PSYCHOLOGY MISCELLANY

No.232 - January 2026

Mostly Health 3

Kevin Brewer

ISSN: 1754-2200

orsettpsychologicalservices@phonecoop.coop

This document is produced under two principles:

1. All work is sourced to the original authors. The images are all available in the public domain (most from http://commons.wikimedia.org/wiki/Main_Page). You are free to use this document, but, please, quote the source (Kevin Brewer 2026) and do not claim it as you own work.

2. Details of the author are included so that the level of expertise of the writer can be assessed. This compares to documents which are not named and it is not possible to tell if the writer has any knowledge about their subject.

This document is presented for human readers.

Kevin Brewer BSocSc, MSc

An independent academic psychologist, based in England, who has written extensively on different areas of psychology with an emphasis on the critical stance towards traditional ideas.

A complete listing of his writings at http://psychologywritings.synthasite.com/. See also material at https://archive.org/details/orsett-psych.

CONTENTS

1. BIRTH ETC

1.1. ABORTION

Isosorbide mononitrate (ISMN) is a nitric oxide donor which dilates blood vessels. One of its uses is to terminate pregnancy.

Makvandi et al (2024) reported a review of seven randomised controlled trials of first and second trimester non-medical abortion using vaginal ISMN and misoprostol compared to misoprostol alone. The combined treatment significantly reduced the induction abortion interval, and increased the odds of a completed abortion. A "successful abortion" was defined as "the complete expulsion of all pregnancy-related products without the need for surgical intervention" (Makvandi et al 2024 p2).

In terms of side effects of the treatment: "In some included trials, the rate of side effects, including abdominal pain, fever, and diarrhoea, were less in the combination therapy group than in the comparison of only misoprostol. On the other hand, the rate of headache in the combination therapy group was higher than in the misoprostol alone group" (Makvandi et al 2024 p10).

The studies in the review were not particularly large with samples ranging from 54 to 160 participants, and they came from four countries - two from India, three from Egypt, and one each from the UK and Greece.

Reference

Makvandi, S et al (2024) Efficacy and safety of isosorbide mononitrate plus misoprostol compared to misoprostol alone in the management of the first and second trimester abortion: A systematic review and meta-analysis BMC Pregnancy and Childbirth 24, article 419

1.2. PRE-ECLAMPSIA

Pre-eclampsia leads to high blood pressure and cardiovascular disease risk for those pregnant as well as potentially harming the foetus. Symptoms usually appear later in the pregnancy (eg: after 20 weeks), so a way of detecting it before this would be ideal (Thompson 2025).

Elovitz et al (2025) reported a blood test that was

linked to certain genes that overexpress in hypertensive disorders of pregnancy, like pre-eclampsia. The study involved 9000 pregnant individuals, but only between 17 to 22 weeks into the pregnancy. Identifying the risk in order to start with aspirin would need to occur earlier (Kathryn Gray of the University of Washington in Seattle in Thompson 2025).

References

Elovitz, M.A et al (2025) Molecular sub-typing of hypertensive disorders of pregnancy Nature Communications 16, article 2948

Thompson, J (2025) Blood test suggests pre-clampsia risk New Scientist 19th April, p17

2. DIET ETC

2.1. GUT MICROBIOME AND MICROBIOTA

Rinninella et al (2023) began: "The human gut microbiota is an ecological entity that includes bacteria, yeast, viruses and parasites, yielding around 100 trillion micro-organisms in total. At birth, the human gut is almost sterile, and gets rapidly colonised by the mother microbiome. The type of delivery, vaginal or caesarean, plays a major role in shaping the microbiome of the newborn. The composition of the healthy gut microbiota is dominated for up to 90% by the phyla Firmicutes and Bacteroidetes" (p1) [1].

` What is a healthy microbiota? A distribution of different species of bacteria is the simple answer, known as "alpha diversity" (Rinninella et al 2023).

Diet is key among the variables that impact it, as well as age, genetics, environment, and lifestyle. "While different compositions of diet can lead to changes of microbiota profiles, an unbalanced diet consumed over a period of time accompanied by an unhealthy lifestyle can leave traces of evidence on the microbiota as well. Generally, subjects with obesity and overweight tend to show a lower diversity of gut microbiome. Genus-specific variations have been mostly observed in mice models, indicating a decreased abundance of Bacteroidetes in obese mice, while there was an increase in Firmicutes and Bifidobacterium noted" (Rinninella et al 2023 p2).

Summarising the research, Rinninella et al (2023) noted the importance of fibres and microbiota-accessible carbohydrates (MACs), while high levels of animal proteins, and saturated fats have negative consequences on health. Put simply, different diets lead to different compositions of bacteria (eg: high fat diet and increased abundance of Bifidobacterium).

Research has studied different dietary patterns, including (Rinninella et al 2023):

a) Western diet - high in saturated fats, animal proteins, refined sugars, and processed foods.

[1] Bacteria live in other parts of the body than the gut (eg: 700 species of bacteria in the mouth; Geddes 2024) (appendix 2A).

b) Mediterranean diet (MD) - high fibre intake (via whole grains, vegetables, fruit, and legumes), olive oil, and nuts.

c) Vegan/vegetarian diets - excludes all meat (and fish), and animal products like milk (vegan).

d) Gluten-free diet - excludes all gluten products.

e) Low-FODMAP diet - excludes foods containing fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs).

f) Ketogenic diet - high fat and protein, and low carbohydrate intake.

Taking the example of Bifidobacteria, these are increased with the MD and gluten-free diet, but reduced by all the others. Only the MD is known to increase microbial diversity and abundance (Rinninella et al 2023).

The long-term effects of specialised diets, like gluten-free (eg: for coeliac sufferers), low-FODMAP (eg: with irritable bowel disease), and ketogenic diets (eg: with drug-resistant epilepsy patients) need more research (Rinninella et al 2023).

2.1.1. Other People

The bacterial make-up of the gut microbiome is a product of diet, lifestyle, medications, and environment, including other people through physical contact. Concentrating on the latter, Berghini et al (2025) mapped the composition and diversity of the microbiome of 1787 adults in eighteen isolated villages in Honduras in 2020. There was evidence of "strain-sharing" of bacteria based on social interactions. Individuals' social networks were constructed from self-reports of relationships.

"Pairs of people with diverse sorts of relationships (spouse, father, mother, sibling, child, close friend, free time, personal or private conversations) share significantly more microbial species and strains with each other than other pairs of people from within the same village with no relationship..." (Berghini et al 2025 p168). The researchers continued: "More intimate relationships share more strains, and strain-sharing rates increase monotonically based on the frequency with which a pair of people shares meals or free time

together" (Berghini et al 2025 p174).

It is known that gut bacteria can influence the individual, and so the researchers observed that "groups of interconnected people might share phenotypes not only because of shared genes or transmitted behaviours, but also because of shared microbes" (Berghini et al 2025 p174).

2.1.2. Tests

The popularity of tests of stools of humans (and their pets) to give information about the gut microbiome has grown (known as microbiota tests). "Whether these kits actually tell us anything useful is a matter of debate, given the challenges in defining what comprises an optimum microbiome - and how to achieve it. Simply proving causality - that a particular community of organisms is directly implicated in a medical condition - has been a huge barrier. 'We have some evidence from animal models and some evidence from intervention trials, but there are not many' {Nicola Segata of the University of Trento, Italy]" (Robson 2025 p14).

The reliability of the tests vary.

Also the microbiome varies between individuals, and the behaviour of a microbe depends upon its neighbours as well as the age and diet of the individual. "None of the bacteria work in isolation. For these reasons, it doesn't make sense to talk about a single 'healthy microbiome'. There are many configurations that may each be associated with a higher or lower risk of certain conditions at different stages of life" (Nicola Segata in Wong 2025).

However, there are some emerging patterns from studies. For example, Fackelmann et al (2025) found that vegans have higher levels of certain bacteria that produce short-chain fatty acids like butyrate, and are associated with lower inflammation. This study showed different gut microbiome patterns (signatures) between vegans, vegetarians, and omnivores/meat-eaters in a sample of over 21 000 individuals. The data came from the ZOE PREDICT and two Italian cohorts where stool samples were collected for genome analysis. There were around 650 vegans and just over one thousand vegetarians in the sample.

The gut microbiome make-up was associated with health. For example: "Red meat was a strong driver of omnivore microbiomes, with corresponding signature microbes (for example, Ruminococcus torques, Bilophila wadsworthia and Alistipes putredinis) negatively

correlated with host cardio-metabolic health. Conversely, vegan signature microbes were correlated with favourable cardio-metabolic markers and were enriched in omnivores consuming more plant-based foods" (Fackelmann et al 2025 p41).

Note that "the application of gut microbiome research in clinical practice remains minimal because of a number of factors, including the complexity of the microbiota and associated sequencing data sets, the difficulties in disentangling correlation from causation, the reliance on pre-clinical models with low generalisability to humans, the limited knowledge most clinicians have about this field, the absence of any validated test to enable therapeutic follow-up, and the absence of established regulations and framework for the clinical translation of this research" (Porcari et al 2025 p154).

By contrast, these authors observed, patients have embraced microbiome-based testing, particularly in direct-to-consumer tests. "This trend raises several concerns about the absence of a standardised framework relating to the indications and methods of these tests, which limits their interpretability and applicability, with considerable waste of patient and health-care system resources, (eg: due to inappropriate requests for medical exams or inappropriate subsequent prescribing of supplements and medications). Moreover, these tests can generate false hopes in patients who are often living with severe disorders, with potentially detrimental consequences. Finally, due to the absence of a formal postgraduate clinical education in microbiome science, most physicians and other health-care professionals are not adequately trained to interpret a microbiome test and therapeutically manipulate the gut microbiome or to distinguish a well conducted test from an inappropriate one" (Porcari et al 2025 p154).

Porcari et al (2025) reported the convening of an expert panel in July 2022 to produce an international consensus statement on microbiome testing in clinical practice. The following key issues emerged:

i) The general principles of microbiome testing, particularly for commercial test providers - eg: "Providers of microbiome testing should communicate a reasonable, reliable, transparent, and scientific representation of the test, making customers clearly aware of the scarce evidence for its applicability in clinical practice" (p156).

ii) The appropriate situation in which to use such tests - eg: patients should not suspend physician-based treatment after using a microbiome test at home independently.

iii) The process of testing (eg: collection of stool samples).

iv) The process of analysis of gut microbiome, including what to include and what not.

2.1.3. Intestinal Gases

Intestinal gases give "[A] window into the health of our guts, they help govern our gut microbiome, influence our gut function and perhaps even that of other organs too" (Ainsworth 2024 p43).

Sampling intestinal gases is usually via tubes inserted into the mouth or anus, which is "inconvenient and invasive" (Kalantar-zadeh et al 2016 p37). Kalantar-zadeh et al (2016) described an alternative, a swallowable indigestible gas capsule to perform in vivo gas measurements as it travels along the gastrointestinal tract. The capsule contains a wireless transmitter to send data every five minutes. Differences in gases were found between pigs on high or low fibre diets in an experiment.

Intestinal gases as manifest in flatulence can be "potential biomarkers of microbiota activity in health and disease" (Freire er al 2022 p1). But this requires knowledge of a "healthy flatulence volatilome" (Freire et al 2022).

Freire et al (2022) explained that "determining a standard healthy pattern of intestinal gas is challenging due to the large differences in the volume and composition of intestinal gases between individuals. These differences are attributed to the nature of human gut microbiota, which is responsible for much of the production of intestinal gas. Certainly, the human gut microbiota is extremely diverse both within and between individuals" (p1).

The difference in flatulence between individuals can be due to variations in five gases - oxygen, nitrogen, carbon dioxide, methane, and hydrogen (Freire et al 2022).

2.1.4. Appendix 2A - Oral Microbiome

There is growing evidence of links between the oral microbiome and (non-oral) diseases (eg: Alzheimer's diseases; cancer).

For example, one study (Kwak et al 2024), using saliva samples of nearly 16 000 US adults, found a correlation between certain bacterial species in the mouth and head and neck cancers. These bacteria could hinder the immune system and allow cancer cells to grow (Geddes 2024). Note that causation was not established - "these bacteria thrive in environments where there's a lot of inflammation, and inflammation is a known risk factor for cancer" (Miguel Reis Ferreira at Kings College London in Geddes 2024).

2.1.5. References

Ainsworth, C (2024) Fartcatchers New Scientist 14/21st December, 43-44

Beghini, F et al (2025) Gut microbiome strain-sharing within isolated village social networks Nature 637, 167-175

Fackelmann, G et al (2025) Gut microbiome signatures of vegan, vegetarian and omnivore diets and associated health outcomes across 21,561 individuals Nature Microbiology 10, 41-52

Freire, R et al (2022) Quantitative GC-TCD measurements of major flatus components: A preliminary analysis of the diet effect Sensors 22, article 838

Geddes, L (2024) Oral microbiome linked to cancer New Scientist 23rd November, p11

Kalantar-zadeh, K et al (2016) Intestinal gas capsules: A proof-of-concept demonstration Gastroenterology 150, 37-39

Kwak, S et al (2024) Oral microbiome and subsequent risk of head and neck squamous cell cancer JAMA Oncology 10, 11, 1537-1547

Porcari, S et al (2025) International consensus statement on microbiome testing in clinical practice Lancet Gastroenterology and Hepatology 10, 2, 154-167

Rinninella, E et al (2023) The role of diet in shaping human gut microbiota Best Practice and Research in Clinical Gastroenterology 62-63, 101828

Robson, D (2025) What makes a healthy gut microbiome? New Scientist 25th January, p14

2.2. VEGETARIAN AND PLANT-BASED DIETS

Vegetarian diets, defined as "dietary patterns solely/mostly composed of plant-based foods, excluding specific or all animal-derived foods from the diet" (Jigeer et al 2025 p1), are associated with health benefits (eg: low risk of cardiovascular diseases in younger and middle-aged adults). But there is a risk of negative consequences for older adults, "a vulnerable group at risk of malnutrition when following a strict vegetarian diet due to the potential inadequate intakes of protein, vitamin B12, calcium, iron, and essential omega-3 fatty acids. Given age-related physiological changes in digestive and metabolic systems among older adults, vegetarian diets may result in muscle loss and bone fracture, key contributors to physical disability. Additionally, evidence regarding the associations between vegetarian diets and other health outcomes, such as mortality, major chronic diseases, cognitive function, and mental health in older adults, is scarce and remains controversial" (Jigeer et al 2025 p1).

Jigeer et al (2025) investigated this topic with data from the "Chinese Longitudinal Healthy Longevity Survey" (CLHLS), which began in 1998 with over 60s from twenty-two of the 31 provinces of mainland China. The participants were surveyed approximately every two years. There were nearly 35 000 participants at baseline, but Jigeer et al (2025) concentrated on 2888 healthy individuals at that time (of which 376 were classed as vegetarian).

Overall, the non-vegetarians ("omnivores"), after controlling for socio-demographic and lifestyle factors (eg: sex; household income; smoking status; alcohol use), were more likely to be healthy at follow-up (an average of six years) compared to vegetarians. "Additionally, the health effects of vegetarian diets may vary depending on diet quality, with vegetarians of higher diet quality not significantly differing in terms of overall healthy ageing and individual outcomes when compared to omnivores. Accordingly, this finding highlights modest inclusion of animal-based foods may improve the overall health status of healthy older adults" (Jigeer et al 2025 p1).

Jigeer et al (2025) found that vegetarian diets were associated with impaired physical functioning with age, and cognitive impairment at eighty years old.

Other studies, of all age groups, have tended to be conducted in Western countries, and they "did not account for the diet quality within vegetarian patterns, which

may partly explain the inconsistent findings regarding the health effects of vegetarian diets" (Jigeer et al 2025 p3).

Jigeer et al (2025) accepted the following two key limitations with their research:

a) The measure of diet - ie: "dietary intake data were collected using a non-quantitative dietary questionnaire, subject to measurement error in diet assessment, making it impossible to adjust for total energy intake. This limitation also means that vegetarians were defined based solely on the frequency of animal product consumption. However, the frequency of intake may be more important than portion size to distinguish between high and low consumption of fruits and vegetables..." (Jigeer et al 2025 p4).

b) Self-reporting of health and illness - ie: "healthy ageing" was defined as "survival to at least 80 years, coupled with no self-reported major chronic disease and no impairment in cognitive function, physical function, or mental health" (Jigeer et al 2025 p5).

2.2.1. Diversity

"Plant-based" diets vary in their composition, but they include less consumption of animal-source foods, and more of food groups like fruits and vegetables, wholegrains, and nuts. "While there is a significant body of evidence in support of the effects of increasing quantity of plant-based food consumption for health, the effects of increasing diversity of plant-based food consumption are less well understood. Diversity can be defined as the number of different food items consumed in a defined time- period" (Creedon et al 2025 p48).

Creedon et al (2025) investigated the health benefits of diverse plant-based food consumption with data from the UK "National Diet and Nutrition Survey" (NDNS) (year 9 collected in 2016-2017). Six hundred and seventy-seven adults provided detailed dietary information for a four-day period, and the researchers scored the quantity and diversity of plant-based foods therein. The median diversity was eight counts per day (ie: different plant-based groups). The sample was divided into low (2-6 counts per day), moderate (7-9 counts), and high diversity (10-18 counts). The most consumed foods in order were plant-based drinks (eg: tea and coffee), vegetables, and fruits.

Cardiometabolic health outcomes were measured (eg: cholesterol levels).

Higher diversity was associated with better cholesterol measures, though this was not statistically significant after adjusting for body mass index (BMI).

The categorisation of foods was a potential limitation of the research, and the researchers admitted: "The analysis did not consider the quality of plant-based foods derived from food products or composite dishes included in the database, for example both whole fruit and fruit eaten as an ingredient in a dessert contributed towards diversity in the same manner" (Creedon et al 2025 p59).

2.2.2. References

Creedon, A.C et al (2025) Characterising the diversity of plant-based food and beverage consumption in adults, and exploring associations with cardiometabolic health outcomes: A cross-sectional study Clinical Nutrition 52, 47-61

Jigeer, G et al (2025) Vegetarian diet and healthy ageing among Chinese older adults: A prospective study npj aging 11, article 25

2.3. FATS

The general relationship between dietary fats, cholesterol, and cardiovascular disease risk is "well established", but less so for specific fats, like interestified (IE) fats (rich in palmitic acid and stearic acid) [2], which was Hall et al's (2025) focus.

A randomised, double-blind, crossover study was undertaken. Forty-seven adults performed both conditions of the the study for six weeks each - palmitic acid-rich or stearic acid-rich margarine spreads and muffins. These were calculated to provide 10% of daily energy needs. Blood cholesterol readings were the outcome measures.

There was no significant differences in cholesterol measures between the two conditions. The conclusion was that IE fats consumed at 10% of energy for six weeks do not adversely impact cholesterol.

The study was short-term only, involving middle-aged healthy volunteers in the UK and the Netherlands. It depended upon the compliance of participants in the consumption of the appropriate amount of IE fats.

[2] IE fats are altered fats that can be used in food applications as an alternative to trans fats particularly (which are known to have negative health effects) (Berry et al 2019).

Compliance was measured by food diaries, and return of empty packaging. There was a four-week "washout" period between the two conditions, which were counterbalanced, but no control group.

References

Berry, S.E et al (2019) Interestified fats: What are they and why are they used? A briefing report from the roundtable on interestified fats in foods Nutrition Bulletin 44, 4, 363-380

Hall, W.L et al (2025) The effects of consumption of interestified fats rich in palmitic acid compared with stearic acid on intermediary markers of cardio-metabolic disease risk: A randomised controlled trial in healthy adults American Journal of Clinical Nutrition 122, 5, 1361-1373

3. COMMUNITY WATER FLUORIDATION

Community water fluoridation (CWF) [3] has been common in many countries for many years in order to combat tooth decay/dental caries, and studies have shown effectiveness here. But there are health risks of excessive fluoride exposure, particularly for the foetus and newborn (Till et al 2025).

"Ingested fluoride is rapidly absorbed in the stomach and intestines, with plasma fluoride concentrations reaching a peak within 20–60 min. Infants and young children retain 80–90% of absorbed fluoride compared with 50% in healthy adults. About 99% of the body's fluoride is strongly bound to mineralised tissues (mainly bone); about 1% is found in soft tissues, including calcified parts of the pineal gland" (Till et al 2025 p255).

For newborns, the adequate intake of fluoride is 0.01 mg/day, while the maximum recommended level is 0.7 mg/day. For adults, 0.05 mg per kg of body weight is the accepted level (Till et al 2025).

CWF has been associated with a 25% relative reduction in dental caries for children and adults (eg: Griffin et al 2007). A review (Iheozor-Ejiofor et al 2015), however, found the evidence of low quality in terms of methodology, particularly for studies prior to 1975. Subsequent studies have found benefits much lower (eg: 2% difference in number of decayed teeth between fluoridated and non-fluoridated water areas) (eg: Moore et al 2024) (Till et al 2025).

In terms of detrimental effects of systemic fluoride exposure, these include bone strength, thyroid function, and cognitive development for the foetus and newborn.

Till et al (2025) that "[I]n an environment where fluoride is available from multiple sources, community-based administration of systemic fluoride may pose an unfavourable risk–benefit ratio for pregnant women and young children" (p253). Restricting sugar consumption could be as effective for tooth decay.

REFERENCES

Griffin, S.O et al (2007) Effectiveness of fluoride in preventing caries in adults Journal of Dental Research 86, 5, 410-415

Iheozar-Ejiofor, Z et al (2015) Water fluoridation for the

[3] Fluoride is also found in fluoridated salt and some foods (Till et al 2025).

prevention of dental caries Cochrane Database of Systematic Reviews 10, CD01856

Moore, D et al (2024) How effective and cost effective is water fluoridation for adults and adolescents? The LOTUS 10-year retrospective cohort study Community Dentistry and Oral Epidemiology 54, 4, 413-423

Till, C et al (2025) Health risks and benefits of fluoride exposure during pregnancy and infancy Annual Review of Public Health 46, 253-274

4. PAIN

4.1. BASICS

With an estimated one-third of people living with chronic pain, understanding pain is vital, including the subjective experience of it (The leader 2022). "We need pain for survival and yet it can drive us to utter despair. We experience pain as a physical process and yet the sensation of pain is created in the brain. What's more, this physical experience is deeply intertwined with our emotional state - indeed, emotional pain is a very real phenomenon" (Cover Story 2022 p38).

A special report in the "New Scientist" in 2022 addressed the key questions:

1. What is pain?

Put simply, sensory neurons collect information about the body and the environment, and certain types of stimuli activate nociceptors, which are processed as "pain" (Sutherland 2022a).

Growing knowledge has shown the gene TRPV1 that makes cells sensitive to heat, the gene SCN9A which sends signals of pain to the brain (and is mutated in individuals with the rate condition of "congenital insensitivity to pain" CIP), and the "pain network" (insula, thalamus, and anterior cingulate cortex) in the brain (Sutherland 2022a).

"The International Association for the Study of Pain currently defines pain as 'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'. This definition does not capture the fact that pain may be both protective and pathological and also misses key features of clinical pain conditions; pain may arise either in the absence of any stimulus or in response to a stimulus that would normally only evoke an innocuous sensation. Finally, it doesn't readily serve non-verbal individuals as it requires the experience to be described" (Tracey et al 2019 p785).

2. What are the boundaries between emotions and pain?

Isolating distinct brain areas involved in pain is complicated because emotions are involved. For example, brain scans show activity in the pain network responding to psychological pain in the same way as to physical pain (Thomson 2022).

Individuals with chronic pain also experience anxiety and depression. In a meta-analysis of 320 MRI (magnetic resonance imaging) studies Brandl et al (2022) found common changes in the brain in individuals with major depressive disorder, anxiety disorders, or chronic pain (as well as disorder-specific changes). Reductions in the grey matter volume in the insula and medial prefrontal cortex areas of the brain were the main common changes.

This study as a meta-analysis combined data from a variety of methodological situations, particularly as technology has advanced with time. The researchers admitted to thirteen limitations to their findings. For example, "study quality has generally increased over the last two decades (eg: regarding normalisation accuracy or noise correction), so older studies might confound results" (Brandl et al 2022 p1078), or differences in medications taken by participants and inconsistency in the reporting about it, or the diagnoses of the conditions.

3. The third type of pain.

The first type of pain is nociceptive pain (response to an injury), the second is neuropathic pain (caused by damage to sensory nerves), and the "third category of pain" is nociplastic pain (NP) (Lawton 2022). "Nociplastic pain is when... system goes wrong, a state known as central sensitisation. The brain's pain centre becomes hypervigilant and responds disproportionately to minor injuries or inflammation, converting them into excruciating pain. In some cases, there is no nociceptive pain at all, but the brain still out extreme pain signals. Negative mental states, such as anxiety or tiredness, can also be converted into pain" (Lawton 2022 p41).

NP was proposed in 2016 as "chronic pain states not characterised by obvious activation of nociceptors or neuropathy, 'but in whom clinical and psychophysical findings suggest altered nociceptive function' [Kosek et

al 2016]. Nociplastic pain can be mechanistically defined as pain arising from the altered function of pain-related sensory pathways in the periphery and CNS [central nervous system], causing increased sensitivity. Nociplastic pain can occur in isolation or as a co-morbidity in individuals with chronic pain conditions that are primarily nociceptive or neuropathic" (Fitzcharles et al 2021 p2098).

NP ("syndrome" has been added) has come to cover a diverse range of conditions (table 4.1), but it is challenging for physicians: "the pain complaint is often difficult to describe, there are associated subjective symptoms, and pathognomonic clinical findings or biomarkers are absent. Nociplastic pain conditions are frustrating for both healthcare professionals and patients, with physicians uncertain regarding diagnosis and patients resentful that their symptoms are doubted" (Fitzcharles et al 2021 p2099). However, there is evidence of overlap with other types of chronic pain (Fitzcharles et al 2021).

- Chronic widespread pain and fibromyalgia
- Complex regional pain syndrome (with or without identifiable nerve injury)
- Chronic primary headaches and orofacial pain (eg: chronic migraine; chronic tension-type headache)
- Chronic visceral pain syndromes (eg: irritable bowel syndrome; abdominal; bladder)
- Chronic primary musculo-skeletal pain (eg: low back; thoracic)

(Source: Fitzcharles et al 2021)

Table 4.1 - Nociplastic pain syndrome categories.

The prevalence of NP varies from 5 to 15% depending on the study, but most agree that the prevalence among females is higher (eg: ten times more than in males at the highest) (Fitzcharles et al 2021).

Common predisposing factors in NP include a family and/or individual history of pain, and psychological, physical, and sexual abuse, while triggers include stress, and specific infections (eg: gastrointestinal). "However, the causal relationship between a patient-reported inciting event and a chronic pain condition is often unclear, because many patients identify precipitating events that do not have a pathoanatomical basis" (Fitzcharles et al 2021 pp2101-2102).

Delay in diagnosis is a common experience. Clark et

al (2013), for instance, in a survey of 900 patients, found that a diagnosis of fibromyalgia took an average of 35 months and interactions with 4.5 different physicians (Fitzcharles et al 2021).

Two types of explanations have been proposed. Firstly, a normal pain trigger "balloons beyond all proportion" (Lawton 2022 p41) (a bottom-up explanation). Or a top-down explanation, where there is no pain trigger, but an abnormality in the nervous system (Lawton 2022).

Advising physicians about the diagnosis of NP, Fitzcharles et al (2021) noted some "non-pain" symptom clues including anxiety and/or depression, hypersensitivity to environmental stimuli, and general fatigue and/or cognitive problems as well as high use of healthcare services (eg: many different doctors seen), and poor response to conventional medications for pain relief.

Because of the lack of obvious tissue damage with NP and the stigma for some patients of "made-up" pain, Fitzcharles et al (2021) emphasised that symptoms should be acknowledged as real, first and foremost by physicians. Non-pharmacological treatments hold promise, including patient education and realistic self-management, psychological therapy, and healthy behaviours generally (eg: diet and weight management; sleep hygiene) (Fitzcharles et al 2021).

4. What is chronic pain?

Pain that lasts for three months or longer is classified as chronic (Osborne-Crowley 2022). Whether it is a stubborn version of acute pain or a separate form of pain is debated [4].

One possibility is a rewiring of the brain to produce pain signals without a stimulus (known as "central sensitisation"; Woolf 1983). The rewiring occurs due to pain without relief for an extended period (Osborne-Crowley 2022).

Alternatively, chronic pain may be a product of physical sensation, emotional trauma and memory (Warraich

[4] Tracey et al (2019) observed: "The recognition that most chronic pain is maladaptive and mechanistically quite different from acute protective pain has been a major conceptual breakthrough within the pain field. Nevertheless, it is hard to manage chronic pain effectively because the processes in the nervous system driving the pain are not easily identified and targeted for treatment. Pain in these circumstances is not simply a symptom of some distinct disease pathology but rather the expression of a pathologically functioning nervous system" (p784).

2022), which allows for chronic pain without physical injury. Simply, an oversensitivity to fear and danger manifest as chronic pain (Osborne-Crowley 2022).

"Pain Reprocessing Therapy" (PRT) is one treatment option. It aims to reconceptualise the pain as "a brain-generated false alarm" (Ashar et al 2022 p14) with educational sessions. For example, Ashar et al (2022) reported a study with 151 adults experiencing low back pain randomised to PRT, placebo (a saline injection in the back), or usual care with follow-up at one year. At baseline, the overall pain rating was 4.1 out of 10, while at follow-up the average was 1.6 in the PRT group, 2.8 in the placebo group, and 3.0 in the usual care group.

5. How can you measure someone's pain?

Pain can be measured along two core dimensions: intensity (magnitude) and unpleasantness (effect) (Tracey et al 2019). Subjective measures are common for the former (eg: ten-point scales for current pain). The "McGill Pain Questionnaire" is a more sophisticated version, based on the choice of 78 descriptor words (Demming 2022).

Alternatively, there is "qualitative sensing testing" where heat, say, is applied to the skin and an individual says when to stop. This "score" can be compared to the average (Demming 2022).

Where self-reports are not possible (eg: babies; animals), indirect measures can be used (eg: crying; grimacing; guarding of injured body areas) as well as physiological measures like increased heart rate. "For all these assessments, absence of signs does not necessarily mean absence of pain; similarly, their presence may also not reflect the experience of pain. Some measures in animals are closely related to the ethogram of the animal and others are surrogates of human clinical measures. For translational success from pre-clinical to man, it is important to have metrics that are also translatable. This is where composite pain biomarkers can help us" (Tracey et al 2019 p787).

In terms of objective measures, Tracey et al (2019) reported on differences in responses to opioids in brain scans depending on the pain. While neuroimaging studies have found the "neurological pain signature", and the "pain-analgesic network" in the brain (Tracey et al 2019).

Accepting the above, Tracey et al (2019) admitted:

"Similar to other complex neurological diseases like Alzheimer's, it is highly unlikely that one biomarker will be able to capture 'pain' in its entirety. Exploiting advanced analytical tools like neural networks, artificial intelligence, or machine-learning algorithms to combine multiple objective biomarkers into 'composite pain biomarker signatures' is more likely to be successful for understanding pain and developing new treatments" (p785).

6. How do you treat pain?

Drugs are the first response response often - non-steroidal anti-inflammatory drugs or opioids, for instance. Side effects are a problem, including addiction and overdose risk with opioids, and efficacy can vary with the type of pain (Sutherland 2022b).

The search for new treatments has focused on finding genes involved in pain (eg: SCN9A; Cox et al 2006). Work with individuals with CIP has isolated gene variants. For example, Woods et al (2025) reported three such individuals. The authors described their experiences of CIP thus: "No peripheral pain was felt, for example, painless bone fractures and self-amputation of the tongue tip and lips, however, defecation produced significant discomfort. Furthermore, whereas temperature within the normal range could be perceived, variations in temperature such as a gust of cold wind were distinctly unpleasant. These were the only experiences of 'pain' that the individuals describe" (Woods et al 2015 p561).

A surprising possibility is bacterial toxins. Chiu et al (2013) found that bacteria (eg: Staphylococcus aureus) can directly activate nocioceptors, while anthrax toxins can regulate pain neurons (ie: reduce activity) (Yang et al 2022).

Treating the physical pain may be limited in success without a psychological element to a treatment programme (eg: "My Surgical Success" (MSS)). It was reported as reducing the time to cessation of opioids after breast cancer surgery compared to controls in a pilot study (Darnall et al 2019). MSS is an online programme involving a ninety-minute psycho-education video, personalised planning, and relaxation audio material. "Video content included information and skills to regulate cognition, emotion, and physiologic hyper-arousal related to pain, including relaxation, thought

reframing, and behaviours that modulate attention and counteract helplessness about pain" (Darnall et al 2019 p2229).

In the case of chronic low back pain, Darnall et al (2021) compared "empowered relief", health education, and cognitive behavioural therapy (CBT). The focus was "pain catastrophising" ("a cognitive and emotional pain response pattern that includes increased attention and feelings of pain helplessness"; Darnall et al 2021 p2).

Empowered relief, based upon CBT, included pain education, "self-regulating skills" (eg: cognitive reframing; self-soothing), and mindfulness. In the study there was a two-hour single session. The health education condition was a matched session on back pain, general nutrition, and medication, while the CBT group received eight 2-hour sessions.

The participants were 263 adults recruited in the San Francisco Bay Area of California, and the study took place between 2017 and 2020. The main outcome measure was the "Pain Catastrophising Scale" (PCS) (Sullivan et al 1995) score at three months after treatment [5].

The empowered relief and CBT groups had significant reductions in PCS score compared to health education (mean reduction in PCS scores: -9.1, -10.9, and -4.6 respectively).

The study involved unblinded conditions, and the participants were volunteers "consisted mainly of White individuals and those who were highly educated and of higher socio-economic status" (Darnall et al 2021 p12).

The study established that a single session of CBT-based empowered relief can be beneficial in pain catastrophising.

A "out of left field" possibility to treat pain is placebo - both "hidden", where individuals think they are receiving a painkiller when given an inert sugar pill, and "open" ("when people are explicitly told that a treatment is inert"; Sutherland 2022b p45).

4.2. LOW BACK PAIN

Chronic low back pain (LBP) is experienced by around one-third of people worldwide, and it "ranks the highest of all chronic conditions in terms of years lived with disability, with its prevalence and burden increasing

[5] The PCS has thirteen items, like "It's awful and I feel that it overwhelms me", each scored o ("not at all") to 4 ("all the time"), to give a total score from 0 to 52 (Darnall et al 2021).

with age" (Parisien et al 2022 p1).

In terms of the causes of chronic pain, a variety of genes are involved, and "a complex interplay between the nervous and immune systems; that is, chronic pain is a neuro-inflammatory disorder mediated by neuronal and non-neuronal cells alike" (Parisien et al 2022 p1).

In a study using both human and mouse data, Parisien et al (2022) found that the early treatment of LBP with steroid or non-steroid anti-inflammatory drugs (NSAIDs) led to prolonged pain despite the benefits in the short term. It seemed that "despite analgesic efficacy at early time points, the management of acute inflammation may be counter-productive for long-term outcomes of LBP sufferers" (Parisien et al 2022 p1).

Put simply, medications that reduce immediate pain by inhibiting inflammation "might interfere with the natural recovery process, thus increasing the odds for chronic pain" (Parisien et al 2022 p5).

The human data came from the UK Biobank project, and individuals with acute LBP given NSAIDs were nearly twice as likely to develop chronic back pain compared to individuals not taking NSAIDs. There was no difference for other types of analgesic medications.

There were clear differences in gene expressions between individuals with resolved pain (at three months) and those with persistent pain in another human sample from Italy.

Jones et al (2023) were clear: "The use of opioids for the management of acute low back pain and neck pain is not supported by direct and robust evidence" (p304). Despite this point, and concerns about dependency and overdose, opioids prescription rates in the USA, for example, are high at 43.3 prescriptions per 100 people in 2020 (Jones et al 2023).

In Australia, Jones et al (2023) undertook a clinical trial on opioids for the management of acute non-specific LBP and neck pain (the OPAL trial). Participants were recruited from 157 clinics and hospitals in Sydney. Between February 2016 and March 2022 347 adults were involved, randomly assigned to a medication (oxycodone-naloxone) or placebo group for six weeks. "Eligible participants had low back pain (pain between the 12th rib and buttock crease) or neck pain (pain below the occiput to the most distal cervical spine), or both, with or without radiation to the leg (for low back pain) or arm (for neck pain); a current episode of pain for 12 weeks or less and preceded by at least a 1-month period free from back and neck pain; and

at least moderate pain severity (as measured by adaptations of item 7 of the 36-Item Short Form Health Survey [SF-36]— ie: how much low back pain or neck pain [none, very mild, mild, moderate, severe, or very severe] the participant had experienced in the previous week)" (Jones et al 2023 p305).

The main outcome measure was pain severity at six weeks on the ten-point scale of the "Brief Pain Inventory". The mean score was 2.78 in the opioid group compared to 2.25 in the placebo group (which is not a statistically significant difference). One-third of the medication group reported at least one adverse event (eg: constipation).

The conclusion was that "not only are opioids not going to benefit individuals with back and neck pain, but they might also cause worse outcomes even after short-term judicious use" (Jones et al 2023 p305).

4.3. POST-SURGERY

Elyad Ekrami reported to the annual meeting of the "American Society of Anaesthesiologists" in October 2022 the finding that people who used cannabis in the month before surgery experienced greater pain after that surgery as compared to non-cannabis users in the month before the operation (Wade 2022) [6].

The dataset involved over 34 500 US adults who underwent surgery between 2010 and 2021 at the Cleveland Clinic in Ohio. Of them, 1683 reported cannabis use in the thirty days before surgery.

Participants rated their pain level 24 hours after surgery on a ten-point scale. The mean for the use group was 5.5 compared to 4.1 for non-users. The difference was statistically significant, controlling for age, and surgery type, for instance (Wade 2022).

The use of cannabis was self-reported, and Michael Alaia noted that "people could have misreported their cannabis use over fears of being judged or having their procedure cancelled" (quoted in Wade 2022).

4.4. REFERENCES

Ashar, Y.K et al (2022) Effect of pain reprocessing therapy or placebo or usual care for patients with chronic back pain: A randomised clinical trial JAMA Psychiatry 79, 1, 13-23

[6] This research has subsequently been published as Ekrami et al (2024).

Brandl, F et al (2022) Common and specific large-scale brain changes in major depressive disorder, anxiety disorders, and chronic pain: A transdiagnostic multi-modal meta-analysis of structural and functional MRI studies Neuropsychopharmacology 47, 1071-1080

Chiu, I.M et al (2013) Bacteria activate sensory neurons that modulate pain and inflammation Nature 501, 52-57

Clark, P et al (2013) A patient and physician survey of fibromyalgia across Latin America and Europe BMC Musculoskeletal Disorders 14, article 188

Cover Story (2022) Special report: Pain New Scientist 19th November, p39

Cox, J.J et al (2006) An SCN9A channelopathy causes congenital inability to experience pain Nature 444, 894-896

Darnall, B.D et al (2019) "My Surgical Success": Effect of a digital behavioural pain medicine intervention on time to opioid cessation after breast cancer surgery - a pilot randomised controlled clinical trial Pain Medicine 20, 11, 2228-2237

Darnall, B.D et al (2021) Comparison of a single-session pain management skills intervention with a single-session health education intervention and eight sessions of cognitive behavioural therapy in adults with chronic low back pain: A randomised clinical trial JAMA Network Open 4, 8, e2113401

Demming, A (2022) How can you measure someone's pain? New Scientist 19th November, 43-44

Ekrami, E et al (2024) Association between cannabis use and opioid consumption, pain, and respiratory complications after surgery: A retrospective cohort analysis Anesthesia and Analgesia 139, 4, 724-733

Fitzcharles, M-A et al (2021) Nociplastic pain: Towards an understanding of prevalent pain conditions Lancet 397, 2098-2110

Harraich, W (2022) The Song of Our Scars: The Untold Story of Pain New York: Basic Books

Jones, C.M.P et al (2023) Opioid analgesia for acute low back pain and neck pain (the OPAL trial): A randomised placebo-controlled trial Lancet 402, 304-312

Kosek, E et al (2016) Do we need a third mechanistic descriptor for chronic pain states? Pain 157, 1382-1386

Lawton, G (2022) The third type of pain New Scientist 19th November, p41

Osborne-Crowley, L (2022) What is chronic pain? New Scientist 19th November, p42

Parisien, M et al (2022) Acute inflammatory response via neurotrophil activation protects against the development of chronic pain Science Translational Medicine 14, eadj9954

Sullivan, M.J et al (1995) The Pain Catastrophising Scale: Development and validation Psychological Assessment 7, 524-532

Sutherland, S (2022a) What is pain? New Scientist 19th November, 38-39

Sutherland, S (2022b) How do you treat pain? New Scientist 19th November, 44-45

The leader (2022) All in the mind New Scientist 19th November, p5

Thomson, H (2022) What are the boundaries between emotions and pain? New Scientist 19th November, p40

Tracey, I et al (2019) Composite pain biomarker signatures for objective assessment and effective treatment Neuron 101, 783-800

Wade, G (2022) Cannabis users experience more pain after surgery New Scientist 29th October, p13

Woods, C.G et al (2015) The phenotype of congenital insensitivity to pain due to the Nav1.9 variant p.L811P European Journal of Human Genetics 23, 561-563

Woolf, C.J (1983) Evidence for a central component of post-injury pain hypersensitivity Nature 306, 686-688

Yang, N.J et al (2022) Anthrax toxins regulate pain signalling and can deliver molecular cargoes into Antxr2+ DRG sensory neurons Nature Neuroscience 25, 2, 168-179

5. MENTAL HEALTH ETC

5.1. SUICIDE

Various studies have found associations between meteorological variables (MVs) and suicide rates (eg: temperature; rainfall; humidity). Though there is inconsistency in some findings - eg: increased suicide during high or low temperatures (Qi et al 2015).

Qi et al (2015) reported an Australian study of suicide and MVs as well as socio-economic variables (eg: unemployment) in eight state capital cities. Official data for 1985 to 2005 were used. MVs were taken from the Australian Bureau of Meteorology.

Temperature difference (ie: "the difference in mean temperature between current month and previous one month"; p1) was positively associated with suicide in four cities, while unemployment rate and suicide were also positively associated in three of the cities (Sydney, Melbourne and Brisbane). These two variables interacted in these cities such that increased temperature amplified the relationship between unemployment and suicide. There was no consistent association between suicide and other MVs (eg: rainfall; hours of sunshine).

This was the first study to investigate MVs, unemployment and suicide in Australian cities, according to the authors, but it did not include non-capital urban, rural and remote areas. Public data after 2005 were not available at that time.

The researchers accepted two key limitations of using general official data. "Firstly, more detailed personal information of each suicide case, eg: health status and mental disorder before suicide, consumption of alcohol at the individual level, economic condition, intake of omega-3 fatty-acid, were not available in the dataset. Secondly, using monthly meteorological data may mask some extreme weather conditions, eg: short term heat waves, which may have potential impact on mental health among population" (Qi et al 2015 p11).

Reference

Qi, X et al (2015) Associations between climate variability, unemployment and suicide in Australia: A multi-city study BMC Psychiatry 15, article 114

5.2. MENTAL ILLNESS STIGMA

The "Attitudes to Mental Illness" (AMI) survey in England has been used to assess stigma towards mental health problems. The period 2008 to 2019 showed improvements (Henderson et al 2020) (compared to general population surveys in 1994 to 2003), but subsequently there has been "signs of increasing desire for social distance" (Ronaldson and Henderson 2025). The "Time to Change" stigma reduction programme ran between 2009 and 2021, aimed at adults aged 25 to 44 years, and is "likely to have contributed" to the improvement in attitudes (Ronaldson and Henderson 2025).

The AMI survey began annually in 2008, and involved a national representative sample of around 1700 adults. It contained three main elements - stigma-related knowledge, attitudes to mental illness, and the desire for social distance. The latter was measured by using two vignettes of mental health problems (depression and schizophrenia), and six domains - living next door, socialising, forming a friendship, working together as colleagues, accepting them as a family member by marriage, and trusting them to provide childcare for a relative (Ronaldson and Henderson 2025).

References

Henderson, C et al (2020) Mental illness stigma after a decade of Time to Change England: Inequalities as targets for further improvement European Journal of Public Health 30, 3, 526-532

Ronaldson, A & Henderson, C (2025) One year later: Tracking the continued growth of mental illness stigma in England medRxiv (https://www.medrxiv.org/content/10.1101/2025.10.10.25337746v1)

5.3. SEVERE SKIN REACTIONS AND MENTAL HEALTH

"Severe cutaneous adverse reactions" (SCARs) are "severe drug-induced skin eruptions" (p1755) (eg: Stevens–Johnson syndrome–toxic epidermal necrolysis (SJS-TEN), drug reaction with eosinophilia and systemic

symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP) and generalised bullous fixed drug eruption (GBFDE)), which are rare (eg: less than ten cases per million per year) (Hong et al 2025).

There is a psychological impact of SCARs (eg: anxiety, depression, and post-traumatic stress disorder (PTSD)). Hong et al (2025) reviewed the evidence, and found 24 relevant studies (published before late 2024). The prevalence rates found were as follows: anxiety 44-63%, depression 21-50%, and PTSD 17-51%, depending on the type of SCARs, and the study.

The studies also showed impacts on everyday life (eg: unemployment), reduced quality of life, fear of medications of any kind, and feeling misunderstood by friends, family, and doctors. "Interestingly, there was no evidence of an association between severity of SJS-TEN and an increased risk of adverse psycho-social outcomes. Common markers of severity, such as ICU [intensive care unit] admission and percentage body surface area involved, may not be reliable predictors of future psy-cho-social outcomes" (Hong et al 2025 p1762).

The methodology of the studies varied in quality, including small samples (less than 20 participants), measurements of variables, and control of confounders. Only studies published in English were included in the review, while 88% of studies investigated SJS-TEN and the remainder DRESS.

The conclusion was that survivors of SCARs should receive psychological monitoring and help after discharge from hospital.

Reference

Hong, S et al (2025) Mental health and psycho-social outcomes in survivors of severe cutaneous adverse reactions: A scoping review Clinical and Experimental Dermatology 50, 1755-1765

6. HUMAN CYTOMEGALOVIRUS

Human cytomegalovirus (CMV) is generally "harmless" to healthy individuals, but a risk to immune compromised individuals in particular. But it is common in low-income settings, and to a lesser extent in high-income settings (Yates et al 2025). CMV leads to "direct" tissue change (ie: there are histopathological hallmarks of the virus), but Rubin (1989) suggested "indirect" effects of CMV (ie: it is "associated with a range of pathology absent evidence of end organ disease"; Yates et al 2025 p1). The indirect effects included increased cardiovascular disease, and susceptibility to co-infections, and altered vaccine response (Yates et al 2025).

Introducing a special issue of the "Philosophical Transactions of the Royal Society B" on the indirect effects of CMV, Yates et al (2025) summed up thus: "It seems possible that individuals with CMV end organ disease might concurrently suffer from indirect effects. However, the evidence that CMV is causally associated with many of these outcomes remains sparse" (p2).

CMV is a herpes virus, which "persists at virtually undetectable levels for the duration of the host's lifespan" (Bremke et al 2025 p1). This means that the virus can reactivate, say, when there is a compromised immune system as in HIV. CMV has been shown to be associated with worse outcomes in HIV (Ellis et al 2025a). For example, increased progression to AIDS-defining events (Deayton et al 2004), and increased mortality (Ellis et al 2025b).

Immunosuppressed organ transplant recipients are especially vulnerable to CMV reactivation, and it has been estimated that four-fifths of bone marrow stem cell transplant recipients suffer from CMV-related diseases (Jackson et al 2025).

The return of CMV in older people is also evident due to immunosenescence (ie: the decline of the immune system with age) (Jackson et al 2025). Jackson et al (2025) explained: "Effective control of HCMV [human CMV] infection depends on a finely tuned interplay between multiple components of the immune system" (p9).

CMV has been associated with inflammatory disease processes, like atherosclerosis and ischaemic heart disease (Bremke et al 2025). The link to cardiovascular disease generally, and all-cause mortality has been proposed, though the results are mixed. Doorly et al (2025) noted three large cohort studies showing an

increase in all-cause mortality for individuals with CMV anti-bodies in their blood compared to those without the anti-bodies. The presence of anti-bodies is taken as evidence of the presence of CMV in the body at some time if not currently. Two cohort studies found no increase (Doorly et al 2025). Among such studies, there are methodological weaknesses including that they "lacked sufficient control for confounders, had short follow-up times or the populations studied had significant co-morbidities at baseline" (Doorly et al 2025 p2).

Hamilton et al (2021) analysed UK Biobank data on 8500 middle-aged adults, "finding no association with either ischaemic heart disease (IHD) or stroke when adjusting for confounders encompassing socioeconomic background, general physical health and activity" (Doorly et al 2025 p2). Doorly et al (2025) updated this study (with 8740 participants, of which 58% were CMV seropositive at baseline), and again found no association with cardiovascular disease, IHD or all-cause mortality and CMV. However, Yates et al (2025) pointed out that "the analysis does not account for selection effects that might be expected to bias CMV—disease associations towards the null" (p2). Doorly et al (2025) admitted that it was not possible to know when individuals had been infected with CMV, and infection duration was a potential confounder.

Tuberculosis (TB) is another disease influenced by CMV. The progression from Mycobacterium tuberculosis (Mtb) infection to TB disease in children is not inevitable, but CMV infection is suggested to aid this progression (Johnson et al 2025).

Johnson et al (2025) explored this idea with a sample of children in the UK. The data were available for 75 children from six hospitals, who were divided into those with TB disease (n = 21), those with Mtb infection (n = 27), and those exposed to TB (eg: family member with the disease) (n = 27). Blood samples were analysed for CMV-specific anti-bodies.

Contrary to previous research, no relationship was found between CMV-specific anti-bodies and TB. But the study did find evidence of CMV in more of the sample than previous research in the UK (49% vs 21%; eg: Pembrey et al 2019).

The sample was small, and the UK is a low-TB burden setting were reasons proposed for the negative findings by Johnson et al (2025).

In a study with two small samples in Africa (25 children in Uganda and 22 in the Gambia), Stockdale et al

(2025) found an increased risk of TB disease with CMV in one country but not the other. The positive relationship was found in the Ugandan sample, where previous work on a wider cohort had shown 2-4 times greater risk of TB disease where CMV is present (Stockdale et al 2020). This has been confirmed in South African studies (eg: Martinez et al 2021).

Infection with CMV is associated with changes in the immune system, and subsequently with cancer, specifically "a protective role against metastatic melanoma" (Bremke et al 2025 p1).

While Labeb et al (2025), in a small-scale study, found immune system differences in cardiovascular disease patients with CMV. The sample was eleven patients undergoing cardiac surgery in a Nashville hospital in the USA.

Glioblastoma is "an incurable and highly aggressive brain tumour with a poor prognosis" (Soderberg-Naucler et al 2025 p1), and tumours have been found to contain CMV (originally reported by Cobbs et al 2002). "Subsequent studies by many research groups have confirmed the frequent presence of HCMV proteins and nucleic acids in glioblastomas, as well as in other tumour types, such as colon, breast, prostate, ovarian cancer, medulloblastoma, neuroblastoma and sarcoma" (Soderberg-Naucler et al 2025 p3).

However, some studies have not found CMV in tumours (eg: Loit et al 2019) (Soderberg-Naucler et al 2025).

Peredo-Harvey et al (2021) reviewed the evidence of CMV in glioblastoma, and overall 84% of tumour samples included CMV. Other work suggests that CMV can "modify both tumour cell behaviour and the micro-environment, which may enhance tumour growth and promote immune evasion" (Soderberg-Naucler et al 2025 p1). This led Soderberg-Naucler et al (2025) to recommend anti-virals as part of the treatment programme for glioblastoma.

CMV may both amplify the response to influenza vaccines as well as the infection (eg: Furman et al 2015) (Bremke et al 2025).

Paarwater et al (2025) attempted to "join the dots" linking HIV and CMV during pregnancy to the early health outcomes of the child. Vertical transmission of CMV (ie: from mother to foetus) is estimated at 40% overall (Paarwater et al 2025). "When primary CMV infection occurs during the first trimester of pregnancy, a

transmission rate to the fetus of 24% has been reported, of whom 38.4% develop severe central nervous system impairment. Although transmission is more common in the second trimester(38%), rising to 72% in the third trimester, severe sequelae are only seen in 3.4% and 0% of infants infected in these trimesters, respectively. This is unsurprising and probably reflects disruption of embryogenesis during the first trimester, coupled with a lack of immune protection by the foetus" (Paarwater et al 2025 p2) [7].

Primary CMV is acquiring the virus for the first time, while non-primary CMV is latent in the mother (or reactivated). Vertical transmission is less than 10% here (Paarwater et al 2025).

HIV in pregnant women adds extra pressure upon the immune system, while "CMV-induced immune activation and disruption of placental barrier integrity may create a more permissive environment for HIV-1 entry, replication and potentially transmission to the foetus. Additionally, CMV can increase HIV transmission risk by promoting immune activation, increasing viral load, causing damage to mucosal barriers and interacting with HIV in ways that further compromise the immune system" (Paarwater et al 2025 p3).

Paarwater et al (2025) extended the idea of vertical transmission of CMV with the concept of the "vertical transmission of inflammation (or inflammation transmission)". The virus is not transmitted directly to the foetus, but maternal inflammation caused by CMV impacts the foetus and the child's subsequent health. Again, the presence of maternal HIV will exacerbate the process.

REFERENCES

Bremke, J et al (2025) The immunomodulatory role of human cytomegalovirus in cancer in the era of checkpoint immunotherapy Philosophical Transactions of the Royal Society B 380, 20240413

Cobbs, C.S et al (2002) Human cytomegalovirus infection and expression in human malignant glioma Cancer Research 62, 3347-3350

Deayton, J.R et al (2004) Importance of cytomegalovirus

[7] Because CMV can lead to developmental problems like sensori-neural hearing loss, screening for CMV may be a strategy. Schleiss (2024) considered the options of targeted screening (high-risk groups only), expanded targeted screening (high- and medium-risk groups), or universal screening (ie: everybody). Relevant issues for any screening programme include its cost-effectiveness, the accuracy (eg: undue anxiety for parents with false positives), and distinguishing between CMV infection that will or will not harm the child's development (Schleiss 2024).

viraemia in risk of disease progression and death in HIV-infected patients receiving highly active anti-retroviral therapy Lancet 363, 2116-2121

Doorly, R et al (2025) Acyclic graphs to define models of relationships between human cytomegalovirus, cardiovascular disease and all-cause mortality in UK Biobank Philosophical Transactions of the Royal Society B 380, 20240415

Ellis, J et al (2025a) Vaglanciclovir for cytomegalovirus viraemia in advanced HIV disease: A phase 2b randomised placebo-controlled trial of vaglanciclovir for cytomegalovirus viraemia in adults and adolescents with advanced HIV disease Philosophical Transactions of the Royal Society B 380, 20240402

Ellis, J et al (2025b) Epstein-Barr and cytomegalovirus co-infection and mortality risk in patients with HIV-associated cryptococcal meningitis: A post-hoc analysis of a prospective nested cohort in the AMBITION-cm randomised controlled trial Lancet HIV 10, 691-e700

Furman, D et al (2015) Cytomegalovirus infection enhances the immune response to influenza Science Translational Medicine 7, 281ra43

Hamilton, E.M et al (2021) Human cytomegalovirus and risk of incident cardiovascular disease in United Kingdom Biobank Journal of Infectious Diseases 225, 1179-1188

Jackson, S.E et al (2025) The immune response to human cytomegalovirus: Impact of age, co-morbidities and the significance of anti-viral activity assessment Philosophical Transactions of the Royal Society B 380, 20240408

Johnson, S.M et al (2025) Does cytomegalovirus infection increase the risk of tuberculosis in UK children? Philosophical Transactions of the Royal Society B 380, 20240457

Labeb, C et al (2025) Mapping CMV-related immune signatures in blood, aorta and perivascular mediastinal adipose tissue Philosophical Transactions of the Royal Society B 380, 20240401

Loit, M.P et al (2019) Multi-modal techniques failed to detect cytomegalovirus in human glioblastoma samples Journal of NeuroVirology 25, 50-56

Martinez, L et al (2021) Cytomegalovirus acquisition in infancy and the risk of tuberculosis disease in childhood: A longitudinal birth cohort study in Cape Town, South Africa Lancet Global Health 9, e1740-e1749

Paarwater, B et al (2025) Joining the dots, maternal cytomegalovirus, HIV and the placenta Philosophical Transactions of the Royal Society B 380, 20240400

Pembrey, L et al (2019) Age at cytomegalovirus, Epstein Barr virus and varicella zoster virus infection and risk of atopy: The Born in Bradford Cohort, UK Pediatric Allergy and Immunology 30, 6, 604-613

Peredo-Harvey, I et al (2021) Presence of the human cytomegalovirus in glioblastomas - a systematic review Cancers 13, article 5051

Rubin, R.H (1989) The indirect effects of cytomegalovirus infection on the outcome of organ transplantation JAMA 261, 3607-3609

Schleiss, M.R (2024) Newborn screening for congenital cytomegalovirus (cCMV) infection: Universal, targeted, expended-targeted, or none-of-the-above? Neonatology Today 19, 8, 3-12

Soderberg-Naucler, C et al (2025) Does human cytomegalovirus provide a novel therapeutic target for patients with glioblastoma? Philosophical Transactions of the Royal Society B 380, 20240403

Stockdale, L et al (2020) Cytomegalovirus anti-body responses associated with increased risk of tuberculosis disease in Ugandan adults Journal of Infectious Diseases 221, 7, 1127-1134

Stockdale, L et al (2025) Quantitative measures of human cytomegalovirus infection and their associations with tuberculosis disease progression and Mycobacterium tuberculosis infection Philosophical Transactions of the Royal Society B 380, 20240410

Yates, T.A et al (2025) The indirect effects of cytomegalovirus infection - mechanisms and consequences Philosophical Transactions of the Royal Society B 380, 20240398

7. ASSOCIATIONS

7.1. HEIGHT

An individual's height has been found to associate with certain health conditions (eg: taller and less risk of heart disease). "Such epidemiologic associations of height with disease endpoints are susceptible to confounding as adult height is also influenced by environmental factors, including nutrition, socio-economic status, and demographic factors" (Raghavan et al 2022 p3).

Raghavan et al (2022) attempted to isolate cause and effect using genetic data from 275 000 US Veterans Affairs Million Veteran Programme (MVP) participants. Around 350 health conditions or traits were associated with height, but statistical analysis suggested that about 130 of them were predicted by height (eg: coronary heart disease; hypertension; diabetes). The conclusion was that "height may be an unrecognised but biologically plausible risk factor for several common conditions in adults" (Raghavan et al 2022 p2).

Reference

Raghavan, S et al (2022) A multi-population phenome-wide association study of genetically-predicted height in the Million Veteran Programme PloS Genetics 18, 6, e1010193 (Freely available at https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1010193)

7.2. APICAL PERIODONTITIS AND GENERAL INFLAMMATION

An inflammatory condition in the root canal system in the mouth, like apical periodontitis (AP) has wider consequences for the individual's health. "In recent years, emerging evidence [eg: Bakhsh et al 2022] has implicated potential links between AP and cardio-metabolic disorders" (Zhang et al 2025 p2).

Working backwards, does treatment of AP improve cardio-metabolic conditions like metabolic syndrome? Zhang et al (2025) studied AP patients undergoing

endodontic treatment at a London dental hospital. Blood samples were taken pre-operation, three months, six months, one year, and two years post-operation for inflammatory biomarkers. Thirty-seven adults completed the study.

Significant post-operation changes in glucose and lipid metabolites were found. In other words, reduced systemic inflammation after the AP treatment, and this would mean reduced risk of cardio-metabolic disease.

The study was small in sample size to begin (n = 65), and the failure to complete was nearly half of these. There were no control groups - either individuals with AP who did not receive treatment and/or individuals without AP. The researchers admitted that this limitation "precluded us from assessing whether baseline metabolomic profiles in AP differ from those of healthy individuals or whether adverse metabolic states persist or even worsen in unsuccessful cases" (Zhang et al 2025 p12). There was also not complete control of confounders like dietary habits, admitted Zhang et al (2025).

On the positive side, the study was longitudinal with five measurement points, including a pre-operation baseline, and an analysis of 44 metabolites. The treatment of AP was standard, and individuals with cardio-metabolic disease at baseline were excluded.

In conclusion, 24 of the 44 metabolites showed significant post-operation changes.

References

Bakhsh, A et al (2022) The impact of apical periodontitis, non-surgical root canal retreatment and periapical surgery on serum inflammatory biomarkers International Endodontic Journal 55, 9, 923-937

Zhang, Y et al (2025) Successful endodontic treatment improves glucose and lipid metabolism: A longitudinal metabolomic study Journal of Translational Medicine 23, article 1195

7.3. FAECAL METABOLITES

"The interplay between diet and gut microbiome composition is complex. Faecal metabolites, the end products of human and microbial metabolism, provide insights into these interactions" (Pope et al 2025 p1). The analysis of faeces also predicts disease risk (eg: atherosclerotic cardiovascular disease at ten years) (Pope et al 2025).

Pope et al (2025) analysed 54 faecal metabolites from participants in two cohorts - 1810 individuals from "TwinsUK" (Verdi et al 2019), and 837 from "ZOE PREDICT1" (Personalised Response to Dietary Composition Trial) (Berry et al 2020).

References

Berry, S.E et al (2020) Human post-prandial responses to food and potential for precision nutrition Nature Medicine 26, 964-973

Pope, R et al (2025) Faecal metabolites as a readout of habitual diet capture dietary interactions with the gut microbiome Nature Communications 16, article 10051

Verdi, S et al (2019) TwinsUK: The UK adult twin registry update Twin Research and Human Genetics 22, 523-529

7.4. PRE-DIABETES

Pre-diabetes is associated with increased risk of cardiovascular disease and mortality. Lifestyle interventions can limit pre-diabetes from developing into full type 2 diabetes, so can these interventions also reduce cardiovascular disease and mortality?

Vazquez Arreola et al (2025) analysed data from two diabetes prevention trials - the "Diabetes Prevention Program Outcome Study" (DPPOS), and the "DaQing Diabetes Prevention Outcomes Study" (DaQingDPOS) (table 7.1). Both programmes involved changes in diet and increased exercise.

From both studies individuals classed as pre-diabetes in remission (n = 275) were compared to those without remission (n = 2127) after one year of the intervention, and then follow-up for approximately twenty years for cardiovascular disease hospitalisation and mortality. The remission group was significantly less likely to experience the cardiovascular outcomes. "Reaching pre-diabetes remission is linked to a decades-long benefit, halving the risk of cardiovascular death or hospitalisation for heart failure in diverse populations" (Vazquez Arreola et al 2025 p1).

The limitations of the study included "the analyses being post hoc, although cardiovascular outcomes were pre-specified in both trials. Baseline characteristics differed between individuals who reached remission and those who did not; moreover, remission was more likely among individuals with baseline glycaemic values closer to the threshold for normal glucose regulation than among

those nearer the diagnostic threshold for type 2 diabetes, which might also have influenced the results" (Vazquez Arreola et al 2025 p10).

STUDY	DETAILS	REFERENCE
DaQingDPOS	Begun in 1986 in DaQing, China, with six years of lifestyle intervention	Gong et al (2011)
DPPOS	Begun in 2002 as long-term follow-up on the "Diabetes Prevention Program Trial" (1996-2003) in 23 clinics in the USA with sixteen sessions of intensive lifestyle intervention	Goldberg et al (2022)

Table 7.1 - Details of two studies in analysis by Vazquez Arreola et al (2025).

References

Goldberg, R.B et al (2022) Effects of long-term metformin and lifestyle interventions on cardiovascular events in the Diabetes Prevention Program and its outcome study Circulation 145, 1632-1641

Gong, Q et al (2011) Long-term effects of a randomised trial of a six-year lifestyle intervention in impaired glucose tolerance on diabetes-related microvascular complications: The China DaQing Diabetes Prevention Outcome Study Diabetologia 54, 300-307

Vazquez Arreola, E et al (2025) Pre-diabetes remission and cardiovascular morbidity and mortality: Post-hoc analyses from the Diabetes Prevention Program Outcome study and the DaQing Diabetes Prevention Outcome study Lancet Diabetes and Endocrinology (https://www.thelancet.com/journals/landia/article/PIIS2213-8587(25)00295-5/fulltext)