Driving and obstructive sleep apnoea

John Stradling

Driving is a skill requiring many simultaneous cerebral activities, mainly eye-hand coordination with accurate speed and direction computations.[1] This high level of activity requires full concentration, as evidenced by the higher accident rates in those who use mobile phones while driving.[2] There is very good evidence that inadequate sleep is an important cause of fatigue-related driving accidents, possibly causing up to 20% of all accidents.[3] Most of these sleep-related accidents are due to lifestyle issues such as driving without having had adequate sleep, and happen at times when vigilance is naturally low (eg, in the afternoon and at night).[3] Furthermore, accidents are extremely expensive to society, with fatal accidents costing over £1 million.[4] For nearly 20 years the part played by sleep disorders—particularly obstructive sleep apnoea (OSA)—has been recognised.[5] OSA can grossly fragment sleep and produces excessive daytime sleepiness that is likely to cause the increased road traffic accident rates seen in patients with OSA. However, it is not entirely clear what aspects of sleep fragmentation in OSA lead to poorer driving ability: is it just sleepiness and inevitable "microsleeps" at the wheel or is there also general impairment of driving skills including eye-hand coordination such as occurs with excess alcohol? The evidence suggests mixed effects during simulated driving.[6]

As with arguments over OSA and cardiovascular risk,[7] there may be confounders influencing any apparent relationship between OSA and driving accidents. For example, obesity itself is a cause of excessive sleepiness without necessarily the presence of OSA.[8] Obesity may influence mechanical aspects of driver ability such as proper scanning of the road (particularly to the sides), as well as fully effective braking and steering in hazardous situations. Other risk factors for OSA such as alcohol consumption may also be important confounders. In certain studies the occurrence of an accident or near-accident may have provoked investigation for sleep apnoea and falsely raised the apparent association. Given the highly plausible hypothesis that OSA causes accidents, what studies are available which demonstrate a cause and effect relationship?

A recent meta-analysis reviewed the 40 or so relevant studies in this area, both in commercial and non-commercial drivers.[9] The original cohort studies on patients with OSA were sometimes small, often had relatively unmatched controls and were based on self-reported accidents rather than an objective record. These studies suggested that the excess accident rate was as high as four times the rate in controls. George and Smiley[10] were the first to study over 1000 patients and controls using objective data from a central accident record system. An increased accident rate was found in patients with OSA, but only at the more severe end of the spectrum (apnoea-hypopnoea index (AHI) >40) where the rate was about double the control figure. A more recent cohort study from Japan also found a dose-response effect of both AHI and Epworth Sleepiness Scale (ESS) in a group of 448 subjects attending a sleep laboratory, with an accident rate nearly three times higher in those with AHI >30 than in those with AHI <5.[11] Case-control studies starting with patients having accidents (n = 102) rather than OSA suggested that those with OSA were 4–7 times more likely than control subjects (n = 152) to have had an accident, despite controlling for some potential confounders.[12] However, there seemed to be no AHI "dose-response" effect or relation to sleepiness but, interestingly, recent alcohol consumption was a synergistic factor with OSA. A Spanish study also found a more than twofold higher accident rate in 60 patients with OSA compared with 60 control subjects, but again there was no dose-response effect either with the AHI or subjective sleepiness as measured using the ESS.[13]

Cross-sectional studies on normal populations have also shown an association with sleep apnoea. In the Wisconsin cohort study (n = 913) there was a small increase in the accident rate (particularly considering multiple accidents) over 5 years in those with an AHI >15. Single accidents rates showed no real "dose-response" effect with AHI.[14]

Cross-sectional studies are prone to the effect of confounding variables and therefore randomised and controlled intervention studies would be more robust. However, it would be unethical to run such a study and expect a control group of untreated symptomatic patients to continue driving, awaiting their accidents. What is the best that has been possible? An early study looked at patients with OSA and compared 36 subjects compliant with continuous positive airway pressure (CPAP) with 14 non-compliant with CPAP (control subjects). A sevenfold higher rate compared with the average rate in the area was found before treatment, which only subsequently fell to below local area rates in the patients compliant with CPAP.[15] However, numerous studies have shown that patients non-compliant with medical advice are different from compliant patients, and this is therefore an important confounder.[16] George[17] performed a similar study comparing driving accident rates before and after prescribed CPAP for subjects with OSA versus matched controls using independent records of the actual accidents. The accident rate was about three times higher than control levels before treatment, falling to control levels after treatment but only in those compliant with CPAP. A significant problem with these studies is that the diagnosis of OSA itself may be effective in reducing accident rates by alerting the patients (and relatives) to the extra risk, leading to a more responsible attitude to driving when sleepy.

An alternative approach to understanding the accident risk—and perhaps the mechanism of any increased risk—has been the use of driving (or, more usually, steering) simulators. These clearly demonstrate impaired steering ability compared with control subjects, with increased wandering from the road and delayed responses to additional distracting events.[18 19] The poorer performance of patients with OSA appeared to be a combination of increasing sleepiness as well as poor eye-hand coordination.[6] Simulated steering ability has also been shown, in randomised controlled trials of patients with moderate to severe OSA, to improve in those treated with CPAP but not in those treated with ineffective sham CPAP.[20]

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In this issue of *Thorax* a study by Mulgrew *et al*[21] compares 3-year accident rates in 783 patients attending a sleep laboratory with suspected OSA and 783 matched control subjects (***see page 536***). In British Columbia there is a monopoly insurance provider where all accidents leading to claims are logged. In addition, the severity of the accident is categorised (<$1000 damage, >$1000 damage and those involving injury, with some details of the actual crash being available such as pedestrian involvement). There were 252 crashes in the patients and 123 in the control subjects (an approximate doubling). Adjusting the results for body mass index (BMI) reduced the apparent effect considerably, rendering it non-significant. However, correcting for BMI is a major problem since it correlates closely with OSA and controlling for it may represent an inappropriate "over-correction". Indeed, BMI may in fact carry substantial information about the likelihood of sleep-disordered breathing, better in some ways than a one-night AHI measurement. There is no way of unravelling this problem in such a case-control study. Similar to some of the studies described earlier, there also appeared to be little or no overall dose-response effect between the crash rate and OSA severity (as assessed by the AHI) except in the subgroup of subjects having accidents involving personal injury. However, if the patients with AHI values of <5 were used as the "control" population, then there was a higher rate in those with AHI >5 but very little further dose-response effect within those with AHI >5. Furthermore, there was no overall relationship with the ESS. The authors conclude that any degree of OSA adds extra risk (perhaps particularly for more severe accidents), and that simple estimates of sleepiness are no help in identifying those at risk in clinical practice.

What can be concluded and how should those involved in the care of these patients respond to these worrying data? Overall there certainly seems to be an increased risk, on average between two and three times control levels. In some studies the risk depends on sleep study measured severity, and in others not. In some the stated sleepiness is predictive, but in others not. Even in those studies where the AHI (or an equivalent) and/or the ESS were predictive, the variation was considerable and largely unhelpful at an individual level. Should we suggest to all patients with "abnormal" sleep studies that they should not drive unless treated? This is clearly ridiculous given that, in some epidemiological studies, up to 20% of randomly selected middle-aged men have "sleep apnoea" when monitored overnight.[22] It is clearly wrong to destroy someone's livelihood on the basis of extremely poorly predictive tests. Furthermore, Findley[23] showed that fear of losing one's licence would inhibit patients from coming forward, and thus drive the problem underground. As in many other areas of medicine, one simply has to do one's best given the limited evidence. It seems right to assess a patient's likelihood of having a future accident using a composite of several sources of information. These include the patient's own report of sleepiness while driving, a spouse's assessment, any previous accidents due to sleepiness, an assessment of their attitude to the problem (including their stated intention to avoid driving while sleepy), the sleep study itself and, perhaps, objective measures of sleepiness (although we use these tests more to inform and educate rather than as arbitrators of competence to drive—an unproven use).

Decision thresholds about continued driving would clearly be different between those who drive a car for only short distances and occasionally, and those who drive long distance coaches: professional drivers, of course, require a higher standard of medical fitness. Interestingly, there is some evidence that OSA may be more common in commercial drivers but the accident rate is again low and, in the sleepiest 5% of drivers, it is about double the control rate.[24] The American College of Chest Physicians has recently pronounced on the management of driving issues in patients with OSA who drive commercially, giving some non-evidence based guidance with suggested arbitrary thresholds but, sensibly, it concludes that drivers have to be individually assessed by the medical examiner and that there are no tests that allow an easy way out.[25] Screening strategies to identify OSA in commercial drivers have been suggested, based on simple identifiers such as upper body obesity followed by home oximetry.[26] To allow driving following treatment, it is clearly important to demonstrate both objective compliance with CPAP as well as subjective resolution of sleepiness.

Ultimately, in law, it is the patient's responsibility not to drive if sleepy, although this central tenet has recently been undermined by two cases where patients with OSA, who caused death by falling asleep at the wheel, were essentially considered non-culpable because of their subsequent diagnosis of OSA.[27 28] This grayness of the decision-making process over who can still drive happens in other areas of medicine too—for example, certain neurological disorders are not an absolute ban to driving, with discretion given to the clinician.[29] Given that the accident rate falls on successful treatment, the solution is of course greater awareness, rapid diagnosis and immediate treatment where appropriate. This is partly the responsibility of those involved with medical examinations of drivers and their licensing, as well as general practitioners who will see these patients first; improved strategies for earlier diagnosis will greatly reduce the period of driving with potential risk. The recent technology appraisal of CPAP for OSA by the National Institute for Health and Clinical Excellence (NICE)[30] which states that CPAP should be made available to those with symptomatic OSA is a major step forward in solving the problem.

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Prenatal nutrition and asthma: hope or hype?

Seif O Shaheen

David Barker's ''fetal origins'' hypothesis has changed the way we think about the aetiology of adult onset diseases, such as coronary heart disease and type 2 diabetes.[1] Underpinning the epidemiological evidence are recent animal data which suggest that fetal programming of these diseases by prenatal nutrition may be mediated through epigenetic mechanisms.[2] If adult onset disease is partly programmed in utero, it seems even more plausible that the prenatal environment influences the inception of asthma, which may first manifest in infancy. A number of exposures during pregnancy have been implicated[3–5] and, although data are conflicting, associations with birth anthropometry prompted speculation that prenatal nutrition might programme fetal lung and immune development leading to asthma and atopy.[6] Given that the diet of pregnant mothers has clearly changed considerably while asthma has been rising, the notion that it might be modified as a strategy for the primary prevention of asthma has considerable appeal.[7] This has perhaps been reinforced by recent disappointments with dietary interventions aimed at secondary prevention of adult asthma.[8]

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NUTRIENTS, FOODS OR DIETARY PATTERNS?

Trying to measure prenatal nutrition presents a major challenge for epidemiologists. Estimating maternal dietary intake in pregnancy, usually using a semiquantitative food frequency questionnaire on one occasion, leads to considerable exposure misclassification, and fetal nutrition will depend, not just on maternal intake, but also on nutrient absorption by the mother, placental transfer and fetal demand. Nutrients measured in maternal blood during pregnancy may be useful to validate dietary intake, and biomarkers measured in umbilical cord blood, cord tissue or deciduous tooth enamel may estimate fetal exposure more precisely. Furthermore, biomarkers may be the best way to capture the overall status of nutrient exposures such as vitamin D which are not exclusively determined by diet.

Initial epidemiological interest focused on the antioxidant hypothesis,[9] and birth cohort studies have reported associations between wheezing in early childhood and low prenatal selenium status,[10 11] and low maternal intakes of vitamin E and zinc.[12–14] Following the observation of a link between low maternal intake of vitamin D and early wheezing,[15 16] it has been proposed that vitamin D deficiency in pregnancy is the main cause of the asthma epidemic in the West.[17] However, given that asthma was not common during the industrial revolution when rickets was rife in cities, this idea would appear to give, at best, an incomplete account of the rise in asthma. Low intakes of apples and fish in pregnancy have also been associated with an increased risk of wheezing, asthma and other atopic outcomes in the offspring.[18–20]

One disadvantage of studying multiple nutrients and foods is that many are highly correlated with each other, making it difficult to disentangle independent effects. Another is that analysis of multiple exposures and outcomes inevitably leads to numerous statistical comparisons. An alternative approach is to relate dietary patterns to disease outcomes. This has the advantage of reducing a large number of dietary measurements down to a small number of overall features of diet which are uncorrelated. Dietary patterns can be derived either by data driven methods such as principal components analysis or by defining a priori scores, as has been used to describe a ''Mediterranean'' diet. In this issue of *Thorax*, Chatzi and colleagues[21] have examined relations between adherence to a Mediterranean diet in pregnancy and wheeze and atopic outcomes in the offspring in a relatively small birth cohort in Menorca ***(see page 507)***. A high diet score was negatively associated with persistent wheeze, atopic wheeze and atopy at 6.5 years of age although, as the score was condensed into two categories, it is not possible to determine whether there are ''dose response'' relations that would favour a causal interpretation. In fact, when the score was analysed as a continuous variable, only one of the three associations remained significant. A key component of a Mediterranean diet is fish, and it would be of interest to know to what extent the apparent effect of a Mediterranean diet on atopic outcomes was explained by a high intake of fish in pregnancy, as the latter was shown to be negatively associated