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Health and Mind Topics

Kevin Brewer

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Orsett Psychological Services
PO Box 179
Grays
Essex
RM16 3EW
UK

orsettpsychologicalservices@phonecoop.coop

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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/.

CONTENTS

1. TYPE 2 DIABETES AND PREGNANCY

Type 2 diabetes mellitus (T2DM) is rising in sub-Saharan Africa due to increased obesity, reduced physical activity, poor nutrition, and HIV anti-retroviral therapy-induced lipodystrophy (Chivese et al 2019).

For women, hyperglycaemia (high blood sugar) first detected in pregnancy (HFDP) (or gestational diabetes mellitus; GDM) is a high risk for future T2DM (as well as adverse birth outcomes) (eg: Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) Study; Lowe et al 2018) [1]. Though the HAPO Study included participants from ten countries, there were no data from Africa (Chivese et al 2019).

Chivese et al (2019) analysed data from the Groote Schuur Hospital in Cape Town, South Africa. The sample was 498 pregnant women in 2010-11 followed-up in 2016-17. The purpose was to see who with HFDP in 2010-11 progressed to T2DM later.

Only 220 women agreed to participate, of which 105 (48%) had T2DM in 2016-17. The factors associated with progression to T2DM included significantly higher blood sugar levels in pregnancy, less education, and larger waist circumference.

The prevalence of T2DM found was much higher than in South African women generally (around 10%), or women in Cape Town (15-30%) (Chivese et al 2019), which suggested the importance of HFDP. Around the world, progression from HFDP to T2DM varies between less than 10% (eg: non-indigenous Australians; Chamberlain et al 2016; table 1.1; Finland - RADIEL Study; Huvinen et al 2018 [2]) to over 50% (eg: India; Kale et al 2004; table 1.2) (Chivese et al 2019).

The follow-up group was less than half of eligible women for various reasons (figure 1.1). The most common problem was the inability to find the women, which is "partly explained by a highly mobile population in the Western Cape, where in-and-out migration is common" (Chivese et al 2019 p13).

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[1] Pre-pregnancy weight is also a risk factor for future offspring's weight (appendix 1A).

[2] The RADIEL Study was set up in Finland to prevent GDM, and it involved three maternity hospitals between 2008 and 2014 (Rono et al 2014). Half of the women at high GDM risk were given a lifestyle programme (appendix 1B), and benefited compared to the control group (the other half of the women) (Koivusalo et al 2016). Huvinen et al (2018) followed up the women 4-6 years after birth (n = 333). In total, 3.6% of the women were diagnosed with T2DM, but this figure was higher for obese women.

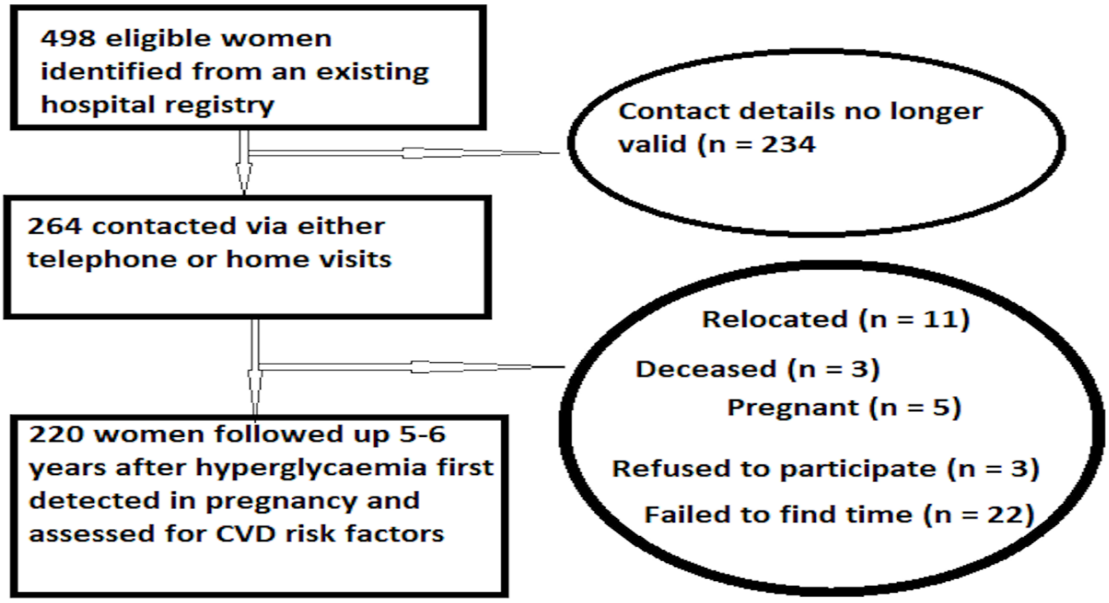
- All women who gave birth at Cairns Hospital in Queensland, Australia, between 2004 and 2010 who were diagnosed with HFDP were recruited for this study.

- Of these, after birth, 483 women were tested for T2DM, of which 155 self-identified as "Indigenous" (Aboriginal and Torres Strait Islander peoples in Australia).

- At three years, post-birth, 22% of Indigenous women and 4% of non-Indigenous women were diagnosed with T2DM, and the figures were 26% and 6% at five years post-partum, and 43% and 14% at seven years, respectively.

- The progression of T2DM was increased by larger body mass index (BMI) - overweight and obese women were 2-3 times more likely to be diagnosed with T2DM.

Table 1.1 - Chamberlain et al (2016).



(CVD = cardiovascular disease)

(Source: Chivese et al 2019 figure 1)

Figure 1.1 - Details of sample.

- Sample - 126 women who gave birth at one hospital in Pune, India, since 1994 and were diagnosed with GDM. The women were followed up in 2002 (between 2-7 years after delivery).

- Findings - 65 women (52%) were diagnosed with T2DM at follow-up. This compared to 4% eight years post-birth among another sample from the same hospital who did not have GDM (Yajnik et al 2003).
  Kale et al (2004) found that the women with T2DM were "more obese and more centrally obese" (but similar in BMI) than the rest of their sample.

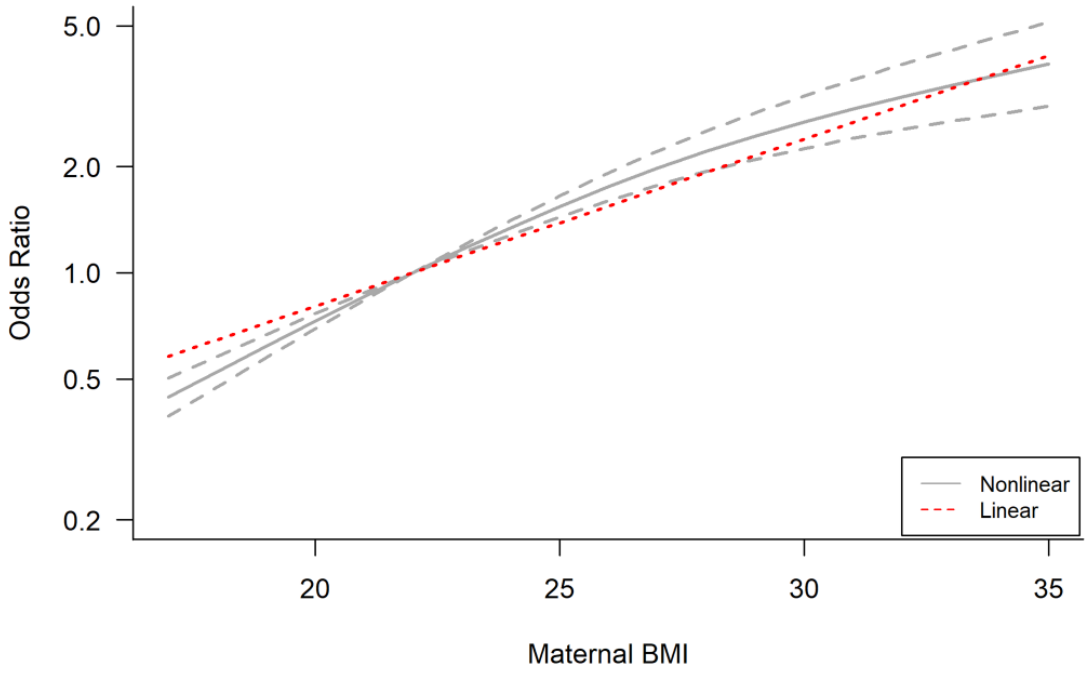
Table 1.2 - Kale et al (2004).

Chivese et al (2019) pointed out some other limitations - "our study did not follow up women until diabetes developed, and therefore we do not have time to development of diabetes, as well as being unable to establish temporality for any of the risk factors we identified. The lack of a control group of women with normoglycemic pregnancies at the same time as our sample is a further limitation" (p13).

APPENDIX 1A - MATERNAL PRE-PREGNANCY WEIGHT

Heslehurst et al (2019) performed a review and meta-analysis of the relationship between maternal pre-pregnancy body mass index (BMI) and future offspring obesity in childhood. Seventy-nine relevant studies covering 59 cohorts were found.

There was a statistically significant relationship between the woman being overweight or obese before pregnancy and her future offspring's risk of obesity in childhood. For example, if the pre-pregnant woman had a BMI of 27 kg/m² (overweight), child obesity was nearly twice as likely as compared to normal weight women (BMI 22 kg/m²), and the risk of offspring obesity was over three times for women with a BMI of 35 kg/m² (obese) (figure 1.2).



(Non-linear = categorical measurement of childhood weight (eg: obesity = ≥95th percentile for age group); Linear = continuous BMI score)

(Source: Heslehurst et al 2019 figure 3)

Figure 1.2 - Relationship between maternal pre-pregnancy BMI and odds ratio for childhood obesity of future offspring.

Heslehurst et al (2019) found "an association between child obesity and increasing child age, which may reflect the combination of in utero and child life course exposures. The development of obesity involves a complex interplay between physiological, environmental, psychological, social, and behavioural exposures. For example, there is evidence of epigenetic processes in utero that contribute to offspring obesity, including alterations in DNA methylation and the gut microbiome. Additional life course exposures include socio-economic status, food production and marketing, food insecurity, and obesogenic environments, which promote unhealthy lifestyles to which some individuals are genetically more susceptible. If mothers were exposed to these complex factors, contributing to their own obesity development, then their children are also likely to be exposed to the same complex factors, which exacerbate in utero development and predisposition to obesity" (pp10-11).

Meta-analyses are only as good as the studies included, and there were a number of methodological issues including (Heslehurst et al 2019):

i) Different outcome measures - child BMI or obesity were measured as continuous or categorical variables.

ii) Heterogeneity between studies in controlling other variables (eg: socio-demographic factors; age of child).

iii) Obesity grouped as one (ie: BMI $\geq$30 kg/m^2) rather than distinguishing between levels of obesity. "Obesity is not a homogeneous group and in order to better understand the differences within obesity, future research should use obesity classes when defining categories" (Heslehurst et al 2019 p11).

iv) Studies published in English only.

v) Little data from low- and middle-income countries.

APPENDIX 1B - PHYSICAL ACTIVITY

Physical activity (PA) prior to, or in early pregnancy reduces the risk of GDM, according to a meta-analysis (Tobias et al 2011).

The Soweto First 1000 Days Study (S1000) was designed to investigate PA in pregnancy and GDM in Africa. GDM is believed to be higher in Africa than in some high-income countries (Khan et al 2016).

GDM and obesity together are a significant risk for

later metabolic syndrome. Furthermore, children born to mothers with GDM have a greater risk of obesity, T2DM, and metabolic syndrome in childhood and adolescence (Yogev and Visser 2009).

The S1000 recruited eighty pregnant, non-diabetic women in Soweto, South Africa. PA was measured by questionnaire, and by wearing an accelerometer for seven days. Blood glucose level was measured at 24-28 weeks of pregnancy.

Physical Activity Generally

Adults are recommended to take part in 150 minutes of moderate to vigorous physical activity (PA) each week by the World Health Organisation, for example, and individuals who do not meet that level have a greater risk of all-cause mortality (eg: nearly one-third higher risk; Lee et al 2012).

Running is one way to achieve the recommended PA. But what is the best "dose" of running? "Dose" can be defined as frequency (eg: three times per week), overall duration (eg: thirty minutes per week), pace (eg: 5 km/h), or total volume (metabolic equivalent (MET) of running at a given pace) (eg: 800 MET-min/wk) (Pedisic et al 2019).

Schnohr et al (2015) proposed a U-shaped relationship between the dose of running and the risk of mortality, with individuals who ran less than 2.5 hours per week, less than four times per week, or a slow to average pace had the greatest benefits compared to non-runners [3]. This study took place in one city (Copenhagen).

Pedisic et al (2019) performed a meta-analysis on studies of running and all-cause mortality. Fourteen relevant articles were found covering six cohorts [4].

Overall, running participation was associated with a reduction in all-cause mortality risk of 27% compared to non-running (with a 34% reduction for women and 27% for men). No significant dose-response relationship was found. In other words, any running is beneficial, with the smallest dose being once a week, less than 50 minutes per week, less than 6 mph, and less than 500 MET-min/wk. Increased running did not reduce mortality risk further.

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[3] "The U-shaped relationship may be explained by possible pathological changes in cardiovascular tissues induced by extreme doses of endurance sports over a long term — for example, the development of patchy myocardial fibrosis, creating a substrate for heart arrhythmias" (Pedisic et al 2019 p2).

[4] The cohorts were: Aerobics Center Longitudinal Study (USA) (3 articles); Copenhagen City Heart Study (Denmark) (4 articles); Health Survey for England and the Scotland Health Survey (UK) (2 articles); National Health and Nutrition Examination Survey (USA) (1 article); Shanghai Men's Health Study (China) (1 article); 50+ Runners Association and Stanford University Lipid Research Clinics Prevalence Study (USA) (3 articles).

All studies included in the meta-analysis had good methodological quality, though there were still some issues, including:

a) Residual confounding - eg: adjusting for PA other than running in the analysis. "Not adjusting for this variable might have led to an incorrect estimation of the effects of running – that is, an overestimation, if physical activity other than running was higher among runners than among non-runners, or an underestimation, if physical activity other than running was higher among non-runners than among runners" (Pedisic et al 2019 p7). Other confounders included health status, unhealthy lifestyle, and socio-demographics factors.

b) Information about non-runners - eg: do not run/jog by choice or due to illness.

c) Selection of participants (eg: convenience sample), particularly the control group, and the size of the sample (ranged from 961 to 80 306).

d) The change in running habit and length of follow-up. Three studies included persistence in running behaviour.

e) Measurement of distance ran (only included in one study).

f) Self-reports of running participation.

g) Length of follow-up ranged from 5.5 to 35 years.

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2. CONTESTED CONDITIONS

2.1. "DISEASE"

Powell and Scarffe (2019a) began: "'Disease' is one of the most foundational concepts in medicine, and yet it is also one of the most intractable. Debates over the concept of disease are no closer to a resolution than when they began several decades ago" (p579) [5]. Part of the problem for these authors is that "disease" straddles many disciplines including biology, medicine, morality, and culture.

A "naturalism" approach (eg: Boorse 1977 [6]) to the term "disease" argues that it describes "underlying biological matters of fact, not evaluative judgments" (Powell and Scarffe 2019a p579). Though such an approach attempts to be moral value-free, terms "unwittingly incorporate moral values, or evaluative judgements that advert to well-being, flourishing, opportunity and the like. The assertion is that in concept and/or in practice, disease classifications are shaped, often insidiously, by covert value judgements of the robustly normative kind" (Powell and Scarffe 2019a p580). Evidence is provided in the form of behaviours/conditions once classed as "disease" which are not now.

An alternative approach to "disease" is "normativism" (eg: Sedgwick 1980), which takes the opposite position to "naturalism", and sees "health" and "disease" as nothing more than value judgments of the

[5] Agar (2019), for example, argued that "the needs of mental health are better served by eliminating the concept of disease altogether and focusing directly on traits that today promote human flourishing" (p591).

[6] For example, Boorse (1977) used the notion of "normal function". "When traits depart from normal functional efficiency by some stipulated degree, they are deemed dysfunctional — and hence diseased — against the idealised standard of what he calls ‘normal species design’" (Powell and Scarffe 2019a p580).

culture and time (appendix 2A). "Diseased biomedical states are simply those we devalue or wish to avoid" (Powell and Scarffe 2019a p581).

But this leads to the problem of disease classification as "spatio-temporally contingent" - "different cultures will value diseases differently, and thus the same state can be a disease in one culture but not in another; and since patterns of evaluation change within societies over time, the same state can be a disease at one time in a culture and not at another time" (Powell and Scarffe 2019a p581).

"Hybrid" approaches try to combine both of the above (eg: Wakefield 1992). Wakefield (1992) saw "disease" as "equated with 'harmful dysfunction', where 'harmful' is an evaluative term determined by social values, and 'dysfunction' is a scientific term referring to the failure of a mechanism to perform its evolutionary function" (Powell and Scarffe 2019a p581) [7].

Powell and Scarffe (2019a) proposed their own "hybrid" approach to "disease" - "a biomedical state is a disease only if it implicates a biological dysfunction that is, or would be, properly devalued" (p582) [8].

Carel (2019) focused on the problem of "who deliberates and who decides whether a condition is justifiably labelled as 'disease'" (p592).

Defending the approach, Powell and Scarffe (2019b) emphasised the importance of "retaining a unified concept of disease across human medicine", particularly as "acknowledging underlying dysfunction can help reduce the stigma of mental illness by disabusing people of the belief that mental health illnesses are less significant, less real, or less unchosen than their physiological counterparts" (p597).

2.2. PHYSICAL VERSUS MENTAL

The clear distinction in health services and medicine is made between physical and mental illness. "Although when questioned directly, most clinicians likely would adhere to a monistic model that asserts that all health problems have both physical and mental

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[7] Wakefield and Conrad (2019) defended Wakefield's (1992) "harmful dysfunction analysis" as pointing out that "social values or standards are not synonymous with the attitudes or opinions that predominate at any given moment. Rather, they are part of a cultural value system that has a complex multi-layered structure and that is open to critical scrutiny and revision in the course of a dialectic about which of a culture's many often-conflicting value commitments are most basic, how to adjudicate between competing values, whether some seeming values are really just rationalisations of unjust power or blind prejudice, and how changing circumstances should alter these judgements" (p594).

[8] Describing how students in a bioethics class feel, Tekin (2019) argued that debate "seldom makes direct contact with the common uses of the disease concept in the medical, social, moral and institutional contexts in which the students are heavily embedded" (p589).

(psychological, emotional or cognitive) dimensions, there is evidence that even psychiatrists maintain dualistic thinking about everyday clinical situations. Some problems tend to be viewed as more biological (and hence due to mechanisms beyond the individual's direct control), while other conditions are seen as more psychological or behavioural (and hence, potentially under the individual's conscious control). Problems of substance use or addiction are located somewhere in the middle, reflecting ongoing debates about the nature of habits, but the notion that addictions reflect weakness in character persists" (Kirmayer and Gomez-Carrillo 2019 p170).

One response to the mind-body distinction has been to explain all disorders (physical and mental) with biological causes (the "bio-bio-bio" approach; Read et al 2009). With such an approach, agency, responsibility, and blame are less of an issue - a biological basis to illness places control outside the individual.

But the "emphasis on biological parameters is underwritten by an epistemic dualism that sharply distinguishes objective physical signs from subjective (psychological) complaints and that, in turn, supports the ontological distinction between 'real' bodily illness and 'imaginary' psychological distress. The lack of biomarkers for many conditions then threatens the 'objective' reality of illness. This is evident in the special stigma experienced by patient's with medically unexplained or contested symptoms and syndromes" (Kirmayer and Gomez-Carrillo 2019 p171).

Kirmayer and Gomez-Carrillo (2019) considered "resignation syndrome" (RS) as an example of a medically unexplained condition. This is a condition that has afflicted some refugee children in Sweden, and is characterised by "depression and behavioural withdrawal that progresses to stupor and finally a state of apparent unconsciousness, with loss of pain response, requiring nasogastric tube feeding and intensive care" (Kirmayer and Gomez-Carrillo 2019 p173). The National Board of Health and Welfare in 2013 proposed six models of RS (Kirmayer and Gomez-Carrillo 2019):

i) Medical - a diathesis-stress model which explains RS as a product of predisposed/vulnerable individuals triggered by stress/environment.

ii) Family - dysfunctional family dynamics "described as overprotective, overanxious and mistrusting parents with difficulties in setting limits and in tolerating separateness. The family model thus emphasised how parents' health and stability affected the child, and noted parental mistrust of the medical system when medical evidence revealed no organic cause for the

child's symptoms" (Kirmayer and Gomez-Carrillo 2019 p173).

iii) Psychological - overwhelming uncontrollability and learned helplessness, and personality traits of the child like perfectionism.

iv) Political - a product of the asylum process.

v) Cultural - conflict between the cultural or religious background of the migrants and that of the host country.

vi) Intentional - "the symptoms as deliberate behaviour and invoked secondary gain from the illness as the underlying causal mechanism, suggesting that having a severe illness increased the likelihood of asylum approval" (Kirmayer and Gomez-Carrillo 2019 p174).

"Each approach to explaining the syndrome raised its own questions about clinical epistemology (ie: how to validate diagnostic explanation with the kinds of knowledge available in clinical contexts), intervention and prevention. The struggle to validate and explain the syndrome also revealed important social and political dynamics related to the local and global refugee crisis, the path to permanent resident status, the rising costs to the healthcare system, and the threat to Sweden's image as a welcoming place for refugees" (Kirmayer and Gomez-Carrillo 2019 p174).

In terms of RS as a medically unexplained condition, Kirmayer and Gomez-Carrillo (2019) argued that it "reveals some of the tensions and contradictions that continue to trouble psychiatry. Notwithstanding the conceptual advances in medicine, neuroscience and psychology, RS elicited doubt, contestation and a struggle for legitimation similar to that of other medically unexplained symptoms and syndromes (which, like the antiquated construct of hysteria, now fall under the somatic symptom disorder in DSM-5 or bodily distress disorder in ICD-11). This reflects broader tensions in the notion of psychosomatic explanation, seen in debates over the appropriate response to medically unexplained symptoms. In each case, invoking psychological, behavioural or social explanations is viewed as questioning the validity of distress and not according it the same seriousness and attention as 'bona fide' medical illness. Real distress needs a physiological explanation and a biomarker. The lack of medical validation then results in social stigma and added suffering" (p175).

Kirmayer and Gomez-Carrillo (2019) argued for an integrative, multi-level explanation - ie: both physiological and social factors. This would help in

"[U]nderstanding the embedding of the brain in the social world [which] requires a detailed mechanistic account of the interactive loops between body, person and environment, niche or lifeworld" (Kirmayer and Gomez-Carrillo 2019 p176).

2.3. POST-TRAUMATIC STRESS DISORDER

"Post-traumatic stress disorder" (PTSD) appeared officially in the American Psychiatric Association's DSM-III in 1980, and it was seen as the clarification of earlier ideas like "shell shock". Young (1995) noted: "When I ask clinicians and researchers to describe the origins of PTSD, the most common reply is that the disorder emerged spontaneously at some point in the course of human evolution, and it would exist as a pan-human disorder even if psychiatry had never discovered it" (p287).

Young (1995), however, disagreed, and saw PTSD as a product of a particular time and place (post-Vietnam war USA).

Unique to PTSD (compared to depression, anxiety disorders, and other traumatic and stress responses) is "the eponymous event" - ie: the specific traumatic event that triggered the symptoms. "For example, intrusive ruminations are a common feature of major depression, and phobias, such as the irrational fear of crowds, are a common symptom of anxiety disorder. But when either symptom is connected, during diagnosis, to an antecedent trauma-class stressor, its meaning is transformed: ruminations turn into intrusive 're-experiences' of the aetiological experience, and phobias become symptomatic 'avoidances' of environmental stimuli that trigger these re-experiences" (Young 1995 p289).

There is also a social contract related to the event. "For example, the medical branch of the US Department of Veterans Affairs is obligated designate this syndrome a 'service-connected' disability if it can be determined that the aetiological event occurred in the course of the veteran's military duties. The service-connected designation means, in turn, that the veteran is entitled to free psychiatric care and to compensation if it is determined that his disorder has reduced his capacity to earn a living. Shifting responsibility to external agency can also change the moral meaning of the syndrome, providing the patient with the means to re-narrate an often troublesome period between the onset of his psychiatric problems and the point when he was given a PTSD diagnosis. Re-narration may include liberation from highly stigmatising diagnoses, such as 'schizophrenia, paranoid type'" (Young 1995 p289).

Young (1995) argued that in psychiatry the triggering event is presented as cause and PTSD is the effect, rather than the event as a reason. The concept of cause-effect can drive the search for biological markers of PTSD.

2.4. PSYCHOSOMATIC MEDICINE

Building on Sigmund Freud, Felix Deutsch in the 1950s believed that the mind-body distinction could be overcome "in the context of a new science called 'psychosomatic medicine'" (Greco 2019 p108).

However, the mind-body dualism was "resilient" - "Instead of spearheading a revolution in medical thought and practice, the impulse of psychosomatic medicine has therefore itself been reabsorbed and reconverted into the dualist mainstream" (Greco 2019 p108).

Greco (2019) argued for the mind-body dualism as embedded in Western societies, and in particular the growth (dominance) of science since the seventeenth century. "Bifurcation" is a better term in the modern dualism, Greco (2019) suggested: "The bifurcation of nature produces a situation whereby our primary experience of reality in perceptual knowledge — where the qualitative richness of sensory impressions is intimately tied with evaluations of experience — is regarded as a secondary epiphenomenon, comparatively unimportant, and liable to being disqualified as a delusion when it does not correlate with knowledge mediated by physico-mathematical abstractions" (p109).

Is patient involvement a way to resolve the dualism? "Patient involvement, participation and empowerment are keywords at the forefront of the politics of contemporary healthcare. While the precise scope and meaning of these concepts can be a matter of debate, they now inform a wide range of activities and associated technologies at different levels, from individual doctor-patient consultations to the development of clinical guidelines and research programmes" (Greco 2019 p112).

Greco (2019) continued: "Discourses of participatory medicine envisage a future where 'networked patients shift from being mere passengers to responsible drivers of their health', and involve a double emancipatory promise. On the one hand, there is the promise of a democratisation of power relations in the clinical encounter and beyond... On the other hand, the promise of participatory medicine concerns the possibility of addressing the clinical shortcomings of a reductive biomedical model by incorporating the 'patient's point of view' — an expression that can refer to a variety of more specific concepts ranging from choice and preferences to experience and narratives" (p112). Unfortunately,

Greco (2019) did not see a resolution.

2.5. FEATHER DUVET LUNG

Liu-Shiu Cheong et al (2019) described a condition called "feather duvet lung" (FDL), where inhaling organic dust from duck or goose feathers in duvets and pillows produces lung inflammation. Symptoms include systemic malaise, influenza-like ones, and acute breathlessness.

It is a form of hypersensitivity pneumonitis (HP), similar to "bird fancier's lung" seen in pigeon breeders.

Liu-Shiu Cheong et al (2019) believed that many cases of FDL are missed or misdiagnosed as lower respiratory tract infection, as in the case study presented by the authors. A middle-aged man showed worsening breathlessness over three months after, it was later discovered, buying a feather duvet and pillow, having previously used synthetic bedding. "Given its heterogeneous and non-specific presentation, HP is often challenging to diagnose. The key is taking a meticulous history" (Liu-Shiu Cheong et al 2019 p4).

The patient described his symptoms at their worse: "I was unable to stand or walk for more than a few minutes at a time without feeling like I was going to pass out. Going upstairs to bed was a 30 min activity as I could only manage two stairs at a time and then needed to sit and rest. I was signed off work and spent most of the time asleep (day and night)" (quoted in Liu-Shiu Cheong et al 2019).

Correct diagnosis, steroids, and removal of the bedding lead to the situation where the patient reported: "my life is pretty much as it was before" (quoted in Liu-Shiu Cheong et al 2019).

2.6. CHRONIC FATIGUE SYNDROME

"Contemporary medicine distinguishes between illness and disease. Illness refers to a person's subjective experience of symptoms; disease refers to objective bodily pathology. For many illnesses, medicine has made great progress in finding and treating associated disease. However, not all illnesses are successfully relieved by treating the disease. In some such cases, the patient’s suffering can only be reduced by treatment that is focused on the illness itself" (Sharpe and Greco 2019 p183).

Fatigue is an example of a symptom of many illnesses which goes beyond the disease. It can be reduced by psychological therapies. "However, while these treatments are typically welcomed by patients with cancer, some patients with CFS [Chronic Fatigue Syndrome] reject them" (Sharpe and Greco 2019 p183).

Sharpe and Greco (2019) argued that this rejection is based on "the moral and social connotations of different kinds of illnesses" (p183). The "objective" symptoms of disease "ensures that the illness is considered 'genuine'; a moral validation allows patients to claim the benefits of the sick role, including sympathy and exemption from duties, as well as permission to access publicly funded healthcare and other financial benefits. Consequently, patients are able to see the application of psychological and behavioural treatments for their fatigue as a benefit" (Sharpe and Greco 2019 p184). But in the case of illnesses where disease symptoms have not yet been established (as in CFS), sufferers "find themselves in a much more morally uncertain position. They face the possibility that their experience of illness will be rejected as 'not real', with all the implications for acceptance, care and financial support that such a judgement implies" (Sharpe and Greco 2019 p184).

The case of "illness-without-disease" (Sharpe and Greco 2019) also highlights the distinction between objective and subjective, which has been described as the "bifurcation of nature" (Whitehead 1920). With the growth of science since the seventeenth century, knowledge established through scientific methods gained status over that which is in the mind or imagination of the individual. "The bifurcation of nature therefore produces a paradox whereby the concrete reality we experience can be dismissed as merely delusion, unless it corresponds with objectively known reality identified only through the mediation of technical apparatus. Illnesses that do not correspond to an identified disease pathology are a prime example of this paradox: how can an illness be patently real, sometimes severely so, when doctors can find no good objective evidence of bodily disease to account for it?" (Sharpe and Greco 2019 p185).

Two responses emerge from this situation - to deny the illness as "real" versus the disease symptoms will eventually be established. Sharpe and Greco (2019) offered their solution - "Instead of thinking of illness and disease in terms of the hierarchical difference between subjective (or mental) and objective (or physical) realities, we propose that we could think of them in terms of different degrees and forms of abstraction from the totality of what is real. 'Abstraction' is a term Whitehead uses to refer to the activity of abstracting, selecting or bringing something into focus. Abstraction in this sense is a process that all organisms engage in as an aspect of their relationship with their environment: our digestive system abstracts 'food' from the substances we ingest, for example, while discarding the rest as irrelevant 'background'. Similarly discrete thoughts are abstracted

from an otherwise undifferentiated stream of consciousness, in connection with the demands or features of specific situations" (p185). The authors continued: "This redescription allows us to appreciate that illness and disease are both equally concrete realities, and both equally 'organic' (ie: of the organism)" (Sharpe and Greco 2019 p185).

Sharpe and Greco (2019) ended with three practical steps: "The essential first step is to compassionately validate the reality of the patient's suffering, even in the absence of a demonstrable disease. The second step is to develop the dialogue of the consultation beyond a preoccupation with the presence or absence of disease, towards a consideration of the illness itself. The third step is to explore with the patient, how their illness might be improved and how they might manage the paradox of illness-without-disease in their own life" (p186).

2.7. BIOSECURITY THREATS

Some diseases have been viewed as "security" risks to governments (eg: Ebola), mainly because of the infectious and contagious aspects, as opposed to serious non-infectious diseases (eg: cancer) [9]. But "the adoption of a security-oriented approach to preventing or responding to disease outbreaks is not necessarily a good thing [...] Appealing to security concerns can be a device not only for raising public awareness but also for maintaining security" (Enemark 2017 pxv; pxvi).

This is "biosecurity". Enemark (2017) defined it as "the safeguarding of populations within and among states against selected infectious disease risks. These risks include both the natural occurrence of deadly disease outbreaks and the deliberate dissemination of pathogenic micro-organisms (that is, biological weapons)" (pxvi).

Koblentz (2010) saw biosecurity as full of trade-offs. "For example, would preventing scientists from perpetrating biological attacks serve to reduce a population's overall vulnerability to infectious disease outbreaks, or would such efforts increase that vulnerability by impeding scientists' ability to make lifesaving discoveries about the organisms that cause disease?" (Enemark 2017 pxvi). Stern (2003) raised concerns about reactive government policies "whose costs may exceed their benefits" (quoted in Enemark 2017).

[9] "Probability neglect" (Sunstein 2003) has been used to refer to "when people's emotions are intensely engaged, they are often far more concerned about dramatic risks (eg: terrorism or an Ebola outbreak) than about statistically larger risks that are confronted in everyday life (such as car fatalities or air pollution)" (Enemark 2019 pxvii).

Enemark (2017) considered four "biosecurity dilemmas" for policymakers:

i) "Protect or proliferate" - Research conducted by one state in the context of biodefence (ie: defending against biological attacks) can be seen by another state as threatening.

ii) "Secure or stifle" - Limiting research on certain pathogens may restrict potential life-saving findings.

iii) "Remedy or overkill" - The response to an outbreak as a national emergency may gain a critical advantage in "the form of extraordinary power, effort, or resources", but may "transgress normal rules in a way that is unjust and counter-productive to public health" (Enemark 2017 pxx) (eg: travel restrictions).

For example, in 2007 the US Government prevented 34 of its citizens with infectious tuberculosis (TB) from flying. This decision was linked to the case of Andrew Speaker, who had flown despite being on a "no-fly" list, and this raised concerns about "potentially a walking biological weapon" (according to a US Senator) (Enemark 2017). "Henceforth, just as the US government could take the extraordinary measure of restricting freedom of movement for counter-terrorism purposes, so too could it now address a public health risk using the same regulatory mechanism. A possible downside of this approach, however, is that the social stigma of having TB might be worsened by associating it so directly with the threat of terrorism" (Enemark 2017 pp115-116).

Closing borders is one strategy, and "'the widespread perception of microbes as invaders... maps neatly onto a pre-existing idea of national security involving the protection of populations against external threats' [Elbe 2011]. Because it is people who carry these microbes, keeping out a dreaded disease can sometimes seem to require keeping out people" (Enemark 2017 p117).

But such an approach can "fuel people's irrational yet habitual association of foreignness with disease" (p118), and the "racist habit" of blaming others (eg: Mexicans and "swine flu" in 2009; West Africans and Ebola in 2014) (Enemark 2017). Enemark (2017) pointed out: "In taking an excessively self-interested, beggar-thy-neighbour approach to disease- control, some states perpetuate the false and harmful message that a deadly and contagious disease is not a globally shared problem" (p129).

Lee and Fidler (2007) observed that "public officials may feel compelled to adopt measures to demonstrate to domestic constituencies that they are

'doing something'" (quoted in Enemark 2017).

iv) "Attention or neglect" - The focus on the "dreaded diseases" at the expense of mundane, everyday illnesses, particularly in poorer countries.

This is also seen in "a degree of political concern about 'new' risks that is greater than the concern about ongoing risks of similar magnitude" (Enemark 2017 p163). For example, in 2013 in the USA, four cases of plague, and no cases of anthrax or smallpox were reported ("Tier 1" biological "selected agents") compared to 35 000 HIV infections (Enemark 2017). A number of critics have highlighted the diversion of resources from high public health risks to low-probability events.

Enemark (2017) argued for "dual-benefit biodefence": "In the face of a strong, popular desire to be protected against the possibility of deliberate infection with a dreaded disease, a better approach would be to allow efforts toward that end to proceed and to demand that such efforts be protective also against infectious disease risks of natural origin" (p175).

2.8. LEGIONNAIRES' DISEASE

Poor drinking water quality can be responsible for diseases linked to gastrointestinal microbes, and the respiratory pathogen Legionella pneumophila (Legionnaires' disease; LD) (Zahran et al 2018).

An outbreak of LD in 2014-5 in Flint, Michigan, showed the problem that US national water regulations were concerned only with gastrointestinal disease risks (Zahran et al 2018).

In the Flint outbreak of LD, there were 87 disease cases, and these coincided with changes in the source and treatment of drinking water - from treated Lake Huron water to treated Flint river water (ie: less chlorine in the water). "During the period that treated Flint River water was distributed to Flint residents, poor water quality and extended periods of low chlorine residual may have enabled legionellae growth in the distribution system" (Zahran et al 2018 pE1732).

LD cases were found by Zahran et al (2018) to be negatively correlated with level of chlorine in the water.

2.9. BUYING-SELLING DISORDER

The International Classification of Diseases (ICD-11) produced by the World Health Organisation in 2018 includes something called "buying-selling disorder" (BSD) as part of "other specified impulse control disorders".

BSD is "characterised by extreme preoccupations

with and craving for buying/shopping and by irresistible and identity-seeking urges to possess consumer goods" (Muller et al 2019 p1) [10].

Muller et al (2019) painted a picture of sufferers: "Patients with BSD buy more consumer goods than they can afford, and those are neither needed nor frequently used. The excessive purchasing is primarily used to regulate emotions, eg: to get pleasure, relief from negative feelings, or coping with self-discrepancy. In the long run, the recurrent breakdown in self-control leads to extreme distress, psychiatric co-morbidity, familial discord, clutter due to pathological hoarding of goods, indebtedness and in many cases even in deception and embezzlement in order to continue overspending despite growing financial problems" (p1). Maraz et al (2016) estimated a point prevalence of 5% in their meta-analysis.

Muller et al (2019) investigated online BSD with data from two previous studies (Muller et al 2015 appendix 2B; Vogel et al 2018) in Germany and Switzerland (n = 122 treatment-seeking patients with BSD). About one-third of the sample were classed as having "probable online BSD". Online BSD correlated with BSD generally.

2.10. APPENDIX 2A - IDIOMS OF DISTRESS

"Idioms of distress" (Nichter 1981) refers to "the languages that individuals of certain socio-cultural groups use to express suffering, pain, or illness" (Mendenhall et al 2019 p621). These idioms go beyond biomedical concepts because they "convey more than a medical diagnosis, often pointing to 'interpersonal, social, political, economic, and spiritual sources of distress' (Nichter 2010)" (Mendenhall et al 2019 p621).

The local idioms are part of an interaction with more global idioms. For example, Western psychiatric disorders in new contexts (eg: anorexia in Hong Kong), or the use of biomedical terms to access health care systems (eg: Mexican immigrants in the USA) (Mendenhall et al 2019). "In these ways, the idioms of distress people use are never removed from global flows of ideas within biomedicine that influence how cultural idioms are conceived, understood, and expressed" (Mendenhall et al 2019 p622).

Mendenhall et al's (2019) work focused on Kenya, and local idioms like "huzuni" and "dhiki", and global "equivalents" like stress and depression. One hundred

[10] Emil Kraepelin described "impulsively driven oniomania" in 1909 (Muller et al 2015).

attendees at a public hospital in Nairobi were interviewed.

"Huzuni", for example, was associated with sorrow of the loss of a loved one. "Although people who report huzuni may well be depressed, the terms are not interchangeable and reflect different social phenomena" (Mendenhall et al 2019 p635). "Depression", though, was used by participants to mean "a lot of problems", "thinking too much", or "being pressed in life". As this global term was taken into the local language, it took on a meaning primarily related to the mind.

Abramowitz (2010) described the idea of "Open Mole" (or "hole in the head") in Liberia, with its wide-ranging symptoms of pain, dizziness, headache, confusion, and social withdrawal, for instance [11]. "Open Mole is understood to be a soft spot in the centre of the skull similar to the soft areas in an infant's unformed skull, or the sunken fontanel associated with infant dehydration... However, in contrast to the infant skeletal development processes and the dehydration-induced softening with which the Western medical literature is familiar, Open Mole is understood to be an acquired disease state that can occur to adults who experience a sudden fright or shock or who endure chronic adversity and stress" (Abramowitz 2010 p356).

Among locals, some believe Open Mole to be contagious (others not), some believe it is "caused by tampering with dangerous spiritual forces, practicing witchcraft or having a dangerous nightmare, while others believe that it can be caused by sharing a hairbrush or a headscarf, getting caught in the rain or sitting in the sun too long. Some believed that Open Mole is caused by committing an act of wrongdoing (like violence, theft or sorcery), while others believed that Open Mole is a victim’s affliction, carried by those who have had wrong done to them" (Abramowitz 2010 p356).

Western psychiatry has viewed, not necessarily helpfully, Open Mole as somatised mental illness (Abramowitz 2010).

Pillen (2016) considered that the experience of trauma may not be expressible and translatable: "Overwhelming events outside of ordinary human experience lead to 'speechless terror'. Such experiences cannot be organised on a linguistic level. There is a failure to arrange memories in words and symbols, yet they persist at a somatosensory level — as somatic sensations, images, nightmares, flashbacks, or bodily reenactments. Terrifying experiences 'therefore cannot be easily translated into the symbolic language necessary for

[11] Abramowitz (2010) listed 26 symptoms.

linguistic retrieval' [van der Kolk and van der Hart 1995]. Such experiences cannot be reproduced in words or narrated; they remain mute, unsymbolised, unverbalised. In contrast, stories can be told about ordinary experience; one can look back at what happened and give such experiences a place in one's life history or personality... Traumatised persons have the impression of living in two different, parallel worlds: the realm of violence or disaster, and the realm of ordinary life. It seems impossible to bridge the two realms of experience, which for many survivors constitute a simultaneity of utterly incompatible worlds... Trauma could thereby be defined as an ongoing embodiment and bodily awareness of an incompatible world of extreme experience. Such an awareness of another possible world is non-linguistic, does not exist in narrative form, and defines survival" (p98).

2.10.1. Cultural Embeddedness

Lewis and Ozaki (2009) showed the cultural embeddedness of language with a comparison of the Japanese term "amae", and "mardy" from the English Midlands. The former refers to "a need to receive affection", while mardy means "soft or spoilt".

Questionnaires were given to twenty native Japanese-speaking individuals, and fifteen English speakers (half from the Midlands), which asked for specific incidents when they or another person had behaved amae/mardy.

In terms of the subjective experience of these emotions, "both involve a subtle blend of pleasant and unpleasant feelings (the latter more salient in the case of mardy). Unpleasant feelings of guilt and embarrassment are common in the descriptions of amae. However, there is also an element of self-assertion or self-indulgence (this is why one feels guilt and embarrassment), which can be 'a feeling of relief'; this is the pleasurable side. The subjective experience of feeling mardy is largely unpleasant, statements such as 'upsetting – felt like crying' provide a strong theme. However, as with amae, there is also an occasional positive feeling: the brief pleasure of self-indulgence or self-assertion" (Lewis and Ozaki 2009 pp924-925).

There were some similarities between the two terms. Lewis and Ozaki (2009) concluded: "It is not true to say that the human need to be indulged, loved, or looked after is only noticed, conceptualised, and given a word in Japanese. Our results suggest that it is recognised in both the cultures considered here. In England, however, because of the social emphasis on independence..., mardy is a term used to deride and therefore discourage the behaviour, or expression of this need, rather than to accept, foster, or indulge it. Mardy

appears to address a similar area of emotional experience as amae, but it is generally regarded as undesirable; there is no word for 'good mardy'. The fact that both good and bad forms of amae are described by the same word sometimes blurs the distinction between them, contributing to the potential for selfishness or manipulativeness" (p932).

It is believed that there are universal word meanings (eg: 60 - "good", "all", "you"), though the evidence is usually limited to a subset of studied language (Enfield 2019). Enfield (2019) argued that "huh?" (expressing confusion) was a universal (found in 31 languages from sixteen language families).

Dingemanse et al (2013) argued that "huh?" is the product of convergent evolution, where independently the same "solution" to a "problem" evolved (eg: echolocation in bats and dolphins). "'Huh?' has a similar form across languages because the same set of conditions leads in all languages to something like the 'huh?' word being produced. In the flow of conversation, people need to be sure that others know when they failed to understand. Time runs by quickly in conversation, and there is only a short window in which to signal a comprehension problem. In that situation, one needs a syllable that is fast and easy to pronounce. 'Huh?' does the job" (Enfield 2019 p182).

2.11. APPENDIX 2B - MULLER ET AL (2015)

Muller et al (2015) preferred the term "pathological buying" (PB). "Maladaptive spending serves as a way to manage negative mood states, to escape from anxiety and tension and to enhance poor self-esteem" (Muller et al 2015 p2).

Muller et al (2015) evaluated the psychometric instruments for measuring PB, including:

a) Compulsive Buying Scale (CBS) (Faber and O'Guinn 1992) - Seven items to give a single score (ie: PB viewed as unidimensional) (eg: "Bought things even though I couldn't afford them").

- Outdated items (eg: "Wrote a cheque when I knew I didn't have enough money in the bank to cover"). Cheque use uncommon today.

- PB not unidimensional. Edwards (1993), for example, proposed five dimensions: tendency to spend, compulsive/drive to spend, feelings about shopping and spending, compulsion/drive to spend, and post-purchase guilt.

- Original sample - 388 self-identified individuals with PB and 292 consumers.

b) Richmond Compulsive Buying Scale (RCBS) (Ridgway et al 2008) - Based on the theoretical conceptualisation of obsessive-compulsive spectrum disorders.

- No items assess long-term negative consequences of PB. Muller et al (2015) stated: "Ridgway et al (2008) argued that not all individuals with PB suffer from financial or psychiatric problems, and that those with PB tendencies but without negative long-term consequences have been neglected by other instruments. In our opinion, this approach is problematic given that the proposed diagnostic criteria we favour for PB clearly include the serious destructive effects on a person's life (eg: psychological distress, impairments, financial problems)" (p4).

- Risk of "overestimating tendencies toward PB" (Muller et al 2015 p4).

- Original sample - 352 undergraduates, 551 university staff, and 309 customers of women's retail website.

Muller et al (2015) designed the 20-item Pathological Buying Screener (PBS). Based on the weakness of previous questionnaires, and their literature review, Muller et al (2015) included the following concepts - "preoccupation/craving, loss of control, emotion regulation, not using purchased goods/hiding purchases/lying about spending/deception, degree of suffering, interference with other life aspects and financial aspects/consequences, and resistance against excessive spending" (pp4-5). The original sample was over 2500 German individuals.

Factor analysis of the responses produced two underlying factors - loss of control/consequences, and excessive buying behaviour.

Table 2.1 compares the items and concepts of the PBS with three other measures of compulsive buying.

	Compulsive Buying Scale [20]	German Addictive Buying Scale [28]*	Richmond Compulsive Buying Scale [24]	Pathological Buying Screener
Indicated time period	n/a	n/a	n/a	past 6 months
Proposed facets of pathological buying				
Preoccupation / craving	n/a	Six items concerning the strong urge to buy something*	"I buy something for myself almost every day."	Q 1 …that you can't stop thinking about buying?
			"Much of my life centers around buying things."	
Loss of control	n/a	n/a	"I buy things I did not plan to buy."	Q 11…that you cannot stop buying things despite financial problems?
			"I buy things without thinking."	Q 10…that you buy more than you had planned?
			"I am a bit reckless about what I buy."	Q 4…that you spend more time buying than you intended?
Emotion regulation	"Bought something in order to make myself feel better."	One item concerning escape from unpleasant everyday life*	n/a	Q 5…that at times you don't feel good and that you feel better when you go buying?
	"Felt anxious or nervous on days I didn't go shopping."[1]			
Buying of unneeded goods / of more than needed / not using purchased goods	n/a	One item concerning buying something that remained unused*	"My closet has unopened shopping bags in it."	Q 7…that you buy more things than you need?
			"I buy things I don't need."	
Reaction of others / hiding purchases / lying about spending / deception	"Felt others would be horrified if they knew of my spending habits."	One item concerning not daring to show purchased goods due to expected uncomfortable responses*	"Others might consider me a 'shopaholic'."	Q 9…that you hide your buying habits from others?
				Q 2…that you feel embarrassed when others ask you about your buying behavior?
Financial aspects	"If I have any money left at the end of the pay period, I just have to spend it."	Three items concerning financial aspects*	n/a	Q 3…that you have financial difficulties due to your buying habits?
	"Bought things even though I couldn't afford them."			
	"Wrote a check when I knew I didn't have enough money in the bank to cover it."			
	"Made only minimum payments on my credit cards."			
Post-purchase guilt	n/a	Two items concerning post-purchase doubts/guilt*	n/a	n/a
Self-concept about consume habits	n/a	One item concerning the self-perception of being wasteful *[2]	"I consider myself an impulse purchaser."	n/a
Other	n/a	One item concerning the fact that advertising letters are of interest*	n/a	n/a
Facets that were not directly included in prior questionnaires				
Interference with other life aspects	n/a	n/a	n/a	Q 6…that you have problems at work or school or in other areas due to your buying behavior?
				Q 13…that you have problems with other people due to your buying habits?
Resistance to PG	n/a	n/a	n/a	Q 12…that you try to limit your buying and can't?
Degree of suffering	n/a	n/a	n/a	Q 5…that you suffer distress from your buying habits?

*Given that the GABS is copyrighted the original items were not listed.

[1]This item could also be assigned to the facet *withdraw*.

[2]This item could also be assigned to the facet *loss of control*.

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(20 = Faber and O'Guinn 1992; 28 = Raab et al 2005 (in German; quoted in Muller et al 2015; 24 = Ridgway et al 2008)

(Source: Muller et al 2015 table 3)

Table 2.1 - A comparison of the PBS and three other measures of compulsive buying based on conceptualisations used by the PBS.

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3. UNIVERSAL HEALTH COVERAGE, DISEASES AND HEALTH INEQUITY

3.1. DEFINING HEALTH AND HEALTH SECTOR

The World Health Organisation (WHO) was established in 1948, and it began with the definition of health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO 1948 quoted in Larsen 2017).

Larsen (2017) argued that this definition, rather than being a conceptual one, was a "health political objective": "It sets a high yardstick for health policies at all levels and also expands the scope of what health authorities should be concerned with" (p2). The document that included this definition did "not directly advocate 'socialised medicine' or universal health insurance, but it is not far from it either. The core ideas in WHO's constitution clearly point to a strong government involvement in health care provision and social security. This appears somewhat surprising and directly at odds with the 'cold war politics' (Packard 2016), the 'medical McCarthyism' (Brickman 2013) as well as the uncontested 'sovereignty' of the organised medical profession (Starr 1982) during this time" (Larsen 2017 p3).

Quoting from Leopold (1949), Goldberg and Patz (2015) pointed out that "the health of each of us is linked to the health of all the rest" (pe38). But, they continued, "Might the recent proliferation of global health organisations in academia, government, and the private sector, tied to institutions driven by economic incentives, actually be impeding the development of a global health ethic?" (Goldberg and Patz 2015 pe38) (appendix 3A).

Mackintosh et al (2016) described the global private health sector as "very heterogeneous, ranging from itinerant medicine sellers, through millions of independent practitioners — both unlicensed and licensed

– to corporate hospital chains and large private insurers" (p596). This sector is a challenge for policies of universal health coverage (UHC), particularly in low- and middle-income countries. In other words, what role does the private sector play?

Mixed health systems combine both the public and private sector, and Mackintosh et al (2016) distinguished five types:

i) Dominant private sector (eg: India, Nigeria) - low government spending on health and/or scarce resources "forces patients to turn elsewhere" (Mackintosh et al 2016).

ii) A non-commercialised (free) public sector and complementary private sector (eg: Sri Lanka, Thailand) - private hospitals provide "specialist services" that the public health system cannot.

iii) A private system for the rich and a public sector for the rest (eg: Argentina, South Africa) - "providing high-quality care at the top of a stratified health system in which the poor generally rely on lower quality public provision" (Mackintosh et al 2016 p600).

iv) A highly commercialised (ie: fee-charging) public sector (eg: China) - public health care facilities are "not privatised in the sense that the assets are still owned by the state, so the facilities had a public identity, yet their daily operations took on a business nature, focusing on revenue generation from charging users, translated into private gains through hospitals' internal bonus allocation system" (Mackintosh et al 2016 p602).

v) A stratified private sector based on income and a fee-based public sector (eg: Tanzania, Malawi) - the quality of the service based on income with good quality hospitals and clinics for the rich, and the equivalent of "low-cost treatment from untrained shop assistants" for the rest (Mackintosh et al 2016).

3.1.1. Global Governance

The Lancet-University of Oslo Commission on Global Governance for Health (Ottersen et al 2014) considered that "health inequity increasingly results from transnational activities that involve actors with different interests and degrees of power: states, transnational corporations, civil society, and others. The decisions, policies, and actions of such actors are, in turn, founded on global social norms. Their actions are not designed to harm health, but can have negative

side-effects that create health inequities" (p630). So health inequity can be reduced by changing the "global political determinants of health" (eg: economic crises and austerity policies; international treaties; violent conflict) [12].

In other words, "[R]ecognising that major drivers of ill health lie beyond the control of national governments and, in many instances, also outside of the health sector" (Ottersen et al 2014 p631).

Global governance is an important concept here. Thakur and Weiss (2006) defined it as the "complex of formal and informal institutions, mechanisms, relationships, and processes between and among states, markets, citizens, and organisations, both inter-governmental and non-governmental, through which collective interests on the global plane are articulated, rights and obligations are established, and differences are mediated" (quoted in Ottersen et al 2014).

Health consequences are often an unforeseen effect of global governance behaviour. For example, the "1994 World Trade Organisation (WTO) Agreement on Agriculture", which aimed neither to harm or promote health, "reduced the competitiveness of small-scale farmers in developing countries; it could thus be argued that the policy caused food insecurity, malnutrition, and associated health outcomes, and hence negatively affected health" (Ottersen et al 2014 p633).

Ottersen et al (2014) showed the consequences to health from seven policy intervention areas:

- Trade and investment - eg: attempts by governments to control tobacco use legally challenged by the manufacturers as a violation of trade agreements (Philip Morris vs Uruguay government).

- Finance and economic regulation - eg: austerity measures by the Greek government after 2007-08 financial crash as a requirement of international loans.

- Labour - eg: policies on unemployment benefits.

- Intellectual property - eg: Indian government licences to authorise lower-cost generic versions of patented

[12] Whitehead (1992) described health equity thus: "ideally everyone should have a fair opportunity to attain their full health potential and, more pragmatically, that no one should be disadvantaged from achieving this potential, if it can be avoided. The aim of policy for equity and health is not to eliminate all health differences so that everyone has the same level and quality of health, but rather to reduce or eliminate those that result from factors considered to be both avoidable and unfair" (quoted in Ottersen et al 2014).

drugs.

- Environment - eg: toxic waste dumping in countries, like Ivory Coast, with under-regulation of environmental issues.

- International security - eg: civilian casualties in armed conflicts.

- Human rights - eg: negative treatment and policies towards irregular migrants (refugees).

Ottersen et al (2014) outlined five "systemic dysfunctions that impede global governance for health":

i) "Democratic deficit" - "global governance arrangements too often do not reflect basic democratic norms, such as equal rights of participation, fair representation, transparency, and accountability" (Ottersen et al 2014 p655).

ii) Weak accountability - "Accountability for the health effects of rules, norms, and policies that emanate from global governance processes can lie with a range of different actors, rather than with any one in isolation" (Ottersen et al 2014 p655).

iii) "Institutional stickiness" - International organisations often entrenched and difficult to reform.

iv) Inadequate space for health - "Regime complexity" (Alter and Meunier 2009) is the increasing number of international bodies and treaties (nearly 5000; Ottersen et al 2014), "which can blur obligations and responsibilities, and complicate accountability" (Ottersen et al 2014 p656), as well as simply squeeze out health as a consideration.

v) Missing institutions - "Economic globalisation has outpaced political globalisation – ie: the development of institutions that could govern the global market effectively and protect societies against market failures. As seen in the case of food security, speculation in food commodity markets led to food price volatility, and the absence of effective institutions to prevent or counteract this problem created food insecurity for already vulnerable populations" (Ottersen et al 2014 p657).

3.1.2. Neoliberalism

Larsen and Stone (2015) described the neoliberal [13] reforms in health care in the West in the last few years around three elements: "(1) transferring public health insurance and public delivery systems to private, for-profit companies; (2) introducing market competition where formerly there had been public-sector dominance or monopoly; and (3) enabling citizens to choose among multiple insurance plans and/or medical service providers" (pp941-942).

These changes appear to weaken the role of government in health care services, but Larsen and Stone (2015) applied Bachrach and Baratz's (1962) idea of the "two faces of power". "The first face entails promotion of private markets and consumer choice in formerly public sectors, programs, and resources and may be understood as a retrenchment of the state. The second face entails a specific mode of governing the public sector through incentives and competition and may be understood as an expansion of the state" (Larsen and Stone 2015 p942).

This "governing through incentives" can be linked to Foucault's (2008) idea about the "technologies of governing". "Rather than simply strengthen markets with laissez-faire policies, as classical liberalism does, neoliberalism generalises the model of market competition to all spheres of society... It is not only that business markets have to be actively constructed but that competition becomes the main principle of governing any social sphere" (Larsen and Stone 2015 p946).

In relation to health care, health insurance and private systems are presented as improving choice. But health insurance scheme limit the options to their "managed care plans", or by "cream skimming" - "selecting healthy people as policyholders, refusing to insure sick and potentially high medical care users, and denying claims and dumping policyholders once they begin to incur high costs... Given this well-known behaviour, the promise that competition would drive commercial insurers to deliver better services for less money was somewhat disingenuous, if not delusional" (Larsen and Stone 2015 p960).

Among the lessons from neoliberal health reforms, Larsen and Stone (2015) noted that such policies "do not create efficient private markets, but they take the efficiency of private markets for granted. Nonetheless,

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[13] Neoliberals "claim that if certain free market reforms are followed, economic productivity and innovation will increase and therefore social welfare will also improve... Neoliberals also hold individual freedom as the highest political value and believe that freedom is a zero-sum quantity — the more power the state has, the less the individual can have... Freedom becomes redefined as the capacity to exercise discrete consumption choices, with scant attention to how poverty and powerlessness constrain those choices" (Larsen and Stone 2015 pp944-945).

neoliberalism purports to create mechanisms to make the public sector efficient" (p965).

3.2. EBOLA VIRUS DISEASE

Around two-thirds of human infectious diseases are zoonotic (animal-borne) (appendix 3B) (Redding et al 2019). Ebola virus disease is one of those, first identified in 1976, and since then 23 recognised outbreaks have been recorded (Redding et al 2019). EVD is caused by one of four pathogenic strains, which may originate from fruit bats. It is a non-specific febrile illness than can cause haemorrhagic fever, and has a high fatality rate among patients (Redding et al 2019).

The EVD has seen two large outbreaks in recent years - 2013-16 West Africa, and currently Democratic Republic of Congo. "It is difficult to assess the efficiency of current health systems in detecting, treating, and preventing onward transmission of EVD, as the number of unobserved outbreaks is by definition unknown" (Glennon et al 2019 p2).

Glennon et al (2019) performed a statistical modelling exercise to assess the number of unobserved outbreaks and cases of EVD. Data from three West African countries in 2014 were analysed. It was estimated that at least half of "spillover events" and small outbreaks were unreported to international health authorities. Factors involved might include very low human population density, and low-transmitting versions of EVD.

Glennon et al (2019) ended: "Our estimates suggest that most spillover events and small outbreaks of EVD are not reported to international bodies but rather are handled locally, likely as fevers of unknown origin or mischaracterised as more common causes of fever (eg: malaria). Supporting core public health and sanitation infrastructure in the areas where spillover is likely to occur may prove vital to preventing the onward transmission of these unseen index cases. Furthermore, promoting the safe management of fever and enhancing local diagnostic capacity has the potential to improve facility-based national surveillance systems and ultimately increase the chance of early detection of EVD outbreaks, both large and small" (p7).

Redding et al (2019) performed a modelling exercise about future outbreaks using data on the Zaire strain of EVD. They found that most of West and Central Africa could be at risk, and 3-4-fold increase in epidemics in the next fifty years. Key factors are human population growth and land-use conversion (increased contact between humans and animal hosts of the disease), climate change, and poor healthcare services to combat outbreaks.

Population movements across the continent would exacerbate any outbreaks.

Specifically, bush-meat hunting is an important process as it is a way in which humans come into contact with bats. While poverty in general is another variable as EVD is slowed by socio-economic development (Redding et al 2019).

Testing experimental treatments and vaccines for EVD in the field is not helped by the fact that the ongoing outbreak in the Democratic Republic of Congo (DRC) is in a conflict zone. One microbiologist reported: "You are doing this [medical work] and people are shooting" (quoted in Maxmen et al 2019).

"Every aspect of the outbreak is affected by the area's long history of conflict and trauma. Residents have endured more than two decades of terror from armed groups, along with resource exploitation and political instability. That has bred distrust of authorities - and conspiracy theories about why Ebola is thriving. One popular rumour alleges that Ebola responders inject people with deadly substances at treatment centres and vaccination sites" (Maxmen et al 2019 p7). This has led to 200 attacks on medical staff in 2019 including seven deaths, while vaccinated individuals have faced violence from neighbours (Maxmen et al 2019).

3.3. CANCER

Breast cancer survival is poorer for women from ethnic minorities and/or socio-economic disadvantaged groups in the USA (eg: 5-year survival rate after diagnosis of 92% for White women, but 83% for Blacks; Phillips 2019). The reasons are multi-level and complex, including screening and lower resourced facilities, delays in care, and lower quality treatment and follow-up (Warnecke et al 2019).

Warnecke et al (2019) showed ethnic group disparity with data from Chicago collected between 2005 and 2008 (the Breast Cancer Care in Chicago study; BCCC). All patients newly diagnosed with breast cancer in the study period aged 30-79 years old were approached, and 989 agreed to participate. In terms of ethnicity, 42% self-identified as non-Hispanic Black (NHblack), 40% non-Hispanic White (NHwhite), and the remainder as Hispanic.

Different measures were taken:

a) Medical records for details of cancer. Five stages were scored - 0 (no cancer cells in breast tissue), 1 (smaller tumours in breast), 2-4 (larger tumours and spread to other organs). 0 and 1 were coded as "early stage", and the others as "late stage".

b) Index of concentrated disadvantage for neighbourhood (eg: proportion of residents below poverty line) (appendix 3C).

c) Index of medical underservice (eg: primary care providers per 1000 population).

d) Patient details (eg: medical records; co-morbidity of conditions; demographic information).

e) Screening facilities (eg: "diagnosis delay" - "more than 60 days between self-reported date of first medical presentation and the date of a definitive diagnosis/biopsy"; Warnecke et al 2019).

"After adjustment for policies affecting neighbourhood context, mode of detection, and facility accreditation/resources, there was no significant disparity in later stage breast cancer diagnosis between NHblack or Hispanic patients compared with NHwhite patients. The results suggest that racial/ethnic differences in mode of detection [14] and facility accreditation/resources account for most of the disparity in stage at diagnosis" (Warnecke et al 2019 p63) [15].

A key difference, then, was the screening facility resources. Poorer resourced facilities would take longer to see patients, and thus lead to diagnosis delay, for instance.

The findings fit with other studies of disadvantaged women who "were more likely to be screened at lower resourced and non-accredited facilities, to experience delays in care, and less likely to be referred to comprehensive care centres for follow-up" (Warnecke et al 2019 p65).

Warnecke et al (2019) ended: "Optimal design of multi-level interventions addressing disparities in later stage breast cancer diagnosis should focus on the health care system and would benefit from enhanced understanding of pathways to detection and diagnosis available to patients in medically underserved communities and potential incentives for improvements that enhance the process" (p65).

The key limitations of the study included:

- Self-reported, cross-sectional data.
- Limited information in medical records (eg: "no information on the systemic aspects of the process,

[14] Mode of detection was via screening or self-discovery (eg: lump; pain).

[15] Uninsured women referred to county hospitals, for example, with less resources and "state-of-the-arr diagnostic capability", as well as less routine screening generally (Phillips 2019).

particularly the patterns of interaction between patients, primary care providers, and specialists"; Warnecke et al 2019 p64).

- Response rate of 54% of those eligible to participate.

3.4. "RACIAL HEALTH DISPARITIES"

Gutin (2019) criticised the "essentialist medicine" of health "disparities" and "inequities" between Black and White individuals in the USA (ie: biological explanations for the social differences).

The first White explorers of Africa described the Black population as "savage", and saw their "unhealthiness" in "tainted blood" (as opposed to the purity of "White blood") (Gutin 2019). "Though our preoccupation with blood has faded, and the scientific understanding of health has evolved, there remains a persistent interest in attributing a biological origin to racial differences and disparities in health and, increasingly, medicine" (Gutin 2019 p224).

Gutin (2019) continued: "Despite calls for an improved conceptualisation of race in biomedical research, scientists continue to adopt an 'essentialist' framework in interpreting the significance of race in their work by imbuing the same centuries-old, phenotypically informed and socially constructed categories of race with genetic meaning" (p225).

Today in the USA, there is a drive for inclusion in biomedical research as a means to combat "racial health disparities". "The intention behind inclusion mandates, and the personalised medical research they are intended to support, is noble; given the well-documented racial variation in the efficacy of medical treatment, greater diversity can begin addressing racial disparities during the research and development process. Yet many scholars argue that the growth of biogenetic research coupled with social, economic, regulatory and legislative pressures has given rise to a form of colour-blind racial science; the phenotypic differentiation of race (ie: skin colour) has been replaced by genotypic variation in biomedical research. Inclusionary policies presume a priori that racial differences exist and thus encourages the search for these disparities with no clear theory or expectation of the importance of race or underlying causal mechanisms. Consequently, any observed racial differences are interpreted as genetic rather than socio-environmental, further essentialising race as a biological, rather than socially constructed, category" (Gutin 2019 p226).

3.5. HOMELESSNESS AND TRAUMATIC BRAIN INJURY

Homeless individuals experience disproportionately poorer mental and physical health than the general population. One particular disadvantage is traumatic brain injury (TBI). "Emerging evidence suggests that the risk factors for TBI closely align with the social determinants of health and causes of social exclusion, including poverty and marginalisation" (Young and Hughes 2020 pe4).

TBI among homeless and marginally housed populations is difficult to measure [16]. For example, Topolovec-Vranic et al's (2012) review of eight studies published between 1996 and 2012 found lifetime prevalence ranging from 8 to 53% (as compared to 22% in the general population, for example; Corrigan et al 2008). But methodological issues include the use of medical records misses cases that do not seek help, and the definition and measurement of TBI (Stubbs et al 2020).

Stubbs et al (2020) performed a more extensive review covering the homeless and marginally housed, or individuals using services for homeless people. The means of measuring TBI included self-reports, medical records, and specific questionnaires and interviews. Thirty-eight relevant studies were found (published between 1995 and 2018).

The overall lifetime prevalence of TBI was 53.4%, and 24.9% for moderate or severe TBI (though there was great variety between the individual studies). This is 2.5 to four times higher than the general population (depending on the study), and ten times higher for moderate or severe TBI.

"Studies that used loss of consciousness as a minimum criterion for defining TBI... and used a screening tool to ascertain history of TBI... were associated with lower estimated TBI prevalence. The age of the study sample..., total sample size..., and using a structured interview (vs a single question or series of questions) to ascertain history of TBI... were associated with higher estimated prevalence" (Stubbs et al 2020 pe23) [17].

Key methodological differences between the studies

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[16] "The identification of TBI among homeless or marginally housed people is likely to be particularly challenging because of a high prevalence of severe mental illness, harmful substance use, and profound multi-morbidity among this group, and probable diagnostic overshadowing" (Young and Hughes 2020 pe4).

[17] "Among the studies that reported age of first TBI, Stubbs and colleagues calculated a weighted mean age of first TBI of 15·8 years... and younger age at first homelessness was consistently associated with a history of TBI among the included studies. These findings suggest that providing individuals, particularly young people, with stable housing is important for preventing TBI" (Young and Hughes 2020 pe4).

in Stubbs et al's (2020) review included:

i) Sample

- Age - eg: "study samples with a higher proportion of older individuals evaluate individuals with a longer time at risk of TBI" (Stubbs et al 2020 pe28).

- Place of recruitment - eg: hostel; clinic for homeless people.

- Specialist - eg: homeless military service personnel; males only.

- Country - Australia, Canada, Japan, South Korea, UK, and USA.

ii) TBI

- Definition - eg: "loss of consciousness"; "alteration of consciousness"; "period of being dazed or confused".

- Measurement - eg: structured interviews, like Ohio State University TBI assessment method (OSU TBI-ID), find higher prevalence than a single question; MRI scans.

iii) Almost all the studies were retrospective and cross-sectional.

A number of associations with TBI were found by Stubbs et al (2020) in some of the studies:

a) Physical health - eg: memory problems; poorer self-reported physical health.

b) Mental health - eg: psychiatric diagnosis; poorer self-reported mental health.

c) Suicidality - eg: five studies reported higher risk of suicidal ideation.

d) Mortality - eg: two studies reported higher a standardised mortality ratio for homeless individuals with TBI than without.

e) Neurocognition - mixed results for cognitive impairment.

f) TBI linked to homeless - between 51-92% of participants experienced first TBI while homeless or marginally housed.

g) Miscellaneous - eg: association with childhood abuse, and general victimisation; involvement in criminal justice system.

"It is becoming increasingly clear that TBI can be both a cause and consequence of homelessness. The functional and socio-economic consequences associated with TBI can present challenges to finding and retaining stable housing. Conversely, a dose-dependent relationship exists between the duration of homelessness and the occurrence of TBI (ie: the longer a person is homeless, the higher the risk of TBI)" (Young and Hughes 2020 ppe4-e5).

3.6. APPENDIX 3A - MEDICAL TOURISM

Epidural stimulation is the electrical stimulation of the spinal cord in individuals with injuries to that area (eg: paraplegia). Experiments with small numbers of patients in the USA, for example, have shown promise, but no large-scale clinical trials have been performed yet (Willyard 2019).

However, this treatment is available privately vua "medical tourism" (eg: US$ 70 000 in a Thai hospital; Willyard 2019). One company behind such treatments emphasised the bureaucracy of US health regulators, which they were free from, and could perform their "successful treatments". Experts cautioned about such private clinics where therapies that might not work are offered, along with the risk of side-effects (Willyard 2019).

3.7. APPENDIX 3B - MOSQUITOES

Mosquito-borne viruses, like dengue and Zika, are a human public health threat, and controlling the vectors (mosquitoes) seems the best strategy. Two techniques are commonly used - population suppression, which reduces the mosquito numbers, and population replacement. The latter makes "wild mosquitoes unable to transmit infectious diseases by spreading genetic modifications or bacterial infections through natural populations" (Armbruster 2019 p39).

Zheng et al (2019), for example, combined both techniques. The researchers infected male Asian tiger mosquitoes with a bacteria that is transmitted to females during mating and it reduces reproductive success (ie: eggs do not hatch). Compared to control sites, in the experimental sites, the number of viable eggs declined by 94%, and the rate of human biting decreased by over 90% (Armbruster 2019).

3.8. APPENDIX 3C - SOCIAL CATEGORISATIONS

The "symbolic categorisation of social groups" describes "the ways in which people continuously construct and negotiate identities and belongings to groups, as well as how they reconstruct the existence of groups, categories, hierarchies and value by connecting to and distancing themselves from other people" (Harrits and Pedersen 2019 p862). These categories can include socio-economic ones (based on income or occupation, for example), cultural (eg: knowledge; tastes), or moral groupings (eg: values and ethics). Also the "categories can be constructed both as distinct groups with clear boundaries (us/them) and as blurrier hierarchical orderings (above/below)" (Harrits and Pedersen 2019 p863).

For example, Skarpenes and Sakslind (2010) suggested that in Norway, where egalitarianism means similarities in socio-economic and cultural categories, moral categories were most important for middle-class identities (Harrits and Pedersen 2019).

While in Denmark, Harrits and Pedersen (2019) found that socio-economic categories were used to describe society most of all. This research was based on focus groups, and a survey, and there was some variety in the findings. For instance, where moral categories were used to order society, it is different to socio-economic hierarchies. The survey asked respondents to describe the sort of person who was working-class, middle-class or upper-class, and a "warmth" index was developed from the answers. Working-class individuals were perceived as warmer than the other classes. Harrits and Pedersen (2019) concluded that the "moral categorisations do not profoundly challenge the socio-economic order of society; rather, they seem to legitimise economic and cultural inequality by establishing an alternative hierarchy on which lower socioeconomic groups can base their worth" (p874).

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4. DEMENTIA FROM DIFFERENT ANGLES

4.1. OFFICIAL DATA

Official figures for England and Wales for 2018 put dementia as the leading cause of death (13% of all registered deaths) (Wilson 2019).

But there are problems with this statement, including (Wilson 2019):

a) Recent changes in categorisation by the Office for National Statistics (ONS) mean that any death certificate that includes dementia, even if as a contributing factor, is classed as caused by dementia.

b) The different types of dementia are grouped as one category by the ONS, whereas cancer is recorded by type. If cancer was grouped as one category, then 28% of deaths would be due to it (2016 figures; Cancer Research UK in Wilson 2019).

4.2. ANIMAL STUDIES

Excessive salt consumption is linked to health problems including stroke and dementia.

Faraco et al (2019) was able to show a causal link between high-salt diet (HSD) and Alzheimer's disease (AD) via tau accumulation in cells in the hippocampus. This accumulation has been found in the brains of Alzheimer's sufferers.

Mice were fed regular chow or chow with an 8-16-fold increase in salt (HSD) for twelve weeks. Memory was tested via recognition of novel objects and spatial memory for a maze (table 4.1).

Method	Details
Novel object recognition test	A mouse is placed in an enclosure with two plastic objects of varying colour and shape for five minutes. This is the habituation phase. Later the mouse returned to the enclosure with two objects (one the same, one novel) (the test phase). Mice explore novel objects more than older ones (eg: sniff; touch). Recall of the old object will result in more time spent exploring the novel object. Forgetting is seen in equal time exploring the two objects in the testing phase. Faraco et al (2019) found that the mice in the control condition spent around 80% of the time in the testing phase exploring the novel object compared to 55% in the HSD condition.
Barnes maze test	A mouse is placed in a bright, loud enclosure, which they dislike, with the option of twenty circular holes on the sides, of which one is the escape hole to a dark confined space. The animal is placed in the enclosure a few times to learn the position of the escape hole (learning phase). Memory is then tested by the time taken for the mouse to go into the escape hole. With recall of the position, they will be quicker and with less errors each time, while this will not improve with forgetting. Faraco et al (2019) found that control mice on the fifth day in the maze took an average of twenty seconds to reach the escape hole compared to sixty seconds for HSD animals.

Table 4.1 - Details of methods of testing memory in mice.

4.3. SLEEP

The brain pathology of AD begins "roughly 20 years" before symptoms like memory loss (Wallis 2019). Troubled sleep could be an early symptom, as well as troubled sleep increasing AD risk. It is a bidirectional relationship (Lucey et al 2019).

In terms of the effect of poor sleep, Holth et al (2019), for example, presented a mouse model that lack of sleep increased tau protein in nerve cells, which is a characteristic of AD. Deliberate sleep deprivation led to a twofold increase in tau levels in the brain interstitial fluid. Twenty eight days of severe sleep deprivation produced greater tau in areas of the brain connected to the hippocampus, but not in the hippocampus itself.

Lucey et al (2018) reported an increase in tau in the cerebrospinal fluid of humans deprived of one night's sleep.

Could changes in sleep patterns and architecture be used as a predictor of AD? Animal studies (eg: Holth et al 2017) have found reduced non-rapid eye movement (NREM) sleep with increasing tau pathology.

Lucey et al (2019) confirmed the reduction in NREM sleep in a longitudinal study with 119 US participants aged 60 years and above. Sleep was monitored over six nights with a portable device for measuring brainwave patterns (which allowed pinpointing of sleep stages). PET scans were used to assess changes in the brain.

NREM sleep decreased with increasing tau accumulation in the brain. Lucey et al (2019) stated: "Given that our study participants were predominantly cognitively normal, this suggested that changes in NREM SWA [slow wave activity], especially at 1 to 2 Hz, might be able to discriminate tau pathology and cognitive impairment either before or at the earliest stages of symptomatic AD" (p1).

Note that only 38 participants underwent PET scans. Also the authors admitted that they could not "establish whether or not sleep disturbances preceded or followed the development of AD pathology" (Lucey et al 2019 p9).

4.4. EPIDEMIOLOGY

The risk of dementia is a combination of genes (eg: apolipoprotein E gene) and lifestyle factors (eg: reduced risk with healthy diet and physical exercise) (Lourida et al 2019). So, is it possible that genetic risk could be offset by positive lifestyle factors?

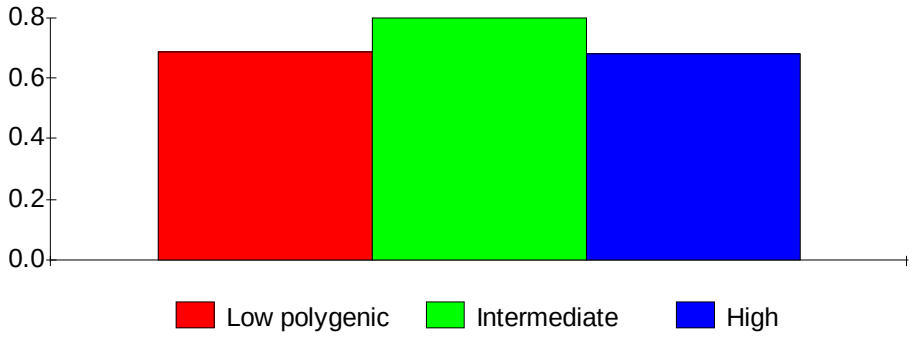
Two studies have produced inconsistent results (table 4.2), and Lourida et al (2019) noted that they had "limited statistical power, making their findings difficult to interpret" (p435).

STUDY	DETAILS
Kivipelto et al (2008)	Cardiovascular Risk Factors, Aging and Dementia Study in Finland. Individuals with an unfavourable lifestyle in midlife and a high risk gene for Alzheimer's disease were significantly more likely to develop dementia in later life compared to favourable lifestyle/high genetic risk individuals.
Gelber et al (2012)	Honolulu-Asia Aging Study (Japanese-American men). No significant association between lifestyle in midlife and dementia among high genetic risk individuals, but an association among low genetic risk individuals.

Table 4.2 - Two studies on dementia risk and lifestyle.

But Lourida et al (2019) offered an affirmative answer from their large population-based cohort study. Data from the UK Biobank covering over 50 000 participants were analysed. A polygenic risk score was calculated for AD based on genetic fingerprinting, and a healthy lifestyle score was constructed from four measures (smoking, physical activity, diet, and alcohol consumption). Physical activity was defined as at least 150 minutes of moderate activity per week or 75 minutes of vigorous activity per week. Health diet was based on consumption of at least four of seven recommended foods (eg: fruit and vegetables). Actual dementia diagnosis was taken from hospital inpatient records as this was a retrospective study. Full data were available on around 200 000 over 60 year-olds.

In the "worst" group (ie: highest quintile polygenic risk score and unfavourable third healthy lifestyle score), around 2% of individuals developed dementia compared to 0.5% in the "best" group (ie: lowest quintile polygenic score and favourable third healthy lifestyle score). "Favourable lifestyle" reduced the risk of dementia at all levels of genetic risk (figure 4.1). Lourida et al (2019) speculated: "Healthy lifestyle may contribute to dementia risk through cardiovascular and cerebrovascular mechanisms, including reduced oxidative damage, anti-thrombotic and anti-inflammatory effects, and increased cerebral blood flow" (p435).



(Unfavourable lifestyle score is 1.00 in each category of polygenic score risk)

(Data from Lourida et al 2019 table 4 p435)

Figure 4.1 - Hazard ratio of dementia based on polygenic score and favourable healthy lifestyle.

The authors noted a number of weaknesses with their study including:

a) Limitations of "healthy lifestyle score", particularly as the data were self-reported.

b) The possibility of unmeasured confounding variables (including other lifestyle factors), and reverse causation (eg: dementia status causes lifestyle).

c) Dementia cases missed or misdiagnosed.

d) Sample restricted to volunteers of European ancestry aged 60 to 73 years old tested in the UK in 2006-10.

e) Follow-up lasted eight years, and participants were on average in their early 70s at this point, "which limited the number of incident dementia cases" (Lourida et al 2019 p435).

To sum up: "Among older adults without cognitive impairment or dementia, both an unfavourable lifestyle and high genetic risk were significantly associated with higher risk of dementia. A favourable lifestyle was associated with a lower dementia risk among participants with a high genetic risk" (Lourida et al 2019 p435).

4.5. ARTIFICIAL INTELLIGENCE

Neuroimaging (eg: PET scans) allows early diagnosis of AD (eg: minor reduction in activity in certain areas of the brain in the prodromal stage of AD - mild cognitive impairment (MCI)). But the scans require interpretation by specialists, and not all individuals with MCI progress to AD (Ding et al 2019).

Ding et al (2019) reported the use of artificial intelligence (AI) (a deep learning algorithm; appendix 4A) to interpret the scans. PET scans from over 1000 patients were used to train the algorithm, and forty patients as the subsequent test (seven were clinically diagnosed with AD, seven with MCI, and 26 neither (non-AD/MCI) in follow-up of up to seven years).

The algorithm was 100% correct in predicting the AD cases in the test, but less accurate for the other two conditions [18]. The algorithm was better than three radiology specialists, except for the non-AD/MCI scans.

The algorithm "apparently utilised the whole brain with varying degrees of influence from various anatomic areas to make its final decision. This highlights the strength of the deep learning algorithm that considers the brain as a pixel-by-pixel volume in its classification, implying that the deep learning algorithm arrives at the diagnosis distinct from how humans interpret the imaging studies" (Ding et al 2019 pp462-

[18] The MCI and non-AD/MCI cases may have developed AD with longer follow-up (Ding et al 2019).

463). But this means that there was no "human interpretable imaging biomarker" for AD (Ding et al 2019).

The test sample was small, and involved individuals referred to a clinic for a PET scan in the USA.

"'This is one of the first promising, preliminary applications of deep learning to the diagnosis of Alzheimer's... The model performs very well when identifying patients with mild or late' diagnoses... but catching it in the earlier stages 'remains one of the most critical open issues in this field'" (Christian Salvatore quoted in McCullom 2019).

4.6. CHANGING THE BRAIN

4.6.1. Brain Oscillations and Memory

Brain oscillations are the synchronised interactions of groups of neurons, and memories are the product of changes in synchrony between neurons. "Therefore, brain oscillations arguably are centrally important for memory processes" (Hanslmayr et al 2019 p485). Oscillations (ie: electrical activity) can be measured by electroencephalography (EEG) and magnetencephalography (MEG).

Stimulation to the brain to produce entrainment (ie: "whereby two interacting oscillating systems, which have different periods when they function independently, assume a common period"; Hanslmayr et al 2019) could improve memory. Three main approaches to entrainment have been used (Hanslmayr et al 2019):

i) Sensory stimulation - stimuli containing a regular rhythm. For example, older adults receiving auditory stimulation timed to slow-wave activity in sleep had better recall of pre-sleep information than controls (Papalambros et al 2017).

ii) Non-invasive transcranial electrical stimulation (tES) or repetitive transcranial magnetic stimulation (rTMS) - electrical or magnetic stimulation on the scalp. Stimulating different parts of the brain can disrupt as well as improve working memory, for example.

iii) Invasive electrical stimulation - electrodes placed in the brain as in deep brain stimulation (DBS). Often individuals with epilepsy and small samples have meant early studies "have been called into question" (Hanslmayr et al 2019).

In terms of the application of these techniques to improving memory for individuals with dementia, ethical concerns have meant that animal studies are the main

method (eg: stimulation of neurons in the hippocampus in the "AD mouse model" and reduced amyloid plaques) (Hanslmayr et al 2019).

4.6.2. Memory Editing

"Science fiction notions of altering problematic memories are starting to become reality as techniques emerge through which unique memories can be edited" (Phelps and Hofmann 2019 p43). This is particularly attractive for traumatic memories, but also for "diminishing cravings that are induced by drug cues in addicts or enhancing education" (Phelps and Hofmann 2019 p43).

Such a process requires knowledge of the physiology of how memories are formed. In invertebrates and with simple associative memories, it is synaptic changes in the brain, which can be altered (Phelps and Hofmann 2019). But "the neural representations of memories are far more complex in vertebrates", and the "methods that have been used to alter synaptic plasticity in animal models are not safe for use in humans" (Phelps and Hofmann 2019 p43).

One of the core issues of "memory editing" with humans is that "a memory for a single event can be expressed in several ways, each of which is linked to a distinct neural representation" (Phelps and Hofmann 2019 p43). A traumatic event will be encoded as the conscious recollection of what happened (episodic memory), and as automatic reactions to cues related to the event, for instance (defensive responses, habitual actions and subjective feelings). So, "targeting one type of memory representation for editing may or may not alter other forms of memory for the same event" (Phelps and Hofmann 2019 p43).

The most promising avenue for editing is episodic memory, which involves the hippocampus (while emotional responses to memories are linked to the amygdala), and includes the processes of consolidation (initial storage of the memory) and reconsolidation (re-storage after retrieval). In animal studies, amnestic agents that inhibit protein synthesis, say, after learning prevent synaptic changes and thus consolidation. These agents/drugs tend to impair memory generally, and so are not safe for human use (Phelps and Hofmann 2019).

But consolidation of traumatic memories is strengthened by stress humans, and so drugs that reduce the stress reaction could help (eg: propranolol (beta blocker)). Hoge et al (2012) found that individuals receiving propranolol after a traumatic event had less physiological arousal when recalling it later than controls, but there was no difference in the likelihood

of developing post-traumatic stress disorder (PTSD) symptoms (Phelps and Hofmann 2019).

Other techniques that alter consolidation show that "there are many potential ways to enhance the strength of a unique memory and a few ways to weaken it" (Phelps and Hofmann 2019 p45). Often the issue is treatment before memory consolidation has completed (ie: immediately after the traumatic event).

In the case of reconsolidation, re-storage after recall strengthens the memory. Rats, for example, were given an inhibitor of protein synthesis before a threatening cue that had been learned, and this reduced the reaction to the cue subsequently (Nader et al 2000). In effect, this was the erasing of previously consolidated memories. But similar substances given to PTSD sufferers after the traumatic event is recalled have had limited success (Phelps and Hofmann 2019).

Again in rats, extinction training has worked. The animals learn an association between a tone and a mild electrical shock (through the principles of classical conditioning), and so the tone ("traumatic memory") produces the physiological reaction before the shock. Extinction training is the presentation of the tone without the subsequent shock (ie: re-learning no association) (eg: Monfils et al 2009). The application to human is limited because memories are complex and distributed in the brain, meaning new information is added to old information rather than substitution, and memories are part of narratives (rather than just a list of words or simple word association) (Phelps and Hofmann 2019).

Techniques that concentrate on the feelings of the memory may offer more promise with humans. Linking to cognitive oriented therapies, the aim is to change how the individual thinks (and consequently feels) about the traumatic memory. One therapeutic technique is "imagery rescripting" (Arntz 2012), where the individual is encouraged to think about the traumatic event, but imagine a different ("happy") outcome. For example, an individual who had been physically assaulted could imagine defeating the attacker or being rescued by a superhero. "This rescripted scenario is not usually based on reality, or even realistic. Rather, it is an alternative and desirable story that shares many of the features of the original trauma memory. The mechanism of imagery rescripting is not well understood" (Phelps and Hofmann 2019 p48).

Phelps and Hofmann (2019) ended: "The idea that human memories can be selectively targeted for editing is no longer just science fiction. However, in this case, truth (or research) is stranger, more complicated and

more nuanced than fiction. Unlike in films, current memory-editing techniques appear to modify aspects of memories, rather than erase them. These modifications may be subtle at times, but could still be of clinical consequence. Relatively little is known as yet about how any of the techniques... might most effectively be applied to clinical treatments" (p49).

4.7. BRAIN-AGE

"While everyone ages chronologically at the same rate, this is not true biologically; some individuals experience accelerated age-related biological degeneration" (Elliott et al 2019 p2). Franke et al (2010) proposed the idea of "brain-age" as a way to quantify biological ageing. It is the difference between an individual's predicted age based on a machine-learning algorithm analysis of structural magnetic resonance imaging (MRI) of the brain and the chronological age (known as the brain age gap estimate; brainAGE). An older brainAGE (ie: the brain age is older than the chronological age) has been linked to cognitive decline in later adulthood (Elliott et al 2019).

Elliott et al (2019) investigated this idea with data from the Dunedin Longitudinal Study in New Zealand (a birth cohort from 1972-73). There were 869 of the original 1037 participants still available. MRI scans and cognitive testing were done in the mid 40s. Other data were available from regular studies over the lifespan.

The average chronological age of the cohort was 45.15 years old at the time of testing, and the mean brain-age was 40.93, but with a range of 23.84 to 71.63 years. Individuals with older brainAGE scored lower on cognitive testing at 45 years old.

Looking backwards, individuals with older brainAGE had lower cognitive scores in childhood and "poorer brain health already at age 3 years" (p7) [19], as well as signs of faster ageing bodies in early adulthood.

The algorithm used to estimate brainAGE was trained on cross-sectional comparisons of individuals of different ages, "which do not distinguish cohort effects (cohort differences in exposures from developmental changes)" (Elliott et al 2019 p8), and on particular types of MRI scans. The test-retest reliability of the brainAGE algorithm on twenty participants over 2-3 months was 81%.

[19] Put another way, individuals with the highest cognitive test scores at three years old had the youngest brainAGE at 45 years old. James Cole, however, urged caution here: "Acceleration or delay could be positive or negative... If a 60 year-old has a brain that looks 70, that's bad, but if a 3 year-old has a brain that looks 5, that might be a good thing" (quoted in Hamzelou 2019).

The findings supported two theories of biological ageing (Elliott et al 2019):

i) "Geroscience perspective" (Kennedy et al 2014) - Ageing is "the result of deterioration across multiple organ systems and that furthermore this deterioration is the root cause of age-related disease" (Elliott et al 2019 p2).

ii) "Early system-integrity perspective" (Dreary 2012) - Individuals vary in brain and body health from birth onwards.

4.8. STIGMA AND OTHERING

There is a growth in campaigns to raise awareness about dementia and to challenge stigma for sufferers. It is assumed that "dementia and the people diagnosed with it are stigmatised, and that this worsens the experiences of those affected" (Fletcher 2019 p2).

Research in relation to this point tends to focus on public and carer perceptions rather than the individuals with dementia's experiences of stigma. While latter studies "mostly operationalise stigma via scales rather than accessing detailed experiential accounts, and therefore offer limited insight into stigma" (Fletcher 2019 p3).

Fletcher (2019) continued: "Authors have extrapolated stigma from dubious examples such as the use of negative language (eg: 'suffering'), poor knowledge of dementia amongst healthcare professionals and a lack of service availability... Arguments that a lack of understanding is evidence of stigma are deeply suspect. That people do not understand a collection of complex neurodegenerative conditions is not necessarily evidence of stigma. Similarly, poor service availability is likely indicative of resource constraints and/or competing priorities rather than stigma" (p3).

Scrambler (1989), initially in relation to epilepsy, distinguished between felt and enacted stigma. The latter includes behaviours by others, whereas felt stigma "entails the self-perception of one's own stigma, encompassing feelings of shame regarding one's own perceived shortcomings and fears of experiencing enacted stigma" (Fletcher 2019 p4).

Awareness campaigns are a reaction to apparent stigma. Fletcher (2019) questioned the use of "unusually young and articulate spokespeople who have themselves been diagnosed with dementia" (p5). These spokespeople are in their late 50s and early 60s, whereas the average age of dementia onset is the 80s. "It is somewhat inevitable that patient-advocates will be

unrepresentatively able, because the effective fulfilment of their role requires various capabilities that even some people without dementia might find challenging. This entails a sanitised presentation of dementia. Such sanitisation is politically useful because it contradicts negative historic assumptions about people with dementia. However, the downside of overly positive portrayals of dementia is that they risk obscuring the experiences of the many people who do suffer due to dementia. Worse still, it promotes an ethic of wellness in which dementia is shown to be potentially unproblematic, implicitly ascribing a type of failure to those who do not live well" (Fletcher 2019 p5).

Fletcher (2019) emphasised his point: "there is a danger that well-meaning initiatives to destigmatise dementia through awareness-raising unwittingly contribute to felt stigma through repeatedly asserting the severity of enacted stigma and implicitly attributing a certain notoriety to dementia" (p6).

Rose suggested that "all the anti-stigma campaigns, the fun runs, the celebrities speaking out, the argument that mental ill-health is, on the one hand, part of everyday experience and, on the other, just an illness like any other" create a "benevolent othering", "whereby certain groups are publicised in a compassionate manner to elicit public sympathies, unintentionally signifying their otherness... Conspicuous anti-stigma campaigns risk positioning dementia as a substantial societal problem and portraying people with dementia as exceptional, widely abused and in need of special treatment, ultimately othering dementia" (Fletcher 2019 p6).

Fletcher (2019) added: "I do not suggest that dementia is not stigmatised... [but]... While awareness campaigns may be a suitable response to enacted stigma, they risk exacerbating felt stigma and hence worsening people's experiences" (p7).

4.9. APPENDIX 4A - ALGORITHMS

Algorithms (used with machine learning) are "powerful pattern finding and prediction tools", but they can also "turn up fool's gold - false positives, blind alleys or mistakes" (Riley 2019 p27).

Riley (2019) highlighted three pitfalls with machine learning:

i) Splitting data inappropriately - Training and testing sets involve randomly broken up data for convenience, whereas real-life data are more holistic, embedded, and not necessarily random.

ii) Hidden variables - Machine learning may pick up

unintentional variables, not the variables that researchers are interested in. For example, an early algorithm to spot tanks learned well from the photographs of the vehicle, but failed in real-life cases. It seems that the training set included tanks on a sunny day, say, and the algorithm focused on aspects of the weather rather than the object of interest (Riley 2019).

iii) Mistaking the objective - Focusing on an easy objective with clear data and labels helps the machine learning, but may not be the answer to the right question. For example, an algorithm may be able to screen for specific diseases based on X-rays, but the real question is whether the individual needs to see a doctor.

Example

Acute kidney injury (AKI) is often spotted too late by concentrations of creatinine in the blood (Topol 2019). Tomasev et al (2019) developed an algorithm to detect such injury 1-2 days earlier and thus enable effective treatment. The algorithm was trained with US data for over 700 000 adults between 2011 and 2015.

Prediction accuracy was 56% for mild AKI, but around 90% for serious forms (requiring dialysis). However, there were many "false positives" (2 false alerts to every one true alert), and the study was retrospective (Topol 2019).

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5. EVOLUTION OF MECHANISMS AND BEHAVIOURS RELATED TO PAIN

5.1. INTRODUCTION

"No human experience is more compelling than that of intense pain. It seems safe to assume that pain did not appear de novo in humans – that the functions and mechanisms of human pain are products of prior evolution" (Walters and Williams 2019 p1). Understanding pain in an evolutionary context is growing in interest, and Walters and Williams (2019) introduced articles from the first international meeting in February 2019 on the evolution of pain. "The focus was on the evolution of pain behaviour and associated mechanisms as revealed by comparisons of pain-related phenomena across diverse invertebrate and vertebrate species, including humans" (Walters and Williams 2019 p1).

The first issue that arose was how to define pain. With humans, the International Association for the Study of Pain (ISAP) definition is commonly used - "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (quoted in Walters and Williams 2019). While Zimmerman (1986 quoted in Walters and Williams 2019) defined pain as "an aversive sensory experience caused by actual or potential injury that elicits protective motor and vegetative reactions, results in learned avoidance and may modify species-specific behaviour, including social behaviour". But what about pain in other species, particularly non-verbal ones?

One answer is to focus on the physiology. If an animal has the same physiological processes as related to pain in humans, then it must experience pain (appendix 5A).

Alternatively, a definition can be based on behaviour. If the animal shows the behaviour known to be associated with pain, then it must be experiencing pain

[20].

Because of the subjective aspect of pain in humans [21], some researchers prefer to use other terms like "nociception" or "nociceptive sensitisation" (Walters and Williams 2019).

Another issue in relation to the evolution of pain is the study of the evolution of physiological mechanisms involved.

In terms of the evolutionary function of pain, it would seem to be maladaptive. But there is evidence that "chronic pain-like alterations can be adaptive under appropriate conditions" (Walters and Williams 2019 p5) (appendix 5B).

Then there is pain-related social behaviour. For example, pain evolved to elicit care, and so empathy evolved alongside this (Walters and Williams 2019).

5.2. NOCICEPTION

"Injury to sensory neurons causes an increase in the excitability of these cells leading to enhanced action potential generation and a lowering of spike threshold. This type of sensory neuron plasticity occurs across vertebrate and invertebrate species and has been linked to the development of both acute and persistent pain" (Mihail et al 2019 p1). Specifically, specialised sensory neurons detect potentially damaging stimuli, and these cells "can display remarkable sensitisation when they are activated by stimuli to which they respond (eg: inflammatory mediators) or when they are injured (eg: by axonal crush)" (Mihail et al 2019 p1). This nociceptor sensitisation drives protective behaviour that allows tissues to heal without reinjury, but this sensitisation can persist after the tissues are healed (leading to chronic pain disorders) (Mihail et al 2019).

Nociception is crucial for health and survival. For instance, fruit fly larvae (Drosophila) produce different nociceptive responses depending on whether the noxious

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[20] Pain in rats, for example, is measured in experiments by offering choice (eg: conditioned place preference or self-administered analgesia) (Williams 2019). In conditioned place preference, an area of the cage is associated with pain via mild electric shocks, say, while another area is neutral. It is assumed that if the animal chooses the neutral area, then pain, which is undesirable, was experienced in the conditioned area.

[21] "Pain is defined as a highly subjective experience, yet, it can be communicated to the social environment by what Fordyce (1976) called ‘pain behaviours’. Usually, pain behaviours are classified into verbal pain behaviours such as exclaiming, reporting or describing pain and non-verbal pain behaviours such as vocalisations, facial expressions, body movements or physiological changes. Pain behaviours are commonly considered to serve either a communicative function, such as self-report or facial expression, or a protective function, such as limping" (Kappesser 2019 p1).

stimulus is thermal (hot or cold), mechanical (eg: touch), or chemical (eg: acid [22]). Mechanical stimulation produces fast crawling behaviours, while cold provokes contractions of the head and the tail towards the middle of the body, for example (Lopez-Bellido et al 2019).

Himmel et al (2019) studied the same larvae to show that certain cellular and molecular processes had an origin beyond 550 million years ago [23]. Menthol is aversive to fruit flies and this was used as the noxious stimulus in experiments. The larvae produced a rolling response to menthol, similar to noxious heat and mechanical stimulation.

Concentrating on fish, Sneddon (2019) stated that "ample evidence to demonstrate that it is highly likely that fish experience pain and that pain-related behavioural changes are conserved across vertebrates" (p1). The evidence includes:

a) Molecular biology of nociception - Physical processes involved in mammalian pain are found in fish species (acid sensing ion channels; Sneddon 2019).

b) Behaviours - eg: nocifensive reflexes, like instantaneous withdrawal from damaging stimuli. Also prolonged changes in behaviour after painful stimulation (eg: less swimming distance in zebrafish; Deakin et al 2019) [24].

The immune system responses to nociceptor signals, and also produces behaviour changes to promote survival as well as healing. For example, nociceptive sensitivity enhances anti-predator behaviour as Adamo and McMillan (2019) showed in a caterpillar (Tobacco hornworm moth; Manduca sexta).

When poked on the posterior, the caterpillar's head whirls around and strikes out with its mandibles, known as a "defensive strike". Adamo and McMillan (2019) injected the caterpillars with heat-killed pathogens to produce an immune response. These caterpillars were more sensitive to touch (ie: produced defensive strike) than controls or pre-injection.

Without this enhanced anti-predator behaviour, sick or injured individuals are more likely to be caught by

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[22] Nociception does not require complex nervous systems as seen in the response of "simple" organisms, particularly to chemical changes. Acid, for example, can damage cells, and nemtatode worms avoid acidic environments (Pattison et al 2019).

[23] This is the time of a major split in early organisms (protostome-deuterostome split) (Himmel et al 2019).

[24] A typical method for studying sensitivity with fruit flies involves amputation of part of a leg. After recovery, the speed of jumping is measured in response to a hot stimulus. This technique can also be used to test painkillers (Khuong et al 2019).

predators. So, it is a compensation mechanism, at least partly (Adamo and McMillan 2019).

Howard et al (2019) pointed out that, for humans and rats, it is "widely accepted that injury and painful experiences in the early neonatal period induce plasticity in nociceptive pathways that is expressed as disordered pain experience, particularly the development of chronic or aberrant pain in later life" (p1). These researchers found a similar pattern in experimental work with a squid species, which "indicate an adaptive value for long-lasting plasticity arising from early-life injury, and suggest that injuries inflicted in very early life may signal to the nervous system that the environment is highly dangerous. Thus, neonatal pain plasticity may be a conserved pattern whose purpose is to set the developing nervous system's baseline responsiveness to threat" (Howard et al 2019 p1).

Howard et al (2019) used sixty-eight Hawaiian bobtail squids (Euprymna scolopes), who received a crush injury to the fin with forceps (or a sham injury of being touched by the forceps) at two, six, or thirteen weeks old. The defensive reaction of the squid was recorded in response to a robotic fish 2-3 weeks after healing of the injury.

5.2.1. Endocannabinoid System

"Nociception is likely one of the nervous system's most ancient and adaptively significant functions. Consequently, there is considerable interest in the elements of nociception that have been conserved over the course of animal evolution. Comparative approaches to study and understand conserved signalling and modulatory processes might be leveraged to understand basic biological principles of nociception and develop potential therapeutics to treat pain" (Paulsen and Burrell 2019 p1).

One possibility is the use of cannabis-based treatments working on the endocannabinoid system in the body (ie: neurotransmitters in the central nervous system).

An evolutionary perspective on this system can be seen in comparative studies (ie: organisms that are evolutionary ancestors, like invertebrates). For example, a leech (Hirudo verbana) shares a number of features with mammalian endocannabinoid synapses (though there are also differences) (Paulsen and Burrell 2019).

There are rare cases of individuals with a genetic mutation in an enzyme linked to cannabinoid receptors, for example, who feel no pain (eg: Habib et al 2019). The enzyme is fatty acid amide hydrolase (FAAH), which

controls the release of a brain lipid called anandamide (called the "bliss molecule" as animals injected with it appear "spaced out"). Loss of FAAH function and consequently increased anandamide are associated with reduced pain sensitivity, less anxiety, accelerated wound healing, but poorer short-term memory (Crompton 2019).

5.2.2. Epigenetics

Early-life stress, for example, can produce chemical changes to genes known as epigenetics. Individuals who have experienced trauma as children have a specific epigenetic change to a gene and a protein that makes them susceptible to post-traumatic stress disorder (PTSD) as adults (Klengel et al 2013).

Geranton (2019) considered whether there was a parallel for chronic pain [25]. "It is now known that pain in early life can enhance the duration of the pain response to subsequent injury in animal models, depending on both the nature and timing of the neonatal trauma" (Geranton 2019 p3). One gene that is well studied in terms of epigenetic changes is FKBP5, which plays a role in the hypothalamic-pituitary-adrenal (HPA) axis. Put simply, epigenetic changes caused by childhood trauma, say, alter the body's stress response and sensitivity to pain, which can manifest as chronic pain. The exact physiological process is still being studied in animals and humans (Geranton 2019).

There is also evidence that epigenetic changes may be intergenerational. But Geranton (2019) noted: "While epigenetic modifications can be transmitted across generations, the transmission seems more likely to occur via social interactions than biological inheritance. Indeed, considering the fast dynamics of epigenetic mechanisms that allow the adaptation to the environment within a lifetime, one could question the advantage of a biological transmission of epigenetic traits (for humans at least)" (p5) [26].

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[25] Establishing the existence of chronic pain in non-humans has proved difficult, such that Williams (2019) concluded: "It remains unclear whether chronic pain is a dysfunction of the pain system, a sustained false alarm, or an artefact of modern life, or some combination. The paucity of reports of chronic pain in free-living animals could be due to lack of observations, lack of behavioural indicators or rarity of survival with chronic pain. It would be perverse to propose that injured non-human animals do not feel pain as do humans, given the common anatomy and neurophysiology and plentiful evidence of recovery and healing. Peripheral and central sensitisation are part of this phase, as rodent studies show. We know less of changes in the brain, or whether the contribution of anxiety, important in driving avoidance of activity and therefore increasing disability, is uniquely human" (p5).

[26] Mitochondria (the powerhouses of cells) have gained interest recently, and their genomes are implicated in mitochondrial disease that affects 1 in 5000 people, it is estimated (Ghiselli and Milani 2019). While the "mother's curse hypothesis" (eg: Gemmell et al 2004) suggested the accumulation of mitochondrial DNA mutations that are "harmful to males but benign/beneficial to females" (Ghiselli and Milani 2019).

5.3. MISCELLANEOUS

Hearn and Williams (2019) performed a "thought experiment" on the response of dinosaurs to serious injuries. Based on 196 papers suggesting limping gait or injury, say, from the fossil records, Hearn and Williams (2019) made the following observations: "Clearly, many dinosaurs survived injuries that would have seriously hampered mobility, impairing hunting or escape from predators, and affecting social interactions. Recovery from severe injuries implies pain-mediated responses. Rates of healing seem faster than for other reptiles, possibly aided by warm-bloodedness. Nesting was often communal, raising the possibility of parental and group protection for injured young" (p1).

Pain is not all negative, and there are situations where humans show "the discounting of pain or reinterpretation of sensations as 'not painful' for activities that are repeatedly undertaken voluntarily" (Finlay 2019 p4). These situations include "runner's high" (or high intensity effort), cosmetic procedures like body hair removal, and self-harm.

Finlay (2019) described three characteristics of these situations: "First, the activity generating the ambiguously painful stimulus should be self-enacted, or at least, self-chosen at the time of the activity. Second, the event should occur repeatedly, over an extended period. Third, the events should be plausibly ambiguous, not life-threatening injuries" (p5).

Finlay (Finlay and Syal 2014) also talked of "the pain of altruism" to describe the idea "that pain, and sickness behaviour had become systematically increased in humans compared with our primate relatives, because human intense sociality allowed that we could ask for help and have a reasonable chance of receiving it" (Finlay 2019 p6). So, increased pain encourages social bonding in humans, according to this idea.

Both these views on the experience of pain in humans show differences to other species based on the role of autonomy, and social bonding.

5.4. APPENDIX 5A - CRUSTACEANS

"Wounded animals often show activities such as rubbing, guarding of wounds and limping, and these activities are interpreted as being consistent with pain. They indicate an awareness of the site of a wound (not necessarily implying consciousness but at least some perception of the afflicted site) and maybe an attempt to alleviate pain. Similar activities have been reported for crustaceans" (Elwood 2019 p2).

Examples include the glass prawns which groom and

rub antenna or eyes where acid was applied, or shore crabs that scratch mouthparts touched by acid (Elwood 2019).

These behaviours seem more complex than nociceptive reflexes, and along with avoidance learning, could be evidence of the pain experience. Elwood (2019) stated: "The idea of pain in crustaceans was traditionally rejected because they were thought to respond to noxious stimuli purely by reflex. This is clearly not the case but that does not mean that pain is proved. There may be alternative explanations that do not depend on the idea of negative feelings commonly implied in studies of human pain. We simply do not know, and probably never will know, what crustaceans feel when exposed to noxious stimuli" (p5).

5.5. APPENDIX 5B - EVOLUTIONARY EXPLANATION

Nesse and Schulkin (2019) offered an evolutionary perspective on excessive pain - the mechanisms that evolved pain as a positive warning sign are "vulnerable to failure". These authors stated: "Many different genes and molecules interact to make pain possible, and most of them are also involved in many other bodily processes. Nervous system and brain pathways involved in pain are only somewhat specific. While specific spinal cord pathways mediate pain transmission, many brain regions and circuits are involved. The entire system provides a fine example of how systems shaped by natural selection are characterised by organic complexity that is fundamentally different from the complexity in systems designed by engineers" (Nesse and Schulkin 2019 p1).

Nesse and Schulkin (2019) argued that the evolutionary benefits of pain are seen in people born unable to feel pain. They "accumulate increasing tissue damage, especially to their skin and joints, and they fail to get full defence against diseases and trauma. The result is deformity, mobility problems, and early death" (Nesse and Schulkin 2019 p2).

In terms of excessive pain, the "smoke detector principle" (Nesse 2005) has been applied. "In technical terms, natural selection shapes mechanisms that regulate defences based on the principles of signal detection, the mathematical theory that describes the costs and benefits of responding or not responding in situations of uncertainty" (Nesse and Schulkin 2019 p3). Put simply, you want a system that is accurate (ie: not too many false alarms), and, most importantly, signals a serious threat.

Sensitisation of a body area after injury is like the smoke alarm. Pain warns the individual of potential re-injury. "The sensitisation of mechanisms that detect damage is an adaptation in the short run to facilitate

tissue healing, and it may also be useful in the long run to provide extra protection in environments that are especially dangerous. However, such protection comes at the risk of the system going into a positive feedback loop in which the experience of pain lowers the pain threshold to cause chronic pain. Mismatch with modern environments may also play important roles in chronic pain, via routes as varied as the effects of exercise, the use of analgesics, and even the frequency of menstrual cycling" (Nesse and Schulkin 2019 p4).

Pain evolved as a smoke detector which does give false alarms because of the high cost of failure to detect noxious stimuli, and we live in a modern world very different from the environment in which pain mechanisms evolved. This is an evolutionary explanation of excessive pain.

Walters (2019) offered a slightly different evolutionary perspective for chronic pain. Chronic or maladaptive pain defined as "dysfunctional pain that 'neither protects nor supports healing and repair [Costigan et al 2009]. Maladaptive pain encompasses numerous types of pain, including peripheral and central neuropathic pain, fibromyalgia, irritable bowel syndrome, interstitial cystitis and inherited pain disorders such as paroxysmal extreme pain disorder. While maladaptive pain has diverse causes, virtually all forms are chronic (lasting from three months to a lifetime) and are highly resistant to treatment. At least some forms of maladaptive pain are now considered diseases in their own right, caused by prolonged or permanent malfunction of the somatosensory system" (Walters 2019 p1).

Predators often seek out injured prey. "Ongoing pain and anxiety persisting long after severe injury continue to enhance vigilance and behavioural caution, decreasing the heightened vulnerability to attack that results from motor impairment and disfigurement, thereby increasing survival and reproduction (fitness)" (Walters 2019 p1).

Evolutionary explanations can often be speculations or "just-so stories". Stearns and Medzhitov (2016) offered four criteria for assessing an evolutionary approach (Walters 2019):

i) National selection across generations "is not germane because it cannot be applied to a complex mammalian trait that already has evolved" (Walters 2019 p6).

ii) Experimentally manipulate the trait and observe the changes in fitness.

iii) Show that "the trait increases its expression in response to functional demand" (Walters 2019 p6).

iv) Natural selection for a trait "is more likely if the trait is precise and complex" (Stearns and Medzhitov 2016 quoted in Walters 2019).

Walters (2019) believed that his evolutionary explanation fulfilled these criteria.

Concentrating on facial expressions, Kappesser (2019) explored the evolutionary explanation that "pain is expressed in the presence of supporting others and suppressed in the presence of adversaries, in order to elicit help from supporting others and to avoid showing vulnerability to adversaries" (p2).

Is there experimental evidence to support this idea? A review by Krahe et al (2013) found nine experimental studies that compared facial expression of pain in the presence of "friends" and "strangers". Kappesser's (2019) review of these studies concluded that the findings were inconsistent, and methodological issues contributed to this. The issues included:

- Operationalisation of social context - "Experimental manipulations range from the mere presence of other individuals to specific behaviour of the social partner to engender threat or to reinforce participants' pain. As a construct, 'social context' is broad and lacks a convincing and acknowledged definition; hence any attempt to define social context top-down by breaking it down into different aspects that would be easier to operationalise would be a valuable first step" (Kappesser 2019 p5).

- Measurement of facial expressions - "People differ in their facial expressiveness depending on their awareness of being videotaped, so all studies using facial expression as an outcome should report whether their participants were aware of being videotaped. Furthermore, results may differ depending on which coding system was used, since most use the presence and intensity of muscle movements, yet differ in which muscle movements they consider and whether they combine two or more into single units, while others code the duration of the movements rather than the presence and intensity. If possible, it is ideal to blind coders to study aims since this may impact on their coding. Lastly, a substantial minority of participants are regularly found in experimental studies to display no facial expressions at all, possibly owing to comparatively weak stimulus intensities in experimental settings, and a wide variation in the threshold at which individuals express their pain facially" (Kappesser 2019 p5).

- The ecological validity of experimental studies.

5.5.1. Evolutionary Psychiatry

Abed et al (2019) argued for the importance of evolutionary perspectives in psychiatry: "Evolutionary perspectives clarify the formulation of questions regarding the causes of human vulnerability to mental disorder. Importantly, recognising that natural selection works through survival and reproductive success and not through good health, happiness or longevity, explains the nature of many psychobiological phenomena including those accompanied by great suffering" (p699).

These authors described some of the key ideas relevant to psychiatry, including:

a) Anxiety and the "smoke detector principle" (Nesse 2019), which states that "when the cost of activation of defences is trivial, (even when the risk is absent) but there is a massive cost of defence failure (if a risk is present and lethal), multiple false alarms will be allowed, which may then be misclassified as illness" (Abed et al 2019 p699).

b) "Differential susceptibility" (Belsky and Pluess 2013), which describes the interaction between genes and environments. "Hence, the less-sensitive individuals thrive regardless of the quality of their early physical or emotional environment, whereas the highly sensitive individuals do worse when the circumstances are harsh, but do exceptionally well in propitious environments. Thus, the predisposition to environmental sensitivity will be selected for despite their harmful effects under adverse circumstances" (Abed et al 2019 p699).

c) The mismatch between the environment where behaviours evolved among early humans, and the modern world.

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6. VACCINATION

6.1. RELUCTANCE

Reluctance or refusal to vaccine children is growing in some parts of the world, but Asani (2019) warned that "vaccine mistrust isn't monolithic. To fully and respectfully engage with people, the reasoning behind different communities' doubts must be unpacked with nuance" (p23).

One theme in Africa is vaccination as a ploy for sterilising local populations (appendix 6A). But vaccine boycotts for such reasons can be avoided through engagement with community leaders, local public awareness campaigns, and locally based ethics committees that take account of cultural norms (Asani 2019).

Medical advice adapted to the cultural norms of a group can be seen in the USA and the Somali-American community in Minnesota. In 2017 there was an outbreak of measles, and a Somali-American member of the Minnesota Department of Health was able to recommend parents stayed at home with their children if they did not want to have them vaccinated (Whyte 2019).

Interventions to improve childhood immunisation uptake can be grouped into three types (Oyo-Ita et al 2016):

- Recipient-oriented - eg: educate parents.
- Provider-oriented - eg: training providers.
- Health systems - eg: extend clinic hours for immunisation.

Oyo-Ita et al (2016) performed a review of studies on ways to boost childhood immunisation in low- and middle-income countries (LMICs). They found fourteen relevant studies, which, altogether, showed health education (at village meetings, at home, or at clinics) was effective. But household monetary incentives "may have little or no effect on full immunisation coverage" (Oyo-Ita et al 2016 p2).

In terms of the certainty of the evidence, health education was moderate ("a good indicator of the likely effect"), whereas other interventions were only low-

certainty ("some indication of the likely effect") (Oyo-Ita et al 2016).

The studies in the review included different types of interventions, including:

i) Recipient-oriented:

- Health education - eg: evidence-based discussions in the community in Pakistan on childhood measles (Andersson et al 2009; table 6.1); posters and leaflets in the community in India.

- Monetary incentives - eg: small cash transfer for up-to-date immunisations by five years old in Zimbabwe.

Setting	Lasbela, Belochistan Province in Pakistan (2006-7).
Intervention	Trusted members of the community in 94 villages selected to join discussions of cost-benefits of immunisation. These individuals later discussed immunisation with community members. A control condition with no discussions involved some villages.
Outcome	Proportion of 12-23 month-olds who received measles vaccine, and full coverage of DTP3 within one-year follow-up. Uptake was higher among individuals in the intervention condition than the control condition - over twice greater for measles vaccine, and over three times greater for DTP3.
Strengths	* Random allocation of villages to intervention or control condition. * Researchers collecting the outcome measures blind to condition.
Weaknesses	* Immunisation uptake based on mothers' recall. * Little control over dissemination of information by trusted members of the community.

Table 6.1 - Details of Andersson et al (2009).

ii) Provider-oriented - eg: training staff in Georgia.

iii) Health system interventions - eg: integrating immunisation service delivery with child preventive malaria treatment.

The different outcome measures used in the studies included:

- Proportion of children who received diphtheria-tetanus-pertussis (DTP3) by one year old.

- Proportion of children who received all recommended increases by two years old.

- Number of children under five years old fully immunised with all scheduled vaccinations.

6.2. REFUSAL TO TREAT

In 2015 a US doctor (Mike Ginsberg) made it known that he would not treat unvaccinated children who had no medical grounds for not being vaccinated. This behaviour has become more widespread (eg: 1 in 6 unvaccinated children refused care in Australia) (Forster 2019).

Medical practitioners who refuse to treat unvaccinated children argue that there is a risk to medically compromised patients from unvaccinated children. Is the behaviour of these doctors ethical?

The Australian Medical Association (AMA), for example, has suggested that it is unethical, but, at the same time, the AMA accepts a doctor's right to conscientious objection (CO) (ie: "a doctor's refusal to take a certain action due to it contravening his or her personal beliefs or morals, even if the action is a legal and generally accepted part of the duties of a doctor"; Forster 2019 p553). There must be alternative healthcare providers available, and it is not an emergency (Forster 2019).

Stahl and Emanuel (2017), however, argued against a doctor's right to CO, asserting that doctors "entered their profession voluntarily, and thus must provide all services and treatments that are part of the usual duties of the profession" (Forster 2019 p553).

Refusal to treat unvaccinated children as CO has consequences, including placing an unfair burden on doctors who do treat such children, and "concerns have been raised that conscientious objection may lead to some groups being disadvantaged, inconvenienced or otherwise harmed, and may facilitate discrimination in certain circumstances" (Forster 2019 p553). Potential discrimination is heightened as the unvaccinated children have not chosen to remain unvaccinated (Forster 2019).

It has been argued that voluntary refusal to vaccinate a child is medical neglect by the parent. Forster (2019) challenged this argument by pointing out that neglect and mistreatment of children is dealt with by government authorities usually, not by individual doctors refusing treatment, so referral to the relevant agency is the appropriate action. Furthermore, "if a child were "neglected or abused by a parent in any other manner, it is anathema to suggest that the doctor would hesitate to treat the child" (Forster 2019 pp554-555).

Forster (2019) concluded that "refusal to treat

unvaccinated children is unethical and would be an invalid application of the right to conscientious objection, and represents unjustified discrimination against these children" (p555).

6.3. APPENDIX - POLIO VACCINATION IN NIGERIA

In 2003 three states in northern Nigeria boycotted the polio immunisation campaign ("Kick Polio Out of Africa" by WHO). Political and religious leaders in the states discouraged parents from vaccinating their children by saying that the vaccine contained anti-fertility agents, HIV, or cancerous substances. One Muslim leader said: "We believe that modern-day Hitlers have deliberately adulterated the oral polio vaccines with anti-fertility drugs and... viruses which are known to cause HIV and AIDS" (quoted in Jegede 2007) [27]. Other Muslim leaders, however, did criticise this view (Jegede 2007).

Jegede (2007) explained the suspicion of the immunisation campaign due to certain factors:

a) Historical context.

- Less use of official health-care services in northern Nigeria compared to the south.
- Population and fertility programmes in the 1980s.
- Suspicion of mass campaigns. A US journalist made this comparison: "From a Nigerian's perspective, to be offered free medicine is about as unusual as a stranger's going door to door in America and handing over $100 bills. It does not make any sense in a country where people struggle to obtain the most basic medicines and treatment at local clinics" (quoted in Jegede 2007).

b) Political context.

- State governments control their own healthcare policies and the northern states were controlled by opposition parties to the central government ruling party.
- General political tension between the north and south of the country.

[27] The live, weakened polio virus used in the vaccine can mutate and spread as "vaccine-derived virus infection" (eg: fifteen cases in Nigeria in 2019). It was caused by Type 2 polio strain, which replicates faster provoking most immunity, but in 2016 the vaccine was changed to Types 1 or 3 (MacKenzie 2019).

c) Previous Western health scandals - eg: "Trovan trial" (Wise 2001).

US pharmaceutical company, Pfizer was accused of testing a new anti-biotic ("Trovan") in Kano (northern Nigeria) in 1996 without ethical approval.

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7. DRUGS AND TREATMENTS

7.1. ANTI-BIOTIC PRESCRIBING

Drug resistance (appendix 7A) can be addressed by reducing inappropriate prescribing. Shallcross et al (2017) used UK data to assess anti-biotic (AB) prescribing.

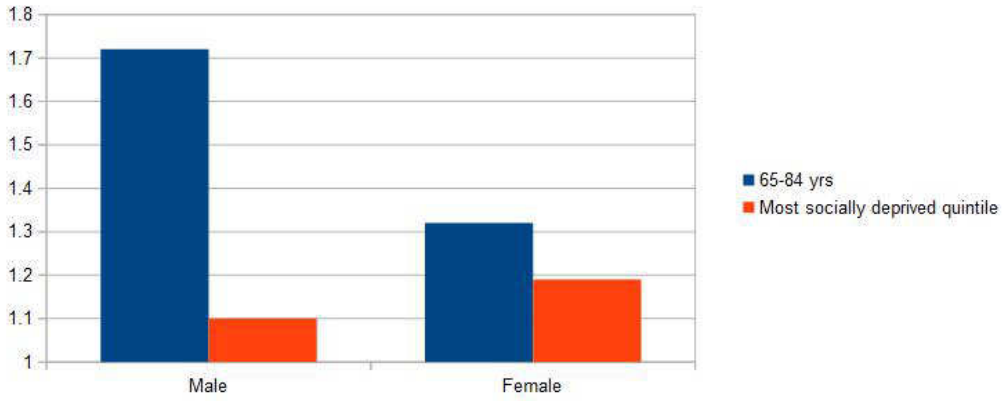
Data were available on 1.9 million adults in 385 general practices via The Health Improvement Network (THIN) ("electronic health records"), and the three-year period 2011 to 2013 was analysed. In total, there were 3.9 million AB prescriptions.

Around one-third of patients (30.1%) were prescribed at least one AB per year, and just under a half (46.1%) had no prescription during the study. The majority of prescriptions (53.3%) went to a small number of patients (9%).

AB prescribing increased with age, particularly for men, and for the most socially deprived quintile (figure 7.1), and smokers generally. Prescriptions were higher for individuals with multiple conditions (co-morbidities).

It was estimated that if the rate of prescribing among patients with co-morbidities, and smoking patients could be reduced to that of the general population average, there would be a total reduction in prescribing of about one-tenth.

Reducing AB prescribing is crucial in impacting anti-microbial resistance. "Patients with frequent anti-biotic exposure are likely to be at greatest risk of anti-microbial resistance, not only through their increased exposure to anti-biotics, but also because they are more likely to be admitted to hospital, where they may be exposed to drug-resistant pathogens. In the context of international initiatives to reduce inappropriate anti-biotic use, it may be important to



(1 = 18-44 year-old age group, or least socially deprived quintile)

(Data from table 2 p1820 Shallcross et al 2017)

Figure 7.1 - Adjusted relative rate of anti-biotic prescribing based on selected age, and on social deprivation quintile.

assess the feasibility of reducing the rate of anti-biotic prescribing to patients with the highest frequency of anti-biotic use" (Shallcross et al 2017 p1823).

7.2. MEDICINAL CANNABINOIDS AS TREATMENT FOR MENTAL DISORDERS

7.2.1. Hype

Hamzelou (2019) described the popular claims made for cannabidiol (CBD) generally: "'It will cure, eliminate or definitely help any disease', an assistant in a shop... in London tells me. Although these extraordinary claims aren't made on the product's packaging, the substance it contains is quickly gaining a reputation among consumers as a cure-all" (p20) [28] [29].

The US market for CBD products was worth $1.5 bn in 2018, according to estimates, and over one million people use such products in the UK (Hamzelou 2019).

[28] Purported benefits include analgesic, and anti-inflammatory, while side effects are reported as mild and infrequent, with a low risk of interactions with other medications, and no evidence of dependency or abuse (Millar et al 2019).

[29] Stockings et al's (2018) review found that cannabinoids were beneficial for pain associated with multiple sclerosis, and with nerve damage. But for other types of pain, the studies were limited in number and/or quality (Wallis 2019). "It would be easy to conclude, as medical experts and health columnists so often do, that patients should simply wait for better data and better products. But chronic pain is an urgent problem for millions of people..." (Wallis 2019 p16).

Generally, there is a lack of evidence on appropriate dosage of CBD (appendix 7B), as well as concerns about product quality. For example, the UK Centre for Medicinal Cannabis found great variety in CBD levels (including 0%) in thirty shop-bought products (Hamzelou 2019).

Other issues include medical advice from unqualified sellers of CBD products, and the potentially harmful effects of the cannabis plant's ability to suck metals and pesticides up from the soil (Hamzelou 2019).

7.2.2. Evidence

Cannabinoids are increasingly used for medicinal purposes. What about their use as treatment for mental disorders?

Black et al (2019) clarified the terminology - "medicinal cannabinoids" (MCs) covers plant-derived and synthetic derivates of the cannabis plant, while "pharmaceutical cannabinoids" refers to extracts with standardised tetrahydrocannabinol (THC) and cannabidiol (CBD) content, for example.

Black et al (2019) performed a systematic review and meta-analysis with studies published between 1980 and mid-2018. Studies involving any type and formulation of MC were considered, and categorised into pharmaceutical-grade THC, pharmaceutical-grade CBD, and medicinal cannabis. Studies with adults (18 years old and above) diagnosed with depression, anxiety, attention-deficit hyperactivity disorder (ADHD), Tourette syndrome, post-traumatic stress disorder (PTSD), or psychosis were included.

Eighty-three eligible studies were found, of which the majority covered depression and anxiety. Half of the total studies were randomised controlled trials (RCTs), but most of these were small (10-39 participants) and short-term (eg: 4-5 weeks). Many of the mental disorders were secondary diagnosis (eg: multiple sclerosis sufferer diagnosed with depression).

Overall, the researchers stated: "There is a notable absence of high-quality evidence where mental disorders are the primary target of treatment, and most evidence is derived from studies where mental disorders are secondary to another medical condition, commonly chronic non-cancer pain and multiple sclerosis" (Black et al 2019 p1007).

Here is a summary of the findings for each mental disorder:

i) Depression (42 studies; 23 RCTs [30]) - None of the

[30] Some studies covered more than one mental disorder.

three categories of MCs significantly improved symptoms compared to a placebo or an active comparator.

ii) Anxiety (31 studies; 17 RCTs) - Pharmaceutical THC did reduce symptoms significantly more than placebo, but the quality of evidence was rated low. Little evidence for the other two categories of MCs.

iii) ADHD (3 studies; 1 RCT) - Not enough evidence.

iv) Tourette syndrome (8 studies; 2 RCTs) - No significant benefits found.

v) PTSD (12 studies; 1 RCT) - Not enough evidence.

vi) Psychosis (11 studies; 6 RCTs) - A small increase in adverse effects.

Black et al (2019) summed up: "There is scarce evidence to suggest that cannabinoids improve depressive disorders and symptoms, anxiety disorders, attention-deficit hyperactivity disorder, Tourette syndrome, post-traumatic stress disorder, or psychosis. There is very low quality evidence that pharmaceutical THC (with or without CBD) leads to a small improvement in symptoms of anxiety among individuals with other medical conditions. There remains insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders within a regulatory framework. Further high-quality studies directly examining the effect of cannabinoids on treating mental disorders are needed" (p995).

7.3. DRUGS

7.3.1. Approval

Wieseler et al (2019) began: "Medicines regulators around the world are pursuing a strategy aimed at accelerating the development and approval of drugs. These approaches are based on the assumption that faster access to new drugs benefits patients. The rhetoric of novelty and innovation creates an assumption that new products are better than existing ones" (p1). These authors challenged this assumption with data from Germany.

The official body that assesses new medicines in that country is the IQWiG (Institute for Quality and Efficiency in Health Care), which considered 216 drugs between 2011 and 2017. Of the total, one-quarter were judged to have "a considerable or major added benefit" over existing medicines, and 16% had an added benefit that was "either minor or could not be quantified", but for the remainder (58%) "the available evidence did not prove an added benefit over standard care for mortality,

morbidity, or health related quality of life in the approved patient population" (Wieseler et al 2019 p2).

Concentrating on a specific area of medicine, newer drugs for psychiatry/neurology were the worst with only 6& having added benefit.

Wieseler et al (2019) commented: "Some people have argued that limited information at the time of regulatory approval (and thus widespread use by patients) is the price to be paid for early access to innovative drugs. This argument suggests that research conducted after market entry will ultimately prove the benefit for patients. The reality, however, looks quite different. For instance, a systematic evaluation [Davis et al 2017] of cancer drugs approved by the EMA between 2009 and 2013 showed that most had been approved with no evidence of clinically meaningful benefit on patient relevant outcomes (survival and quality of life), and several years later the situation had little changed" (p2).

Part of the problem is "me-too-drugs" - ie: "a commercially successful drug with a new mode of action is often followed by several similar drugs, not real innovation" (Wieseler et al 2019 p2).

Wieseler et al (2019) advocated that health authorities drive the demand for new drugs based on what is needed (eg: Drugs for Neglected Diseases initiative; DNDi) rather than waiting for pharmaceutical companies to "decide what to develop".

7.3.2. Translational Problems

Creating drugs from discovery to bringing to market is a difficult process. Yezierski and Hansson (2018) noted that fourteen therapeutic targets for pain relief, for example, have failed at clinical trial. "A fair accounting of this unenviable record would, however, note that: (i) not all of these targets were abandoned because of lack of efficacy in humans (some failed because of poor tolerability or the presence of rare but serious side effects), (ii) some of the targets may not actually be permanently abandoned, (iii) in very few cases were drug exposure levels actually determined, and (iv) decisions surrounding the design of many of these trials may have been based more on marketing considerations than scientific ones" (Mogil 2019 p1).

For some, these failures are part of a "replication crisis" (Baker 2016) "bought on by poor incentives, poor scientific reporting, and sloppy and/or inappropriate statistical practices" (Mogil 2019 p1).

Others blame the poor fit between animal models and human testing. "Suffice it to say that pain researchers have made, in retrospect, some arguably ill-advised choices regarding their choice of subject sex (male),

genotype (inbred C57BL/6), age (young), time of testing following injury (soon after), method of inducing pain (artificial) and outcome measures (evoked and reflexive)" (Mogil 2019 p1). Animal models make the "translational assumption" (ie: "mouse = rat = human") (Mogil 2019).

Still concentrating on pain, Mogil (2019) lamented the paucity of direct clinical comparisons between rodents and humans, and between mice and rats. In relation to the latter studies, "all should be treated with caution, as it is difficult to distinguish a true species difference from a difference between one strain of rat versus one strain of mouse. For example, a study [Mogil et al 2000] of thermal pain sensitivity in three rat strains and three mouse strains revealed increased sensitivity in female Long Evans rats and Swiss Webster mice compared to males, decreased sensitivity in female Sprague Dawley rats compared to males, and no sex differences in Wistar Kyoto rats, CD-1 or ND4 mice" (Mogil 2019 p2).

7.3.3. Limbic Capitalism

Courtwright (2005) began: "All researchers agree that individuals can become intoxicated by and dependent on alcohol, tobacco, and other psychoactive drugs [ATODs]. But they have disagreed over whether, and to what extent, drug pathologies comprise a unitary medical problem. Most critically, does addiction have a biological common denominator? Consensus on this question has shifted back and forth" (p105).

Historically, in the late nineteenth and early twentieth centuries, ATODs were treated together as "inebriety". This was seen as a trait, which, once acquired, could be passed on as degenerate tendencies. "The drunkard's child might be an opium addict, his grandchild an epileptic, his great grandchild a congenital idiot. Though inebriate degeneration might assume many forms, its final end was always ruin. It was crucial, therefore, to keep the young from acquiring inebriate habits, for their sake and for posterity's. Drugs were literally 'germ poisons' that threatened the 'race' by corrupting sperm and ova" (Courtwright 2005 pp108-109).

By the mid-20th century, this idea had disappeared, and, with the growth of medical science, alcohol and tobacco became viewed separately from other drugs, particularly with the social acceptability of their personal use. Courtwright (2005)asserted: "The decoupling of alcohol and tobacco from other drugs was no accident. It was at least partly the result of a deliberate campaign by powerful and fiscally important industries, which spent millions on advertising and public relations to promote and defend their products" (p113).

Towards the end of the 20th century, ATODs became unified as "chemical dependency" or "substance abuse" with the growth of genetic and neuroscientific evidence. This evidence suggests that "drug consumption is synergistic and crosses licit-illicit lines" (Courtwright 2005 p120).

Alongside these changes has been the development of what Courtwright (2005) called "limbic capitalism". He stated: "By that I mean the reorientation of capitalist enterprise from basic services and durable goods to the more profitable business of providing transient but habitual pleasures, whether drugs or pornography or gambling or even sweet and fatty foods. In global terms limbic capitalism first became important in the age of transoceanic empire building. Were it not for the trade in sugar, tobacco, tea, and opium, there never would have been a British Empire, with all that entailed for modern history. Limbic capitalism has become even more conspicuous and lucrative in our own advanced (if that is the word) consumer societies. Entrepreneurs exploit evolved drives and then provide the goods and services to cope with the damage. Alcohol sells aspirin, cigarettes sell nicotine patches, sugar sells insulin, heroin sells Naltrexone, which costs addicted patients between $100 and $150 a month" (Courtwright 2005 p121).

7.3.4. Drug Rediscovery Protocol

The Drug Rediscovery protocol (DRUP) was set up to collect data on cancer patients treated with drugs "outside of their approved label". Systematic data are collected for on-label use only (van der Velden et al 2019).

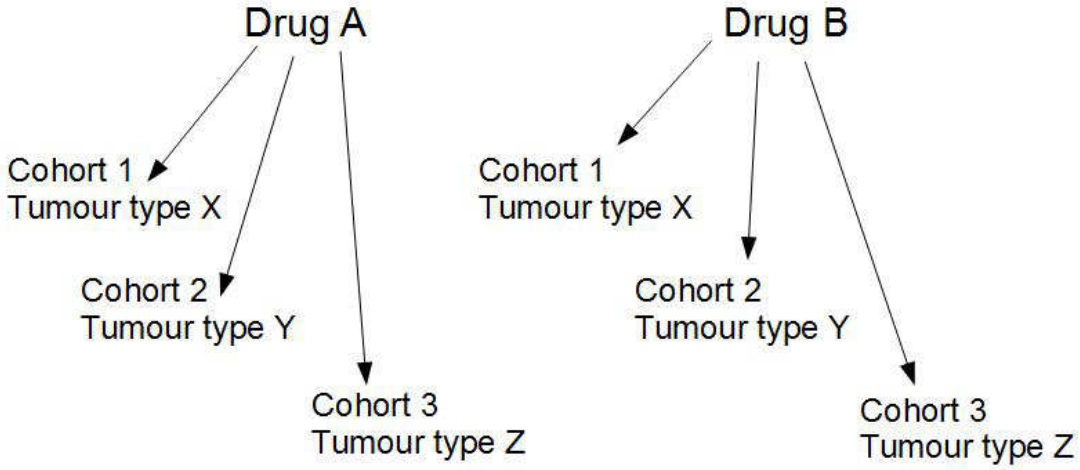
The DRUP is particularly important for patients with rare sub-types of cancer, where no on-label drugs may exist, and it is part of the growth of personalised medicine.

van der Velden et al (2019) reported the details of the DRUP based in the Netherlands. Between 2016 and 2018, 215 patients with advanced tumours were recruited. Overall, one-third showed benefits from an off-label drug (eg: nivolumab). The study design does not include a control group.

The DRUP is based on parallel cohorts (figure 7.2). Eight patients with a particular tumour are given a particular drug (stage I of the clinical trial), and if there are signs of clinical benefits, sixteen more patients will be added in stage II (figure 7.3). If stage I shows no benefit, the cohort is closed, but the results are made public. On most occasions, data on failures are not published. van der Velden et al (2019) stated that "the importance of publicly reporting negative results cannot be underestimated, as it prevents patient exposure

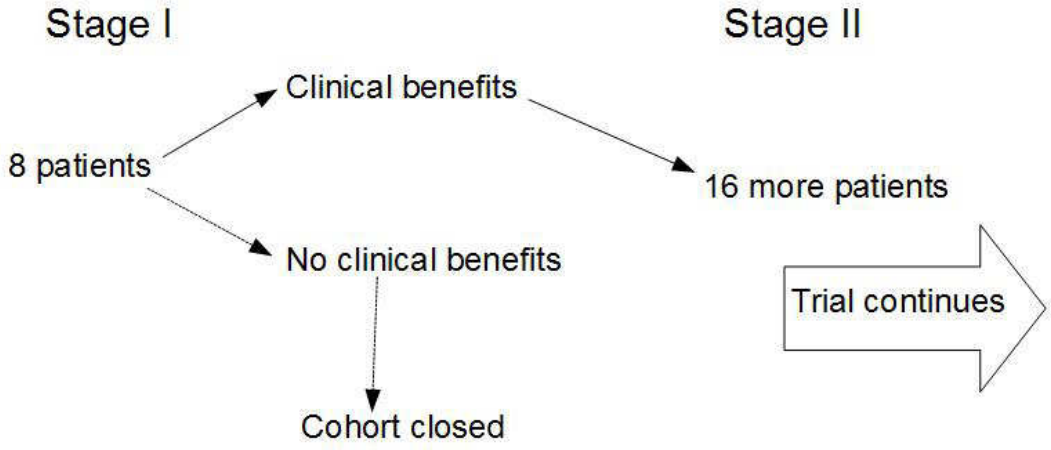
to ineffective agents with all their accompanying toxicities and financial costs" (p131).

On the positive side, the DRUP is faster than traditional clinical trials with the "rapid incorporation of new drugs and scientific insights into clinical practice" (van der Velden et al 2019 p131).



(Based on figure 1 p128 van der Velden et al 2019)

Figure 7.2 - Basic overview of DRUP.



(Based on figure 1 p128 van der Velden et al 2019)

Figure 7.3 - Simon-like design (Simon 1989) of the DRUP.

7.4. HIV TRANSMISSION

There is always a risk of transmission of HIV for individuals with HIV-negative status who have unprotected

sex with HIV-positive partners (ie: serodifferent couples). But virally suppressive anti-retroviral therapy (vsART) taken by the HIV-positive partner reduces this risk, as shown by the PARTNER study.

This was a prospective, observational study in fourteen European countries. The first part of the study (PARTNER1) (between 2010 and 2014) found no transmission of HIV among 548 heterosexual and 340 gay serodifferent couples reporting condomless sex where the HIV-positive partner was taking vsART (Rodger et al 2016).

Phase 2 (PARTNER2) concentrated on gay male couples only (between 2014 and 2017 (Rodger et al 2019). Seven hundred and eighty-two eligible couples were recruited. Rodger et al (2019) summed up: "Our findings provide conclusive evidence that the risk of HIV transmission through anal sex when HIV viral load is suppressed is effectively zero. Among the 782 serodifferent gay couples followed for almost 1600 eligible couple-years of follow-up, which included more than 76 000 reports of condomless sex, we found zero cases of within-couple HIV transmission. In the absence of ART, on the basis of the frequency and type of sex, for receptive condomless anal sex acts alone approximately 472 transmissions... would have been expected" (p2434).

The researchers accepted the limitations of their sample - namely, median age of 38 years old for HIV-negative participants (whereas most HIV transmission is in under 25s), predominantly White ethnicity, and most HIV-positive participants has been on vsART for several years. Other studies have suggested that the risk of HIV transmission remains during the first six months of vsART "because of incomplete viral suppression in blood and genital compartments... The effectiveness of ART in preventing HIV transmission is dependent on maintaining full virological suppression in plasma" (Rodger et al 2019 p2435) (eg: <200 copies of plasma HIV-1 DNA virus per mL).

Rodger et al (2019) advocated early testing and treatment of HIV from their findings, but also "to tackle stigma, discrimination, and criminalisation laws that continue to affect HIV-positive people" (p2436).

7.5. APPENDIX 7A - RESISTANCE

AB resistance depends on the ability of different species of bacteria to swap genetic material (Baraniuk 2019).

Wang et al (2019) reported that five commonly used non-AB drugs (eg: ibuprofen) made it easier for bacteria to absorb each other's DNA.

This was a controlled laboratory study, and outside the laboratory many other chemicals may be involved in gene transfer (Katherine Duncan in Baraniuk 2019).

7.6. APPENDIX 7B - DOSAGE

"Hemp-derived CBD is commercially available and is currently used as a health and food supplement commonly for anxiety and pain relief. This market represents a flourishing industry expected to rise financially and globally. However, the blurred lines between CBD as a licensed medicine and CBD as an over-the-counter remedy contribute to the overall lack of understanding of what dose of CBD may be considered therapeutic. This is further hampered by the lack of standardisation in over-the-counter CBD products and their unregulated labelled doses" (Millar et al 2019 p1889).

Millar et al (2019) reviewed thirty-five relevant studies on CBD dosage (of which fifteen were RCTs). Doses ranged from <1 to 50 mg/kg/d (milligram per kilogram weight of person [31] per dose). Plasma concentrations were not provided, and this fitted with a lack of detailed clinical trials.

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8. SELF VS OTHERS' RISK

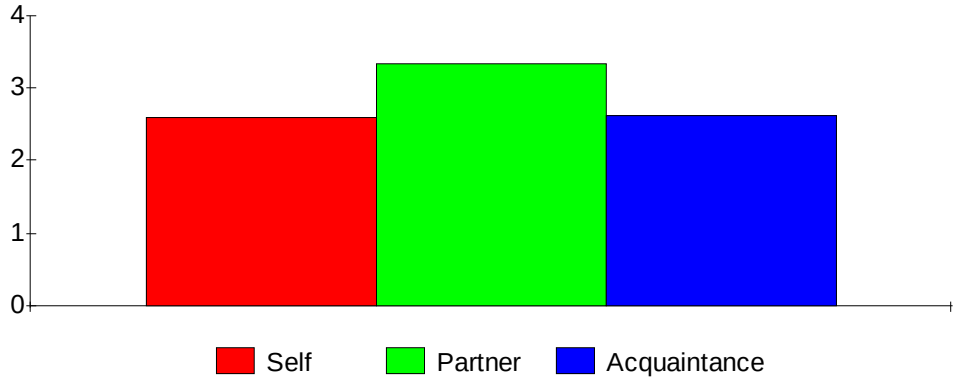
Ghassemi et al (2020) argued that "when our partner, child, or parent engages in a behaviour that involves risk, we feel more anxious than when we intend to engage in the same behaviour ourselves" (p1).

Part of the reason for this anxiety is a cognitive bias called "unrealistic comparative optimism" (or "optimistic bias") (Weinstein 1980). This is the tendency to "believe that negative events (eg: accidents, natural disasters) are less likely to happen to oneself than to other people, while positive events are perceived as more likely to happen to oneself than to others" (Ghassemi et al 2020 p2). Add to this another cognitive bias in the form of "illusion of control" (Lange 1975), which describes an individual's overestimation of their control of an uncontrollable situation that they are involved in (eg: driving a car vs being a passenger).

Ghassemi et al (2020) investigated the anxiety over the perceived risk for a significant other in five studies.

Study 1 - 150 participants, who were in a committed romantic relationship, were recruited online at a Swiss university. Individuals read nine short scenarios about everyday risks (eg: flying with a low-budget airline) and rated their feelings. The participants were divided into three groups for the independent variable (who the scenario was about) - the self, romantic partner, or distant acquaintance.

Anxiety related to the scenarios was significantly higher for the partner condition than the other two conditions (figure 8.1). This study established that individuals perceive the same situation as riskier for a loved one than for themselves or an acquaintance.



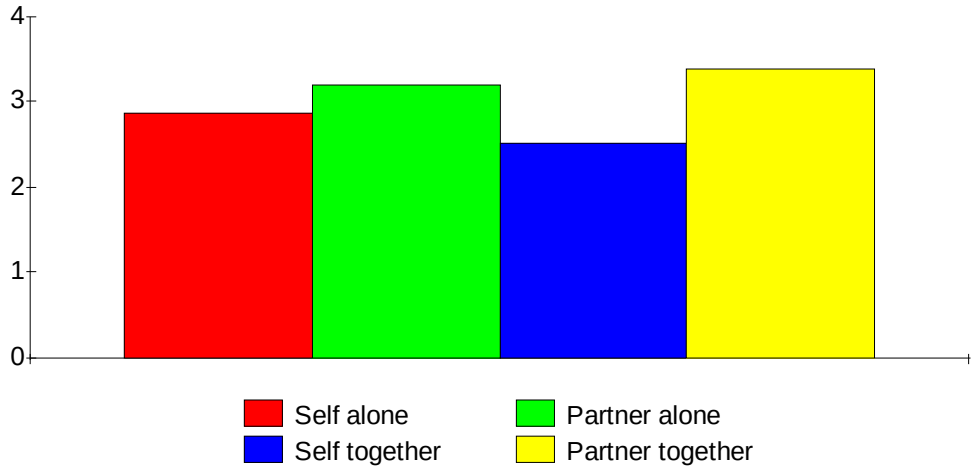
(Data from table 1 p4 Ghassemi et al 2020)

Figure 8.1 - Mean total rating of anxiety for risk scenarios (out of 5) in Study 1.

Study 2 - 193 more participants in a committed romantic relationship read ten risk scenarios (eg: walking through an unsafe area of a city). There were four independent groups that the participants were allocated to:

- Apply to self
- Apply to partner
- Self and partner together but focus on risk for self
- Self and partner together but focus on risk for partner.

Perceived risk was higher for the partner than the self (whether alone or together) (figure 8.2). "Lack of control over the partner's outcomes, operationalised by own absence, did not account for the effect: Irrespective of whether individuals were described to be present or not, they were more anxious about their partner's (vs own) risk. In fact, when individuals engaged in the risk behaviour together with their partner, they felt less anxious about themselves, resulting in an even more pronounced self-partner discrepancy" (Ghassemi et al 2020 p6).



(Data from table 1 p4 Ghassemi et al 2020)

Figure 8.2 - Mean total rating of anxiety for risk scenarios (out of 5) in Study 2.

Study 3 - This study investigated whether the self-partner discrepancy in anxiety was due to perceived consequences (ie: fearing worse consequences for the partner than the self). The participants were 150 individuals in a committed romantic relationship recruited from a German online panel. The design was the same as Study 1, except that participants generated three consequences of each scenario before rating their

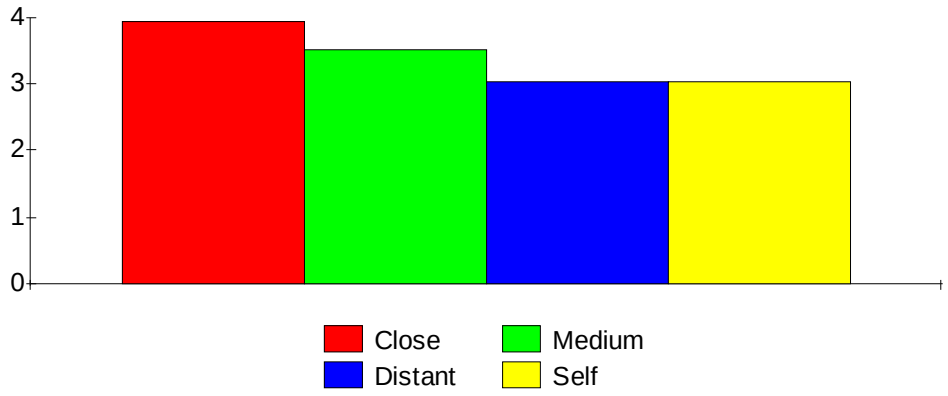
anxiety.

Anxiety about risk was significantly higher in the partner condition (mean 3.66) than in the self condition (mean 3.09), but anxiety in the acquaintance condition was also high (mean 3.38). More severe consequences were generated in the partner and acquaintance conditions than in the self condition.

So, a "higher severity of imagined consequences partly explained individuals' higher anxiety about their partner's (vs their own) risk taking" (Ghassemi et al 2020 p8).

Study 4 - This study varied the level of closeness of relationships with 194 students at a Swiss university. Participants were asked to think of a significant other (close), a person who they knew but not close (medium), and a regular acquaintance (distant). Participants read the scenarios used previously in relation to one of the three levels of relationship or themselves. It was an independent groups design.

Anxiety about the risk was the same for the self and distant individuals, which were significantly less than the close and medium conditions (figure 8.3). "This study showed that the discrepancy in anxiety in response to own versus others' risk behaviour increases with relationship closeness" (Ghassemi et al 2020 p9).



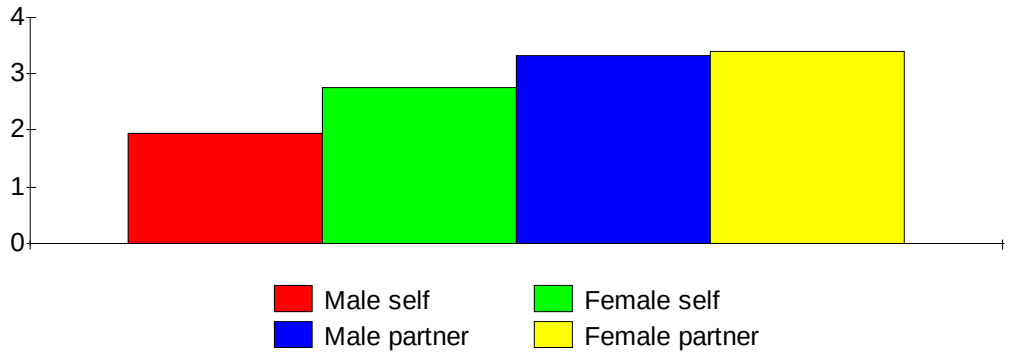
(Data from table 2 p7 Ghassemi et al 2020)

Figure 8.3 - Mean total rating of anxiety for risk scenarios (out of 5) in Study 4.

Study 5 - The previous studies involved hypothetical scenarios, whereas this one was based on a real situation - driving a car. Fifty-four romantic couples were recruited to test a car at a local car dealers in Switzerland. Each member of the couple completed the one-hour drive alone, but prior to it they each rated the

risks for themselves and their partners.

Participants were anxious about their partner's drive than for themselves, and there was a gender difference with women being more anxious generally (figure 8.4).



(Data from table 3 p10 Ghassemi et al 2020)

Figure 8.4 - Mean total rating of anxiety for risk scenarios (out of 5) in Study 5.

Overall, the five studies showed a self-other discrepancy in perception of risk. Though the studies used controlled experimental designs, the participants were volunteers (non-representative of the general population, particularly with more women), and the measures were single-item (eg: "How anxious are you that something bad will happen to...?").

People giving advice to others which they do not follow for themselves has been called "action hypocrisy" (Howell et al 2014). Ghassemi et al (2020) felt that their findings could explain such behaviour.

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9. SCHIZOPHRENIA AND PSYCHOSIS

9.1. PHYSICAL HEALTH PROBLEMS

9.1.1. First Episode of Psychosis

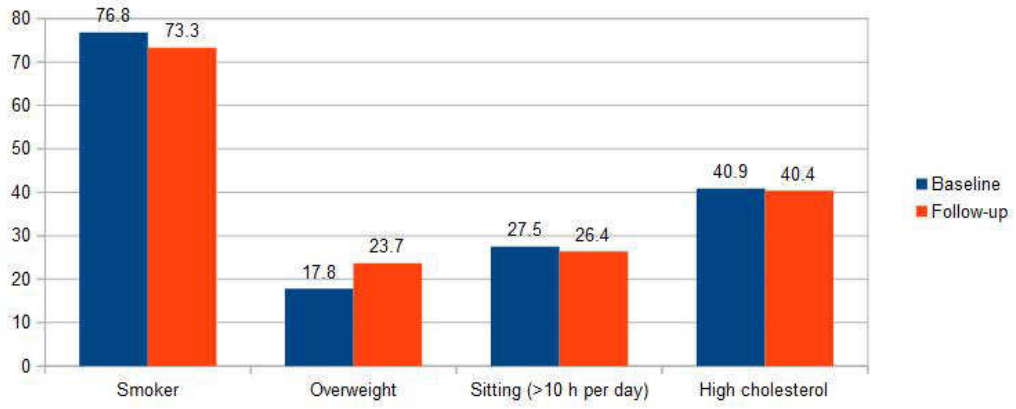
Gaughran et al (2019) investigated physical health in the year following the first episode of psychosis (FEP). Cardiometabolic dysregulation is a problem, partly because anti-psychotic medication affects metabolism (eg: clozapine and glucose dysregulation; Hoares et al 2004). What is the role of lifestyle factors here?

Gaughran et al (2019) recruited 293 individuals in England who were followed up for twelve months after their FEP. The cardiometabolic measures included body mass index, blood pressure, glucose and insulin levels, and cholesterol.

Over the twelve months negative cardiometabolic changes were common (eg: increased weight, diabetes, and cholesterol levels). Unhealthy lifestyle choices were high (eg: three-quarters of the sample smoked; high consumption of sugar-sweetened beverages and tea with sugar; salt added to food and take-away meals regularly; low levels of exercise) (figure 9.1). However, there was no significant association between lifestyle at baseline and cardiometabolic outcomes one year later.

Gaughran et al (2019) concluded: "our results identify that cardiometabolic risk factors are already pronounced in those presenting to FEP services and worsen over the first year under standard care. No baseline behaviour predicted risk of worsening cardiometabolic parameters, but a greater degree of emergent glucose dysregulation was observed in those from BME groups" (p718).

Table 9.1 summarises the main strengths and weaknesses of the study.



(Data from Gaughran et al 2019 table 2 p716)

Figure 9.1 - Selected unhealthy lifestyle factors at baseline and twelve months later (%).

STRENGTHS	WEAKNESSES
1. Prospective study with one year follow-up. 2. Standardised cardiometabolic measures and definitions used. Clear eligibility criteria (eg: within six months of first presentation to mental health services with psychosis), and exclusion (eg: major medical illness). 3. Diverse sample (46% White, 37% Black, 8% Asian) of both in-patients and individuals in the community. 4. Details of medication from electronic medical records.	1. Self-reported data for exercise, substance use, and food consumed in previous week. 2. 125 participants completed the study (from 293 starters and 971 approached as eligible). 3. "Over half our patients required acute inpatient care at the time of recruitment and many had received treatment for some weeks before being well enough to consent to inclusion. To minimise this effect and minimise missing data, we therefore sought permission to use clinical data, where available and comparable, as well as adjusting for the number of days prescribed anti-psychotics before baseline in our analyses" (Gaughran et al 2019 p718). 4. The "number of statistical tests carried out was reasonably large and although we took a more conservative threshold of statistical significance, we cannot completely discount the possibility of type I errors" (Gaughran et al 2019 p718).

Table 9.1 - Main strengths and weaknesses of Gaughran et al (2019).

9.1.2. Lung Cancer

Individuals diagnosed with schizophrenia are more likely to be tobacco smokers than the general population (Zhuo et al 2019). So, does that mean such individuals have a higher risk of lung cancer?

Studies are inconclusive, and fall into two categories (Zhuo et al 2019):

i) Higher risk - eg: Lichtermann et al (2001) cohort study.

ii) Lower risk - eg: meta-analysis by Catts et al (2008); genetic study in Turkey (Ozbey et al 2011).

To clarify the situation, Zhuo et al (2019) performed an up-to-date meta-analysis of twelve cohort studies (both retrospective and prospective) (covering nearly half a million individuals with schizophrenia). Follow-up durations spanned 10 to 29 years, and a total of 2151 lung cancer cases were diagnosed among patients.

Overall, compared to the general population from the same country, individuals with schizophrenia at baseline were not significantly associated with lung cancer risk. This did not differ by gender. But the studies varied, including in their methodological quality. For example, one study found nearly a fivefold greater risk for individuals with schizophrenia, while, at the other end, a 25% less risk in another study.

Methodological issues of the studies included:

a) Not controlling for confounding factors (eg: body mass index; occupation; diet). Many studies did not control for tobacco smoking as it was not their focus.

b) Different diagnostic criteria for schizophrenia, and for lung cancer.

c) Details lacking about anti-psychotic medication, management and course of schizophrenia (eg: some studies included only in-patients).

d) Control group - a few studies used matched controls (eg: age; gender).

Only studies published in English covered by the main medical databases were included in the meta-analysis. The studies came from developed countries - Australia, Western Europe (5 studies), USA, Israel (3), and China (2).

9.1.3. Healthcare Provision

Because of the evidence that individuals with psychosis die earlier than the general population from physical health problems, annual health checks were introduced in England in 2014 with financial incentives for health trusts (Crawford et al 2019).

Crawford et al (2019) evaluated these financial incentives using data from the National Audit of Psychosis in England and Wales in 2011, 2013, and 2017. The first two years were prior to incentives to be compared to 2017 three years after their introduction. There was an increase of around one-fifth in health screenings for individuals with psychosis after the introduction of financial incentives.

Crawford et al (2019) stated: "We cannot be certain that it was the introduction of the financial incentive that was responsible for this improvement, but a number of related findings suggest that it was. First, only modest improvements were seen in the quality of physical healthcare delivered to people with psychosis in England between 2011 and 2013... Second, we found no evidence of significant improvements in the quality of other aspects of care received by people with psychosis during this period, and some evidence of falling standards of care. Third, the scale of the improvement between 2013 and 2017 was far greater in England than it was in Wales where no financial incentive was offered" (p722).

The data covered nearly 18 000 over 18s with a clinical diagnosis of schizophrenia or schizoaffective disorder receiving care from mental health services in England and Wales. The outcome measure was the proportion of patients screened for seven risk factors for poor physical health (eg: tobacco use; hypertension) according to documentary evidence. Though clinical records were audited independently, there is always the question of their reliability (Crawford et al 2019).

9.2. EARLY INTERVENTION IN PSYCHOSIS

Amos (2014) talked of "spin" and "bias" to misrepresent the advantages of early intervention in psychosis (EIP) [32]. Amos (2019) particularly criticised a review by Aceituno et al (2019) (appendix 9A) for "ignoring evidence of systematic bias [and] the failure to identify limitations of specific articles".

Aceituno (2019) took Amos's (2019) criticism of

[32] EIP includes specialised multi-disciplinary teams offering low doses of medication, and psychosocial interventions (eg: cognitive-behaviour therapy; vocational rehabilitation).

"cherry-picking" of studies for the review and used it on him in Amos (2012 and 2014) [33].

Much of the debate is around the cost-effectiveness of treatment to prevent the transition to psychosis (ie: FEP) [34]. Amos (2019) stated: "If a treatment is not effective, it cannot be cost-effective". But Aceituno (2019) replied that treatments not reaching statistical significance for effectiveness could be cost-effectiveness in the short-term, say, or because "costs and effects are measured with uncertainty".

There are other outcomes for Aceituno (2019), including: "engage young people with services, reduce co-morbidities (including substance misuse disorders), decrease the duration of untreated psychosis and ameliorate the impact of the FEP by, for example, using less admissions to hospital and compulsory admissions" (p745).

Amos (2012) distinguished the different measures of cost-effectiveness:

a) Cost-effectiveness analysis (CEA) - compares treatments for incremental costs of achieving a health outcome (eg: reduction of one unit on psychosis scale).

b) Cost-utility analysis (CUA) - similar to CEA but compares the costs for units of quality-adjusted life years (QALYs) [35], for instance.

c) Cost-benefit analysis (CBA) - costs and consequences of a treatment are translated into monetary equivalents.

d) Cost-minimisation analysis (CMA) - reports the difference in costs between treatments.

CUA and CEA report an incremental cost-effectiveness ratio (ICER) (ie: "the difference in cost divided by the difference in effect or utility"; Amos 2012 p721). For example, Cocchi et al (2011), in Italy, calculated an

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[33] Amos (2012) found nine articles for his review, and they mostly showed no difference between EIP and standard care in costs. Most of the studies were case-control designs, with "clear significant bias". Amos (2012) concluded: "Extant economic evaluations of EI are not adequately designed and powered to answer the questions they propose. Small sample sizes, reliance upon biased case-controls, and inaccurate outpatient cost estimation mean that there are no reports which report the actual costs and the feasible reduction of costs by substituting outpatient for inpatient care. There would appear to be little value in future research which relies upon case-control designs" (p733).

[34] Reduction of the duration of untreated psychosis (DUP) is a key concept here.

[35] "A QALY is a weighted average of time spent at a particular quality of life compared to perfect health, where perfect health is 1.0 and death is 0.0. This is used as a proxy for utility, an abstract concept associated with the preferences of an individual or group. The higher the preference of an individual or group for a set of conditions, the higher the utility of that set of conditions, relative to other possible sets" (Amos 2012 p721).

ICER of Euros 1204 net saving for EIP per unit reduction on the Health of the Nation Scale, while Zhang et al (2014), in China, reported a saving of US$ 1820 per QALY gained.

An alternative method to ICER is cost-effectiveness acceptability curves (CEACs) which represent graphically the probability of one treatment being more cost-effective than another (Amos 2012).

9.3. PRE-NATAL MATERNAL STRESS

Pre-natal maternal stress (PNMS) may increase the risk of later mental health problems for the foetus. But how to test this idea? It is unacceptable (if not unfeasible) to deliberately stress one group of pregnant women as in a laboratory experiment and compare them to an unstressed group. However, a natural experiment is possible (table 9.2). This is where researchers take advantage of a natural-occurring event to study its impact.

ADVANTAGES	DISADVANTAGES
Studying the effects of natural events. Gives clues to cause and effect. Some things not possible to control or study in an experiment. Not unethical.	Lack of control of confounding variables, and not replicable. No random allocation of participants to groups. No baseline measure of behaviour, and limited information about participants. Susceptible to retrospective bias.

Table 9.2 - Main advantages and disadvantages of the natural experiment.

For example, Guo et al (2019) used the Great Tangshan Earthquake (GTE) in July 1976 in Hebei province in China (which killed around a quarter of a million people), and the risk of later schizophrenia among foetuses at the time [36]. Data were analysed from the China National Sample Survey on Disability (CNSSD) covering 2.5 million individuals in 2006. Individuals born between October 1975 and May 1979 were the focus. The earthquake was covered in the news and it was assumed that "almost all of the Chinese people living at the time were aware of it and were affected by the earthquake in some way"

[36] Other mental health problems have been studied in relation to the GTE (appendix 9B).

(Guo et al 2019 p721). However, whether individuals had felt the earthquake or personally experienced the destruction was noted.

Four birth cohorts were distinguished for analysis purposes:

a) Pre-earthquake - born before earthquake and exposed to it in first year of life (n = 25 453).

b) Earthquake - in gestation during earthquake and exposed in the womb. This group was sub-divided into three depending on the stage of gestation at the time of the earthquake (n = 23 530).

c) Post-earthquake - conceived in year after (ie: August 1976-77) (n = 22 596).

d) Reference/controls - conceived two years after the earthquake (ie: August 1978-79) (n = 22 831).

Compared to the reference cohort, individuals in the earthquake cohort were over three times more likely to be diagnosed with schizophrenia, and over seven times more likely if the stress was during the first trimester of pregnancy. Felt exposure to the earthquake was key (as opposed to news information only).

The findings fit with the "foetal origins hypothesis" (Glover 2011) - ie: "the origins of many adults' physical and mental health outcomes can be traced back to the in utero period, when rapid changes in the structure and function of the foetal brain and body take place based on the intra-uterine and extra-uterine environments" (Guo et al 2019 p733).

Guo et al (2019) explained the biological processes behind the findings as "neuroendocrine mechanism, epigenetic modifications and alteration of the hypothalamic-pituitary-adrenal axis (HPA-axis). During the first trimester, the neurogenesis and self-renewal of neural stem cells vigorously occur; disturbance of the neuronal proliferation and migration during this period may underlie the increased susceptibility to schizophrenia. Stress can also affect the epigenetic modifications, such as DNA methylation and histone modification. They are critical mechanisms for regulating gene expression and are associated with an increase in susceptibility to schizophrenia when affected. Furthermore, foetal programming by glucocorticoids is known to occur early in gestation. The changes in HPA-axis programming through glucocorticoids as a result of antenatal stress may program a trajectory of abnormal brain growth, from foetal brain development through puberty and into adulthood" (p734).

Other PMNS studies and schizophrenia include flood

(eg: Selten et al 1999 [37]) and terrorism (eg: Weinstein et al 2018 [38]).

The study by Guo et al (2019) was a retrospective analysis of secondary data. Certain information was not available, like non-earthquake-related PNMS, or access to social support. "Moreover, earthquake is an acute population-level stressor, so the generalisability to chronic or individual-level sources of stress remains a question" (Guo et al 2019 p734).

The CNSSD did not include individuals living in institutions, including the army, though it was a nationally representative survey of households.

9.4. URBANICITY

Psychosis rates are higher in urban areas (than rural), among men, and minority ethnic and migrant groups (Del-Ben et al 2019). But these findings are based on studies in high-income countries.

The limited number of studies in low- and middle-income countries (LMICs) have varied results. For example, two studies in Brazil show the differences - in Sao Paulo city the incidence of FEP was lower than expected for a metropolis (Menezes et al 2007), but the findings in another city in Sao Paulo state (Ribeirao Preto) were more nuanced (Del-Ben et al 2019).

Del-Ben et al (2019) reported data on all individuals aged 16-64 years having first contact with mental health services between 2012 and 2015 in the Ribeirao Preto catchment area [39]. The incidence of FEP (adjusted by gender and age) was 19.46 per 100 000 person-years (compared to 15.8 in Menezes et al's 2007 study). The incidence was higher for younger individuals, men, and Black and minority ethnic individuals (figure 9.2).

FEP incidence was 25% less in the main city compared to the 25 municipalities of the catchment area (ie: less population dense towns).

Del-Ben et al (2019) commented: "This finding is opposite to the association between urbanicity and risk of psychosis consistently described in some European populations, but is similar to results recently reported in Italy [Jongsma et al 2018], and is also in agreement with a recent published data showing no association

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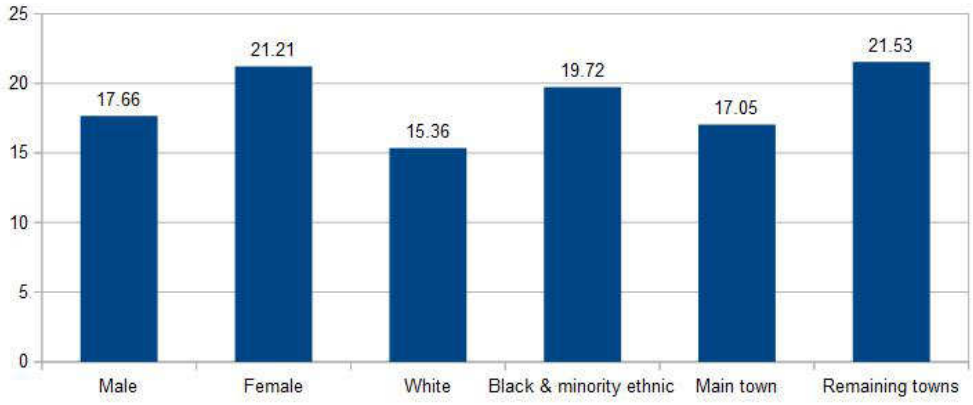
[37] Children in 1953 after a major flood disaster in Holland were more likely to develop psychosis than those born in two subsequent years.

[38] In Israel, children of mothers who experienced terrorism during pregnancy were more likely to develop adult schizophrenia than controls.

[39] There was also "leakage study" in the following year that reviewed the medical records of possible cases.

between urbanicity and psychosis in LMICs [DeVylder et al 2018]" (p727).

One reason here is that municipalities with lower population density in Brazil tend to show poor socio-economic indicators, so, Del-Ben et al (2019) admitted, "the observed association between urbanicity and risk of FEP in the region of Ribeirao Preto suggests a possible effect of socio-economically deprived contexts in the incidence of psychosis. It is important to highlight that this is an initial and exploratory study where we considered population density as a proxy of urbanicity; we did not include more direct measures of urbanicity" (p728).



(Data from Del-Ben et al 2019 table 2 p728)

Figure 9.2 - Adjusted incidence of FEP per 100 000 inhabitants in selected groups.

9.5. REPRODUCTIVE HEALTH

The reproductive health of women with schizophrenia (WS) is little studied. "Because of hyperprolactinemia [40]associated with first-generation anti-psychotics and segregation of many women with schizophrenia in institutions, childbearing rates in this population were low historically. With introduction of community-based care and fertility-sparing second-generation anti-psychotics, women with schizophrenia are now increasingly experiencing pregnancy" (Brown et al 2019 p736).

"Induced abortion", defined as "a pregnancy termination that is carried out by medication or surgery" (Brown et al 2019 p736), is one aspect of reproductive health. How do WS compare to the general population here?

[40] High levels of the hormone prolactin, which is normally associated with breast milk production, and the upshot is a "natural contraceptive".

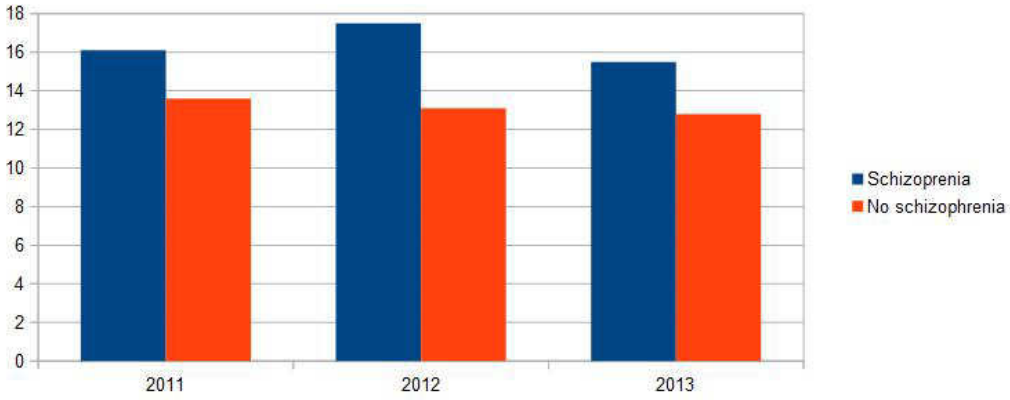
For example, a Finnish study (Simoila et al 2018) had mixed findings. The rate of induced abortion did not vary between WS (22.9 per 1000 follow-up years) and age- and place of birth-matched healthy controls (24.9). However, WS were more likely to terminate a pregnancy (60% vs 26%). This study involved over 1500 WS and nearly 8000 controls (Brown et al 2019).

Brown et al (2019) reported a larger study involving all female residents of Ontario in Canada aged 15-44 years between 2011 and 2013. The data were analysed in different ways - cross-sectional and longitudinal [41].

i) Cross-sectional comparison of WS and not in 2011, 2012, and 2013:

- Abortion rate per 1000 women of reproductive age: Overall, higher among WS (maximum 1.33 times greater), but due to large differences among younger women (15-24 years) (maximum nearly three times greater) (figure 9.3) [42].

- Abortion rate per 1000 live births: As above (overall maximum three times greater) (figure 9.4).

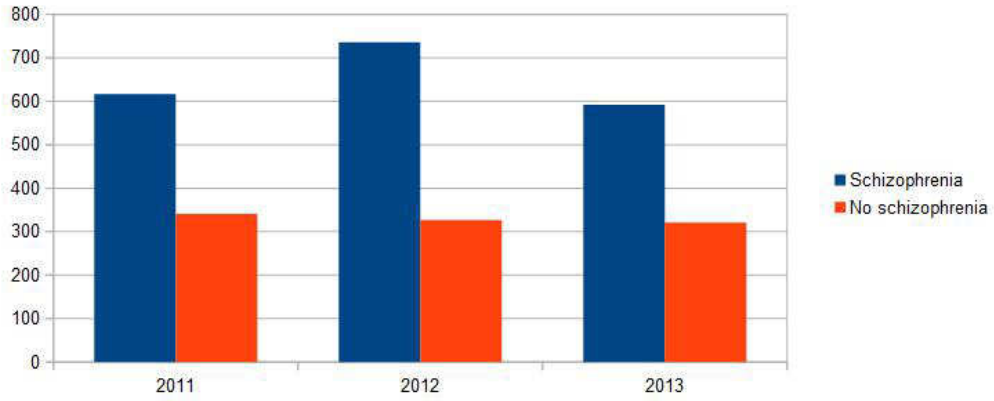


(Data from Brown et al 2019 table 1 p738)

Figure 9.3 - Abortion rate per 1000 women aged 15-44 years.

[41] The study did not include abortions outside the three-year window, private terminations or those by individuals who travelled outside of Ontario for the procedure, and women misclassified as another mental disorder than schizophrenia (Brown et al 2019).

[42] Note that some of the differences were not statistically significant because of small numbers in each age group (Brown et al 2019).



(Data from Brown et al 2019 table 1 p738)

Figure 9.4 - Abortion rate per 1000 live births among women aged 15-44 years.

ii) Longitudinal analysis over three years for predictors of abortion vs no abortion among WS: younger (<25 years), multi-parous (ie: not first pregnancy), and co-morbid mental disorder, including substance use. "Neighbourhood income quintile, region of residence, severity of schizophrenia, and stable and unstable chronic medical conditions were not associated with induced abortion risk" (Brown et al 2019 p738) [43].

In terms of the Finnish and Canadian data, the legal situation for abortions is different which limits the comparability (Brown et al 2019).

Other research has considered the reasons for the greater risk of abortion among WS. Brown et al (2019) explained that "compared with women without schizophrenia, women with schizophrenia are less likely to use contraception and, among those who do use contraception, are at greater risk for inconsistent or improper use. Data suggest that women with schizophrenia experience difficulty negotiating with male partners in the use of barrier methods and other family planning issues; 40% of women with schizophrenia report discussing family planning with their partners compared with 90% of women without schizophrenia [Pehlivanoglu et al 2007]. Women with schizophrenia are also more likely than those without to experience sexual assault and intimate partner violence, and to be under the influence of drugs or alcohol during sex" (pp739-740).

[43] A number of variables were controlled for (eg: neighbourhood income; severity of schizophrenia), but information was missing on others (eg: ethnicity; relationship status; intimate partner violence) (Brown et al 2019).

9.6. NEW TREATMENTS

Recent research has suggested a link between glutamatergic N-methyl-D-aspartate receptors (NMDAR) in the brain and psychotic symptoms. The upshot is potential new drugs (glycine reuptake inhibitors), like Bitopertin (Curtis 2019).

This drug is being tested. Bugarski-Kirola et al (2014) reported an early trial with some success. All groups improved in hospital, but more patients receiving bitopertin (and the olanzapine group) were ready for discharge at week 4 than in the placebo group (Curtis 2019).

Sarcosine is a dietary supplement which has similar effects. Small-scale trials with schizophrenia (eg: Strzelecki et al 2018) are varied: "In some studies sarcosine on its own or as adjunctive therapy is superior to placebo and in others there are no significant differences" (Curtis 2019 p697).

"Sarcosine differs from the drugs that can be prescribed to treat schizophrenia in that patients can obtain it for themselves... "It should be borne in mind that some patients may see sarcosine as a relatively attractive option. They may regard it as a 'natural' product and they may feel more autonomy in consuming something that they purchase for themselves rather than only taking a medication that is prescribed to them" (p697).

Curtis (2019) continued: "A potential risk is that patients might try taking sarcosine instead of, rather than as well as, their usual medication. This could well lead to deterioration or relapse and patients should be advised against trying this without close supervision. Another risk is that patients with unsatisfactory symptom control might try to self-medicate with high doses. It is unclear what, if any, problems this might cause but it seems sensible to advise caution" (p698).

9.7. APPENDIX 9A - ACEITUNO ET AL (2019)

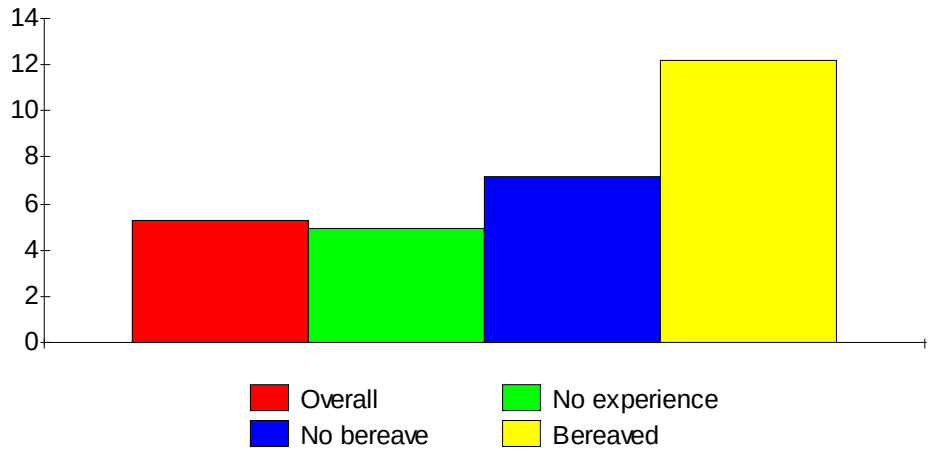
Aceituno et al (2019) found sixteen relevant studies of the cost effectiveness of EIP services with psychosis. Compared to standard care, EIP was rated as cost effective with FEP. But the studies reviewed were "heterogeneous and sometimes methodologically flawed" (p388).

For example, the studies used different methods to calculate cost effectiveness. Some studies calculated the saving per unit of quality-adjusted life years (QALYs) gained, and others the saving per year, and others the percentage difference in costs.

9.8. APPENDIX 9B - DEPRESSION AND GTE

Gao et al (2019) reported depression among bereaved survivors of the GTE 37 years after the earthquake. This study concentrated on the Jidong cohort (>9000 participants) (60 km from the epicentre) interviewed in 2013-14. Three groups were distinguished - no earthquake experience, earthquake experience with bereavement (n = 98), and no bereavement (n = 543).

After adjusting for variables like age at time of earthquake, the bereaved group were nearly three times more likely to be depressed than the no earthquake experience group (figure 9.5). There was no significant difference for non-bereaved earthquake experience group [44]. The risk of depression was higher for women in both the bereaved and non-bereaved earthquake groups (as compared to the no experience group), but not for men. Individuals aged eighteen years or older at the time of the earthquake (bereaved and non-bereaved) also had a higher risk of depression.



(Data from Gao et al 2019 table 1)

Figure 9.5 - Percentage of individuals with depression based on earthquake experience.

This study confirmed the long-term effect of the disaster. Gao et al (2019) explained: "The earthquake afflicted the survivors with not only the loss of their homes but also, more importantly, the tension and fear brought by the disaster itself, the loss of loved ones, the complete destruction of social networks and a sense of despair. During the long-term urban

[44] A difference between bereaved and non-bereaved survivors was also reported fourteen years after the MS Estonia Disaster (sinking in 1994 in the Baltic Sea) (Arnberg et al 2011). Non-bereaved survivors recovered from the trauma, whereas those with "traumatic bereavement" did not.

reconstruction process, all these effects of the disaster might lead to long-term adverse psychological effects on the survivors. In addition, the Tangshan earthquake broke out at the end of the decade of the Cultural Revolution. The consequences of the Cultural Revolution, which include a fragile economic foundation, low economic compensation, lack of societal acknowledgement and destruction of the healthcare service network, may have delayed recovery" (p6).

Other studies of the long-term impact of disaster and depression include:

- Alexander Kielland (Norwegian) oil platform collapse (in 1980) 27 years later (Boe et al 2011).

- Piper Alpha oil platform disaster in North Sea (in 1988) ten years on (Hull et al 2002).

While Green et al (1994), for instance, reported no long-term mental health problems among children at the time, seventeen years after the Buffalo Creek dam collapse in West Virginia (in 1972).

Gao et al's (2019) study had the following limitations:

a) No controlling for other traumatic events.

b) Only survivors still alive in 2013-14. "Premature death may be related to depression and disease" (Gao et al 2019 p6).

c) Did not include individuals who had moved away from the area.

d) No details about the anti-depressant medications taken.

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10. AIR POLLUTION AND MENTAL DISORDERS: CAUSE OR CORRELATION?

Ioannidis (2019) began: "The search for causes of mental diseases is notoriously difficult. Mental disorders are challenging to define and measure. Non-genetic factors may be a major determinant for their occurrence. However, the implicated exposures are heavily correlated and/or confounded. Moreover, time lag, dose–response, and susceptible periods in life can only be speculated about" (p1). These points are seen in the idea of air pollution causing mental disorders, though recent research in the USA and Denmark by Khan et al (2019) found associations.

The physical impact of air pollution has been widely researched, including historical events like the "1952 Great London Fog" event (eg: Logan 1953) ("in which a multiple day temperature inversion concentrated coal-based air pollutants and resulted in thousands of deaths"; Khan et al 2019 p2), or the New Delhi smog in 2017 (Terry et al 2018).

Khan et al (2019) analysed two large datasets:

a) IBM Health MarketScan Commercial Claims and Encounters Database 2003-13 - Over 151 million health insurance claims in the USA. The researchers concentrated on bipolar disorder, major depression, personality disorder, schizophrenia, epilepsy, and Parkinson disease.

b) Danish national treatment and air pollution registers - Around 1.5 million individuals born between 1979 and 2003. Research was concentrated on bipolar disorder, schizophrenia, personality disorder, and depression.

In the USA, air quality was significantly associated with bipolar disorder. For example, the worst air quality according to US Environmental Protection Agency scores was associated with an increase in bipolar disorder of about one-quarter. There was some association for major depression.

In Denmark, air pollution experienced up to 10 years old was associated with the four mental disorders studied. For example, the rate of schizophrenia in adulthood was 1.5 times higher in the worst air polluted septile (top 7th) compared to the best quality septile, and bipolar disorder was 1.3 times higher.

In explaining the relationship between air pollution and mental disorders, Khan et al (2019) offered three pathways from studies with animals (eg: healthy feral dogs living in cities; Calderon-Garciduenas et al 2002):

i) Indirect - Fine particulate matter (PM) in the lungs triggers inflammation, which "results in the production of brain cytokines, activation of microglia, and genomic oxidative damage" (Khan et al 2019 p15). These all have an impact on the brain.

ii) Direct - Reactions of the immune system to the PM in the body impacting on the brain.

iii) Direct - Breathing in pollutants through the nose, so the "olfactory neurons transport fine PM directly to the brain, producing direct toxic damage to the limbic system and brain degeneration due to oxidative stress" (Khan et al 2019 p15).

All three pathways impact on the brain, which leads to the psychiatric problems.

Ioannidis (2019) evaluated the Khan et al (2019) study: "Both datasets harness enormous sample sizes, but this offers no guarantee of validity. Analysis of big data can draw absurd conclusions because of fundamental deficiencies in the quality of the data. The US database is approximately 100-fold larger than the Danish one, but the latter is of better quality" (p1).

Air pollution exposure was measured with eighty-seven variables in the US data, but only fourteen in the Danish case. "It is uncertain whether it is better to have more or fewer variables to define air pollution, let alone if only some (and if so, which) of these correlated variables might cause disease" (Ioannidis 2019 p2).

In establishing causation from epidemiological (observational/correlational) data, Hill (1965) proposed a set of criteria (Ioannidis 2019) (table 10.1):

- Strength of association.
- Consistency of findings across datasets.
- Specificity - establishing a specific relationship between A and B. "Patterns of causation are likely to be complex and non-specific because these diseases are correlated and overlapping between each other, and the same applies for environmental exposures" (Ioannidis 2019 p2).
- Temporality - the order in time. Ioannidis (2019) explained: "Measurements of exposure to air pollution mostly precede the psychiatric diagnoses. However, exceptions may exist, eg: IBM MarketScan diagnoses made in 2003–2005 may predate some air pollution exposure data. Moreover, recorded dates of psychiatric disease

diagnosis may not represent disease onset. The disease process may have started years earlier" (p3).

- Biological gradient (or dose-response) (ie: greater pollution leads a greater effect on mental health).

- Plausibility - a biological mechanism between air pollution and mental disorders. Ioannidis (2019) was unsure about animals experiments and studies: "the problem with such in vivo and in vitro data is that almost always, they are not systematically collected. Their publication is usually driven by the urge to present convincing 'narratives'. Selection biases in this literature are probably rampant but extremely difficult to quantify, given the lack of registration or widely accepted rules on what should be reported" (p3).

- Coherence - agreement between different methods, particularly experimental findings and epidemiological data.

- Experimental evidence as the nest for establishing causality because of the control of variables.

- Analogy - similarities between observations and other associations.

Criteria/Consideration	*Mental Health*	*Mortality*
Strength	+/–	+/–
Consistency	– (+ for bipolar)	+
Specificity	–	–
Temporality	+/–	+
Biological gradient	+	+
Plausibility	+/–	+
Coherence	(+)	+
Experiment	–	–
Analogy	(+)	(+)

+, criterion mostly fulfilled; +/–, criterion fulfilled but caveats exist; –, criterion not fulfilled; (+), criterion likely to be at best weakly informative in this setting.

https://doi.org/10.1371/journal.pbio.3000370.t001

(Source: table 1 Ioannidis 2019)

Table - Application of Hill's (1965) criteria to the Khan et al (2019) study.

During peer review of the Khan et al (2019) study before publication, there was disagreement about the

methodology and the findings. Ioannidis (2019) complimented Khan et al for responding to the criticisms, and for having "offered a brilliant exploratory analysis with interesting hypotheses-generating hints for bipolar disorder and possibly other psychiatric diagnoses" (pp5-6).

Overall, the evidence was stronger for the link between air pollution and bipolar disorder and schizophrenia, but transparency and reproducibility will help. "It has now become evident that in many observational data sets, there are so many different ways to analyse the same data on the same question that the resulting spread of results ('vibration of effects'; Guloksuz et al 2018) can allow almost any conclusion to be generated. Therefore, trust increases when the data are publicly available so that other analysts can examine them, when other analysts (including those with contrarian viewpoints) have analysed them and reached the same conclusions, when the main inferences are not substantially modified with different modelling and analytical assumptions, and when it has been pre-specified how analyses will be performed in a protocol that is ideally pre-registered" (Ioannidis 2019 pp4-5).

APPENDIX - MAGNETITE

Maher et al (2016) reported the "abundant presence" of magnetite nanoparticles in the human brain via air pollution. Magnetite is a natural iron-oxide mineral, and is released in air pollution. "As a result of atmospheric circulation, the airborne particles in a given environment can be derived from both local and distant sources, such as dry lakes, deserts, fires, smoke stacks, traffic, or mining operations. Magnetite is an abundant constituent of atmospheric PM [particulate matter] pollution, especially in the urban environment, where it has been identified in diesel exhaust, as brake-abrasion particles, in the air of underground stations, along railway lines, at welding workplaces, and in the emissions from industrial combustion processes" (Giere 2016 p11986).

APPENDIX - USE OF MASKS

Huang and Morawska (2019) questioned the effectiveness of flimsy gauze face masks for combating air pollution. Though these masks are commonly worn in some parts of the world, like China, individuals may stay longer outside in the pollution because of the false sense of security of the mask. These are medical masks usually, which were designed to capture droplets in the breath or air not PM. "Many factors need to be

considered, including the sizes and sources of particles, the type of mask and the face shape and behaviour of the wearer" (Huang and Morawska 2019 p30).

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