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Probiotics and prebiotics: prospects for public health and nutritional recommendations

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Probiotics and prebiotics are useful interventions for improving human health through direct or indirect effects on the colonizing microbiota. However, translation of these research findings into nutritional recommendations and public health policy endorsements has not been achieved in a manner consistent with the strength of the evidence. More progress has been made with clinical recommendations. Conclusions include that beneficial cultures, including probiotics and live cultures in fermented foods, can contribute towards the health of the general population; prebiotics, in part due to their function as a special type of soluble fiber, can contribute to the health of the general population; and a number of challenges must be addressed in order to fully realize probiotic and prebiotic benefits, including the need for greater awareness of the accumulated evidence on probiotics and prebiotics among policy makers, strategies to cope with regulatory roadblocks to research, and high-quality human trials that address outstanding research questions in the field.

Keywords: probiotics; prebiotics; dietary guidelines; public health policy; healthy diet

Introduction

This paper addresses the prospects for public health and nutritional recommendations for probiotics and prebiotics. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.[1] A dietary prebiotic is a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefits upon host health.[2] Evidence for health and therapeutic benefits of probiotics include preventing morbidity and mortality associated with necrotizing enterocolitis in preterm, very low-birth-weight newborns;[3,4] preventing antibiotic-associated diarrhea;[5] reducing the duration of infectious diarrhea;[6–8] regulation of intestinal transit;[9] improvement in blood lipid composition;[10] reduced incidence of atopic dermatitis in infants;[11] relief of symptoms of irritable bowel syndrome (IBS);[12,13] and reducing the incidence of common upper respiratory tract infections.[14] Prebiotic benefits include improved calcium absorption with ingestion of prebiotic formulations;[15] reduced duration, incidence, and symptoms of traveller's diarrhea;[16,17] alleviation of IBS symptoms;[18] prevention of specific allergies;[19] reduction in energy intake and markers of insulin resistance and improved body weight management;[20–22] and increased satiety and reduced appetite.[23,24] Additionally, the association of aberrant human microbial colonization patterns with numerous disease states (gastroenteritis, type 2 diabetes, allergy, obesity, and inflammatory bowel diseases, among others) provides important targets

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for probiotic and prebiotic interventions to influence human health.[25]

A group of experts (Table 1) met on June 13, 2013 at the New York Academy of Sciences at a meeting hosted by the International Scientific Association for Probiotics and Prebiotics (ISAPP) to discuss nutritional guidelines and make public health policy recommendations on the topic of "Evidence of probiotic and prebiotic benefits to public health: State of the science and regulatory expectations."

Evidence of benefits relevant to public health

Public health and dietary guidance recommendations focus on disease prevention and health maintenance. In this context, foods containing live microbes (including both foods containing defined probiotics and fermented foods such as yogurts, cheeses, and unpasteurized fermented vegetables), as well as foods containing prebiotics (natural or fortified), are associated with certain health benefits (Table 2). These include maintenance of healthy gut function, improved tolerance to antibiotics, increased calcium absorption, improved markers of glucose homeostasis and lipid metabolism, and overall reduced risk for different chronic diseases. The effect sizes (in many cases with tight confidence intervals) for probiotic interventions across a range of clinical endpoints have been estimated in meta-analyses (Table 3). A recent Norwegian

Table 1. Participants of the workshop to discuss "Evidence of probiotic and prebiotic benefits to public health: state of the science and regulatory expectations" held during the 11th annual meeting of the International Scientific Association for Probiotics and Prebiotics (ISAPP)

Name	Affiliation	Country
Mary Ellen Sanders (co-chair)	Dairy & Food Culture Technologies	United States
Seppo Salminen (co-chair)	University of Turku	Finland
Irene Lenoir-Wijnkoop (co-chair)	Utrecht University/Danone Research	Netherlands/France
Bruno Pot	Center for Infection and Immunity Lille	France
Max Nieuwdorp	University of Amsterdam	The Netherlands
John Hutton	University of York	United Kingdom
Ambroise Martin	University of Lyon	France
Dan Merenstein	Georgetown University Medical Center	United States
Paul Jacques	Tufts University	United States
Ian Jeffery	University College Cork	Ireland
Daniel Tancredi	University of California	United States
Alexandra Meynier	Mondelez International R&D	France
Niklas Larsson	Probi AB	Sweden
George Tzortzis	Clasado	United Kingdom
Gregory Leyer	UAS Laboratories	United States
Melanie Lalonde	BioK+	United Kingdom
John Brett Theroux	Glycom A/S	Denmark
Miguel Freitas	Dannon	United States
Chris Cifelli	Dairy Research Institute	United States
Hideyuki Shibata	Yakult	United States
Stephan Theis	Beneo Institute	Germany
Roula Papaioannou	P&G	United States
Eric Johansen	Chr. Hansen A/S	Denmark
David Keller	Ganeden Biotech	United States
Pascal Molimard	Merck	France
Jingru Li	Kimberly Clark Corporation	United States
Terhi Ahlroos	Valio	Finland
Bryon Petschow	Transcend Biomedical Communications LLC	United States

Table 2. Examples of public health benefits associated with probiotics or foods containing live microbes, fermented dairy products, or prebiotic supplements. Studies include both observational and RCTs

Health Outcome	Dietary	Impact of dietary probiotic or fermented dairy product
Healthy gut function	Probiotic	Improved tolerance to lactose in lactose maldigesters[54]
		Improved gut homeostasis[55]
		Normalized intestinal transit time[9]
	Prebiotic	Reduced duration, incidence, and symptoms of traveller's diarrhea[16,17]
		Reduced episodes of diarrhea in subjects with *Clostridium difficile*–induced diarrhea[56]
		Improved symptomology and gut microbiota composition in irritable bowel syndrome[57]
		Favorable shifts in chronic intestinal inflammation, with relevance for inflammatory bowel disease[58]
Healthy metabolic function	Probiotic	Reduced plasma LDL levels[59,60]
	Prebiotic	Reduction in energy intake and markers of insulin resistance and improved body weight management[20,21]
		Increased satiety and reduced appetite[23,24]
	Fermented dairy products	Reduced risk for type 2 diabetes or improved markers for glucose homeostasis[61–63]
		Less weight gain over time in a prospective study of $>$ 120,000 adults[64]
		Fermented milk reduced risk of CVD[65]
		Cheese intake was significantly associated with decreased CVD risk in women[65]
		High intakes of total and low-fat dairy were associated with a lower risk of CHD among participants without hypertension[66]
		Fermented dairy was associated with a reduced risk of stroke[66]
		Dairy products other than cheese, cheese alone, and calcium were associated with lower diastolic blood pressure[67]
		High yogurt consumption was associated with a significant decrease in diabetes risk[68]
		Yogurt intake was associated with lower common carotid artery intima-media[69]
		Yogurt consumption was associated with reduced weight gain and waist circumference[70]
Healthy immune function	Probiotic	Regulation of the immune system[71,72]
	Prebiotic	Regulation of the immune system[73]
Overall health	Probiotic	Reduced common upper respiratory tract infections[14]
	Prebiotic	Improved mineral absorption and bone mineral density[74–76]
	Fermented dairy products	Reduced risk of overall mortality[77]

family-based study examined associations between consumption of probiotic milk products in pregnancy and infancy with questionnaire-reported atopic eczema, rhinoconjunctivitis, and asthma in 40,614 children.[26] This population-based cohort study demonstrated that consumption of probiotic milk products was related to a reduced incidence of atopic eczema and rhinoconjunctivitis.[26]

Although some meta-analyses pool data from heterogeneous studies (e.g., meta-analyses on probiotics often pool data on different microbial strains), the numerous positive reviews speak to the effectiveness of a broad range of strains, validating the very definition of probiotics: the ability to confer a health benefit on the host. Furthermore, the level of scientific support for both prebiotics and probiotics, combined with an excellent safety profile, is at least comparable to the amount of support available for a variety of other foods or dietary ingredients that are currently recommended for their health benefits (e.g., whole grains[27,28] or monounsaturated fats[29,30]). Growing evidence suggests that some of the benefits observed with whole grain consumption may be attributable to its prebiotic effects.[31–33]

The accumulating data demonstrate sufficient scientific, clinical, and public health weight and relevance to justify modifying current clinical practices or to include probiotics and prebiotics in public health policy and/or nutritional recommendations.

Clinical recommendations for probiotics and prebiotics

Interest in the benefits of probiotics and prebiotics has grown within the medical community as a result of accumulating clinical evidence and increased awareness of products and their use by both healthy subjects and patients. In 2011, the World Gastroenterology Organisation published guidelines for the use of probiotics and prebiotics globally by gastroenterologists and other health professionals.[34] Importantly, the guidelines indicate that there is evidence of efficacy for probiotics and prebiotics and suggest their consideration for clinical use for specific health outcomes, such as antibiotic-associated diarrhea, necrotizing enterocolitis, and atopic dermatitis. Workshops held at Yale University, most recently in 2011, have likewise issued recommendations for probiotic use.[35] A survey of practitioners, mainly specializing in gastroenterology, found that all 56 (100%) physician respondents considered probiotics to be safe for most patients and all but one felt that probiotics have a role in treating gastrointestinal illnesses or symptoms.[36] Family physicians have been advised to pair a probiotic with an antibiotic prescription,[37] and an updated systematic review and meta-analysis supports a change in practice by recommending probiotics to prevent necrotizing enterocolitis in premature infants.[3] Effect sizes estimated in various meta-analyses suggest that cost-effective gains could be generated from probiotic use in improving tolerance to antibiotics, reducing antibiotic prescriptions, decreasing *C. difficile* infection rates in hospitals, and reducing the risk of common upper respiratory tract infections (Table 3). In regards to prebiotic effects, a recent Cochrane review and meta-analysis reported that prebiotics were associated with a significant reduction in eczema; however, the authors state that additional research is warranted before a recommendation can be made.[19] Taken together, probiotics and prebiotics are being recognized as useful therapeutic clinical tools for healthcare providers.

Dietary recommendations for probiotics and prebiotics

Authoritative health policy or nutritional recommendations are mixed in their approach to recommendations of probiotics, prebiotics, or live microbes. The full report of the 2010 Dietary Guidelines Advisory Committee[38] included the following statement: "Foods high in prebiotics and probiotics are linked to health benefits. For example, fiber is a prebiotic linked to health benefits. Many probiotic-containing foods, such as dairy foods, are also linked to health benefits and are recommended for inclusion in the diet." However, the finalized *2010 US Dietary Guidelines* made no reference to probiotics or prebiotics. Similarly, no mention was made of probiotics by EU member states in their answers to open questions concerning 2009 dietary recommendations.[39] In 2004, the French nutrition health policy[40] for seniors with digestive problems stated about yogurts: ". . . they provide lactic acid bacteria that can help you," while the British dietetic association provided a grade B recommendation for probiotics, saying that they are "worth trying." However, various medical organizations are beginning to recommend probiotics for specific clinical conditions[34,37,41–43] or infant nutrition.[44] In

Table 3. Effect sizes of clinical applications of probiotics. Results shown are from systematic review and meta-analyses used where available

Endpoint	Effect reported	Relative risk (RR) or Odds Ratio (OR)	Context	Reference
Reducing incidence of common URTI Reducing antibiotic prescriptions	Probiotics reduced the number of patients with at least one acute URTI episode by 42% and antibiotic prescriptions by 33%	OR 0.58 (95% CI 0.36−0.92)	A systematic review of 10 trials including 3451 participants Meta-analysis of subsets	14
Reducing incidence of antibiotic-associated diarrhea (AAD)	Probiotic administration reduced AAD by 42%	RR 0.58 (95% CI 0.5−0.68)	A systematic review and meta-analysis of 63 randomized controlled trials with 11,811 participants	78,79
Prevention of *C. difficile* infection (CDAD) in hospitalized elderly	Significant reduction of CDAD risk by 64%	RR 0.34 (95% CI 0.24−0.49)	A systematic review and meta-analysis Medical recommendation	80
Prevention of necrotizing enterocolitis (NEC)	Significant reduction in incidence of severe NEC by 65%, with a number needed to treat of 25 Significant reduction in infant mortality by 60% with a number needed to treat of 25	Severe NEC (stage II or more) (typical RR 0.35, 95%, CI 0.24−0.52); mortality (typical RR 0.40, 95% CI 0.27−0.60).	A systematic review and meta-analysis of 16 eligible trials randomizing 2842 infants Medical recommendation	3
Improved symptoms of IBS	Overall symptoms improved	OR 1.6 (95% CI 1.2−2.2)	A systematic review and meta-analysis Dietary recommendation, medical recommendation	12,13
Excessive infant crying	*L. reuteri* DSM 17938 decreased crying time	−65 minutes/day (95% CI −86 to −44)	A systematic review and meta-analysis of probiotics; positive association for improvement found only for subgroup analysis on *L. reuteri* DSM 17938, not on probiotics as a whole Dietary recommendation, medical recommendation	81

Continued

Table 3. ***Continued***

Endpoint	Effect reported	Relative risk (RR) or Odds Ratio (OR)	Context	Reference
Prevention of atopic dermatitis in infants	Probiotic use decreased the incidence of atopic dermatitis by 21%	RR 0.79 (95% CI 0.71−0.88)	A systematic review and meta-analysis Dietary recommendation, medical recommendation	11
Reduced LDL cholesterol in hypercholesterolaemic adults	Cholesterol levels reduced Total cholesterol: −6.40 mg dl^{-1} LDL cholesterol: −4.90 mg dl^{-1} HDL cholesterol: −0.11 mg dl^{-1}	(95% CI −9.93 to −2.87) (95% CI −7.91 to −1.90) (95% CI −1.90 to 1.69)	Meta-analysis of 13 human clinical trials of 485 participants with high, borderline high, and normal cholesterol levels	10

addition, there is an increasing awareness that even small benefits of probiotics and prebiotics can positively affect healthcare expenditures, not only in hospitals but also in the community (Table 3).[33,34]

Types of evidence used to support public health policy recommendations

Health policy recommendations have multiple purposes. They aim to provide guidelines for healthcare professionals on safe, high-quality, preventive or therapeutic approaches to patient care, while encouraging cost-effective management. In this mostly clinical setting, randomized controlled trials (RCTs) and subsequent meta-analyses are considered to be the gold standard for providing reliable data on efficacy and effectiveness. Another purpose of health policies is the promotion and improvement of the health status in the general population. The information obtained through RCTs under strict protocol conditions with well-defined (restrictive) inclusion criteria can be enhanced by sets of evidence that reflect more heterogeneous populations and contextual aspects.[45,46] Many modern nutrition intervention trials are now designed in accordance with good clinical practice standards. While this will increase our understanding of causality between food consumption and health, it does not always provide complete information related to the multifactorial confounders that are observed in the real-world environment.[47–49] Adapted approaches to grading evidence have been proposed,[50] which consider the different types of research needed to answer different types of clinical questions. Therefore, both RCTs and well-controlled observational studies are regularly used to inform public policy.

Overall outcomes of the expert meeting

For nutrition or public health policy recommendations to incorporate probiotics or prebiotics, the ISAPP group recommended (1) increasing efforts by stakeholders in the probiotic and prebiotic fields to communicate to policy-setting organizations the value of the broad concept of beneficial cultures to health of the general population, which includes broad beneficial effects of probiotics; and (2) clarity from government entities (or the committees charged with advising them) on the type and level of evidence that would be acceptable to support health policy recommendations on probiotics and prebiotics.

Broad concept of beneficial cultures

The term probiotic has divergent meanings among scientific, regulatory, and consumer audiences. The widely accepted scientific definition of probiotics[1] has generally been interpreted to apply to defined strains of well-characterized microbes that are the subject of controlled human studies. However, we conclude that evidence is sufficient to support the concept of *potentially beneficial live microbes*, for which some plausible benefits are reasonable to

expect, including strains of microbes that have not been specifically tested for health benefits but are members of well-studied genera or species. Evidence for this conclusion comes from three sources: (1) controlled intervention studies with defined probiotics; (2) observational studies with fermented dairy products; and (3) human microbiome research, which identifies numerous human disease conditions associated with aberrant colonizing microbiota. Whether such use falls under the umbrella definition of probiotic is a discussion that is needed within the broader scientific community.

The primary purpose of this concept would be to inform the consumer of the safety and possible benefits of consuming high levels of particular types of live microbial cultures, which are traditionally and/or naturally present in our foods. This conceptual group of products, however, could be distinguished from other types of products containing defined microbial strains supported by scientific evidence for specific indications consistent with regulatory requirements. Current regulatory classifications for probiotics include drug, food, dietary (nutritional) supplement, or medical food, based on the intended use of the product as defined by claims, labeling, promotions, and endpoints of clinical investigations, although the separation between the different categories is not always clear. The regulatory classification of more generalized benefits or claims, however, would be limited to foods and dietary/nutritional supplements.

For prebiotics, the available evidence from clinical intervention studies, comprehensive reviews, and meta-analyses is more limited than for probiotics. Available evidence supports the notion that prebiotics provide health benefits to infants at risk of food allergy and to subjects with IBS-type symptoms or bone mineral issues. People suffering from IBS lack satisfactory options for managing symptoms and they stand to benefit from information on effective dietary options for their condition. Recent evidence from intervention studies further supports the beneficial effects of particular food products with prebiotic properties on energy homeostasis, satiety regulation, and body weight gain.[51]

Collectively, the available evidence suggests that authorities with responsibility for developing dietary guidelines and public health recommendations (e.g., U.S. Dietary Guidelines Advisory Committee, European Food Safety Authority, and others) should consider the following: (1) the balance of evidence with regard to practical beneficial impacts of foods containing live microbes and probiotics as part of the healthy diet on long-term health maintenance and reduction in disease risk; and (2) the balance of evidence with regard to practical beneficial impacts of dietary prebiotics to promote intestinal health, improve bone mineral density, and contribute to body weight management.

Clarity in the evaluation and translation of the available evidence

Dietary recommendations for probiotics and prebiotics can be justified based on the currently available scientific evidence. However, gaps do exist and a better understanding is needed of mechanisms of action, translation of results from strictly controlled clinical trials into real life settings, methodology for population interventions that manage confounding factors, and analysis to quantify possible economic benefits to public health policy recommendations.

Efficient translation of science into useful public health messages is paramount. The average citizen is increasingly health conscious and searches for information on health-enhancing benefits of food in general, with particular attention to probiotics and prebiotics. Clear, evidence-based messages (such as those previously mentioned)[34–43] are much preferred over what can be gleaned through less reliable sources, such as internet surfing.[52] When considering the outstanding safety record amassed for probiotics consumed by the general population, it is important to remember that a strong recommendation may be made when the plausible potential benefits clearly outweigh plausible potential risks.

Challenges exist in terms of effectively engaging government agencies and clinical societies to consider probiotics and prebiotics in nutritional guidelines and health policy recommendations. Scientific credibility of probiotics and prebiotics will gain widespread recognition and endorsement by healthcare providers and public health policy institutions with continued commitment by researchers to fully register trials a priori (e.g., clinicaltrials.gov), to appropriately design and carry out studies, and to report studies in an unbiased fashion using established guidelines (e.g., CONSORT[53]). As additional evidence is generated, multidisciplinary dialogue among regulatory authorities, clinical societies, thought leaders, and healthcare providers

should lead to effective communication of the science to stakeholders.

Recommendations

The following action steps are needed to help advance the science and recognition among healthcare providers of the value of probiotics and prebiotics in a public health context:

1. Refine the concept of probiotic:
   (a) Preserve the FAO/WHO definition of probiotics, which encompasses strain-specific effects for precise health claims.
   (b) Promote the category of *live microbes associated with fermented foods* that provide more generalized physiological benefits for overall health.
2. Stimulate research into probiotics and prebiotics. Properly controlled, well-conducted, and accurately reported human intervention studies are needed to address outstanding research questions, such as clarifying the magnitude of expected effects, characterizing responders and non-responders, and exploring important new health endpoints. Emerging evidence suggests that probiotics and prebiotics may play a role in alleviating type 2 diabetes mellitus and cardiovascular events like myocardial infarction. Clinical trials are needed. The use of accepted surrogate endpoints when available, such as oral glucose tolerance tests or blood lipid profiles, will facilitate such research.
3. Promote existing standards for conducting high-quality human trials. Reinforce the importance of conducting and reporting human studies according to best practices (e.g., CONSORT) and minimizing bias through a priori registration of trials. This will provide the primary means of establishing causality.
4. Recognize the value of observational studies, designed to minimize bias, for forming hypotheses to test in RCTs and providing supplementary, real world evidence of efficacy.
5. Evaluate health economic endpoints to aid in documenting societal benefits as well as long term public health consequences. Population-wide health technology assessments and quality-of-life assessments are also needed to better quantify the public health benefits.
6. Expand public policy/dietary guidelines. Include recommendations for consumption of foods containing live microbes and prebiotics, especially in cases where the preponderance of evidence indicates improved health outcomes (e.g., yogurt and chronic disease risk, (Table 2)).
7. Clarify regulatory classifications. Work to shift regulatory attitudes towards probiotics and prebiotics to better enable communication of research relevant to the general population and in-need subgroups within the context of safe, effective probiotic and prebiotic interventions and to continue to conduct research on probiotic foods and supplements.

Conflicts of interest

M.E.S. consults with numerous food and dietary supplement companies conducting business in the probiotic industry. She does not have any ownership role or serve on governing boards for any company. She serves on Scientific Advisory Boards for The Dannon Company and New Chapter Inc. and on the Yogurt in Nutrition Board, sponsored by Danone Institute International. I.L.W. is employed by Danone Research. S.S. has received honoraria as an invited speaker in scientific meetings sponsored by food companies. D.M. has been an expert witness for numerous probiotic class action lawsuits. B.W. P. consults with several medical food companies and is a paid medical writer. B.P. consults occasionally for probiotic-producing companies and obtained fundamental research and travel funding from different companies but has no ownership role for any company. P.F.J is a member of the Bay State Milling Nutrition and Science Advisory Council and the Dannon Yogurt Advisory Board. C.J.C. works for the Dairy Research Institute. GRG has had research funding from several probiotic and prebiotic companies, none of which influenced the content herein.

References

1. FAO/WHO. 2001. Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria. http://www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf
2. Gibson, G.R., K.P. Scott, R.A. Rastall, *et al.* 2010. Dietary prebiotics: current status and new definition. *Food Science and Technology Bulletin: Functional Foods* **7:** 1–19.

3. Alfaleh, K., J. Anabrees, D. Bassler, *et al.* 2011. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database Syst. Rev.* CD005496.
4. Jacobs, S.E., J.M. Tobin, G.F. Opie, *et al.* 2013. Probiotic Effects on Late-onset Sepsis in Very Preterm Infants: A Randomized Controlled Trial. *Pediatrics* **132:** 1055–1062.
5. Goldenberg, J.Z., S.S. Ma, J.D. Saxton, *et al.* 2013. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. *Cochrane Database Syst. Rev.* **5:** CD006095.
6. Bernaola, Aponte G., C.A. Bada Mancilla, N.Y. Carreazo, *et al.* 2013. Probiotics for treating persistent diarrhoea in children. *Cochrane Database Syst. Rev.* **8:** CD007401.
7. Dinleyici, E.C., M. Eren, M. Ozen, *et al.* 2012. Effectiveness and safety of Saccharomyces boulardii for acute infectious diarrhea. *Expert Opin. Biol. Ther.* **12:** 395–410.
8. Allen, S.J., E.G. Martinez, G.V. Gregorio, *et al.* 2010. Probiotics for treating acute infectious diarrhoea. *Cochrane Database Syst. Rev.* CD003048.
9. Miller, L.E. & A.C. Ouwehand. 2013. Probiotic supplementation decreases intestinal transit time: meta-analysis of randomized controlled trials. *World J. Gastroenterol.* **19:** 4718–4725.
10. Guo, Z., X.M. Liu, Q.X. Zhang, *et al.* 2011. Influence of consumption of probiotics on the plasma lipid profile: a meta-analysis of randomised controlled trials. *Nutr. Metab. Cardiovasc. Dis.* **21:** 844–8450.
11. Pelucchi, C., L. Chatenoud, F. Turati, *et al.* 2012. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. *Epidemiology* **23:** 402–414.
12. Hoveyda, N., C. Heneghan, K.R. Mahtani, *et al.* 2009. A systematic review and meta-analysis: probiotics in the treatment of irritable bowel syndrome. *BMC Gastroenterol* **9:** 15.
13. Moayyedi, P., A.C. Ford, N.J. Talley, *et al.* 2010. The efficacy of probiotics in the treatment of irritable bowel syndrome: a systematic review. *Gut.* **59:** 325–332.
14. Hao, Q., Z. Lu, B.R. Dong, *et al.* 2011. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database Syst. Rev.* CD006895.
15. Whisner, C.M., B.R. Martin, M.H. Schoterman, *et al.* 2013. Galacto-oligosaccharides increase calcium absorption and gut bifidobacteria in young girls: a double-blind cross-over trial. *Br. J. Nutr.* 1–12.
16. Cummings, J.H., S. Christie & T.J. Cole. 2001. A study of fructo oligosaccharides in the prevention of travellers' diarrhoea. *Aliment. Pharmacol Ther.* **15:** 1139–1145.
17. Drakoularakou, A., G. Tzortzis, R.A. Rastall, *et al.* 2010. A double-blind, placebo-controlled, randomized human study assessing the capacity of a novel galacto-oligosaccharide mixture in reducing travellers' diarrhoea. *Eur. J. Clin. Nutr.* **64:** 146–152.
18. Whelan, K. 2011. Probiotics and prebiotics in the management of irritable bowel syndrome: a review of recent clinical trials and systematic reviews. *Curr. Opin. Clin. Nutr. Metab. Care* **14:** 581–587.
19. Osborn, D.A. & J.K. Sinn. 2013. Prebiotics in infants for prevention of allergy. *Cochrane Database Syst. Rev.* **3:** CD006474.
20. Vulevic, J., A. Juric, G. Tzortzis, *et al.* 2013. A mixture of trans-galactooligosaccharides reduces markers of metabolic syndrome and modulates the fecal microbiota and immune function of overweight adults. *J. Nutr.* **143:** 324–331.
21. Parnell, J.A. & R.A. Reimer. 2009. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. *Am. J. Clin. Nutr.* **89:** 1751–1759.
22. Delzenne, N.M., A.M. Neyrinck & P.D. Cani. 2011. Modulation of the gut microbiota by nutrients with prebiotic properties: consequences for host health in the context of obesity and metabolic syndrome. *Microb. Cell Fact.* **10**(Suppl 1)**:** S10.
23. Cani, P.D., E. Lecourt, E.M. Dewulf, *et al.* 2009. Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. *Am. J. Clin. Nutr.* **90:** 1236–1243.
24. Cani, P.D., E. Joly, Y. Horsmans, *et al.* 2006. Oligofructose promotes satiety in healthy human: a pilot study. *Eur. J. Clin. Nutr.* **60:** 567–572.
25. Backhed, F., C.M. Fraser, Y. Ringel, *et al.* 2012. Defining a healthy human gut microbiome: current concepts, future directions, and clinical applications. *Cell Host. Microbe.* **12:** 611–622.
26. Bertelsen, R.J., A.L. Brantsaeter, M.C. Magnus, *et al.* 2013. Probiotic milk consumption in pregnancy and infancy and subsequent childhood allergic diseases. *J. Allergy. Clin. Immunol.* [Epub ahead of print] PMID: 24034345.
27. Ye, E.Q., S.A. Chacko, E.L. Chou, *et al.* 2012. Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. *J. Nutr.* **142:** 1304–1313.
28. McKeown, N.M., P.F. Jacques, C.J. Seal, *et al.* 2013. Whole grains and health: from theory to practice–highlights of The Grains for Health Foundation's Whole Grains Summit 2012. *J. Nutr.* **143:** 744S–758S.
29. Schwingshackl, L., B. Strasser & G. Hoffmann. 2011. Effects of monounsaturated fatty acids on cardiovascular risk factors: a systematic review and meta-analysis. *Ann. Nutr. Metab.* **59:** 176–186.
30. Estruch, R., E. Ros, J. Salas-Salvado, *et al.* 2013. Primary prevention of cardiovascular disease with a Mediterranean diet. *N. Engl. J. Med.* **368:** 1279–1290.
31. Higgins, J.A. 2012. Whole grains, legumes, and the subsequent meal effect: implications for blood glucose control and the role of fermentation. *J. Nutr. Metab.* **2012:** 829–238.
32. Borneo, R. & A.E. Leon. 2012. Whole grain cereals: functional components and health benefits. *Food Funct.* **3:** 110–119.
33. Fardet, A. 2010. New hypotheses for the health-protective mechanisms of whole-grain cereals: what is beyond fibre? *Nutr. Res. Rev.* **23:** 65–134.
34. WGO Practice Guideline–Probiotics and Prebiotics. 2011. http://www.worldgastroenterology.org/probiotics-prebiotics.html

35. Floch, M.H., W.A. Walker, K. Madsen, *et al.* 2011. Recommendations for probiotic use-2011 update. *J. Clin. Gastroenterol.* **45**(Suppl)**:** S168–S171.
36. Williams, M.D., C.Y. Ha & M.A. Ciorba. 2010. Probiotics as therapy in gastroenterology: a study of physician opinions and recommendations. *J. Clin. Gastroenterol.* **44:** 631–636.
37. Rodgers, B., K. Kirley & A. Mounsey. 2013. PURLs: prescribing an antibiotic? Pair it with probiotics. *J. Fam. Pract.* **62:** 148–150.
38. Dietary Guidelines Advisory Committee Report. 2010. http://www.cnpp.usda.gov/DGAs2010-DGACReport.htm
39. Scientific Opinion on Establishing Food-Based Dietary Guidelines. 2010. http://www.efsa.europa.eu/en/efsajournal/pub/1460.htm
40. French National Nutrition and Health Program. 2010. http://www.gken.org/Synopses/CI_10008.pdf
41. Guarino, A., F. Albano, S. Ashkenazi, *et al.* 2008. European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases: Evidence-based Guidelines for the Management of Acute Gastroenteritis in Children in Europe. http://espghan.med.up.pt/pdf_files/ESPGHAN_ESPID_Guidelines%20for%20the%20Management%20of%20Acute%20diarrhea_JPGN2008.pdf
42. Christian, Braegger B., A. Chmielewska, T. Decsi, *et al.* 2011. Supplementation of Infant Formula With Probiotics and/or Prebiotics: A Systematic Review and Comment by the ESPGHAN Committee on Nutrition. http://www.espghan.med.up.pt/position_papers/JPGN_CoN_Infant_formula_probotics_prebiotics.pdf
43. Hungin, A.P., C. Mulligan, B. Pot, *et al.* 2013. Systematic review: probiotics in the management of lower gastrointestinal symptoms in clinical practice – an evidence-based international guide. *Aliment. Pharmacol. Ther.* **38:** 864–886.
44. Mugambi, M.N., A. Musekiwa, M. Lombard, *et al.* 2012. Synbiotics, probiotics or prebiotics in infant formula for full term infants: a systematic review. *Nutr. J.* **11:** 81.
45. Dobrow, M.J., V. Goel, L. Lemieux-Charles, *et al.* 2006. The impact of context on evidence utilization: a framework for expert groups developing health policy recommendations. *Soc. Sci. Med.* **63:** 1811–1824.
46. Teutsch, S.M. & J.E. Fielding. 2013. Rediscovering the core of public health. *Annu. Rev. Public Health* **34:** 287–299.
47. Romio, S., M. Sturkenboom & G. Corrao. 2013. Real-world data from the health decision maker perspective. What are we talking about? *Epidemiology Biostatistics and Public Health* **10**(3). http://ebph.it/article/download/8979/8115
48. Lock, K., R.D. Smith, A.D. Dangour, *et al.* 2010. Health, agricultural, and economic effects of adoption of healthy diet recommendations. *Lancet.* **376:** 1699–1709.
49. Ioannidis, J.P. 2013. Implausible results in human nutrition research. *BMJ* **347:** f6698.
50. Glasziou P., J.P. Vandenbroucke & I. Chalmers. 2004. Assessing the quality of research. *BMJ* **328:** 39–41.
51. Roberfroid, M., G.R. Gibson, L. Hoyles, *et al.* 2010. Prebiotic effects: metabolic and health benefits. *Br. J. Nutr.* **104**(Suppl 2)**:** S1–S63.
52. Brinich, M.A., M.B. Mercer, & R.R. Sharp. 2013. An analysis of online messages about probiotics. *BMC Gastroenterol.* **13:** 5.
53. CONSORT Statement Website. 2013. www.consort-statement.org/
54. de Vrese, M., A. Stegelmann, B. Richter, *et al.* 2001. Probiotics–compensation for lactase insufficiency. *Am. J. Clin. Nutr.* **73:** 421S–429S.
55. van Baarlen, P., J.M. Wells & M. Kleerebezem. 2013. Regulation of intestinal homeostasis and immunity with probiotic lactobacilli. *Trends Immunol.* **34:** 208–215.
56. Lewis, S., S. Burmeister, & J. Brazier. 2005. Effect of the prebiotic oligofructose on relapse of Clostridium difficile-associated diarrhea: a randomized, controlled study. *Clin. Gastroenterol. Hepatol.* **3:** 442–448.
57. Silk, D.B., A. Davis, J. Vulevic, *et al.* 2009. Clinical trial: the effects of a trans-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritable bowel syndrome. *Aliment. Pharmacol. Ther.* **29:** 508–518.
58. Leenen, C.H. & L.A. Dieleman. 2007. Inulin and oligofructose in chronic inflammatory bowel disease. *J. Nutr.* **137:** 2572S–2575S.
59. Jones, M.L., C.J. Martoni, M. Parent, *et al.* 2012. Cholesterol-lowering efficacy of a microencapsulated bile salt hydrolase-active Lactobacillus reuteri NCIMB 30242 yoghurt formulation in hypercholesterolaemic adults. *Br. J. Nutr.* **107:** 1505–1513.
60. Amar, J., C. Lange, G. Payros, *et al.* 2013. Blood microbiota dysbiosis is associated with the onset of cardiovascular events in a large general population: the D.E.S.I.R. study. *PLoS One* **8:** e54461.
61. Tong, X., J.Y. Dong, Z.W. Wu, *et al.* 2011. Dairy consumption and risk of type 2 diabetes mellitus: a meta-analysis of cohort studies. *Eur. J. Clin. Nutr.* **65:** 1027–1031.
62. Struijk, E.A., A. Heraclides, D.R. Witte, *et al.* 2013. Dairy product intake in relation to glucose regulation indices and risk of type 2 diabetes. *Nutr. Metab. Cardiovasc. Dis.* **23:** 822–828.
63. Sluijs, I., N.G. Forouhi, J.W. Beulens, *et al.* 2012. The amount and type of dairy product intake and incident type 2 diabetes: results from the EPIC-InterAct Study. *Am. J. Clin. Nutr.* **96:** 382–390.
64. Mozaffarian, D., T. Hao, E.B. Rimm, *et al.* 2011. Changes in diet and lifestyle and long-term weight gain in women and men. *N. Engl. J. Med.* **364:** 2392–2404.
65. Sonestedt, E., E. Wirfalt, P. Wallstrom, *et al.* 2011. Dairy products and its association with incidence of cardiovascular disease: the Malmo diet and cancer cohort. *Eur. J. Epidemiol.* **26:** 609–618.
66. Dalmeijer, G.W., E.A. Struijk, Y.T. van der Schouw, *et al.* 2013. Dairy intake and coronary heart disease or stroke–a population-based cohort study. *Int. J. Cardiol.* **167:** 925–929.
67. Fumeron, F., A. Lamri, N. Emery, *et al.* 2011. Dairy products and the metabolic syndrome in a prospective study, DESIR. *J. Am. Coll. Nutr.* **30:** 454S–463S.
68. Margolis, K.L., F. Wei, I.H. de Boer, *et al.* 2011. A diet high in low-fat dairy products lowers diabetes risk in postmenopausal women. *J. Nutr.* **141:** 1969–1974.
69. Ivey, K.L., J.R. Lewis, J.M. Hodgson, *et al.* 2011. Association between yogurt, milk, and cheese consumption and common carotid artery intima-media thickness and cardiovascular disease risk factors in elderly women. *Am. J. Clin. Nutr.* **94:** 234–239.

70. Wang, H., L.M. Troy, G.T. Rogers, *et al.* 2013. Longitudinal association between dairy consumption and changes of body weight and waist circumference: the Framingham Heart Study. *Int. J. Obes. (Lond)*. doi: 10.1038/ijo.2013.78. [Epub ahead of print]
71. Brestoff, J.R. & D. Artis. 2013. Commensal bacteria at the interface of host metabolism and the immune system. *Nat. Immunol.* **14:** 676–684.
72. Chu, H. & S.K. Mazmanian. 2013. Innate immune recognition of the microbiota promotes host-microbial symbiosis. *Nat. Immunol.* **14:** 668–675.
73. Lomax, A.R. & P.C. Calder. 2009. Prebiotics, immune function, infection and inflammation: a review of the evidence. *Br. J. Nutr.* **101:** 633–658.
74. Abrams, S.A., K.M. Hawthorne, O. Aliu, *et al.* 2007. An inulin-type fructan enhances calcium absorption primarily via an effect on colonic absorption in humans. *J. Nutr.* **137:** 2208–2212.
75. Holloway, L., S. Moynihan, S.A. Abrams, *et al.* 2007. Effects of oligofructose-enriched inulin on intestinal absorption of calcium and magnesium and bone turnover markers in postmenopausal women. *Br. J. Nutr.* **97:** 365–372.
76. Whisner, C.M., B.R. Martin, M.H. Schoterman, *et al.* 2013. Galacto-oligosaccharides increase calcium absorption and gut bifidobacteria in young girls: a double-blind cross-over trial. *Br. J. Nutr.* **110:** 1292–1303.
77. Soedamah-Muthu, S.S., G. Masset, L. Verberne, *et al.* 2012. Consumption of dairy products and associations with incident diabetes, CHD and mortality in the Whitehall II study. *Br. J. Nutr.* 1–9.
78. Hempel, S., S.J. Newberry, A.R. Maher, *et al.* 2012. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA* **307:** 1959–1969.
79. Carvalho, B.M., D. Guadagnini, D.M. Tsukumo, *et al.* 2012. Modulation of gut microbiota by antibiotics improves insulin signalling in high-fat fed mice. *Diabetologia* **55:** 2823–2834.
80. Johnston, B.C., S.S. Ma, J.Z. Goldenberg, *et al.* 2012. Probiotics for the prevention of Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. *Ann. Intern. Med.* **157:** 878–888.
81. Sung V., S. Collett, T. de Gooyer, *et al.* 2013. Probiotics to prevent or treat excessive infant crying: systematic review and meta-analysis. *JAMA Pediatr.* **167:** 1150–1157.