Boxing and the risk of chronic brain injury

Evidence is inconclusive but the absolute risk in modern day boxing is still low . . .

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RESEARCH, p 809

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In this week's *BMJ*, a systematic review of observational studies by Loosemore and colleagues assesses the risk of chronic traumatic brain injury with amateur boxing.[1] It finds that the quality of evidence is too poor to come to any definite conclusions. So, do we need to worry about the health of modern boxers, amateur or professional?

Concern over injury to fighters has been a persistent theme throughout the history of boxing. Although boxing was popular in early Rome, the practice was banned by Caesar Augustus, supposedly because of the high rates of injury in Roman legionnaires. The sport resurfaced in England during the 17th century in the form of bare knuckle boxing or prize fighting. The most famous of the rules introduced to protect the injured or incapacitated boxer were the 1867 Queensberry rules, which dictated that fights should be "a fair stand-up boxing match." Each fighter was given a 10 second count if he was knocked down and the length of bouts was time limited. Gloves of a "fair size" were introduced, which changed the nature of the sport, as bouts became longer and more strategic, with greater importance attached to defensive manoeuvres such as slipping, bobbing, countering, and angling.

As the changing nature of the sport and the use of protective equipment reduced acute injuries, concern began to develop about the chronic neurological risks of boxing. This was fuelled by a study published in 1928, which introduced the lay term "punch drunk" into medical terminology; this term has since become synonymous with impaired boxers.[2] Surprisingly, the only clinical case examined in that study concerned idiopathic Parkinson's disease.

Chronic traumatic brain injury has since been described in more detail. In the early stages of the condition, symptoms reflect lesions affecting the pyramidal, cerebellar, and extrapyramidal systems. In the later stages, cognitive and behavioural impairment predominate. About one third of cases are progressive.[3-5] The pathological features of the condition are similar to Alzheimer's disease, although some specific differences exist.[6 7]

The crucial risk factor for chronic traumatic brain injury is exposure to head impact. The largest and best of the neuropathological studies included 15 ex-boxers, 12 of whom were professionals.[6 7] These boxers had fought in the period 1900-40, and eight of them were national champions or world champions in their weight division. Although the study had methodological flaws—for example, all demographic and boxing exposure data were collected retrospectively—the most striking feature was the fighters' high exposure to boxing. The number of career fights ranged from 400 to 700. Many boxers also worked in fairground boxing booths and had up to 30 or 40 fights each day over several years. The pathological features described have become the essential diagnostic criteria for chronic traumatic brain injury.

These injuries are unlikely to be seen in boxers today because of their relatively short careers. More recent studies of professional boxers find that 95% of registered boxers have fewer than three fights in their careers, and that the theoretical risk of concussive injury from sparring is almost non-existent.[8]

The other major risk factor for chronic traumatic brain injury is genetic. Recent studies show that boxers with the apolipoprotein E4 (apoE4) allele are susceptible to chronic neurological deficits.[9 10] Male boxers who have 12 or more professional fights, as well as the ApoE4 allele are 16 times more likely to have neurological deficits than those without the allele. The ApoE4 allele has also been linked to poor neurological outcome after traumatic brain injury from any cause.[11]

The precise incidence of chronic traumatic brain injury is difficult to measure, and it may largely be a condition of historical interest. Few prospective epidemiological studies have been performed in boxers, and often they do not distinguish between amateur boxing and professional boxing. A dose-response effect has been suggested, whereby professional boxers have a higher rate of chronic traumatic brain injury than amateurs because of greater exposure to head impacts—bouts are longer (12 rounds versus three rounds) and they do not wear protective headgear. However, this has never been formally tested. Given the quality of the published literature, it is not surprising that Loosemore and colleagues find little conclusive evidence for chronic traumatic brain injury in amateur boxing.[1]

The difficulty with extrapolating early studies to today's sport is that the nature of the sport has changed substantially. In the 1930s to 1950s, boxers' careers generally lasted 10-20 years, started in childhood, and involved up to 1000 professional fights. Many boxers also became professional sparring partners or boxers in tents and booths, where they fought up to 30-40 unsupervised bouts each day. Fighters were not matched by skill or weight, they had no medical supervision, and they fought with 6 oz gloves. Bouts were often not stopped even when a boxer was overmatched, and bouts lasted longer (up to 20 rounds of two minutes

each). There was no mandatory exclusion after a knockout or head injury. Because of the depression in the 1930s, financial reasons kept many boxers competing, despite the onset of neurological symptoms.

No compelling evidence is available to suggest that regular magnetic resonance imaging of the brain, rigorous medical supervision, or currently practised safety measures will influence or prevent the development of chronic traumatic brain injury. However, because today's boxers have shorter careers and reduced exposure to repetitive head trauma, the likelihood of this condition developing is probably low. Whether governing bodies should recommend or mandate genetic testing for the ApoE4 allele in prospective boxers is an ethical question that needs to be debated. One of the reasons for doing so would be to provide an opportunity to counsel boxers about their risk of injury.

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Breast feeding and the risk of allergy and asthma

New trial shows no reduction in risk

RESEARCH, p 815

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The possibility that breast feeding might protect against allergy and asthma has generated interest for 70 years. In this week's *BMJ*, a cluster randomised trial by Kramer and colleagues assesses whether exclusive and prolonged breast feeding reduces the risk of asthma and allergy at 6 years of age.[1] It found no significant difference in allergy and asthma symptoms reported by parents or the results of allergy skin prick tests.

Hospitals in Belarus were randomised to promotion of breast feeding or usual care, and mothers intending to breast feed were eligible. The intervention increased the total duration of breast feeding and exclusive breast feeding in the intervention group. Six years later, parents answered seven questions about wheezing, hay fever, itchy rash, and whether their child had ever had asthma or eczema. The children also had skin prick tests to determine hypersensitivity to five airborne allergens. Overall, 10% of parents reported that their child ever wheezed, 5% that they ever had symptoms of hay fever, and 1% that they ever had asthma, with no significant difference between intervention and control groups. Positive skin prick tests were more common, with 27% of children having more than one positive test, but again there was no significant difference between the two groups.

The trial overcomes many of the challenges inherent in studying the influence of breast feeding on health outcomes. Assigning mothers to breastfeeding promotion or usual care eliminates the confounding inherent in observational studies. The cluster design allows better estimation of effects within each intervention group. Furthermore, the design includes prospective collection of high quality data on feeding when the children were 3, 6, 9, and 12 months, with standardised definitions for exclusive and any breast feeding.

The limitations of this study include a highly selected sample, comparison of two relatively similar breastfeeding groups, and the validity of the outcome measures. It is appropriate to select mothers intending to breast feed when testing the efficacy of a programme to promote breast feeding as this improves the duration of total and exclusive breast feeding. However, it limits external validity, because women who choose to breast feed may differ from those who do not in characteristics related to allergy and asthma outcomes, such as geography and socioeconomic status.

Although large differences were seen between the duration of breast feeding in the two groups, all women started breast feeding, and even in the control group 36% were still breast feeding at 6 months. Only 6.4% of the control group were exclusively breast feeding at 3 months compared with 44.3% of the intervention group, but many more may have been exclusively breast feeding at an earlier time point, such as 6-8 weeks. Hypothetically, exclusive breast feeding in the early weeks might be protective. It is possible that the groups were not divergent enough to answer the question of whether breast feeding protects against allergy and asthma.

The outcome measures also need to be considered. The reported prevalence of asthma was five times lower than the expected rate in the United Kingdom or the United States.[2 3] Possible explanations include a lower prevalence of childhood asthma in this sample from Belarus compared with the UK and US; under-reporting or underdiagnosis of asthma in this sample; or lower prevalence of asthma in both the intervention group and the control group related to a

common factor, such as the high initial breastfeeding rate. The second outcome, positive skin prick tests, is also problematic. Skin prick tests are better negative predictors than positive predictors and in clinical practice are recommended only as confirmatory tests for people with symptoms.[4] A test with a positive predictive value of 11.9% for hay fever may not have adequate specificity to determine if breast feeding is associated with allergy.[5]

The finding that promoting breast feeding did not reduce hay fever, eczema, or asthma reported by parents or result in fewer positive skin prick tests despite large increases in the duration of exclusive breast feeding calls into question previous findings of associations between breast feeding and decreased risk of allergy and asthma. Although this study must be interpreted cautiously—taking into account its limitations—previous work on this question is conflicting.[6 7]

For the moment, promotion of breast feeding should include evidence that it reduces the incidence of a wide range of infectious diseases, including diarrhoeal diseases and lower respiratory tract infections.[8 9] Evidence that it reduces the incidence of other conditions including diabetes, obesity, and some cancers is emerging.[10-13] Furthermore, breast feeding has health benefits for the mother. Therefore, there is already ample evidence to promote breast feeding as a public health measure. None the less, the claim that breast feeding reduces the risk of allergy and asthma is not supported by evidence.

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Reporting of observational studies

New recommendations should help researchers, journal editors, and readers

ANALYSIS, p 806

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In this week's *BMJ*, von Elm and colleagues report the STROBE (strengthening the reporting of observational studies in epidemiology) statement, which recommends what should be included in an accurate and complete report of an analytical observational study.[1]

Observational epidemiology has made an immense contribution to our understanding of the causes and treatment of disease. Numerous causal associations between risk factors and disease have been identified (see box on bmj.com). Most of these observations have led to substantial improvements in public health by causing changes in policy or by leading to the development of effective treatments.

Observational studies are also essential for effective clinical practice. Cohort studies allow us to improve the reliability of diagnosis; to understand prognosis; to develop and validate risk scores to target treatment appropriately; to monitor the safety of treatments in routine practice; to identify treatment effects (adverse or beneficial) that are not reliably detected in trials (perhaps because they are too rare, have too long a latency, or are confined to people excluded from trials); and to estimate the effects of interventions in circumstances in which randomised trials are not feasible.

To make the most of the enormous potential of observational epidemiology to transform clinical practice and improve public health, studies must be designed and reported as rigorously as possible. However, as with other areas of research, including laboratory sciences[2 3] and randomised controlled clinical trials,[4] the design and reporting of epidemiological studies can be poor, with consequences for the reliability of results.[5 6]

Quality control is unlikely to improve in the near future, given the ever increasing number of medical journals, and the consequently reduced influence of peer review on the likelihood that poor quality research will be published. The STROBE guidelines on the reporting of epidemiological studies are therefore welcome.[1] The summary paper published in this week's journal will be backed up by a more detailed document, which will explain the background and justification for each guideline. Such guidelines inevitably have limitations, and there is always a risk that poorly designed studies will be made more difficult to spot by superficial improvements in the way they are reported. However, experience with similar guidelines for reporting randomised trials and

systematic reviews has generally been positive.

Are there any matters that are not covered by the STROBE guidelines or that deserve particular emphasis? Firstly, the definition and prespecification of outcomes is crucial, particularly in cohort studies, where composite outcomes are often used to increase statistical power. For example, outcomes such as "coronary events" and "cardiovascular events" are often used in studies of potential new risk factors for cardiovascular disease. However, these composites have no widely accepted standard definitions. In our systematic review of published studies of seven new vascular risk factors,[7] of 266 eligible studies (167 case-control studies and 99 cohort studies), 56 (21%) reported a risk association based on a composite outcome. The 23 studies reporting composites of different coronary events used 11 different terms and 21 different composites. The 33 studies reporting composites of cardiac and extracardiac events (usually termed cardiovascular events) used 25 different composites, and seven studies gave no information on what events were included in their composite outcome. Only one composite was used by two different studies, and these had the same authors. Such variation between studies undermines the potential to compare studies and perform meta-analysis. It also raises the possibility of post hoc choices of composites that are dependent on data—by far the most effective way to increase the "statistical power" of a study.

Secondly, the importance of reporting data on the precision of measurement of the exposure(s) under study also deserves particular emphasis, whether it is a physiological parameter or a behavioural risk factor. For example, in a recent systematic review of case-control studies of the use of aspirin and risk of colorectal cancer, only studies that collected and reported detailed exposure data stratified by dose, frequency, and duration of aspirin use identified the same strong protective effect of aspirin that was found by long term follow-up of randomised trials.[8] Interestingly, smaller studies tended to have the most discriminating measures of exposure, resulting in a highly asymmetrical funnel plot, which could be misinterpreted as evidence of publication bias. The potential advantages of smaller more rigorous epidemiological studies over larger simpler studies have been outlined previously.[5]

Finally, the design of studies and the interpretation of results must have expert clinical input. Just as clinical studies can suffer from a lack of statistical and epidemiological expertise, epidemiological studies can suffer from a lack of clinical expertise. A statement about the extent of any input from people with relevant clinical expertise might be an additional future STROBE recommendation. Overall, however, the STROBE guidelines are an important and timely initiative, which researchers and journals should support and put into practice.

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Ototoxicity caused by aminoglycosides

Is severe and permanent in genetically susceptible people

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Aminoglycoside antibiotics are widely used for the treatment of Gram negative sepsis. It is well known that they can cause dose related renal toxicity and ototoxicity, which occur in almost everyone who receives a sufficiently toxic dose.[1] It is less well known that some people have an inherited predisposition that renders them highly sensitive to the ototoxic effects of these antibiotics: aminoglycosides taken at levels that are well within the therapeutic range can result in rapid, profound, and irreversible hearing loss. Even a single dose in a predisposed individual can result in permanent hearing loss.[2]

In countries that use aminoglycosides widely, a quarter of people with hearing loss induced by aminoglycosides have maternal relatives who also have deafness related to drug induced ototoxicity.[3] In the familial cases of hearing loss, individuals received antibiotics for a much shorter period than those without a family history of ototoxicity, suggesting the presence of an inherited predisposing mutation. The most common predisposing mutation is now known as m.1555A>G, a mitochondrial DNA mutation. This will be inherited by every child of a mother who has the mutation as a consequence of mitochondrial DNA being exclusively maternally inherited. This mutation accounts for at least 33-59% of aminoglycoside ototoxicity, according to studies from China, where use of aminoglycosides in the community is widespread owing to their low cost.[4] The mutations responsible for the remainder are being studied.

Aminoglycosides exert their antibacterial effects by binding to bacterial ribosomes, leading to errors in bacterial protein synthesis. Human mitochondrial ribosomes bear a structural resemblance to bacterial ribosomes.

Mutation at position 1555 of human mitochondrial DNA makes the human mitochondrial ribosome even more similar to the bacterial one, which facilitates aminoglycoside binding. Once bound, aminoglycosides have a long half life in the hair cells of the inner ear (several months), which increases the risk of ototoxicity. How common is the m.1555A>G mutation? To date, no large prevalence studies have been performed and data can only be extrapolated from small studies. In the US state of Texas, screening of blood spots from 1161 newborns found one positive case, and in New Zealand there was one positive case among 206 random blood samples screened (0.48%; 95% confidence interval 0.01 to 2.75).[5 6] This prevalence is much higher than previously suspected from calculations of its contribution to childhood deafness.

In the United Kingdom about 1 in 1000 children are born deaf; half of these cases have a genetic cause, with about 80-85% caused by recessive genes, 10% by dominant genes, and 2-5% caused by the m.1555A>G mutation.[7] This indicates a prevalence of the m.1555A>G mutation of 1 in 40 000. The discrepancy between this and the prevalence in New Zealand and Texas implies that either the prevalence in the UK is very much lower or penetrance of the mutation is very low, meaning that more people have the mutation but are not deaf. As aminoglycosides in the UK are used only in hospitals, penetrance is likely to be low in the absence of exposure to aminoglycosides. A genuine population frequency of between 1 in 206 and 1 in 1161 would have substantial implications for clinical practice in terms of the numbers of people at risk of ototoxicity.

Even in the absence of exposure to aminoglycosides, some families carrying this mutation may also develop deafness, albeit at a later age and with a lower penetrance. The variable penetrance of the m.1555A>G mutation may be attributable partly to the presence of a modifying nuclear genetic mutation.[8] In some populations, the m.1555A>G mutation seems to be a common cause of deafness. In Spain, 27% (19/70) of families with at least two deaf individuals were positive for this mutation.[9] Everyone with the mutation who was exposed to aminoglycosides became deaf. The probability of becoming deaf by the age of 30 years if an individual had received such antibiotics was 96.5% compared with 39.9% if they had never been treated. Thus aminoglycosides are a major environmental modifier of the m.1555A>G mutation. Because penetrance of the mutation is very low in some families (0-18%), exposure to aminoglycosides may cause drug induced deafness that may be erroneously categorised as sporadic.[10 11]

Is it cost effective to screen for this mutation before aminoglycosides are given? Cost effectiveness is determined by the cost of a screening test and the prevalence of the mutation versus the cost of not screening. The current cost of testing for this mutation in the UK is about £35 (€52; $71) per test, based on a small number being performed (generally in those who have already lost their hearing after aminoglycoside administration). However demand for more tests would reduce the unit costs, and single nucleotide genotyping in the commercial sector costs pennies per genotype. Conversely, the cost to the health service of providing a cochlear implant for a child who becomes deaf before acquiring language and of maintaining the implant for 15 years is estimated to be about £47 000 per child, rising to £61 000 over a child's lifetime.[12] Educational costs for a profoundly deaf child with a cochlear implant are estimated at about £18 000 a year.[13] However, the cost of not providing a cochlear implant to a profoundly deaf child is even greater in terms of educational costs and eventual earning power. In the US, the total lifetime cost to society for a child with prelingual onset of profound deafness has been estimated to exceed $1m.[14]

Hearing loss induced by aminoglycosides in individuals with the m.1555A>G mutation is in theory preventable. The mutation is well known among doctors who see patients who already have hearing loss. However, the general medical community is not aware of this susceptibility and that mutation testing is available through regional genetics centres. We recommend that the true prevalence of the mutation in the UK be ascertained to determine the cost effectiveness of screening everyone prescribed aminoglycoside antibiotics. In the meantime, patients who are likely to receive multiple courses of aminoglycosides—for example, patients with leukaemia and newborns admitted to special care baby units—should be screened. Genetic testing needs to be turned around rapidly, and consideration should be given to using an alternative antibiotic until the result of genetic testing is known.

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Management of chronic knee pain

Acupuncture has no additional benefit in people taking a course of exercise

RESEARCH, p 812

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Two papers have recently been published on bmj.com on the treatment of osteoarthritis of the knee.[1 2] The first is a randomised trial of adding acupuncture to a course of advice and exercise delivered by physiotherapists[1]; the second, which is also published in this week's *BMJ*, is a systematic review of the effectiveness of physiotherapy after elective total knee arthroplasty in people with osteoarthritis.[2]

Clinical trials conducted over the past decade have helped to define the role of acupuncture in various clinical conditions. A particular focus of these trials has been the use of acupuncture for chronic knee pain or osteoarthritis of the knee.[3]

The findings of randomised trials of acupuncture have caused much debate. Positive trials have been criticised because of inadequate blinding. Negative trials have been criticised because the intervention was not administered by properly trained practitioners or because control interventions may have had analgesic effects. However, a systematic review of high quality randomised controlled trials suggests that acupuncture can reduce pain and disability in people with chronic pain.[3]

Despite this evidence the role of acupuncture in the management of chronic knee pain is still unclear. Foster and colleagues[1] argue that acupuncture is useful only if it adds to the benefits of the first line treatments of exercise and advice. They investigated whether acupuncture is useful for people receiving exercise and advice by randomising 352 adults with osteoarthritis of the knee to advice and exercise, advice and exercise plus acupuncture, and advice plus sham acupuncture.

The trial found that acupuncture did not significantly reduce pain (measured on the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) subscale) at six months compared with sham acupuncture when combined with advice and exercise. This finding agrees with another large well designed trial that compared acupuncture with sham acupuncture given in addition to exercise in people with knee osteooarthritis.[4] A pooled estimate from these two studies shows that acupuncture does not significantly reduce pain compared with sham acupuncture (reduction in pain score on the 10 point WOMAC subscale 0.1 points, 95% confidence interval 0 to 0.2).

A systematic review by Minns Lowe and colleagues,[2] published in this week's *BMJ*, assesses the effects of physiotherapy exercise programmes given after total knee replacement surgery in people with osteoarthritis. The review found a small to moderate effect of functional exercise on joint motion and quality of life at three to four months after surgery, but the effect was not sustained at one year.

The findings should be considered provisional at best. In four of the six included trials, all study participants received an exercise or physiotherapy programme after discharge from the acute hospital[5-8]; these trials cannot tell us about the effectiveness of such programmes because the control groups also received an exercise intervention. The two remaining trials[9 10] focused on the effects of outpatient programmes on the range of knee flexion and found little or no effect on this outcome. Most of the trials evaluated low intensity exercise programmes provided soon after surgery. More lengthy and intensive physiotherapy exercise programmes may be needed to overcome the considerable deficits in muscle strength and endurance that are evident in these patients.

What conclusions can be drawn from these studies? The findings of the trial by Foster and colleagues suggest there is little point in recommending acupuncture to people with chronic knee pain who are already undertaking a course of exercise.[1] Acupuncture might be recommended to people who do not exercise.[3] It is difficult to make clinical recommendations on the basis of Minns Lowe and colleagues' review, although it does highlight the lack of research into the effectiveness of physiotherapy exercise programmes after total knee replacement.[2]

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