Cardiovascular disease

Exercise in middle age may reduce risk of heart failure

Two years of high intensity exercise training, in previously sedentary healthy middle-aged adults, improved maximal oxygen uptake (VO_2max) and reduced left ventricular (LV) stiffness, in a study from the United States. The investigators conclude that regular exercise training may protect against the future risk of heart failure with a preserved ejection fraction (HFpEF) by preventing the increase in cardiac stiffness caused by sedentary aging.

A total of 61 healthy, sedentary adults were recruited to a prospective, parallel group, randomised controlled trial. Their mean age was 53 ± 5 years and around half (48%) were male. Participants were randomly assigned to either two years of aerobic exercise and resistance training (n = 34) or a control group (n = 27). Aerobic exercise was carried out for at least 30 minutes, 4-5 days per week, and included at least one high-intensity weekly interval session. Participants also undertook two weekly strength training sessions. Those in the control group performed yoga, balance, and strength training three times a week for two years.

Right heart catheterisation and 3D echocardiography were performed with preload manipulations to define LV end-diastolic pressure-volume relationships and Frank-Starling curves. LV stiffness was calculated by curve fit of the diastolic pressure-volume curve. VO_2max was recorded to measure changes in fitness.

Of the initial 61 participants, 53 completed the study and the majority of participants in the exercise group (mean 88% ± 11%) adhered to the exercise programme.

In the exercise group, VO_2max significantly increased by 18% (95% CI: 15-22%; P < 0.001), whereas there was no improvement in VO_2max in the control group. LV stiffness was significantly reduced in the exercise group (P = 0.0018) but no change was seen in the controls. Exercise also increased LV end-diastolic volume (P < 0.001) whereas pulmonary capillary wedge pressure was unchanged, providing greater stroke volume for any given filling pressure (P = 0.007).

Poor fitness in middle age is associated with poor health and has been linked to the development of heart failure particularly HFpEF. This is likely to be mediated through increased LV stiffness.

The study authors conclude: 'Two years of intensive exercise training, at levels consistent with current public health recommendations, increases maximal oxygen uptake and decreases cardiac stiffness in previously sedentary but otherwise healthy middle-aged adults.

'Regular exercise training may provide protection against the future risk of HFpEF by preventing the increase in cardiac stiffness attributable to sedentary aging.'

This study, although small, provided clear objective evidence of the beneficial physiological adaptations of exercise in middle-aged adults. The reduction in LV stiffness provides a mechanism to prevent the onset of HFpEF — a condition for which there is little effective pharmacological intervention in comparison with heart failure with a reduced ejection fraction.

It is certainly encouraging to have evidence to support exercise as a preventative measure. Furthermore, regular exercise is also beneficial in maintaining a healthy blood pressure and with hypertension as an additional mediator for increased LV stiffness via LVH this may provide another mechanism for preventing the onset of HFpEF.

DR PETER SAVILL

Howden EJ, Sarma S, Lawley JS et al. Reversing the cardiac effects of sedentary aging in middle age - a randomized controlled trial: implications for heart failure prevention. *Circulation* 2018 Jan 8 pii: CIRCULATIONAHA.117.030617. doi:10.1161/CIRCULATIONAHA.117.030617 [Epub ahead of print]

Addiction

Marked regional variations identified in primary care opioid prescribing

Opioid prescribing rates are increasing and show notable geographical variations across England. They are highest in the North and in areas of social deprivation, a study on primary care prescribing has shown. Virtually all the low prescribing areas were in the south of England and nine of the ten highest prescribing areas were northern clinical commissioning groups (CCGs).

The investigators assessed opioid prescribing in primary care in England between August 2010 and February 2014 using mg morphine equivalent as the measure of quantity. They adopted this strategy on the basis that because of the association between adverse effects and opioid dose it is more appropriate to analyse risk relating to dose rather than prescription count (as has been done in a number of previous studies).

Eight opioids were included in the study: buprenorphine, codeine, dihydrocodeine, fentanyl, methadone, morphine, oxycodone and tramadol. Primary care prescribing data were obtained from the Health and Social Care Information Centre.

Over the study period total opioid prescribing showed a steady increase. Tramadol was the most prescribed opioid, followed by buprenorphine and then methadone. Fentanyl was the drug least prescribed.

Buprenorphine, codeine, oxycodone and tramadol prescribing showed the greatest rates of increase while

Table 1

Absolute amount and mean grams of each opioid prescribed over the study period, and the linear correlation between monthly total and time

Opioid	Total amount prescribed over study period (g)	Mean g/month prescribed in England	Increase or decrease over time (Spearman's r)
Buprenorphine	92,500.3	2,151.2	0.86
Codeine	27,922,622.7	649,363.3	0.89
Dihydrocodeine	22,190,184.3	516,050.8	-0.27
Fentanyl	2,489.5	57.9	0.18
Methadone	1,931,295.7	44,913.8	-0.97
Morphine	4,835,679.9	112,457.7	0.75
Oxycodone	2,719,720.2	63,249.3	0.86
Tramadol	139,222,060.4	3,237,722.3	0.80

methadone and dihydrocodeine prescribing decreased, see table 1, above.

Virtually all the low prescribing areas were in the south of England. Nine of the ten highest prescribing areas were northern CCGs, the exception being Bristol in the south west. Comparison of prescribing rates with scores on the Index of Social Deprivation showed a strong relationship ($r = 0.56$, $P < 0.0001$). When latitude was included as a covariate, the correlation was stronger ($r = 0.43$, $P < 0.001$).

The authors acknowledge that their data were not able to identify prescriptions issued specifically for chronic non-cancer pain as opposed to other indications. However, the paper does identify a number of important trends.

Tramadol prescribing is increasing in England and there are potential associated public health risks as tramadol-related deaths are also increasing.

The authors provide three possible explanations for the increase in prescribing: tramadol has filled the 'void' created by the withdrawal of co-proxamol; tramadol is being prescribed in preference to NSAIDs because of concerns about complications associated with the latter; and tramadol is perceived as a drug that lies in between weak and strong opioids, avoiding the risks and stigma associated with strong opioid medications.

This paper provides an overall summary of opioid prescribing in England, its rate of change, and regional differences in prescribing. It shows a north-south gradient and that opioid prescribing rates are highest in areas of social deprivation.

The authors conclude: 'This study exposes increasing rates of prescription of a class of drugs whose use for chronic pain is controversial, with potential for abuse, and an association with serious adverse effects and premature death.'

DR JEZ THOMPSON

Mordecai L, Reynolds C, Donaldson LJ, de C Williams AC. Patterns of regional variation of opioid prescribing in primary care in England: a retrospective observational study. *Br J Gen Pract* 2018; DOI: https://doi.org/10.3399/bjgp18X695057

Obstetrics and gynaecology

Bicarbonate for dystocia improves maternal and fetal outcomes

Administering a drink of sodium bicarbonate dissolved in water to women with dystocia an hour before oxytocin treatment resulted in better outcomes for both mother and child, compared with standard oxytocin treatment alone, a small trial from Sweden has found.

Two hundred consecutive women presenting with dystocia (poor or no progress in labour) were recruited to the trial. All were primigravid, at term, and with uncomplicated pregnancies.

When dystocia was diagnosed they were randomised either to usual management (immediate commencement of an oxytocin infusion to augment labour), or a 4.26 g dose of sodium bicarbonate dissolved in 200 ml of water to drink, with reassessment one hour later. The women given the bicarbonate drink were given oxytocin an hour after the drink.

Maternal blood pH and amniotic fluid lactic acid levels (AFL) were measured at the point of randomisation and repeated in all women one hour later. At delivery the cord blood pH was measured.

Because the presence of blood in amniotic fluid rendered AFL measurement impossible only 90 women randomised to the bicarbonate group completed the study. Completed data were available for 99 women randomised to immediate oxytocin augmentation.

Compared with those in the usual treatment group, in the women given bicarbonate normal unassisted vaginal »

Table 1

Outcome of labour: bicarbonate vs no bicarbonate

	Spontaneous vaginal delivery	Vacuum/forceps delivery	Emergency caesarean section	Post-partum haemorrhage
Bicarbonate n = 90	76 (84.4%)	6 (6.7%)	8 (8.9%)	0 (0%)
No bicarbonate n = 99	67 (67.7%)	24 (24.2%)	8 (8.1%)	16 (16.2%)
Significance	P < 0.01	P < 0.01	NS	-

delivery rates improved, see table 1, above, and additionally, neonatal condition at birth was better, as were measures of acidosis, see table 2, right.

Administration of bicarbonate was associated with a significant reduction in mean AFL levels after one hour of 0.7 mmol/L (from 8.6 to 7.9 mmol/L), and in those with a high baseline level (> 10 mmol/L) there was a mean decrease of 1.0 mmol/L (from 10.9 to 9.9 mmol/L). A significant increase in maternal blood pH (P < 0.001) was seen in the bicarbonate group. There were no changes in AFL levels or pH in the usual treatment group. Cord blood pH was higher compared with those not exposed to bicarbonate.

This small study certainly deserves to be repeated, particularly in other populations and with larger numbers of participants. If a simple and inexpensive mineral supplement can measurably improve labour and neonatal outcomes in dystocia in the first stage of labour the implications are significant.

DR CHRIS BARCLAY

Table 2

Neonatal outcomes: bicarbonate vs no bicarbonate

	Apgar score < 7 at 5 min	Cord pH at delivery	Transfer to neonatal intensive care unit
Bicarbonate	0	7.27	2
No bicarbonate	2	7.23	6
Significance	-	P = 0.01	NS

Wiberg-Itzel E, Wray S, Åkerud H. A randomized controlled trial of a new treatment for labor dystocia. *J Matern Fetal Neonatal Med* 2017 Jun 22:1-8. doi: 10.1080/14767058.2017.1339268. [Epub ahead of print]

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