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Gut *Prevotella* as a possible biomarker of diet and its eubiotic versus dysbiotic roles: a comprehensive literature review

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Abstract

The gut microbiota has a profound impact on human health. Emerging data show that dietary patterns are associated with different communities of bacterial species within the gut. *Prevotella* species have been correlated with plant-rich diets, abundant in carbohydrates and fibres. Dysbiosis within the gut ecosystem has been associated with the development of non-communicable diseases such as obesity, the metabolic syndrome, inflammatory bowel disease, irritable bowel syndrome, colorectal cancer, type 1 diabetes, allergies and other diseases. The purpose of this comprehensive literature review was to evaluate the available data on the impact of diet on the *Prevotella* genus, as a dietary fibre fermenter in the gut as well as its implications as a potential biomarker for homeostasis or disease state through its metabolite signature. Studies were identified by conducting PubMed, Web of Science Core Collection and Google Scholar electronic searches. We found eighty-five publications reporting the impact of dietary patterns on gut microbial communities, including *Prevotella* or *Prevotella/Bacteroides* ratio in particular. Moreover, the role of *Prevotella* species on health status was also evaluated. *Prevotella* possess a high genetic diversity, representing one of the important groups found in the oral cavity and large intestine of man. The gut commensal *Prevotella* bacteria contribute to polysaccharide breakdown, being dominant colonisers of agrarian societies. However, studies also suggested a potential role of *Prevotella* species as intestinal pathobionts. Further metagenomic studies are needed in order to reveal health- or disease-modulating properties of *Prevotella* species in the gut.

Key words: **Dietary patterns: Gut microbiota: *Prevotella***

In the last decades, researchers started to understand that the gut microbiota is a key player affecting human health, being an essential key in human health and disease[1]. The focus shifted on understanding what constitutes a health- (eubiotic) or disease-promoting (dysbiotic) microbial community[1]. Emerging evidence shows that alterations in the intestinal microbial balance could lead to dysbiosis and play a pathological role, contributing to the development of non-communicable diseases such as obesity, the metabolic syndrome (MetS), inflammatory bowel disease, irritable bowel syndrome, colorectal cancer, type 1 diabetes, rheumatoid arthritis, allergies, autism and major depressive disorders[1–6].

The human intestinal microbiota was shown to play a role as a vital regulator of basic human biological processes such as modulating the metabolic phenotype, extracting nutrients and energy from our diets, programming host immune system and regulating epithelial development[7]. These core functions are linked to the production of essential and extremely diverse metabolites such as vitamins (vitamin B_{12}, folic acid or vitamin K), bile acids, neurotransmitters (serotonin, dopamine, acetylcholine) and SCFA (acetic acid, propionic acid and butyric acid). These metabolites result from undigested fibre fermentation by the gut microbiota[8,9].

More than 90 % of the entire population of the human gut microbiota are represented by two phyla, Firmicutes (which includes mainly *Clostridium, Enterococcus, Lactobacillus* and *Faecalibacterium* genera) and Bacteroidetes (which includes notably *Bacteroides* and *Prevotella* genera)[5,10].

Preliminary studies showed that some microbial species from the gut ecosystem had been linked to specific dietary habits. To illustrate, strong research efforts initiated by projects such as the European Metagenomics of the Human Intestinal Tract (MetaHIT) (http://www.metahit.eu) project, the American Human Microbiome Project (HMP) (http://hmpdacc.org) or the Asian Microbiome Project (http://www.asiangut.com/) had emphasised a higher diversity of the gut microbes of rural and preagricultural or isolated populations compared with westernised or industrialised populations.

In this regard, observational studies on these populations highlighted that these communities are characterised by an

Abbreviations: MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; TMAO, urinary trimethylamine oxide.

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Table 1. Detailed search strategies for PubMed, Web of Science Core Collection (WoS CC) and Google Scholar

WoS CC (final screen: 4 November 2018, 240 hits)	PubMed (final screen: 4 November 2018, 233 hits)	Google Scholar (final screen: 4 November 2018, 9580 hits)
(diet* OR dietary habit* OR Eating habit* OR dietary pattern OR plant-based diet* OR dietary fibre*) AND TOPIC: (gut microbiota OR intestinal microbiota*) AND TOPIC: (*Prevotella*) AND TOPIC: Health	(‘diet’[MeSH Terms] OR ‘diet’ [All Fields]) OR (‘diet’[MeSH Terms] OR ‘diet’ [All Fields] OR ‘dietary’ [All Fields]) AND patterns[All Fields]) OR (‘feeding behaviour’ [MeSH Terms] OR (‘feeding’ [All Fields] AND ‘behaviour’ [All Fields]) OR ‘feeding behaviour’ [All Fields] OR (‘eating’ [All Fields] AND ‘habits’ [All Fields]) OR ‘eating habits’ [All Fields]) OR (‘dietary fibre’ [All Fields] OR ‘dietary fibre’ [MeSH Terms] OR (‘dietary’ [All Fields] AND ‘fibre’ [All Fields]) OR ‘dietary fibre’ [All Fields])) AND (‘gastrointestinal microbiome’ [MeSH Terms] OR (‘gastrointestinal’ [All Fields] AND ‘microbiome’ [All Fields]) OR ‘gastrointestinal microbiome’ [All Fields] OR (‘gut’ [All Fields] AND ‘microbiota’ [All Fields]) OR ‘gut microbiota’ [All Fields])) AND (‘prevotella’ [MeSH Terms] OR ‘prevotella’ [All Fields]) c (‘health’ [MeSH Terms] AND (‘1 January 2008’ [PDAT]: ‘4 November 2018’ [PDAT])	(diet* OR dietary habit* OR eating habit* OR dietary pattern OR plant-based diet* OR dietary fibre*) AND (gut microbiota OR intestinal microbiota*) AND *Prevotella* AND health

abundance of *Prevotella* species within the gut, whereas westernised populations harbour higher levels of *Bacteroides* than *Prevotella*[11–20].

To date, limited information is available linking microbiota or specific microbial species like the *Prevotella* genus to health markers; however, several studies have established a correlation between microbial taxa and disease[3,4,7]. Regarding *Prevotella*, studies focused on the associations between the diverse species, genome and habitats with dietary patterns, health and disease. Characterisation of the healthy human microbiota by using next-generation sequencing techniques has revealed a prevalence of *Prevotella* species at mucosal sites, within the respiratory system, oral and gut ecosystem. Evidence revealed beneficial effects of some *Prevotella* strains in the gut such as not only improving CVD risk factor profile and glucose metabolism[21,22], but also pathobiontic properties of some strains which promoted diseases like the MetS, obesity, inflammatory bowel disease or other inflammatory diseases (rheumatoid arthritis, asthma, bacterial vaginitis, HIV infection)[23].

The necessity of larger cohort studies in order to establish a disease-triggering role of *Prevotella* species is highlighted, since inflammatory diseases are multifactorial and *Prevotella* is also considered beneficial due to its abundance in healthy gut microbiota and association with plant-rich diets[24–26].

Therefore, the selection of the *Prevotella* genus from the gut as the main subject for this systematic review lies in its significance as commensal of the human gut and its characteristic as dietary fibre fermenter. We decided to further examine eligible studies that focus on unravelling the association between dietary habits, food products and the presence of *Prevotella* species and their metabolite signature as well as the relevance of this bacterial genus in health status.

Experimental methods

Literature search

We conducted our literature review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[27]. The literature search was conducted independently by both authors, with disagreements resolved by consensus.

We searched the scientific electronic databases PubMed, Web of Science Core Collection (WoS CC) and Google Scholar for potentially eligible articles. We developed a systematic search strategy, which included the following descriptors from PubMed: ‘diet’, ‘gut microbiota’, ‘*Prevotella*’ and ‘health’. In addition, we considered free-text terms like ‘dietary pattern’, ‘eating behaviour’, ‘plant-based diet’, ‘dietary fibre’, ‘gastrointestinal microbiome’, ‘health status’ and ‘disease’. The logical connectives ‘and’, ‘or’ and ‘and not’ were systematically used to combine descriptors and terms used to trace the publications. For the WoS CC database and Google Scholar, we adapted our final PubMed search strategy. In Table 1, we provide the exact search strategies of the literature databases. We also explored for additional articles by checking the references cited in the primary eligible studies included in this systematic review. The final search on 4 November 2018 resulted in 274 hits (Fig. 1) from the databases after excluding 9811 duplicates identified using Endnote (Thomson Reuters). An initial screening of the titles and abstracts of articles was then performed to exclude irrelevant studies. During the systematic evaluation, study data were reviewed, where possible, in relation to dietary patterns and levels of *Prevotella*, changes in the intestinal microbiota, the role of *Prevotella* in the gut system, the metabolite signature and any reported metabolic consequence of the *Prevotella* genus in rodents and human studies. Then, the full texts of potentially eligible studies were reviewed before definitive inclusion.

Study selection

Table 2 provides an overview of the *a priori* defined inclusion and exclusion criteria that we applied to select eligible articles.

We (G. P. and D.-C. V.) independently screened all 274 abstracts. By applying inclusion/exclusion criteria to the information contained in the abstract, we reduced the pool of potentially eligible articles to 155 (Fig. 1). We evaluated the retrieved full-text articles applying the same inclusion and exclusion criteria that were used for the abstract selection. Any disagreements during the selection process were discussed among all the reviewers and unit consensus was reached. Finally, we included eighty-five full-text articles into our review, after we excluded seventy articles that did not meet the inclusion criteria.

Table 2. Inclusion and exclusion criteria for the systematic review

Inclusion criteria for systematic review	Exclusion criteria
• Studies published in the last 10 years, from 1 January 2008 to 4 November 2018 were included in the search; • English language; • Studies reporting the impact of diet, geography on the presence of the *Prevotella* genus within the gut ecosystem or studies comparing the impact of long- and short-term diets on gut microbiota, or studies reporting the metabolite signature of *Prevotella* species; • Studies reporting the correlation between host health and the presence of *Prevotella* species in the gut ecosystem; • Human and animal (rodent) studies	• Articles screening the *Prevotella* species from other animals (not rodents); • Datasets which did not provide information related to eating habits, dietary interventions and associated nutritional properties and levels of the *Prevotella* genus in the gut or association of *Prevotella* ssp. with health status; • Failure to provide data for *Prevotella* presence within the gut ecosystem

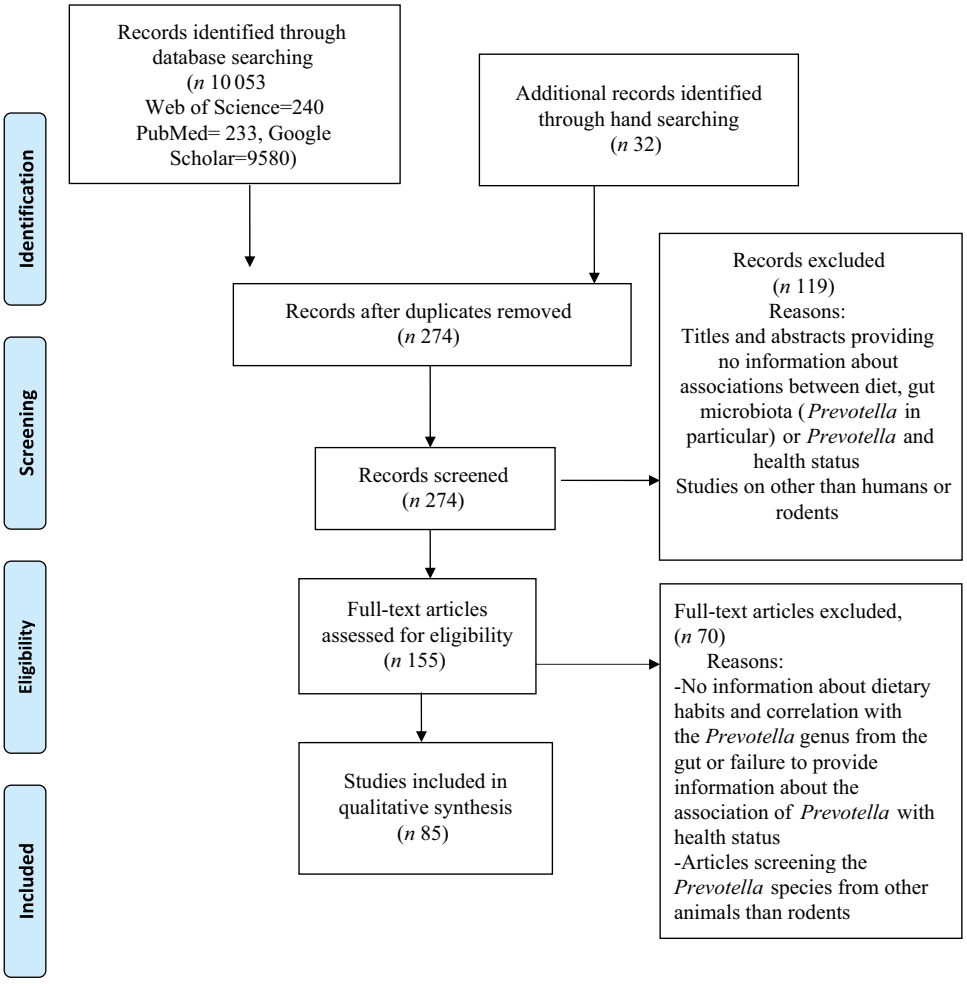

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process.

Review statistics

A total of eighty-five studies extracted from 155 articles met the inclusion criteria and were analysed in the systematic review. The detailed steps of the systematic review article selection process are given as a flow chart in Fig. 1.

Risk of bias within studies

The risk of bias was unclear in all trials. Lack of information precluded a proper evaluation of the risk of bias for all studies.

Results

We identified sixty-eight articles and seventeen literature reviews published between 2008 and 2018 that have investigated the impact of different dietary habits on gut microbial communities, in particular on *Prevotella* levels or *Prevotella*/*Bacteroides* ratio. Moreover, the influence of urbanisation, industrialisation and geographical or ethnic factors on shaping the gut ecosystem as well as the role of gut microbiota in different diseases were evaluated (online Supplementary File S1)[8,12–16,18,20,22,29–34,38,43–45,47,55,62,63,66–68,70–74,79,82–114].

The studies described significant differences in the gut microbial ecosystem, influenced by dietary habits, lifestyle, geography and environmental factors, by using molecular techniques such as 16S rDNA pyrosequencing and shotgun metagenomic data[10–12]. Most of the gut bacteria (approximately 60 %) cannot be cultured due to their particular requirements for anaerobiosis and nutritional needs. Therefore, the development of these techniques provided new knowledge on the composition and functionality of the gut microbiome as an ecosystem and its variation across the world[10].

Dietary patterns shape the gut microbiota composition

Specifically, studies on the human microbiome have suggested that long-term dietary habits, geographical and ethnic factors could shape the gut microbiota into the so-called 'enterotypes' that were not specific to certain continents or nations[12,21]. The 'enterotypes' hypothesis was introduced in 2011 by Arumugam *et al.* as a useful method to stratify human gut microbiomes[28]. Wu *et al.* used shotgun sequencing of the faecal samples from American individuals and used multiple clustering techniques, but found only two of the three original clusters: *Bacteroides* and *Prevotella*[29]. The third cluster was not distinct in their data, with *Ruminococcus* (Clostridiales order) equally abundant in both of the first two enterotypes. They compared their findings with a previously published study on Italian and rural African children, wherein Italian children had *Bacteroides*-dominated gut microbiomes and African children had *Prevotella*-dominated gut microbiomes[29]. Although consensus that these enterotypes are the result of long-term dietary behaviour is usually accepted, the concept itself has also been challenged, since other studies have proposed the existence of microbial community gradients rather than distinct enterotypes[30]. Studies highlighted afterwards only two community types: one dominated by *Prevotella* and one dominated by *Bacteroides* or members of the Firmicutes *Bifidobacterium*[26].

De Filippo *et al.*[20] reported a considerable difference in gut microbiota at a phylum level, namely Firmicutes/Bacteroidetes ratio, between African children who followed a low-fat high-fibre diet and Italian children who consumed a high-fat and high-protein modern diet. The African children were living in a village of rural Burkina Faso, in an environment close to that of Neolithic subsistence farmers, while the Italian children were living in Florence, in an environment typical of industrialised Europe. The African children showed a significant enrichment in Bacteroidetes and depletion in Firmicutes ($P < 0{\cdot}001$) with abundance of *Prevotella* and *Xylanibacter* bacteria and more SCFA ($P < 0{\cdot}001$) compared with European children. The authors assumed that the polysaccharide-rich diets of African people shaped their gut microbiota in a way that helped to maximise energy intake from fibre while also protecting them from inflammation and non-infectious colonic diseases[20].

Several other observational and cohort studies underlined the abundance of *Prevotella* species in Indian[31], Chinese, Kazaks[32], Turks, Moroccans[33], Indonesian, Thai[12], Filipinos[14], African (Malawian, Egyptian[34], Tanzanian and BaAka hunter–gatherers[15,18]) and Venezuelan rural or isolated populations[35], whereas *Bacteroides* were abundant in populations from western countries in Europe and America[11–14,19,29,34]. The abundance of the *Prevotella* genus in these populations is determined by its capacity to digest complex carbohydrates and by the genetic and enzymatic potential to break down cellulose and xylan from foods[19]. A specific strain, *Prevotella copri*, has been shown to be an important biomarker for diet[13,36]. Nakayama *et al.* have underlined in a study on Filipino children that the growth of *P. copri* and *P. stercorea* were stimulated by vitamin A and β-carotene from bananas and mangos[14]. The authors also outlined that not only these two species of Prevotellaceae, but also species of Veillonellaceae (*Dialister succinatiphilus*) and Erysipelotrichaceae have a positive correlation with dietary carbohydrate. A high intake of fat positively correlated with *Bacteroides, Ruminococcus*, *Blautia*, *Dorea*, *Megamonas* and negatively correlated with *Prevotella*[14,31]. Moreover, Li *et al.* showed in their study on healthy Chinese herdsmen that *Prevotella* gradually decreased with the degree of urbanisation, while *Bacteroides*, *Faecalibacterium*, *Blautia*, *Collinsella*, *Ruminococcus*, *Coprococcus* and *Dorea* increased with the degree of urbanisation[32]. In addition, Mancabelli *et al.* highlighted in their meta-analysis of publicly available shotgun datasets of human faecal samples collected from urbanised and traditional preagricultural populations that industrialisation has shaped the gut microbiota through the acquisition and/or loss of specific gut microbes, thereby potentially impacting on the overall functionality of the gut microbiome[21]. For example, *Xylanibacter* (Bacteroidetes) and *Treponema* (Spirochaetes) were only found in individuals from agricultural communities, which indicate that they could be symbionts lost in urban-industrialised societies[14,19]. Enrichment in *Succinivibrio* and *Treponema*, which also possess a high-fibre degrading potential, is important for agrarian populations like the Africans, as the typical diet is high in fibre and complex carbohydrates[14].

Overall, people living in African countries have higher gut microbiota diversity dominated by Actinobacteria (*Bifidobacterium*); Bacteroidetes (*Bacteroides–Prevotella*); Firmicutes (*C. histolyticum, Eubacterium*, *Oscillibacter, Butyricicoccus* and *Sporobacter);* Proteobacteria (*Succinivibrio, Shigella* and *Escherichia*) and Spirochaetes (*Treponema*) and depleted in only Actinobacteria (*Bifidobacterium catenulatum*), Firmicutes (*Clostridium difficile* and *Akkermansia muciniphila*). Meanwhile, for people living in Western countries such as in Europe and America, gut microbiota is enriched in Firmicutes (*Blautia, Dorea, Roseburia, Faecalibacterium*, *Ruminococcus, Oscillospira, C. perfringens, C. difficile* and *S. aureus);* Bacteroidetes (*Bacteroides)*, Actinobacteria (*B. adolescentis* and *B. catenulatum*) and Verrucomicrobia (*A. muciniphila*)[20,21].

Association of dietary habits with microbial and metabolic profiles and the link with health or disease states

The distinct dietary habits of populations living in different geographical areas are reflected in their microbial diversity and metabolic profile. To exemplify, Western diet is characterised by high consumption of animal proteins and fat (meat, fish, dairy products), refined carbohydrates (processed foods, sweets)

and low levels of fibre intake from plants[9,37]. In contrast, Eastern diet consists of staple foods such as rice or noodles, soup and several dishes with a lot of vegetables. Populations living in isolated areas (like preagricultural populations) have a diet based on foods gathered and/or hunted from their proximate environment rich in carbohydrates and fibre[14,20].

Even though *Prevotella* has been linked with a vegetable-rich diet and *Bacteroides* with protein/fat rich diets, little is known about the composition of the gut microbiota in people with specific dietary patterns like vegetarian, vegan, Mediterranean or omnivorous[13].

In the last 10 years, few studies have reported the differences in faecal microbiota of individuals following a vegetarian, vegan or omnivorous diet, but studies on large cohorts are missing. Vegetarian, ovo-lacto vegetarian, lacto-vegetarian or vegan diets have increased in popularity lately, as studies reported beneficial effects on human health in terms of prevention of CVD, cancer and diabetes[38]. The Mediterranean diet is characterised by a high intake of vegetables and fruits, legumes and whole grains combined with a moderately high consumption of fish, low intake of saturated fat, meat and dairy products and regular but moderate consumption of red wine and the use of olive oil as the principal source of dietary lipids[39]. This type of diet has also been linked to protective roles against several diseases like obesity, type 2 diabetes, inflammatory diseases and CVD[39–41]. On the contrary, the omnivore diet which is typical for Western diets from industrialised countries apparently led to a composition of the microbiota that is more associated with different types of diseases like obesity, insulin resistance, dyslipidemia and inflammatory disorders[42].

Most studies reported that vegetarians harbour higher numbers of *Prevotella* species as well as a high *Prevotella*/*Bacteroides* ratio compared with non-vegetarians (omnivores)[38,43]. However, one study by Wu *et al.*[44] reported that levels of *Prevotella* were not significantly different between omnivores and vegans from the USA, as the residence in a westernised culture might determine a more 'restrictive' microbiota structure. Ferrocino *et al.* showed in a cross-sectional study that vegans and vegetarians have an abundance of Prevotellaceae and ovo-lacto vegetarians were characterised by the presence of *P. micans*, *B. vulgatus* and *Faecalibacterium prausnitzii*. *P. copri* was also found in a characteristic bacteria of the omnivore subjects, which is consistent with its presence in non-agrarian diets[38,45]. *B. vulgatus* is associated with agrarian diets, being well known for its ability to encode the largest number of enzymes which target the degradation of pectin[6,46]. *F. prausnitzii* was found to be a characteristic species in the faecal samples of the subjects who followed a vegetarian diet[47], and it has recently been shown that it has the probiotic ability to produce vitamin B_{12} and to hydrolyse lactulose and galacto-oligosaccharides[48]. *F. prausnitzii* has also been recognised as being one of the most abundant butyrate producers in human faeces[48].

Moreover, it has frequently been reported that SCFA (acetate, propionate and butyrate) are produced by intestinal microbiota during the fermentation of undigested polysaccharides. In contrast, non-digested proteins are broken down into smaller peptides or amino acids, in the end resulting in branched-chain fatty acids (valerate, caproate), phenolic compounds, amines and ammonia[49]. It has been demonstrated that these microbial metabolites help controlling the colon pH, regulating energy control and prevent pathogen bacteria growth as well as modulating bacterial gene expression leading to the production of enzymes involved in amino acid metabolism[7,50].

Evidence shows that SCFA levels were higher in native Africans on agrarian diet compared with African Americans or European children (Italian)[14,19]. Propionate was positively correlated with the presence of *Prevotella* in African children and negatively correlated with *Bifidobacterium*, *Blautia* and Lachnospiraceae[14]. Specifically, propionate is formed mostly through the succinate pathway that is characteristic of Bacteroidetes[51] and has been shown to be metabolised in the liver. Its implications in reducing serum cholesterol and decreasing hepatic lipogenesis, thus preventing weight gain in overweight adult humans, was demonstrated[52].

Butyrate was enriched in European children and positively correlated with *Bifidobacterium, Bacteroides, Blautia, Dorea* and *Faecalibacterium*[13]. Butyrate is frequently produced via butyryl-CoA:acetate CoA-transferase with consumption of acetate and is mainly characteristic of the Firmicutes phylum. Butyrate promotes barrier function and reduces inflammation when present in sufficient quantity[53]. It becomes the major fuel source for colonic epithelial cells, reducing the need for energy allocation to these cells from the host[53,54]. In addition, Chen *et al.*[55] analysed the fibre utilisation capacities of *Prevotella* or *Bacteroides* by testing fibres (arabinoxylans from sorghum bran, arabinoxylans from maize bran and fructo-oligosaccharides) in an *in vitro* fermentation system. The authors highlighted that through the fermentation of the mentioned substrates, *Prevotella* produced two to three times more propionate than the *Bacteroides*-dominated microbiota. Conversely, lower levels of butyrate were obtained[55]. Acetate is a fermentation product for most gut anaerobes and consistently reaches the highest concentrations among the SCFA in the colon. Approximately, 70 % of the acetate is used as an energy source by the liver, but is also used as a substrate for the synthesis of cholesterol and long-chain fatty acids[56]. Moreover, it was revealed to act as an appetite regulator and thus aid in reducing obesity[57].

Thus, the amount and relative abundance of SCFA may be considered as biomarkers of a healthy status[12].

De Filippis *et al.* showed that vegetarians and vegans had a high-level adherence to the Mediterranean diet, which positively associated to *Prevotella* and increased levels of SCFA (acetic, propanoic or butanoic acids) and negatively correlated to urinary trimethylamine N-oxide (TMAO) levels[13]. In contrast, consumption of proteins and fat in omnivorous diets positively associated to higher levels of branched-chain fatty acids (valerate, caproate) and urinary TMAO[13]. TMAO is a metabolite which has been recently shown to increase the risk of cardiovascular and atherosclerosis in both mice and humans independently of traditional cardiometabolic risk factors and through inhibiting hepatic bile acid synthesis[58,59]. TMAO results from carnitine and choline found in animal products (eggs, beef, pork and fish), which are converted by the gut microbiota to trimethylamine, oxidised in the liver and released into circulation as TMAO[58]. In addition, the content of choline and L-carnitine in

the traditional Mediterranean diet is more than 50 % lower than in a typical Western diet[12].

Interestingly, Chen *et al.* showed in a study on mice that TMAO levels were decreased by resveratrol, a natural polyphenol found in grapes, berries and wine, which attenuated TMAO-induced atherosclerosis[60]. The authors further explained that resveratrol increased hepatic bile neosynthesis via gut microbiota remodelling (increased levels of *Lactobacillus, Bifidobacterium, Akkermansia*, but decreased levels of *Prevotella*)[60].

Thus, while it is still unknown what constitutes a healthy gut microbiome, some studies have linked a microbial dysbiosis to some disease states. High levels of *Prevotella* were linked to obesity[61] and significantly associated with BMI[62], insulin resistance in non-diabetic people[61,63], hypertension[64] and non-alcoholic fatty liver disease (NAFLD)[65]. Furthermore, *Prevotella* were also linked to high blood pressure and impaired glucose metabolism[46]. However, other studies did not find correlations between obesity[13,66,67], type 1 or type 2 diabetes[68,69] and lower levels of *Prevotella*. In fact, Hjorth *et al.* reported that subjects with increased waist circumference and high *Prevotella/Bacteroides* ratio could easier lose body fat on diets high in fibre and whole grain than subjects with a low *Prevotella/Bacteroides* ratio[70]. In addition, *Prevotella* and *Bacteroides* levels were decreased at baseline in MetS subjects and increased after an intervention with Mediterranean diet and low-fat diet. In contrast, no significant microbiota changes after the dietary intervention were observed in the group of obese subjects without the MetS[66]. Furthermore, studies in mice indicate that *Prevotella* can determine features of the MetS. Colonisation of germ-free mice with a *Prevotella*-rich microbiota from patients with hypertension induced higher blood pressure compared with mice receiving microbiota from a normotensive donor[64].

P. copri colonisation in mice on a high-fat diet promoted increased insulin resistance[63]. Furthermore, Kovatcheva-Datchary *et al.*[71] showed that after a dietary intervention with barley, kernel-based bread (BKB), blood glucose and serum insulin responses improved compared with the group that received white wheat bread. Moreover, they compared the faecal microbiota of individuals who showed the least or no improvement in glucose or insulin responses (non-responders) to those who showed the most pronounced improvement (responders). They observed an abundance of Bacteroidetes (*Prevotella*) and high P/B ratio after BKB intervention in responders, but not in non-responders. *Dorea* and *Roseburia* initially increased at baseline but decreased in responders after BKB intervention. Regarding the SCFA profile, no significant differences were observed between the two groups. To investigate the effect of *Bacteroides* and *Prevotella* species on glucose metabolism, germ-free mice were colonised with human faeces-derived *Bacteroides thetaiotaomicron* and *P. copri* for 14 d and fed a standard chow diet. The levels of *Prevotella* were higher in mice colonised with responder versus non-responder donor microbiota, which suggested that *Prevotella* may contribute to the BKB-induced improvement in glucose metabolism[71]. Similarly, De Vadder *et al.*[72] showed that mice colonised with the succinate producer *P. copri* exhibited metabolic benefits, which could be related to succinate-activated intestinal gluconeogenesis (IGN). They concluded that the activation of IGN is positively correlated with *Prevotella*, which could in fact account for the beneficial metabolic effects such as improved glucose metabolism, by increased glucose tolerance[72].

Likewise, Vitaglione *et al.* showed that after an intervention with whole grain products, levels of *Prevotella* increased and a significant positive correlation was identified between SCFA and the abundance of Bacteroidetes in obese subjects[73].

Furthermore, levels of *Prevotella, Bacteroides* and *Dorea* were favourably correlated with an improved CVD risk factor profile, such as BMI, waist circumference, triglyceride levels and blood pressure, in a randomised crossover study design with 3 g of high molecular weight β-glucan for 5 weeks[22]. In contrast, Kelly *et al.* highlighted recently that some species of *Prevotella* (*Alloprevotella, Paraprevotella, Prevotella 7*) were associated with CVD risk[74].

Moreover, Henao-Meija *et al.* elucidated the role of *Prevotella* in non-alcoholic fatty liver disease, which is a hepatic manifestation of the MetS and has a leading role in triggering chronic liver disease in the Western world. They outlined that a *Prevotella*-rich dysbiosis was finally associated with pathology of the liver[75].

Discussion

The objective of this qualitative systematic review was to evaluate the available data revealing the modulation of the *Prevotella* genus from the gut ecosystem by different dietary habits as well as its implications as a potential biomarker for homeostasis or disease state through its metabolite signature. Moreover, the association with other bacterial species like *Bacteroides* and its role as a dietary fibre fermenter in the gut were also assessed.

The results of this review indicate that some *Prevotella* strains such as *P. copri* or *P. stercorea* were associated with plant-based diets, rich in polysaccharides and fibres, typical for rural communities, whereas the *Bacteroides* genus was correlated with a high-fat, high-protein modern diet, typical in Western countries. Moreover, *P. copri* was highlighted as an important biomarker for diet and lifestyle, due to its abundance in different populations across the world[13,36]. The abundance of *Prevotella* species were shown in many populations with fibre-rich diets, due to its potential to digest and breakdown complex carbohydrates from foods[76]. Therefore, observational studies outlined high levels of *Prevotella* species in Indian[31], Chinese, Kazaks[32], Turks, Moroccans[33], Indonesian, Thai[12], Filipinos[14], African (Malawian, Egyptian[34], Tanzanian and BaAka hunter–gatherers[15,18]) and Venezuelan rural or isolated populations[35], whereas *Bacteroides* were abundant in populations from Western countries in Europe and America[11–14,19,29,34]. In addition, vegetarian, vegan and Mediterranean diets were also linked with high levels of *Prevotella* and a high *Prevotella/Bacteroides* ratio[12].

Evidence reported that these diets might have beneficial effects on human health, in terms of protecting against several diseases such as obesity, type 2 diabetes, inflammatory diseases and CVD[39,41]. These diets were positively correlated with increased

levels of SCFA, which are produced by the intestinal microbiota during fermentation of undigested polysaccharides and have well-documented beneficial roles[77,78]. *Prevotella* species were shown to be positively associated with propionate production that has important roles in preventing weight gain by reducing serum cholesterol and decreasing hepatic lipogenesis[52].

Prevotella strains are classically considered commensal bacteria due to their extensive presence in the healthy human body and their rare involvement in infections. However, emerging studies have linked increased *Prevotella* abundance and specific strains to inflammatory disorders, suggesting that at least some strains exhibit pathobiontic properties[23].

Several limitations should be considered when interpreting the results of this study. First, assessing the way dietary habits or specific nutrients like dietary fibre impact the gut microbial composition could lead to different bias, as the bacterial communities have a great diversity and the interactions between specific nutrients and commensal bacteria from the gut are still not very well known. Moreover, the great inter-individual variability between different populations, the lack of in-depth metagenomic studies and small sample sizes for interventional studies could also increase the risk of bias.

A review from 2017 underlined the interaction between *P. copri* and the immune system, revealing pathobiontic properties such as releasing inflammatory mediators from immune and stromal cells and promoting inflammatory diseases (periodontitis, rheumatoid arthritis, asthma, bacterial vaginosis, HIV infection, the MetS and inflammatory bowel disease)[23]. At the same time, inflammatory diseases are highly heterogeneous and the complex interactions between host genetic risk factors and environmental exposures are also important.

Some studies positively correlated *Prevotella* levels with obesity, type 2 diabetes and NAFLD[65], while others did not find any correlations between these diseases and abundance of *Prevotella*[80,81]. In addition, high levels of *Prevotella* were positively associated with glucose improvement in mice or improved CVD risk factor profile in humans[13,66,67].

Another recent review by Ley[25] analysed the possible beneficial and detrimental implications of *Prevotella* strains from the human gut on host health. It emphasises the importance of better understanding of *Prevotella*'s wide genetic diversity, ecology and interaction with other commensal bacteria from the gut, in order to be able to modulate its levels[25].

Prevotella may only play a part in certain disease endotypes, since they may exhibit different properties due to a high genetic diversity within and between species. These discrepancies in different studies may be due to the complex interrelatedness of the diseases, and additional investigations of immune mechanisms in metabolic disease are needed in humans. Thus, there is a need for more studies in humans to ascertain a causal and potential disease-triggering role for *Prevotella*[23].

Conclusion

As *Prevotella* is a genus with high genetic diversity within and between species, they could explain its abundance in human healthy microbiota and only certain strains may exhibit pathobiontic properties. Nevertheless, there is a need for more studies in humans to ascertain a causal and potential disease-triggering role for *Prevotella* and more in-depth metagenomic studies are needed in order to reveal the health- or disease-modulating properties.

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Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114519000680

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