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Obstructive sleep apnoea: new associations and approaches

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An important new finding has come from an observational study linking obstructive sleep apnoea with cancer mortality.[1] Based on 22 years of follow-up data from the Wisconsin Sleep Cohort, investigators reported that relative to controls, mortality was higher for people with mild obstructive sleep apnoea (hazard ratio [HR] 1·1, 95% CI 0·5–2·7), moderate obstructive sleep apnoea (HR 2·0, 95% CI 0·7–5·5), and severe obstructive sleep apnoea (HR 4·8, 95% CI 1·7–13·2). Cancer mortality in this context refers to all types of cancer, with lung cancer the most frequent. The researchers cited preclinical studies showing that chronic or intermittent hypoxia—the latter mimicking clinical obstructive sleep apnoea—can lead to tumour growth and resistance to radiotherapy. This new research provides a possible mechanistic link between obesity and cancer, and will help to increase awareness of obstructive sleep apnoea by broadening its potential detrimental outcomes beyond the cardiovascular system. Whether the purported effects of obstructive sleep apnoea on cancer mortality will be reported in other cohorts or can be mitigated by intervention is unclear.

In cardiovascular medicine, Colish and colleagues[2,3] reported evidence that treatment of patients with severe, symptomatic obstructive sleep apnoea with continuous positive airway pressure (CPAP) is associated with a reduction in right atrial and ventricular size and left ventricular mass as measured by cardiac MRI and transthoracic echocardiography. The beneficial structural changes detected with MRI were evident as early as 6 months after the start of treatment, with confirmation of continued improvement by 12 months. However, use of CPAP might be associated with improved health behaviours—ie, diet, exercise, adherence to drugs—rather than improved cardiovascular risk.[4] Because this study did not include a control group, definitive conclusions cannot be made about the direct effects of CPAP on ventricular size and mass.

Because the benefits of CPAP are well-established, assignment of symptomatic patients to an untreated control group is ethically and logistically problematic; therefore, recent studies have instead included patients with minimally symptomatic or mild obstructive sleep apnoea, in whom the possible benefits of CPAP have not been conclusively established. Weaver and colleagues[5] reported that patients with mild or moderate obstructive sleep apnoea who were assigned to CPAP had a greater improvement in subjective functional capacity after 8 weeks than did patients given placebo (adjusted mean change of Functional Outcomes of Sleep Questionnaire score 0·89 *vs* –0·06; p=0·006). Likewise, Craig and colleagues' study[6] of patients with asymptomatic obstructive sleep apnoea randomly assigned to 6 months of CPAP or usual care noted a significant difference between groups in the change in daytime sleepiness (adjusted mean difference in Epworth Sleepiness Scale score change –2·0, 95% CI –2·6 to –1·4); however, vascular risk did not differ significantly between groups. Although these studies were randomised, that of Craig and colleagues was open-label and therefore at risk of bias caused by the placebo effect. The vulnerability of

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studies of CPAP to a large placebo effect was shown by Crawford and colleagues,[7] who reported that although adherent use of CPAP has real benefit, a significant proportion of the improvement in subjective daytime sleepiness in randomised placebo-controlled trials might be caused by expectation of benefit.

Accumulating evidence of the detrimental outcomes of obstructive sleep apnoea—in terms of sleepiness, cardiovascular and metabolic disease, and now possibly cancer—coupled with little improvement in objective outcomes in randomised controlled trials, suggests that: (1) residual confounding might be present in association studies; (2) the effects of obstructive sleep apnoea are at least partly irreversible; or (3) the first-line treatment—CPAP—might be only partly effective because of varying degrees of adherence. If the effects of obstructive sleep apnoea are shown to be irreversible, studies should focus on identification of young patients with less developed disease while also trying to curb reversible risk factors, most notably obesity. Irrespective of the explanation, and despite substantial benefits of CPAP for some patients with obstructive sleep apnoea, alternative treatment strategies should be explored.

To this end, Dixon and co-workers did the first randomised trial comparing two weight-loss strategies for people with severe obstructive sleep apnoea.[8] The 30 people assigned to bariatric surgery lost significantly more weight over 2 years than did the 30 participants assigned to an exercise, diet, and behavioural weight-loss programme (mean weight loss 27·8 kg, 95% CI 20·9–34·7 *vs* 5·1 kg, 95% CI 0·8–9·3). However, this substantial difference did not result in a significant improvement in disease severity. These results show the multifactorial nature of the pathogenesis of obstructive sleep apnoea, which is often primarily attributed to the mechanical effects of obesity. One potential treatment option addressing a different cause of obstructive sleep apnoea is implantable hypoglossal nerve stimulation, which has been substantially refined and tested. Schwartz and colleagues[9] reported the results of a study in which people with obstructive sleep apnoea were given hypoglossal nerve stimulation of increasing intensity.[9] They reported a substantial dose–response association between stimulation and increase of inspiratory airflow without arousal from sleep, leading to normal flow in most patients. The feasibility of hypoglossal nerve stimulation as a potential treatment for obstructive sleep apnoea has led to several ongoing multicentre randomised trials to test the effectiveness of this technique. Further research into the mechanisms underlying obstructive sleep apnoea is likely to lead to new treatment approaches including new drugs and devices.

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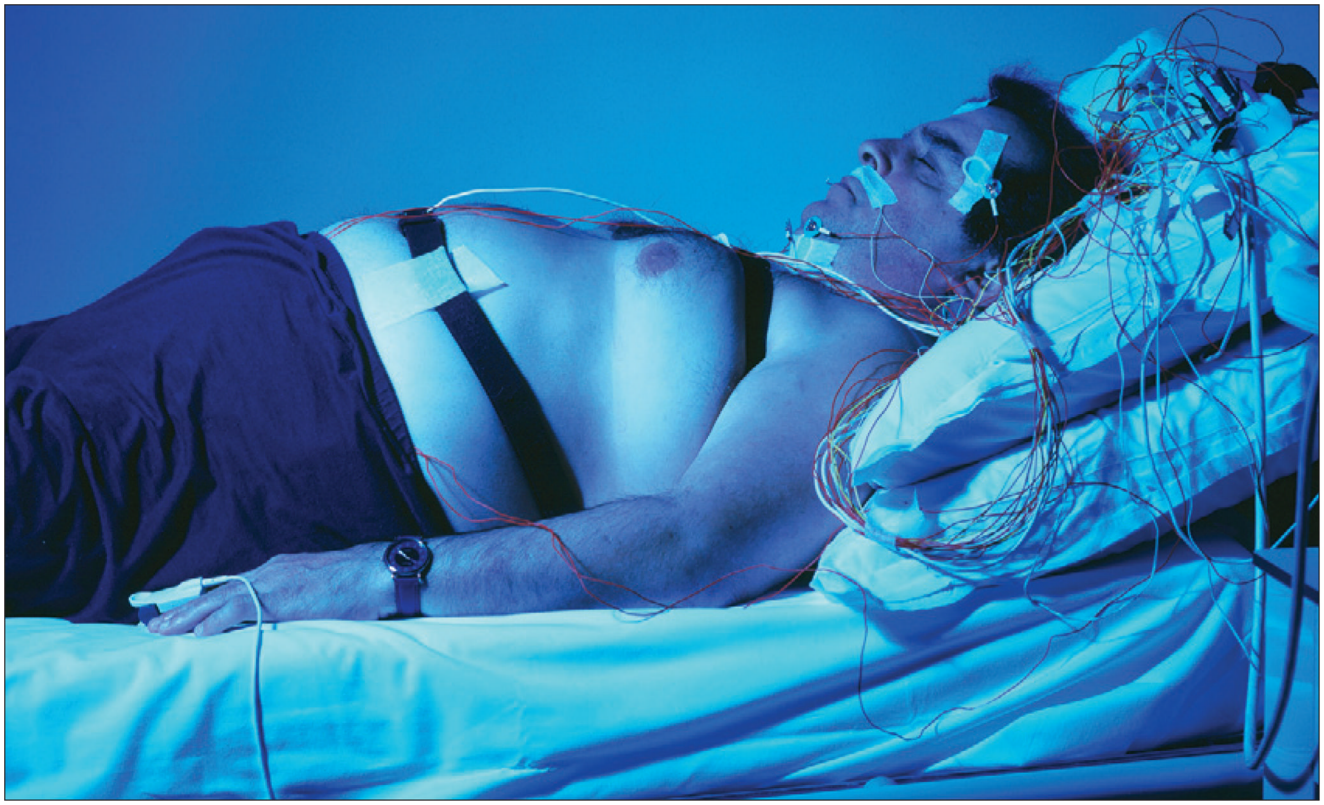

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Figure 1.