Welcome to issue 118 of GP Research Review.

Canadian research reports that when a randomly selected sample of adults who had been diagnosed with asthma in the past 5 years were prospectively evaluated with home peak flow and symptom monitoring, spirometry, and serial bronchial challenge tests, about one-third had no evidence of current asthma. The study concludes that in patients such as these, it may be worthwhile reassessing the asthma diagnosis.

Smoking even a small number of cigarettes per day has substantial negative health effects, report researchers from the US National Cancer Institute. Their analysis found that people who consistently smoked on average <1 cigarette per day over their lifetime were 64 times more likely to die early than never smokers, while those who smoked between 1 and 10 cigarettes a day had an 87% higher risk of earlier death than never smokers. Risks were lower among former low-intensity smokers compared to those remained smokers, and risk fell with earlier age at quitting. “There is no safe level of cigarette smoking”, conclude the researchers.

The first study in the Natural Health section helps to clarify the role of gut bacteria on neural function and behaviour. In a mouse model of chronic stress and depression, a single orally administered bacteria strain, \textit{Lactobacillus rhamnosus} \text{JB-1}, attenuated stress-induced behavioural deficits, including changes in sociability and anxiety-like behaviour, and prevented immunoregulatory alterations associated with the stress phenotype. The study researchers suggest that their evidence supports microbe-based interventions for stress-related disorders.

I hope you enjoy this issue and I welcome your comments and feedback.

Kind Regards
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Independent commentary by Associate Professor Jim Reid.

Jim Reid has a private family medicine practice at the Caversham Medical Centre, Dunedin, New Zealand. For full bio CLICK HERE.

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For more information, please go to http://www.medsafe.govt.nz
Reevaluation of diagnosis in adults with physician-diagnosed asthma

Authors: Aaron SO et al.

Summary: This Canadian investigation, conducted from January 2012 through February 2016, recruited 701 adults with physician-diagnosed asthma established within the past 5 years. The primary outcome was the proportion of participants in whom a diagnosis of current asthma could be ruled out, defined as participants who exhibited no evidence of acute worsening of asthma symptoms, reversible airflow obstruction, or bronchial hyperresponsiveness after having all asthma medications gradually tapered off (over 4 study visits) and after a study pulmonologist established an alternative diagnosis. Of the 613 participants who completed the study, current asthma was ruled out in 203 (33.1%). Serious cardiopulmonary conditions were identified in 12 subjects who had previously been misdiagnosed and after an additional 12 months of follow-up, 181 subjects continued to exhibit no clinical or laboratory evidence of asthma. Fewer than half (43.8%) of subjects in whom current asthma was ruled out underwent testing for airflow limitation in the community at the time of initial diagnosis, compared with 55.6% of those whose asthma diagnosis was confirmed.

Comment: The reviewer could not agree more with the sentiments of the authors of this paper. The statement that “all those who wheeze do not necessarily have asthma” needs reinforcing. It is sobering that 33% of this cohort could not be shown to have asthma at the time of testing, and following stopping all medication, after 1 year 29% continued to show no sign of asthma. Those who did not have current asthma were less likely to have had formal testing. Maybe in New Zealand, because we are so asthma conscious, we also over diagnose asthma? Do 20% of our children really have asthma, or did they occasionally wheeze from other causes?


Predictors and causes of long-term mortality in elderly patients with acute venous thromboembolism: a prospective cohort study

Authors: Fallier N et al.

Summary: This prospective follow-up involving 991 patients aged ≥65 years with acute venous thromboembolism sought to determine long-term predictors and causes of death. During a median 30 months of follow-up, 206 patients (21%) died. Multivariate analysis identified the following independent predictors of overall mortality: age (HR 1.32; 95% CI, 1.05 to 1.65, per decade), active cancer (HR 5.80; 95% CI, 4.22 to 7.97), systolic blood pressure <100 mm Hg (HR 2.77; 95% CI, 1.56 to 4.92), diabetes mellitus (HR 1.50; 95% CI, 1.02 to 2.22), low physical activity level (HR 1.92; 95% CI, 1.38 to 2.66), polypharmacy (HR 1.41; 95% CI, 1.01 to 1.96), anaemia (HR 1.48; 95% CI, 1.07 to 2.06), high-sensitivity C-reactive protein ≥40 mg/L (HR 1.88; 95% CI, 1.36 to 2.60), ultra-sensitive troponin >14 pg/mL (HR 1.54; 95% CI, 1.06 to 2.25), and D-dimer >3000 ng/mL (HR 1.45; 95% CI, 1.04 to 2.01). Death was most commonly attributed to cancer (34%), pulmonary embolism (18%), infection (17%), and bleeding (6%).

Comment: In my experience, acute venous thromboembolism is not particularly common in older patients. However, in those who do suffer from this condition, long-term survival is precarious. This study showed that there are a number of factors contributing – polypharmacy (maybe these patients had multimorbidity), low physical activity, cancer, diabetes, and low blood pressure. A number in this study had multiple risk factors, which compounded the risk.


Heavy cannabis use is associated with low bone mineral density and an increased risk of fractures

Authors: Sophocleous A et al.

Summary: This UK study enrolled 200 people who smoke cannabis regularly for recreational purposes and 114 non-users (cigarette smokers who served as controls). Cannabis users were classified as moderate (n=56) or heavy smokers (n=144), depending on whether they reported fewer or more than 5000 cannabis smoking episodes during their lifetime. Heavy cannabis users had lower total hip bone mineral density (BMD; mean Z-score: −0.20 vs +0.2; p<0.0005) and lower spine BMD (−0.5 vs 0.0; p<0.0005) and lower BMI (26.5 vs 29.0; p=0.01) than controls. Heavy users also had a higher fracture rate (rate ratio = 2.17; 95% CI, 1.59 to 2.95; p<0.001) and higher concentrations of cross-linked C-telopeptide of type I collagen (CTX) concentrations (0.3 vs 0.2 pg/mL; p=0.045) and N-terminal propeptide of type 1 procollagen (PII NP; 47.1 vs 41.2 pg/mL; p=0.01), compared with controls. Heavy users had lower serum total 25-hydroxyvitamin D concentrations compared with controls (25.3 vs 36.9 nmol/L; p=0.002).

In multiple regression analysis, heavy cannabis use predicted for spine BMD and accounted for 5.4% of the variance (p=0.035), and predicted for total hip BMD, which accounted for 5.8% of the variance (p=0.001). No such effects were observed with moderate cannabis use.

Comment: The conclusion says it all with respect to bone density. Heavy use of cannabis = low bone density due to high bone turnover and low BMI. There seems to be an independent impact from both low BMI and the use of cannabis itself, both of which compound in the rate of hip fractures.


Intermittent nitrate use and risk of hip fracture

Authors: Misra D et al.

Summary: This study examined the association of incident use of short-acting nitrate formulations (nitroglycerin sublingual/spray/ointment or isosorbide dinitrate injection/patch) with incident hip fracture risk, using data from patients aged ≥60 years with ischemic heart disease and without history of hip fracture from The Health Improvement Network, an electronic medical records database in the UK. The analysis included 14,451 pairs of matched nitrate users and non-users. 573 fractures were recorded during follow-up (257 nitrate users; 316 non-users). Hip fracture was 33% lower among short-acting nitrate users than non-users (HR 0.67; 95% CI, 0.53 to 0.85; p=0.008). Competing risk analysis by death did not change effect estimates.

Comment: Fascinating. Since the advent of interventional management of angina of effort, the use of nitrates as antianginal agents has waned (at least in this country). However, this large study provides pretty convincing evidence of benefit from hip fractures and warrants further research for use in their own right, as a preventative measure.


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Association between gout and aortic stenosis

**Authors:** Chang K et al.

**Summary:** This retrospective case-control study identified 112 cases of aortic stenosis through a review of 1085 outpatient transthoracic echocardiography (TEE) reports. Charts were reviewed to identify diagnoses of gout and the earliest dates of gout and aortic stenosis diagnosis. Cases were age-matched with 112 nonaortic stenosis controls; cardiovascular comorbidities were similar between the groups. Nearly twice as many cases as controls had a history of gout (21.4% vs 12.5% (unadjusted OR 1.90); 95% CI, 1.05 to 3.48; p=0.038). Multivariate analysis retained significance only for gout (adjusted OR 2.08; 95% CI, 1.00 to 4.32; p=0.049). Among subjects with aortic stenosis and gout, gout diagnosis preceded aortic stenosis diagnosis by a mean 5.8 years. The age at onset of aortic stenosis was similar among patients with and without gout (78.7 vs 75.8 years).


Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care

**Authors:** Agar MR et al.

**Summary:** Outcomes are reported for 2027 patients (mean age, 74.9 years) receiving palliative care from inpatient hospice or hospital palliative care services. All patients had life-limiting illness, delirium, and a delirium symptoms score (sum of Nursing Delirium Screening Scale behavioural, communication, and perceptual items) of ≥1. Treatment consisted of age-adjusted titrated doses of oral risperidone (n=82), haloperidol (n=81), or placebo solution (n=84) every 12 hours for 72 hours, based on symptoms of delirium. Patients also received supportive care, individualised treatment of delirium precipitants, and subcutaneous midazolam hydrochloride as required for severe distress or safety. At day 3, delirium symptom scores were significantly higher in the risperidone arm versus the placebo arm (on average 0.48 Units higher; p=0.02), as were scores in the haloperidol arm (on average 0.24 Units higher vs placebo; p=0.009). Compared with placebo, active treatment was associated with more extrapyramidal effects (risperidone, 0.73; 95% CI, 0.09 to 1.37; p=0.03; and haloperidol, 0.79; 95% CI, 0.17 to 1.41; p=0.01). Overall survival was significantly better with placebo than with haloperidol (HR 1.73; 95% CI, 1.20 to 2.50; p=0.003), whereas the between-group difference was not significant for placebo versus risperidone (HR 1.29; 95% CI, 0.91 to 1.64).

**Comment:** In this study, both haloperidol and risperidone did not contribute to control of distressing delirium. Added to this was an increase in extrapyramidal effects, and those in the placebo group had better overall survival. Rather than attempting to suppress delirium symptoms, greater effort needs to be made in establishing and eliminating cause.

**Reference:** JAMA Intern Med. 2017;177(1):34-42

**Goodfellow Gems**

**Antibiotics – shorter courses (5 days) are better (pneumonia and cellulitis)**

A JAMA editorial comments on a trial of 5 versus 10 days of antibiotics for patients hospitalised with community-acquired pneumonia. After 5 days of antibiotic treatment, patients were randomised to either continuing antibiotics, or stopping antibiotics (if afebrile for 48 hours and no more than 1 sign of clinical instability such as hypotension, tachycardia, tachypnoea or hypoxia). The shorter duration group did better at 30 days. Equivalence has also been shown for cellulitis with 5 versus 10 days of antibiotics. There is no evidence that taking antibiotics beyond the point at which a patient’s symptoms are resolved reduces antibiotic resistance. Prolonged antibiotic treatment may instead cause “increased selective pressure driving antibiotic resistance among our colonising microbial flora.”

This Gem has been checked by Associate Professor Mark Thomas, Infectious Disease Physician Auckland City Hospital and the University of Auckland.

**References:**
3. Heptonstall MJ et al., Comparison of Short-Course (5 Days) and Standard (10 Days) Treatment for Uncomplicated Cellulitis. Arch Intern Med 2004. Click here

Gems are chosen by the Goodfellow director Dr. Bruce Arroll to be either practice changing or practice maintaining. The information is educational and not clinical advice.

**Reference:** Lancet. 2017;389(10065):157-66

**Abstract**
Association of long-term, low-intensity smoking with all-cause and cause-specific mortality in the National Institutes of Health–AARP Diet and Health Study  

Authors: Inoue-Choi M et al.  

Summary: These researchers sought to clarify the effects of long-term, low-intensity smoking (<10 cigarettes per day [CPD]) on mortality from all causes and for specific causes of death, using data from 290,215 adults (mean age 71 years) in the National Institutes of Health–AARP Diet and Health Study who were aged 59–82 years at the start of the study. Participants were asked about their smoking behaviours during 9 periods across their lives (from <15 years to ≥70 years). Among current smokers, 159 reported smoking <1 CPD consistently throughout the years that they smoked; 1493 reported consistently smoking between 1 and 10 CPD. In each of these groups, all-cause mortality risk was substantially higher than for never smokers (HR 1.64; 95% CI, 1.07 to 2.51, and HR 1.87; 95% CI, 1.64 to 2.13, respectively). Associations were similar between genders for all-cause mortality and were observed across a range of smoking-related causes of death, with a particularly strong association for lung cancer mortality (HR 9.12; 95% CI, 2.92 to 28.47, and HR 15.9; 95% CI, 1.27 to 1.59) for consistent smokers of <1 and 1–10 CPD, respectively). Former consistent smokers of <1 and 1–10 CPD who quit at an older age had a higher all-cause mortality risk than those who quit at a younger age, with a median follow-up of 5.3 years, regular tea drinkers had a slower progression of coronary artery calcium compared with never drinkers in adjusted multivariable analysis, which correlated with a statistically significant lower incidence of cardiovascular events for regular tea drinkers (adjusted HR 0.71; 95% CI, 0.53 to 0.95). Compared with never coffee drinkers, regular coffee intake was not statistically associated with coronary artery calcium progression or cardiovascular events (adjusted HR 0.97; 95% CI, 0.78 to 1.20). Caffeine intake was marginally inversely associated with coronary artery calcium progression.  

Comment: This large study (290,215 participants) looked at those who currently smoked between 1 and 10 cigarettes a day. But a large number of these admitted to heavier smoking earlier in life, which may have influenced the study outcome. However, 1/5 of all those in the study had historically been light smokers and this group also had a higher all-cause mortality than non-smokers. In addition, in those light smokers who had ceased, all-cause mortality was reduced progressively with ceasing at a younger age. So, all cigarette smoking increases risk.  

Abstract

EVIDENCE-BASED NATURAL HEALTH BY DR CHRIS TOFIELD

Oral treatment with Lactobacillus rhamnosus attenuates behavioural deficits and immune changes in chronic social stress  

Authors: Bharwani A et al.  

Summary: In this model of chronic stress and depression, male C57BL/6 mice were treated orally over 28 days with either Lactobacillus rhamnosus (JB-1)™ or vehicle. During the final 10 days of treatment, all animals were subjected to chronic social defeat and assessed for alterations in behaviour and immune cell phenotype. JB-1 attenuated stress-induced anxiety-like behaviour and prevented immunoregulatory alterations associated with the stress phenotype, but did not alter development of aggressor avoidance following social defeat. Microbial treatment attenuated stress-related activation of dendritic cells and increased levels of IL-10 regulatory T cells. JB-1 also modulated the effect of stress on faecal metabolites with neuroactive and immunomodulatory properties.  

Comment: The pace of Westerners’ lifestyles has increased dramatically over the last few decades, and with it we are seeing an increase in stress-related disorders such as anxiety, for which anxiolytics don’t always cut the mustard. Admittedly, we can’t draw any firm conclusions from this study in mice, but it makes physiological sense that the beneficial immunomodulatory and neurological changes seen in the Lactobacillus rhamnosus group should translate into similar effects in humans.  

Abstract

Associations of coffee, tea, and caffeine intake with coronary artery calcification and cardiovascular events  

Authors: Miller PE et al.  

Summary: This analysis examined coffee and tea data from 6506 ethnically diverse participants in the Multi-Ethnic Study of Atherosclerosis (a medical research study involving more than 6000 men and women from 6 communities in the US) with intake for each beverage classified as never, occasional (<1 cup/day), and regular (≥1 cup/day). Over a median follow-up of 5.3 years, regular tea drinkers had a slower progression of coronary artery calcium compared with never drinkers in adjusted multivariable analysis, which correlated with a statistically significant lower incidence of cardiovascular events for regular tea drinkers (adjusted HR 0.71; 95% CI, 0.53 to 0.95). Compared with never coffee drinkers, regular coffee intake was not statistically associated with coronary artery calcium progression or cardiovascular events (adjusted HR 0.97; 95% CI, 0.78 to 1.20). Caffeine intake was marginally inversely associated with coronary artery calcium progression.  

Comment: So, tea looks to be better for heart health than coffee. Regular tea intake, as compared to no tea intake, slowed coronary artery calcium build-up in this US study, and importantly also reduced the incidence of cardiovascular events over a sizeable 11 years. On the downside, occasional coffee intakers had a higher risk of cardiovascular events, whereas regular coffee drinkers (≥1 cup a day) showed neither reduction nor increase in risk. Sigh of relief for some of us?  

Abstract

Dr Christopher Tofield  

Dr Tofield completed his medical training at St Bartholomew’s and the Royal London Hospital in London. He now works part time in general practice in Tauranga, is involved with clinical research, has published several medical papers and a textbook on pharmacology, and is clinical advisor to Bay of Plenty District Health Board.  

For full bio CLICK HERE.

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