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More Bioethics and Health Topics

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A complete listing of his writings at http://psychologywritings.synthasite.com/.

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1. REPRODUCTION, PREGNANCY AND CHILDBIRTH ISSUES

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1.1. TRANSNATIONAL REPRODUCTIVE TRAVEL

Transnational reproductive travel (TRT) "flourishes, in part, by capitalising on differences in legal regimes, wages and standards of living, and cultural and ethical norms" (Baylis and Downie 2014 p1).

TRT is partly about "travel to places where there are no (or very few) restrictions on what reproductive goods (ie: gametes) and services (ie: gestational services) can be purchased" (Baylis and Downie 2014 p1), but also for other reasons like cost, better quality of services, or accessing services not available at home generally or for some groups.

The complexity of TRT is seen in cases like a gay male Israeli couple who "contracted with an Indian woman to bear and birth a child for them, using the egg of another Indian woman whom they selected from an online database" (Baylis and Downie 2014 p2).

Women are at the heart of the TRT industry, particularly poorer ones who offer their "services". Thus, Baylis and Downie (2014) argued, the need for a feminist perspective. These authors highlighted some key ethical issues to address, including whether women in poorer countries benefit from increased employment opportunities or risk exploitation and coercion, the payment of women for eggs, the motivations of individuals who engage in TRT, and rules about the import and export of reproductive materials.

Martin (2010) introduced the idea of self-sufficiency in reproductive resources. This is the provision of reproductive goods and services (ie: donor gametes and gestational surrogacy) for all citizens in a country, such that individuals do not need to travel abroad. It is assumed that reproductive goods and services at home are provided within a framework of mutual care and relatedness, which Martin and Kane (2014) called the POLIS model: "Public health, for the prevention and treatment of needs; Organisation, with a national authority taking responsibility for oversight and co-ordination of various strategic elements and infrastructure; Legislation, to protect interests of intending parents, donors and children; Information, through systematic and transparent collection of data to inform policy and practice through quality and safety evaluation; and Societal engagement, through debate and education to encourage solidarity and enfranchise all members of the community in opportunities to donate or receive resources when needed" (quoted in Baylis and Downie 2014).

Attempting to regulate what is a global marketplace in reproductive goods and services has left regulators as "dogs with no teeth" (Carney 2011). On this basis, Crozier et al (2014) argued that commercial transnational gestational surrogacy should be recognised as legal paid work. "The pivotal issues then are how to value and compensate social reproductive labour that includes much unpaid or invisible biological and emotional labour, and how to establish a fair wage for surrogates so that these women don't find themselves in that uneasy space between potential exploitation and economic gain" (Baylis and Downie 2014 p4).

Ballantyne (2014) did not see all poorer women who provide reproductive services as exploited. She distinguished between "harmful exploitation" ("when a person is made worse off by her participation in some activity/transaction"; Baylis and Downie 2014), "coercive exploitation" ("when a person is deceived or forced into participation in some activity/transaction"), and "mutually advantageous exploitation" ("when a person receives less than her fair share of the benefits from participation in some activity/transaction") (Baylis and Downie 2014).

1.2. REPRODUCTION TECHNOLOGIES

Cavaliere and Palacios-Gonzalez (2018) began with the observation that "the main purpose of bioethics is to demarcate morally acceptable applications of biomedical technologies" (p835). They gave the example of genetic modifying interventions, which "bioconservatives" (eg: Sandel 2009) see as morally acceptable for curing disease, but not for enhancement (eg: increasing height or strength) (appendix 1A).

Reproductive screening techniques, like pre-implantation diagnosis, and reprogenetics techniques (eg:

mitochondrial replacement techniques; MRTs [1]) are increasing in use. MRTs replace eggs containing mitochondrial DNA abnormalities (eg: leading to neuromuscular disease) with eggs without the abnormalities (Cavaliere and Palacios-Gonzalez 2018). Put simply, the healthy DNA of the mother is placed in another egg (of the woman herself or more likely another woman) with healthy mitochondrial DNA, and fertilised by the sperm from the intended father. Technically, there is the DNA of three individuals in some cases. There are different assisted reproductive techniques for doing this process.

Arguments against MRTs include the limited information about the health and well-being of children produced in this way (eg: Baylis 2013).

Supporters of MRTs emphasise its therapeutic use (eg: Wrigley et al 2015) in an argument that goes like this: "we are morally required to prevent the suffering and premature death of innocent individuals. MRTs can prevent the suffering and premature death of existing innocent individuals. Hence, we are morally required to carry out MRTs" (Cavaliere and Palacios-Gonzalez 2018 p837).

There are differences between MRTs as therapy and as "enhancement" as seen in the case of lesbian couples who could use the technology to produce a child that genetically related to both women. Cavaliere and Palacios-Gonzalez (2018) summed up some of the negative consequences of this case proposed by critics (genetic-relatedness objection by consequences; GRO-c): "concerns for the resources needed to develop new technologies and how these resources may be employed for other more pressing medical needs; the reinforcement of ideas on the importance of genetic kinship for family-making and on the role of genetics more generally to determine our identities; the medicalisation of a social preference and the reinforcement of the two-parent (heterosexual) genetically based model of the family (ie: bionormative conception of the family)" (p840).

Cavaliere and Palacios-Gonzalez (2018) considered each of these arguments, and concluded: "We do not want to defend here the wish for genetic kinship as an absolute good that trumps other considerations and nor do we believe that reinforcing a family-making process that includes a genetic element is without costs. However, we remain convinced that these considerations cannot be employed solely to bar access to MRTs by lesbian couples, a group with an already limited range of reproductive options, as this would be immoral from an equality standpoint" (p841).

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[1] Newson and Wrigley (2017) preferred the term "mitochondrial targeting techniques".

Some feminists have argued that assisted reproductive technologies (ARTs) "increase rather than decrease women's subservience to biological destiny", and reinforce conventional gender roles (Meskus 2015).

Such technologies have been explored in relation to women's agency. Meskus (2015) discussed "agential multiplicity" in the study of women in Finland undergoing in vitro fertilisation (IVF) via a website supporting such individuals (ie: peer support) [2].

Firstly, there is hormonal therapy to stimulate the growth of follicles in the ovary. "When preparing for the treatment, purchasing medication in advance is an important event for many. With the medication ready and waiting in the cupboard, the longed-for 'action time' feels much closer. When one peer group member writes: 'I'm so impatient. I already went to the pharmacy today and bought the drugs for the next treatment', another member replies: 'Aren't the treatments so much closer when you have the drugs at hand!'" (Meskus 2015 p76).

Some of the women on the website referred to the "hatchery" at this point, as they waited for "egg collection". One writer said: "The harvest was 20 eggies [eggs], and now we're on tenterhooks whether we had enough spermies [sperm] and how many were fertilised" (pp76-77).

The eggs are fertilised in the laboratory, and then grown to see which will be viable embryos before transfer to the woman. One woman wrote: "Tomorrow the biologist will call and tell us how the eggs have fertilised. The day was quite awful, but we survived it! Now we are nervously waiting to hear how the embryos are doing!" (p77).

In Finland, one or two embryos are transferred to the woman, and then comes "the days of torment" waiting to see if the embryo(s) develops in the womb. The process of implantation in the uterus wall was described with expressions like "'the pal takes a grip' or with a wish that 'the traveller has really sticky paws'" (Meskus 2015 p78).

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[2] IVF has created a new ethical situation because "more IVF embryos are created per cycle than can reasonably be transferred in the cycle in which they were created. While practice differs between IVF clinics, in many countries the current norm is to transfer no more than three IVF embryos per cycle (unless there are sound clinical reasons to increase this to four or five), and increasingly there is a move towards single embryo transfer (which is now legislated in some jurisdictions). IVF embryos not transferred in the cycle in which they were created can be discarded; donated or sold for reproductive, teaching, or research use by others; or cryopreserved (hereafter, frozen) for later own reproductive use (provided they are deemed suitable for transfer). If, at some later date, these frozen IVF embryos are no longer wanted by the prospective social parent(s) (i.e., those who planned to care for the child(ren) born of IVF and embryo transfer), then they can be transferred to a third-party for their reproductive use; an IVF clinic to improve assisted human reproduction or to provide instruction in assisted human reproduction; or a research team to pursue basic science or clinical research" (Baylis 2011 p357).

Meskus (2015) noted the anthropomorphism here (ie: "endowing cellular entities with personhood"). This was part of the embodied experience of undergoing IVF treatments, and the agencies that the women do and do not have during the process.

Camporesi (2018) noted that "scientists seem to always have to justify research on human embryos in terms of learning more about the causes of miscarriage and infertility" (p8). This is what Thompson (2005) called "strategic naturalising" - ie: "couching the research in terms that are appealing to the public" (Camporesi 2018). Camporesi (2018) argued for the expansion of "the justification of said research to include shedding light on the early development of human embryos outside the human body, about which we know very little? Or what if we said that research on human embryos is particularly interesting as it could illuminate the potentialities of ectogenesis, ie: of growing an embryo (later, a foetus) outside the human body?" (p8).

Many of the rules about research on embryos are presented as a compromise between different moral positions [3]. However, critics have suggested that certain of these rules are not useful as in "a speed limit faster than anyone could drive is not a compromise, not indeed is it a rule in any meaningful sense" (Nuffield Council of Bioethics 2017 quoted in Camporesi 2018).

Often the technical feasibility view wins out in terms of morals and laws (ie: "when something is possible, somebody, somewhere will do it"; Camporesi 2018), but Cavaliere (2017), for example, challenged this idea as "an optimistic view of scientific progress, research and technologies", among other arguments.

1.2.1. Choosing a Boy

Neogi et al (2017) described a sad situation in India where tradition and culture mean that parents have "the need to have a son by all means" ("son syndrome"; Rai et al 2018) (table 1.1) [4] [5]. Sex selection techniques

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[3] The moral status of the embryo is debated between the extremes of human "from the moment of conception" (eg: Catholic Church) to "the developing human embryo is just human material; it is a collection of cells, similar to skin, blood, bone marrow, and other bodily tissues; it has no moral status" (Baylis 2011 p358).

[4] Estimates of the gender imbalance globally due to the "son syndrome" includes 80 million fewer females because of selective abortions and infanticides, while in China, for instance, there are 117 boys to every 100 girls born (Rai et al 2018).

[5] "Given the economic and social ramifications of raising a daughter in the developing world, people have been opting for different primitive and advanced scientific techniques to ensure a small family size with the only child being a boy. Apart from gender selection being harmful to the woman and her growing foetus, how much these attribute to the skewing of sex ratios in India and elsewhere remains

to aid this desire include a specific diet, or intercourse on particular days of the month, while "infanticide received social sanction in some communities" (Neogi et al 2017) [6].

- 933 women to 1000 men India in 2001 census (Manchanda et al 2011).
- Based on data of children born at one hospital in Dehli, in 2008-9 (n = 3975 mothers), Manchanda et al (2011) found a sex ratio of 806 girls to 1000 boys. If the mother already had a girl, the sex ratio for girls was 720, and 178 for the third child after two previous girls.
- Accepting that "parents are unlikely to incriminate themselves by telling the investigator about ante-natal sex determination", 0.5% overall admitted to taking traditional medicine, compared to 40% of those with two previous girls.
- Sen (2003) distinguished between "mortality inequality", including female infanticide, and neglect of girls leading to early death, and "natality inequality" (eg: termination of female foetuses after sex determination tests).

Table 1.1 - Example of India.

"Sex-selection drugs" (SSDs) prescribed by traditional healers, for example, are also taken in large amounts during pregnancy. These "medicines", a mix of herbal and non-herbal ingredients, are consumed by nearly half of pregnant women to get a male child if she already has two daughters in India, for instance (Neogi et al 2017).

But SSDs are not benign, with a link to a quarter of babies born with birth defects and around 16% of stillbirths in parts of India. Chemical analysis of SSDs showed very high levels of phytoestrogens and testosterone (Neogi et al 2017).

Rai et al (2018) reviewed the techniques and measures (traditional and medical) used around the world to choose a baby's gender.

1. Techniques based on natural methods:

i) Timing of intercourse:

a) Shettles method - Y-chromosome sperms (Y-sperms) have a better chance of fertilising the egg in a more

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unexplored and hence unknown" (Rai et al 2018 p557).

[6] "Sex selection is comparable to racial preference, which is strongly prohibited under human rights. This brings up another question of demeaning the opposite sex’s value in society" (Rai et al 2018 pp555-556).

alkaline environment (ie: closer to ovulation). The upshot is intercourse on the day of ovulation is recommended for a male child. Other advice includes that men wear loose clothing because the heat generated with tight underpants can kill Y-sperm, and intercourse should involve rear entry as the sperm has a lesser distance to travel. This method claims an 80% success rate for boy children (Rai et al 2018).

b) Whelan method - This is the biochemical opposite to the Shettles method, and recommends intercourse 4-6 days before ovulation (ie: less alkaline reproductive environment).

c) Billings ovulation method - Intercourse on the peak day of fertilisation will provide an environment most beneficial to fast moving Y-sperms. Claims a 95% success rate (Rai et al 2018).

ii) Pre-conception diet - A woman's diet will influence the acidity of the reproductive tract, and an alkaline environment is recommended for Y-sperm. Foods rich in sodium, potassium, and protein are thus advised (eg: meat, eggs, banana).

iii) "Pregnancy kits" (eg: "Smart Stork") - A combination of techniques include measurement of acidity of reproductive tract, diet, and herbal supplementation. Claims a 95% success rate (Rai et al 2018).

iv) "SSDs".

2. Techniques based on assisted reproductive technology:

i) Sperm sorting - From a sample of semen, the Y-sperms are separated before artificial fertilisation. Success rates of 75-80% (Rai et al 2018).

ii) In vitro fertilisation pre-implantation genetic diagnosis (IVF PGD) - Embryos are developed through IVF and male eight-celled embryos are implanted in the woman. A success rate of almost 100% (Rai et al 2018).

The side effects of IVF PGD include vaginal infections, and disorders like ovarian hyperstimulation syndrome from repeated cycles of hormonal supplementation and egg extraction procedures.

There are ethical concerns about the embryos created and never implanted in the woman (Rai et al 2018).

1.2.2. Fertility Preservation

Paton (2018) explored the issues of oncofertility (cancer and fertility) and fertility preservation (FP) (eg: storing eggs for after cancer treatment) in eleven detailed interviews with women diagnosed with cancer in Britain. Six of the women were aged over 35, and two key themes emerged from these interviews.

a) "Avoiding early menopause" - The cancer treatment had induced early menopause for these women, and in "discussing FP techniques in the interviews the women understood these techniques as possible options that might have helped them avoid their early menopause. In many cases this was a misunderstanding of what FP offers, however it did not change the importance that FP had for the women. Avoiding the menopause was desirable for all the women interviewed as they felt that early menopause would be (and was) a difficult burden to bear for their physical and mental well-being post-cancer" (Paton 2018 p97).

Paton (2018) noted that by "expressing desires to retain their fertility and ovarian functions it is possible that these women were also expressing desires to retain their femininity" (p99). This is seen in "Monica's" comments when doctors recommended double mastectomy and hysterectomy (and consequently early menopause): "It just makes you feel like there is nothing left that makes you a woman. Nothing that defines you as a woman. Everything that is textbook defines you as a woman is gone. To get the menopause as well is just icing on the cake!" (p98).

b) "HCP [health care professionals] assumptions about who wants fertility preservation" - "Angela's" comments are a good example here: "But the subject of fertility... Nothing was said at first... I'd hung on to my ovaries deliberately... and [the doctor] said, 'Well chemo is going to stop your ovaries working... and that will be it'... nobody said 'Do you want to hang on to your fertility'... nothing was actually mentioned" (p99).

She continued: "I would have wanted someone to make a bigger effort to talk about fertility, not just say 'Oh, this is going to happen'... I would have seriously wanted someone to talk about saving some eggs somewhere along the line... I would have wanted someone to save my fertility" (p99).

Receiving information about their disease and treatment options would aid women in "informed, autonomous patient decision-making". "By holding back information they think would be irrelevant, HCPs may be forcing patients to make decisions from a restricted or incomplete set of options" (Paton 2018 p101).

Paton (2018) summed up: "The women in this study understood 'fertility' to go beyond child-bearing; preserving fertility was about choice preservation for the future, and in particular, not going into early menopause after cancer" (p102).

1.2.3. The Future

El-Toukhy (2019) reflected on issues for reproductive medicine in the 2020s, including:

i) Continued improvement of success rates of IVF - eg: 14% live-birth rate per IVF cycle in 1991, and 26-28% in 2016 in the UK (UK Human Fertilisation and Embryology Authority 2016 quoted in El-Toukhy 2019).

ii) Safety of the mother and baby in IVF treatment.

For example, infants born following ARTs have an increased risk of lower birth-weight, and of being small for gestational age compared to naturally conceived babies. This is partly due to multiple pregnancies with ARTs, but these risks are still present for single births (Bay et al 2019a).

But do these children continue to have height and weight problems as they grow? IVF was introduced in 1978, so the early cohort has grown up by now. Bay et al (2019a) found twenty studies on the long-term development of individuals born via IVF and other similar techniques (nearly 4000 individuals).

With a mean follow-up of 22 years, there was no significantly lower weight or height in childhood between IVF- and naturally-conceived individuals found. Any differences were only up to pre-school age. In other words, infants been with lower birth-weight catch up.

iii) The provision of good-quality evidence for a technology before its use in clinical practice.

iv) Ante-natal monitoring - eg: a higher incidence of stillbirths in low-risk singleton pregnancies after fertility treatment than in naturally conceived pregnancies (Bay et al 2019b).

One technique of ART is frozen embryo transfer (FET), which was introduced in 1984, and there have been concerns about the long-term effects on children conceived by this method (eg: epigenetic modifications which may affect cognitive development) (Spangmose et al 2019).

Spangmose et al (2019) reported on a cohort of children in Denmark conceived by FET between 1995 and 2001. Now adolescents (n = 423), they were compared to individuals conceived by fresh embryo transfer (ET) (n = 6072) on academic performance. The two groups were similar in profile (eg: low birth weight). In their analysis, the researchers adjusted for variables like maternal age, and parents' education level and employment. Other studies have found that maternal IQ predicted child's IQ, but this information was not available here (Spangmose et al 2019).

There was no difference between the two groups on overall mean school test scores at 15-16 years old, nor for individual subjects like mathematics and English.

The test scores were a proxy for cognitive development, though "the Danish 7-point grading scale may lack the sensitivity to detect subtle but clinically relevant differences in cognitive development" (Spangmose et al 2019 p265).

A limited number of similar studies have previously been performed (Spangmose et al 2019):

a) Mains et al (2010) - Individuals conceived by FET in Iowa, USA, showed no difference in cognitive performance aged 8-17 years old to fresh ET children. But no adjustment was made for parental background, and the sample was small (n = 57) (Spangmose et al 2019).

b) Sandin et al (2013) - Among a Swedish cohort, FET by ICSI (intra-cytoplasmic sperm injection), but not FET by IVF, was a significant risk for cognitive impairment compared to standard IVF with fresh ET. The sample was large (n = 4422 FET children), and covered individuals aged up to their 20s. The analysis adjusted for parental psychiatric history, but not socio-demographic factors (Spangmose et al 2019).

c) Bay et al (2013) - No difference between FET-conceived and naturally conceived children in mental, behavioural and emotional disorders aged 8-17 years old in Denmark (n = 686 FET children).

1.3. GENETIC TESTING

Determining the sex of a foetus can be done by a search for Y-chromosomes in maternal blood. Their presence is a sign of a male foetus, as Y-chromosomes are only present in the cells of males, and their absence a female foetus.

Non-invasive prenatal testing (NIPT) was introduced in 2011, and it is based on the knowledge that cell-free foetal DNA from the placenta is circulating in the pregnant woman's blood (Birko et al 2018).

Santa Rita et al (2018) reported a test based on blood collected by fingertip puncture of the mother (ie: non-invasive) with 101 pregnant volunteers 8-20 weeks gestational age. Initially, there were false-positives for male DNA, which were maternal skin contamination (ie:

male DNA on the fingertip from external sources- eg: contact with male partner). Skin cleansing before the test was thus important. After resolution of this issue, the fingertip blood test proved 100% accurate at predicting the sex of the child.

This test collected capillary blood as opposed to venous blood sampling (from a vein in the arm, say). The authors listed three advantages of their method: "(a) It is considered less invasive and more comfortable to the mother allowing samples to be collected from women with phobia of needles or high anxiety about giving blood, (b) it requires a smaller amount of blood and allows sampling in cases where phlebotomy may be difficult, and (c) it can be performed quickly and easily allowing samples to be collected in areas where there is no phlebotomist present (eg: rural areas)" (Santa Rita et al 2018 p622).

Birko et al (2018) considered the ethical issues involved with such routine NIPT. On the positive side, testing can occur earlier in the pregnancy, and with greater accuracy. There is the possibility of whole-genome sequencing from such NIPT in the future.

"Paradoxically, while being touted as enhancing choice, prenatal screening has, from its infancy, been criticised for undermining parents' autonomy" (Birko etal 2018 p3). Societal pressure to screen, to diagnose, and then to terminate a pregnancy challenge the autonomy of the parents. "Many people, when faced with the decision of whether to pursue prenatal screening, may believe that it would be irresponsible to decline participation in a publicly funded program seemingly designed for the benefit of society as a whole. After all, the implementation of such tests by the medical system 'establishes screening as a legitimate use of scarce medical resources and thereby surreptitiously underlin[es] its importance' [Seavilleklein 2009]" (Birko et al 2018 p4).

There is also the implicit assumption that "women whose foetuses are found to be affected will abort the pregnancy, since for most of the conditions for which screening can be done there is, at present, no treatment" (Lippman 1985 quoted in Birko et al 2018).

The amount of information provided by prenatal screening can produce "information overload", and thus anxiety and stress rather than improved choice. "Additionally, this 'bewilderment' applies not only to results provided by prenatal screening but also to information provided about prenatal screening at various stages of the process. Hence, while Press and Browner (1994) pointed out that prospective parents prefer not to dwell on the social and ethical dimensions of prenatal screening, Kukla (2005) suggested that parents often make a conscious choice to defer decisions to healthcare practitioners as a way of avoiding the burdens of information overload and decision-making regarding screening" (Birko et al 2018 p6).

Seavilleklein (2009) concluded that "'there is incontrovertible evidence that women are not making free informed choices about prenatal screening', that 'whether choice is interpreted narrowly as informed consent or broadly as relational, there are reasons to worry that women's autonomy is not being protected or promoted by the routine offer of screening' and that 'incorporating the offer of prenatal screening into routine prenatal care for all pregnant women is not supported by the value of autonomy and ought to be reconsidered'" (quoted in Birko et al 2018).

1.4. CHILDBIRTH

"Childbirth can be extremely painful. Thus the provision of effective pain relief during labour is an important element of a positive maternal experience" (Wilson et al 2018 p662). But what pain relief to use?

Wilson et al (2018) reported a randomised controlled trial (RCT) in the UK comparing the opioid drug pethidine injected into the muscles in the body and remifentanil (synthetic opioid) as intravenous patient-controlled analgesia (PCA).

The RCT was called RESPITE, and was open-label across fourteen maternity units. Between May 2014 and September 2016, 401 women were randomised to remifentanil (intervention group) or pethidine (control group) after consenting to participate. The primary outcome measure was the need for further pain relief in labour (ie: epidural analgesia).

In the remifentanil group, half as many women had an epidural as the control group (19 vs 41%). Self-reported pain was significantly lower in the intervention group as well.

Wilson et al (2018) reflected on the key weakness of the study - ie: "the inability to mask clinical staff and women to the treatment allocation, made inevitable by the dissimilar technical aspects of intravenous PCA and intramuscular injection. Masking trial participants and clinical staff to the group allocation was impossible without the use of a double-dummy design and sham interventions, which would have included intravenous PCA with an inactive placebo and an inactive intramuscular injection. These possibilities were explored thoroughly at the study design stage. Sham interventions were ultimately rejected as a result of strongly negative opinions expressed by women in the Patient and Public Involvement group assisting in the study design. Clinical staff were also unwilling to administer inactive, invasive procedures required for sham intervention or control" (p669). A limitation of open-label RCTs is, thus, that double-blinding is not possible.

Wilson et al (2018) responded: "The limitations of an open-label study design in terms of potential for performance or ascertainment bias were mitigated by precluding research staff from any involvement in the request for or decision to proceed to epidural, or any additional or subsequent clinical care of the mother and baby, after randomisation" (p669).

Sandall et al (2018) began: "Although caesarean section (CS) can be a life-saving intervention for mothers and children, it can also lead to short-term and long-term health consequences" (p1349). These researchers reviewed the evidence on the health consequences of CS.

1. Mother's health - "The absolute risk of maternal death associated with CS is known to be low in high-resource settings, and higher in low-resource settings" (Sandall et al 2018 p1350).

Increased risk of severe acute maternal morbidity (SAMM) (eg: uterine rupture). Also a higher risk of adverse outcomes in subsequent pregnancy than with vaginal birth.

There is some evidence of psychological effects, like guilt because the women could not give birth vaginally, less satisfaction with the birth experience, and the presence of a scar.

2. Infant's health - "There is emerging evidence that babies born by CS have different hormonal, physical, bacterial, and medical exposures, and that these exposures can subtly alter neonatal physiology. Short-term risks of CS include altered immune development, an increased likelihood of allergy, atopy, and asthma, and reduced intestinal gut microbiome diversity" (Sandall et al 2018 p1349).

Where there is no health risk to mother or child, birth before 39 weeks of gestation is associated with more negative outcomes than delivery at full term (Parikh et al 2014). This conclusion, however, is "derived largely from observational studies in which labour induction was compared with spontaneous labour" (Grobman et al 2018 p514).

Grobman et al (2018) reported the ARRIVE trial (A Randomised Trial of Induction Versus Expectant Management), where over 6000 low risk pregnant women in the USA were randomly assigned to undergo labour induction at 39 weeks (induction group) or wait until 41 weeks (expectant management group). The outcome measure was perinatal death or severe neonatal complications.

In the induction group 4.3% of cases had negative outcomes compared to 5.4%. "These findings contradict the conclusions of multiple observational studies that have suggested that labour induction is associated with an increased risk of adverse maternal and perinatal outcomes" (Grobman et al 2018 p522).

The number of women who had CS was significantly lower in the induction group.

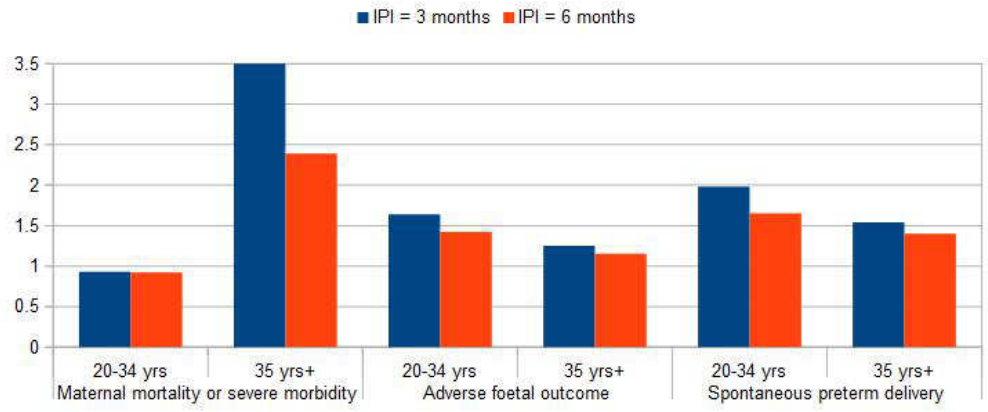
The inter-pregnancy interval (IPI) is the time between delivery of one child and conception of the next, and a period of less than eighteen months is associated with increased risks for the second pregnancy. A number of studies have shown this relationship generally (Schummers et al 2018).

Schummers et al (2018) concentrated on older mothers(ie: 35 years and over) in a study of Canadian data. All women with at least two consecutive singleton pregnancies in British Columbia between 2004 and 2014 were studied based on the age of the mother (<20 years vs 20-34 years vs ≥35 years - 7184 vs 123 821 vs 17 539 pregnancies). The IPIs were categorised in six-monthly groups (eg: 12-17 months).

The increased risks of negative birth outcomes for IPIs of six months or less varied with age:

- Maternal morbidity or severe morbidity - greater risk for older women.
- Adverse foetal outcomes - greater risk for 20-34 year-olds.
- Spontaneous pre-term delivery - greater risk for 20-34 year-olds.
- Low birth weight - no age difference (figure 1.1).

Short IPI, overall, was more of a risk for birth outcomes than the age of the mother.



(Data from Schummers et al 2018 table 3)

Figure 1.1 - Adjusted risk ratio for short IPIs based on age (where IPI of 18-23 months = 1.00)

Methodological strengths (and weaknesses) of this study include:

1. Large population cohort.

But: One province in one country.

2. Use of validated medical records.

But: Misses individuals not in health databases.

3. IPI calculated by subtracting birth date of first child from birth date of second child, and adjusting for gestational age at birth.

But: Calculation of IPI algorithm-based estimate including last menstrual period.

4. During statistical analysis, confounding variables (eg: socio-demographic variables, smoking during pregnancy, neighbourhood income) controlled for.

But: Variables not controlled for or no information (eg: maternal alcohol use, pregnancy environment, stress).

5. Excluded spontaneous or induced abortion, stillbirth, and neonatal death cases.

6. Multiple birth outcomes used, and all with standardised definitions (eg: World Health Organisation's International Classification of Diseases).

But: Some outcomes small - eg: 5 maternal deaths in whole sample.

7. IPIs categorised in five groups - <6, 6-11, 12-17, 18-23, and ≥24 months.

But: no information on IPI as choice or not (pregnancy intention).

But: Three age categories not of equal size (ie: less pregnancies after 34 years old). Why use age categories chosen, and not others?

1.5. CONTRACEPTION

Fertility awareness-based (FAB) methods of contraception are based on knowing when a woman is fertile each month and abstaining from sex at that time. FAB methods use indicators like basal body temperature, as in the case of the "Natural Cycles" smartphone app, which also records dates of menstruation (and luteinising hormone tests results as optional extra) (Berglund-Scherwitzl et al 2017).

Berglund-Scherwitzl et al (2017) reported a prospective study of the Natural Cycles app (which two of the researchers had invented). Data on all paying users of the app between August 2014 and March 2017 were included (n = 22 785). The aim was to show the effectiveness of the app (ie: the number of unplanned pregnancies).

It was calculated that the "perfect use" would lead to seven pregnancies per 100 woman-years, while "typical use" gave a pregnancy rate of 8.3% per year. Other FAB methods vary from 1.6% to 20% per year (Berglund-Scherwitzl et al 2017).

This type of FAB method offers an alternative to the hormone-based pill or condoms, which are the main contraceptive methods of the ten available (table 1.2).

The success of the Natural Cycles app as a contraception depends on the users, who must record their temperature every day, and take note of the fertility probability information (eg: use a condom on "red" (fertile) days) (Sarchet 2018).

Maureen Cronin (of Ava, a competitor company to Natural Cycles) (Sarchet 2018) criticised the Berglund-Scherwitzl et al (2017) study for its self-selecting sample (ie: women who choose to use the app), and the fact that only 6944 of the sample used the app for at least one year (ie: "perfect use").

Method *	Perfect Use	Typical Use
Progestogen injection	1	6
Vaginal ring	1	9
Combined pill	1	9
Progestogen-only pill	1	9
Natural family planning (or rhythm method)	1	24
Male condoms	2	18
Diaphragms and caps	4-8	12-29

(* contraceptive implant and copper coil (IUD) less than 1 (perfect use); female sterilisation 0.5 (lifetime risk))

(Source: Sarchet 2018 diagram p20)

Table 1.2 - Number of women (out of 100) who are likely to get pregnant in a year using a contraceptive method.

1.6. APPENDIX 1A - CHOOSING DISABILITY

Glover(1992) stated: "Consider the theoretical possibility of screening to ensure that only a disabled child would be conceived. This would surely be monstrous. And we think it would be monstrous because we do not believe it is just as good to be born with a disability" (quoted in Camporesi 2010).

In a survey of 190 fertility clinics in the USA, 3% said that they would "select an embryo for the presence of a disability" (Baruch et al 2006 quoted in Camporesi 2010).

Concentrating on one condition, Camporesi (2010) asked: "Do we need to define 'deafness' as a disability to argue that it is morally wrong to choose deaf children with PGD [pre-implantation genetic diagnosis]?" (p87). She answered by using Oliver's (1996) distinction between "disability" and "impairment". The latter is "'lacking part or all of a limb, or having a defective limb, organ or mechanism of the body' whereas 'disability' is defined as 'the disadvantage or restriction of activity caused by a contemporary social organisation which takes no or little account of people who have physical impairments and thus excludes them from participation in the mainstream of social activities'. Therefore, impairment has to do exclusively with the body; disability also necessarily involves other factors" (.Camporesi 2010 p88).

However, Camporesi (2010) still argued that choosing deafness with PGD is morally wrong. She offered an argument of justice towards the future child. The parents' decision to choose deafness is a "direct danger to other citizens" (ie: future child) in that being hearing impaired will restrict the choices of the child.

1.6.1. Wrongful Life

DeGrazia (2012) talked of the concept of "wrongful life". "The basic idea of wrongful life is that some diseases and perhaps some circumstances (eg: slavery in especially brutal conditions) are so awful for the affected individuals that their lives are not worth living; moreover, knowingly to allow children to be born with such conditions or in such circumstances is to wrong them grievously. This idea compels us to consider whether, in creating children through procreation, we can wrong them" (DeGrazia 2012 p139).

But the alternative to the wrongful life is non-existence. "Non-existence is not a state of an individual, but rather the fact that there is no individual. So how can we say that bringing the child into existence — or failing to end her existence with abortion — made her worse off? Worse off than what? How could she have been better off?" (DeGrazia 2012 p140).

DeGrazia (2012) also described the idea of "permissible procreation" - "that there is good reason to expect the individual to be created will come to appreciate and enjoy her life, feeling glad to be alive, without her judgment being deluded" (p161). So, "cases of wrongful life are precisely those in which it is predictable that the individual to be created would have a life filled with suffering and dysfunction with negligible prospect for compensating satisfaction or meaning. Someone living such a life, if capable of evaluating and communicating about her life, would not (in the absence of severe delusion) express gladness about her life as a whole" (DeGrazia 2012 p161).

When making a procreation decision, it is accepted that all human lives will involve harms, but the benefits of existence will be sufficient to compensate for the harms, and so life will be worth living.

Benatar (2006) made the distinction between "a life worth starting" and "a life worth continuing": "For instance, while most people think that living life without a limb does not make life so bad that it is worth ending, most (of the same) people also think that it is better not to bring into existence somebody who will lack a limb. We require stronger justification for ending a life than for not starting one" (quoted in DeGrazia 2012). DeGrazia (2012) was "not persuaded that the distinction is significant. Why should it matter whether one already exists when the question of whether one's life is worth living is raised?" (p144).

1.6.2. Body Integrity Identity Disorder (BIID)

BIID describes individuals who feel "a consistent sense of non-contiguity between body and self" (Sullivan 2015 p582). Put another way, individuals feel that part of their body is not "right". The upshot is a request for amputation of a healthy limb, say.

Sullivan (2015) considered the ethics of such "elective amputation".

One way to view BIID is as a "disabled person trapped in a non-disabled body" ("wannabes"). However, "the insanity objection" (Partridge no date in Sullivan 2015) is made: "no one 'but a severely mentally disturbed person would want a healthy leg, arm, hand, or foot cut off' and that 'such people need treatment, not amputation'" (Ryan 2009 quoted in Sullivan 2015).

Muller (2009) argued that the desire for amputation is caused by an underlying neuropsychological problem, and so the decision is not autonomous. She argued that if an individual's desire for amputation could be shown to be autonomous, then the operation would be ethical. Sullivan (2015) was critical: "close examination of Müller's attempts to substantiate her claim that wannabes lack autonomy reveals that her perception of wannabes (and their desires) is underpinned and shaped by an obvious prejudice which links amputation with 'disability', and the desire for 'disability' (as, by definition, undesirable) with 'madness'" (p585).

Sullivan (2015) preferred the position that "what may be good for one person may not be appropriate for another" (p588). She continued: "Accepting that amputation (for patients with BIID) may not be a universally unethical practice does not mean that amputations should or would be performed without due care, nor does it mean that surgeons opposed to such a practice would be required to perform it" (Sullivan 2015 p588).

A rights-based conception of justice would "give due consideration to the individual's right to self-determination, and to the cost of denying that right, or at least a particular manifestation of that right" (Sullivan 2015 p589).

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2. SEASONAL INFLUENZA VACCINE

Appendix 2A - Ethical issues and RCTs
References

Seasonal influenza vaccinations for older adults is common today in many countries. The general claim is that for every 200 vaccinations one life over 65 is saved (Taylor 2008).

But how to estimate the exact benefit of such a vaccination programme? A randomised clinical trial (RCT) that randomly vaccines some individuals but not others is the ideal method to answer this question, but this is viewed as unethical because of the deliberate withholding on beneficial treatment from some people (appendix 2A). It is, thus, easier to compare those who choose not to be vaccinated with the vaccinated. The latter group are much more likely to die over a winter period (Taylor 2008).

But Taylor (2008) pointed out that the percentage of the flu deaths in the USA of older adults, for instance, has not changed over thirty years (ie: 5% of winter deaths) [7], which is a period of vaccination for few to the majority (eg: Simonsen et al 2005).

Jackson et al (2005) argued (based on a Seattle medical database) that extremely ill and frail older adults are more likely to die but less likely to be vaccinated, "making vaccination appear more beneficial than it actually is" (Taylor 2008 p18).

Concerning one version of the influenza vaccine, Domnich et al's (2017) meta-analysis reported it "effective in reducing several influenza-related outcomes among the elderly, especially hospitalisations due to influenza-related complications" (p513).

The outcome measures varied in the eleven studies included in the meta-analysis - laboratory-confirmed influenza, and hospitalisation for pneumonia/influenza (most common), hospitalisation for acute coronary syndrome, influenza-like illness, and hospitalisation for cerebrovascular accidents. The study populations varied between older adults living in the community, and in long-term care facilities.

The pooled data suggested the vaccine reduced hospitalisation for pneumonia/influenza by over 50% compared to no vaccination, and laboratory-confirmed influenza was reduced by 60%. In other words, a vaccinated individual was half as likely as a non-vaccinated individual. These figures are "in-field vaccine effectiveness" (VE) estimates, which is

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[7] On the other hand, 90% of all influenza-related deaths occur in senior citizens (Domnich et al 2017).

calculated when RCTs are not used (ie: no directly comparable treatment and placebo groups).

Observational (epidemiological) studies (ie: not RCTs) have weaknesses as described by Verhees et al (2018): "the risk of bias and confounding is increased because of differences in characteristics between vaccinated and unvaccinated groups. Moreover, indirect, subjective and non-specific outcome measures are often used to determine the effect on prevention of influenza and the complications attributed to influenza. This hinders the interpretation of studies and leaves researchers to draw different conclusions for various endpoints" (p2992).

Verhees et al (2018) summarised the "existing knowledge": "There are multiple observational studies, systematic reviews and meta-analyses that support a beneficial effect of vaccination on mortality, but the evidence is predominantly of poor quality. Since vaccination prevents influenza, it is plausible that vaccination also prevents severe complications related to influenza (eg: pneumonia, heart failure and myocardial infarction) and mortality. Expert opinion, as reflected by leading health organisations and medical associations, states that influenza vaccination as such should be recommended. However, some health organisations are cautious in ascribing effects of vaccination to mortality reduction" (pp2992, 2994).

APPENDIX 2A - ETHICAL ISSUES AND RCTS

There is debate over whether it is ethical to perform RCTs with seasonal influenza vaccinations and over 65s, particularly frail, especially with an outcome measure of mortality (Verhees et al 2018).

A limited number of RCTs with community-dwelling older adults have been performed. Two of them showed a reduction of about 50% for clinical influenza, another reported a decrease in self-reported influenza-like illness, and two placebo-controlled trials found benefits for older adults with cardiovascular disease (Verhees et al 2018). "No RCTs on the prevention of influenza among elderly diabetics or institutionalised elderly have been published. Trials large enough to draw conclusions on the efficacy of influenza vaccination in the elderly on mortality attributed to influenza are non-existent" (Verhees et al 2018 p2992).

In terms of the ethics, Verhees et al (2018) referred to the concept of "clinical equipoise" (Freeman 1987) (ie: genuine uncertainty about a treatment). If this exists, then denying some individuals treatment as in the placebo group of a RCT is not unethical. But, Verhees et al (2018) pointed out: "Health institutes, professional medical associations, practicing physicians and elderly patients seem to support influenza vaccination to a high extent. Thus, it seems difficult to maintain that there is equipoise regarding the effect of vaccination on preventing influenza. Therefore, influenza vaccination is considered 'competent care'; it encompasses the norms for practice that derive from practices accepted by the community of expert practitioners. Since physicians are obliged to provide their patients with competent care, influenza vaccination cannot be denied to the elderly in a research setting. Denying vaccination fails to meet the principle of beneficence [8] since this would substantially increase their risk for influenza and its possible complications. It is also unjust, as it denies them what they are entitled to" (p2994).

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[8] Treatments should be beneficial to patients.

3. PSYCHOSIS

3.1. The meta-analysis of two possible causes of psychosis
  3.1.1. Tobacco use
  3.1.2. Childhood trauma
3.2. Schizophrenia and creativity
3.3. Creating visual hallucinations
3.4. References

3.1. THE META-ANALYSES OF TWO POSSIBLE CAUSES OF PSYCHOSIS

3.1.1. Tobacco Use

Individuals with psychosis (eg: schizophrenia) are more likely to smoke tobacco than the general population. The reason for this is "still unclear", but a number of "theories have been proposed, many focusing on the idea of self-medication – ie: smoking corrects a pharmacological abnormality (such as excessive dopamine blockade induced by anti-psychotics), counteracts negative or cognitive symptoms of schizophrenia, or relieves boredom or distress" (Gurillo et al 2015 p718). But what about the possibility that tobacco use causes psychosis?

Gurillo et al (2015) undertook a meta-analysis of studies to answer this question. Studies between 1980 and 2014 were included, with the focus on daily tobacco use/regular smoking, and onset/first episode of psychotic illness. There were sixty-one relevant studies in English, which used case-control, longitudinal or cross-sectional methodology.

The main findings were:

i) "Compared with controls, the overall prevalence of smoking in people presenting with their first episode of psychosis was three times higher" (Gurillo et al 2015 p720). Eleven case-control studies provided this information. But concentrating on the three studies that specified "daily smoking", "the association disappeared".

ii) Daily smokers were twice as likely as controls (non-smokers) to have a first episode of a psychotic disorder. This conclusion was based on five prospective longitudinal studies.

iii) Daily smokers who had psychotic illness had an earlier age of onset than non-smokers who had psychosis (mean: 24.25 vs 25.63 years old). This observation was based on 23 studies. "These findings conflict with previous reports, in which no relation was noted between smoking status and age at onset of psychosis" (Gurillo et al 2015 p721).

iv) There was no significant difference in age of initiation of smoking between patients and controls (based on twelve studies). The difference was less than half a year earlier.

Gurillo et al (2015) felt that their study "calls into question the self-medication hypothesis" [9], and so the "possibility of a causal link between tobacco use and psychosis merits further examination".

Bradford Hill (1965) proposed a number of criteria for distinguishing causation from association, including:

- Strength of the relationship - modest here.
- Consistency between different populations - eg: different countries.
- Temporality - smoking appears before the psychosis.
- Biological plausibility - eg: a relationship between nicotine and dopamine, and excess dopamine has been linked to psychosis.

In terms of the limitations with this meta-analysis, as always it is dependent on the quality of studies included. Gurillo et al (2015) noted the small number of prospective longitudinal studies, which is the best method to establish causation (and rule out reverse causality)(outside of controlled experiments), and the limited control of potential confounders, like consumption of other drugs. Also the exact measurement of smoking varied between studies (eg: "daily", "regular", "sporadic", "nicotine dependence").

3.1.2. Childhood Trauma

Read et al (2005) performed a literature review (of studies published in English up to November 2004 [10]) on child sexual abuse (CSA) and/or child physical abuse (CPA), and psychosis/schizophrenia. Child abuse has been linked to various mental disorders, and to increased severity (Read et al 2005).

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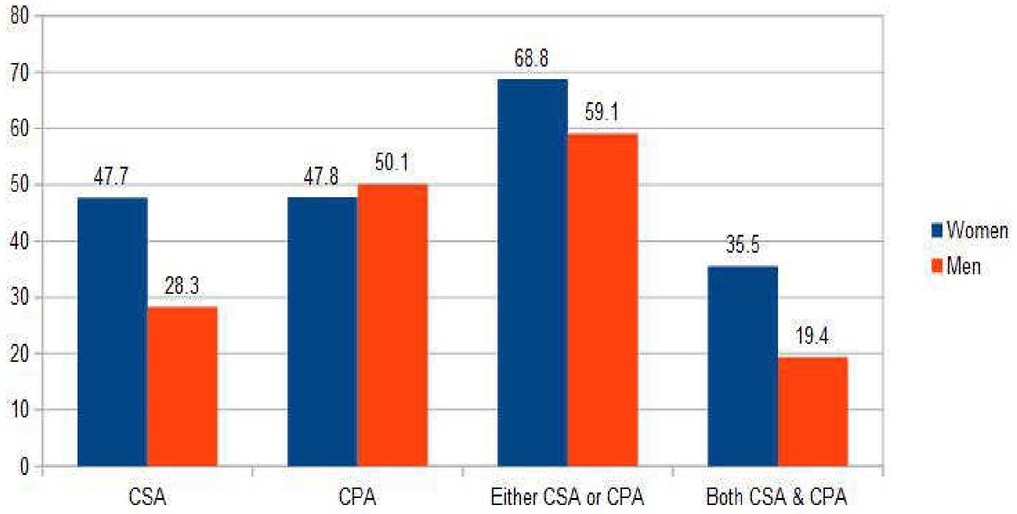
[9] Prochaska et al (2008) argued that "the tobacco industry monitored or directly funded research promoting the self-medication hypothesis, in particular, biological research" (Gurillo et al 2015 p722).

[10] Forty-six studies covered women and 31 studies men.

Among individuals with psychosis, 69% of women and 59% of men (weighted averages) had experienced either CSA or CPA (figure 2.1). Most studies used self-reports of abuse, without corroborating evidence (which may not exist anyway).



(Data from Read et al 2005 table 1 p332 and table 2 p333)

Figure 2.1 - Weighted average of childhood abuse among individuals with psychosis (%).

Other methodological issues included:

- Exclusion of emotional abuse and neglect (physical and emotional).

- Many studies did not exclusively focus on psychosis, and included other mental disorders, so Read et al (2005) included samples "where at least half were diagnosed psychotic".

- Under-reporting of abuse, especially CSA by men, by psychiatric in-patients generally, and cultural differences.

- How psychosis is defined and measured.

- The relationship between child abuse and specific symptoms (eg: hallucinations).

- Controlling for other variables (eg: adult revictimisation; other mental health problems; substance abuse).

- The inclusion of control groups.

- Age and duration of child abuse. The latter is the "dose-effect" (Read et al 2005) (eg: longer duration of abuse leads to more severe psychosis).

A key question is how does child abuse lead to psychosis? Read et al (2005) summarised two types of theories to answer this question:

a) Cognitive-based models - eg: negative beliefs about the self; confusion between inner and outer experiences ("source monitoring difficulties").

b) Biological-based models - eg: traumagenic neurodevelopmental (TN) model (Read et al 2001) - ie: "childhood trauma can cause long-standing neurodevelopmental, cognitive and interpersonal deficits of the kind found in people diagnosed as schizophrenic" (Read et al 2005 p344).

Varese et al's (2012) meta-analysis focused more widely on adverse childhood events (ACEs), which includes child maltreatment (ie: abuse) as well as bullying/peer victimisation, and parental loss and separation.

These researchers looked for prospective cohort studies, large population-based cross-sectional studies, and case-control studies published up to 2011. For inclusion, the adversity had to be experienced before eighteen years old, and the psychosis had to be formally diagnosed. Forty-one studies were relevant [11].

Overall, psychosis was over twice as likely after ACEs than not. "With the exception of parental death, statistically significant associations were observed between all types of childhood adversity and psychosis" (Varese et al 2012 p665) (figure 2.2).

The key methodological issues included:

1. Measurement of ACEs - self-report (with or without corroboration).

2. Types of ACEs and definitions - eg: "parental separation" varied from two weeks to parental death.

3. Diagnosis of psychosis - eg: which DSM system [12] or ICD used [13]; who does the diagnosis (psychiatrist or

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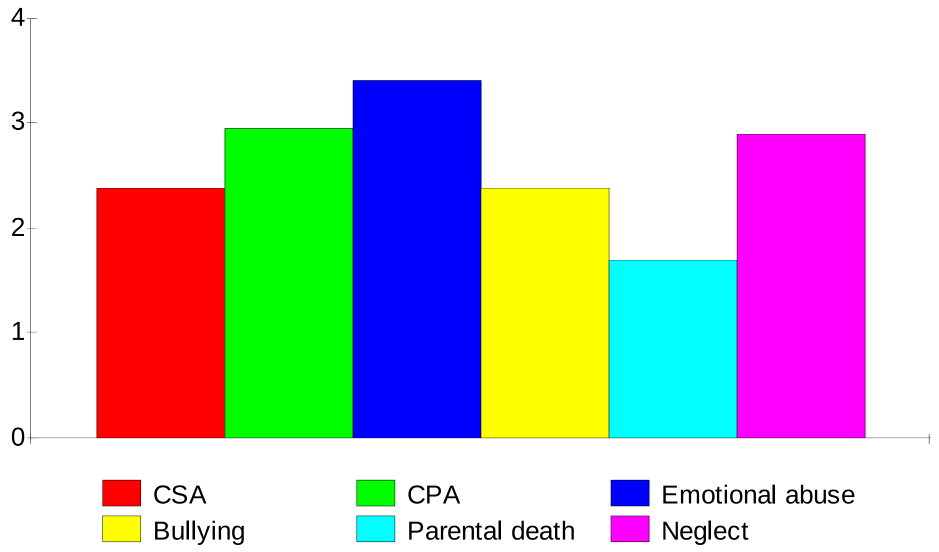
[11] Included the search of electronic databases for unpublished material (eg: conference papers), and as well as articles published in English, those in Dutch, French, German, Italian, Portuguese, and Spanish.

[12] DSM = Diagnostic and Statistical Manual of Mental Disorders produced by the American Psychiatric Association, and has versions from I to 5.

[13] ICD = International Classification of Diseases produced by the World Health Organisation.



(Data from Varese et al 2012 table 2 p668)

Figure 2.2 - Odds ratio of psychosis based on childhood event (where 1 = not experienced the event).

other).

4. Controlling of other variables - eg: drug use; urban dwelling; family history of psychosis.

5. Multiple or single ACEs, and age and duration of events.

6. Presence of single or multiple symptoms of psychosis - Varese et al (2012) stated that "the psychosis literature has tended to focus exclusively on hallucinatory and delusional symptoms and not on other symptoms. Therefore, the existing data did not allow us to test whether adversity was specifically associated with the development of specific symptoms" (pp668-669).

3.2. SCHIZOPHRENIA AND CREATIVITY

Schizophrenia spectrum disorders have a heritable component, and they are conditions that impair an individual's health (mental and physical), thereby reducing the probability of reproduction. "This naturally raises an evolutionary puzzle. Reduced fitness in sufferers would be expected to lead to the disappearance of the heritable traits predisposing individuals to the condition. The fact that this does not appear to happen has lead many commentators to speculate that there must be other, beneficial effects of the traits, most probably manifest in healthy relatives" (Nettle and Clegg 2006 p611).

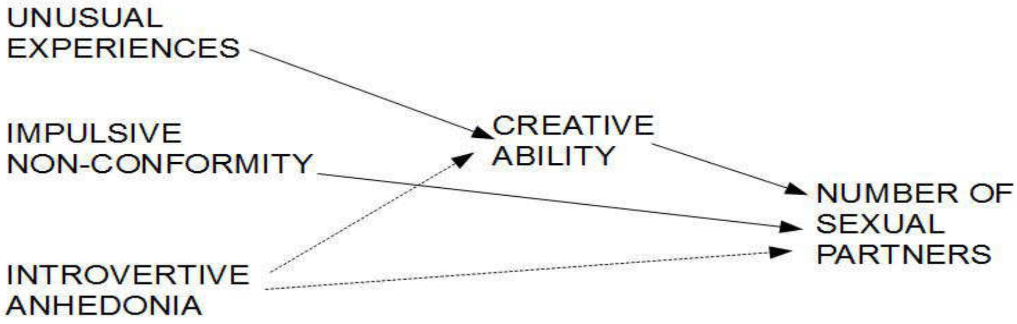
One possibility is creativity, particularly in the arts. Schizotypal traits [14] or schizophrenia-proneness have been found to be more common in individuals active in the creative arts (eg: Schuldberg et al 2000).

Miller (2001) proposed the idea that human artistic ability is similar to a peacock's tale - namely, a costly display of genetic quality to attract mates ("aesthetic fitness").

Thus, a "direct prediction would seem to be that successful engagement in artistic production should be correlated with achieved number and/or quality of sexual partners" (Nettle and Clegg 2006 p611).

Nettle and Clegg (2006) tested this prediction with a sample of 239 British adults from the general population, and 186 British poets and visual artists. All participants completed a questionnaire measuring schizotypy, and self-reported number of sexual partners since eighteen years old.

Analysis of the data found a positive relationship between two schizotypal traits and "mating success" (ie: more sexual partners) - impulsive non-conformity (directly), and unusual experiences (via creative activity) - ie: "those high in unusual experiences produce poetry or art more seriously, and this in turn increases mating success" (Nettle and Clegg 2006 p613). Introvertive anhedonia had a negative relationship with creative ability, and number of sexual partners (figure 2.3).



(Thick line = positive relationship; dashed line = negative relationship)

(Based Nettle and Clegg 2006 figure 2 p613)

Figure 2.3 - Significant relationships between schizotypal traits, creative activity, and number of sexual partners.

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[14] Four schizotypy dimensions have been focused upon - unusual experiences (eg: hearing voices), cognitive disorganisation, impulsive non-conformity (eg: recklessness), and introvertive anhedonia (eg: lack of pleasure in normal activities) (Nettle and Clegg 2006).

Nettle (2006) went further: "Poets and artists score as highly on unusual experiences and impulsive non-conformity as schizophrenia patients do... They are differentiated from patients only by their low scores on introvertive anhedonia" (Nettle and Clegg 2006 p614).

3.3. CREATING VISUAL HALLUCINATIONS

Dissociative states involve "symptoms of gaps in memory not caused by ordinary memory loss, out of body experiences and other distortions of the sense of one's own body, distortions in visual perception, such as seeing things as if they are in a tunnel or seeing things in black and white, and fragmentation of the sense of the self" (Caputo 2015 p659).

Attempts have been made to study this experimentally. For example, by staring at a black dot for ten minutes (eg: Miller et al 1994), or gazing at one's own face in a mirror (eg: Caputo 2010).

Caputo (2015) used interpersonal gazing, where two individuals (one metre apart) stared into each other's eyes for ten minutes in low light. Among forty Italian student volunteers, symptoms of dissociation were subsequently reported (eg: strange-face-like hallucinations; feelings of disconnection with the body; distortions of colours and time).

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4. DEPRESSION

4.1. Physical activity
4.2. Responding to treatment
4.3. Withdrawal side effects
4.4. Transcranial magnetic stimulation
4.5. Chronic pain
4.6. Multiple sex partners
4.7. Suicide
4.8. Appendix 4A - Algorithms
4.9. Appendix 4B - Transcranial magnetic stimulation
4.10. Appendix 4C - NCISH data
4.11. References

4.1. PHYSICAL ACTIVITY

Individuals with major depression are less likely to be physically active compared to those without depression [15], while physical activity can reduce the future depressive episodes (Schuch et al 2018).

Schuch et al (2018) reported a meta-analysis on the nature of the latter. Forty-nine unique prospective studies published before October 2017 were found. The studies had to include a follow-up of at least one year, and participants were depression-free at baseline.

The most physically active individuals were significantly less likely to be depressed in the future as compared to the least active (odds ratio: 0.84). Completing 150 minutes per week of moderate to vigorous physical activity was beneficial for all ages.

The inevitable question then, Schuch et al (2018) noted, was "how might physical activity offer protection against depression onset"? They answered: "It is likely that no single mechanism can explain this relationship. A range of biochemical and psychosocial factors are likely responsible, including biological mechanisms through which exercise increases neurogenesis and reduces inflammatory and oxidant markers and activates the endocannabinoid system... Also, physical activity may directly increase psychological factors such as self-esteem or perceptions of physical competence. Finally, an improved level of fitness leads to both subjective and objective improvements in physical health status" (pp639-640).

In another meta-analysis of eleven prospective studies, Zhai et al (2015) found that sedentary behaviour

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[15] Eg: half as likely to perform at least 150 minutes of moderate-intensity physical activity each week (Schuch et al 2017).

was associated with an increased risk of future depression. Schuch et al (2018) pointed out that "while sedentary behaviour and physical activity are related constructs – with the former existing at the low end of the physical activity spectrum – it is of clinical relevance to quantify the pooled relationships of physical activity with subsequent depression onset independently of sedentary behaviour" (p639).

Meta-analysis is dependent on the studies included, and so methodological limitations exist, including (Schuch et al 2018):

- Self-reported measures of physical activity, and of depression.

- Though the participants were depression-free at baseline, there were few details of previous lifetime episodes of depression.

- Different definitions of high and low physical activity, and measures of physical activity (eg: intensity, frequency).

- Relevant variables were not controlled or measured (eg: family history of depression; obesity; poor diet).

- The studies were observations, meaning an association can be established, but not causation.

What about exercise as a treatment for individuals with depression? In one of the first studies, Blumenthal et al (1999) found that relapse was lower among older adults with depression who exercised regularly compared to those who did not. This finding has been confirmed by subsequent studies, and meta-analysis (eg: Schuch et al 2016).

Two questions have emerged - which type of exercise is best, and how much exercise? Dunn et al (2005), for example, found that higher intensity exercise (eg: aerobic exercise - walking, running, cycling) over three months reduced depression more than lower intensity (eg: stretching). Consequently, these researchers recommended three 45-60-minute sessions at 50-85% maximum heart rate per week (Jabr 2017). However, other researchers are not as sure about the specifics (Jabr 2017).

4.2. RESPONDING TO TREATMENT

Predicting who will respond to treatment is a highly desirable ability, particularly in relation to mental disorders.

The analysis of an individual's speech is one possibility, particularly when paired with machine learning algorithms (appendix 4A). For example, Bedi et al (2015) used a computerised analysis of speech incoherence to predict successfully which psychosis "at-risk" individuals would develop symptoms.

Carrillo et al (2018) applied natural speech analysis to individuals with treatment-resistant depression to see who would respond to psilocybin (a hallucinogenic drug that works on serotonin) as treatment. The responses to an autobiographical memory test by seventeen patients and eighteen healthy controls were analysed by an automated algorithm called "emotional analysis" (Carrillo et al 2016). This programme quantifies the emotional content of speech to give a positive or negative emotional sentiment score.

The algorithm, firstly, distinguished patients from controls as the former used significantly fewer positive words. Secondly, the algorithm could distinguish between patients who responded to psilocybin (41% of patients) (ie: decline in depression) and those who did not. The authors stated: "On closer inspection of the data, it was found that responders used fewer emotional words at baseline (and fewer positive words especially) than non-responders, potentially reflecting a greater capacity for change in the responders that rendered them particularly sensitive to this treatment" (Carrillo et al 2018 p86).

4.3. WITHDRAWAL SIDE EFFECTS

In England in 2017, there were 65 million prescriptions of anti-depressants (ADs) for over seven million individuals, half of whom had been taking them for longer than two years. In the USA, there were about 37 million users (Davies and Read 2018).

Around one-third of individuals taking ADs for longer than two years may have "no evidence-based clinical indicators for continuing to take them", which produces around one million users in England and six million in the USA (Davies and Read 2018).

But there are withdrawal effects when long-term users stop ADs. Traditional reactions include increased anxiety, flu-like symptoms, insomnia, nausea, and headaches, though the level of effects can vary from short-term and mild to long-lasting and severe (Davies and Read 2018).

Official advice from the American Psychiatric Association (APA) in the USA and the National Institute for Health and Clinical Excellence (NICE) in the UK suggest only mild side effects lasting 1-2 weeks.

Davies and Read (2018) challenged these guidelines with findings from a systematic review. Twenty-four relevant studies on withdrawal effects after stopping ADs were found.

The incidence rates for withdrawal effects varied between 27% and 86% with a median of 56%. The most extreme level of severity was an average of 46% (but this figure came from four studies). The duration of effects varied, but lasted more than two weeks. It was "not uncommon for people to experience withdrawal for several months and beyond" (Davies and Read 2018).

A few studies collected qualitative data, which included this statement: "It took me two months of hell to come off the anti-depressants. Was massively harder than I expected" (quoted in Davies and Read 2018).

The findings of Davies and Read's (2018) review led to headlines in early October 2018 in the UK, like "painful price of coming off drugs for depression" and "millions are warned over 'severe' side effects while coming off anti-depressants..." (quoted in NHS 2018).

Davies and Read's (2018) review, like any combining other research, included a diverse range of studies, including in duration, AD, and size. Studies include those asking the patients, and asking doctors to rate the withdrawal effects. There were online surveys, which can overestimate the problem because of who responds (ie: selection bias) (NHS 2018).

Read et al (2019) reported an online survey of 752 UK AD users recruited via the mental health charity "Mind" ("Medication for Mental Health Survey"). About one-third of respondents had stopped taking ADs. The majority of these individuals took less than three months to come off, and only 5% over a year. Overall, one-third found coming off "very easy", half "fairly easy", and the remainder "not easy at all".

Read et al (2017) reported more details from "Medication for Mental Health Survey" with responses from 1008 users of ADs, but concentrated on the side effects of taking the medication (eg: weight gain; concentration problems; fatigue), and on polypharmacy. Over half of the respondents were taking more than one psychiatric medication, and about half of those reported wider side effects (eg: on social life and close relationships).

Larsen-Barr et al (2018) analysed the responses of 105 New Zealand adults to an anonymous online survey on stopping anti-psychotic medication (AM) [16].

Just over half of the respondents reported successfully stopping AMs, and one-third resumed taking them. Overall, negative withdrawal effects were reported

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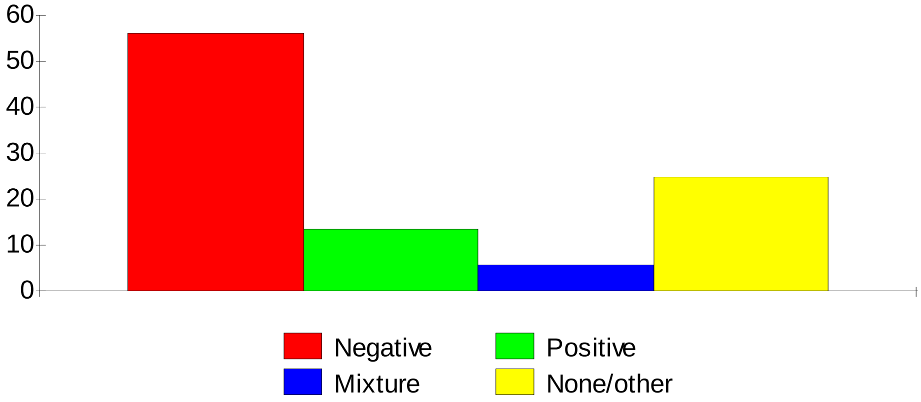
[16] "The experiences of anti-psychotic medication survey".

by about two-thirds of the sample (eg: panic, nausea, headache, relapse of psychotic symptoms). A small number of people had positive withdrawal effects (eg: clearer thinking, more energy) (figure 4.1).

Slow withdrawal was key as "people who withdrew gradually across more than a month were significantly more likely than those who withdrew in a month or less to successfully stop AMs, and report no current use. They were also less likely to report experiencing relapse of psychosis or mania during withdrawal..." (Larsen-Barr et al 2018 p372).



(Data from Larsen-Barr et al 2018 table 4 p371)

Figure 4.1 - Percentage of respondents reporting withdrawal effects.

4.4. TRANSCRANIAL MAGNETIC STIMULATION

Herwig et al (2007) reported a randomised double-blind placebo-controlled trial of repetitive transcranial magnetic stimulation (rTMS) for individuals with depression (appendix 4B).

Herwig et al (2007) explained the process: "Transcranial magnetic stimulation depolarises neurons in targeted cortex areas focally and non-invasively through induction of a transient electromagnetic field that is generated by a pulsed electrical current running through a wound copper coil. The induction of local and trans-synaptically mediated metabolic and biochemical changes in pathophysiologically relevant brain areas was suggested as a rationale for an anti-depressant effect" (p445).

One hundred and twenty-seven adults (aged 18-75 years) diagnosed with moderate or severe major depression at seven university clinics in Germany and Austria received real or sham rTMS, which was applied above the left dorsolateral prefrontal cortex on fifteen subsequent working days. Sham rTMS involved a very weak pulse.

There was no difference between the two conditions in number of participants who improved (31%), and in decrease in depression rating scores before and after the trial.

These findings were in contrast to other studies that found a positive effect. There are methodological issues related to different studies, including:

- rTMS was an add-on to anti-depressant medication in the Herwig et al (2007) study. Thus, differences in anti-depressant medication used, and whether dosage changed during the study.

- The stimulation parameters of rTMS (eg: 15 Hz or 10 Hz in this study), and timing (eg: three times per week for 4-6 weeks in another study).

- Samples - characteristics (eg: gender, age, severity of depression), and size.

- Definitions and measures of depression, and outcome measures.

- Nature of the placebo or sham condition (eg: no current rTMS; electrodes placed over the scalp to mimic skin sensation of rTMS).

- Single or multi-centre trial.

The mean response rate in placebo groups in RCTs with anti-depressant medication is 40% (Razza et al 2018), but what is the situation with rTMS RCTs? In order to answer this question, Razza et al (2018) performed a meta-analysis of rTMS RCTs for depression published in England up to March 2017. Sixty-one relevant quantity studies were included.

The improvement in depression symptoms in the sham rTMS groups were large. The response was larger in more recent studies, and was linked to the response in the active rTMS group. "Taken together, these findings suggest factors such as increased clinical attention to participants within a trial, increased expectation of improvement, and exclusion of more severe/symptomatic patients may operate in most RCTs, regardless of the modality of the intervention or the investigated condition" (Razza et al 2018 p110).

They continued: "For instance, in early years of rTMS trials, it was common to use coils without refrigeration, which often overheated and had to be changed during the sessions, instead of refrigerated-coil systems, that are now the standard. In early studies, little attention was paid to sensory artefacts (ie: sound, tactile sensation on the scalp) of active rTMS, which more recent RCTs try to mimic in their sham controls. Moreover, coils were originally held by the staff, and not by mechanical devices; and TMS devices were less developed than the present ones. These aspects, if put together, might have contributed to increasing rTMS sham response over time; considering that, if sham method improves, response in both groups increases" (Razza et al 2018 p110).

But the sham response was not influenced by the angle of the rTMS to the head (45 vs 90°).

In terms of the limitations of this meta-analysis, there was heterogeneity between the studies, and around three-quarters had methodological issues that risked bias (eg: imprecision in randomisation; imperfect blinding) (Razza et al 2018).

4.5. CHRONIC PAIN

Chronic pain affects millions of people in the world (eg: 100 million in the USA), and many of these individuals also experience anxiety and depression at the same time (Descalzi et al 2017).

There is evidence that the long-term pain produces physiological changes which lead to depression. For example, neuroimaging studies of chronic pain patients show changes in areas of the brain (eg: medial prefrontal cortex) associated with depression (Descalzi et al 2017).

Causation has been established in studies with rats as depression-like behaviours do not appear until at least six weeks after the experimentally-induced injury to produce chronic pain (Descalzi et al 2017).

Descalzi et al (2017) showed that chronic pain induced in mice leads to changes in gene expression that affects depression in three brain areas. Spared nerve injury is a standard technique used to induce chronic pain. This involves surgery on the sciatic nerve in the leg. Depression-like behaviours are measured by tests like the forced swim test. An animal is placed in a pool of water and must swim to an island. Depression-like behaviour is measured by immobility (ie: time spent making no effort to swim to the island).

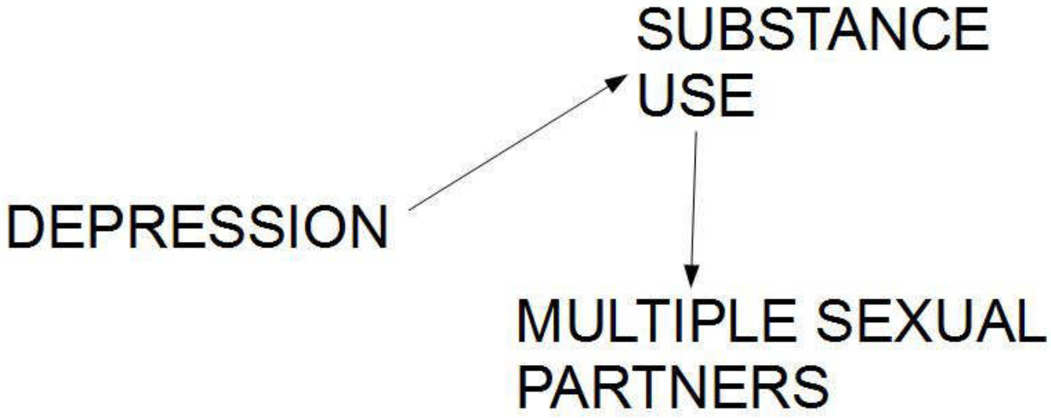
Descalzi et al (2017) proposed that the chronic pain produced stress, which altered signalling processes, like glucocortocoids, and these in turn induce changes in gene expression leading to depression.

4.6. MULTIPLE SEX PARTNERS

There are health inequalities in many countries with ethnic minorities, like between the Northwest Territories (NWT) and Canada as a whole in, for example, youth sexually transmitted infection (STI) rates (ten times greater), and youth suicide rates (double) (Logie et al 2018).

Depression, substance use, and sexual partners (eg: multiple partners) are linked to STI risk. Logie et al (2018) explored this in a survey of 199 female 13-17 year-olds in seventeen NWT communities. The survey included questions on number of sexual partners ever, depression, and substance use. Thirty-two individuals (16%) reported a history of multiple sexual partners (MSP), while 63% overall had depression symptoms. One-third of the sample used substances.

Depression was directly associated with substance use, but not with MSP. However, depression was indirectly associated with MSP via the direct link between substance use and MSP (figure 4.2).



(Based on Logie et al 2018 figure 1 p605)

Figure 4.2 - Significant direct relationships found by Logie et al (2018).

A statistical model was produced which showed that every one standardised unit increase in depression led to 0.02 standardised unit increase in substance abuse, and 0.5 standardised unit increase in MSP. Put simply, depressed individuals are more likely to consume alcohol or other drugs, which is associated with causal sex among Indigenous adolescent women in the NWT. Together, this produces a STI vulnerability.

No details were collected on actual STIs, and the sample was volunteers who had attended sexual health workshops. The respondents reporting MSP was small. It was not possible to establish causality because the study was a cross-sectional one.

4.7. SUICIDE

It is estimated that there are around one million deaths globally per year from suicide, which is greater than homicides, car accidents, war, and death from AIDS. Furthermore, there are 25 million suicide attempts, and 140 million individuals thinking about it (Franklin et al 2017). Three-quarters of the suicides are in developing countries, including one-fifth of the total in India (Carleton 2017).

The high rate of suicide in India is linked to agricultural problems and farmers' debts (Carleton 2017). Carleton (2017) analysed data for 1967 to 2013 from the National Crime Records Bureau (NCRB), which covers reported suicides in the thirty-two states and union territories of India, and from the Indian Ministry of Agriculture on crop yields, as well as climate data.

Carleton (2017) summed up the statistical findings that "temperature during India's main agricultural growing season has a strong positive effect on annual suicide rates... For days above 20°C, a 1°C increase in a single day's temperature during the growing season increases annual suicides by 0.008 per 100,000 people, causing an additional 67 deaths, on average across India; this amounts to a 3.5% increase in the suicide rate per SD [standard deviation] increase in temperature exposure. In contrast, temperatures in the non-growing season have no identifiable impact on suicide rates" (p8747).

Das (2018) accepted Carleton's (2017) calculations, but argued that the view that "the causality works through an agricultural channel is flawed" (pE116). Das (2018) continued: "Probably high temperature and high humidity stimulate suicidal tendencies, especially of people having health problems" (pE116). This author felt that temperatures would have to be above 35°C to have a negative impact on crop yields. "In a tropical country like India a heat wave day is declared if temperature goes beyond 40-42°C, which means, dermatologically, a temperature around 20°C is pleasant weather in India and unlikely to induce any extreme decision like suicide" (Das 2018 pE116).

Murari et al (2018) were critical of Carleton's (2017) methodology and data, including:

- The under-reporting of suicides to the police (NCRB).

- The inclusion of data on urban suicides in the analysis. "Can one relate the rate of urban suicides to climate factors?" (pE115).

- Crop data did not include cotton, "a major crop in the regions with concentrations of farmer suicides" (Murari et al 2018 pE115).

- Different crops respond to different temperatures.

- The distinction between the growing and non-growing seasons is not clear-cut.

Murari et al (2018) saw farmer suicides as "an outcome of multiple factors", not just temperature-related crop yields.

Plewis (2018) questioned Carleton's (2017) use of overall suicide rates among farmers across India as the outcome measure. Plewis's (eg: 2014) analysis "for the nine cotton-growing states that account for over 40% of India's rural population, male farmer suicide rates initially rose and then fell between 1996 and 2011 and female farmer suicide rates fell markedly for the same period. There is, however, spatial heterogeneity, with male rates increasing in Andhra Pradesh and Haryana but falling in Gujarat, with no consistent evidence for a trend in the other six states" (pE117).

Identification of risk factors for suicidal thoughts and behaviours (STBs) is key to prevention. Kraemer et al (1997) described a risk factor as "a special type of correlate that precedes the outcome of interest and can be used to divide the population into high- and low-risk groups" (Franklin et al 2017 p190). On the other hand, there are protective factors which reduce the likelihood of the outcome.

Many different risk factors and "warning signs" are listed by organisations working for suicide prevention. For example, the American Association of Suicidology has three risk factors for adults - anticipated or actual losses or life stresses, and prior suicide attempts, and more than one of the following warning signs: "Increased substance use; no reason or purpose for living; anxiety, agitation, or sleep problems; feeling trapped; hopelessness; social withdrawal; rage and anger; reckless or risky behaviours; dramatic mood changes" (Franklin et al 2017 p189).

Franklin et al (2017) outlined sixteen broad risk and protective factor categories (eg: demographics - age, marital status; social factors - history of abuse), and investigated them with a meta-analysis of 365 English language studies published up to 2015.

The most unexpected finding was that "at least within the narrow methodological limits of the existing literature, existing risk factors are weak and inaccurate predictors of STBs" (Franklin et al 2017 p213). Predictive ability had not improved in newer studies, nor by the length of follow-up. Furthermore, Franklin et al (2017) reported that "no risk factor category or sub-category is substantially stronger than any other; there is no compelling evidence that any specific STB outcome is associated with a unique set of risk factors; and protective factors are rarely studied and are generally weak" (p214). Despite these findings, the researchers emphasised the importance of risk guidelines and warning signs in everyday life.

The main issue with this and any meta-analysis was the heterogeneity in the methodology of the studies included. In this case, methodological differences included:

a) Outcome measure and assessment for suicide attempts and thoughts.

b) How the statistical level of risk was calculated (eg: hazard ratio or odds ratio).

c) Length of follow-up from presence of risk factor(s) to STBs.

d) Sample characteristics and size (eg: general or clinical population).

e) Inclusion of previous suicide attempts.

f) Single or combined factors - "For example, few would expect hopelessness measured as an isolated trait-like factor to accurately predict suicide death over the course of a decade. But many might expect that, among older males who own a gun and have a prior history of self-injury and very little social support, a rapid elevation in hopelessness after the unexpected death of a spouse would greatly increase suicide death risk for a few hours or days. Yet, most of the existing literature has tested the former hypothesis rather than the latter" (Franklin et al 2017 p217).

"Zero suicide" has become the target of many healthcare professionals among others (ie: to prevent all suicides). The idea is to prevent suicides by making it harder (eg: removal of guns from homes), and "suicide screening" to proactively identify potential individuals. "Zero suicide" comes from a Detroit-based healthcare provider (Henry Ford Health System) (Wilson 2018).

A number of criticisms have been made of the "zero suicide" idea, including (Wilson 2018):

- The accuracy of screening (eg: half of suicides are classed as low risk individuals; Wilson 2018).

- Many individuals who commit suicide have not had contact with mental health services beforehand, so "it is a tall order to expect doctors to save the lives of people they haven't met" (Wilson 2018 p23).

- The risk of more compulsory psychiatric hospitalisation.

- The effect on bereaved families of being told that "all suicides are preventable".

- The effects on medical staff with impossible targets.

A number of maternal deaths during pregnancy and the first year after birth are suicide (estimated at 5-20% in high-income countries and 1-5% in poorer ones) (Khalifeh et al 2017).

In high-income countries, most women who commit suicide around pregnancy time have a history of mental illness, but this period may also exacerbate symptoms (eg: post-natal deterioration; stopping medication during pregnancy) (Khalifeh et al 2017).

Research on this topic has certain limitations, including (Khalifeh et al 2017):

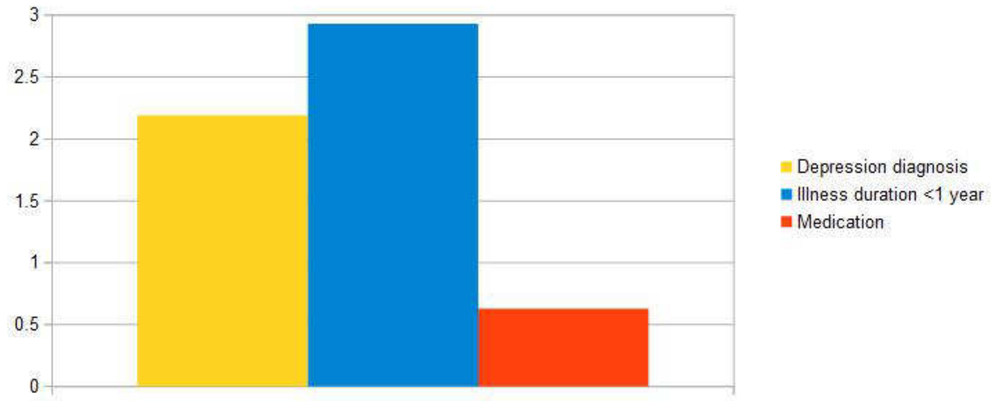
- Small sample.
- Short pre-suicide period of study.
- Lack of comparison group (ie: non-pregnant women).

Aiming to overcome these limitations, Khalifeh et al (2017) used data from the UK National Confidential Inquiry into Suicide and Homicide by People with Mental Illness (NCISH) (appendix 4C) for 1997 to 2012. NCISH covers all suicides by individuals ten years old or above who had contact with psychiatric services in the twelve months prior to death. Khalifeh et al (2017) compared all female suicides in pregnancy or the first year after birth (perinatal suicides) (n = 98) with female suicides outside this situation (non-perinatal suicides) (n = 4687) matched by age (16-50 years old).

Around 1 in 50 female suicides were during the perinatal period. Khalifeh et al (2017) commented: "Over the course of the study, we recorded a modest downward trend in the number of women dying by suicide in the non-perinatal period, but not in the perinatal period" (p238).

The perinatal suicides were significantly more likely to have a diagnosis of depression, recent onset of the illness, not to have received a psychiatric admission or treatment, but no history of alcohol abuse (figure 4.3).

This study has a large sample over fifteen years of women in contact with psychiatric services, and many potential confounders were controlled for in the analysis (eg: socio-demographic characteristics). But it involved only women in contact with psychiatric services (which is estimated at around two-thirds of perinatal suicides; Khalifeh et al 2017).



(Data from Khalifeh et al 2017 table 4 p239).

Figure 4.3 - Odds ratios for selective differences (where 1.00 = non-perinatal suicide group).

It was not possible to assess suicide risk factors. Khalifeh et al (2017) commented: "The correlates of perinatal suicides reported in this study could reflect a difference in the baseline prevalence of examined characteristics, or a difference in the nature or strength of the association between a given factor and suicide timing. Clarification of the above requires large epidemiological studies, which are difficult to do because of the rarity of perinatal suicides and the limitations of routinely available data" (pp240-241).

Data about the women were based on patient records. "Information might be particularly insufficient when the patient has had only short-term contact with psychiatric services, which could lead to data errors or to reporting bias" (Khalifeh et al 2017 p241). Some key information was missing in a small number of cases (eg: medication details at time of death).

Some potential confounders were not addressed, like birth complications, or history of partner violence.

4.8. APPENDIX 4A - ALGORITHMS

An algorithm is "a self-containing step-by-step set of operations that computers and other 'smart' devices carry out to perform calculation, data processing, and automated reasoning tasks" (Garfinkel 2017 p326). They are becoming increasingly used in decision-making tasks, but there are concerns about "algorithmic bias".

Garfinkel (2017) advocated for algorithmic transparency and accountability with a set of principles:

1. Awareness - All parties involved (from designers

to users) should be aware of the potential biases and the implications of these.

2. Access and Redress - A means of redress for affected individuals and groups.

3. Accountability - Institutions are responsible for the decisions made by the algorithms they use.

4. Explanation - Institutions explain how they use algorithms.

5. Data provenance - Details of how the machine learning occurred (ie: training data) [17].

6. Auditability - Decisions should be recorded to allow future auditing.

7. Validation and Testing - Rigorous validation of the algorithms before general use.

4.9. APPENDIX 4B - TRANSCRANIAL MAGNETIC STIMULATION

In terms of the efficacy of rTMS for improvements in resistant auditory hallucinations among individuals with schizophrenia, Aleman et al's (2007) ten-study meta-analysis reported benefits. The studies were published up to 2006, and were RCTs of rTMS over the left temporoparietal cortex.

But "rTMS did not improve positive symptoms in general. Thus, the observed effect was specific to auditory hallucinations" (Aleman et al 2007 p419).

There were some differences between the studies in the meta-analysis, including:

- Duration of rTMS - eg: 15 minutes continuous vs 5 x 1-minute stimulation with 1-minute intervals.

- Number of treatment sessions.

- Design of RCT - parallel-groups (intervention vs placebo) or crossover design (all participants involved in both conditions - intervention then placebo vs placebo then intervention). In the crossover design an individual is their own control, and confounding factors are reduced.

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[17] In the case of machine learning to spot breast cancer in mammograms, bias can occur if the training uses "noisy data" (eg: examples where cancer was missed or misdiagnosed by humans). Also the representativeness of the population in the examples (eg: less African-American women) (Whyte 2018).

- Measures of hallucinations - eg: four-point or 20-point rating scales).

- Differences in sham rTMS.

Impaired empathy often accompanies serious mental illness. Yang et al (2018) reported a meta-analysis of studies of rTMS and empathy. Twenty-two relevant studies were found, of which 21 of them involved healthy volunteers. Overall, there was "a significant but small overall effect on empathy in healthy participants and this effect varied according to empathy domains..." (Yang et al 2018 p746) [18]. The "most encouraging finding" was that rTMS enhanced affective empathy. However, the studies included in the meta-analysis were both RCTs and non-RCTs.

Empathy was measured in various ways between the studies, including facial expression recognition in photographs or videos, or the false belief task.

Huang et al (2017) reported two individuals in Taiwan who showed "transient anger attacks" after tDCS. "Ms A", after the first session of tDCS, "experienced an abrupt onset of unrestrained anger with verbal outbursts and body tension, accompanied by irritability and restlessness, of which the nursing staff and herself reported rather distinct from her prior inhibited personality. She even needed seclusion management owing to intense agitation and an impulse to 'tear everything apart'. This intensity of anger attack attenuated after 4 hours, however, residual irritability and restlessness persisted for 4 weeks and an increase of energy made her insomniac and 'always keyed up'" (p981).

"Ms B" "experienced abrupt anger attacks with loud cursing, crying and fist clenching sustaining for 20e30 minutes, which was unusual to her submissive personality and demanded seclusion management" (p981), after the second and third sessions of tDCS.

Huang et al (2017) noted that animal studies with tDCS had shown increased dopamine levels, which "might trigger the behavioural excitability and acting-out anger observed in our patient" (p981).

4.10. APPENDIX 4C - NCISH DATA

Data from NCISH for 2003 to 2013 showed that 6% of homicides convictions were individuals with a diagnosis of schizophrenia, and 17% of suicides were such

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[18] Cognitive empathy is the ability to attribute desires and intentions to others, while affective empathy is the emotional experience.

individuals (Baird et al 2018).

Are individuals with schizophrenia who commit homicide similar or different to those who commit suicide? Baird et al (2018) analysed the NCISH data further for male patients between 1997 and 2011.

There were 168 male patients diagnosed with schizophrenia who committed homicide and 777 suicides. The former group were more likely to have a history of prison, violent offending or drug misuse, be non-White, to have missed recent appointments with mental health services, and have a co-morbidity of a personality disorder.

The suicides were more likely to have had contact with mental health services (including inpatient care), have a history of self-harm, a co-morbidity of an affective disorder, and to be receiving psychological treatment.

There were no differences in history of alcohol misuse, living alone/unmarried, or being unemployed, for example.

Though the data were extensive and equivalent information was available for both groups, the study "was descriptive and was therefore unable to establish causality" (Baird et al 2018 p684). Information on key variables was not available (eg: death of a parent during childhood; family history of violence or suicide), as well as the researchers "lacked indicators of schizophrenia sub-types, course of illness and negative symptoms, and more detailed information on positive symptoms and specific type of previous self-harming behaviour would have been optimal" (Baird et al 2018 p685).

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