University of Reading

The gut microbiota and cardiovascular health benefits: a focus on wholegrain oats

Article

Published Version

Creative Commons: Attribution 4.0 (CC-BY)

Open Access

Kristek, A., Schar, M. Y., Soycan, G., Alsharif, S., Kuhnle, G. G. C. ORCID: https://orcid.org/0000-0002-8081-8931, Walton, G. ORCID: https://orcid.org/0000-0001-5426-5635 and Spencer, J. P. E. ORCID: https://orcid.org/0000-0003-2931-7274 (2018) The gut microbiota and cardiovascular health benefits: a focus on wholegrain oats. Nutrition Bulletin, 43 (4). pp. 358-373. ISSN 1471-9827 doi: 10.1111/nbu.12354 Available at https://centaur.reading.ac.uk/80682/

It is advisable to refer to the publisher's version if you intend to cite from the work. See Guidance on citing.

To link to this article DOI: http://dx.doi.org/10.1111/nbu.12354

Publisher: Wiley-Blackwell

All outputs in CentAUR are protected by Intellectual Property Rights law, including copyright law. Copyright and IPR is retained by the creators or other copyright holders. Terms and conditions for use of this material are defined in the End User Agreement.

University of Reading

www.reading.ac.uk/centaur

CentAUR

Central Archive at the University of Reading

Reading's research outputs online

Nutrition Bulletin

REVIEW

DOI: 10.1111/nbu.12354

The gut microbiota and cardiovascular health benefits: A focus on wholegrain oats

A. Kristek, M. Y. Schär, G. Soycan, S. Alsharif, G. G. C. Kuhnle, G. Walton and J. P. E. Spencer

Department of Food and Nutritional Sciences, University of Reading, Reading, UK

Abstract

Existing scientific data suggest that a high intake of wholegrain foods contributes to improved gut health and a reduced risk of cardiovascular disease. Wholegrain oats are rich in dietary fibre and an important source of many bioactive components, including minerals, vitamins and phenolic compounds. The oat β-glucans have been reported to lower low-density lipoprotein cholesterol through their ability to increase the viscosity of intestinal chime, change the gut microbiota composition and increase the production of short-chain fatty acids, which may contribute to the inhibition of hepatic cholesterol synthesis. Oats are also a rich source of phenolic acids, which are predominantly bound to cell wall polysaccharides through ester bonds. This bound state within oats means that phenolic acid bioavailability will largely be determined by interactions with the colonic microbiota in the large intestine. However, results from *in vitro*, animal and human studies have been inconsistent in relation to the impact of oats on the gut microbiota, possibly due to differences in experimental techniques and because compounds in oats, other than β-glucans, have not been considered. This review focuses on the interaction of oat β-glucans and phenolic acids with gut microbiota, and the subsequent link to cardiovascular health.

Keywords: cardiovascular disease, gut health, gut microbiota, oat, phenolic acids, β-glucans

Introduction

A high intake of wholegrains is related to improved gut health (Cooper *et al.* 2015) and reduced risk of cardiovascular disease (CVD) (Thies *et al.* 2014b; Aune *et al.* 2016). The health benefits of wholegrains might be due to effects on inflammation (Nilsson *et al.* 2008a; Singh *et al.* 2013), fasting blood glucose (Pick *et al.* 1996; Jensen *et al.* 2006) and markers of lipid metabolism (Pins *et al.* 2002; Behall *et al.* 2004; Jonnalagadda *et al.* 2011; Johansson-Persson *et al.* 2014; Tang *et al.* 2015; Aune *et al.* 2016). A recent meta-analysis of observational studies indicates that diets rich in wholegrains are associated with a 21% reduction [relative risk (RR) = 0.79 (95% CI: 0.74, 0.85)] in CVD risk (Ye *et al.* 2012). However, the median daily wholegrain intake in the UK, estimated from secondary analysis of data from the *National Diet and Nutrition Survey* Rolling Programme 2008/2009–2010/2011, is 20 g/day for adults and 13 g/day for children, which is higher than in 2000/2001 but remains low and well below the US wholegrain recommendation of 48 g/day (no UK wholegrain dietary reference value exist) (Mann *et al.* 2015).

It has been suggested that the cardiovascular protective effects of wholegrain oats are mainly due to their

Correspondence: Prof. Jeremy Paul Edward Spencer, Department of Food and Nutritional Sciences, School of Chemistry, Food and Pharmacy, University of Reading, Reading, UK.
E-mail: j.p.e.spencer@reading.ac.uk

© 2018 The Authors. *Nutrition Bulletin* published by John Wiley & Sons Ltd on behalf of British Nutrition Foundation
This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

dietary fibre content, in particular, soluble oat β-glucans, with established blood cholesterol- and glucose-lowering properties (Tappy *et al.* 1996; Tosh 2013; Whitehead *et al.* 2014; Tosh & Chu 2015). However, oats are also a rich dietary source of phenolic acids and avenanthramides (a class unique to oats) and several randomised, controlled, crossover studies have suggested that a range of phenolic compounds may be responsible for some of oat's health effects (Lamport *et al.* 2017; Lockyer *et al.* 2017; Mills *et al.* 2017). However, the phenolic acids in oats are linked to cell wall polysaccharides by ester linkages and this means their absorption will be limited until they reach the large intestine where they may undergo extensive bioconversion by colonic microbiota to yield various bioactive metabolites that express local intestinal effects in the gut, and also systemic effects following absorption (Vitaglione *et al.* 2008; Williamson & Clifford 2017). Previous data have suggested that, in addition to fibre and non-digestible carbohydrates, phenolics may beneficially modulate the gut microbiota composition and activity (Connolly *et al.* 2012b, 2016), which may play role in the prevention of chronic diseases (He & Shi 2017). For example, the secreting metabolites, such as secondary bile acids (BAs), short-chain fatty acids (SCFAs) and trimethylamine-N-oxide (TMAO), act as hormone-like factors and are sensed by dedicated receptor systems in the human host to play a role in the pathogenesis of CVD (Brown & Hazen 2015). In this review, we provide a concise introduction into human gut health and the contribution that the microbiota play in influencing markers of CVD pathophysiology, before outlining the cardiovascular benefits of oat intake and how these are mediated, in part, by the gut microbiome.

Gut health and the host gut microbiota

The human gastrointestinal tract is a diverse and dynamic microbial ecosystem, comprising approximately 10^{14} bacterial cells and up to 1000 different species (Thursby & Juge 2017). Firmicutes and Bacteroidetes are the two dominant phyla, representing more than 90% of all the phylotypes, followed by lower relative abundances of Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia (Robles Alonso & Guarner 2013; Power *et al.* 2014; Zhang *et al.* 2015). Commonly considered as the most beneficial bacterial genera are bifidobacteria, lactobacilli and butyrate producers, such as *Eubacterium rectale*, *Roseburia* species (Robles Alonso & Guarner 2013). An appropriate balance between harmful and health-promoting gut microbiota can support human health by: (1) maintaining host immune homeostasis; (2) increasing the efficiency of energy production in the gut through fermentation of non-digestible dietary compounds; (3) synthesising vitamins, such as B_{12} and K; (4) controlling intestinal epithelial cell proliferation (Clarke *et al.* 2014); (5) stimulating immunological defence; (6) creating a protective barrier; and (7) inhibiting the growth of potential pathogens (Gibson & Roberfroid 1995; Gibson 1998; Gong & Yang 2012; Ahmed Nasef *et al.* 2014; D'Argenio & Salvatore 2015; Okumura & Takeda 2017).

Conversely, an unfavourable gut microbiota composition and function (*i.e.* dysbiosis) can trigger the development of diseases through intestinal-derived endogenous endotoxins, such as lipopolysaccharides, indoxyl sulphate and L-carnitine (Prakash *et al.* 2011). These metabolites may potentiate the development of acute diseases, such as diarrhoea and chronic diseases, including obesity, metabolic diseases, cancer and CVD (Tang & Hazen 2014; Tuohy *et al.* 2014; Dao *et al.* 2015). There has been a long understanding of the interaction between environmental factors and gut microbiota, including that of pH, peristalsis, redox potential and nutrient availability (Nicholson *et al.* 2012). Dietary changes are thought to be responsible for around 57% of the variation in the gut microbiota, compared with only 12% for genetics (Brown *et al.* 2012). For example, a study showed that the microbiota of mice fed a low-fat, polysaccharide-rich diet markedly increased in populations of Firmicutes, and decreased in levels of *Clostridium*, *Eubacterium*, *Enterococcus* and *Bacteroides* spp when the mice were switched to a high-sugar/high-fat diet (Turnbaugh *et al.* 2009; Nguyen *et al.* 2015). On the other hand, a high-fibre diet can limit the growth of potentially pathogenic *E. coli.* (Zimmer *et al.* 2012), which has been observed in humans within 24 hours following a change from a high-fat/low-fibre diet to one which is low-fat/high-fibre (Wu *et al.* 2011).

The role of the gut microbiota in the pathophysiology of cardiovascular disease

Prebiotic effects

Shifts in the gut microbiota composition have been associated with a wide variety of diseases, including CVD (Garcia-Mantrana *et al.* 2018). The promotion of the growth of specific beneficial gut microbiota is believed to have preventative effects on CVD due to the influence of these bacteria on human physiology/metabolism, including the ability to reduce total serum

cholesterol, low-density lipoprotein (LDL) cholesterol and inflammation (Sun & Buys 2015; Ejtahed *et al.* 2011). Dietary substrates which induce changes in the growth of favourable bacteria are referred to as 'prebiotics', which pass largely unmetabolised in the upper gastrointestinal tract and are selectively utilised by host microorganisms conferring a health benefit (Gibson *et al.* 2017). Established prebiotics are carbohydrate-based but other substances, such as polyphenols (Tzounis *et al.* 2011; Queipo-Ortuño *et al.* 2012) and polyunsaturated fatty acids (Kankaanpaa *et al.* 2001; Peluso *et al.* 2014), might also fit the updated definition as they can affect the gut microbiome, although more studies are needed to show subsequent health effects. Prebiotics may reduce risk factors of CVD through the stimulation of growth of *Bifidobacterium* and *Lactobacillus*, and the subsequent production of SCFAs (LeBlanc *et al.* 2017), or possibly through the reduction in plasma cholesterol (Hooper *et al.* 2002) and/or fasting plasma glucose and insulin (Ooi & Liong 2010; Saini *et al.* 2010; Ruan *et al.* 2015). Furthermore, consumption of prebiotics has been linked to improved intestinal function, such as reduced gastrointestinal inflammation (Laparra & Sanz 2010; Vieira *et al.* 2013) and mineral absorption, and modulation of energy metabolism, satiety and immune function (Gibson & Roberfroid 1995; Gibson 1998; Pereira & Gibson 2002; Nicholson *et al.* 2012).

Structural effects

The large gut's enormous surface area helps to absorb nutrients, water and electrolytes from food but at the same time, it needs to provide a tight barrier against harmful substances and pathogens. One way in which the gut microbiota may confer health effects is via their potential to maintain large gut integrity (Konig *et al.* 2016). Gut hyperpermeability (leaky gut) results from structural changes induced by Gram-negative bacteria, which allows bacterial cell wall products, such as lipopolysaccharide and peptidoglycans, to enter into the bloodstream and activate macrophages. Also, gut microbiota-derived lipopolysaccharide can induce foam cell formation, and this can reduce reverse cholesterol transport and increase insulin resistance, hyperlipidaemia, vascular inflammation (Aki *et al.* 2008) and thus increase CVD risk.

Bile acid synthesis/clearance/metabolism

BAs have indirect (through cholesterol metabolic pathways) and direct effects (through interaction with myocytes) on blood cholesterol levels, atherosclerotic plaque formation and myocardial function and thus are hypothesised to reduce CVD risk (Khurana *et al.* 2011). Figure 1 illustrates the pathways of BA synthesis and cholesterol biotransformation in the liver (Ridlon *et al.* 2006). Primary BAs are further metabolised via conjugation to glycine or taurine in the liver, synthesised to bile salts and transported to the gallbladder. Following a meal and the release of cholecystokinin from the duodenum, the gallbladder contracts resulting in bile salts flowing into the duodenum, which in turn promotes the absorption of dietary lipids (Wahlstrom *et al.* 2016). The bacteria in the lower intestine are capable of converting primary BAs, by deconjugation and hydroxyl group oxidation at C-3, C-7, and C-12, and 7a/b-dehydroxylation, to secondary BAs, which predominate in human faeces (Sagar *et al.* 2015; Wahlstrom *et al.* 2016). Even though some are lost in faeces, most BAs are absorbed in the ileum and return to the liver where they are deconjugated and released into the small intestine (Ridlon *et al.* 2006). The genera of the gut microbiota involved in BA metabolism are *Bacteroides, Bifidobacterium, Clostridium, Lactobacillus* and *Eubacterium* (Gérard 2014). BA metabolites resulting from microbial transformation may act as signalling molecules and regulate cardiovascular function through the TGR5 (G-coupled protein receptor) and FXR (farnesoid x receptor), thus potentially inhibiting inflammation and maintaining epithelial cell integrity (Miyazaki-Anzai *et al.* 2014), and modifying vascular tone (Nie *et al.* 2015; Wahlstrom *et al.* 2016). Furthermore, *Bacteroides fragilis*, *B. vulgatus*, *Clostridium perfringens*, *Listeria monocytogenes* and several species of *Lactobacillus* and *Bifidobacterium* interfere with cholesterol absorption from the gut by deconjugating bile salts, via bile salt hydrolases (Jones *et al.* 2008), which means cholesterol is less easily absorbed and more likely to be excreted in faeces, resulting in lowered blood cholesterol (Hofmann 1999; Ridlon *et al.* 2006; Nicholson *et al.* 2012; Tuohy *et al.* 2014).

Short-chain fatty acids

SCFAs are the major end product of both carbohydrate and amino acid bacterial fermentation in the human large intestine (Morrison & Preston 2016). The main SCFAs are acetate, propionate and butyrate; less common are formate, valerate, caproate and branched-chain fatty acids (Macfarlane & Macfarlane 2003; Nicholson *et al.* 2012). Butyrate can be metabolised by colonocytes or absorbed and metabolised further in the liver, where they are metabolised

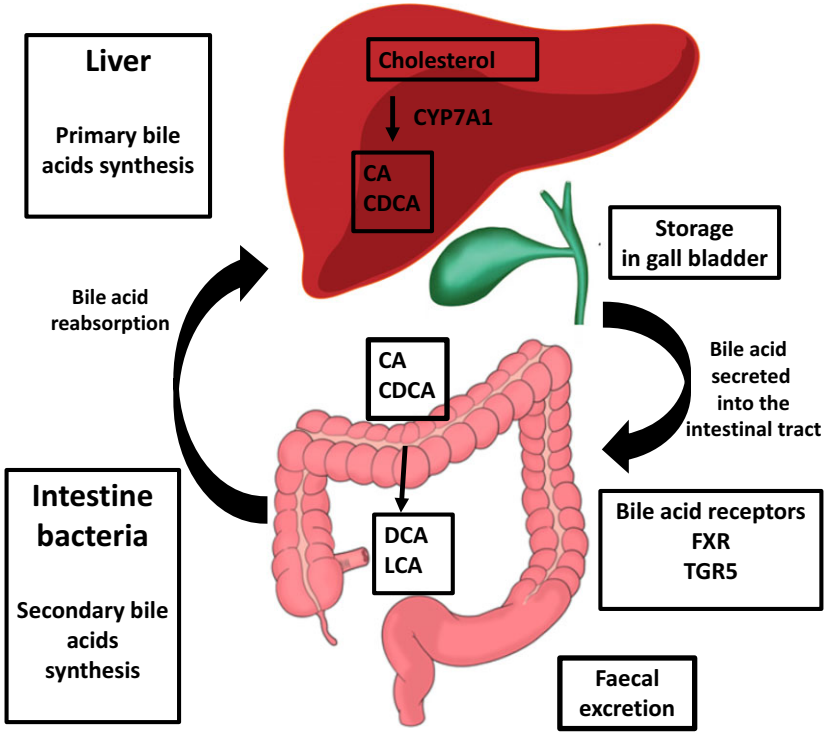

Figure 1 Bile acid biosynthesis. Primary bile acid synthesis in the liver: cholesterol is synthesised to cholic acid (CA) and chenodeoxycholic acid (CDCA) by the cholesterol 7 alpha-hydroxylase (CYP7A1) enzyme. In the intestinum, the bacterial 7 alpha-dehydroxylase converts the CA and CDCA to deoxycholic acid (CDA) and lithocholic acid (LCA), respectively. The bile acid receptors FXR farnesoid x receptor (FXR) and G protein-coupled bile acid receptor (TGR5) regulate bile acid synthesis, glucose homeostasis and lipid metabolism. [Colour figure can be viewed at wileyonlinelibrary.com]

(Ríos-Covián *et al.* 2016). SCFAs can act as an energy source for gut epithelial cells, improve intestinal defence against pathogens, modulate inflammation and possibly influence satiety (Russell *et al.* 2013). Butyrate may play a key role in regulating gene expression, inflammation and maintaining homeostasis of colonic mucosa through stimulating the production and release of the gut hormone glucagon-like peptide-2 (GLP-2) in enteroendocrine L cells (Tappenden *et al.* 2003; Hamer *et al.* 2008; Louis & Flint 2009). In addition, SCFAs decrease systemic levels of blood lipids by inhibiting hepatic cholesterol synthesis and/or redistributing cholesterol from plasma to the liver (Pereira & Gibson 2002). SCFAs are also thought to bind to specific G protein-coupled receptors, leading to the favourable regulation of lipid and glucose metabolism in the context of CVD (den Besten *et al.* 2013; Canfora *et al.* 2015; Kasubuchi *et al.* 2015). Another gut microbiota metabolism-dependent effect is the microbial conversion of choline and L-carnitine to trimethylamine (TMA) to TMAO. TMAO is thought to increase atherosclerotic CVD by altering cholesterol transport, potentially increasing macrophage activation (Randrianarisoa *et al.* 2016).

Oat components

Oats (*Avena sativa*) are unique among cereals due to their multifunctional characteristics and nutritional profile (Table 1). They supply protein, carbohydrate (primarily starch), crude fat, dietary fibre, unique antioxidants and vitamins and minerals (Welch 1994; Sadiq Butt *et al.* 2008; Menon *et al.* 2016). Oats have been grown for thousands of years, mainly as an animal feed crop, but during the 19th century, oats gained recognition as a 'healthy' food (Menon *et al.* 2016). Numerous reviews suggest that diets rich in oats may reduce inflammatory bowel disease and coeliac disease (Haboubi *et al.* 2006; Thies *et al.* 2014), attenuate CVD progression (Ruxton & Derbyshire 2008; Thies *et al.* 2014), and regulate glucose control in type 2 diabetes (Connolly *et al.* 2012b; Hou *et al.* 2015).

The nutrient profile and quality of oats depend on several factors, such as growth environment, genotype and the interaction between environment and genotype (Peterson *et al.* 2005). The main constituent (60%) of oat grains is starch (rapidly digestible, slowly digestible and resistant), located in the

Table 1 Nutritional composition of raw oat bran. Data from the US Department of Agriculture National Nutrient Database (USDA 2015)

Nutrient	Value per 100 g
Energy (kcal)	246
Protein (g)	17.30
Total fat (g)	7.03
Fatty acids, total saturated (g)	1.6
Fatty acids, total monounsaturated (g)	2.38
Fatty acids, total polyunsaturated (g)	2.77
Total carbohydrate (g)	66.22
Sugar (g)	1.45
β-glucans (g)*	4.5–5.6
Arabinoxylans (g)*	3.83–13.20
Non-starch polysaccharide (g)	7.1
Calcium (mg)	58
Iron (mg)	5.41
Potassium (mg)	566
Sodium (mg)*	4
Magnesium (mg)	235
Zinc (mg)	3.11
Thiamine (mg)	1.17
Riboflavin (mg)	0.22
Niacin (mg)	0.93
Vitamin B (mg)	0.16
Folate (μg)	52
Vitamin E (mg)	1.01
Vitamin K (μg)	3.2
Total phenolic (mg)*	35.1–87.4

*Data from Shewry *et al.* (2008).

endosperm. Resistant starch is recognised as a fermentable fibre source for gut microbiota, which results in the production of SCFAs in the colon (Ovando-Martínez *et al.* 2013; Gangopadhyay *et al.* 2015; Rasane *et al.* 2015). Moreover, oats are a source of high-quality protein, lipids (especially unsaturated fatty acid such as oleic, linoleic and palmitic acid), traces of minerals (mainly calcium and iron), B and E vitamins and phenolic compounds (Gangopadhyay *et al.* 2015; Rasane *et al.* 2015; Menon *et al.* 2016).

Oat phytochemicals

Dietary phenolics, such as hydroxycinnamic, hydroxybenzoic acids and avenanthramides, are natural phenolic components in oats (Shewry *et al.* 2008). They are found in three different forms within the oat food matrix: as soluble free acids; as soluble conjugates esterified to low molecular weight components such as sugars; and as insoluble bound acids esterified to high molecular weight components, including lignin, cell wall polysaccharides such as arabinoxylan (Stevenson *et al.* 2012) and storage proteins in the aleurone layer and the pericarp (Shewry *et al.* 2008). The main hydroxycinnamic acids present in oats include ferulic acid, caffeic, p-coumaric (Fig. 2), o-coumaric and sinapic acids. Hydroxybenzoic acid derivatives are protocatechuic, syringic, vanillic, *p*-hydroxybenzoic and gallic acids (Kern *et al.* 2003; El-Seedi *et al.* 2012; Kumar & Pruthi 2014; Yang *et al.* 2014).

Hydroxycinnamic acids all have a C_6C_3 carbon skeleton with a double bond in the side chain that may have a cis or trans configuration. By far the most abundant hydroxycinnamic in oats is the trans-ferulic acid, with contents ranging from 95 to 386 μg/g (Shewry *et al.* 2008). Analytical data indicate that, on average, 19% of these phenolic acids (range: 50–110 μg/g) are present in the soluble state, 34% as conjugates (range: 111–314 μg/g) and 47% bound (range: 131–640 μg/g) (Shewry *et al.* 2008). Another phenolic group specific to oats are the avenanthramides (AVA) (Fig. 3), consisting of an amide conjugate of anthranilic acid and hydroxycinnamic acids. The three major subgroups are avenanthramide-A (AVA-A), avenanthramide-B (AVA-B) and avenanthramide-C (AVA-C), which occur in the bran or outer layers of the kernel (Manach *et al.* 2004). Total contents of avenanthramides in oats range from 42 to 91 μg/g (Emmons & Peterson 1999; Liu *et al.* 2004; Manach *et al.* 2004; Chen *et al.* 2007).

Fibre

Wholegrain oats are typically 10%–12% fibre, of which roughly 40% is soluble and 60% insoluble (cellulose) (Menon *et al.* 2016). Mixed-linkage (1-3)(1-4)-β-D-glucans (β-glucans) (82% water-soluble fraction) together with arabinoxylans are important sources of soluble as well as insoluble dietary fibre (Shewry *et al.* 2008; El Khoury *et al.* 2012). The soluble β-glucans located throughout the subaleurone cell walls are one of the most commonly studied components of oats (Kim *et al.* 2006; Cloetens *et al.* 2012; Rebello *et al.* 2014; Zhang *et al.* 2016). A 100 g of oats contains 3–6 g β-glucans (Shewry *et al.* 2008).

Bioavailability of phytochemicals and physiological effects of β-glucans

It has been estimated that only 5%–10% of dietary polyphenols are absorbed in the small intestine, with the remaining fraction reaching the large intestine where they are metabolised by the gut microbial community (Manach *et al.* 2005; Cardona *et al.* 2013).

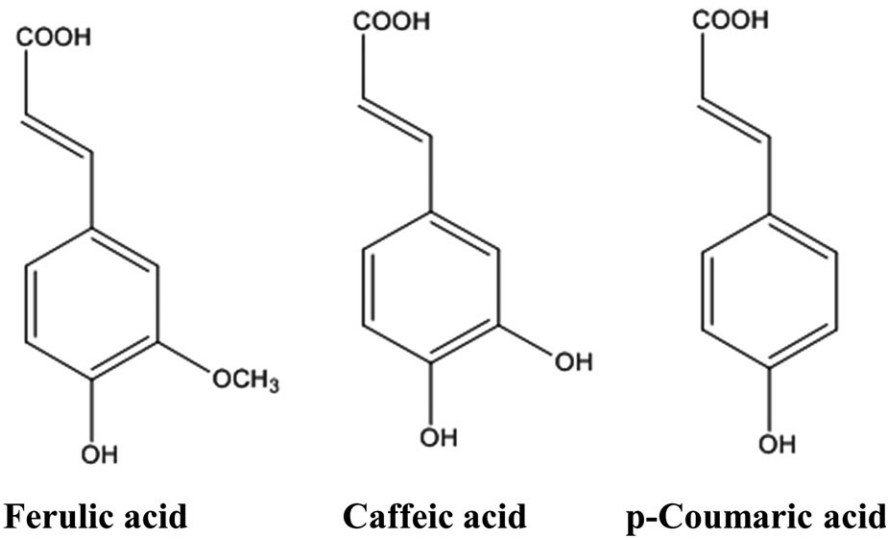

Figure 2 Chemical structure of the main hydroxycinnamates in oats.

The absorption and metabolism of ferulic acid can be affected by the form of food matrix ingested (Kern *et al.* 2003; Rein *et al.* 2013). Counterintuitively, fibre-bound ferulic acid in wheat bran has been observed to be more bioavailable than free ferulic acid (Rondini *et al.* 2004). The differences observed in their absorption may relate to the rapid cleavage of the fibre–phenolic ester bond by the intestinal microbiota, which generates a higher amount of free phenolic acids in the large gut, increases their time in the plasma and decreases the level of urinary excretion (Chesson *et al.* 1999; Rondini *et al.* 2004). Our group reported intake of 60 g oat bran (2.5 mg avenanthramides, 28.6 mg phenolic acids) resulted in elevated urinary excretion of 30 phenolic acids metabolites, amounting to total recovery of 22.9% ± 5.0%, mainly between 0–2 and 4–8 hours (Schar *et al.* 2017). The predominant metabolites included vanillic acid, 4- and 3-hydroxyhippuric acids and sulphate conjugates of benzoic and ferulic acid (accounting for two-thirds of total phenolic excretion). The results suggest that bound phenolic acids present in oats are rapidly released by the microbiota. Similarly, another human study (Zhang *et al.* 2017) showed peak plasma concentrations of avenanthramides between 2 and 3 hours after high (229.6 mg/kg) AVA intake and 1 and 2 hours for low AVA intake (32.7 mg kg). AVA-B demonstrated a longer half-life and a slower elimination rate than AVA-A and AVA-C. The bioactive properties of polyphenols are greatly dependent on their bioavailability (Chen *et al.* 2004; Kroon *et al.* 2004; Manach *et al.* 2004; Chen *et al.* 2007). These polyphenols have been observed to inhibit vascular smooth muscle cell proliferation and enhance nitric oxide production (Nie *et al.* 2006).

The physiological activity of β-glucans is in part related to their effects on bile reabsorption and through their ability to increase intestinal chyme viscosity, effects that are dependent on both the concentration and molecular weight of the β-glucans consumed (Shewry *et al.* 2008; Menon *et al.* 2016). The molecular weight of β-glucans varies between 100 000 and 1 200 000 g/mol, and those of a small molecular size (370 000 g/mol) have been reported to be less effective at reducing cholesterol levels (Kim *et al.* 2006) compared with those of high molecular weight

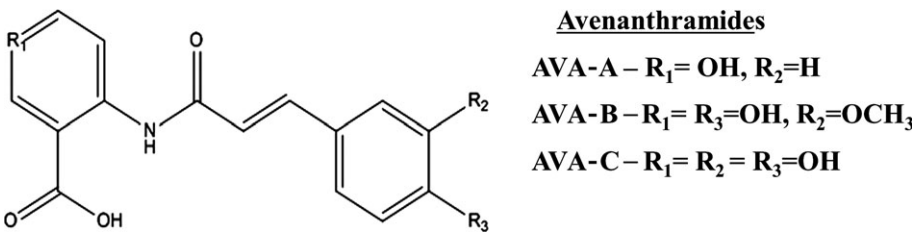

Figure 3 Chemical structure of the avenanthramide in oats. Avenanthramide-A (AVA), avenanthramide-B (AVB) and avenanthramide-C (AVC).

© 2018 The Authors. *Nutrition Bulletin* published by John Wiley & Sons Ltd on behalf of British Nutrition Foundation

(Braaten *et al.* 1994). The solubility of β-glucans is another important factor influencing their physiological activity (El Khoury *et al.* 2012). Their ability to form highly viscous small intestinal chyme likely contributes to the health benefits of β-glucans, as it has been reported that there is an inverse linear relationship between measures of postprandial blood glucose and insulin responses (to an oral glucose load) and the viscosity of the chyme (Wood *et al.* 2000; Chen & Raymond 2008; Wolever *et al.* 2018).

Cardiovascular benefits of the oat intake

Atherosclerosis is one of the main underlying pathophysiological processes in CVD development (Stamler *et al.* 1986; Shepherd *et al.* 1995), with several different actions, such as oxidation of LDL cholesterol, adhesion of monocytes across the endothelial surface, development of monocytes to macrophages and the formation foam cells (Andersson & Hellstrand 2012). The potential modulation of atherogenic pathways following oat intake has been suggested and may involve anti-inflammatory activity, the maintenance of endothelial function and the reduction in plasma cholesterol (Fig. 4) (Ryan *et al.* 2007, 2011; Jonnalagadda *et al.* 2011; Thies *et al.* 2014; Whitehead *et al.* 2014; Shen *et al.* 2016). Additionally, oat fibre and phenolics are capable of interacting directly with the gut microbiota, leading to a shift in their profile and composition, secondary changes in cholesterol and bile metabolism, and the production of key metabolites such as SCFAs and phenolic acids metabolites (Fig. 4).

Effects of oat intake on microbiome composition – *in vitro* and animal data

Several *in vitro* fermentation (Table 2) and animal studies (Table 3) suggest that increased oat intake leads to gut microbiota alterations. *In vitro* fermentation of oat grains has been shown to increase *Bifidobacterium* and *Lactobacillus* populations (Connolly *et al.* 2010) and *Bacteroides* and *Prevotella* groups (Chappell *et al.* 2015), whilst decreasing clostridia levels (Kedia *et al.* 2009). However, although oat-derived β-glucans extracts increased *Lactobacillus–Enterococcus* after 5 hours and *Bacteroides* after 24 hours in one *in vitro* study, they were found to not influence bifidobacterial growth (Hughes *et al.* 2008). In another *in vitro* study, it has been reported that the

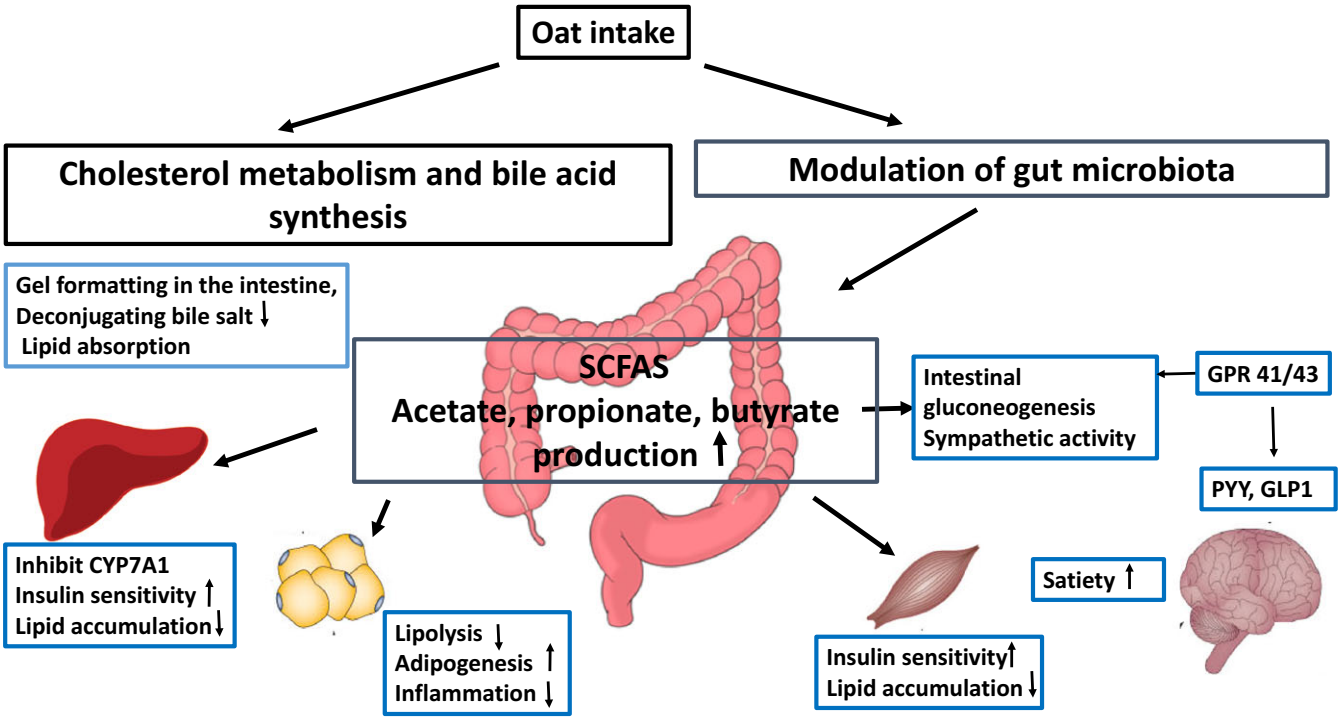

Figure 4 Potential mechanisms in the digestion system of the cardiovascular benefits of oats. Oats may interact directly with the gut microbiota leading to a shift in their profile and composition, changes in cholesterol and bile metabolism, and the production of key metabolites such as short-chain fatty acids. Abbreviations: SCFAs (short-chain fatty acids), GPR41 and GPR43 (G protein-coupled receptor), PYY (peptide YY), GLP1 (glucagon-like peptide 1) and CYP7A1 (cholesterol 7 alpha-hydroxylase). [Colour figure can be viewed at wileyonlinelibrary.com]

Table 2 The impact of oats on the gut microbiota and short-chain fatty acid (SCFA) production based on data from *in vitro* studies at 24 hours

Reference	Intervention	Effects on bacterial composition	Effects on SCFA production
Hughes *et al.* (2008)	Oat-derived β-glucans Low molecular weight (LMW) 150 kDa High molecular weight (HMW) 230kDa	*Atopobium* ↑ - LMW and HMV *Bacteroides – Prevotella* ↑ - LMV *Lactobacillus/Enterococcus* ↓ - LMV and HMV *Clostridium histolyticum* ↑ - LMV and HMV	Acetate ↑ - LMV, HMV Propionate ↑ - LMV, HMV
Kedia *et al.* (2009)	Oat bran fraction (OB) Whole oat flour (WOF)	*Bifidobacterium* ↑ - OB and WFO *Lactobacillus/Enterococcus* ↑ - OB *Clostridium* ↓ - 24 hours, OB *Clostridium* ↑ - 24 hours, WOF	Acetate, butyrate, propionate ↑ - OB, WOF
Kim and White (2009)	Oat-derived β-glucans Low β-glucans (LB) – 5.31% β-glucans High β-glucans (HB) – 7.70% β-glucans	No data	Acetate, butyrate, propionate ↑ - LB, HB No significant differences between LB vs. HB
Connolly *et al.* (2010)	Oat grain flakes 0.53–0.63 mm (size 23) 0.85–1.0 mm (size 25–26)	*Bifidobacterium* genus ↑ - size 25–26 *Eubacterium* ↑ - sizes 23 and 25–26	Acetate ↑ - size 23 Acetate, propionate, butyrate ↑ - size 25–26
Connolly *et al.* (2012b)	Wholegrain oat-based cereals • Jumbo porridge oat (JPO) • 100% wholegrain aggregate (WGA) • Granola (G) • 70% wholegrain loops (WGL) • Instant porridge (IP)	JPO, IP, G, WGA *Bifidobacterium* ↑ JPO, G – *Atopobium* ↑ G, WGA, IP, WGL - *Bacteroides, Prevotella* ↑ G, WGA, WGL - *Lactobacillus/Enterococcus* ↑ P, WGA – *Clostridium* ↓	Acetate, propionate ↑ - JPO, IP, WGA, WGL, IP Butyrate ↑ - IP, WGA
Connolly *et al.* (2012a)	Toasted (T), partially toasted (PT) and raw (R) wholegrain wheat flakes	*Bifidobacterium* genus ↑ - T, PT and R *C. hystolyticum* subgroup, *Lactobacillus* ↑ - R	Acetate, propionate ↑ - T, PT R
Chappell *et al.* (2015)	Belinda oats	Bacteroides ↑ Firmicutes ↓	Acetate, propionate, butyrate ↑

β-glucans are fermented by *Bacteroides* spp but not by *Lactobacillus* and *Bifidobacterium* (Crittenden *et al.* 2002). The fermentation of oats in anaerobic, pH-controlled, faecal batch cultures has been shown to increase SCFA production, with significant increases in acetate, propionate and butyrate levels (Hughes *et al.* 2008; Kedia *et al.* 2009; Kim & White 2009; Connolly *et al.* 2010, 2012b).

Consumption of oats by rodents has been reported to result in many specific changes in their microbiota, such as increases in the growth of *Prevotellaceae*, *Lactobacillaceae* and *Alcaligenaceae* families 175.5% ($P = 0.03$), 184.5% ($P = 0.01$) and 150.0% ($P = 0.004$). However, these results are not consistent with the findings from other animal studies that indicate oat bran intake increases only *Bifidobacterium* and *Lactobacillus* growth (Drzikova *et al.* 2005; Berger *et al.* 2014). The range of oat products used in these studies, including oat flour and bran (Drzikova *et al.* 2005), or insoluble fibre and soluble fibre combinations (Zhou *et al.* 2015), might explain the reported variability in microbiota growth in rodents. Hence, further well-designed *in vitro* and human studies are required to examine which oat components may result in beneficial changes to the microbiota.

Overall, these studies indicate inconsistent findings regarding the influence of oats on the growth of the microbiota and their diversity, which might be partly explained by the various different study and experimental designs. It is also important to note that these studies considered only the influence of the β-glucans fraction within oats and not other oat bioactives, such as polyphenols, which have also been observed to

Table 3 Animal studies examining the effects of oat intake on growth of gut microbiota and short-chain fatty acid (SCFA) production

Reference	Intervention (*duration*)	Oat effects on bacterial composition and/or SCFA production compared to control	Animals
Drzikova *et al.* (2005)	Oat flour (F); oat bran (B); oat flour (F) (autoclaved) (*6 weeks*)	*Bifidobacterium* genus ↑ - F, B *Bacteroides* ↑ - F	Rats
Immerstrand *et al.* (2010)	Oat bran (OB; β-glucans – 1800 kDa or 2348 kDa) Processed oat bran (POB; β-glucans – 1311 kDa, 241 kDa, 56 kDa, 21 kDa, 10 kDa) (*4 weeks*)	Acetate, propionate, butyrate ↑ - OB, POB	Mice
Berger *et al.* (2014)	High fat diet – barley husks, rye bran, fibre residue from oat milk (*4 weeks*)	*Lactobacillus* ↑ propionate, butyrate ↑	Mice
Zhou *et al.* (2015)	Wholegrain oat flour (WGO), Low bran oat flour (LBO) (*8 weeks*)	Prevotellaceae, Lactobacillaceae, and *Alcaligenaceae* families relative abundance – ↑ - WBO Clostridiaceae, Lachnospiraceae families – ↑ - LBO	Mice

interact with the gut microbiota (van Duynhoven *et al.* 2011; Cardona *et al.* 2013; Kay 2015).

Effects of oat intake on microbiome composition – human trials

Whilst *in vitro* (Kedia *et al.* 2009; Connolly *et al.* 2010, 2012a) and animal studies (Immerstrand *et al.* 2010; Berger *et al.* 2014) indicate that oat intake increases the production of SCFAs, these effects are difficult to quantify in humans as SFCAs are rapidly absorbed or utilised in the large intestine. For example, butyrate is almost entirely used by the colonocytes as their preferred energy substrate (Cummings *et al.* 1987), propionate is primarily absorbed and removed by the liver (Hong *et al.* 2005), whilst acetate passes into the peripheral circulation (Roediger 1980). The use of *in vitro* tools can help to investigate whether various substrates lead to increased SCFA generation, as faecal SCFA measurements are an uncertain estimate of colonic SCFA production (Valeur *et al.* 2016).

Findings from human trials on the effects of oats on the microbiota vary, possibly due to differences in study design (*i.e.* intervention dose, study duration, study population, the method of microbial enumeration) and because these studies assessed the effects of fibre but not the polyphenols in oats (Table 4). Two randomised controlled trials provide evidence that wholegrain wheat may exert effects on gut microbiota (Costabile *et al.* 2008; Vitaglione *et al.* 2015). A daily intake of 48 g of wholegrain wheat significantly increased the growth of *Bifidobacterium* (0.8 $\log_{10}$ cells per g faeces) and *Lactobacillus* (0.6 $\log_{10}$ cells per g faeces) and increased plasma ferulic acid levels (Costabile *et al.* 2008). In contrast, intake of 70 g per day of wholegrain wheat was found not to increase levels of *Bifidobacterium*, although faecal ferulic acid levels were found to be associated with an increase in *Bacteroides*, Firmicutes and a reduction in *Clostridium* (Vitaglione *et al.* 2015). To date, no human trials have studied the direct effects of extracted or purified oat phenolic acids on the growth of the microbiota, or whether they contribute to the prebiotic effects of wholegrain intake, although data do exist on the impact of flavanols, which have been found to promote the growth of specific beneficial bacteria (Tzounis *et al.* 2011). These data suggest that phenolic acids present in wholegrain cereals may potentiate gut microbiota diversity; however, further research is required to distinguish between the effects of fibre and polyphenols on gut health.

Impact of oat intake on cholesterol metabolism and bile acid synthesis

Oat β-glucans have been suggested to lower cholesterol by causing an increased viscosity of the intestinal chime (Ryan *et al.* 2007). The gel formed is thought to act as a physical barrier to lipid (triglycerides) absorption in the small intestine, in particular that of cholesterol reabsorption (Bae *et al.* 2010; Andersson & Hellstrand 2012; Bao *et al.* 2014). β-glucans have also been shown to bind to luminal BAs, which increases the excretion of bile in the faeces and triggers an increase in hepatic conversion of cholesterol into BAs, thereby decreasing blood cholesterol levels (Lia *et al.* 1995; Bae *et al.* 2010; Grundy *et al.* 2017). It has been reported that the intake of 75 g of

Table 4 The relationship between oats, the growth of gut microbiota and short-chain fatty acid (SCFA) production based on data from human intervention trials

Reference	Intervention (*duration*)	Oat effects on bacterial composition and/or SCFA production compared to control
Bridges *et al.* (1992)	20 (38–73 years) hypercholesterolaemic men Oat bran – 34 g/day total fibre and 13.4 g/day soluble fibre Control – 14 g/day total fibre and 3 g/day soluble fibre (*3 weeks*)	SCFA in peripheral serum Serum acetic acid ↑
Mårtensson *et al.* (2005)	56 adults (20–70 years, 24 men/32 women) with moderately increased plasma cholesterol levels Fermented oat-based products (FO) (3–3.5 g/day – β-glucans) Fermented ropy, oat products (FRO) Fermented dairy-based product (control) (*Control – 3 weeks, treatment – 5 weeks*)	Total bacteria count ↑ *Bifidobacterium* ↑ - FO, FRO
Nilsson *et al.* (2008b)	25 healthy adults (20–47 years, 10 men/15 women) 40 g β-glucans enriched oat bran (40 g oat bran, 20 g dietary fibre, 10 g glucan in four slices of bread) Control – baseline samples, week 0 (*12 weeks*)	SCFAs in faeces Acetic, propionic, butyric, isobutyric, isovaleric - ↑
Valeur *et al.* (2016)	10 healthy adults (22–49 years, 2 men/8 women) 60 g oatmeal porridge (8.5 g fibre, 4.7 g glucans) Control – baseline samples, day 1 (*1 week*)	Intestinal gas production SCFAs and no changes – faeces β-galactosidase and urease - ↓ Rectal level of PGE_2 – no significant difference
Connolly *et al.* (2016)	32 mild or hypercholesterolaemia adults (23–64 years, 12 men/20 women) Wholegrain oat granola (WGO) - 45 g granola breakfast cereals (6.3 g fibre, 2.9 g glucans) Non-wholegrain (NWG) – 45 g non-wholegrain breakfast cereals (control) (3 g fibre, no glucans) (*6 weeks*)	SCFAs no significance differences Total bacteria count ↑ *Bifidobacterium* ↑ *Lactobacilli* ↑

extruded oat bran (11 g β-glucans) resulted in a near doubling of serum 7 alpha-hydroxy-4-cholesten-3-one concentration within 8 hours, which lead to increased BA synthesis (Andersson *et al.* 2002). BA excretion is well known to stimulate cholesterol uptake from the circulation, resulting in a decreased serum cholesterol concentration (Grundy *et al.* 2017).

Oat intake and short-chain fatty acid production

SCFA production is highly dependent on the donor and availability of substrates (Cook & Sellin 1998). The ability of oats (and isolated β-glucans) to increase SCFA production is well established (Connolly *et al.* 2010, 2012a; Berger *et al.* 2014). After 12 hours of *in vitro* fermentation, oat bran (containing 22% oat β-glucan) induced significantly higher concentrations of propionate compared to other prebiotic dietary fibres, such as inulin and xylooligosaccharide (Carlson *et al.* 2017). The production of SCFAs in the large intestine following oat consumption has been reported and postulated to contribute to reductions in serum lipids and other CVD risk markers (Andersson & Hellstrand 2012). As such, SCFAs may act as mediators of the beneficial effects of wholegrain oat intake of human CVD. These effects might be dependent on SCFAs' ability to: (1) affect liver and muscle cellular metabolism via their potential to increase insulin sensitivity and decrease lipid accumulation in liver (Oda *et al.* 1994; Ulmius *et al.* 2011; Zhang *et al.* 2012; Chang *et al.* 2013; McNabney & Henagan 2017); (2) suppress cholesterol synthesis, increase fatty acid

oxidation and decrease *de novo* fatty acid synthesis in the liver (Andersson *et al.* 2002, 2017; Cloetens *et al.* 2012; Han *et al.* 2015); (3) increase adipogenesis and decrease lipolysis (Gao *et al.* 2015; Heimann *et al.* 2016); (4) modulate satiety through their potential to bind to G protein-coupled receptors (GPR41, GPR43), leading to the increased production of the gut hormones glucagon-like peptide-1 and peptide YY (Hooda *et al.* 2010; Koh *et al.* 2016; Rebello *et al.* 2016) and regulate satiety centrally (Bridges *et al.* 1992; Canfora *et al.* 2015; Canfora & Blaak 2017); and 5) improve colon and liver glucose homeostasis via their induction of intestinal gluconeogenesis (den Besten *et al.* 2013; Bourassa *et al.* 2016; Cheng *et al.* 2017; Jayachandran *et al.* 2018) (Fig. 4). In addition, butyric acid has been reported to increase phenolic acid absorption in the colon (Ziegler *et al.* 2016), which subsequently may induce endothelium-dependent vasodilation (Suzuki *et al.* 2002, 2007; Choi *et al.* 2012). Recent studies have also indicated that the ratio of acetate and propionate may be important for defining the precise effects of SCFAs on various physiological systems. For example, a high serum acetate:propionate ratio has been associated with reductions in total serum cholesterol in men (Weitkunat *et al.* 2017; Boets *et al.* 2017; Wolever *et al.* 1996).

Conclusions

Evidence suggests that wholegrain oats may reduce CVD risk due to their influence on lipid metabolism and plasma cholesterol levels. Oat β-glucans are likely to be partly responsible for any effects as they can change the gut microbiota composition, increase cholesterol excretion in the gut and increase the levels of SCFAs, which may inhibit hepatic cholesterol synthesis and affect glucose homeostasis in adipose tissues and muscle cells. However, inconsistent findings from *in vitro*, animal and human studies have been reported regarding the influence of oat intake on these outcomes, possibly due to differences in experimental techniques and the focus on β-glucan rather than other compounds present in oats, such as phenolic acids and avenanthramides, which may also contribute to beneficial changes in the gut microbiota and lipid/cholesterol metabolism. Clinical, observational and experimental studies to date have not explored the extent to which cardiovascular benefits are dependent on oat fibre or phenolic acid levels. Hence, further randomised, controlled trials are required to examine the relative effects of oat phenolics on microbial pathways and cardiovascular risk markers.

Conflict of interest

The authors declare no conflict of interests.

References

Ahmed Nasef N, Mehta S & Ferguson LR (2014) Dietary interactions with the bacterial sensing machinery in the intestine: the plant polyphenol case. *Frontiers in Genetics* **5**: 64.

Aki D, Minoda Y, Yoshida H *et al.* (2008) Peptidoglycan and lipopolysaccharide activate PLCgamma2, leading to enhanced cytokine production in macrophages and dendritic cells. *Genes to Cells* **13**: 199–208.

Andersson KE & Hellstrand P (2012) Dietary oats and modulation of atherogenic pathways. *Molecular Nutrition & Food Research* **56**: 1003–13.

Andersson M, Ellegard L, Andersson H *et al.* (2002) Oat bran stimulates bile acid synthesis within 8 h as measured by 7alpha-hydroxy-4-cholesten-3-one. *American Journal of Clinical Nutrition* **76**: 1111–6.

Andersson KE, Chawade A, Thuresson N *et al.* (2017) Wholegrain oat diet changes the expression of genes associated with intestinal bile acid transport. *Molecular Nutrition & Food Research* **61**: 1600874.

Aune D, Keum N, Giovannucci E *et al.* (2016) Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ* **353**: i2716.

Bae IY, Kim SM, Lee S *et al.* (2010) Effect of enzymatic hydrolysis on cholesterol-lowering activity of oat beta-glucan. *New Biotechnology* **27**: 85–8.

Bao L, Cai X, Xu M *et al.* (2014) Effect of oat intake on glycaemic control and insulin sensitivity: a meta-analysis of randomised controlled trials. *British Journal of Nutrition* **112**: 457–66.

Behall KM, Scholfield DJ & Hallfrisch J (2004) Lipids significantly reduced by diets containing barley in moderately hypercholesterolemic men. *Journal of the American College of Nutrition* **23**: 55–62.

Berger K, Falck P, Linninge C *et al.* (2014) Cereal byproducts have prebiotic potential in mice fed a high-fat diet. *Journal of Agriculture and Food Chemistry* **62**: 8169–78.

den Besten G, van Eunen K, Groen AK *et al.* (2013) The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *Journal of Lipid Research* **54**: 2325–40.

Boets E, Gomand SV, Deroover L *et al.* (2017) Systemic availability and metabolism of colonic-derived short-chain fatty acids in healthy subjects: a stable isotope study. *Journal of Physiology* **595**: 541–55.

Bourassa MW, Alim I, Bultman SJ *et al.* (2016) Butyrate, neuroepigenetics and the gut microbiome: Can a high fiber diet improve brain health? *Neuroscience Letters* **625**: 56–63.

Braaten JT, Wood PJ, Scott FW *et al.* (1994) Oat beta-glucan reduces blood cholesterol concentration in hypercholesterolemic subjects. *European Journal of Clinical Nutrition* **48**: 465–74.

Bridges SR, Anderson JW, Deakins DA *et al.* (1992) Oat bran increases serum acetate of hypercholesterolemic men. *American Journal of Clinical Nutrition* **56**: 455–9.

Brown JM & Hazen SL (2015) The gut microbial endocrine organ: bacterially-derived signals driving cardiometabolic diseases. *Annual Review of Medicine* **66**: 343–59.

Brown K, DeCoffe D, Molcan E *et al.* (2012) Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. *Nutrients* **4**: 1095–119.

Canfora EE & Blaak EE (2017) Acetate: a diet-derived key metabolite in energy metabolism: good or bad in context of obesity and glucose homeostasis? *Current Opinion in Clinical Nutrition and Metabolic Care* **20**: 477–83.

Canfora EE, Jocken JW, Blaak EE *et al.* (2015) Short-chain fatty acids in control of body weight and insulin sensitivity. *Nature Reviews Endocrinology* **11**: 577–91.

Cardona F, Andrés-Lacueva C, Tulipani S *et al.* (2013) Benefits of polyphenols on gut microbiota and implications in human health. *The Journal of Nutritional Biochemistry* **24**: 1415–22.

Carlson JL, Erickson JM, Hess JM *et al.* (2017) Prebiotic dietary fiber and gut health: comparing the *in vitro* fermentations of beta-glucan. Inulin and xylooligosaccharide. *Nutrients* **9**: 1361.

Chang HC, Huang CN, Yeh DM *et al.* (2013) Oat prevents obesity and abdominal fat distribution, and improves liver function in humans. *Plant Foods for Human Nutrition* **68**: 18–23.

Chappell AJ, Thies F, Martin P *et al.* (2015) The effect of *in vitro* fermentation of oats (*Avena sativa*) and barley (*Hordeum vulgare*) on the faecal gut microbiota. *Proceedings of the Nutrition Society* **74**: E32.

Chen J, Raymond K (2008) Beta-glucans in the treatment of diabetes and associated cardiovascular risks. *Vascular Health and Risk Management* **4**: 1265–72.

Chen CY, Milbury PE, Kwak HK *et al.* (2004) Avenanthramides and phenolic acids from oats are bioavailable and act synergistically with vitamin C to enhance hamster and human LDL resistance to oxidation. *Journal of Nutrition* **134**: 1459–66.

Chen CY, Milbury PE, Collins FW *et al.* (2007) Avenanthramides are bioavailable and have antioxidant activity in humans after acute consumption of an enriched mixture from oats. *Journal of Nutrition* **137**: 1375–82.

Cheng Y, Zhang J, Luo K *et al.* (2017) Oat bran β-glucan improves glucose homeostasis in mice fed on a high-fat diet. *RSC Advances* **7**: 54717–25.

Chesson A, Provan GJ, Russell WR *et al.* (1999) Hydroxycinnamic acids in the digestive tract of livestock and humans. *Journal of the Science of Food and Agriculture* **79**: 373–8.

Choi S, Il Kim H, Hag Park S *et al.* (2012) Endothelium-dependent vasodilation by ferulic acid in aorta from chronic renal hypertensive rats. *Kidney Research and Clinical Practice* **31**: 227–33.

Clarke G, Stilling RM, Kennedy PJ *et al.* (2014) Minireview: gut microbiota: the neglected endocrine organ. *Molecular Endocrinology* **28**: 1221–38.

Cloetens L, Ulmius M, Johansson-Persson A *et al.* (2012) Role of dietary beta-glucans in the prevention of the metabolic syndrome. *Nutrition Reviews* **70**: 444–58.

Connolly ML, Lovegrove JA & Tuohy KM (2010) *In vitro* evaluation of the microbiota modulation abilities of different sized whole oat grain flakes. *Anaerobe* **16**: 483–8.

Connolly ML, Lovegrove JA & Tuohy KM (2012a) *In vitro* fermentation characteristics of whole grain wheat flakes and the effect of toasting on prebiotic potential. *Journal of Medicinal Food* **15**: 33–43.

Connolly ML, Tuohy KM & Lovegrove JA (2012b) Wholegrain oat-based cereals have prebiotic potential and low glycaemic index. *British Journal of Nutrition* **108**: 2198–206.

Connolly ML, Tzounis X, Tuohy KM *et al.* (2016) Hypocholesterolemic and prebiotic effects of a whole-grain oat-based granola breakfast cereal in a cardio-metabolic "at risk" population. *Frontiers in Microbiology* **7**: 1675.

Cook SI & Sellin JH (1998) Review article: short chain fatty acids in health and disease. *Alimentary Pharmacology & Therapeutics* **12**: 499–507.

Cooper DN, Martin RJ & Keim NL (2015) Does whole grain consumption alter gut microbiota and satiety? *Healthcare* **3**: 364–92.

Costabile A, Klinder A, Fava F *et al.* (2008) Whole-grain wheat breakfast cereal has a prebiotic effect on the human gut microbiota: a double-blind, placebo-controlled, crossover study. *British Journal of Nutrition* **99**: 110–20.

Crittenden R, Karppinen S, Ojanen S *et al.* (2002) *In vitro* fermentation of cereal dietary fibre carbohydrates by probiotic and intestinal bacteria. *Journal of the Science of Food and Agriculture* **82**: 781–9.

Cummings JH, Pomare EW, Branch WJ *et al.* (1987) Short chain fatty acids in human large intestine, portal, hepatic and venous blood. *Gut* **28**: 1221–7.

Dao MC, Everard A, Aron-Wisnewsky J *et al.* (2015) Akkermansia muciniphila and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. *Gut* **65**: 426–36.

D'Argenio V, Salvatore F (2015) The role of the gut microbiome in the healthy adult status. *Clinica Chimica Acta* **451**: 97–102.

Drzikova B, Dongowski G & Gebhardt E (2005) Dietary fibre-rich oat-based products affect serum lipids, microbiota, formation of short-chain fatty acids and steroids in rats. *British Journal of Nutrition* **94**: 1012–25.

van Duynhoven J, Vaughan EE, Jacobs DM *et al.* (2011) Metabolic fate of polyphenols in the human superorganism. *Proceedings of the National Academy of Sciences of the United States of America* **108**(Suppl 1): 4531–8.

Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A *et al.* (2011) Effect of probiotic yogurt containing Lactobacillus acidophilus and Bifidobacterium lactis on lipid profile in individuals with type 2 diabetes mellitus. *Journal of Dairy Science* **94**: 3288–94.

El Khoury D, Cuda C, Luhovyy BL *et al.* (2012) Beta glucan: health benefits in obesity and metabolic syndrome. *Journal of Nutrition and Metabolism* **2012**: 851362.

El-Seedi HR, El-Said AM, Khalifa SA *et al.* (2012) Biosynthesis, natural sources, dietary intake, pharmacokinetic properties, and biological activities of hydroxycinnamic acids. *Journal of Agriculture and Food Chemistry* **60**: 10877–95.

Emmons CL & Peterson DM (1999) Antioxidant activity and phenolic contents of oat groats and hulls. *Cereal Chemistry Journal* **76**: 902–6.

Gangopadhyay N, Hossain MB, Rai DK *et al.* (2015) A review of extraction and analysis of bioactives in oat and barley and scope for use of novel food processing technologies. *Molecules* **20**: 10884–909.

Gao C, Gao Z, Greenway FL *et al.* (2015) Oat consumption reduced intestinal fat deposition and improved health span in Caenorhabditis elegans model. *Nutrition Research* **35**: 834–43.

Garcia-Mantrana I, Selma-Royo M, Alcantara C *et al.* (2018) Shifts on gut microbiota associated to Mediterranean diet adherence and

specific dietary intakes on general adult population. *Frontiers in Microbiology* **9**: 890.
Gérard P (2014) Metabolism of cholesterol and bile acids by the gut microbiota. *Pathogens* **3**: 14–24.
Gibson GR (1998) Dietary modulation of the human gut microflora using prebiotics. *British Journal of Nutrition* **80**: S209–12.
Gibson GR & Roberfroid MB (1995) Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *The Journal of Nutrition* **125**: 1401–12.
Gibson GR, Hutkins R, Sanders ME *et al.* (2017) Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nature Reviews Gastroenterology & Hepatology* **14**: 491–502.
Gong J & Yang C (2012) Advances in the methods for studying gut microbiota and their relevance to the research of dietary fiber functions. *Food Research International* **48**: 916–29.
Grundy MML, Quint J, Rieder A *et al.* (2017) The impact of oat structure and β-glucan on *in vitro* lipid digestion. *Journal of Functional Foods* **38**: 378–88.
Haboubi NY, Taylor S & Jones S (2006) Coeliac disease and oats: a systematic review. *Postgraduate Medical Journal* **82**: 672–8.
Hamer HM, Jonkers D, Venema K *et al.* (2008) Review article: the role of butyrate on colonic function. *Alimentary Pharmacology & Therapeutics* **27**: 104–19.
Han S, Jiao J, Zhang W *et al.* (2015) Dietary fiber prevents obesity-related liver lipotoxicity by modulating sterol-regulatory element binding protein pathway in C57BL/6J mice fed a high-fat/cholesterol diet. *Scientific Reports* **5**: 15256.
He M & Shi B (2017) Gut microbiota as a potential target of metabolic syndrome: the role of probiotics and prebiotics. *Cell & Bioscience* **7**: 54.
Heimann E, Nyman M, Pålbrink A-K *et al.* (2016) Branched short-chain fatty acids modulate glucose and lipid metabolism in primary adipocytes. *Adipocyte* **5**: 359–68.
Hofmann AF (1999) The continuing importance of bile acids in liver and intestinal disease. *Archives of Internal Medicine* **159**: 2647–58.
Hong YH, Nishimura Y, Hishikawa D *et al.* (2005) Acetate and propionate short chain fatty acids stimulate adipogenesis via GPCR43. *Endocrinology* **146**: 5092–9.
Hooda S, Matte JJ, Vasanthan T *et al.* (2010) Dietary oat beta-glucan reduces peak net glucose flux and insulin production and modulates plasma incretin in portal-vein catheterized grower pigs. *Journal of Nutrition* **140**: 1564–9.
Hooper LV, Midtvedt T & Gordon JI (2002) How host-microbial interactions shape the nutrient environment of the mammalian intestine. *Annual Review of Nutrition* **22**: 283–307.
Hou Q, Li Y, Li L *et al.* (2015) The metabolic effects of oats intake in patients with type 2 diabetes: a systematic review and meta-analysis. *Nutrients* **7**: 10369–87.
Hughes SA, Shewry PR, Gibson GR *et al.* (2008) *In vitro* fermentation of oat and barley derived beta-glucans by human faecal microbiota. *FEMS Microbiology Ecology* **64**: 482–93.
Immerstrand T, Andersson KE, Wange C *et al.* (2010) Effects of oat bran, processed to different molecular weights of beta-glucan, on plasma lipids and caecal formation of SCFA in mice. *British Journal of Nutrition* **104**: 364–73.
Jayachandran M, Chen J, Chung SSM *et al.* (2018) A critical review on the impacts of β-glucans on gut microbiota and human health. *The Journal of Nutritional Biochemistry* **61**: 101–10.
Jensen MK, Koh-Banerjee P, Franz M *et al.* (2006) Whole grains, bran, and germ in relation to homocysteine and markers of glycemic control, lipids, and inflammation 1. *American Journal of Clinical Nutrition* **83**: 275–83.
Johansson-Persson A, Ulmius M, Cloetens L *et al.* (2014) A high intake of dietary fiber influences C-reactive protein and fibrinogen, but not glucose and lipid metabolism, in mildly hypercholesterolemic subjects. *European Journal of Nutrition* **53**: 39–48.
Jones BV, Begley M, Hill C *et al.* (2008) Functional and comparative metagenomic analysis of bile salt hydrolase activity in the human gut microbiome. *Proceedings of the National Academy of Sciences of the United States of America* **105**: 13580–5.
Jonnalagadda SS, Harnack L, Liu RH *et al.* (2011) Putting the whole grain puzzle together: health benefits associated with whole grains–summary of American Society for Nutrition 2010 Satellite Symposium. *Journal of Nutrition* **141**: 1011s–22s.
Kankaanpaa PE, Salminen SJ, Isolauri E *et al.* (2001) The influence of polyunsaturated fatty acids on probiotic growth and adhesion. *FEMS Microbiology Letters* **194**: 149–53.
Kasubuchi M, Hasegawa S, Hiramatsu T *et al.* (2015) Dietary gut microbial metabolites, short-chain fatty acids, and host metabolic regulation. *Nutrients* **7**: 2839–49.
Kay CD (2015) Rethinking paradigms for studying mechanisms of action of plant bioactives. *Nutrition Bulletin* **40**: 335–9.
Kedia G, Vazquez JA, Charalampopoulos D *et al.* (2009) *In vitro* fermentation of oat bran obtained by debranning with a mixed culture of human fecal bacteria. *Current Microbiology* **58**: 338–42.
Kern SM, Bennett RN, Mellon FA *et al.* (2003) Absorption of hydroxycinnamates in humans after high-bran cereal consumption. *Journal of Agriculture and Food Chemistry* **51**: 6050–5.
Khurana S, Raufman JP & Pallone TL (2011) Bile acids regulate cardiovascular function. *Clinical and Translational Science* **4**: 210–8.
Kim HJ & White PJ (2009) *In vitro* fermentation of oat flours from typical and high β-glucan oat lines. *Journal of Agricultural and Food Chemistry* **57**: 7529–36.
Kim SY, Song HJ, Lee YY *et al.* (2006) Biomedical issues of dietary fiber beta-glucan. *Journal of Korean Medical Science* **21**: 781–9.
Koh A, De Vadder F, Kovatcheva-Datchary P *et al.* (2016) From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell* **165**: 1332–45.
Konig J, Wells J, Cani PD *et al.* (2016) Human intestinal barrier function in health and disease. *Clinical and Translational Gastroenterology* **7**: e196.
Kroon PA, Clifford MN, Crozier A *et al.* (2004) How should we assess the effects of exposure to dietary polyphenols *in vitro*? *American Journal of Clinical Nutrition* **80**: 15–21.
Kumar N & Pruthi V (2014) Potential applications of ferulic acid from natural sources. *Biotechnology Reports* **4**: 86–93.
Lamport DJ, Pal D, Macready AL *et al.* (2017) The effects of flavanone-rich citrus juice on cognitive function and cerebral blood flow: an acute, randomised, placebo-controlled cross-over trial in healthy, young adults. *British Journal of Nutrition* **116**: 2160–8.
Laparra JM & Sanz Y (2010) Interactions of gut microbiota with functional food components and nutraceuticals. *Pharmacological Research* **61**: 219–25.

LeBlanc JG, Chain F, Martín R *et al.* (2017) Beneficial effects on host energy metabolism of short-chain fatty acids and vitamins produced by commensal and probiotic bacteria. *Microbial Cell Factories* **16**: 79.

Levy L & Tedstone A (2017) UK dietary policy for the prevention of cardiovascular disease. *Healthcare* **5**: 9.

Lia A, Hallmans G, Sandberg AS *et al.* (1995) Oat beta-glucan increases bile acid excretion and a fiber-rich barley fraction increases cholesterol excretion in ileostomy subjects. *American Journal of Clinical Nutrition* **62**: 1245–51.

Liu L, Zubik L, Collins FW *et al.* (2004) The antiatherogenic potential of oat phenolic compounds. *Atherosclerosis* **175**: 39–49.

Lockyer S, Rowland I, Spencer JPE *et al.* (2017) Impact of phenolic-rich olive leaf extract on blood pressure, plasma lipids and inflammatory markers: a randomised controlled trial. *European Journal of Nutrition* **56**: 1421–32.

Louis P & Flint HJ (2009) Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine. *FEMS Microbiology Letters* **294**: 1–8.

Macfarlane S & Macfarlane GT (2003) Regulation of short-chain fatty acid production. *Proceedings of the Nutrition Society* **62**: 67–72.

Manach C, Scalbert A, Morand C *et al.* (2004) Polyphenols: food sources and bioavailability. *American Journal of Clinical Nutrition* **79**: 727–47.

Manach C, Williamson G, Morand C *et al.* (2005) Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *American Journal of Clinical Nutrition* **81**: 230s–42s.

Mann KD, Pearce MS, McKevith B *et al.* (2015) Low whole grain intake in the UK: results from the National Diet and Nutrition Survey rolling programme 2008–11. *The British Journal of Nutrition* **113**: 1643–51.

Mårtensson O, Biörklund M, Lambo AM *et al.* (2005) Fermented, ropy, oat-based products reduce cholesterol levels and stimulate the bifidobacteria flora in humans. *Nutrition Research* **25**: 429–42.

McNabney SM & Henagan TM (2017) Short chain fatty acids in the colon and peripheral tissues: a focus on butyrate, colon cancer. Obesity and insulin resistance. *Nutrients* **9**: 1348.

Menon R, Gonzalez T, Ferruzzi M *et al.* (2016) Oats-from farm to fork. *Advances in Food and Nutrition Research* **77**: 1–55.

Mills CE, Flury A, Marmet C *et al.* (2017) Mediation of coffee-induced improvements in human vascular function by chlorogenic acids and its metabolites: two randomized, controlled, crossover intervention trials. *Clinical Nutrition* **36**: 1520–9.

Miyazaki-Anzai S, Masuda M, Levi M *et al.* (2014) Dual activation of the bile acid nuclear receptor FXR and G-protein-coupled receptor TGR5 protects mice against atherosclerosis. *PLoS ONE* **9**: e108270.

Morrison DJ & Preston T (2016) Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes* **7**: 189–200.

Nguyen TLA, Vieira-Silva S, Liston A *et al.* (2015) How informative is the mouse for human gut microbiota research? *Disease Models and Mechanisms* **8**: 1–16.

Nicholson JK, Holmes E, Kinross J *et al.* (2012) Host-gut microbiota metabolic interactions. *Science* **336**: 1262–7.

Nie L, Wise ML, Peterson DM *et al.* (2006) Avenanthramide, a polyphenol from oats, inhibits vascular smooth muscle cell proliferation and enhances nitric oxide production. *Atherosclerosis* **186**: 260–6.

Nie Y-f, Hu J & Yan X-h (2015) Cross-talk between bile acids and intestinal microbiota in host metabolism and health. *Journal of Zhejiang University Science B* **16**: 436–46.

Nilsson AC, Ostman EM, Holst JJ *et al.* (2008a) Including indigestible carbohydrates in the evening meal of healthy subjects improves glucose tolerance, lowers inflammatory markers, and increases satiety after a subsequent standardized breakfast. *Journal of Nutrition* **138**: 732–9.

Nilsson U, Johansson M, Nilsson A *et al.* (2008b) Dietary supplementation with beta-glucan enriched oat bran increases faecal concentration of carboxylic acids in healthy subjects. *European Journal of Clinical Nutrition* **62**: 978–84.

Oda T, Aoe S, Imanishi S *et al.* (1994) Effects of dietary oat, barley, and guar gums on serum and liver lipid concentrations in diet-induced hypertriglyceridemic rats. *Journal of Nutritional Science and Vitaminology* **40**: 213–7.

Okumura R & Takeda K (2017) Roles of intestinal epithelial cells in the maintenance of gut homeostasis. *Experimental & Molecular Medicine* **49**: e338.

Ooi L-G & Liong M-T (2010) Cholesterol-lowering effects of probiotics and prebiotics: a review of *in vivo* and *in vitro* findings. *International Journal of Molecular Sciences* **11**: 2499–522.

Ovando-Martínez M, Whitney K, Reuhs BL *et al.* (2013) Effect of hydrothermal treatment on physicochemical and digestibility properties of oat starch. *Food Research International* **52**: 17–25.

Peluso I, Romanelli L & Palmery M (2014) Interactions between prebiotics, probiotics, polyunsaturated fatty acids and polyphenols: diet or supplementation for metabolic syndrome prevention? *International Journal of Food Sciences and Nutrition* **65**: 259–67.

Pereira DI & Gibson GR (2002) Effects of consumption of probiotics and prebiotics on serum lipid levels in humans. *Critical Reviews in Biochemistry and Molecular Biology* **37**: 259–81.

Peterson DM, Wesenberg DM, Burrup DE *et al.* (2005) Relationships among Agronomic Traits and Grain Composition in Oat Genotypes Grown in Different Environments. *Crop Science* **45**: 1249–55.

Pick ME, Hawrysh ZJ, Gee MI *et al.* (1996) Oat bran concentrate bread products improve long-term control of diabetes. *Journal of the American Dietetic Association* **96**: 1254–61.

Pins JJ, Geleva D, Keenan JM *et al.* (2002) Do whole-grain oat cereals reduce the need for antihypertensive medications and improve blood pressure control? *Journal of Family Practice* **51**: 353–9.

Power SE, O'Toole PW, Stanton C *et al.* (2014) Intestinal microbiota, diet and health. *British Journal of Nutrition* **111**: 387–402.

Prakash S, Rodes L, Coussa-Charley M *et al.* (2011) Gut microbiota: next frontier in understanding human health and development of biotherapeutics. *Biologics* **5**: 71–86.

Queipo-Ortuño MI, Boto-Ordóñez M, Murri M *et al.* (2012) Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. *American Journal of Clinical Nutrition* **95**: 1323–34.

Randrianarisoa E, Lehn-Stefan A, Wang X *et al.* (2016) Relationship of serum Trimethylamine N-Oxide (TMAO) levels with early atherosclerosis in humans. *Scientific Reports* **6**: 26745.

Rasane P, Jha A, Sabikhi L *et al.* (2015) Nutritional advantages of oats and opportunities for its processing as value added foods - a review. *Journal of Food Science and Technology* **52**: 662–75.

Rebello CJ, Chu YF, Johnson WD *et al.* (2014) The role of meal viscosity and oat beta-glucan characteristics in human appetite control: a randomized crossover trial. *Nutrition Journal* **13**: 49.

Rebello CJ, O'Neil CE & Greenway FL (2016) Dietary fiber and satiety: the effects of oats on satiety. *Nutrition Reviews* **74**: 131–47.

Rein MJ, Renouf M, Cruz-Hernandez C *et al.* (2013) Bioavailability of bioactive food compounds: a challenging journey to bioefficacy. *British Journal of Clinical Pharmacology* **75**: 588–602.

Ridlon JM, Kang DJ & Hylemon PB (2006) Bile salt biotransformations by human intestinal bacteria. *Journal of Lipid Research* **47**: 241–59.

Ríos-Covián D, Ruas-Madiedo P, Margolles A *et al.* (2016) Intestinal short chain fatty acids and their link with diet and human health. *Frontiers in Microbiology* **7**: 185.

Robles Alonso V & Guarner F (2013) Linking the gut microbiota to human health. *British Journal of Nutrition* **109**(Suppl 2): S21–6.

Roediger WE (1980) Role of anaerobic bacteria in the metabolic welfare of the colonic mucosa in man. *Gut* **21**: 793–8.

Rondini L, Peyrat-Maillard MN, Marsset-Baglieri A *et al.* (2004) Bound ferulic acid from bran is more bioavailable than the free compound in rat. *Journal of Agriculture and Food Chemistry* **52**: 4338–43.

Ruan Y, Sun J, He J *et al.* (2015) Effect of probiotics on glycemic control: a systematic review and meta-analysis of randomized. Controlled trials. *PLoS ONE* **10**: e0132121.

Russell WR, Hoyles L, Flint HJ *et al.* (2013) Colonic bacterial metabolites and human health. *Current Opinion in Microbiology* **16**: 246–54.

Ruxton CHS & Derbyshire E (2008) A systematic review of the association between cardiovascular risk factors and regular consumption of oats. *British Food Journal* **110**: 1119–32.

Ryan D, Kendall M & Robards K (2007) Bioactivity of oats as it relates to cardiovascular disease. *Nutrition Research Reviews* **20**: 147–62.

Ryan L, Thondre PS & Henry CJK (2011) Oat-based breakfast cereals are a rich source of polyphenols and high in antioxidant potential. *Journal of Food Composition and Analysis* **24**: 929–34.

Sadiq Butt M, Tahir-Nadeem M, Khan MK *et al.* (2008) Oat: unique among the cereals. *European Journal of Nutrition* **47**: 68–79.

Sagar NM, Cree IA, Covington JA *et al.* (2015) The interplay of the gut microbiome, bile acids, and volatile organic compounds. *Gastroenterology Research and Practice* **2015**: 1–6.

Saini R, Saini S & Sharma S (2010) Potential of probiotics in controlling cardiovascular diseases. *Journal of Cardiovascular Disease Research* **1**: 213–4.

Schar MY, Corona G, Soycan G *et al.* (2017) Excretion of avenanthramides, phenolic acids and their major metabolites following intake of oat bran. *Molecular Nutrition & Food Research* **62** : 1700499.

Shen XL, Zhao T, Zhou Y *et al.* (2016) Effect of oat beta-glucan intake on glycaemic control and insulin sensitivity of diabetic patients: a meta-analysis of randomized controlled trials. *Nutrients* **8**: 39.

Shepherd J, Cobbe SM, Ford I *et al.* (1995) Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *New England Journal of Medicine* **333**: 1301–7.

Shewry PR, Piironen V, Lampi AM *et al.* (2008) Phytochemical and fiber components in oat varieties in the HEALTHGRAIN Diversity Screen. *Journal of Agriculture and Food Chemistry* **56**: 9777–84.

Singh R, De S & Belkheir A (2013) Avena sativa (Oat), a potential nutraceutical and therapeutic agent: an overview. *Critical Reviews in Food Science and Nutrition* **53**: 126–44.

Stamler J, Wentworth D & Neaton JD (1986) Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* **256**: 2823–8.

Stevenson L, Phillips F, O'Sullivan K *et al.* (2012) Wheat bran: its composition and benefits to health, a European perspective. *International Journal of Food Sciences and Nutrition* **63**: 1001–13.

Sun J & Buys N (2015) Effects of probiotics consumption on lowering lipids and CVD risk factors: a systematic review and meta-analysis of randomized controlled trials. *Annals of Medicine* **47**: 430–40.

Suzuki A, Kagawa D, Fujii A *et al.* (2002) Short- and long-term effects of ferulic acid on blood pressure in spontaneously hypertensive rats. *American Journal of Hypertension* **15**: 351–7.

Suzuki A, Yamamoto M, Jokura H *et al.* (2007) Ferulic acid restores endothelium-dependent vasodilation in aortas of spontaneously hypertensive rats. *American Journal of Hypertension* **20**: 508–13.

Tang WH & Hazen SL (2014) The contributory role of gut microbiota in cardiovascular disease. *Journal of Clinical Investigation* **124**: 4204–11.

Tang G, Wang D, Long J *et al.* (2015) Meta-analysis of the association between whole grain intake and coronary heart disease risk. *The American Journal of Cardiology* **115**: 625–9.

Tappenden KA, Albin DM, Bartholome AL *et al.* (2003) Glucagon-like peptide-2 and short-chain fatty acids: a new twist to an old story. *Journal of Nutrition* **133**: 3717–20.

Tappy L, Gugolz E & Wursch P (1996) Effects of breakfast cereals containing various amounts of beta-glucan fibers on plasma glucose and insulin responses in NIDDM subjects. *Diabetes Care* **19**: 831–4.

Thies F, Masson LF, Boffetta P *et al.* (2014) Oats and CVD risk markers: a systematic literature review. *British Journal of Nutrition* **112**(Suppl 2): S19–30.

Thursby E & Juge N (2017) Introduction to the human gut microbiota. *Biochemical Journal* **474**: 1823–36.

Tosh SM (2013) Review of human studies investigating the postprandial blood-glucose lowering ability of oat and barley food products. *European Journal of Clinical Nutrition* **67**: 310–7.

Tosh SM & Chu Y (2015) Systematic review of the effect of processing of whole-grain oat cereals on glycaemic response. *British Journal of Nutrition* **114**: 1256–62.

Tuohy KM, Fava F & Viola R (2014) 'The way to a man's heart is through his gut microbiota'–dietary pro- and prebiotics for the management of cardiovascular risk. *Proceedings of the Nutrition Society* **73**: 172–85.

Turnbaugh PJ, Ridaura VK, Faith JJ *et al.* (2009) The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. *Science Translational Medicine* **1**: 6ra14.

Tzounis X, Rodriguez-Mateos A, Vulevic J *et al.* (2011) Prebiotic evaluation of cocoa-derived flavanols in healthy humans by using

a randomized, controlled, double-blind, crossover intervention study. *American Journal of Clinical Nutrition* **93**: 62–72.

Ulmius M, Johansson-Persson A, Krogh M *et al.* (2011) An oat bran meal influences blood insulin levels and related gene sets in peripheral blood mononuclear cells of healthy subjects. *Genes and Nutrition* **6**: 429–39.

USDA (US Department of Agriculture) (2015) Agricultural Research Service, Food Surveys Research Group: Food and Nutrient Database for Dietary Studies. Available at: www.nal.usda.gov/fnic/usda-food-surveys-research-group (accessed 1 September 2018).

Valeur J, Puaschitz NG, Midtvedt T *et al.* (2016) Oatmeal porridge: impact on microflora-associated characteristics in healthy subjects. *British Journal of Nutrition* **115**: 62–7.

Vieira AT, Teixeira MM & Martins FS (2013) The role of probiotics and prebiotics in inducing gut immunity. *Frontiers in Immunology* **4**: 445.

Vitaglione P, Napolitano A & Fogliano V (2008) Cereal dietary fibre: a natural functional ingredient to deliver phenolic compounds into the gut. *Trends in Food Science and Technology* **19**: 451–63.

Vitaglione P, Mennella I, Ferracane R *et al.* (2015) Whole-grain wheat consumption reduces inflammation in a randomized controlled trial on overweight and obese subjects with unhealthy dietary and lifestyle behaviors: role of polyphenols bound to cereal dietary fiber. *American Journal of Clinical Nutrition* **101**: 251–61.

Wahlstrom A, Sayin SI, Marschall HU *et al.* (2016) Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. *Cell Metabolism* **24**: 41–50.

Weitkunat K, Stuhlmann C, Postel A et al. (2017) Short-chain fatty acids and inulin, but not guar gum, prevent diet-induced obesity and insulin resistance through differential mechanisms in mice. *Scientific Reports* **7**: 6109.

Welch RW (1994) Can dietary oats promote health? *British Journal of Biomedical Science* **51**: 260–70.

Whitehead A, Beck EJ, Tosh S *et al.* (2014) Cholesterol-lowering effects of oat beta-glucan: a meta-analysis of randomized controlled trials. *American Journal of Clinical Nutrition* **100**: 1413–21.

Williamson G & Clifford MN (2017) Role of the small intestine, colon and microbiota in determining the metabolic fate of polyphenols. *Biochemical Pharmacology* **139**: 24–39.

Wolever TM, Fernandes J & Rao AV (1996) Serum acetate:propionate ratio is related to serum cholesterol in men but not women. *Journal of Nutrition* **126**: 2790–7.

Wolever TMS, Jenkins AL, Prudence K *et al.* (2018) Effect of adding oat bran to instant oatmeal on glycaemic response in humans - a study to establish the minimum effective dose of oat beta-glucan. *Food and Function* **9**: 1692–700.

Wood PJ, Beer MU & Butler G (2000) Evaluation of role of concentration and molecular weight of oat beta-glucan in determining effect of viscosity on plasma glucose and insulin following an oral glucose load. *British Journal of Nutrition* **84**: 19–23.

Wu GD, Chen J, Hoffmann C *et al.* (2011) Linking long-term dietary patterns with gut microbial enterotypes. *Science* **334**: 105–8.

Yang J, Ou B, Wise ML *et al.* (2014) *In vitro* total antioxidant capacity and anti-inflammatory activity of three common oat-derived avenanthramides. *Food Chemistry* **160**: 338–45.

Ye EQ, Chacko SA, Chou EL *et al.* (2012) Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. *Journal of Nutrition* **142**: 1304–13.

Zhang PP, Hu X-Z, Zhen H-M *et al.* (2012) Oat β-glucan increased ATPases activity and energy charge in small intestine of rats. *Journal of Agricultural and Food Chemistry* **60**: 9822–7.

Zhang YJ, Li S, Gan RY *et al.* (2015) Impacts of gut bacteria on human health and diseases. *International Journal of Molecular Sciences* **16**: 7493–519.

Zhang Y, Zhang H, Wang L *et al.* (2016) The effect of oat beta-glucan on *in vitro* glucose diffusion and glucose transport in rat small intestine. *Journal of the Science of Food and Agriculture* **96**: 484–91.

Zhang T, Shao J, Gao Y *et al.* (2017) Absorption and elimination of oat avenanthramides in humans after acute consumption of oat cookies. *Oxidative Medicine and Cellular Longevity* **2017**: 2056705.

Zhou AL, Hergert N, Rompato G *et al.* (2015) Whole grain oats improve insulin sensitivity and plasma cholesterol profile and modify gut microbiota composition in C57BL/6J mice. *Journal of Nutrition* **145**: 222–30.

Ziegler K, Kerimi A, Poquet L *et al.* (2016) Butyric acid increases transepithelial transport of ferulic acid through upregulation of the monocarboxylate transporters SLC16A1 (MCT1) and SLC16A3 (MCT4). *Archives of Biochemistry and Biophysics* **599**: 3–12.

Zimmer J, Lange B, Frick JS *et al.* (2012) A vegan or vegetarian diet substantially alters the human colonic faecal microbiota. *European Journal of Clinical Nutrition* **66**: 53–60.