented diet (16 g oligofructose/d) or an 8-week placebo-supplemented diet (16 g maltodextrin/d) before cross-over. Washout period: 5 weeks</td>
<td>Satiety</td>
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<tr>
<td>Dehpghan et al. (2013)</td>
<td>Iran, n 49 women with type 2 diabetes (mean age 48-3 years; mean BMI 30-8 kg/m²; time after DM diagnosis &gt; 6 months; mean HbA1c levels 8-3 %)</td>
<td>Parallel RCT double-blinded HMQS: 9</td>
<td>Random assignment to either an 8-week prebiotic-supplemented diet (10 g inulin/d) or an 8-week placebo-supplemented diet (10 g maltodextrin/d)</td>
<td>Postprandial plasma glucagonas</td>
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<tr>
<td>Pourghassem Gargari et al. (2013)</td>
<td>Argentina, n 35 obese women (mean age 40-5 years; mean BMI 33-5 kg/m²)</td>
<td>Parallel RCT double-blinded HMQS: 10</td>
<td>Random assignment to either 17-week consumption of Yacon syrup (approximately 12-5 g FOS/d), n 20, or 17-week consumption of placebo syrup, n 15</td>
<td>Fasting glucose, Energy intake and HbA1c, CRP and TNF-α, Lipopolysaccharide, Malondialdehyde, TAG and SOD activity, Fasting insulin and HOMA-IR, Glutathione peroxidase activity, Total cholesterol, LDL and CRP (only males), Total body weight, HOMA, TAG and HDL, Glucose after OGTT, Insulin after OGTT, Fasting glucose and fasting insulin, HbA1c and HOMA, Lipid levels, CRP, Total body weight, BMI, Waist circumference, Fasting serum insulin, HOMA and serum LDL, Satiety (only qualitative), Fasting serum glucose, Serum total cholesterol, HDL and TAG</td>
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### Table 2. Continued

<table>
<thead>
<tr>
<th>Study</th>
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</table>
| Giacco et al. (2004)\(^{31}\) | Italy, \(n = 30\) adults with plasma cholesterol concentrations between 5-17 and 7.76 mmol/L; 20 men and 10 women (mean age 45-5 years; mean BMI 26.6 kg/m\(^2\)) | Cross-over RCT double-blinded | Random assignment to either a 2-month prebiotic-supplemented diet (10.6 g short-chain FOS/d) or a 2-month placebo-supplemented diet (7.5 g maltodextrin/d) before cross-over. Washout period: not stated | Fasting plasma Lp(a)  
Postprandial serum insulin  
Fasting plasma cholesterol and TAG  
Postprandial glucose, NEFA and TAG |
| Lecerf et al. (2012)\(^{32}\) | France, \(n = 59\) healthy adults: twenty-six men and thirty-three women (age 20 years; mean BMI 21 kg/m\(^2\)) | Parallel RCT double-blinded | Random assignment to a 4-week xylo-oligosaccharide supplement (5 g XOS/d) or a 4-week xylo-oligosaccharide +ulin supplement (1 g XOS + 3 g inulin/d) or 4-week placebo (4 g maltodextrin/d) | Lipopolysaccharide  
IL-1β and TNF-α expression  
IL-13 and IL-10 expression |
| Letexier et al. (2003)\(^{33}\) | France, \(n = 8\) healthy adults: four men and four women (age range 23–32 years; BMI range 19–25 kg/m\(^2\)) | Cross-over RCT double-blinded | Random assignment to either a 3-week prebiotic-supplemented diet (10 g inulin/d) or a 3-week placebo-supplemented diet (10 g maltodextrin/d) before cross-over. Washout period: 4 months | Hepatic lipogenesis  
Plasma TAG  
Total cholesterol, LDL and HDL  
Glucose, NEFA, insulin and glucagon  
Total body weight  
T-cell activation  
NK cell activity  
Cytokine production  
Monocyte respiratory burst  
Basal hepatic glucose production  
Fasting plasma glucose and insulin  
Fasting lipids, Lp(a) and NEFA  
ApoA1 and apOb |
<p>| Lomax et al. (2012)(^{34}) | UK, (n = 43) normal-weight and overweight adults: eleven men and thirty-two women (mean age 55 years; mean BMI 25.6 kg/m(^2)) | Parallel RCT double-blinded | Random assignment to either a 4-week prebiotic-supplemented diet (8 g fructans/d) or a 4-week placebo-supplemented diet (8 g maltodextrin/d) | | |
| Luo et al. (2000)(^{35}) | France, (n = 10) adults with type 2 diabetes: six men and four women (mean age 57 years; mean BMI 28.6 kg/m(^2); mean time after DM diagnosis 11 years; mean HbA1c levels 7.7%) | Cross-over RCT double-blinded | Random assignment to either 4-week prebiotic-supplemented cookies (20 g FOS/d) or 4-week control-supplemented cookies (sucrose) before cross-over. Washout period: nil | | |
| Parnell et al. (2009)(^{36}) | Canada, (n = 39) overweight and obese adults with BMI &gt; 25 kg/m(^2); seven men and thirty-two women (mean age 40 years; mean BMI 30.6 kg/m(^2)) | Parallel RCT double-blinded | Random assignment to either a 12-week prebiotic-supplemented diet (21 g oligofructose/d) or a 12-week placebo-supplemented diet (7.9 g maltodextrin/d) | | |
| Peters et al. (2009)(^{37}) | The Netherlands, (n = 21) normal-weight and overweight adults: five men and sixteen women (mean age 53 years; mean BMI 25.9 kg/m(^2)) | Cross-over RCT double-blinded | Random assignment to 2 d consumption of breakfast prebiotic meal-replacement bar (8 g FOS) or breakfast prebiotic + barley meal-replacement bar (8 g FOS + 8 g barley) or breakfast barley meal-replacement bar (8 g barley) or breakfast control meal-replacement bar (oats) | | |
| Piche et al. (2003)(^{38}) | France, (n = 9) adults with gastro-oesophageal reflux disease: five men and four women (mean age 52 years). | Cross-over RCT double-blinded | Random assignment to either a 1-week prebiotic-supplemented low-residue diet (19.8 g FOS/d) or a 1-week placebo-supplemented low-residue diet (sucrose) before cross-over. Washout period: minimum 3 weeks | | |
| Russo et al. (2008)(^{39}); Russo et al. (2010)(^{40}) | Italy, (n = 15) healthy males (mean age 19 years; mean BMI 22.8 kg/m(^2)); Italy, (n = 19) healthy females (mean age 38 years; mean BMI 25.1 kg/m(^2)) | Cross-over RCT double-blinded | Random assignment to either a 5-week prebiotic-supplemented diet (11% inulin-enriched pasta) or a 5-week placebo-supplemented diet (control wheat pasta) before cross-over. Washout period: 8 weeks | | |</p>
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<td>Russo et al. (2011) (41)</td>
<td>Italy, n = 20 healthy males (mean age 19 years; mean BMI 22.8 kg/m²)</td>
<td>Cross-over RCT double-blinded HMQS: 9</td>
<td>Random assignment to either a 5-week prebiotic-supplemented diet (11% inulin-enriched pasta) or a 5-week placebo-supplemented diet (control wheat pasta) before cross-over. Washout period: 8 weeks</td>
<td>↑ Neurotensin and somatostatin</td>
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<tr>
<td>Russo et al. (2012) (42)</td>
<td>Switzerland, n = 74 elderly adults with mild malnutrition: eighteen males and fifty-six females (mean age 84 years; mean BMI 25 kg/m²)</td>
<td>Parallel RCT double-blinded HMQS: 12</td>
<td>Random assignment to either a 12-week prebiotic-supplemented drink (2–4 g FOS/d) or a 12-week identical drink (without FOS)</td>
<td>↓ IL-6 mRNA and TNF-α mRNA</td>
</tr>
<tr>
<td>Schiffrin et al. (2007) (43)</td>
<td>Germany, n = 38 males: twenty smokers and eighteen non-smokers (mean age 27 years; mean BMI 23.2 kg/m²)</td>
<td>Parallel RCT double-blinded HMQS: 9</td>
<td>Subjects participated in a pre-randomisation run-in period (consumed at least 200 g wheat-rye bread/d for 5 weeks), followed by randomisation to an intervention period (nineteen participants consumed at least 200 g prebiotic bread/d for 5 weeks and nineteen participants consumed at least 200 g prebiotic + antioxidant bread/d), followed by a post-intervention period (all thirty-eight participants received a standard diet for 1 week). Intervention breads contained 4 g inulin/100 g</td>
<td>↑ TRAP</td>
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<td>Tovar et al. (2012) (44)</td>
<td>Mexico, n = 110 overweight and obese women (age range 18–50 years; BMI = 25 kg/m²)</td>
<td>Parallel RCT not double-blinded HMQS: 8</td>
<td>Random assignment to 12-week partial meal replacement diet or 12-week partial meal replacement + prebiotic (10 g inulin/d) or 12-week prebiotic (10 g inulin/d) or 12-week control (no meal replacement or inulin). All the subjects received a low-energy diet</td>
<td>↓ Body weight</td>
</tr>
<tr>
<td>Verhoef et al. (2011) (45)</td>
<td>The Netherlands, n = 29 normal-weight and overweight adults: nine males and twenty females (mean age 28 years; mean BMI 24.8 kg/m²)</td>
<td>Cross-over RCT double-blinded HMQS: 9</td>
<td>Random assignment to either a 13 d prebiotic-supplemented diet (10 g FOS/d or 16 g FOS/d) or a 13 d placebo-supplemented diet (16 g maltodextrin) before cross-over. Washout period: 2 weeks</td>
<td>Outcomes for 16 g FOS/d intervention</td>
</tr>
<tr>
<td>Vulevic et al. (2008) (46)</td>
<td>UK, n = 44 normal-weight and overweight elderly adults: sixteen males and twenty-eight females (age range 64–79 years; BMI range 22–31 kg/m²)</td>
<td>Cross-over RCT double-blinded HMQS: 10</td>
<td>Random assignment to either a 10-week prebiotic-supplemented diet (5.5 g GOS/d) or a 10-week placebo-supplemented diet (5.5 g maltodextrin) before cross-over. Washout period: 4 weeks</td>
<td>↑ Plasma GLP-1</td>
</tr>
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<td>Vulevic et al. (2013) (47)</td>
<td>UK, n = 45 overweight and obese adults with the metabolic syndrome: sixteen males and twenty-nine females (mean age 45 years; mean BMI 31 kg/m²)</td>
<td>Cross-over RCT double-blinded HMQS: 10</td>
<td>Random assignment to either a 12-week prebiotic-supplemented diet (5.5 g GOS/d) or a 12-week placebo-supplemented diet (5.5 g maltodextrin) before cross-over. Washout period: 4 weeks</td>
<td>↑ IL-6, IL-8, and TNF-α production</td>
</tr>
<tr>
<td>Whelan et al. (2006) (48)</td>
<td>UK, n = 11 healthy adults: five males and six females (mean age 28 years; mean BMI 23.5 kg/m²)</td>
<td>Cross-over RCT double-blinded HMQS: 10</td>
<td>Random assignment to either a 2-week prebiotic-supplemented liquid enteral formula (approximately 18 g pea fibre + 10 g FOS/d) or a 2-week placebo liquid enteral formula (standard formula) before cross-over. Washout period: 4 weeks</td>
<td>↓ IL-10, IL-6, and TNF-α production</td>
</tr>
</tbody>
</table>

RCT, randomised controlled trial; HMQS, Heyland Methodological Quality Score, where trials scoring ≥ 8 out of 14 points are considered to be of high methodological quality; FOS, fructo-oligosaccharide; GLP, glucagon-like peptide; NASH, non-alcoholic steatohepatitis; AST, aspartate aminotransferase; DM, diabetes mellitus; CRP, C-reactive protein; TAC, total antioxidant capacity; SOD, superoxide dismutase; HOMA-IR, homeostasis model assessment for insulin resistance; ALA, α-linolenic acid; DGT, oral glucose tolerance test; Lp(a), lipoprotein(a); XOS, xylo-oligosaccharide; XK, natural killer CD; CD, cluster of differentiation; TRAP, total radical-trapping antioxidant parameter; PCL, photosensitive chemiluminescence; ICAM-1, intracellular adhesion molecule-1; GOS, galacto-oligosaccharide; TC, total cholesterol; ↓, significantly lower than that in the comparison diet group after intervention; ↑, significantly higher than that in the comparison diet group after intervention; ↔, no significant difference between the prebiotic-supplemented diet and control diet groups after intervention; HLA-DR, human leucocyte antigen-D-related.
after prebiotic consumption \(^{(57, 46)}\) was not possible in the meta-analysis, as they did not report study data and did not provide results when contacted by the reviewers. An additional trial carried out in obese subjects was also excluded from the meta-analysis because it reported only qualitative improvements in satiety \(^{(50)}\). Of the five trials measuring energy intakes in normal-weight and overweight participants and those with type 2 diabetes, three found a significant reduction in total energy consumption during the prebiotic intervention when compared with placebo \(^{(22, 26, 36)}\). However, reduction in total energy consumption during the prebiotic and those with type 2 diabetes, three found a significant energy intakes in normal-weight and overweight participants placebo were reported by two trials \(^{(30, 36)}\), while no change weight after prebiotic supplementation in comparison with intervention on body weight. Significant reductions in body reported by five trials examining the effect of prebiotic intervention for at least 2 weeks’ duration increases circulating peptide YY concentrations in normal-weight and overweight adults \(^{(23, 36, 46)}\), but the effect was not statistically significant after the meta-analysis \((n = 100)\), with a combined SMD of \(-0.96 \ (95\%\ CI\ -1.98, 0.06;\ P=0.07)\). Of four high-quality trials, two found increased GLP-1 concentrations after prebiotic supplementation in healthy and overweight subjects \(^{(25, 38)}\). The increase in GLP-1 concentrations was not significant after the meta-analysis \((n = 117)\), with a pooled SMD of \(-0.32 \ (95\%\ CI\ -0.87, 0.23;\ P=0.25)\). Each of the trials reported significant reductions in ghrelin concentrations \(^{(36)}\) and increased GLP-2 concentrations \(^{(42)}\) in subjects consuming dietary prebiotics. Contradictory results were reported by five trials examining the effect of prebiotic intervention on body weight. Significant reductions in body weight after prebiotic supplementation in comparison with placebo were reported by two trials \(^{(50, 56)}\), while no change in body weight was observed in three trials \(^{(26, 28, 44)}\). Trials of longer duration (12–17 weeks) were more likely to observe reductions in body weight than shorter trials lasting 4–8 weeks. The meta-analysis \((n = 191)\) indicated a non-significant reduction in body weight after prebiotic supplementation, with a pooled SMD of \(-0.48 \ (95\%\ CI\ -1.19, 0.23;\ P=0.19)\).

### Outcomes associated with glucose homeostasis

Of the four studies measuring the effect of prebiotic supplementation on postprandial glucose concentrations, two reported significant reductions in glucose concentrations \((95\%\ CI\ -1.41, -0.07;\ P<0.05)\), indicating a statistically significant effect supporting that prebiotic consumption results in the reduction of postprandial glucose concentrations (Fig. 3). Of three studies, two reported significant reductions in postprandial insulin concentrations following prebiotic intervention in overweight and hypercholesterolaemic subjects \(^{(31, 36)}\). Meta-analysis of these trials \((n = 121)\) indicated a statistically significant reduction in postprandial insulin concentrations, with a combined SMD of \(-0.77 \ (95\%\ CI\ -1.50, 0.04;\ P<0.05)\) (Fig. 4). Significant delays in gastric emptying times in healthy males consuming prebiotic supplements were found in two trials carried out by the same study group \(^{(40, 41)}\). Studies investigating fasting glucose and fasting insulin concentrations and insulin resistance (HOMA-IR) reported conflicting results. Significant reductions in HbA1c levels in healthy participants after only 5 weeks of prebiotic supplementation \(^{(40)}\) and in women with type 2 diabetes after 8 weeks \(^{(26)}\) were found by two trials, while no change in HbA1c levels in obese women after prebiotic supplementation lasting 3 months was found by another trial \(^{(29)}\).

### Outcomes associated with cardiovascular and hepatic health

There was insufficient evidence to support that prebiotic supplementation reduces total cholesterol or LDL concentrations in healthy, obese or dyslipidaemic individuals, with the

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD (random)</th>
<th>95 % CI</th>
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<tbody>
<tr>
<td>Cani et al. (2006)(^{(22)})</td>
<td>-0.85</td>
<td>-1.77, 0.08</td>
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<tr>
<td>Cani et al. (2009)(^{(23)})</td>
<td>-0.51</td>
<td>-1.78, 0.76</td>
</tr>
<tr>
<td>Whelan et al. (2006)(^{(49)})</td>
<td>-0.37</td>
<td>-1.22, 0.47</td>
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<tr>
<td>SMD</td>
<td>-0.57</td>
<td>-1.13, 0.01</td>
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Fig. 2. Effects of dietary prebiotic supplementation on self-reported satiety. Forest plot of standardised mean differences (SMD, 95 % CI) for individual and pooled trials.
majority of studies finding no change in the concentrations of these lipids after intervention. Of the eleven trials investigating the effect of prebiotic supplementation on circulating TAG concentrations, five reported significant reductions in healthy, overweight or hypercholesterolaemic individuals compared with controls\(^{(24,33,39,45,48)}\). However, the remaining six trials that failed to detect changes in TAG concentrations were also carried out in healthy, overweight or hypercholesterolaemic subjects\(^{(25,28–31,35)}\). These trials were subjected to meta-analysis (\(n=402\)), resulting in a non-significant pooled SMD for TAG concentrations of \(-0.11\) (95% CI \(-0.31, 0.08\); \(P=0.26\)) (Fig. 5). A significant reduction in serum aspartate aminotransferase concentrations was reported by one small trial carried out in people with NASH\(^{(25)}\).

**Outcomes associated with inflammation and immune function**

Of the four trials investigating the impact of dietary prebiotic supplementation on circulating C-reactive protein (a biochemical marker of inflammation) concentrations, three found significant reductions in overweight and obese adults and women with type 2 diabetes in comparison with controls\(^{(26,28,48)}\). Meta-analysis of these trials (\(n=181\)) indicated a non-significant reduction in C-reactive protein concentrations after prebiotic supplementation, however, with a pooled SMD of \(-0.85\) (95% CI \(-2.11, 0.42\); \(P=0.19\)). Studies measuring the production of pro-inflammatory cytokines (TNF-\(\alpha\) and IL) and immune cell activity (T-cell activation and natural killer cell activation) yielded contradictory results. Significant increases in the measures of antioxidant status (total antioxidant capacity\(^{(27)}\), total radical-trapping antioxidant parameter and photosensitive chemiluminescence\(^{(44)}\)) were found by two studies, and a decrease in small-intestinal permeability\(^{(42)}\) following prebiotic interventions was reported by one trial. Significant reductions in circulating lipopolysaccharide (LPS) concentrations after dietary prebiotic supplementation in healthy adults\(^{(32)}\) and women with type 2 diabetes\(^{(26)}\) were identified by two studies.

**Discussion**

Simple, safe and effective interventions are urgently needed to prevent and treat obesity and its associated co-morbidities. The human gut microbiota and its metabolites influence host...
physiology, energy homeostasis, inflammatory processes and immune function both locally and within distal tissues. The use of dietary prebiotic supplements to promote the selective proliferation of beneficial intestinal microbes might represent an important nutritional strategy in the management of metabolic abnormalities and chronic disease.

**Prebiotics and overweight/obesity**

The SCFA acetate, propionate and butyrate are produced as by-products of bacterial prebiotic fermentation in the colon. In addition to representing a source of energy for the host, these SCFA play a number of beneficial roles including the maintenance of human intestinal health and modulation of metabolic and immune processes. SCFA are the only known ligands for two G protein-coupled receptors, GPR41 and GPR43, which are expressed in a variety of gastrointestinal cells and stimulate the secretion of hormones involved in the regulation of energy intake and expenditure. Binding of SCFA to GPR41 increases the production of peptide YY and GLP-1, hormones that reduce appetite, delay gastric emptying and increase insulin sensitivity\(^50\). SCFA also promote the differentiation of intestinal L-cells, contributing to increased endogenous GLP-1 production\(^51\).

In animal studies, dietary supplementation of the SCFA butyrate has been found to prevent diet-induced obesity and improve insulin sensitivity with a concomitant increase in energy expenditure and fatty acid oxidation and an increase in mitochondrial respiration\(^52\). In mice, the selective growth of certain *Lactobacillus* species in the colon has been found to reduce body fat storage through the up-regulation of *Fiaf* (fasting-induced adipose factor) gene expression and inhibition of lipoprotein lipase\(^53,54\). Indeed, several animal studies have demonstrated the protective effects of prebiotics on the development of obesity and insulin resistance\(^55,56\); however, more robust human studies are required to confirm the protective effects of prebiotics on these pathways in human physiology.

The present review found consensus among three of the five high-quality trials supporting that the daily consumption of a prebiotic supplement for a minimum of 2 weeks increases satiety cues in healthy adults. However, these findings were based on self-reports from relatively small numbers of subjects (\(n\) 81) and prebiotic supplementation failed to result in significant weight reduction. Weight reduction was unlikely to be observed in these trials due to the short duration of their prebiotic interventions (2 d–2 weeks). The addition of pea fibre to the prebiotic supplement confounded one trial reporting an increase in satiety after 2 weeks of prebiotic consumption, making it difficult to draw conclusions about the action of either type of fibre individually\(^59\). Of the two trials that did not detect any change in satiety after prebiotic supplementation,
Prebiotics and glucose intolerance

Reduced levels of bifidobacteria and lactobacilli and increased gastrointestinal permeability are found in mice consuming a diet high in saturated fat when compared with those consuming a standard diet. The provision of dietary prebiotic supplements subsequently restores the growth of these beneficial bacterial species and improves the integrity of the gut barrier. Animal studies have shown a causal link between the consumption of a high-fat diet and increased intestinal levels of LPS-containing bacteria, or concentrations of circulating LPS, and the development of obesity and insulin resistance. LPS is the major component of the outer membrane of Gram-negative bacteria and is composed of a hydrophobic lipid (lipid A), a hydrophilic core oligosaccharide and a repeating hydrophilic polysaccharide side chain (O-antigen). In the setting of a high-fat diet, LPS is able to translocate from the intestine into the host circulation, resulting in ‘metabolic endotoxaemia’. LPS stimulates the overproduction of reactive oxygen species and pro-inflammatory cytokines by macrophages, resulting in subclinical systemic inflammation, weight gain and insulin resistance development. Human subjects with type 2 diabetes have been found to possess serum endotoxin levels that are 2-fold higher than those observed in non-diabetic controls. Metabolic endotoxaemia is also positively correlated with total energy intake and fasting insulin concentrations in the non-diabetic population. In mice with high-fat diet-induced metabolic endotoxaemia, nutritional supplementation with prebiotics restores intestinal levels of Gram-positive bacteria, improves glucose tolerance and reduces circulating concentrations of LPS and pro-inflammatory cytokines.

Prebiotics and their fermentation products have been shown to reduce gastrointestinal permeability by a variety of mechanisms. The SCFA butyrate is involved in the maintenance of gut epithelial integrity by acting as the principal fuel for colonocytes and promoting the transcription of tight junction proteins between gastrointestinal cells. Butyrate also reduces gastrointestinal permeability by enhancing the activation of the peroxisomal proliferator-activated receptor gamma (PPARγ) gene, a nuclear factor receptor involved in the attenuation of inflammation in colonic epithelial cells. Prebiotic-induced changes in gut microbiota also increase the endogenous production of GLP-2, which enhances gut barrier function by promoting the proliferation of crypt cells.

The present review found general agreement among trials supporting that the consumption of dietary prebiotic supplements reduces postprandial glucose and insulin concentrations in healthy and overweight individuals. Pooled reductions in postprandial glucose and insulin concentrations were statistically significant after the meta-analysis. High-quality randomised controlled trials conducted in subjects with either impaired glucose tolerance or type 2 diabetes have also found reduced postprandial serum insulin concentrations after the consumption of arabinoxylan (a potential prebiotic fibre). Whether these results were mediated by alterations in intestinal bacterial growth or activity is unclear, as stool samples were not analysed in these trials. Significant delays in gastric emptying times after prebiotic supplementation in healthy males were found by two studies. However, these trials were conducted by the same research group, and it is unclear whether some subjects participated in both the studies. Therefore, further independent research is required before definitive conclusions can be drawn about the effects of prebiotic consumption on gastric emptying. The findings of studies investigating fasting glucose and fasting insulin concentrations and insulin resistance (HOMA-IR) after prebiotic supplementation were contradictory. Long-term prebiotic intervention studies in people with pre-diabetes...
or the metabolic syndrome are now required to determine whether prebiotics confer some protection against the future development of type 2 diabetes in high-risk individuals.

**Prebiotics and dyslipidaemia**

The abundance of particular bacterial species in the gut has been shown to be positively correlated with serum total cholesterol and LDL-cholesterol concentrations in subjects with CVD(75). It has also been hypothesised that bacteria found in atherosclerotic plaques may have originated from the gastrointestinal tract, as the DNA of specific micro-organisms can be found in both the colon and coronary atheroma of the same individual(76). As the development of CVD involves multiple pro-inflammatory pathways, it is plausible that pathogenic microbes may potentiate inflammation within atherosclerotic plaques by delivering macropathies to the arterial wall and stimulating their production of reactive oxygen species and cytokines or their conversion to foam cells(77).

Propionate, a SCFA product of prebiotic fermentation, may play a significant role in the modification of hepatic lipid metabolism. In the liver, propionate is a possible substrate for gluconeogenesis and may contribute to the inhibition of cholesterol synthesis by altering the activity of 3-hydroxy-3-methylglutaryl-CoA reductase(5). In addition, prebiotic supplementation might attenuate cholesterol and TAG production by stimulating the synthesis of cis-9, trans-11-conjugated linoleic acid from PUFA by beneficial bacterial species. This is a form of cis-9, trans-11-conjugated linoleic acid has been shown to reduce cholesterol and TAG concentrations in animal studies(78), but the results of human trials are less conclusive. Gut microbes are also an essential requirement for the production of secondary bile acids in the colon. These bile acids are de-conjugated and are therefore unavailable for enterohepatic recirculation. As a result, the liver is forced to produce additional bile acids from circulating cholesterol(20).

The findings of human intervention studies investigating the effect of dietary prebiotic supplementation on circulating total and LDL-cholesterol concentrations were contradictory. Of the two studies reporting significant reductions in total cholesterol concentrations, one found a reduction in only male subjects and was complicated by the use of an intervention containing both prebiotics and α-linolenic acid(20). α-Linolenic acid may have contributed to the cholesterol-lowering effect in this instance. There is limited evidence to support that prebiotic supplementation reduces total or LDL-cholesterol concentrations in hypercholesterolaemic individuals, as the only two trials conducted in participants with hypercholesterolaemia found no significant changes in total cholesterol, LDL-cholesterol or HDL-cholesterol concentrations(24,31). However, these trials involved short-term prebiotic intervention periods (3–8 weeks’ duration) and studies of longer duration are therefore required.

The present review found conflicting evidence describing the effect of prebiotic supplementation on circulating TAG concentrations in healthy, overweight/obese and hypercholesterolaemic subjects. In addition to a prebiotic supplement, one study(45) provided a low-energy diet co-intervention to all the trial participants, making it difficult to establish whether the TAG-lowering effect was associated with prebiotic-induced intestinal microbial changes alone or whether weight reduction or a reduced fat intake together with the action of the modified microflora produced a synergistic effect. Additional systematic reviews exploring this topic have also reported equivocal conclusions. The use of prebiotics for the reduction of TAG concentrations in humans regardless of health condition was favoured by one review of trials published between 1995 and 2005(30), with the majority of trials being conducted in normolipidaemic individuals. The other meta-analysis of trials published between 1999 and 2010 supported the TAG-lowering effects of inulin in only hypercholesterolaemic subjects(75), but the reduction in TAG concentrations lost significance when results from both hyperlipidaemic and normolipidaemic subjects were combined. The present review also found a non-significant reduction in TAG concentrations after the meta-analysis of pooled trials. Future trials must simultaneously quantify lipid concentrations and gut bacterial growth and activity to determine whether prebiotic-induced modulation of the intestinal flora contributes to the reduction of serum TAG concentrations.

**Prebiotics and non-alcoholic steatohepatitis**

NASH is an asymptomatic disease characterised by fatty infiltration of the liver and inflammation, which can eventually lead to fibrosis, cirrhosis, portal hypertension, hepatocellular carcinoma and liver failure(83). Obesity, dyslipidaemia, insulin resistance and diabetes have frequently been reported to be associated with the development of NASH. Increased plasma endotoxaemia, overproduction of inflammatory cytokines and excessive oxidative stress within hepatic cells are also thought to contribute to the pathogenesis of NASH. The use of dietary prebiotic supplements to restore an optimal microbial balance within the gastrointestinal tract of individuals with NASH may assist in the reduction of TAG accumulation in the liver, attenuate inflammation and promote hepatic secretion of lipoproteins such as VLDL(19). The translocation of Gram-negative bacteria from the intestine into the circulation has been reported to be associated with an increased severity of cirrhosis(82). By maintaining gut barrier function and reducing bacterial translocation, prebiotics may be effective in the management of liver disease complications(83).

Studies exploring the effects of dietary prebiotic consumption on metabolic parameters in individuals with NASH are scarce. In the present review, one small trial involving seven adult males was included, which found a significant reduction in serum aspartate aminotransferase concentrations after prebiotic supplementation(25). This finding was supported by a larger randomised controlled trial (n 66), which administered a symbiotic (fructo-oligosaccharide + Bifidobacterium longum) to participants for 24 weeks(49). In addition to a significant reduction in serum aspartate aminotransferase concentrations, researchers found a reduction in the concentrations of circulating cytokines (TNF-α) and markers of inflammation (C-reactive protein), reduced concentrations of serum LDL-cholesterol and...
endotoxins, an improvement in insulin sensitivity (HOMA-IR) and a reduction in hepatic steatosis (determined by liver biopsy). More research is required in this potentially very promising area of study.

**Prebiotics and immune cell dysfunction**

Gut microbiota, innate immune function and metabolism are inextricably linked, with early pathological processes occurring at the molecular level (subclinical inflammation, immune cell activation, increased oxidative and endoplasmic reticulum stress, altered production of vascular adhesion molecules and advanced glycation end products) contributing to the eventual development of metabolic disturbances such as hyperlipidaemia, atherosclerosis, insulin resistance and weight gain. Colonic bacteria and their prebiotic fermentation products may play a key role in the modulation of immune function by both increasing host resistance to infection and down-regulating inappropriate immune responses in the case of allergic reactions or chronic inflammatory conditions. By maintaining the integrity of the gastrointestinal barrier, prebiotics reduce the invasion of pathogenic intestinal bacteria and their products (including LPS) into the circulation, preventing downstream immune cell activation. Prebiotics are thought to encourage increased intestinal mucin production, protecting the intestinal wall from bacterial adherence and invasion. SCFA produced as a by-product of bacterial prebiotic fermentation interact with GPR41 and GPR43 receptors on neutrophils and inhibit NF-κB activation, reducing the production of pro-inflammatory cytokines. Additional bacterial fermentation products such as polysaccharide A and peptidoglycan exert anti-inflammatory effects on the host immune system.

There is insufficient evidence at present to recommend dietary prebiotics for the modulation of immune function to improve cardiometabolic health. There are very few human trials available, and most have reported contradictory findings. Although individual studies have found significant increases in the measures of antioxidant capacity and reductions in small-intestinal permeability and circulating LPS concentrations after prebiotic interventions, further studies are required to verify these results. Inulin exhibits antioxidant properties independent of altering gut bacterial growth and is able to scavenge a number of reactive oxygen species, which may help to reduce lipid peroxidation in the stomach. Future studies must distinguish between health benefits derived solely from the consumption of soluble fibres and those associated with the growth and activity of beneficial gut microbes. Future intervention studies exploring the effect of dietary prebiotics on immune function need to be conducted in healthy individuals who are subsequently exposed to an immune challenge.

**Conclusions**

Although animal studies have provided convincing evidence to support the beneficial role of prebiotics in metabolic health, the results of human trials to date have been less conclusive. Research involving laboratory animals enables the provision of tightly controlled diets, whereas studies involving free-living humans are complicated by the variety of foods consumed by individuals from day to day. Some human studies have been complicated by the use of nutritional supplements containing prebiotics in combination with additional health-promoting components such as live bacteria, antioxidants and other dietary fibres, making it difficult to attribute changes in metabolism to prebiotics alone. To rule out cardiometabolic benefits associated with concomitant nutrients, prebiotic supplements in their pure form must be used in future trials.

In addition to bifidobacteria and lactobacilli, dietary prebiotics modulate the growth of numerous other gastrointestinal micro-organisms, the identity and function of which have not yet been fully characterised. Different species of bifidobacteria also have a variety of functions, which require further elucidation. Prebiotics are likely to undergo cross-fermentation by other microbial species of unknown benefit to the host. Bacterial analyses of human stool samples provide information only about the micro-organisms inhabiting the colon and are unlikely to accurately reflect the microbial composition of the proximal intestine. Responses to dietary prebiotics are variable in humans, with bifidogenic potential being affected by an individual's age, body weight, antibiotic use, dietary macronutrient intake, physical activity and baseline levels of colonic bifidobacteria. More research is required to determine host lifestyle behaviours capable of promoting intestinal normobiosis and to establish the optimal prebiotic dose required to maximise health benefits.

In conclusion, the present review found convincing evidence from short-term high-quality human trials supporting the use of dietary prebiotics as a potential therapeutic intervention for the regulation of appetite and the reduction of circulating postprandial glucose and insulin concentrations. Further studies are needed to correlate these findings with changes in the growth and function of specific gut bacteria. There is insufficient evidence at present to recommend dietary prebiotics for reducing energy intake and body weight, increasing gastric peptide YY and GLP-1 secretion, improving insulin sensitivity, lowering lipid levels and modulating immune function. Long-term prospective trials investigating primary metabolic end points are now required.

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