Food as Medicine 2021 Review

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Contents

Transformation to healthy diets by 2050 will require substantial dietary shifts. Global consumption of fruits, vegetables, nuts, and legumes will have to double, and consumption of foods such as red meat and sugar will have to be reduced by more than 50%. A diet rich in plant-based foods and with fewer animal source foods confers both improved health and environmental benefits." Prof. Walter Willet MD Harvard T.H. Chan School of Public Health

Introduction

Globally, eleven million deaths every year are attributable to the very food we consume (Lancet, 2017). With the urgency of the growing population and the unprecedented climate emergency, our food in the Anthropocene is the strongest lever in optimizing both planetary and human health. The human lifespan is ever-increasing as we find ways to maximise our health and longevity, yet, despite this, our morbidity is on the rise (Case & Deaton, 2017). This report has four objectives, with the first being to evaluate and summarise the scope of recent research within nutrition science. Secondly, this report will identify where the findings of research from 2021 and that evaluated in the Food As Medicine report in 2020 differ. Thirdly, this report will also identify limitations of the research conducted over the span of 2021. Lastly, this report will showcase New Zealand nutrition science researchers and their research.

Summary of 2020 report

The Food As Medicine 2020 report investigated the influence of food on health and its potential to prevent or treat disease. Five key mechanisms of disease were identified based on New Zealand-specific causes of mortality: inflammation, microbiome, neurogenesis, angiogenesis, and gut health. Research included in this report demonstrated how food could influence health through enabling or inhibiting said mechanisms. Specific components of food were identified throughout these studies that appear to have a positive impact on health. These included polyphenols, antioxidants, omega 3 fatty acids, and unsaturated fats.

To confirm these findings, the diets of the "healthiest" countries, as determined by the Bloomberg Global Health Index, were assessed, and compared to New Zealand. There is no global consensus on what constitutes a healthy diet. However, there are overlapping themes in the nutrient guidelines on the healthiest countries. One can use this and the growing field of literature to create an evidence-based reflection of a healthy diet. Healthy diets emphasise diversity, made up largely of plant-based foods, low amounts of animal-sourced foods. They contain unsaturated fats rather than saturated, whole grains rather than refined, and avoid processed foods. It also considers one's microbiome and eats to maintain eubiosis (a 'balanced' microbiome).

Another exciting and vast developing area of scientific experimentation surrounds the microbiome. The brain-gut-axis and the growing understanding of the significance of gut microbiome health highlighted a potential mechanism connecting intrinsic and extrinsic factors of our health and wellbeing. This body of literature identified the 'case of the missing microbes' – a significant loss of biodiversity within human digestive systems, with evidence of an associated negative consequence to our health. The key conclusions enveloped various systems. Our improved hygiene, anti-septic techniques, use of agrochemicals, antibiotic use, westernised diets, and ever-decreasing contact with microbes has decreased the diversity of our individual microbiomes. Evidence had shown that this diversity was a key indicator of health, and in many cases its absence was associated with morbidities.

Search strategy

Research was conducted using the Google Scholar search function to find papers released solely in 2021 and 2022. Search terms were chosen so as to narrow down the results, and included "inflammation", "microbiome", "antioxidants", "nutrition", "gut health" and "polyphenols". Articles from relevant academic journals were also analysed for this review. A total of 159 studies were found. From this, major categories of research emerged; cardiometabolic outcomes, neurodegenerative diseases, metabolic syndromes, dairy, meat, and dietary patterns.

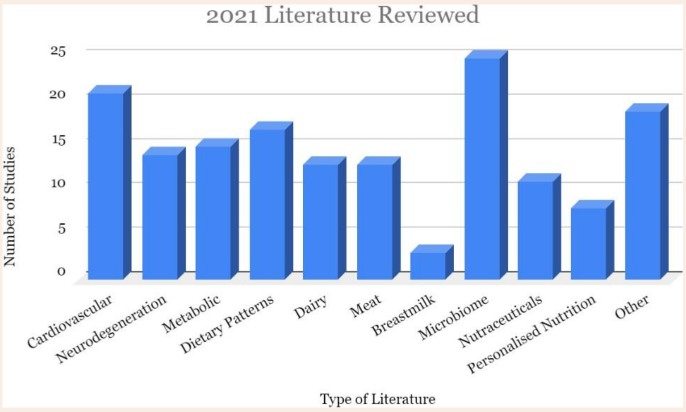

Figure 1. Categories of Literature found

Of the 159 studies reviewed by the author, those discussed in the present report were selected based on their perceived significance to nutrition science and their reflection of the key areas of interest and limitations in nutrition science at present.

Food as medicine

Cardiometabolic outcomes

In 2019 alone, 19.56 million deaths globally were attributable to cardiovascular disease. With such a significant burden of disease, the prevention and treatment of cardiometabolic outcomes remains a point of interest in scientific research. In the 2020 report, diet was established as a tool to be used in the prevention and treatment of such outcomes. Foods of particular interest in 2020 were those high in phytochemicals like polyphenols.

Recommendations for dietary patterns from the 2020 report included an overall reduction in consumption of processed foods, meat, and refined grains. The proposed mechanisms for the links between these dietary changes and health outcomes was associated with the roles of food in decreasing oxidative stress, and as a result, decreasing inflammation which has been linked to cardiovascular disease. Researching 2021 examining this association between diet and health typically fell into one of three categories – evaluating the effect of overall dietary patterns, food groups or specific nutrients on cardiometabolic health.

Dietary patterns

Hu et al (2021) aimed to assess the effect of dietary patterns on incident cardiovascular disease and mortality, and all-cause mortality using the HEI-2015 score. The Healthy Eating Index-2015 (HEI-2015) score measures adherence to the 2015- 2020 Dietary Guidelines for Americans, where a set of foods are rated from 0-100. A score of 100 reflects that the set of foods aligns with the key dietary guidelines; Americans currently have a score of 59 (US Department of Agriculture, 2015). Other dietary patterns assessed by Hu et al. (2021) were the Alternative Healthy Eating Index-2010 (AHEI-2010), alternate Mediterranean(aMed) diet, and the Dietary Approaches to Stop Hypertension (DASH). AHEI-2010 was created to assess the intake of food and beverages associated with chronic diseases.

The aMed diet assesses adherence to a Mediterranean style diet in US populations. The DASH score was designed to assess adherence to the DASH dietary pattern. After adjustment of participant sociodemographic characteristics and health behaviours, those in the highest quintile of HEI-2015 had a 16% lower risk of incident CVD compared to those in the lowest quintile. Additionally, those in the highest quintiles of AHEI-2010, aMed and DASH had respectively, a 15%, 16% and 11% lower risk of CVD compared to those in the lowest quintiles.

All the examined diets emphasise an increased intake of plant-based foods and whole-foods, while minimising consumption of processed foods. These findings support research discussed in the 2020 report and research conducted in 2021 (Yoshida et al, 2021; Mompeoet al 2021, Glenn et al 2021). The main limitation of this study is its use of Food Frequency Questionnaires (FFQ) to measure participant dietary intake. FFQ are susceptible to measurement error and subjective reporting as they rely on a participant's ability to recall dietary information over extended periods of time. Additionally, FFQs were only completed twice throughout the duration of this study (around 6 years apart) and therefore cannot account for fluctuations in dietary intake overtime.

Riccardi et al (2021) conducted a review of the available literature on the associations between food choices and the risk of atherosclerosis. They concluded that low consumption of salt and animal-based foods, along with high consumption of plant-based foods, whole grains, fruits, legumes, and nuts was associated with decreased risk of atherosclerosis. hey recommended replacement of animal fats such as butter, with unsaturated fats and oils. Novelties in literature were also highlighted, as research begins to differentiate between the risks of such animal-based products like dairy and meat. The science on the association between meat and cardiometabolic outcomes is inconsistent, with evidence consistently indicating a relationship between processed meat and coronary heart disease incidence and mortality, but few indicating this relationship with unprocessed meat. Moreover, the association between poultry and cardiometabolic outcomes appears minimal to none. Riccardi et al (2021) argues these differences may be due to differences in composition, as poultry has a lower fat content, and a more favourable fatty acid profile compared to red meat. Riccardi et al (2021) also emphasised the conflicting evidence on dairy, as research appears to indicate no association regardless of fat content.

From their review, Riccardi et al (2021) produced a summary table (Figure 2) that "represents one of the most evidence-based dietary means to reduce the risk of atherosclerosis".

The research conducted on dietary patterns in 2021 was in line with those discussed in the previous report. Despite their consistency with previous thinking and results, the research analysed in this report had limitations owing to the quality of data included the inconsistency in food groups used in the studies, and the high heterogeneity of observations.

Additionally, as the literature reviewed were based on observational studies, there is a lack of concrete conclusions and understanding of the underlying mechanisms controlling the found associations. These limitations suggest experimental studies are required before conclusions on the underlying mechanisms that link diet and health can be made.

Food groups

Du et al (2021) investigated the relationship between cardiometabolic outcomes and intake of highly processed foods. Despite some evidence indicating an association between the intake of highly processed foods and various negative health outcomes,

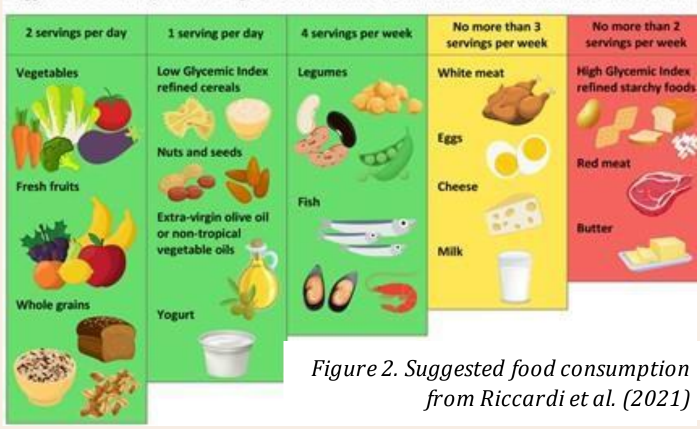

Figure 2. Suggested food consumption from Riccardi et al. (2021)

there is little evidence of this association in prospective studies. 13,548 participants were followed for an average of 27 years. All participants were from the United States, aged 45-60 and were deemed at risk of atherosclerosis. Atherosclerosis is a disease characterised by the deposition of fatty material on the inner arterial walls and is considered a cause of various cardiometabolic outcomes.

Participant's dietary intake was estimated using a food frequency questionnaire (FFQ), and the level of food processing was determined using the NOVA classification. Coronary artery disease incidence was 19.4% greater in the highest group of consumption (70.8 per 10,000 person-years) compared to the lowest quartile of consumption (59.3 per 10,000 person-years). These results were consistent across subgroups by sex, race, BMI categories, hypertension status and diabetes status.

The findings appear consistent with those in the 2020 report, and published studies in 2021 (Silva et al 2021, Zhong et al 2021). They are also consistent with the findings of Hu et al (2021) and Riccardi et al (2021), as the intake of processed foods is decreased in the studied dietary patterns. Limitations of the study include its use of FFQ, and its observational nature.

Whole grain consumption has been linked to a reduced risk of cardiovascular disease. However, few studies have investigated the association between consumption of refined versus whole grains and cardiovascular outcomes.

Sawicki et al (2021) investigated the association with intermediate risk factors of cardiometabolic outcomes for both refined and whole grains and compared them. The intermediate risk factors considered were central adiposity (waist circumference), blood lipid and lipoprotein concentrations, blood pressure, fasting glucose concentrations and insulin resistance. 3121 participants were followed for an average of 18 years, with relevant lifestyle and FFQs completed and collected every four years.

Participants in the highest category of whole grain consumption had a smaller mean increase in waist circumference, fasting glucose concentration and systolic blood pressure each four-year interval when compared to those in the lowest category of whole grain consumption. They also showed greater mean increase in fasting plasma HDL cholesterol concentration and a greater mean decline in fasting plasma triglyceride concentration.

These findings suggest that substitution of refined grains with whole grains may be an effective method to attenuate intermediate risk factors of cardiovascular disease, thereby reducing their risk of cardiometabolic diseases. This is consistent with the dietary recommendations and trends of the 2020 report and are consistent with another research conducted in 2021 (Chung et al, 2022; Seal & Scheers, 2021; Marshall et al, 2021). The findings of Sawiciki et al. also supports the recommendations in Riccardi et al (2021) and Hu et al (2021), of increased whole-grain intake rather than refined grain. Limitations of this study include its use of FFQ to assess dietary intake.

Nutrients

An increased intake of fruits, vegetables, nuts, and whole grains have all individually be associated with lower incidence and mortality of cardiovascular diseases. Despite this, the specific nutrients underlying these associations remain a matter of debate.

Basu et al (2021) investigated the association between phytochemicals specifically polyphenol intake, and cardiovascular disease (CVD) risk factors. The risk factors measured in this study were glycaemic control and serum LDL cholesterol. 33 participants were followed for 14-weeks and randomly assigned to one of three groups - a control powder, a low dose powder (13g of strawberry powder/day) or a high dose (32g strawberry powder/day). The findings revealed significant reductions in fasting insulin and insulin resistance in the high dose group compared to the low dose and control groups. These findings suggest that intake of strawberries (resulting in a higher intake of phytochemicals) can improve insulin resistance, lipid particle profiles and serum PAI-1 in obese adults.

These findings mirror those reported in the 2020 report, and in 2021 research(Zhang et al, 2021; Grosso et al 2022).

Neurodegenerative diseases

As the prevalence of various neurodegenerative diseases continue to rise, the potential prevention and treatment methods continue to be investigated. As established in the 2020 report, evidence shows that neurogenesis (process by which new neurons are formed in the adult brain) can be stimulated through the foods we eat, opening the opportunity for dietary-based interventions.

Brain atrophy is the loss of brain cells and is an early biomarker of cognitive impairment measured using magnetic resonance imaging (MRI) (Heister et al, 2011). Kaplan et al (2022) examined the effect of a Mediterranean diet on age-related brain atrophy, and the differences in this effect if polyphenol content was

specifically targeted. Evidence suggests that polyphenols can cross the blood- brain-barrier and reduce neuroinflammation, induce cell proliferation and induce neurogenesis in the hippocampus (Figueira et al, 2019; Abraham & Johnson, 2009; Dias et al, 2012). Kaplanet al (2021) conducted a randomised controlled trial over an 18-monthperiod. 284 participants were randomly assigned to one of three groups: HDG (control), MED (Mediterranean) or Green-MED (Green Mediterranean). Participants self-reported lifestyle habits and FFQs were completed at baseline. The control group followed standard nutritional counselling to promote a healthy diet and uphold a similar intervention intensity to the other groups.

The Mediterranean group followed a calorie- restricted traditional Mediterranean diet, low in simple carbohydrates, but rich in vegetables. They were also instructed to replace most of their red meat consumption with poultry or fish. Finally, they included 28 g/day of walnuts to ensure a polyphenol intake of 440 mg/day.

The Green-MED intervention group followed the same structure as the MED group but avoided all processed and red meat and consumed more plant-based foods overall. In terms of polyphenols, participants consumed 3-4 cups of green tea a day and 100g of Wolffia globosa (Makai - Duckweed) a day.

The findings of this study suggested that the green-MED diet is potentially neuroprotective against age-related neurodegeneration. The consumption of specific "green" dietary components high in polyphenols such as Makai, green tea, and walnuts, along with the reduced consumption of meat, were specifically associated with a reduced hippocampal occupancy score decline. Moreover, this reduced hippocampal occupancy score decline was associated with improvements in cardiometabolic parameters including glycaemic markers, body weight and blood pressure.

The findings of this study reflect an overall improvement in brain atrophy due to a Mediterranean diet, with further benefits associated with polyphenol intake. These results are consistent with the 2020 report, and other research published in 2021 (Tsan et al, 2021; Gauci et al, 2021).

Multiple studies from 2021 support the theory of polyphenols acting as antioxidants, reducing oxidative stress, and therefore preventing or improving symptoms of various health outcomes. Although compelling, similar literature published in 2021 has also conflicted with these findings (McBean & O'Reilly, 2021), suggesting a need for further research.

Bianchi et al (2021) conducted a systematic review on literature investigating the role of nutrition in the treatment or prevention of neurodegenerative diseases. 79 total studies were included, 28 on the effect of nutrition, 18 on supplements, 16 of polyunsaturated fats, and 13 on vitamins. Studies investigating the effect of nutrition largely focuses on the Mediterranean diet, with most reporting a beneficial effect of this diet on cognitive impairment and Alzheimer's disease (AD) incidence and progression. A few of the researchers studied the effect of nutrition on brain structures' volume and functions. Gu et al (2015) specifically found an association between low adherence to a Mediterranean diet and reduced volume in the evaluated brain structures.

Studies focusing on the effect of supplementation found evidence of an association - that dietary supplementation and education on food intake greatly improved the quality of life and cognitive function in patients with AD, a reduction in the disability scale in patients with multiple sclerosis, and an improvement in movement disorder in patients with Parkinson's.

Contrastingly, some studies found no beneficial effect on reducing cognitive decline in patients with AD and Huntington's disease (HD). Findings from studies investigating the effect of polyunsaturated fatty acids were controversial and conflicting. These findings reflect the inconsistency in the general field, as more researchers call for higher quality research.

Li et al (2021) investigated the effect of anthocyanins on the incidence of neurodegenerative diseases through reviewing published literature. Anthocyanins have the typical flavonoid structure and are established antioxidants, able to cross the blood-brain-barrier. Li et al (2021) references two studies where an association has been made. Kent et al (2017) reported that elderly patients with moderate dementia showed improvement in their memory and cognitive ability after 12 weeks of daily consumption of anthocyanin-rich cherry juice.

Boespflug et al (2018) reported that the blood oxygen of elder patients with mild cognitive impairment increased after a 16-week intervention of blueberry supplements. The primary proposed mechanism of this effect is anthocyanins action as an antioxidant. Oxidative stresses a main factor causing neuronal cell death and therefore neurodegenerative diseases. Their action as an antioxidant could be through scavenging reactive oxygen species (ROS) directly, or by stimulating the expression of antioxidant enzymes in the brain.

These findings are supported by the 2020 report and by other research conducted in 2021 (Annunziata et al, 2021; Morris et al, 2021; Ontario et al, 2022, Luo et al, 2021).

As a meta-analysis, its limitations are determined by the quality of the included studies. Moderate heterogeneity was reported, as well as variation in the cofounders accounted for, meaning factors like physical activity may contribute to some of the reported association.

Melo et al (2021) investigated the association between adherence to the MIND diet and cognitive performance, brain volume and silent brain infarcts. 2092 participants were followed for an average of 6.6 years. The MIND diet is comprised of 10 favourable food groups (green leafy vegetables, other vegetables, berries, nuts, whole grains, fish, beans, poultry, wine and olive oil) and 5 unfavourable food groups (butter and margarine, cheese, red meat, fast fried foods and pastries and sweets).

Based on the participants dietary intake as assessed by FFQs, they were given a score between 0-15. A score of 15 indicates high adherence to the MIND diet. Higher adherence to the MIND diet was significantly associated with improved cognitive performance, and with a lower decline overtime. Specifically, it was associated with better global cognitive function, visual memory, processing speed, and verbal comprehension and reasoning.

These findings support those in Kaplanet al (2022) due to the similarities in dietary patterns. They also support the general recommendations made in the 2020 report. Limitations of this study is its use of FFQ.

Dairy

The health effects of dairy consumption are a point of contention, with evidence supporting both sides of the argument. Disregarding the global environmental health impacts, results on the association between dairy consumption and risk of morbidities such as cardiovascular disease remain inconsistent and contradictory. Thus, dairy emerged as a major theme seen in 2021 research.

Jin et al (2021) conducted a meta-analysis focusing on prospective cohort studies examining the association between dairy consumption and total cancer and cancer-specific mortality. Thirty-four studies were included, covering all dairy products and 3,171,186 participants. Thirteen of the included studies focused on total dairy consumption, and found no significant association, with no significant heterogeneity among the studies.

Seventeen studies focused specifically on milk consumption and reported an association between milk intake and incidence of cancer in females, but not males. When stratified by cancer type, an increased risk was only reported in liver and ovarian cancer. When stratified by fat content, only high-fat milk consumption showed an association. However, there was significant heterogeneity between the studies. Fermented milk consumption was evaluated in 10 studies and it was concluded that there was an inverse association between fermented milk consumption and cancer incidence in females only, with some evidence of a dose-responsive relationship. There was moderate heterogeneity between the studies.

Cheese consumption was investigated in 10 studies, and showed little association, with some indication of a high cheese intake associated with increased risk of colorectal cancer mortality. Little to no heterogeneity was found between studies focusing on cheese intake.

Cruijsen et al (2021) investigated the association between dairy consumption and myocardial infarction mortality. 4364 participants aged 60-80 years old from the Alpha Omega Cohort were followed for an average of 12 years. Participant's dietary intake was measured using an FFQ. Yoghurt consumption showed an inverse association with cardiovascular mortality and all-cause mortality. Associations for milk and all other dairy products were neutral or inconsistent. Multi-omics analyses reveal relationships among dairy consumption, gut microbiota and cardiometabolic health.

Zhang et al (2021) conducted an umbrella review of systematic reviews and meta-analyses on the association between milk consumption and health outcomes. Forty-one meta-analyses were included with forty-five unique health outcomes covered. Milk consumption was more often linked to benefits to health rather than harm, and dose-response analyses revealed that an increment of 200ml a day of milk was associated with a lower risk of cardiovascular disease, stroke, hypertension, colorectal cancer, metabolic syndrome, obesity and osteoporosis. However, milk intake was also associated with a higher risk of prostate cancer, Parkinson's disease, ace and iron-deficiency in infancy.

These three studies (Jin et al, 2021; Cruijsen et al, 2021; Zhang et al, 2021) reflect the inconsistency observed throughout 2021 diary research. The main drivers of these inconsistencies are due to bias, confounding factors, heterogeneity in methodology and the observational nature of research. Scientists are recommending research to shift to focus on biomarkers and metabolites, and an emphasis on randomised control trials, as these will all help to understand the underlying mechanisms of health effects of diary and help to navigate the inconsistencies.

Drouin-Chartier et al (2021) aimed to identify the plasma metabolites associated with dairy consumption, and to determine if these reflected any found association between dairy consumption and the risk of type 2 diabetes. Participants were sourced from three cohorts, with 1833 from the PREDIMED baseline cohort, 1522 from the PREDIMED year 1 cohort and 4932 from a pooled cohort. 87 unique metabolites associated with total or specific dairy consumption were identified, and an inverse association with dairy consumption and type 2 diabetes risk was reported.

Meat

Like dairy, meat has come under growing scrutiny in the past decade. With substantial research indicating an association between meat consumption and colorectal cancer, research investigating the potential side effects of meat consumption has increased dramatically. Although highly publicised, the conclusions of such research are both inconsistent and controversial.

Iqbal et al (2021) investigated the association between meat intake and risk of cardiovascular disease, and the differences in this association between types of meat. 134,297 participants were followed for an average of 9.7 years across 21 low-, middle- and high-income countries. Their dietary intake was assessed at baseline using a country- specific FFQ. Meat was broken into processed meats, meat and poultry. Based on their dietary information, participants were categorised into high consumption(>250g/wk) or low consumption (<50g/wk). Vegetarians were used as the reference group. No association was observed between the higher consumption groups of unprocessed red meat and total mortality, or cardiovascular disease. Similarly, no association between total mortality or cardiovascular disease and poultry was found. Consumption of >150g/wk of processed meat was associated with a higher total mortality and cardiovascular disease risk, when compared to vegetarians (0g/wk).

Zhang et al (2021) investigated the association between meat consumption and dementia incidence. The UK Biobank cohort was used in this study, comprising 502,493 participants. Dietary intake was measured using a FFQ at baseline, followed with repeated 24-hour recall dietary assessments. Participants were followed for an average of 8 years. Zhanget al (2021) reported that the consumption of processed meats was associated with an increased risk of all-cause dementia and Alzheimer's disease, while unprocessed meat was associated with lower risks. Although, they do comment on the inconsistency in related studies, as the differentiations between processed and unprocessed meats are inconsistent. Studies exploring the differences between the types of meat are still mainly observational, as the underlying reasons are only theorised.

Zhang et al (2021) proposes the potential for the protective effect of unprocessed meat to be due to its protein content, as adequate protein intake has been linked to a reduced risk of mild cognitive impairment and dementia in the elderly. Theories of the effects of iron content are similar inconsistent, as some have indicated an association between iron deficiency and decreased cognitive processes, while others have indicated iron deposits in the aging brains impairing cognitive function. Zhang et al (2021) overall posits that the beneficial and negative effects of different meat types on the risk of dementia may exist simultaneously, thus leading to the inconsistency.

Papier et al (2021) also used the UK Biobank cohort to investigate the association between meat consumption and various health outcomes. As the most publicised negative health outcomes associated with meat consumption is cancer, they focused on 25 conditions other than cancer. They reported that unprocessed red meat intake was associated with a higher risk of ischaemic heart disease, pneumonia, and diabetes. Processed meat intake was more significantly associated with a higher risk of ischaemic heart disease, pneumonia, and diabetes as well. Differences in BMI across the categories of meat consumption appear to account for a substantial part of the increased risks, suggesting that residual confounding by adiposity may still operate.

Mofrad et al (2021) examined the relationship between meat consumption and depression, anxiety and psychological distress. 482 women aged 20-50 were included. Dietary intake was evaluated using an FFQ and depression and anxiety was measured using the Depression, Anxiety and Stress Scale (DASS-21). The prevalence and symptoms of depression, anxiety and psychological stress were increased among individuals in the top quartiles of red meat consumption, compared to those in the bottom quartile.

Mofrad et al (2021) proposes multiple mechanisms potentially responsible for this association.
Research conducted on rats found that the consumption of high-fat diets was associated with a higher risk of depression. Another potential mechanism may be the quantity of Arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid(DHA) contained in red meat. While EPA and DHA are known for their anti-inflammatory properties, AA is known to stimulate the synthesis of inflammatory mediators.

Therefore, the balance between these acids determines the inflammation caused by red meat, and inflammation has been established as playing a key role in depression. Teelet al (2021) conducted a meta-analysis on the available literature investigating this association. This study reported inconsistent results as some studies reported higher depression level in meat abstainers compared to meat consumers, while others reported the opposite. Tell et al. (2021) concluded overall that the evidence of an increased depression level in meat abstainers compared to meat consumers was more consistent and compelling.

Dietary patterns

Trimethylamine N-Oxide (TMAO) is a metabolite generated in response (in part) to meat consumption by the gut. TMAO has been linked to poor cardiometabolic health. Argyridouet al (2021) aimed to investigate the effect of a vegan diet intervention of the plasma levels of TMAO, potentially highlighting a mechanism by which vegan diet influences cardiometabolic health. 23 participants with obesity or dysglycemia followed an 8-week vegan diet, followed by a 4-week period of an unrestricted diet. Participant glucose tolerance and plasma TMAO were measured at baseline, week one, week eight and week twelve of the intervention. TMAO levels decreased after weeks 1 and weeks 8 of the vegan diet intervention, they however rebounded at week 12 after their return to an unrestricted diet.

Kaiser et al (2021) investigated the association between a vegan diet and cardiovascular disease through a review of 7 studies, containing 73,000 total participants. Cardiovascular events were defined as total cardiovascular disease (CVD) incidence, coronary heart disease (CHD), acute myocardial infarction, total stroke, haemorrhagic stroke and ischaemic stroke. There was no significant association between adherence to a vegan diet and risk of primary CVD or a CHD event. Some studies reported vegan diets preventing recurrent cardiovascular events, but these studies were of poor quality.

Kaiser et al (2021) suggested the vegan diet had mechanisms to both cause and prevent harm. Lower levels of nutrients such as DHA, selenium, zinc iodine and vitamin B12 seen in vegans have a potential for causing adverse cardiovascular health effects. In contrast, the vegan diet's optimal macro- and micronutrient composition, lower cholesterol and saturated fats, and higher plant sterols and fibre content may be responsible for favourable effects on cardiovascular health.

Marrone et al (2021) investigated the effect of a vegan diet on metabolic syndrome. They argue that the main downfall of vegan diets is the risk of developing nutritional deficiencies of proteins, omega 3 fatty acids, vitamin B12, iron, zinc, iodine, vitamin D and calcium. The debate surrounding protein adequacy of a vegan diet remains inconsistent, as some studies indicate adequacy and others do not. They emphasise the need for nutrient supplementation in vegans as studies indicate lower levels of B12, vitamin D and calcium. Although vegan calcium sources are abundant, the decreased vitamin D levels associated with the vegan diet has been shown to limit absorption of calcium.

Upon analysis of literature examining the health effects of a vegan diet, an association was reported. A vegan diet was reported to be associated with increased satiety, antioxidants levels., and magnesium (Mg^{+}) and potassium (K^{+}) concentration. It was also associated with decreased blood glucose levels, BMI, low-density lipoprotein-cholesterol and lipopolysaccharide levels. Overall, they concluded that a vegan diet appears to be a useful tool in the prevention of metabolic syndrome and cardiovascular diseases.

Coelho-Júnior et al (2021) investigated the influence of the Mediterranean diet on physical performance and cognitive function in older adults. 9 studies were included, and the findings were that high adherence to the Mediterranean diet was associated with better walking speed, knee muscle strength speed, global cognition and memory. The mentioned studies have moderate to low risk of bias.

Guasch-Ferré & Willett (2021) published a comprehensive overview of the impact of the Mediterranean diet on health. The traditional Mediterranean diet comprises a high intake of plant-based foods, minimally processed and locally grown foods, with the principal source of fat being olive oil. Dairy intake is moderate, with cheese and yoghurt intake more prominent, fish and poultry in low to moderate amounts, and red meat in low amounts. Although individual components of the diet have been researched, emphasis is placed on the overall diet itself, highlighting the synergistic interactions between them. A key issue is whether this traditional form of the diet can be generalised to all populations, and as such variations to the Mediterranean diet have emerged.

Guasch-Ferré & Willett (2021) comment that the most consistent and robust evidence of health benefits from the diet is the association observed with cardiovascular risk factors and outcomes. They summarise that the evidence strongly indicates that adherence to a Mediterranean diet reduces the risk of several cardiovascular outcomes and proposes that this association can be explained in part by the beneficial impact of the diet on cardiovascular risk factors like diabetes and metabolic syndrome. As the Mediterranean diet is high in fats, there is some apprehension to recommend the diet to patients with obesity. As such, this has been an area of research. Guasch- Ferré & Willett (2021) summarise that evidence overall indicates no association with obesity and the diet, and that calorie-restricted Mediterranean diet interventions are associated with weight loss. The association with cancer has also been heavily researched. Here they mention Morze et al (2021) study, a meta-analysis containing 117 studies with a total population of 3,202,496 participants.

This meta-analysis concluded that the Mediterranean diet was inversely associated with breast, colorectal, head and neck, respiratory, gastric, bladder and liver cancers (0.94, 0.83, 0.56, 0.84, 0.70, 0.87 and 0.64, respectively). Cognitive function has also been an area of great interest, and the impact of this dietary pattern on it is summarised here. There is strong observational evidence that adherence to the Mediterranean diet can reduce the decline in cognitive function, but the evidence from intervention studies is scarce. Intervention studies examining total mortality and difficult to conduct and rife with ethical dilemmas. Guasch-Ferré & Willett (2021) mention the PREDIMED trial that was stopped due to ethical reasons because of the benefit shown for the primary endpoint 33.

Overall, they summarised the evidence for certain health outcomes through grading. The evidence for cardiovascular disease, diabetes and metabolic syndrome were considered convincing, the evidence for total and breast cancer and cognitive function is highly suggestive, and the evidence for total mortality, overweight and obesity and specific cancers are suggestive.

Metabolic syndromes

A higher intake of vegetables has consistently been associated with improved metabolic health, however the role specific nutrients may play in said association is under-researched (Nguyen et al, 2022; Mumme et al, 2021).

One nutrient of specific interest is nitrate, as evidence has emerged of increasing dietary nitrate intake to improve cardiovascular health. Avoort et al (2021) investigated this theorised association over a 12-week intervention. 77 participants were randomly assigned into either a supplementation group, a vegetable intake group or the control group. Those in the vegetable intake groupware instructed to maintain their usual diet in addition to ~250-300g of nitrate-rich vegetables, that translated to around ~350-400mg of nitrate a day. The supplementation also consumed their usual diets but also were provided with a concentrated beetroot juice that provided them with 400mg of nitrate a day. The control group showed an increase in their systolic blood pressure, while the vegetable intake group showed a significant decrease in systolic blood pressure. The beetroot supplementation groups showed no change in their systolic blood pressure. No groups showed a change in their diastolic blood pressure. Flavonoids are a class of polyphenolic secondary metabolites and have many theorised health benefits including potential protection against type 2 diabetes. Polyphenols specially were indicated in the 2020 report as a compound of interest.

Bondonno et al. (2021) aimed to investigate the association between flavonoid intake and diabetes incidence, while also identifying subpopulations that may receive the greatest benefit from increased flavonoid intake. 54,787 participants aged 50-64 were followed for an average of 23 years. Participant body fat was measured at enrolment using bioelectrical impedance. 6700 of the participants were diagnosed with diabetes during the duration of this study. They concluded that a flavonoid-rich diet was inversely associated with diabetes incidence, although this association plateaued at moderate flavonoid intakes (~400- 600 mg/d). These findings did not appear to be modified by any health behaviours of the individual, with the exception of obesity status, where those with obesity were shown to benefit the most from a higher flavonoid consumption. Cross-sectionally, total flavonoid intake was inversely associated with body fat, thus explaining approximately half of the association between flavonoid intake and diabetes incidence.

Brayner et al (2021) compared the differences in the associations between fat type and the risk of developing obesity and type 2 diabetes. The fat types of interest were saturated fats (SFAs), polyunsaturated fats (PUFAs) and monounsaturated fats (MUFAs). 16,523 participants were followed for an average of 6.3 years. Dietary intake was measured using the Oxford WebQ – a hybrid of a 24-hour dietary recall and an FFQ. From the data collected, two main dietary patterns were identified; DP1 and DP2. The DP1 dietary pattern had a high intake of nuts and seeds, vegetable dishes, and butter. They also had a low intake of fruits, low-fat yoghurt and wine, and overall consumed more of all types of fats, vegetables and animal fats. The DP2 dietary pattern had a high intake of butter, high fat cheese and ice cream, with a low intake of nuts, seeds and vegetables.

Overall, they consumed higher amounts of SFAs and animal fats, and lower amounts of PUFAs and vegetables. The two dietary patterns contained no major differences in carbohydrate, protein and energy intake between them. In terms of obesity, the DP1 dietary pattern showed no association, whereas the DP2 dietary pattern showed strong association for those in the highest quartile of DP2. Neither dietary pattern showed an association with type 2 diabetes.

Bakaloudi et al (2021) performeda review and meta-analysis of observational studies investigating the influence of the Mediterranean diet on metabolic syndrome. 58 studies were included, and factors such as waist circumference, blood pressure, fasting blood glucose, high-density lipoprotein cholesterol and triglycerides were measured. High adherence to the Mediterranean diet was associated with a lower waist circumference and triglycerides. They found no significant difference in fasting blood glucose or blood pressure in this group. High-density lipoprotein cholesterol was reported as significantly higher in the group with a high adherence to the diet, but there was high heterogeneity between the studies.

Current understanding and direction of science

Epidemiological literature has clearly identified associations between specific dietary habits and health outcomes. The identification of the mechanisms responsible for such associations are essential to forming evidence-based recommendations for the public. The current understanding of these mechanisms, and the proposed direction of future research are discussed below.

Health outcomes

Most diseases or disorders are characterised by inflammation in the body (Hunter et al, 2012). Because of this, most of the research into the mechanisms explaining nutrition-associated health benefits focus on how specific dietary components influence inflammation. Inflammation is characterised by an increase in oxidative stress in the body through an excess of reactive oxygen species (ROS). ROSs are by- products of cellular functions throughout the body and can be 'scavenged' by antioxidants and anti- inflammatories (Chatterjee, 2016).

For metabolic health there are two syndromes that are of primary interest - obesity and diabetes. Obesity is considered low-grade inflammation state throughout the body due to an excess of adipose cells (Nani et al, 2021). An increased energy intake and saturated fat intake is shown to increase the production of ROS in the body, thereby triggering an inflammatory pathway that ultimately results in an increased expression of pro-inflammatory cytokines, and a downregulation of the anti-inflammatory molecule AMP-activated protein kinase (AMPK) (Dandona et al, 2005).

Diabetes is linked to an increased intake of fats and carbohydrates along with a decreased fibre intake. However, these dietary components have yet to be linked to the specific mechanisms preventing diabetes or diabetes-related symptoms. Said mechanisms are lower haemoglobin A1c (HbA1c) and fasting glucose levels (Esposito & Giugliano, 2013).

Cardiovascular events are mainly due to atherosclerosis and plaque formation (Balakumar et al, 2016). These in turn are caused by high low- density lipoprotein (LDL) and low high-density lipoprotein(HDL) levels, as well as the susceptibility of the LDL particles to aggregate. A diet high in vitamin E has been shown to reduce this susceptibility, therefore acting as a potential mechanism (Ruuth et al, 2018). Diet interventions have also been shown to directly affect the levels of LDL and HDL, highlighting another potential mechanism. Phytochemicals like polyphenols from an individual's diet may also influence their health through the increase in antioxidant molecules, but also in their stimulation of nitric monoxide (NO) levels (Valeria et al, 2018). NO has been established as having a vasodilating effect, thereby inhibiting platelet aggregation and occlusion of coronary vessels (Loscalzo, 2001).

The mechanisms responsible for the beneficial impact of nutrition on neurodegenerative diseases are significantly understudied, as the cause and clinical treatment of them remains considerably undetermined. One proposed mechanism is that fats may increase the permeability of the blood- brain-barrier and increase the number of beta- amyloid plaques which are associated with Alzheimer's disease (Rajaram et al, 2019).

Polyphenols have also been focused on as they are able to cross the blood-brain-barrier and can therefore exert an antioxidant effect in the brain. One specific polyphenol called Hesperidin has become of interest as it appears to increase cerebral blood flow, thereby preventing cognitive decline (Haiyan et al, 2019). Overall, the mechanisms responsible for the impact of nutrition on any health outcomes are significantly understudied and require further research.

Dairy

The current understanding of the health benefits of dairy reflects the findings throughout published literature - inconsistency. For example, saturated fat intake is recommended to be low and as such, most dietary recommendations suggest consuming low-fat dairy products rather than full-fat products. But emerging research indicating that the characteristics of fatty acids like their carbon length chain and the number and location of the unsaturated double bonds, are what actually determine its impact on health. Therefore, saturated fats with shorter carbon length chains may actually be beneficial to one's health, and in some studies, this has been reported (Hirahatake et al, 2020).

One cannot also ignore the countless studies reporting the effectiveness of dairy products as calcium and amino acid sources. Said amino acids have been linked to reduction in blood pressure and arterial stiffness (Pana et al, 2020). The calcium intake from milk increases the levels in the body, so calcium can be used for maintaining bone health and for muscle contraction. Another mechanism is its influence on the microbiome as a probiotic, stimulating the growth of beneficial bacteria like Lactobacillus and Bifidobacterium.

The health of said microbiome has been linked to the overall health of the body, particularly through its modulation of inflammation (Aslam et al, 2020). Ultimately, the mechanisms by which dairy negatively impacts health are not well understood and require extensive research. One could propose that it is the overconsumption of dairy products that is to blame, and that such negative health impacts are because of the subsequent deficiencies in other vital nutrients. Although, clearly dairy is a good source of calcium and amino acids, it does not offer the same variety of nutrients as plant-based calcium sources do. This would explain the association indicated in observational studies, as individuals who consume more dairy may also consume less vegetables other sources of nutrients besides calcium.

Meat

Meat has long been integral to the human diet and is considered the main element of dishes in the Western world. For many it is the default protein option in their diet. Research on its impact on health is inconsistent and without a clear conclusion.

The proposed beneficial impacts on health are due to its nutrient composition as meat contains all essential amino acids and several vitamins and nutrients (Tielandet al, 2012). The main reason for proposed negative impacts on health are mainly processing and the saturated fat content of meat. Generally saturated fatty acids (SFAs) constitute around half of the fat in meat, and overall contribute to half of the maximum recommended daily intake (Becker et al, 2016; Wyness et al, 2011).

Recent studies have argued that the complexity of saturated fatty acids is not yet understood, and that previous research showing an association between its consumption and negative health outcomes may have been confounded by industrial trans-fats in margarines(Geiker et al, 2021). Similarly, to dairy, the role of the food matrix on health outcomes may be a better method for evaluating the health outcomes related to meat consumption. Meat alone can provide a good majority of many vitamins (selenium, iron, etc) but when consumed in excess, an individual may develop nutrient deficiencies as meat is emphasised over a balanced diet. Further research should focus on standardisation of research protocols and on investigating meat consumption in conjunction with a healthy diet, versus an unhealthy diet as this will help to remove confounding (Becker et al, 2016).

Dietary patterns

The Mediterranean and Vegan diets are both characterised by a high intake of fruits, vegetables, unsaturated fats, and fibre. Both also emphasis the consumption of plant-based foods, and minimal consumption of animal-based foods, although the vegan diet completely avoids them altogether.

The current understanding of the mechanisms responsible for the health benefits associated with these dietary patterns mainly concern their adequacy in nutrient intakes. The intake of plant-based oils and fish increase antioxidant and omega 3 fatty acid intakes, which are assumed to decrease inflammation across the body, and potentially stimulate proliferation and angiogenesis(the formation of new blood vessels). The intake of fibre positively impacts health as it is associated with reduction in insulin resistance and therefore metabolic syndromes like diabetes. Specifically, the high fruit intake provides a great source of soluble fibre, which is responsible for short chain fatty acid (SCFA) production by colonic bacteria in the intestine, contributing to overall gut health.

These dietary patterns are also suggested to garner health benefits through their avoidance of overly processed foods that increase inflammation, and their complete/partial avoidance of meat and dairy. The Mediterranean diet specifically has been heavily researched in the past decade and will continue to be. As climate worries grow research on the Vegan diet will continue to increase, as the possibility of minimising animal-based foods consumption is also investigated.

Polyphenols

Polyphenols are secondary plant metabolites synthesized in both normal conditions, and in response to stress. They are not essential for body metabolism but contribute to overall health and are the most abundant antioxidant compound found in the human body (Chun et al, 2005). The mechanisms by which they contribute to overall health are their antioxidant properties and their interaction with the host's microbiome.

Their ability as an antioxidant is due to their structure containing phenolic hydroxyl groups, which are able to donate a hydrogen atom or electron, and their conjugated aromatic system available for delocalisation of unpaired electrons. These structures mean they can remove free radicals (known as 'reactive oxygen species' or 'ROS') from the body that contribute to inflammation (Galanakis et al, 2015). An increase in ROS and therefore inflammation is linked to various disorders and diseases, illustrating how polyphenols can help prevent or treat them.

Their influence in the gut microbiome is not well understood but is an emerging area of interest. Evidence has shown that they can influence the composition of the microbiome, inhibiting some groups, while leaving others intact, or stimulated (Duda-Chodak et al, 2015). Their inhibition of Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa has been demonstrated, along with their stimulation of Bifidobacterium and Bacteroides (Nakayama et al, 2012; Tzounis et al, 2007).

The mechanisms of this influence need to be investigated further, but the current understanding is that polyphenols alter gut permeability, sensitise bacteria to xenobiotics and exert local anti-inflammatory effects (Singh et al, 2019). Areas of future research pertaining to polyphenols will most likely in regard to such mechanisms, as well as the various factors influencing their bioavailability and bio-efficacy. Their bioavailability is known to be low, but differs between types, so research is needed to understand these differences and the metabolites associated with each. Currently, it is known that only 5-10% of dietary polyphenols can be absorbed into the small intestine, while the rest are absorbed in the large intestine and interact with gut microorganisms (Manachet al, 2005).

2021 Research Conclusions

The research in areas of nutrition and health in 2021 appeared to follow major themes. In terms of 'food as medicine', the key health outcomes of focus are reflected in health statistics, as research is driven by the burden of disease.

Cardiometabolic outcomes, neurodegenerative diseases and metabolic syndromes are among the most researched for both prevention, and correlation. Confirmation of a 'healthy' diet remains prominent, with focus on the discourse of meat and dairy intake, and the impact of key food groups on health. Dietary patterns such as the Mediterranean diet and Veganism are of specific interest. Another area of research was specific food compounds such as polyphenols, and their impact on health.

In science there are never absolute truths, and rarely are there approximate ones. Despite this, science can inform policy, technology, and investment. The large majority of nutrition research published in 2021 supported the initial findings of the 2020 report. However, there were limitations consistent throughout this research that act as key drivers of scepticism and acted as barriers.

Firstly, participant nutrient intake was most commonly measured through food frequency questionnaires (FFQ) and 24-hour recall questionnaires. Besides the obvious benefits of their low administrative cost and ability to assess long periods of time, their validity and accuracy cause dissension. They contain a finite list of food and beverages that rely on a participant's recall of their dietary intake over an extended period. There are numerous variations that differ in their inclusion of serving sizes. They are frequency- based, asking the participant questions like "how often do you eat a specified food?". This results in the opportunity for measurement error or subjective reporting. It also falls short in regard to accuracy as it doesn't reflect fluctuations and changes in an individual's diet, worsened by the minimal number of reports throughout the duration of a study. Overall, the use of food frequency questionnaires brings into question the validity of dietary intake data and therefore any associations found (Kristal et al, 2005).

Another limitation is the observational nature of the mentioned studies. Observational studies can identify correlation but cannot determine causation. Meta-analyses reveal the methodological inconsistencies rife throughout such observational studies. The research remains a good indicator of the associations between two variables, but without the understanding of the mechanisms causing such an association, causation cannot be determined. In short, epidemiological evidence needs to be corroborated with criteria of biological plausibility. This is especially significant in food science, where randomised controlled trials, considered the gold standard for determining causation, are not often feasible. This is because unlike the very clinical scenario of one exposure and one outcome, food is seldom consumed in isolation. Therefore, a drug or therapy-like evaluation of it is not a true reflection of its therapeutic capacity. Instead, a food matrix approach would be more suitable.

A food matrix approach considers the nutrient and non-nutrient components of a food, including the food it is consumed with. It is viewing food further from the individual item and further than the plate. Instead, it considers the synergistic or antagonistic effect other foods may have on it if consumed together. It also considers the bioavailability of its nutrients within the body, acknowledging that the way we prepare, cook and store our foods all influence the bioavailability (Elizalde-Romero et al, 2021). The microbiome is also considered, and subsequently the impact of its composition on the body's ability to absorb and utilise a nutrient. Due to the integration of the microbiome, this approach spans wider than our plates or our kitchens, and back to our adolescence, our birth, and our mother's own diet (Cortes-Macías et al, 2020).

Microbiome

The microbiome is an area of research that has grown substantially in the past decade, and the reported findings suggest that manipulation of gut microbes may be a powerful means to alter diverse aspects of human health. Gut microbiome research in 2021 had many breakthroughs. The COVID-19 pandemic specifically led to a large interest in the role of diet on health, and particularly 'immune boosting'. Though most research was observational, some looked at changes in immune markers in response to a dietary intervention.

Wastyk et al (2021) investigated the impact of two dietary interventions- plant-based fibre and fermented foods, on the human immune system. Across 17 weeks, 39 participants were followed and randomly assigned to either intervention.

Blood and stool samples were collected at each of the four stages of the study. Stage one was prior to the intervention occurring and lasted for three weeks to gather baseline data. Stage two was named the "ramp" stage where participants gradually increased their intake of the respective interventions. Stage three was the maintenance phase where participants maintained high level of consumption for 6 weeks. Lastly, stage four was a 4-week period where participants maintained their diet to their desired extent. Stool samples gathered data on microbiota composition, function and metabolic output. Blood samples generated a systems-level view of the participant's immune system, with measurements of their cytokine levels among others.

The participants' gut microbiota did not differ in alpha or beta diversity at baseline between the two interventions. Food logs were completed by the participants every two weeks. High- fermentation participants showed significant increase in microbiota diversity and a decrease in inflammatory markers upon completion of the study compared to the beginning. High-fibre participants showed a small decrease in inflammatory markers. However, whether the observed changes were due to the intervention alone is not clear. High-fibre participants also increased their intake of soluble and insoluble fibres, carbohydrates, vegetable proteins and various micronutrients. They also decreased their animal protein and sodium intakes. High- fermented participants increased their animal protein intake as they consumed fermented dairy products.

The bacterial members of the microbiome are the predominant interest of most microbiome research. In 2021 however, some focus shifted towards the other members like fungi dubbed the mycobiome. An interesting breakthrough in this field has been the association shown between inflammatory bowel disease (IBD) and the mycobiome composition. Gastrointestinal diseases like IBD have remained elusive and challenging in identifying the underlying microorganisms and potential therapies.

Debaryomyces hansenii is a fungus used for ripening cheese and meat products in the food industry. Jain et al (2021) found that it is enriched in inflamed mucosal tissues of patients with IBD and in mice it causes impaired wound healing. They theorised this involvement to be possibly due to fungal outgrowth caused after use of antibiotics. Mice treated with VNAM (broad- spectrum antibiotic) showed a dominant genus, Debaryomyces, upon analysis of ITS amplicons from their mucosal wounds. In contrast, controls had no detectable levels of this genus in their microbiome. These findings provide a previously uncharacterised host microbial axis that can be targeted to improve healing in IBD cases.

Sepich-Poore et al 2021 reviewed relevant literature on the role the microbiome may play in human cancer. They concluded that strong experimental evidence suggest that microbes play a role in cancer through genotoxin-mediated mutagenesis, or as virulence factors that amplify tumorigenesis. The gut microbiome are known to have broad influence, contributing to host immune tone but may also effect this during tumorigenesis. They have also been shown to modulate immune responses and can influence the efficacy of radiation therapy.

Nejman et al (2020) surveyed 1010 tumours for bacteria across melanoma, lung, ovarian, glioblastoma, pancreas, bone and breast cancer. They reported substantial differences in composition, diversity and inferred metabolic functionality between cancer types, suggesting tumour-specific microbiome. Nejman et al (2020) and Sepich-Poore et al (2021) suggest further research, specifically into modification of the gut and tumour microbiomes as a mechanism to enhance chemotherapies. These findings identify the potential for microbiome-based therapies for cancer, and the potential for the microbiome to be the mechanism connecting diet and cancer, an association observed in recent literature.

Although promising, the field of microbiome research is one laden with gaps of knowledge. Largely due to the mere size and variability of the microbiome, few microorganisms and their genes are fully characterised.

Unlike genetics, the microbiome is amenable and varies both between individuals and within an individual. Samples of the microbiome taken only have a dept of cultivation of around 30-60%, even in the most recent of studies (Segata & Thomas, 2019). The combination of the large gaps in knowledge and the extreme variability and sensitivity of the microbiome brings up the question of the validity of research in this field.

There are concerns about the reproducibility of data due to such gaps in microbial sequencing data dubbed as "dark matter" (Clavel et al, 2021). This is worsened by the lack of standardisation of procedures and gene sequencing in microbiome research. Variation in sample handling, sampling size and DNA extraction methods lead to inconsistent results. As such, there is a call to standardise these methods, and to also collate data to replicate projects like The Human Genome project (Martiny et al, 2019).

One project of interest is the European project 'Microbiome Support' aiming to establish international standards and protocols for microbiome research. This will hopefully address some of the issues in microbiome research. Conference in 27-29 June 2022 "Paving the Microbiome Way for Improved Food Systems" will provide unique insights into how microbiomes can deliver sustainable and innovative solutions that create significant positive impacts on our food systems (Microbiome Support, 2021)

Emerging Science

An emerging science under global focus currently is CRISPR gene editing. This allows scientists to alter DNA sequences and modify gene functions, with the potential to correct genetic defects, treat and prevent the spread of diseases, improve the growth and resilience of crops and more. CRISPR gene editing involves two parts - the CRISPR itself and the protein Cas9. CRISPRs are specialised stretches of DNA, and Cas9 is an enzyme that acts like a molecular pair of scissors, able to cut DNA strands (Live Science, 2021).

CRISPR was first discovered in 1987, but the significance of it was not understood until 2012, when a paper was published, that has since won Nobel prize (Doudna & Charpentier, 2014).CRISPR gene editing was adapted from the natural defence mechanisms of bacteria, where it was observed that the organism uses CRISPR-derived RNA strands and various Cas proteins to inhibit attacks by viruses. The DNA is chopped up by the CRISPR RNA and Cas proteins, and is then stored in the microorganism to be used as a weapon in case of future attack. Because of this, CRISPR regions are likened to "banks" or viral memories.

CRISPR has some apparent ethical concerns as it is gene editing. One example of this is the case of He Jiankui - a biophysicist who announced his team had edited DNA in human embryos, creating the world's first gene-edited babies. He was promptly sentenced to three years in prison and fined 3 million yuan for "practising medicine without a license, violating Chinese regulations on human- assisted reproductive technology and fabricating ethical review documents" (Live Science, 2020).

Besides this sensationalised case, other ethical concerns surround the limits of our knowledge, and therefore the potential for unintended consequences that can be genetically passed on. The potential for lines between therapeutic and enhancement tools to be blurred is also a considered dilemma. Currently, germline editing is recommended to be only done on genes leading to serious diseases when there are no other reasonable treatment alternatives.

As this research is in its infancy, there is very little known about potential long-term consequences. As of today, none have been identified, and many trials are underway for treatments against genetic diseases like Sickle Cell Disease (Washington Post, 2022).

Gerascophobia, or the 'fear of aging', is a fear that plagues most of humanity (Perales-Blum et al, 2014). research in 2021 has made strides in unlocking the secrets of aging. Senescent cells are aged cells that lose their ability to replicate, and instead produce inflammatory substances. They have been shown to increase as an individual ages and are therefore a potential target for anti-aging therapies (Gorgoulis et al, 2019).

Xu et al (2021) investigated the effect of a chemical named procyanidin C1 (PCC1) on the lifespan of mice. PCC1 is a chemical isolated from grape seed extract. At low concentrations it was shown to prevent senescent cells from producing inflammatory substances, and at high doses it killed said senescent cells, while not harming younger cells. Overall, PCC1 appeared to increase the lifespan of the treated mice by 9%, and also increased physical fitness in younger mice. They also investigated the effect of PCC1 on tumours in conjunction with chemotherapy. This is because chemotherapy is known to accelerate the aging of tumour cells. Tumours treated with PCC1 and chemotherapy shrank by 75%, whereas chemotherapy alone shrank tumours by 44%.

Such senescent cells were also targeted by Suda et al (2021), who developed a vaccine against these cells. Senescent cells occur throughout the body and thus look different to one another. Suda et al (2021) focused on senescent vascular endothelial cells, that line the walls of arteries, veins and capillaries. They analysed the surface proteins of these cells, and selected the protein called glycoprotein nonmetastatic melanoma protein B (GPNMB), as the target antigen.

Evidence suggests that in individuals with atherosclerosis have more GPNMB on their vascular endothelial cells, and the potential for the inflammatory substances produced by senescent cells to contribute to the plaque build-up that characterises atherosclerosis. Once injected into the mice, the vaccine prompted the immune system to target cells with GPNMB on their surface and mark them for apoptosis (cell death). GPNMB cells, arterial plaques and inflammatory molecules significantly decreased in the vaccinated mice, and slightly increased their lifespan.

A limitation of this study is the fact that not only senescent cells present GPNMB on their surface, so there is the potential for other cells to become targets of the immune system, although that was not reported in this study.

Nutraceuticals

Nutraceuticals cover any products derived from food sources that provide extra health benefits in addition to their basic nutritional value. They include dietary supplements, but they also contribute to prevention and/or treatment of diseases (Lordonet al, 2021). Although, this term was first defined in 1989, research into them has expanded rapidly in recent times. The balancing act for regulatory bodies is to maintain regulation that is sufficient to protect consumers, but not to the extent of stifling the nutraceutical market. Nutraceuticals are currently governed under food regulations, which can result in little protection for the consumer. Alternatively, classifying nutraceuticals as medication may prevent innovation in the field, especially that done by small groups, due to the cost and scale expected in clinical trials.

In 2020, the global market for nutraceuticals was US$233.9 billion, projected to be US$358.5 billion by 2027. North America, Japan and China are the largest consumers (Unleashed Software, 2020). The nutraceutical market is a controversial one, but clearly, the demand for nutraceutical products is growing. Alongside this growing demand, innovations in how to improve their effectiveness also grow. One of the biggest challenges in the nutraceutical field is ensuring adequate bioavailability of the product in the body. This is where Nano science comes into play.

Nano science involves the development of nanometre-sized products. An innovation of interest is the development of encapsulation technologies. These involve the encapsulation of nutraceuticals within the interior of protein nano- architectures. These work well because most nutraceuticals bind to proteins, forming a complex that improves the stability and bioavailability of nutraceuticals.

The major challenge in this innovation is to determine the appropriate conditions in which the proteins self-assemble into the desired products, as these conditions vary with nutraceutical type, protein type and encapsulation type (Acosta, 2009). A practical application of this innovation would be the successful encapsulation of polyphenols to increase their bioavailability within the body (Oliveira et al, 2021).

Personalised Nutrition

Personalised Nutrition in an era of convenience and innovation; this personalisation of technology for the individual consumer seems inevitable. Examples of this already exist in the algorithms dictating our social media feeds and in services like Function of Beauty (a personalised shampoo and conditioner subscription). An emerging area in this personalisation is nutrition, and the potential to produce products and diets specific to a consumer.

As scientists further our understanding of the complexity of diet and nutrition, it becomes increasingly clear that individual factors influence potential outcomes. The personalisation of nutrition through phenotypic, genotypic and microbiome data, would allow for more effective interventions and treatment. As such, this is an emerging area of research and innovation.

Livingstone et al (2021) investigated the effect of personalised nutritional advice on intake of discretionary foods. Over a 6-month randomised controlled trial, 1609 adults were followed. There were three levels of personalised nutrition - L1, L2and L3 . L1 advice was based on participant's nutrient intake. For example, if a participant's salt intake was high due to their intake of meat-based dishes, the message would say "Reduce your intake of processed meats and pies; swap salami, ham and bacon for turkey or beef."

L2 advice was based on nutrient intake and phenotypic data like BMI, waist circumference and circulating concentrations of fasting blood glucose, omega-3 and carotenoids.

L3 advice was based on nutrient intake, phenotypic data and genotypic data. For example, if a high saturated fat intake was identified primarily due to meat-based dishes, and the participant had high cholesterol and carried the APOE genetic risk variant for Alzheimer's disease, the message may include "You have a genetic variation that can benefit by keeping a healthy intake of saturated fat and a normal level of blood cholesterol. Swap savoury pies and processed meats for lean meats or skinless chicken breast."

Overall, Livingstone (2021) found that personalised nutrition advice helped increase the reductions in discretionary food intake. These findings reflect the opportunity personalised nutrition offers to the individual consumer, and the potential benefits of such technologies.

Although this area of research has great potential, extensive research in this field is required in order to produce evidence-based products. There is currently a huge gap between what we know and what personalised nutrition services offer, and similarly to nutraceuticals, personalised nutrition falls within a grey area, not regulated by food administration laws, so little research and trials are needed before products can be advertised.

New Zealand Science

Dr Lynnette Ferguson obtained her D.Phil.(Oxon) (the equivalent of a PhD) from Oxford University, working on the subject of DNA damage, DNA repair and mutagenesis in yeast.

After her return to New Zealand, she began working as part of the Auckland Cancer Society Research Centre, using mutagenicity testing as a predictor of carcinogenesis, with particular focus on the New Zealand situation. In 2000, she took on a 50% role as Head of a new Discipline of Nutrition at the University of Auckland.

In more recent years, she has considered the interplay between genes and diet in the development of chronic disease, with particular focus on Inflammatory Bowel Disease, a cancer- prone condition, and in prostate cancer.

As programme leader for the multidisciplinary- multiorganization Nutrigenomics New Zealand, she worked with a range of others to bring nutrigenomics tools and potential to the New Zealand science scene. She has supervised more than 40 students to the successful completion of Beach, MSc or PhD. Her laboratory regularly supervises 2-3 summer students each year. She is the author or co-author of more than 350 peer reviewed publications as chapters in books or articles in international journals. She serves on the Editorial Boards of several major journals.

Lynnette's current research considers the interplay between genes and diet in the development of chronic disease, with particular focus on Inflammatory Bowel Disease, a cancer-prone condition and also in both colorectal and prostate cancer. As programme leader for the multidisciplinary-multiorganization Nutrigenomics New Zealand, she has worked with a range of others across The university of Auckland, Plant and Food Research and AgResearch Ltd, to bring nutrigenomics tools and potential to the New Zealand science scene. (University of Auckland, 2021).

Literature published by L. Ferguson:

- A Polyphenol Enriched Variety of Apple Alters Circulating Immune Cell Gene Expression and Faecal Microbiota Composition in Healthy Adults: A Randomized Controlled Trial (2021)
- Diet and nutrition (2021)
- Anticancer Characteristics of Fomitopsis pinicola Extract in a Xenograft Mouse Model—a Preliminary Study (2019)
- Inflammatory bowel disease: why this provides a useful example of the evolving science of nutrigenomics (2020)

Dr Odette Shaw has a PhD in anatomy, with interest in immunology and inflammation pathways. She has a lead role in a Plant & Food Research-led project studying the effect of Boysenberries on inflammatory pathways. Her research focuses on how fruit compounds can support lung health by modifying inflammation. Her researched to the creation of a new co-investment business venture called the Innovation Cell with Anagenix. Anagenix developed BerriQi in 2017, a consumer product aimed at those wishing to protect their lungs against pollution damage.

Also involved in the High-Value Nutrition (HVN) National Science Challenge's Immune Health Priority Research Programmes, which focuses on the influence of diet on lung health. The impact of air pollution and associated threats to health and productivity are significant to Chinese consumers, a key target for New Zealand's export products. As part of the HVN-funded research, Odette has worked with New Zealand-based companies – including Zespri, Manuka Health and Anagenix; to identify existing products in their portfolio that may be beneficial for lung health, including kiwifruit, berry fruit and propolis. She is currently the principal investigator in an HVN-funded project looking to translate the results from the model work into humans through a clinical study measuring the effect of BerriQion lung function after exposure to airborne pollution.
More recently, Odette has engaged with the Rubus breeding team to develop a method for high throughput screening of fruit samples to identify those with inflammation or immunity properties. This cell-based assay platform provides an efficient way to screen the selections in the breeding programme for any varieties that may have beneficial effects and fast track research on those with the best potential for functional food development. By identifying which immune pathways, if any, are activated in the cell model and understanding whether these are primarily involved in improving gut or lung health, for example, trials can be developed that focus on this specific benefit thereby improving the efficiency of food and ingredient R&D. (Plant and Food, 2021).

Literature published by O. Shaw:

- Boysenberry and apple juice concentrate reduced acute lung inflammation and increased M2 macrophage-associated cytokines in an acute mouse model of allergic airways disease (2021)
- Maternal diet impacts on the development of offspring immune response to potential allergens (2019)
- Blackcurrant anthocyanins modulate CCL11 secretion and suppress allergic airway inflammation (2017)

Dr Matthew Barnett graduated from The University of Auckland in May 2005 with a PhD in Biological Sciences, with his thesis research focusing on the importance of a mother's diet during gestation and lactation on the risk of type-2 diabetes in her offspring. Since 2001 he has worked for AgResearch Limited in a range of roles (including Research Associate, FRST Postdoctoral Fellow, and Research Scientist) and on a variety of topics.
He was part of the Nutrigenomics New Zealand collaboration from 2004-2014, working on understanding how diet and genome interact to influence health with a particular focus on intestinal function. While still working for AgResearch, Matthew is currently based at the University of Auckland's Liggins Institute and is involved in several projects investigating the importance of nutrition for health throughout life. While the primary focus of these projects remains intestinal health, other aspects of human health, including cognition and mobility, are increasingly of interest. (Riddet Institute, 2021).

Literature published by M. Barnett:

- A Polyphenol Enriched Variety of Apple Alters Circulating Immune Cell Gene Expression and Faecal Microbiota Composition in Healthy Adults: A Randomized Controlled Trial (2021)
- An update on the role of gut microbiota in chronic inflammatory diseases, and potential therapeutic targets (2018)
- Nutrigenomics: Integrating Genomic Approaches Into Nutrition Research (2017) – worked with L.R. Ferguso

Literature Review

During the course of this research and reporting writing, the following literaturewas reviewed:

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