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Dietary fibre and health: the story so far

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The present paper reviews progress in research on dietary fibre and human health over the past five decades. There is now convincing evidence from prospective cohort studies that diets low in dietary fibre are associated with increased risk of common non-communicable diseases including CVD, type 2 diabetes and colorectal cancer. These findings provide strong support for hypotheses proposed by Denis Burkitt 50 years ago, based on very limited evidence but with considerable imagination and insight. For the first two to three decades of this period, research on dietary fibre was hampered by the lack of consensus about the definition, and measurement, of this complex and diverse dietary component and by the lack of appropriate tools for investigating the gut microbiome that is central to understanding mechanisms of action. Recent technical and scientific advances in microbiome research (based on fast, low-cost, DNA sequencing) are facilitating investigation of the associations between dietary fibre, the gut microbiome and human health. Current challenges include the need for agreement about the characteristics of a healthy gut microbiome. Although the health benefits attributed to higher dietary fibre intake are likely to be shared with most types of dietary fibre, one should anticipate that different sources of dietary fibre and the other components (resistant starch and non-digestible oligosaccharides) that make up dietary fibre will have characteristically different effects on human physiology and disease risk. In conclusion, population-level intakes of dietary fibre are low and there is a public health priority to develop and implement more effective interventions to increase intake.

Key words: Dietary fibre: Denis Burkitt: Cancer prevention

Dietary fibre is one of the top four nutrients (the others are sodium, total fat and saturated fat) that are included frequently in dietary metrics for assessing links between eating patterns and human health[1]. In addition, the recognition that most people, globally, have relatively low intakes of dietary fibre has led to high profile efforts to find ways of supporting individuals to increase their dietary fibre intake[2]. This is a remarkable success story for an area of nutrition research that was ignored until about 50 years ago. The Nutrition Society played a pioneering role in stimulating research on dietary fibre and human health by holding the first symposium on the topic in 1973[3]. Among the speakers at that symposium was Denis Burkitt who deserves much of the

Abbreviations: CRC, colorectal cancer; FAP, familial adenomatous polyposis; GI, gastrointestinal; LS, Lynch syndrome; RCT, randomised controlled trial; RS, resistant starch.

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credit for galvanising early research on dietary fibre and health[4].

Denis Burkitt and research on dietary fibre and health

For much of his professional life, Denis Burkitt had an unremarkable career. After graduating in medicine from Trinity College Dublin in 1935, he completed his surgical training in the UK and in Ireland before being employed as a general surgeon in several hospitals in England and Wales. Driven by his Christian faith and influenced by family members who worked overseas in what was then the British Empire, Burkitt's ambition was to serve humanity. This he did, initially as a surgeon in the British army in Kenya during the Second World War, and later as a Medical Officer or Government Surgeon based in Uganda and employed by the Colonial Medical Service[4]. Although he had no formal training as a scientist, Burkitt was an observant, thoughtful and remarkably persistent individual. When he was introduced to the case of a child with a massively swollen face with 'bizarre' lesions involving both sides of both jaws, he was baffled but intrigued. This incident initiated a series of largely non-scientific, but highly intuitive and informative, investigations by Burkitt that led, very rapidly, to the discovery of a novel childhood cancer, caused by the Epstein–Barr virus, that now bears his name – Burkitt's lymphoma[4].

Much of this pioneering work was illustrated, and new ideas were developed and tested, by drawing maps of the occurrence of the unusual childhood cancer at different locations throughout Africa. Later, Burkitt used the same approach when he began to think about the reasons for the very different patterns of diseases, including diseases that he had treated surgically, in Africa compared with the UK. Influenced by ideas promoted by Peter Cleave, in a paper titled 'Related disease- related cause?', Burkitt proposed the radical idea that a diverse range of diseases and conditions that were common in the Western world including CHD, obesity, diabetes, dental caries, various vascular disorders and large bowel conditions notably cancer, appendicitis and diverticulosis had a common cause[5–7] (Fig. 1). Even more radically, building on work by Peter Cleave, two other physicians (G. D. Campbell and Hugh Trowell), a surgeon (Neil Painter) and a biochemist (Alec Walker), Burkitt hypothesised that it was the lack of fibre in the diet that increased risk of these apparently unconnected diseases[6–8]. Importantly, Burkitt advanced ideas for the mechanisms through which dietary fibre could influence several physiological processes in the gut that could lead to the apparently diverse non-communicable diseases that he associated with fibre-deficient diets in economically developed societies (Fig. 1).

Burkitt conducted a series of epidemiological studies and small-scale experimental studies to test his hypothesis that dietary fibre had profound effects on gut function and used those findings to support his central idea that inadequate intakes of dietary fibre cause many common non-communicable diseases[9]. He suspected that low stool weight and long transit times were causal for gut diseases such as constipation and colorectal cancer (CRC) and he showed clearly that stool weight and gut transit time were both influenced by dietary fibre intake[9]. Although these findings and his other academic

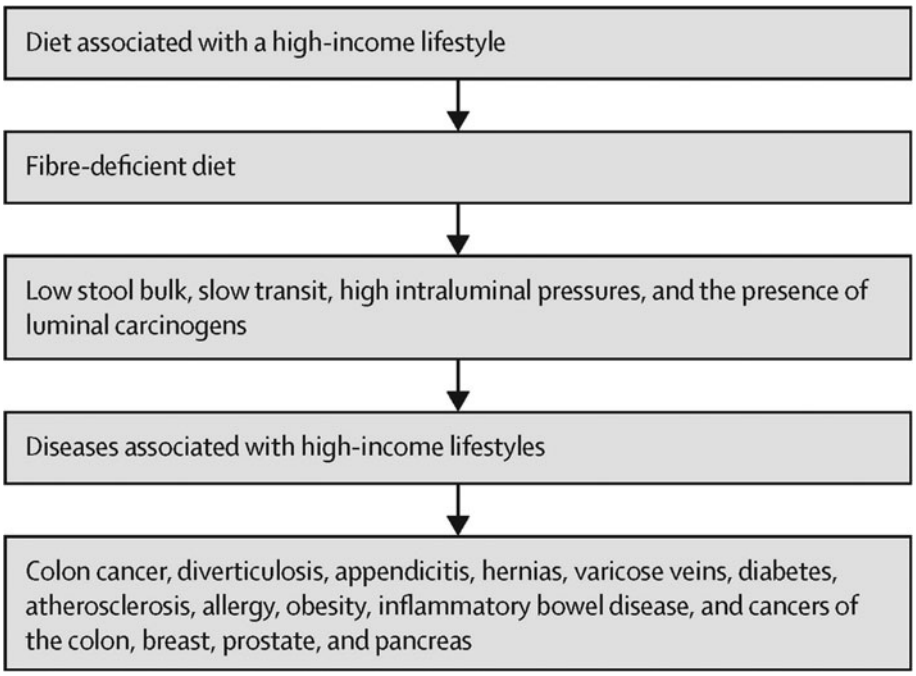

Fig. 1. Rationale for Burkitt's hypothesis that multiple non-communicable diseases may be caused by the lack of fibre in the diet (reprinted with permission from O'Keefe[7]).

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publications were influential, it is probable that his frequent lectures around the globe and, especially, his popular writing (notably his book 'Don't forget fibre in your diet'[10]) played a more significant role in raising awareness of dietary fibre and its importance for health among scientists, health professionals, policy makers and the public[4].

Despite the very limited scientific evidence available to Burkitt when he proposed his dietary fibre hypothesis, findings from subsequent research have supported most of his core ideas. For example, a recent systematic review and meta-analysis of prospective cohort data from >20 million person-years of observation, involving >20 000 cases, has shown a clear inverse association between dietary fibre intake and relative risk of CRC[11]. There are similar dose-dependent, inverse associations between dietary fibre intake and risk of type 2 diabetes[12] and CVD[13]. These findings are strengthened by a very recent meta-analysis of prospective cohort studies examining associations between dietary fibre and chronic disease risk that has shown reduced incidence of CVD (including CHD and stroke), type 2 diabetes and CRC in those with higher dietary fibre intakes[2]. In addition, higher fibre intakes were associated with reduced all-cause mortality and reduced mortality from CVD, CHD and cancer[2].

In their 2015 report on 'Carbohydrates and health'[14], the Scientific Advisory Committee on Nutrition concluded that there is strong evidence from prospective cohort studies that increased intakes of total dietary fibre, and particularly cereal fibre and wholegrain, are associated with lower risk of cardio-metabolic disease and CRC. However, in randomised controlled trials (RCTs), there is no effect of dietary fibre intake on risk factors for CVD or for type 2 diabetes[14]. Although there was some evidence from trials of effects of dietary fibre on constipation and on related physiological outcomes including intestinal transit times and faecal mass, the Scientific Advisory Committee on Nutrition did not discuss any evidence from RCTs on cancer outcomes[14].

Dietary fibre: what is it and how can it be measured?

Fifty years ago, Burkitt and colleagues who were working on dietary fibre and health had a significant problem. There was no clear definition of what dietary fibre is and no reliable methods for its measurement. This meant that there were no data on dietary fibre in tables of food composition which was a severe impediment for anyone attempting to use epidemiological approaches for investigating links between dietary fibre intake and disease. In contrast, there was a long history of research on fibre (often described as crude fibre) in animal nutrition. This was because of the well-recognised impact of fibre on digestion of feeds by monogastric animals and the importance of fibre as a source of energy in diets for ruminants. Consequently, there was considerable focus on methods for fibre determination with major advances made by Peter Van Soest who introduced the use of detergents in assays for the rapid determination of fibre in animal feeds[15].

Nearly 100 years ago, in his pioneering work on the composition of human foods, McCance recognised that not all the carbohydrate in human foods was digestible and he termed the non-digestible component 'unavailable carbohydrate'[16]. However, McCance did not use the term 'dietary fibre' and its introduction to the scientific and medical literature is attributed to Hipsley in 1953 who proposed that higher intakes of dietary fibre may reduce the risk of pregnancy toxaemia (now known as preeclampsia)[17]. Hipsley stated that dietary fibre includes lignin, cellulose and the hemicelluloses[17]. Hugh Trowell, one of Burkitt's collaborators, defined dietary fibre as '… the skeletal remains of plant cells that are resistant to hydrolysis by the enzymes of man…'[18]. David Southgate, McCance's successor as compiler of the UK food composition tables, took up the challenge of defining and assaying dietary fibre. He suggested that '… the definition of dietary fibre is essentially a philosophical one and the term applies to all the indigestible polysaccharides and lignin that may be imagined to reach the large intestine…'[19]. Southgate, in agreement with Trowell, considered that the polysaccharides and associated substances, principally lignin, that make up plant cell walls are fundamental components of dietary fibre and he went on to develop analytical methods for assaying dietary fibre in foods[19]. The resulting data for dietary fibre (known as 'Southgate fibre') were used in compiling the first UK food composition tables that provided information on dietary fibre content.

However, this did not settle the issue. In 1973, the gastroenterologist, John Cummings, published an extensive and critical review of the literature from both human and animal model studies and concluded that '… Dietary fibre is an important component of our food. Its role in the gut has been underestimated because of an incomplete knowledge of its composition and inadequate techniques for the measurement of each constituent…'[20]. Subsequently, Cummings and his collaborator Hans Englyst developed new, robust and much faster, assays for dietary fibre that focused on measurement of NSP[21]. This approach was adopted for use in the UK food composition tables and data for 'Englyst fibre' were included in several editions of McCance and Widdowson's 'The composition of foods'[22].

Although it was clear that NSP were not degradable by endogenous human enzymes and so flowed from the terminal ileum into the large intestine, there was growing recognition that other carbohydrates also escaped small bowel digestion[23]. Studies using ileostomists[23] and healthy volunteers fitted with a multi-lumen tube passed via the nose along the small bowel with the distal end positioned just prior to the ileocaecal junction[24], provided convincing evidence that some dietary starch and also some oligosaccharides flowed from the small intestine into the large bowel. This led to the discovery, and characterisation, of resistant starch (RS) and to investigate the effects of this carbohydrate fraction on human physiology and health[25].

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Resistant starch: definition, occurrence of foods and physiological effects

Research on RS was stimulated by a so-called concerted action, funded by the Commission of the European Communities, titled 'Physiological Implications of the Consumption of Resistant Starch in Man' with the acronym EURESTA, that involved up to forty research groups from eleven European countries over a period of 4 years from 1990[25]. Despite very limited funds to support research directly, the networking and training activities within EURESTA enabled the consortium to make rapid progress. EURESTA defined RS as 'the sum of starch and the products of starch degradation not absorbed in the small intestine of healthy individuals'[25] and undertook detailed physical and chemical characterisation of RS recovered from the human terminal ileum[26].

In vitro and *in vivo* evaluation of the rate and extent of digestion of starches from different food sources revealed that starch is resistant to pancreatic amylase for several reasons including: (a) it is physically inaccessible to human digestive enzymes owing to enclosure in food structures such as partly milled grains or seeds (known as RS1); (b) it is present in intact starch granules occurring in uncooked potatoes and banana (RS2) and (c) it contains retrograded amylose found in processed foods e.g. cooled cooked potato, bread and Kellogg's cornflakes (RS3)[27]. More recently, two further forms of RS have been proposed. These are RS4, defined as chemically modified starch formed by cross-linking, esterification or etherisation and the less well-characterised RS5 that is composed of amylose–lipid complexes[28].

Although, by definition, RS is not digested by the enzymes of the human small intestine, it is fermented to a greater or lesser extent by the bacteria in the large bowel[29,30]. Consequently, the energy value of RS is much lower than that of digestible starch with values of approximately 2 and 4 kcal/g (8 and 16 kJ/g) for RS and digestible starch, respectively[25,28]. EURESTA provided preliminary estimates of RS intake by Europeans noting that these seemed low (approximately 4 g/d) and suggested that there is a considerable potential to increase RS intake if RS proves to be beneficial to the consumer[25].

Towards consensus on the definition and measurement of dietary fibre

Debates and disagreements about the definition of dietary fibre continued for many years and, 30 years after its first symposium on dietary fibre and health, the Nutrition Society published the proceedings of the 7th International Vahouny Fibre Symposium[31]. This included a paper from Jonathan DeVries titled 'On defining dietary fibre' in which he presented views from an expert scientific review committee convened by the American Association of Cereal Chemists[32]. This argued for a broadening of the definition of dietary fibre to include not only NSP but also other carbohydrates that escaped digestion in the small bowel and flowed into the large intestine[32].

At that time, the UK was in a small minority of countries that defined dietary fibre as NSP and that used 'Englyst fibre' for food composition tables and for food labelling. In particular, the UK was out of alignment with the rest of Europe where 'AOAC fibre' (that comprised of all non-digestible polysaccharides and included lignin and RS), as measured by methods developed by the Association of Analytical Chemists (AOAC), was dominant. This was not just a scientific disagreement. Disagreement on how to define and to measure dietary fibre had implications for food regulations and for implementation of free trade policies throughout the European Union.

Eventually, in 2008, the UN's Codex Alimentarius brokered international agreement on a definition of dietary fibre that included NSP plus RS plus non-digestible oligosaccharides[33]. This international consensus has wide implications because Codex sets global standards for food and the agreed definition is used as the basis for analytical methods for dietary fibre, for food labelling, for setting of nutrient reference values and for health claims[33]. However, Codex were not able to agree on exactly which oligosaccharides should be included so that each jurisdiction continues to make individual decisions on this component of the definition and measurement of dietary fibre.

New discoveries: resistant starch and cancer prevention

Although there is substantial evidence from observational studies that dietary patterns are strongly associated with risk of many common cancers[34], there is limited evidence of causality from RCTs. This is unsurprising given the logistical challenges, high cost and required duration of such studies. Unlike the situation for other non-communicable diseases, there are few reliable biomarkers that can be used as surrogate endpoints in cancer prevention trials. More than 30 years ago, in collaboration with John Burn (Newcastle University) and Tim Bishop (University of Leeds), we began to think about novel approaches to this problem. At that time, there were rapid advances in understanding the genetic basis of CRC in both those with hereditary forms of CRC and in so-called sporadic cancer in the general population. We focused on two clinical conditions – familial adenomatous polyposis (FAP) and Lynch syndrome (LS; formerly known as hereditary non-polyposis colorectal cancer). FAP is caused by germline defects in the *APC* gene, a key component of the Wnt signalling pathway. Individuals with FAP develop multiple adenomatosis polyps in the large bowel, often around puberty and, without surgical intervention (usually colectomy), there is close to 100 % probability of progression to CRC by age 35–40 years and a high risk of cancers at other sites, especially in the duodenum[35]. People with LS have a defect in one of the genes encoding the DNA mismatch repair system; this is a consortium of proteins that recognises and repairs copying

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errors that occur during DNA replication. As a consequence, people with LS accumulate multiple mutations in their DNA and are at increased risk of cancer at several sites, including in the large bowel[36].

In our first RCT (the CAPP1 study), we recruited 113 young people (mean age 18 years) with FAP who had an intact colon and randomised them to aspirin and to RS using a 2×2 factorial design[37]. We chose aspirin as one of the intervention agents in the CAPP1 study because there was growing evidence from observational epidemiological studies that those who took aspirin frequently had lower CRC risk[38]. We chose RS as the other intervention agent because there was evidence that RS fermentation in the large bowel results in increased production of butyrate by the gut microbiome which has anti-cancer effects[39]. In addition, its availability as a bland white powder meant that it was possible to randomise young people with FAP to RS, or to a maize-starch placebo, for prolonged periods (at least 1 year). Since polyps are precursors of carcinomas and more, and bigger, polyps increase the risk of CRC, the primary endpoint in the CAPP1 study was polyp number in the rectum and sigmoid colon with the size of the largest polyp as the major secondary endpoint[37]. To our considerable disappointment, we did not find any effects of intervention with RS on either endpoint[37]. However, in further exploratory analyses, we observed that crypt length (crypts are the functional units of the colorectal epithelium) appeared to become shorter over time in those treated with RS[37]. Overall, this study demonstrated the potential for undertaking chemoprevention RCTs in those at higher genetic risk of cancer using dietary (and pharmaceutical) agents.

We used a similar factorial design in the CAPP2 study in which we randomised nearly 1000 adults with LS (mean age 45 years) to aspirin and to RS[40]. We hypothesised that RS may be particularly effective in people with LS because we had seen that cells with defects in the DNA mismatch repair system appear to be more susceptible to the antineoplastic effects of butyrate, an important metabolic end-product of RS fermentation by the gut microbiome[41]. Because LS is relatively rare (estimated to be between 1:370 and 1:2000 in Western populations[42]), recruiting such a large number of people with LS was a significant challenge. Collaboration with colleagues in the International Society for Gastrointestinal Hereditary Tumours[43] allowed us to recruit from, and to deliver the intervention in, multiple centres throughout the UK, across Europe, in Hong Kong, in Australia and in South Africa[40]. At the end of the intervention study (mean 29 months of intervention), we saw no effect of RS on the incidence of colorectal adenoma or carcinoma among people with LS[40]. However, we had anticipated that effects on cancer development might take longer to emerge so we had consented our participants to longer-term follow-up. We carried out a subsequent analysis after a median follow-up of 52·7 months and, again, found no effects of RS on CRC incidence or, indeed, on other cancers that occur typically in people with LS[44]. At that point we concluded that 'Dietary supplementation with resistant starch does not emulate the apparently protective effect of diets rich in dietary fibre against colorectal cancer'[44].

Recently, we completed a further analysis of follow-up data when all participants in the CAPP2 study were at least 10 years post-intervention and we included data for up to 20 years follow-up from participants in England, Finland and Wales[45]. Again, we saw no difference in CRC incidence in those randomised to RS but, surprisingly, we found a large, and highly significant, reduction in incidence of non-CRC (hazard ratio, 0·54; 95 % CI, 0·33, 0·86; $P = 0{\cdot}010$)[45]. We observed this reduction in non-CRC in the first 10 years after intervention and the lower risk continued in the next decade[45] (Fig. 2). The protective effect appeared to be particularly pronounced for cancers of the upper gastrointestinal (GI) tract (stomach, duodenal, bile duct and pancreatic cancers) where we detected just five cancers in five participants in those randomised to RS compared with twenty-one cancers in seventeen participants in the placebo group[45]. The common clinical practice of large bowel screening in those with LS allows early detection and management of neoplastic lesions in this organ. In contrast, it is not usual to undertake regular screening for extracolonic cancers so these are often detected late and are responsible for more cancer deaths than is CRC[46]. Specifically, cancers of the upper GI tract are much more likely to be lethal than are CRC[46]. Consequently, the finding from the CAPP2 study of lower risk of extracolonic cancers in those randomised to RS is likely to have substantial potential benefits for patients with LS.

There are no studies of RS and upper GI cancer in the general population so the findings of the CAPP2 study should be a stimulus to undertake such studies. There is good reason to believe that findings from studies on people with LS will also apply in the general population. For example, we have shown that aspirin reduced CRC in people with LS[47] and a similar effect was seen in long-term follow-up of physicians and others who were randomised to aspirin in trials set-up originally to investigate CVD prevention[48]. In addition, we have observed that, among people with LS, those who are also obese are at higher risk of CRC than those who are not obese[49]. This emulates the well-established association between higher BMI and CRC risk in the general population[50].

Resistant starch and the gut microbiome

Our findings from the CAPP2 study raise questions about the mechanism through which RS reduces risk of upper GI cancers. When we designed the intervention study, we knew that RS was degraded by the gut bacteria and subsequent research has shown that RS is fermented by multiple human colonic bacteria including members of the Ruminococcaceae, Lachnospiraceae, Erysipelotrichaceae and Clostridiaceae families[51] and involves synergy between primary RS degraders and secondary starch scavengers[52]. Importantly, RS leads to greater production of SCFA[51], including the anti-neoplastic butyrate[39]

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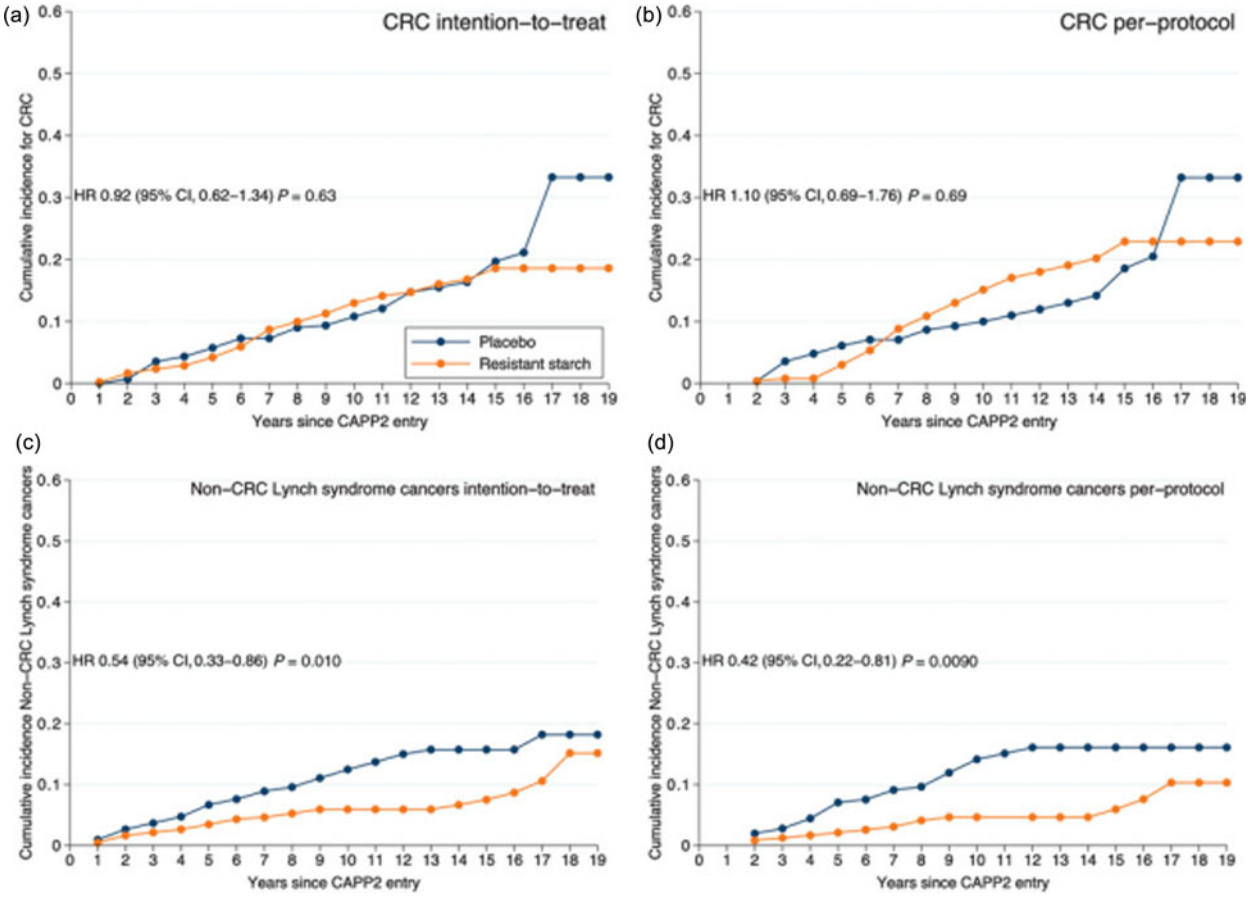

Fig. 2. Lack of effect of supplementation with resistant starch (RS) on colorectal cancer (CRC) in both intention-to-treat (A) and per-protocol (B) analyses in long-term follow-up of people with Lynch syndrome. In contrast, RS supplementation reduced incidence of non-CRC Lynch syndrome cancers both intention-to-treat (C) and per-protocol (D) analyses (reprinted with permission from Mathers *et al.*[45]). 95 % CI, 95 % confidence interval; HR, hazard ratio.

that suppresses growth of cancer cells and may enhance apoptosis[53]. In addition, we have reported evidence that cells defective in mismatch repair may be more susceptible to the anti-neoplastic effects of butyrate[41]. For these reasons, we had expected RS to lower CRC risk in people with LS but, clearly, that did not occur[45].

However, there may be other mechanisms involving interactions between RS and the gut microbiome that could explain our observation of lower risk of upper GI cancers in those randomised to RS[45]. Our current hypotheses focus on the role of RS in reducing conversion of primary bile acids to unconjugated secondary bile acids[54]. Some secondary bile acids can promote carcinogenesis[54] by inducing cancer stem cells[55] and intervention studies in both healthy volunteers[56], and in participants with recent colorectal adenomas[57], showed that RS reduced faecal concentrations of secondary bile acids. In addition to absorption from the ileum, bile salts are absorbed from the large bowel and recycled to the upper intestine via the liver and bile duct, as part of the normal enterohepatic circulation[58,59]. Consequently, reduction in colonic bacterial production of secondary bile acids following RS ingestion would be expected to lower exposure of the upper GI tissues to potentially damaging secondary bile acids and this may explain the significantly reduced risk of upper GI cancers that we observed in the CAPP2 study[45].

In 1973, when Cummings conducted his influential review of dietary fibre, he concluded that it was not known whether fibre is capable of altering bacterial metabolism in the colon[20]. Only 7 years later, from studies directly in human subjects, Stephen and Cummings showed that dietary fibre is extensively degraded in the gut, probably by the colonic microflora, and that this interaction is likely to be important in determining disease susceptibility[60]. Although many research teams, including Cummings and his collaborators, continued to investigate interactions between dietary fibre, the gut microbiome and health, progress over the next 20 years was relatively slow. More recently, technical and scientific advances in microbiome research (based on fast, low-cost, DNA sequencing) have driven investigation of the associations between the gut microbiome and human health, notably on the mechanisms through which the diet, including dietary fibre intake, can modulate these associations.

Much of this work has focused on the role of bacterial end-products of dietary fibre fermentation, especially the

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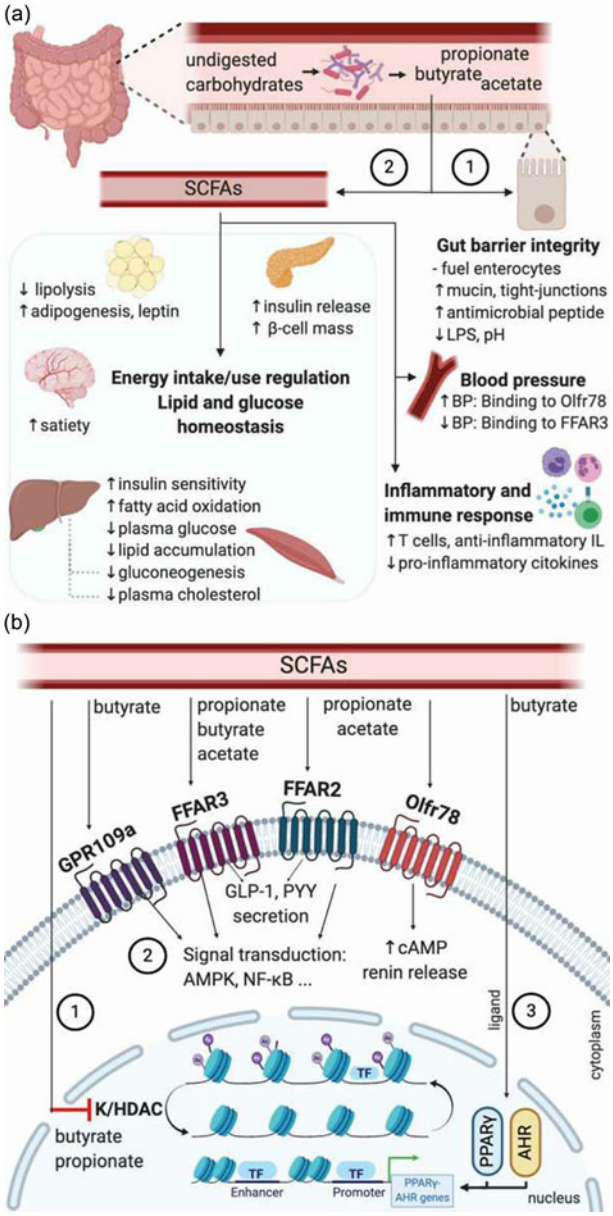

Fig. 3. Molecular pathways through which SCFA produced by bacterial fermentation of dietary fibre (undigested carbohydrates) in the large bowel modulate a wide range of physiological processes including through (2) altered signal transduction and (2) regulation of gene expression via transcription factor-mediated and epigenetic mechanisms (reprinted with permission from Nogal *et al.*[62]). BP, bold pressure; LPS, lipopolysaccharide; GPR, G protein-coupled receptor; OLFR, olfactory G protein-coupled receptor; GLP, glucagon-like peptide-1; PYY, peptide YY; AMPK, 5' adenosine monophosphate-activated protein kinase; cAMP, cyclic adenosine monophosphate; K/HDAC, lysine/ histone deacetylase; TF, transcription factor; AHR, aryl hydrocarbon receptor.

SCFA, in mediating links between the diet, the gut microbiome and a wide range of health outcomes[61,62] (Fig. 3). For example, there is growing evidence that SCFA, bile acids and tryptophan metabolites, produced by the gut microbiota, determine inflammatory and immunological responses with implications not only for gut health[63] but also for function and health throughout the body. In addition, detailed human intervention studies, using multi-omics approaches, reveal the complex relationships between the baseline microbiome and individual inflammatory and immunological responses to higher dietary fibre intake[64]. There is also recent evidence from a clinical trial carried out in Bangladesh that a dietary supplement targeted at the gut microbiome may improve the growth of young children with moderate acute malnutrition and such findings stimulate research into the mechanisms by dietary manipulation of the microbiota that may influence growth[65].

However, progress in this area is currently limited by: (1) the lack of evidence of whether gut dysbiosis (an imbalance in the composition and/or metabolism of the microbiome) is a cause, or a consequence, of disease and (2) the absence of evidence for causal links between specific changes in gut microbiome structure and markers of human function or health[66]. Reaching consensus on defining the characteristics of a healthy gut microbiome is likely to be pivotal in enabling advances in this research area[66].

Public health implications: using resistant starch to increase dietary fibre intake

In the UK, the Scientific Advisory Committee on Nutrition recommends a dietary fibre intake of at least 30 g/d for adults[14]. However, mean dietary fibre intake by adults is less than 20 g/d. Despite sustained campaigns to encourage greater consumption of dietary fibre[67], intake has shown little change over several years[68]. Breads and vegetables are the top two food groups providing dietary fibre in the UK diet, each contributing 15–20 % of total intake, but significant amounts of dietary fibre are also provided by potato products, pasta, rice and other cereal products (including breakfast cereals)[68]. This suggests that there is considerable scope for increasing dietary fibre intake through food choice, especially choice of wholegrain cereal products, and by reformulation of existing products to increase their content of dietary fibre. Sections of the food industry are addressing this challenge through initiatives such as 'Action on fibre'[69] but the glacial rate of change in dietary fibre intake at the population level is disappointing.

Because of its bland flavour, white colour, low water holding capacity and stability during different types of food processing, RS is a potentially attractive ingredient for increasing the dietary fibre content of starchy, and other, foods[70]. When cooked starches are allowed to cool, some of the starch undergoes a process of crystallisation, known as retrogradation, that reduces accessibility of the starch to pancreatic amylase and increases its RS content[71]. However, a wide range of other approaches are available for increasing the RS content of starch foods including conventional selection or genetic manipulation of plants to increase the amylose content of starch, enzymatic hydrolysis, physical treatments,

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chemical modifications, exposure to γ-rays and complexation with lipids[71].

Breeding cereal, or other starchy, crops that have a higher amylose:amylopectin ratio in their seeds or storage organs is a potentially cost-effective and sustainable way of increasing the RS (and, therefore, dietary fibre) content of foods while maintaining their usual appearance, texture and taste. This has been achieved through conventional plant-breeding approaches using mutagenesis and selection but the advent of gene-editing approaches offers new opportunities. Building on evidence from studies showing that down-regulation of isoforms of the starch-branching enzyme (SBE) II (TaSBEIIa and TaSBEIIb), increased amylose content of the wheat grain, Li and colleagues used CRISPR/Cas targeted mutagenesis of TaSBEIIa to generate a range of transgene-free, high-amylose wheat lines[72]. Agronomic characteristics of the gene-edited wheat plants were broadly similar to those of the parental varieties but there was some yield penalty with lower 1000-grain weights in some cases, especially for the triple-null lines (*aabbdd*)[72]. The latter had higher RS content and total dietary fibre content but, when the flour was baked into bread and biscuits, had slightly poorer end-use quality[72]. Such limitations might be mitigated by blending the *aabbdd* triple-null lines with conventional, commercial wheats[72]. The UK Government (2022) plans to introduce legislation that will allow the use of gene-editing approaches (such as CRISPR/Cas9) to support the development and marketing of what they describe as 'precision bred plants and animals'[73]. This could open the way for UK plant breeders (and others) to generate novel foods rich in RS that could contribute to bridging the gap between current intakes of dietary fibre and that recommended by the Scientific Advisory Committee on Nutrition[14].

Conclusions

Research over the past five decades has confirmed much of Burkitt's hypothesis about associations between diets low in dietary fibre and greater risk of a consortium of common non-communicable diseases including CVD, type 2 diabetes and a number of cancers. However, in most cases, it remains unclear whether higher intakes of dietary fibre *per se* reduce disease risk or whether dietary patterns that are characterised by low intakes of dietary fibre amplify risk. Further studies, especially well-designed intervention studies with hard clinical endpoints, will be needed to establish causality. Future mechanistic research is likely to focus on the interaction between dietary fibre, the gut microbiome and human physiological, metabolic and immunological processes since this focus has considerable potential to reveal dietary fibre-related alterations in pathways and processes that have pervasive effects on human function and health[62,74,75]. Although it is probable that the health benefits attributed to higher dietary fibre intake will be shared with most types of dietary fibre, the diversity and complexity of the supramolecular polymer networks containing variable proportions of cellulose, hemicelluloses, pectic substances and non-carbohydrate moieties that make up plant cell walls[76,77] in individual plant foods mean that they have different physicochemical properties within the human gut and, consequently, different effects on health[78]. Similarly, one should anticipate that different types of RS, and of the non-digestible oligosaccharides, that contribute to the dietary fibre in foods will have characteristically different effects on human physiology and disease risk. The inadequate intake of dietary fibre by most populations globally remains a significant, and urgent, public health challenge. This may be addressed by concerted societal action including by plant breeders, by reformulation and improved marketing of dietary fibre-rich foods by manufacturers and retailers and by public health interventions that focus on dietary fibre *per se*. In addition, population level shifts in dietary patterns towards less processed, plant-based diets designed to mitigate the adverse effects of the global human food system on climate change and on biodiversity are also likely to increase dietary fibre intake and to reduce the burden of non-communicable diseases[79].

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Conflict of Interest

None.

Authorship

J. C. M. is the sole author of this article.

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