Cardiovascular disease

How does weight change affect risk of atrial fibrillation?

Putting on weight appears to raise the risk of developing atrial fibrillation (AF), a meta-analysis has concluded. However, no clear evidence emerged as to whether weight loss reduces the risk.

The Oxford-based investigators carried out a systematic review and meta-analysis on data extracted from multiple sources including MEDLINE, Embase, PubMed and the Cochrane Central Register of Controlled Trials. They included randomised controlled trials and cohort studies across all healthcare settings but excluded studies of bariatric surgery.

The primary outcome was the risk of incident AF in relation to weight change.

Data on 108,996 individuals from ten studies were analysed. In a pooled analysis from six populations (five studies), a 5% gain in weight increased the incidence of AF by 13%; HR 1.13 (95% CI: 1.04-1.23).

A pooled analysis from seven populations (five studies) found that a 5% weight loss was not associated with a significant change in incidence of AF; HR 1.04 (95% CI: 0.94-1.30).

Two studies presented subgroup analyses by baseline weight; one reported that weight gain in those who were obese at baseline was associated with a similar increase in risk of AF compared with the whole population and the other that weight gain of 1 kg per annum resulted in a similar increased risk of AF in individuals with a healthy weight (BMI < 25 kg/m^2) compared with the whole study population.

Obesity is associated with the onset of AF and as the prevalence of obesity increases it follows that the prevalence of AF will also increase. This coupled with an ageing population and increased prevalence of other risk factors such as hypertension and diabetes (both of which are also associated with obesity) goes some way to explain the current burden of AF on primary care and hospital services.

Certainly obesity can influence the outcomes of AF treatment strategies and a paper[1] that I reviewed in the November 2018 issue linked obesity with increased failure rates after catheter ablation for AF [Savill P. AF recurrence following catheter ablation more likely in obese patients. *Practitioner* 2018;262(1820):8].

The pathological mechanisms linking excess weight and AF may be mediated by the metabolic syndrome and direct damage to the heart from excess adipose tissue, atrial enlargement and diastolic dysfunction which can alter the electrical properties of the atria.

Strategies to prevent weight gain in the population may reduce the global burden of AF but the authors felt that further research was needed on this subject. They concluded that weight gain may increase the risk of AF, but there was no clear evidence that non-surgical weight loss altered AF incidence.

'Gaining weight increases the risk of incident AF, but the evidence is uncertain whether relatively small amounts of non-surgical weight loss reduces that risk,' the investigators conclude.

'More research is needed to understand the degree of increased risk associated with weight gain, whether non-surgical weight loss can reduce the risk of incident AF and if this depends on baseline weight status, intentionality and amount of weight loss,' they say.

DR PETER SAVILL

Jones NR, Taylor KS, Taylor CJ et al. Weight change and the risk of incident atrial fibrillation: a systematic review and meta-analysis. *Heart* Published Online First: 22 June 2019. doi: 10.1136/heartjnl-2019-314931

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1 Glover BM, Hong KL, Dagres N et al. Impact of body mass index on the outcome of catheter ablation of atrial fibrillation. *Heart* Published Online First: 02 October 2018. doi: 10.1136/heartjnl-2018-313490

Respiratory medicine

High levels of cardiorespiratory fitness associated with reduced risk of COPD

Good cardiorespiratory fitness in midlife may lower the risk of developing and dying from COPD, a prospective cohort study from Denmark has found.

The Copenhagen Male Study recruited 5,286 men aged 40-59 years, mean 48.7, from 14 large workplaces in the city from 1970 to 1971.

The men completed a questionnaire and were asked to describe themselves as never smokers, former smokers or active smokers. Tobacco consumption was calculated from the number of cigarettes smoked a day. Leisure time physical activity was self-reported as low, moderate or high. Those with preexisting COPD, asthma or chronic cough symptoms were excluded.

VO_2 max was measured by standard bicycle ergometer test to determine cardiorespiratory fitness. Categories of cardiorespiratory fitness (low, normal, high) were defined as ± 1 Z-score (± 1 SD) above or below the age-adjusted mean.

The study endpoints were incident COPD, and death from COPD. The sensitivity analyses included tests for reverse causation, which were performed by excluding participants who died within ten years of recruitment.

Participants were followed up for up to 46 (mean 28.3) years. Of 4,730 participants, 4,338 (91.7%) had died by the end of the study. There were 626 (13.2%) participants diagnosed with COPD, and 233 (4.9%) were registered with COPD as a cause of death.

Poor cardiorespiratory fitness was associated with lower levels of self-reported physical activity, higher body mass index, higher alcohol consumption, lower socioeconomic status, and higher incidence of diabetes and arterial hypertension.

An age-adjusted Cox proportional hazard model demonstrated a reduced risk of incident COPD with increased levels of cardiorespiratory fitness. When compared with low cardiorespiratory fitness, the risk of incident COPD was reduced by 18% in participants with normal cardiorespiratory fitness; HR 0.82 (95% CI: 0.66-1.01, P = 0.07), and by 22% for participants with high cardiorespiratory fitness; HR 0.78 (95% CI: 0.60-1.02, P = 0.08).

The age-adjusted risk of death from COPD, relative to low cardiorespiratory fitness, was estimated to be reduced by 27% in participants with normal cardiorespiratory fitness; HR 0.73 (95% CI: 0.52-1.01, P = 0.058) and by 50% in participants with high cardiorespiratory fitness levels; HR 0.50 (95% CI: 0.32-0.80, P = 0.003).

Higher levels of cardiorespiratory fitness were associated with a delay to both diagnosis of COPD and death from COPD. Time to diagnosis was delayed by 1.79 years for men with normal vs low cardiorespiratory fitness (95% CI: 0.14-3.45, P = 0.034), and 1.45 years (95% CI: −0.71 to −3.60, P = 0.19) for those with high vs low cardiorespiratory fitness.

Death from COPD was delayed by 1.28 years (95% CI: 0.04-2.52, P = 0.042) for normal vs low cardiorespiratory fitness, and by 1.8 years (95% CI: 0.19-3.42, P = 0.028) for high vs low cardiorespiratory fitness. Tests for reverse causation did not alter the results.

While no previous studies have examined the association between cardiorespiratory fitness and COPD specifically, several studies have suggested that high levels of physical activity may reduce decline in lung function thereby delaying the progression of COPD. This study offers good evidence in support of that premise.

The message to all individuals at risk from COPD is that maximising cardiorespiratory fitness from middle age onwards can effectively reduce the risk of developing or dying from the condition.

The study authors conclude: 'In individuals at risk of developing COPD, fitness enhancing physical »

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activity should be encouraged not only to reduce dyspnoea but also to delay development, progression and death from COPD.'

DR PETER SAUL

Hansen GM, Marott JL, Holtermann A et al. Midlife cardiorespiratory fitness and the long-term risk of chronic obstructive pulmonary disease. *Thorax* Epub ahead of print. *17 June 2019* doi: 10.1136/thoraxjnl-2018-212821

Mental health

Gabapentinoids may increase risk of suicidal behaviour in young patients

A large Swedish study has suggested that gabapentinoid medications are associated with an increased risk of suicidal behaviour and unintentional overdose in adolescents and young adults.

The investigators conducted a population-based cohort study using data from Swedish registers with complete national coverage.
The population of almost nine million (8,945,712) individuals aged 15 years and over was assessed for gabapentinoid treatment episodes (two consecutive dispensed prescriptions for a gabapentinoid) between 2006 and 2013.

Information on suicidal behaviour, unintentional overdoses, injuries and road traffic incidents was collected from the Swedish Patient Register; deaths from the Swedish Death Register; and criminal activity from the Register of People Suspected of Offences.

Follow-up time was divided into periods of treatment and non-treatment, and the gabapentinoids were analysed both together and individually. Those with identified substance misuse disorders and those who were taking other antiepileptic medication were excluded from some analyses.

Over the study period, 191,973 patients collected two or more consecutive prescriptions for a gabapentinoid, and around 60% of these were for pregabalin.

When treatment and non-treatment periods were compared for the same participant, gabapentinoid prescribing was associated with an increased risk of:

- Suicidal behaviour and death from suicide; age adjusted hazard ratio (HR) 1.26 (95% CI: 1.20-1.32)
- Unintentional overdose HR 1.24 (95% CI: 1.19-1.28)
- Head or body injury HR 1.22 (95% CI: 1.19-1.25)
- Road traffic incidents and offences HR 1.13 (95% CI: 1.06-1.20)

There was no statistically significant association with arrest for violent crime HR 1.04 (95% CI: 0.98-1.11).

When stratified by gabapentinoid type, pregabalin was associated with increased hazards for all outcomes. However, gabapentin treatment was associated with reductions in road traffic incidents and offences HR 0.81 (95% CI: 0.70-0.94) and arrests for violent crime HR 0.80 (95% CI: 0.67-0.95) but not for other outcomes. Results for men and women followed the same general patterns.

Periods of gabapentinoid treatment were associated with increased hazards of suicidal behaviour in people younger than age 55, with the highest risk in those aged 15-24 years, HR 1.67 (95% CI: 1.52-1.84) but reduced or no association in those aged 55 and older. Patterns were similar for other outcomes i.e. younger participants (15-34 years) showed increased hazards, whereas older participants (≥ 55 years) did not.

Over recent years the number of prescriptions issued for gabapentin and pregabalin have risen sharply. Adverse effects with these drugs have been noted including dizziness, somnolence, balance problems, blurred vision, coordination problems and impairment in cognitive performance, and earlier reports have suggested a link to overdose-related death and increased suicidal thinking. However, good quality evidence on the risks of these medications has been relatively limited. Earlier this year gabapentin and pregabalin were reclassified as class 3 controlled drugs in the UK.

The study authors conclude: 'Overall, gabapentinoids seem to be safe for a range of outcomes in older people. However, the increased risks found in adolescents and young adults (ages 15-24 years) prescribed gabapentinoids, particularly for suicidal behaviour and unintentional overdoses, warrant further research.'

DR JEZ THOMPSON

Molero Y, Larsson H, D'Onofrio BM et al. Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: population based cohort study in Sweden. *BMJ* 2019;365:l214

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