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Health Shorts

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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.

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1. PRE-DIABETES

"Pre-diabetes" (P-D), a concept that emerged in the late 1970s, is used to identify individuals who are at risk of developing diabetes in the future. It is "the earliest identifiable stage of glucose dysregulation, characterised by plasma glucose levels that were intermediate between normal glucose tolerance and diabetes" (Echouffo-Tcheugui and Selvin 2021 p60).

In terms of a defining measurement of plasma glucose levels, one method is an oral glucose tolerance test and two hours later a glucose load value is taken. Impaired glucose tolerance (IGT) at this point was defined as 140 - 199 mg/dL in 1979, but this figure became 100 - 125 mg/dL in the 21st century by the American Diabetes Association (ADA) using the fasting blood glucose test. In 2010 an alternative glycosylated haemoglobin-based (HbA_{1C}) definition was introduced (5.7 - 6.4%; ADA) (Echouffo-Tcheugui and Selvin 2021).

The WHO does not support the HbA_{1C} definition, and recommends an IGT measure of 110 - 125 mg/dL. In fact, Echouffo-Tcheugui and Selvin (2021) reported the current existence of five definitions of P-D in clinical use (table 1.1). So, the different criteria will "identify different people and have only moderate overlap, meaning that the same people will be classified as having pre-diabetes by one definition but not by another" (Echouffo-Tcheugui and Selvin 2021 p61). For example, in one study, between a quarter and a half of individuals classed as having IGT by one definition were also classed as P-D by other definitions (Echouffo-Tcheugui and Selvin 2021).

- Using fasting blood glucose test: 100 - 125 mg/dL (ADA in 2010); 110 - 125 mg/dL (WHO in 2006).
- Using 2-hr 75g oral glucose test: 140 - 199 mg/dL (ADA and WHO).
- Using glycosylated haemoglobin: 5.7 - 6.4% (ADA); 6.0 - 6.4% (International Expert Committee in 2009).

(Source: Echouffo-Tcheugui and Selvin 2021 table 1 p61)

Table 1.1 - Different diagnostic criteria for pre-diabetes.

All this makes it difficult to calculate the global prevalence of P-D. One recent estimate was 7.5% of adults

(Saeedi et al 2019), which was probably an under-estimate as IGT was used (not HbA_{1c}) (Echouffo-Tcheugui and Selvin 2021).

Studies in China, for example, using all three tests, find a prevalence ranging from 36 to 50% of adults, while in the USA, figures range from 4 to 44% (Echouffo-Tcheugui and Selvin 2021).

Age and body mass index (BMI) are key risk factors for P-D (ie: over 65s; overweight and obese individuals). Other demographic differences, like higher prevalence among non-Hispanic Blacks and Hispanics in the USA, depend to some degree on the definition of P-D used (Echouffo-Tcheugui and Selvin 2021).

"A significant proportion of individuals with pre-diabetes will develop diabetes over time, though the magnitude of this risk depends substantially on the pre-diabetes definition used" (Echouffo-Tcheugui and Selvin 2021 p64). The relative risk of developing diabetes can vary from 4 to ten times greater for individuals with P-D compared to non-P-D, depending on the definition and the meta-analysis (Echouffo-Tcheugui and Selvin 2021). There is some research on regression (ie: from pre-diabetes to normo-glycaemia), which may be due to early intervention, but again "undoubtedly reflects the known variables in tests of glycaemia" (Echouffo-Tcheugui and Selvin 2021 p64).

Whatever definition is used, P-D is associated with a higher risk of cardiovascular problems (eg: a relative risk of 1.13 to 1.30 in a meta-analysis of 53 prospective studies; Huang et al 2016). All-cause mortality is also higher in similar amounts (Echouffo-Tcheugui and Selvin 2021).

On the positive side, there is evidence that intensive lifestyle modifications can help individuals with P-D. Large trials in China, Finland, the USA, and India, for instance, over a number of years showed benefits (up to 50% reduction in the development of diabetes) with dietary changes and physical activity (eg: moderate-intensity, like brisk walking, at least 150 minutes per week) (Echouffo-Tcheugui and Selvin 2021).

Studies have also shown benefits with pharmaceutical interventions, like metformin (eg: one-third diabetes risk reduction) (Echouffo-Tcheugui and Selvin 2021). Where there is a choice, lifestyle interventions may be better, except for obese individuals (BMI $\geq$35 kg/m^2), say (Echouffo-Tcheugui and Selvin 2021). "The drug effects have tended to wear out after a washout period; their

withdrawal frequently leads to a glycaemic rebound" (Echouffo-Tcheugui and Selvin 2021 p69).

Echouffo-Tcheugui and Selvin (2021) continued: "In trials that assessed the combined effect of lifestyle modification and a pharmacologic intervention (metformin or pioglitazone), no additional benefit beyond lifestyle modification was found. Given the relatively short duration of most diabetes prevention trials, evidence on the long-term benefits of pharmaceutical therapies on outcomes such as cardiovascular disease and mortality is limited" (Echouffo-Tcheugui and Selvin 2021 p69).

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2. HPV VACCINE

The WHO (World Health Organisation) has a global strategy to eliminate cervical cancer using the human papillomavirus (HPV) vaccine. The vaccine has been used in over one hundred countries (Falcaro et al 2021).

It was introduced in England in 2008 for 12-13 year-old females, with a "catch-up" service for older teenagers subsequently. It is a bivalent HPV immunisation programme using "Cervarix" (ie: it stimulates the immune system against two antigens). Falcaro et al (2021) assessed the ten-year impact of the vaccination programme [1].

The researchers compared three groups who had received the vaccine at 12-13, 14-16 or 16-18 years old, and four unvaccinated cohorts. There was a large reduction in cervical cancer rates among the vaccinated groups compared to the unvaccinated ones (between 34-87%). Those vaccinated at 12-13 years old showed the largest reduction.

The data were population-level patterns, and the researchers admitted that "individual-level data for vaccination status were not available so we could not estimate individual-level efficacy. Additionally, we have no information on the HPV type in each of the cancers. As an observational study of routinely collected cancer registry records, there is a risk that the relationship between the offer of the HPV vaccine and subsequent diagnosis of cervical cancer is confounded by factors not accounted for in the analysis" (Falcaro et al 2021 p2090).

The offer of HPV vaccine was based on age when the programme was introduced. This is a potential confounder which the researchers attempted to control with statistical modelling. "Careful modelling was required to accurately define the different birth cohorts and to adjust for changes to cervical screening and possible secular trends in cervical cancer at all ages before assessing the impact of vaccination" (Falcaro et al 2021 p2090).

The researchers continued: "From previous research, we have detailed information on the effect that policy changes of age at first screening and particular events (eg: the death of television celebrity Jade Goody) had on cervical cancer incidence, so in our regression models we made careful adjustment for this confounding. The cohort

[1] A review of 26 randomised placebo-controlled trials of immunisation programmes had found reductions in cervical cancer precursors (Arbyn et al 2018).

effect that we attribute to the offer and uptake of HPV vaccination could mirror changes in the underlying incidence of sexually transmitted infections, but national data on chlamydia, gonorrhoea, and genital herpes in young women between 2010 and 2019 did not show any strong decreasing trends. Thus, we argue that our findings provide an unbiased estimate of the population-level effect of bivalent HPV vaccination (at different ages and with different levels of coverage) on subsequent cervical cancer rates" (Falcaro et al 2021 p2090).

This was an observational study. There has been a follow-up of randomised clinical trial participants in Finland (Luostarinen et al 2018), which showed the protection of the HPV vaccination against HPV-associated cancers. "However, the women did not all receive the same vaccine (some were vaccinated with Cervarix and others with Gardasil) and the number of cases of cancer was too small to estimate efficacy with precision" (Falcaro et al 2021 p2090).

Cruickshank and Grigore (2021) evaluated the study thus: "Although there are limitations in use of routinely collected data and linkage to vaccine records was not possible, the data are based on large cohort numbers and have been modelled to account for recognised confounders and bias" (p2053).

HPV vaccination programmes in low- and middle-income countries face a number of challenges including access to affordable vaccines, delivery (including low-temperature-controlled facilities), and waste disposal. However, Cruickshank and Grigore (2021) stated: "The scale of the HPV vaccination effect reported by this study should also stimulate vaccination programmes in low-income and middle-income countries where the problem of cervical cancer is a far greater public health issue than in those with well established systems of vaccination and screening. The most important issue, besides the availability of the vaccine (related to the decision makers in the health policy), is the education of the population to accept the vaccination because a high rate of immunisation is a key element of success" (p2054).

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3. E-CIGARETTES

E-cigarettes were introduced to help in cessation of tobacco smoking. They "provide a non-combustible source of nicotine, which allows for the inhalation of nicotine without many of the known carcinogens in cigarette smoke. Those who can switch to e-cigarettes without relapsing to cigarette smoking will reduce the health consequences of their nicotine addiction" (Pierce et al 2021 p2).

Whether e-cigarettes do help in cessation and preventing relapse is disputed. In the short-term, daily e-cigarette users have a lower relapse rate (for tobacco cigarette smoking) than non-users (Wang et al 2021).

Pierce et al (2021) noted some problems:

a) The need for long-term evidence.

b) The concern that e-cigarettes may become part of dual-product use (ie: with tobacco cigarettes).

c) Potential uncontrolled confounders. "Using e-cigarettes as part of a quit attempt is more common among those who are younger, less dependent on nicotine, more educated, have higher income, are from non-Hispanic White race and ethnicity, and those who believe e-cigarettes are less harmful than cigarettes. A number of these variables are also related to the probability that a quit attempt will lead to successful cessation..." (Pierce et al 2021 p2).

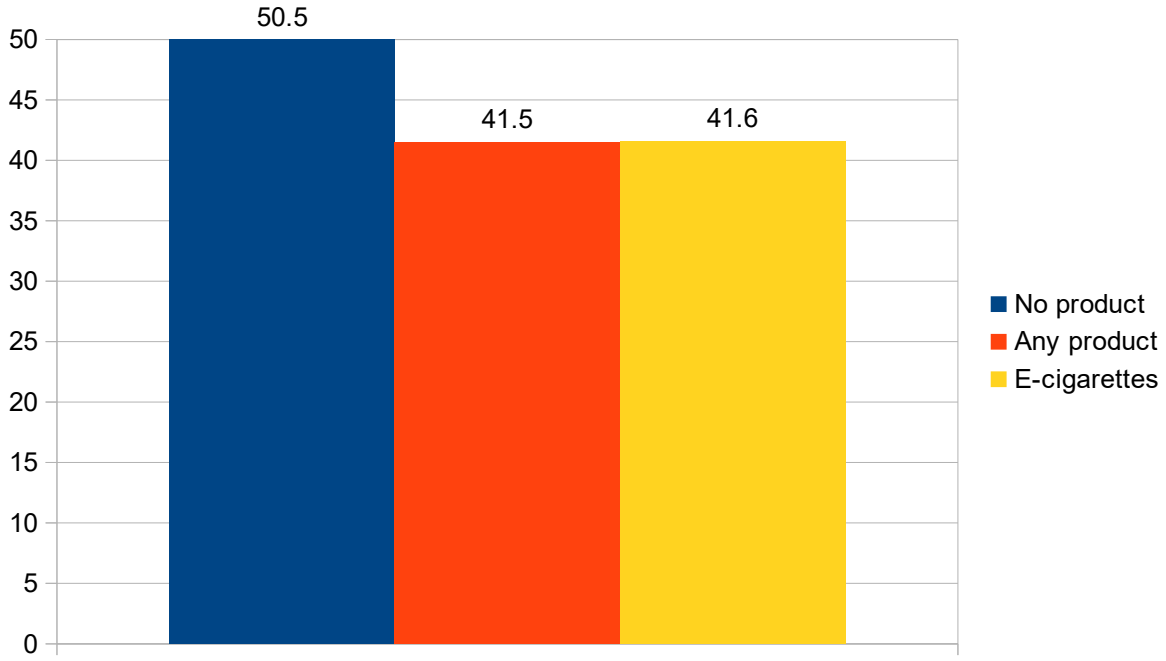
Attempting to overcome these problems, Pierce et al (2021) reported data from the US Population Assessment of Tobacco and Health (PATH) study, which is a nationally representative cohort study began in September 2013. Data up to 2017 were available for four waves of participants. At baseline, 13 604 participants smoked cigarettes (defined as 100 or more cigarettes smoked in their lifetime) (out of 18 049 in the study).

Questionnaires were asked about frequency of smoking, length of cessation, and use of e-cigarettes and other tobacco products. Potential confounders measured included perceived harmfulness of cigarettes, age began smoking, smoking at home by others, addiction and mental health symptoms.

Use of e-cigarettes, and other tobacco products (eg: cigars; pipes; hookah) by former smokers was measured, and these individuals were compared to former smokers who had not used these products.

Relapse rate for tobacco cigarettes was higher among

former smokers who used any tobacco product (including e-cigarettes) compared to "tobacco-free" former smokers. The difference was not statistically significant. In other words, successful quitting was similar whether the former smoker switched to e-cigarettes, an alternative tobacco product, or not (figure 3.1). Use of any tobacco product (including e-cigarettes) was associated with a higher rate of requitting for a three-month period. This confirmed the short-term benefits of e-cigarettes (and other non-tobacco cigarette products) for smoking cessation, but not the long-term benefit.



(Data from table 3 Pierce et al 2021)

Figure 3.1 - Percentage of former smokers still quit after one year based on use of tobacco products.

The sample was self-selected in the sense of alternative nicotine delivery system chosen, whereas a randomised controlled trial would allocate individuals to receive certain products (eg: Eisenberg et al 2020). A randomised controlled trial would allow causal inference which was not possible with this observational study.

This study covered alternative tobacco products, and controlled for nineteen potential confounders associated with e-cigarette use. But "there are undoubtedly other variables that are unmeasured confounders and limit causal inference" (Pierce et al 2021 p8).

In conclusion, Pierce et al (2021) stated that "switching to e-cigarettes (even on a daily basis) was not associated with helping smokers remain abstinent from cigarettes. Indeed, the evidence suggested that switching to alternate tobacco products by recent former smokers may be associated with increased risk of a relapse to cigarette smoking" (pp8-9).

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Wang, R.J et al (2021) E-cigarette use and adult cigarette smoking cessation: A meta-analysis American Journal of Public Health 111, 2, 230-246

4. AIR POLLUTION

4.1. MENTAL HEALTH

"Identifying modifiable risk factors for illness severity and relapse following onset is therefore a crucial research challenge that could inform early-intervention efforts and reduce the human suffering and high economic costs caused by long-term chronic mental illness" (Newbury et al 2021 p678). The authors were referring primarily to psychotic and mood disorders, and to the potentially modifiable risk factor of air pollution. They were reporting their finding that air pollution exposure was associated with mental health service use among individuals with such disorders.

A retrospective cohort study was performed with nearly 14 000 adults who had used a south London mental health service provider between 2008 and 2013. The participants lived in four local boroughs, and air pollution was modelled for those areas.

The outcome measure was mental health service use - in-patient days, and outpatient appointments.

Overall, increased exposure to air pollution was significantly associated with increased mental health service use. This showed a dose-response relationship (ie: more exposure and more service use). It was estimated that reducing air pollution to WHO recommended levels would reduce mental health service use by 2%. In summary, air pollution potentially increases illness severity and relapse for mood and psychotic disorders.

Newbury et al (2021) offered this explanation for the findings: "With potent oxidising and inflammatory properties, it has been suggested that air pollutants could affect the brain directly by translocating along the olfactory nerve and permeating the blood-brain barrier and/or indirectly by eliciting systemic inflammation. Neuroinflammation and oxidative stress are likewise both implicated in the aetiology of psychotic and mood disorders, and therefore a role of air pollution exposure in the severity and
course of psychotic and mood disorders is biologically plausible" (p684).

Table 4.1 summarises the key strengths and weaknesses of the study.

STRENGTHS	WEAKNESSES
1. Two different measures of mental health service use to show illness severity and relapse. 2. Use of official measures of air pollution - mean concentration of three pollutants per quarter. 3. Control for multiple confounders, like seasonal fluctuations in pollution, ethnicity, and neighbourhood deprivation. 4. Large diverse sample with up to seven years follow-up.	1. Mental health service use was a proxy measure of illness severity and relapse. A number of factors influence contact with services, including bed availability, and help-seeking motivation. 2. No information on air pollution during childhood. 3. The exposure to air pollution was an approximation, and ideally individuals would wear monitoring devices for exact measures. 4. Causation cannot be established as this was a retrospective observational study.

Table 4.1 - Key strengths and weaknesses of Newbury et al (2021).

4.2. PROLONGED EFFECT

Analysing the air in London, Resongles and Weiss (2021) found evidence of lead (as from leaded petrol), but unleaded petrol became the norm over twenty years ago in the UK. This means that toxic pollutants remain in the environment for long periods of time. Samples collected in 2014 and 2018 showed a chemical profile similar to the past decade. "The chemical profiles do not vary seasonally, an indication that persistent lead pollution comes from road dust that is thrown into the air rather than from current coal burning..." (Research highlights 2021 p10).

4.3. REFERENCES

Newbury, J.B et al (2021) Association between air pollution exposure and mental health service use among individuals with first presentations of psychotic and mood disorders: Retrospective cohort study British Journal of Psychiatry 219, 6, 678-685

Research highlights (2021) Lead from decades ago dirties London's air today Nature 595, p10

Resongles, E & Weiss, D (2021) Strong evidence for the continued contribution of lead deposited during the 20th century to the atmospheric environment in London of today Proceedings of the National Academy of Sciences, USA 118, 26, e210279118

5. DEPRESSION AND CITIES

"Living in cities changes the way we behave and think" (Stier et al 2021 p1). For many that is negative changes (eg: poorer mental health). Stier et al (2021) challenged this idea, arguing that the research findings were mixed due to differences in methodology and definitions (eg: "urban").

These researchers noted "surprisingly, the per capita prevalence of depression decreases systematically with city size" (Stier et al 2021 p1). Key is the number of connections to others (or socio-economic network structure) in cities, which can lead "to potential mental 'overload' but also, to greater stimulation and choice along more dimensions of life" (Stier et al 2021 p2).

Stier et al (2021) used statistical mathematical modelling with four US datasets, which included prevalence of depression, and Twitter geolocation information.

At the same time, Stier et al (2021) recognised that "the numerous factors that influence depression vary enormously within cities. These variations may influence individuals directly and also, indirectly through the local environments in which they live and work" (p4). These factors might include neighbourhood population density, socio-economic status, and gender. This study also only investigated depression.

REFERENCE

Stier, A.J et al (2021) Evidence and theory for lower rates of depression in larger US urban areas Proceedings of the National Academy of Sciences, USA 118, 31, e2022472118

6. PREDICTING PLACEBO

Meissner et al (2020) investigated the possibility that certain blood proteins could predict susceptibility to the placebo effect. Kokkotou et al (2010), for example, had previously found that "placebo responders" with Irritable Bowel Syndrome (IBS) had higher levels of osteoprotegerin in their blood. Meissner et al (2020) sought a wider "molecular fingerprint of placebo effects in human plasma" (p2). They noted: "Blood plasma is the most sampled and most complex human proteome and comprises immunoglobulins, peptide and protein hormones, proteins secreted by solid tissues (eg: liver proteins), cytokines, lysosomal proteins, tissue leakage proteins (eg: troponin, creatine kinase), and proteins released from tumours and infectious organisms. Depending on their site of origin, plasma proteins can change within minutes to hours" (Meissner et al 2020 p2).

Meissner et al (2020) induced nausea in 100 volunteers with visual effects (figure 6.1) [2], and they were then given a treatment to reduce the nausea (but half received a placebo version [3]) [4]. Patterns in the blood proteins were found among those given a placebo who reported benefits in reducing the nausea. Nausea was self-reported on an eleven-point scale, from 0 ("no nausea") to 10 ("maximal tolerable nausea").

Such knowledge would allow doctors to use milder drugs at lower doses with individuals susceptibility to the placebo (Luana Colloca in Hamzelou 2020).

[2] "Nausea was induced by standardised visual presentation of alternating black and white stripes with left-to-right circular motion at 60 degree/sec. This left-to-right horizontal translation induces a circular vection sensation wherein subjects experience a false sensation of translating to the left. The nauseating stimulus was projected to a semi-cylindrical and semi-transparent screen placed around the volunteer at a distance of 30 cm to the eyes" (Meissner et al 2020 p4).

[3] The placebo was sham acupuncture.

[4] Previously the researchers (Aichner et al 2019) had noticed a significant placebo effect when comparing a treatment and a placebo for experimentally induced nausea.

(Source: Meissner et al 2020 figure 1a)

Figure 6.1 - Drawing of nausea-inducing set-up.

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Kokkotou, E et al (2010) Serum correlates of the placebo effect in irritable bowel syndrome Neurogastroenterology and Motility 22, 3, 285-e81

Meissner, K et al (2020) Molecular classification of the placebo effect in nausea PLoS ONE 15, 9, e0238533 (Freely available at https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0238533)

7. NEW TREATMENTS FOR DEPRESSION

7.1. NITROUS OXIDE

The lifetime prevalence of major depression disorder (MDD) is estimated at 10-20%, but around one-third of those individuals are at risk from treatment-resistant major depression (TRMD) (Nagele et al 2021).

In the search for a treatment for TRMD, nitrous oxide ("laughing gas") was tried by Nagele et al (2015) in a small-scale study. Nagele et al (2021) performed a controlled trial with twenty completing individuals attending the Washington University Department of Psychiatry clinic.

All participants underwent three one-hour sessions of inhalation over three months (ie: one month between each treatment session). One session was a placebo (0% nitrous oxide/100% oxygen), one session was 25% nitrous oxide in oxygen, and one session with 50% nitrous oxide. This was a crossover design.

Data on mood were collected at baseline (ie: before inhalation), 2 hours, 24 hours, 1 week and two weeks after inhalation using standardised measures.

Overall, the sessions with nitrous oxide led to significant improvements in depression scores compared to the placebo session over four weeks. There were also benefits at three months. The magnitude of the improvement was very comparable to that in trials of certain anti-depressants (Nagele et al 2021).

Nagele et al (2021) noted some key points, including "25 or 50% nitrous oxide showed equivalent anti-depressant efficacy; however, 25% nitrous oxide demonstrated a markedly lower rate of adverse side effects" [eg: dizziness, nausea] (p4). They continued: "Although we observed anti-depressant effects in most patients after nitrous oxide inhalation, the response was not uniform. Some patients had minimal or no improvement after nitrous oxide and placebo and should be considered non-responders. Furthermore, some patients had a strong placebo response, which, in some instances, mirrored the response to nitrous oxide" (Nagele et al 2021 p4).

This study had some key limitations, including:

a) Small sample.

b) Short-term follow-up.

c) Limited "wash-out period" (ie: time between sessions). Nagele et al (2021) noted that "some patients had a sustained treatment effect beyond four weeks, which resulted in a carry-over effect" (p4).

d) Blinding problems - ie: "in more than four of five instances, patients correctly guessed their treatment (nitrous oxide versus placebo), which is higher than expected because of chance. Thus, there is potential for bias in the study results..." (Nagele et al 2021 p4). The researchers pointed out: "Given the calming effects of nitrous oxide, it is extremely difficult to completely blind patients to nitrous oxide versus placebo. Concomitant use of a relaxing agent in the placebo group, for instance, benzodiazepines, to artificially mimic the temporary euphoric/anxiolytic effects of nitrous was considered; however, out of concern that this could differentially affect depressive symptoms, we decided not to use this method" (p4).

7.2. PSYCHEDELICS

Mehta (2020) advocated brain scanning as the way to find out how psychiatric drugs are working in the brain. This also allows the search for neurobiological underpinnings of symptoms that cross diagnostic boundaries (eg: psychosis).

Mehta (2020) favours the use of psychedelic drugs as treatments for mental disorders. For example, psilocybin (the active compound of "magic mushrooms") activates a receptor in the brain called 5-HT2A, and this receptor is known to be active in Parkinson's Disease. The consequence in both cases is visual distortions and hallucinations (Mehta 2020).

7.3. REFERENCES

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Nagele, P et al (2021) A phase 2 trial of inhaled nitrous oxide for treatment-resistant major depression Science Translational Medicine 13, eabe1376

8. EXERCISE MIMETIC

The idea that the benefits of exercise could be available without doing the exercise, namely "in a pill", is attractive. Early in the 21st century, it was found that "unfit" mice given an experimental drug (GW1516) became "fit". GW1516 targeted a protein (peroxisome proliferator-activated receptor; PPPR-delta) that is viewed as the "master switch" of a wide range of genes (Marchant 2021).

An alternative approach is targeting a hormone released by muscles during exercise (irisin). This caused white fat in obese mice to be converted into energy-burning brown fat, and so they lost weight (even on a high-fat diet) (Marchant 2021).

Mice have also shown benefits with a molecule called "compound 14" (Marchant 2021).

The term "exercise mimetic" has been used for such substances (Marchant 2021). But critics pointed out that there are many types of exercise with different physiological effects, and one pill cannot cover all the metabolic processes involved (Marchant 2021).

There is also concern over side effects. The above-mentioned substances are experimental, and tested on mice for a reason. GW1516, for example, was abandoned because long-term high usage produced tumours in the mice (Marchant 2021).

REFERENCE

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9. CLINICAL TRIALS

9.1. ARTIFICIAL INTELLIGENCE

"Clinical trials are the main way to determine whether new treatments are safe and effective. Trial success can depend on the timely enrolment of a representative sample of individuals who meet the eligibility criteria. However, enrolling enough people to draw a statistically significant conclusion about a trial result can be a problem" (Weng and Rogers 2021 p512) [5].

The eligibility criteria are usually strict, leaving only participants classed as low-risk (eg: young adults, healthy individuals, or, if a particular disease is required, without co-morbidities). But this approach restricts the participant pool, as well as excluding individuals who could potentially benefit from the treatment being trialled (Weng and Rogers 2021).

An alternative to controlled trials is analysis of real-world data (eg: electronic health records; EHRs). Liu et al (2021) created an AI software tool called "Trial Pathfinder" to analyse EHRs in "trial emulations". Using data from actual clinical trials, the software is able to extrapolate the results to other patients based on relevant characteristics. Then the AI calculated the generalisability of findings. It recommended more women, and older adults being recruited in clinical trials. The dataset related to cancer treatments.

In summary, a wider sample of participants could be used while still maintaining safeguards for patient safety (Liu et al 2021).

9.2. EARLY TRIALS

"Perkins tractors" became a popular treatment for all conditions in the late 18th century. Introduced by Elisha and Benjamin Perkins, it involved lightly stroking the afflicted part of the body with "two narrow metallic rods a few inches long" (Faria 2021 p68). It was claimed that the disease or pain was drawn out of the body (Faria

[5] Over 80% of cancer treatment clinical trials, for instance, fail to complete recruitment of participants in the targeted time (Liu et al 2021).

2021).

Dr John Haygarth was the first person to experimentally test treatments. He did this with tractors. Five rheumatic patients at this infirmary in Bath were stroked with pieces of wood carefully painted to look like tractors. Four of them claimed to feel better afterwards. Haygarth repeated this with actual tractors, as well as other materials, including pieces of bone, slate pencils, and tobacco pipes (all painted to imitate tractors). In every case, the patients reported improving. Haygarth published his findings in 1800 in "Of the Imagination as a Curse and Cure of Disease". "Haygarth was the first to perform a controlled experiment that elegantly and eloquently made clear the power of the psyche" (Faria 2021 p77).

The first double blind trial is attributed to psychologist William Halse Rivers, who in 1907, tested the effects of caffeine on muscular activity (Faria 2020).

9.3. REFERENCES

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Liu, R et al (2021) Evaluating eligibility criteria of oncology trials using real-world data and AI Nature 592, 629-633

Weng, C & Rogers, J.R (2021) An AI tool to make clinical trials more inclusive Nature 592, 512-513

10. SOCIAL MEDIA USE AND DEPRESSION

The relationship between social media use and depressive symptoms has become an important issue in recent years. Cross-sectional studies have confirmed greater levels of anxiety and depression with greater use (eg: Lin et al 2016). But "concern has been raised that reporting bias may result from individuals with greater depressive symptoms over-reporting social media use" (Perlis et al 2021 p1). There are a few short-term longitudinal studies (eg: two weeks; Kross et al 2013).

Perlis et al (2021) explored a longer time period based on data from an internet survey performed every month between May 2020 and May 2021 among US adults. Mental health was measured by the nine-item Patient Health Questionnaire (PHQ-9). This involves nine symptoms of depression each rated for the last two weeks ("not at all" (0) to "nearly every day" (3)), and giving a maximum score of 27.

The researchers analysed two waves of the survey (n = 5395). All participants at the first wave had a low PHQ-9 score (mean 1.29), but 8.9% experienced an increase in score of five points or greater by the second wave (this was the outcome variable). Social media use was significantly associated with this increase. The researchers explained that "the association was not meaningfully changed by number of social supports or face-to-face social interactions at baseline, suggesting it is not mediated by reduction in social interactions more broadly" (Perlin et al 2021 p4).

Looking at specific social media platforms and age, Perlin et al (2021) found the following patterns: "For TikTok and Snapchat, use was associated with depressive symptoms among those ages 35 years or older but not among those younger than age 35 years... For Facebook, the opposite pattern was observed; use was associated with depressive symptoms among those younger than 35 years, but not among those aged 35 years and older" (p3).

This study had a broader age range than previous ones, and the majority of the participants were over 35 years old. Thus, it showed that the association between social media use and depression is not limited to adolescents and young adults.

The data were self-reported. No information was collected about the nature of social media use. "Notably, social media use may simply be a marker of underlying vulnerability to depression" (Perlin et al 2021 p4). The sample was not representative of the US population with over 65% of the respondents being female. The study could

not establish causation. Perlis et al (2021) ended: "These data cannot elucidate the nature of this association, but suggest the need for further study to understand how social media use may factor into depression among adults" (p1).

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11. OVERCOMING PRESENT BIAS

"Individuals often fail to invest in preventive healthcare, even when such interventions cost little and individuals are aware of their benefits" (John and Orkin 2021 p1). One explanation is "present bias" (ie: a focus on the current time or immediate future with little thought to long-term planning).

So, psychological interventions may help. John and Orkin (2021) reported a field experiment in rural Kenya to encourage the use of chlorine for water. A total of 3750 women were allocated to one of four groups:

i) "Visualisation" (V) - Two sessions that involved visualising alternative possibilities for the future.

ii) "Planning" (P) - Two sessions to improve planning skills.

iii) "Active control" (AC) - Two discussion sessions about an irrelevant topic (birds in Kenya).

iv) "Pure control" (PC) - No sessions.

Over the following three years, the household use of chlorinated drinking water increased significantly in the V condition compared to the PC one. Consequently, the number of diarrhea episodes in children decreased in the V group. The P condition showed a small (non-significant) increase in chlorinated water use.

In conclusion, the V condition increased future-oriented behaviours, which included the preventive health measures.

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12. GASTRO-INTESTINAL SYMPTOMS

Individuals with eating disorders often have gastro-intestinal (GI) complaints (eg: abdominal pain, constipation and bloating), and Stein et al (2021) considered whether childhood GI symptoms could be a predictor of later eating disorders.

Recurrent abdominal pain (RAP) is estimated to affect around 10% of 5-16 year-olds, "usually with no identifiable disease pathology" (Stein et al 2021 p916). Apley and Naish (1958) defined RAP as "[A]t least three bouts of pain, severe enough to affect his/her activities, over a period of at least 3 months, with attacks continuing in the year preceding examination" (quoted in Stein et al 2021). Paediatric Functional Abdominal Pain Disorders (FAPDs) is a more recent term, which is defined as "when abdominal pain occurs 4 or more times a month, for at least 2 months, in either an episodic or continuous fashion, and cannot be ascribed to an inflammatory, anatomic, metabolic, or neoplastic process" (Stein et al 2021 p916).

RAP/FAPD is associated with anxiety. in fact, the GI symptoms have often been attributed to generalised anxiety (Stein et al 2021).

But "recent research has shown that visceral hypersensitivity (ie: increased sensitivity to GI sensations) is especially important for developing increased pain sensitivity, hypervigilance, and poor coping responses" (Stein et al 2021 p916). Hypersensitivity about "essentially normal gut sensations" creates a preoccupation with the experiences, fear of pain from them, and food avoidance and restriction. Thus, the possible link between childhood GI symptoms and later eating disorders.

There is a small amount of evidence showing such a relationship. For example, in a Swedish study, childhood GI problems were more common among 51 adults females with anorexia nervosa than in healthy controls (Rastam 1992). While among adults with bulimia nervosa, those who recalled childhood GI complaints had earlier onset of self-induced vomiting behaviour that those without GI symptoms (Gendall et al 2005).

Prospective longitudinal data, however, were lacking until Stein et al's (2021) study. They analysed data from the Avon Longitudinal Study of Parents and Children (ALSPAC) in the UK.

During the regular collection of data in ALSPAC, mothers were asked about their child's abdominal pain, and Stein et al (2021) concentrated on the responses for

seven and nine years old. "Fasting to control weight" was investigated at sixteen years old (table 12.1). Complete data on 3001 children were available.

Mothers asked:

- "Have there been times when your child seems to have had a pain in their stomach in the past 12 months?" (yes/no).

- "How many separate times has this happened in the past 12 months?" (once, twice, 3 or 4 times, 5 or more times, or don't know).

Adolescent asked:

- "During the past year, how often did you fast (not eat for at least a day) to lose weight or avoid gaining weight? (never, less than once a month, monthly, weekly).

Table 12.1 - Key questions from ALSPAC.

Overall, 6.2% of the sample had 5 or more times of RAP (RAP5+) at seven and nine years old according to the mother, and 19% had 3 or 4 times (RAP3+). in total, 12.7% of adolescents reported fasting for at least one day to lose weight. Putting the numbers together, 19% of the RAP5+ group had fasted. After adjusting for variables like maternal anxiety and depression, there was no relationship between RAP5+ and fasting.

But there was a significant association, even after controlling for confounders, for RAP3+ and fasting (an odds ratio of 1.5 compared to no RAP).

Stein et al (2021) offered some possible explanations for the finding that RAP3+ was significantly associated with fasting, but not RAP5+, including:

a) The frequency of RAP is less important than the severity, which was not asked about.

b) "Non-extreme response bias" - This is, Stein et al (2021) explained, "whereby participants tend to avoid selecting the extreme endpoints on a scale, preferring to select the middle values... Thus, by asking the parents to report their child's RAP as 5+ episodes in the past year, we may have inadvertently missed out on important and relevant data" (p921).

All data were maternal-reported for the child or self-reported in adolescence.

Stein et al (2021) ended: "Whilst the independent contribution of RAP to the overall risk of developing an

eating disorder appears to be quite modest, coupled with anxiety and other important psychological factors it may be clinically significant and should be enquired about in the assessment and management of eating disorders" (p922).

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13. SICKNESS DETECTION

Group-living species of animals can detect sick individuals (eg: ants), but what about human beings? This is important with SARS-CoV-2 when individuals are infectious before symptom onset.

Humans respond to obvious disease signs, like skin lesions, with disgust, and "[T]here is some evidence that people can detect sickness from body odours, bodily motion and faces when they belong to the same homogeneous group, but cross-cultural data is necessary to uphold claims of universality" (Arshamian et al 2021 p2).

Arshamian et al (2021) sought such cross-cultural data by showing pictures of Western faces to non-Western participants. The photographs came from Sweden, and were shown to a "home" sample, two groups from global cities (in Thailand and Mexico), and three traditional societies (two hunter-gatherer communities and one from the equatorial rainforest).

The photographs of thirteen individuals included some injected with an antigen to cause the immune system to respond and produce the symptoms of sickness (ie: the initial phase of infection).

Each photograph was rated as "sick" or "healthy", and then to say who was sick in a forced-choice paradigm (sick and healthy photographs side by side).

In the first task, all groups of participants detected a sick face correctly above chance. likewise in the forced-choice paradigm. "Taken together, this suggests that sickness detection is based on deciphering infection cues that are shared across people. Although this study does not address what these cues are or whether sickness cues in White-presenting faces may be more discernible than in faces from other communities, recent data from Swedish participants studying the same faces indicate that low-level features like pale skin and droopy eyelids were the most reliable estimates of sickness [Axelsson et al 2018]" (Arshamian et al 2021 p6).

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14. WHAT-IF-SITUATIONS TEST

The "What-If-Situations-Test (WIST) (Nemerofsky 1986) was developed to measure pre-school children's understanding after sexual abuse prevention programmes. "The test items measure the skills and concepts taught in the prevention program and address skills and concepts thought to be essential in reducing the risk of sexual victimisation" (Nemerofsky and Carran 2010 p5).

It consists of twenty-nine items based around, "What would you do if someone..." - eg: "asked you to touch their private parts" or "touched your private parts". It is scored between 0 and 64, with a higher score showing greater understanding. It should be administered pre-prevention programme and post-programme (Nemerofsky and Carran 2010).

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15. SHAME AND EATING DISORDERS

Researchers are interested in the individual factors that trigger and maintain eating disorder behaviour, and reduce help-seeking and treatment effectiveness. One such factor for all these aspects is the experience of shame. This is "usually defined as a negative painful self-conscious emotion characterised by negative global evaluations of the entire self" (Nechita et al 2021 p1900).

There is growing evidence of the association between shame and eating disorder symptoms. But the relationship may be different between over- and under-eating symptoms. For instance, "it seems that attempts to control eating might be used to prevent shame..., while shame can also be viewed as a consequence of disordered eating behaviours which in turn maintain the problem by triggering further attempts to control weight and shape as a way of regulating this painful emotion" (Nechita et al 2021 p1901).

There are also different types of shame as well as general shame or shame-proneness (Nechita et al 2021). For example, "characterological" (shame about personal abilities and habits), behavioural (shame about problematic behaviours), and body shame (Andrews 1998).

Nechita et al (2021) reported a meta-analysis of 195 studies on the association between shame and disordered eating. Each study was assessed for measurement of shame and eating disorders symptoms, the types of each, and the methdological quality (eg: clear research questions; clear statement of inclusion and exclusion criteria; control of potential confounders).

Overall, shame was significantly associated with all types of eating disorders symptoms, and particularly body shame, and shame around eating.

In terms of the methodology of the different studies:

a) Most of the studies included focused on global eating disorders symptoms rather than the specific ones.

b) "The large majority of the studies included in this meta-analysis were cross-sectional [95%], thus not allowing to draw any conclusions about temporal relationships and causality. Also, the fact that the few longitudinal studies did not adjust for baseline levels might be a potential source of bias" (Nechita et al 2021

p1935).

c) Different measures of shame were used between the studies, and "few studies considered the confounding influence of other variables such as body mass index, depression, or other type of negative affect. In order to uncover the true nature of the association between shame and ED [eating disorders], controlling for these factors might be an important step forward" (Nechita et al 2021 p1935).

d) The samples were predominantly White, educated individuals.

e) Nechita et al (2021) finished on their methodological evaluation saying: "The field would benefit from clear conceptualisations of constructs, adequate measures and straightforward presentation of study approach and sample. This suggestion is in accordance with the data in this meta-analysis indicating a low quality for most studies which is mainly due to the cross-sectional nature of studies, inappropriate description of samples, and lack of sample size estimation" (p1936). Only four studies were rated as "good" in terms of methodological quality, and 43 as "fair".

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