Cardiovascular disease

Raised resting heart rate associated with increased mortality risk

A high resting heart rate and an increase in resting heart rate over a decade are associated with a greater risk of death from cancer and other causes as well as cardiovascular disease (CVD), a study from Australia has found.

The study used data from the Melbourne Collaborative Cohort Study that recruited 41,514 participants (59% women), aged 40-69 years, between 1990 and 1994.

Resting heart rate measurements were recorded at baseline for 41,386 individuals and at follow-up, between 2003 and 2007, changes in resting heart rate were analysed for 21,692 participants. Measurements were carried out by trained staff, using Dinamap monitors. A resting heart rate of < 70 beats per minute was classed as normal.

There were 3,618 deaths from cancer, 2,239 from CVD and 2,573 from other causes during a mean follow-up of 22 years. After adjustment for potential confounders, including blood pressure and known medical conditions (but not arrhythmias such as atrial fibrillation as information on these conditions was not available), raised resting heart rate was associated with a higher risk of death. Similar associations were found for cardiovascular death, cancer and other causes of death:

- All causes - hazard ratio (HR) per 10 beats per minute 1.13 (95% CI:1.11-1.15)
- CVD - HR 1.11 (95% CI: 1.07-1.16)
- Cancer- HR 1.10 (95% CI: 1.06-1.13)
- Other causes - HR 1.20 (95% CI: 1.16-1.25)

Similar results were obtained when participants with pre-existing cardiovascular conditions were excluded.

Higher mortality was observed for most cancer sites, including:

- Breast – HR 1.16 (95% CI: 1.03-1.31)
- Colorectal – HR 1.18 (95% CI: 1.08-1.29)
- Kidney – HR 1.27 (95% CI: 1.03-1.57)
- Lung cancer – HR 1.19 (95% CI: 1.10-1.29)

Temporal increases in resting heart rate were associated with higher mortality, particularly for individuals whose resting heart rate increased by more than 15 beats per minute.

Those participants whose resting heart fell from raised to normal had a similar risk to those who maintained a healthy heart rate.

The cancer association was interesting and a possible mechanism for this is that higher resting heart rates reflect higher levels of sympathetic activity which could lead to an increase in factors that stimulate epithelial cell growth and proliferation.

Resting heart rate is a marker of cardiac function and a good indicator of physical fitness and general health. Most studies investigating the association between resting heart rate and mortality have focused on deaths from CVD and measured resting heart rate at only one time point.

The authors concluded that resting heart rate and changes in resting heart rate over a decade are associated with mortality risk and that this risk is not confined to just cardiovascular causes. The authors propose that the monitoring of resting heart rate may be useful in the identification of those at higher mortality risk.

The study authors conclude: 'Elevated resting heart rate measured at a single point is associated with higher risk of death from most causes, including cancer, independently of blood pressure and the main sociodemographic and lifestyle risk factors. Long-term increases in resting heart rate were also associated with higher mortality.

'Resting heart rate monitored during GP visits or using fitness devices could help identify population subgroups at higher mortality risk.'

DR PETER SAVILL

Seviiri M, Lynch BM, Hodge AM et al. Resting heart rate, temporal changes in resting heart rate, and overall and cause-specific mortality. *Heart* 2018;104:1076-85

Addiction

Patients prescribed opioids for analgesia at risk of dependence

A systematic review and meta-analysis has estimated that the incidence of iatrogenic opioid dependence or abuse in patients prescribed opioids for pain is almost 1 in 20.

Researchers from the University of Dundee carried out systematic searches of six online databases (Embase, Medline, PubMed, Cinahl Plus, Web of Science, and OpenGrey) to find relevant studies. A 'grey' literature search and a manual reference search of included articles were also undertaken.

The study's objective was to estimate the incidence of iatrogenic opioid dependence or abuse in patients with pain who had been prescribed opioid analgesic therapy.

After reviewing more than 3,000 papers, 12 studies, judged as good or fair quality, that met the inclusion criteria were chosen for analysis. These studies covered a total of 310,408 participants. There was little within-study risk for bias, and no significant publication bias was identified. The main measure used was the event rate i.e. the proportion of the total population developing dependence or abuse.

A random effects model (DerSimonian-Laird method) for data analysis provided a pooled incidence of opioid dependence or abuse of 4.7%. However, the authors did note substantial heterogeneity among study effects and the incidence ranged from 0.2% to 34.2%.

Sensitivity analyses indicated that the diagnostic criteria used for opioid dependence or abuse (i.e. differences between DSM-IV and ICD-9 criteria)

accounted for 20% of this variance in study effects and length of exposure to opioid analgesics accounted for a further 18%. Studies deemed of good quality were associated with a significantly lower incidence (3.1%) than those of fair quality (15.1%).

Strong opioids were associated with a significantly lower incidence (0.7%) than weak opioids (5.5%). Rates of dependence and abuse were found to be lower among those prescribed opioids for a longer period, 3 months or more (2.3%), than in those prescribed opioids for a varied period (10.7%).

Prescribing of opioids in the management of chronic non-cancer pain has been increasing in recent years, and prescribers need to balance their desire to provide relief from pain against the risks of contributing to physical dependence, addiction and diversion of prescribed opioids. This paper provides useful additional information that will assist in getting the balance right.

The study authors caution that differences in aetiology, pain severity or the nature of the pain may account for these counter-intuitive findings.

They conclude: 'There is a need for well designed, rigorously controlled, adequately powered prospective experimental studies examining the incidence – rather than prevalence – of iatrogenic opioid dependence and abuse after analgesic prescribing.'

DR JEZ THOMPSON

Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. *Br J Anaesthesia* 2018;120(6):1335-44

Smoking cessation

Can nicotine preloading help smokers quit?

The use of a nicotine patch before quitting may have a modest effect on abstinence, a large pragmatic randomised trial has found.

Patients listed as smokers on their health records were invited to take part in the trial. Pregnant and breast-feeding women, patients with a skin condition that precluded use of the patches and those with medical conditions potentially aggravated by high nicotine levels were excluded.

A total of 1,792 adults were enrolled from Nottingham, Birmingham, Bristol, and London. All were daily smokers with tobacco dependence.

Around half (889) were randomised to the preloading arm and 893 to the control arm. Patients in the former group used a 21 mg/24 hr nicotine patch daily for approximately four weeks before quit day unless there had been night-time problems during a previous attempt in which case day time only use was advised.

Participants in both arms were referred to the NHS stop smoking service and received standard pharmacotherapy and behavioural support to encourage cessation.

Participants were asked to smoke as normal and not reduce consumption as this would probably lower blood nicotine levels, which could make cigarettes more rewarding and thus undermine the potential benefits of preloading.

At baseline participants' smoking history and basic demographic information were recorded. This included two markers of cigarette dependence: the Fagerstrom test for cigarette dependence, which measures consumption of cigarettes and difficulty in refraining from smoking, and the concentration of exhaled carbon monoxide.

Participants returned one week after the baseline appointment (about three weeks before quit day). Adverse events and adherence to preloading were assessed. They were telephoned one week after quit day and about six weeks after baseline, to collect data on adverse events, adherence to preloading, and use of, and adherence to, other smoking cessation pharmacotherapy.

Data on smoking cessation from the NHS stop smoking service or the participant at + 4 weeks were obtained. At six and 12 months participants were telephoned to obtain data on smoking status and health service use. Abstinence was assessed biochemically by measuring the concentration of expired carbon monoxide.

Biochemically validated abstinence at six months was achieved by 157 of 899 participants (17.5%) in the preloading arm and 129 of 893 (14.4%) in the control arm: difference 3.0% (95% CI: – 0.4 to 6.4%), odds ratio (OR) 1.25 (95% CI: 0.97 to 1.62), P = 0.08 in the primary analysis. When varenicline was used as post-cessation treatment this gave an OR for the effect of preloading of 1.34 (95% CI: 1.03-1.73), P = 0.03: difference 3.8% (95% CI: 0.4 -7.2%).

The investigators conclude: 'Nicotine preloading with a 21 mg/24 hr nicotine patch for four weeks seems to be efficacious, safe, and well tolerated, but probably deters the use of varenicline, the most effective smoking cessation drug. If it were possible to overcome this unintended consequence, preloading could lead to a worthwhile increase in long term smoking abstinence.'

DR PETER SAUL

The Preloading Investigators. Effects on abstinence of nicotine patch treatment before quitting smoking: parallel two arm, pragmatic randomised trial. *BMJ* 2018;361:k2164

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