Brain damage in American Football
Inevitable consequence or avoidable risk?

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The subject of brain injury in American football has never been more controversial. For 15 years, the National Football League (NFL) denied any link between football and brain injury or chronic traumatic encephalopathy. It supported this claim with research performed by an NFL appointed committee, which contradicted that of independent researchers. Despite this long history of denial, the NFL recently settled (for $870m (£578m; €822m)) a legal case filed by former players who claimed their neurological deficits were from playing football. It remains unclear whether this was an admission by NFL that football can lead to chronic traumatic encephalopathy or other brain injury or a public relations response to an overwhelming media reaction to deaths of prominent retired football players and a perceived lack of concern for retired NFL players and their families. What is clear is that more research is needed to determine how athletes develop brain injury and whether strategies could protect them.

Chronic traumatic encephalopathy (CTE) was first described in American football players as a progressive neurodegenerative syndrome leading to neuronal loss coupled with protein and plaque deposits in the brain as a result of repeated mild traumatic brain injury. Case series data from autopsy studies, imaging, and animal models have characterised the encephalopathy. Those affected show localised brain atrophy and deposition of Tau protein and neurofibrillary tangles in the cerebral cortex, basal ganglia, or brainstem in a distinctive pattern unlike that of Alzheimer’s disease or other neurological diseases. Clinically, CTE has been associated with memory problems, depression, poor impulse control, anger, apathy, and impaired motor behaviours. Currently, however, diagnosis can be confirmed only at autopsy. We are still lacking a clear clinical picture because there have been no long term prospective studies of the disease spectrum from diagnosis to death, and it is unclear whether any treatment could slow progression of the disease if it was recognised early.

Possible mechanisms
Although all cases of autopsy proved CTE to date have been in people with a history of repetitive blows to the head, not all had a documented history of concussion. This raises concern that an accumulation of undiagnosed subconcussive head trauma may lead to (or be a leading risk factor for) CTE. Retired NFL players who began playing football before age 12 have shown greater levels of cognitive impairment in their 40s-60s than those who started later, which further supports the possible danger of long term exposure to head trauma.

New biophysical data provided by helmet mounted accelerometers have added to our ability to quantify these subclinical blows to the head. High school players can experience over 1000 head impacts per season, many of which are subconcussive and are undetected or unreported by the athletes, medical staff, parents, and coaches. As helpful and informative as these accelerometers seem, the NFL recently suspended their use because of difficulty determining the location and severity of impacts and of disagreement over the reliability of the data. We await improvement in the technology, hoping that it will further our understanding of the burden of repeated head impact attributed to football.

Over the past 60 years there have been only 63 autopsy confirmed cases of CTE in American football players, despite the fact that millions played the sport during this time frame. This makes it difficult to establish causation or relative risk. Some athletes could have other risk factors that predispose them to CTE. However, in their systematic review of all reported cases of CTE, Maroon and colleagues found that there was no evidence to link substance misuse, genetic factors such as apolipoprotein E, or premorbid symptoms to increased risk of CTE. They found that a history of concussive injury was the only risk factor consistently associated with CTE, although clearly an exact risk and tolerance of the brain to developing CTE are impossible to derive from current data.

Improving safety
Despite these uncertainties, strategies to reduce the number of concussive and subconcussive head impacts in American football should be a top priority. Risk reduction has been attempted through legislation requiring qualified licensed health professionals to clear injured athletes and stipulating the time before return to play. Other suggestions have included changing the rules to limit deliberate or avoidable head trauma in contact sports. Long term studies, however, would be needed to determine their effectiveness. Protective equipment has also been studied, and although most reports have found that helmets don’t reduce the incidence of concussion, recent studies suggest that some helmet designs may be effective.

Further work into risk mitigation, paralleled by increased research into the pathophysiology of both concussion and CTE, is needed.

Despite the seemingly easy to recognise clinical signs and symptoms of CTE, there is currently no imaging or other diagnostic test that can confirm the diagnosis of CTE in living people. While cases continue to receive tremendous media attention, the fact remains that current evidence suggests the risk is very low when we consider the total number of athletes who have played American football. The apparent low incidence of CTE makes it challenging to draw definite conclusions on the condition’s risk factors and natural course and on the tolerance of the brain to repetitive head trauma.

Improving the safety of American football with regard to head injury will take time. For now, it seems that the more we learn about CTE, the more questions are left unanswered—it still remains unclear if brain damage is an inevitable consequence or an avoidable risk of American football.
Air pollution, stroke, and anxiety

Particulate air pollution is an emerging risk factor for an increasing number of common conditions

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The effects of air pollution on the lungs and heart are now widely appreciated, with expanding evidence for an important role in cardiac disease. The Global Burden of Disease Study identified fine particulate matter (PM$_{2.5}$) in outdoor air and household air pollution from use of solid fuels as the ninth and fourth leading risk factors, respectively, for disease worldwide, and the World Health Organization attributes one in five deaths to air pollution. The effects of air pollution are not limited to cardiopulmonary diseases. Recent evidence suggests a role in diverse outcomes, including diabetes, low birth weight, and preterm birth. This research stems from improved understanding of the role of air pollution in initiating systemic inflammation, a response that may affect multiple organ systems. Two linked studies add to growing evidence that air pollution is an important risk factor for an increasing number of common diseases.

In the first of the two papers, Shah and colleagues systematically reviewed and meta-analysed 103 studies conducted in 28 countries and including 6.2 million events to assess the role of short term fluctuations in air pollution as a trigger for stroke. Although evidence from several cohort studies of long term exposure to particulate matter indicates associations with stroke mortality, such findings are not universal.

The role of air pollution as a possible trigger for stroke has important implications for disease burden, especially in China where air pollution and the incidence of (especially haemorrhagic) stroke are high. In their analysis, Shah and colleagues found that increases in each of the common gaseous and particulate air pollutants were significantly associated with admission to hospital for stroke or stroke related mortality, with associations strongest for strokes on the same day as exposure; increased ozone was only weakly associated with cerebrovascular events.

Air pollution remained significantly associated with stroke in sensitivity analyses that adjusted for potential biases related to quality of outcome ascertainment, assessment of exposure, and adjustment for confounders. This analysis supports a role for air pollution as a modifiable risk factor for stroke, although associations with air pollution were less precise for haemorrhagic stroke than for ischaemic stroke. The impact of chronic exposure to air pollution on development of carotid atherosclerosis (a precursor for stroke) remains unclear. Although this is not covered in the analysis, evidence of an association is growing.

Since air pollution causes systemic inflammation, it is reasonable that researchers have now turned to the arena of mental health, a leading priority for research given the relative absence of known modifiable risk factors and a high and growing disease burden. In the second linked paper, Power and colleagues exploit rich data in the Nurses’ Health Study cohort to assess the role of particulate pollution on prevalent anxiety symptoms. They found an exposure dependent association between higher levels of PM$_{2.5}$ and increased symptoms of anxiety, and indications that associations were stronger for exposures in the month immediately preceding the scoring of anxiety.

These observations were supported by several sensitivity analyses, which indicated that associations were robust to broad geographical region, health status (to control for the possibility of anxiety as a sequela of cardiopulmonary effects of air pollution), and demographic characteristics, although the study was limited to older women. Power and colleagues’ findings add to a growing literature on the mental health effects of air pollution, including a small but intriguing body of research linking short term variability in air pollution to suicide.

Power and colleagues used spatiotemporal exposure estimates and reported stronger effects for more recent exposures, reducing confounding by spatially varying factors correlated with air pollution. Since effects were observed over all time periods, spatial variation seems to have had an important influence on effect estimates. Furthermore, although effects were observed in all geographical regions, the investigators did not examine other potentially adverse (for example, noise, barometric pressure, solar intensity) or healthy (for example, natural spaces) environmental exposures that may operate at different scales. Indeed, evidence is accumulating that natural spaces may have beneficial effects on stress and social cohesion, both of which deserve further study in relation to mental health.

As with any observational study, questions remain, as the authors acknowledge, and the findings should be replicated in other populations and with other study designs. Moreover, although these observations are biologically plausible, given links between inflammation and anxiety there is a need for greater mechanistic supporting evidence, of the type that now exists for associations between particulate matter and pulmonary, cardiac, and circulatory disease.

The findings of these two studies support a sharper focus on air pollution as a leading global health concern. They also suggest opportunities for reducing the prevalence of two debilitating and common diseases. One of the unique features of air pollution as a risk factor for disease is that exposure to air pollution is almost universal. While this is a primary reason for the large disease burden attributable to outdoor air pollution, it also follows that even modest reductions in pollution could have widespread benefits throughout populations. The two linked papers in this issue confirm the widespread benefits throughout populations. As with any observational study, questions remain, as the authors acknowledge, and the findings should be replicated in other populations and with other study designs. Moreover, although these observations are biologically plausible, given links between inflammation and anxiety there is a need for greater mechanistic supporting evidence, of the type that now exists for associations between particulate matter and pulmonary, cardiac, and circulatory disease.

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Mental health effects of varenicline

Results from a new meta-analysis seem at odds with patients’ real life experiences

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The safety of drugs for smoking cessation, in particular varenicline (Chantix, Champix; Pfizer) and its effects on mental health, has been debated by regulatory authorities, researchers, prescribers, and patients since varenicline was first marketed nine years ago. The debate is likely to be sharpened by the linked paper by Thomas and colleagues, a systematic review and meta-analysis of randomised placebo controlled trials that found “no evidence of an increased risk of suicide or attempted suicide, suicidal ideation, depression, or death with varenicline.”1 This finding seems to be at odds with many patients’ experience of psychiatric adverse effects associated with varenicline, recently summarised in a citizen petition to the US Food and Drug Administration (FDA).2

In the new meta-analysis, about a third of the studies included at least 75% men; two studies had an almost all male population.7 Post-marketing research has also shown that women are over-represented in the group experiencing psychiatric effects.11 Thus the low proportion of women in some trials could reduce the incidence of psychiatric events reported.

There are other important differences between clinical trials and real life. More than half the studies (27/44) in the new meta-analysis investigated 12 weeks of treatment, as recommended in the product information,7 but only a small minority of patients receive exactly 12 weeks’ treatment in real life.12 The number of patients (and outcomes) in randomised controlled trials is usually much smaller than in post-marketing use studies and if an adverse event is rare, even meta-analyses might not have the statistical power to detect differences in rates of these events. Closer monitoring in trials could reduce the risk of certain adverse events. Reporting and analysis of results could also affect safety conclusions: in the linked paper only 46% of the included trials reported data on suicidal ideation7 and combination of the endpoints of completed and attempted suicide for analysis for statistical reasons might not have been clinically appropriate.

What does all this mean for patients considering varenicline for smoking cessation? Continuing reports from real life experience suggest that patients’ and doctors’ concerns are not unfounded, despite the linked paper’s conclusions, and that patients should still be warned of possible psychiatric effects. Patients who notice changes to their mental health while taking varenicline should discuss these with their doctor and consider stopping varenicline; this could resolve adverse psychiatric effects and serious consequences could be prevented.

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DIFFERENCES IN THE SEX DISTRIBUTIONS OF STUDY POPULATIONS MIGHT ALSO BE RELEVANT. IN A POST-MARKETING STUDY IN NEW ZEALAND, VARENICLINE WAS PRESCRIBED TO ROUGHLY EQUAL NUMBERS OF MEN (48%) AND WOMEN (52%).8 IN THE NEW META-ANALYSIS, A BROADNESS OF THE STUDIES INCLUDED AT LEAST 75% MEN; TWO STUDIES HAD AN ALMOST ALL MALE POPULATION.1 POST-MARKETING RESEARCH HAS ALSO SHOWN THAT WOMEN ARE OVER-REPRESENTED IN THE GROUP EXPERIENCING PSYCHIATRIC EFFECTS.11


As healthcare workers we routinely emphasise the nutritional superiority of breast milk for infant feeding to new and expectant mothers. Some women, though, find themselves unable to breast feed. Although some of them turn to clinicians and health visitors for advice, as many as three quarters of new mothers now look to the internet for guidance.\(^1\) Online these women find emotive, moralising discourse around breast feeding and often fear inducing warnings that formula is inferior to human milk for infant feeding.

They may also find sites that facilitate the buying, selling, and trading of breast milk, as well as high profile media sites featuring celebrities who are engaged in this trade. In the absence of warnings about the dangers of buying milk online, this option might seem healthy and beneficial—at the better choice if one can’t breast feed oneself.\(^2\) What mothers, and many healthcare workers, don’t realise is that this market is dangerous, putting infant health at risk.

The online market in human milk, growing fastest in the United States, is now also gaining popularity elsewhere, largely among mothers ineligible for milk from milk banks. Although a narrow group of adult consumers (including people with cancer, gym enthusiasts, and fetishists) buy milk online, most buyers are parents who require other women’s milk for supplementation or as the sole source of nutrition for their infants. In countries such as the United States where milk banks charge up to $4 (£2.7; €3.7) an ounce, online milk is often the cheaper option. Unlike regulated bank milk, no expense is incurred in routine pasteurisation or testing for disease or contamination, and collection, storage, and shipping requirements are negotiated between buyer and seller, enabling prices to be kept lower.\(^3\)

Troublingly, these cost saving measures lead to a high risk of communicable disease transmission, contamination, and tampering.\(^4\) Unlike donors at licensed milk banks online sellers are not required to undergo any serological screening, meaning that diseases such as hepatitis B and C, HIV, human T cell lymphotropic virus, and syphilis may not be detected.\(^5\)\(^ 6\)\(^ 7\) One study comparing milk bought online with that from licensed milk banks found that 21% of the samples bought online were positive for cytomegalovirus, compared with only 5% of bank samples.\(^6\)

Samples bought online also showed higher overall bacterial growth, with only nine of the 101 samples not having detectable bacterial growth. This is partly owing to the lack of pasteurisation but also to poor shipping and storage conditions. One study of 102 samples purchased online found that 25% of samples arrived with severely damaged packaging and were no longer frozen, leading to more rapid bacterial growth and contamination.\(^8\) Other studies identified occasional contamination with bisphenol A\(^9\) and illicit drugs\(^5\) and tampering including the addition of cows’ milk or water to increase volume (as milk is sold online per ounce).\(^7\) Such contamination cannot easily be detected before infant feeding.

**Health professionals must take action**
What can healthcare workers do to help smarter and safer infant feeding choices? They should increase their awareness of the market and how it operates so that they can pass good information on to caregivers. Professional bodies and institutions currently do not advise on this practice, and training for healthcare professionals does not cover the online market in breast milk.\(^7\) Trusts and professional groups need to formulate their responses to this growing market and to supply accurate information to healthcare providers and service users. Mothers need to feel confident to discuss the various barriers to breast feeding with health professionals so that, if necessary, healthy and safe alternatives to their own milk can be discussed.

In paediatrics, general practice, and community care, post-birth check-ups offer an excellent opportunity to inquire about feeding difficulties and practices. New mothers experiencing difficulties breast feeding, and those who cannot breast feed, can learn of options that are much safer than the online market in breast milk.\(^8\) Healthcare professionals should also provide advice on the best storage and use of expressed milk.

However, our work must not end in the professional setting. Healthcare workers must also drive and inform the urgent implementation of regulation to ensure safety and quality of human milk.\(^9\) Legal regulation to ensure the safe collection, processing, shipping, and quality of human milk is needed, as are mechanisms to obtain redress against those who knowingly contaminate or dilute milk for profit. Moreover, women need legal protection against their exploitation in the production of breast milk for sale.

Although breast milk holds many known benefits, seeking out another’s milk rather than turning to instant formula poses risks. When breast milk is screened and treated appropriately, as the World Health Organization states, it remains second to a mother’s own milk as best for infant feeding.\(^10\) At present milk bought online is a far from ideal alternative, exposing infants and other consumers to microbiological and chemical agents. Urgent action is required to make this market safer.

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