# GP RESEARCH REVIEW™

Making Education Easy

Issue 181 – 2021


## In this issue:



**Abbreviations used in this issue**
**ACEI** = angiotensin-converting enzyme inhibitor
**AF** = atrial fibrillation
**aHR** = adjusted hazard ratio
**ARB** = angiotensin II receptor blocker
**BMI** = body mass index
**CI** = confidence interval
**COVID-19** = coronavirus disease 2019
**CRP** = C-reactive protein
**HR** = hazard ratio
**IBD** = inflammatory bowel disease
**LVEF** = left ventricular ejection fraction
**NYHA** = New York Heart Association
**OR** = odds ratio
**RCT** = randomised controlled trial
**RR** = risk ratio

# Welcome to issue 181 of GP Research Review.

A large population-based study from Ontario, Canada confirms that vaccination with two doses of mRNA COVID-19 vaccine is not only highly effective against symptomatic infection, but is also highly protective against severe outcomes in patients testing positive for SARS-CoV-2. A large international study has found that the risk of dementia in old age is lower in people with cognitively stimulating jobs than in those with non-stimulating jobs. In our Natural Health section, Dr Chris Tofield has reviewed two interesting studies, one investigating the use of probiotics in the treatment of functional abdominal pain in children, and the other, the potential effects of pomegranate on rheumatoid arthritis.

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

Kind regards,
Jim


**Assoc Professor Jim Reid**
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## Effectiveness of BNT162b2 and mRNA-1273 Covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe Covid-19 outcomes in Ontario, Canada

**Authors:** Chung H et al.


**Summary:** This study used data from Ontario to assess COVID-19 mRNA vaccine effectiveness against symptomatic infection and hospital admission or death among 324,033 people with symptoms of COVID-19. In total, 53,270 (16.4%) people were positive for SARS-CoV-2, of whom 2479 (4.7%) were admitted to hospital or died, and 21,272 (6.6%) had received at least one dose of vaccine. From 14 days after one dose, vaccine effectiveness against symptomatic infection was 60% (95% CI 57-64) and increased from 48% (95% CI 41-54) after 14-20 days to 71% (95% CI 63-78) after 35-41 days. Effectiveness ≥7 days after two doses was 91% (95% CI 89-93). Effectiveness against hospital admission or death ≥14 days after one dose was 70% (95% CI 60-77) and increased from 62% (95% CI 44-75) at 14-20 days to 91% (95% CI 73-97) at ≥35 days. Vaccine effectiveness ≥7 days after two doses was 98% (95% CI 88-100). Among adults aged ≥70 years, vaccine effectiveness was lower shortly after one dose but was similar to that in younger people after 28 days. Vaccine effectiveness was high against variants with the E484K mutation after two doses.


**Comment:** If only the vaccination doubters could read and have the ability to interpret the outcome of many studies like this that are appearing in the literature. There can now be no doubt of the effectiveness of COVID-19 vaccination, especially after two doses, including protection against the delta mutation. Will people never learn? Some of us remember polio, and for those younger, measles. Vitamin C and herbal remedies were a fat lot of use.

***Reference: BMJ. 2021;374:n1943***
Abstract


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## Cognitive stimulation in the workplace, plasma proteins, and risk of dementia: Three analyses of population cohort studies

**Authors:** Kivimäki M et al.

**Summary:** This multinational analysis examined the relationship between cognitively stimulating work and dementia risk among 107,896 participants in 7 population-based prospective cohort studies from the IPD-Work (individual-participant data meta-analysis in working populations) consortium. Over 1.8-million-person years, 1143 people were diagnosed with dementia. Risk of dementia was lower among participants with high- versus low-cognitive stimulation at work (incidence 4.8 vs 7.3 per 10,000 person years; aHR 0.77; 95% CI 0.65-0.92) and the relationship was robust to adjustment for education, smoking, heavy alcohol consumption, physical inactivity, job strain, obesity, hypertension, diabetes, coronary heart disease and stroke (aHR 0.82; 95% CI 0.68-0.98). Higher cognitive stimulation at work was associated with lower levels of proteins that inhibit central nervous system axonogenesis and synaptogenesis (slit homologue 2 [SLIT2], carbohydrate sulfotransferase 12 [CHSTC], peptidyl-glycine α-amidating monooxygenase [AMD]) and an increased dementia risk was associated with SLIT2 (aHR per standard deviation 1.16; 95% CI 1.05-1.28), CHSTC (aHR 1.13; 95% CI 1.00-1.27) and AMD (aHR 1.04; 95% CI 0.97-1.13).

**Comment:** Mmmmmmm. And I was thinking about retiring – one day. These studies suggest that riding off into the sunset increases the risk of dementia. Perhaps time to reflect and reconsider. If only golf and fishing were as stimulating as seeing patients – I still learn something every single day and long may I be privileged for it continue.

***Reference: BMJ. 2021;374:n1804***
Abstract

## Risk factors and management of pulmonary infection in elderly patients with heart failure: A retrospective analysis

**Authors:** Peng Q & Yang Q

**Summary:** This single-centre, retrospective study (2018-20) evaluated pulmonary infection clinical characteristics and risk factors in 201 elderly heart failure patients. Incidence of pulmonary infection was 23.88% and there were differences ($p < 0.05$) in age, diabetes status, NYHA grade, LVEF, and CRP between infection and non-infection groups. There were no differences in sex, BMI, alcohol intake, smoking, hypertension, hyperlipidaemia, and length of hospital stay between the groups. Logistic regression analyses suggested that age ≥70 years, diabetes, NYHA grade III, LVEF ≤55%, and CRP ≥10 mg/L were independent risk factors for pulmonary infection. The most common pathogens were *Pseudomonas aeruginosa* (34.48%), *Staphylococcus aureus* (19.57%), and *Klebsiella pneumoniae* (15.22%).

**Comment:** This study looked at 201 patients and showed that over a 2-year period, just over one-fifth of those in heart failure developed a pulmonary infection. There were large differences in the demographics of the group but the risk factors that particularly increased infection risk were age (>70 years) NYHA failure grade III, LVEF <55%, and CRP >10mg/L. Not so important were diabetes, alcohol consumption, hypertension, and hyperlipidaemia.

***Reference: Medicine (Baltimore) 2021;100(38):e27238***
Abstract

## The efficacy and safety of alpha-adrenergic blockers for medical expulsion therapy in patients with ureteral calculi: A meta-analysis of placebo-controlled trials

**Authors:** Yu Z-W et al.

**Summary:** This meta-analysis examined the use of α-adrenergic blockers as a medical expulsive therapy (MET) in patients with ureteral calculi based on 8 placebo-controlled studies (n = 2284). Overall, α-adrenergic blockers had no effect on clearance of stones in the urinary tract (RR 1.05; 95% CI 1.00-1.11). Subgroup analysis suggested that α-adrenergic blockers may be effective for distal urinary tract stones (RR 1.08; 95% CI 1.02-1.15). The combination of MET with α-adrenergic blockers was associated with dizziness (RR 1.37; 95% CI 1.06-1.79) and retrograde ejaculation (RR 3.10; 95% CI 1.81-5.29).

**Comment:** α-adrenergic blockers are recommended in New Zealand in Pathways to assist in treatment of ureteric stone clearance. This study was a meta-analysis of their use as compared to placebo. Eight studies were included with 2284 patients. And the outcome – α-adrenergic blockers were no more effective than placebo, but subgroup analysis demonstrated that there was a marginal effect when the stone was distally placed. There was an expected large number of adverse effects in the blocker group, including dizziness (read postural hypotension).

***Reference: Medicine (Baltimore) 2021;100(37):e27272***
Abstract



## Over-prescription of short-acting beta agonists in the treatment of asthma

**Authors:** Looijmans-van den Akker I et al.

**Summary:** This multicentre retrospective analysis of data from Dutch electronic medical records (n = 1161) examined the use of asthma medication in primary care and whether excessive short-acting β2-agonist (SABA) use (≥400 inhalations per year) was associated with poor asthma control and exacerbations. Among SABA recipients (n = 766), 193 (25%) overused SABAs, among whom 19% had an exacerbation versus 7% of appropriate SABA users. Among patients using asthma medication, the odds of having an exacerbation were 2.9-fold higher when using an inappropriate number of SABA inhalations (OR 2.897; 95% CI 1.87-4.48).

**Comment:** The fact that overuse of SABAs can lead to tachyphylaxis has been known since the early 80s. It has also been known since that time that the more they are used, the more unstable the asthma becomes. This study showed that 19% of inappropriate users suffered an exacerbation compared with 7% of those using them appropriately. Of all those using SABAs, 25% were using them inappropriately. The fact that they can provide instant gratification with relief of wheeze is a compelling reason for their use, but clinicians must get the message across that it is better to treat the cause of the symptoms rather than the symptoms themselves.

***Reference: Fam Pract. 2021;38(5):612-616***
Abstract

## Association between angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and community-acquired pneumonia: A nationwide population propensity-score matching study

**Authors:** Lin S-Y et al.

**Summary:** This Taiwanese database analysis of community-acquired pneumonia examined its relationship with angiotensin-converting enzyme inhibitor (ACEI; n = 58,062) or angiotensin II receptor blocker (ARB; n = 67,944) use. The HR of community-acquired pneumonia for ARB users relative to non-ARB users was 0.33. The HR of community-acquired pneumonia was 0.71 in ACEI users versus nonusers. Stratification analysis suggested that ARB and ACEI both exhibited a protective effect for community-acquired pneumonia across age and sex. Recipients of ARBs for <100 days had a greater reduction in the risk of community-acquired pneumonia (adjusted HR [aHR] 0.58) than the non-ARB cohort, while ACEI recipients for 121-450 days were less likely to have community-acquired pneumonia (aHR 0.50).

**Comment:** ACEIs have long been associated with a side effect of cough, as have, to a much lesser extent, ARBs. This study looked at possible association with community-acquired pneumonia. In short, it showed that both had a protective effect on acquiring infection, with ARB users having an HR of 0.33 and ACEI patients having an HR of 0.71.

***Reference: Int J Clin Pract. 2021;75(10):e14476***
Abstract

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## Goodfellow Gems

### Long covid in patients who were not hospitalised

This is from an Arizona cohort of 303 non-hospitalised patients.[1] While some patients recover quickly, persistent symptoms are not uncommon. All patients had a positive covid test and were followed for a median of 61 days (range 30 to 250).

The paper reports on 28 symptoms. After 30 days, fatigue was reported in 37.5% of patients, and after 60 days, it was 47.1% (some lost to follow up). For breathlessness for those time periods, it was 37.5% and 45.5%. The 5th most common symptom was changes in smell or taste, 26.4% and 24.8. High blood pressure was present in 11.1% and 14.1%, respectively. The median number of symptoms was 3 (range 1 to 20).

The response rate to the initial questionnaire was 55.8% and was completed by 24/2/2021, so it is not clear if this included the delta variant.

**References:**
1. Post-acute sequelae of COVID-19 in a non-hospitalized cohort: Results from the Arizona CoVHORT. Plos One (2021) View 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. www.goodfellowunit.org/gems**

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## The influence of constipation on asthma: A real-world, population-based cohort study

**Authors:** Huang Y-C et al.

**Summary:** This Taiwanese, nationwide, population-based cohort study of 86,860 constipated patients and 86,860 controls assessed the risk of asthma in constipated patients who might have altered gut microflora contributing to asthma via the gut-lung axis. Asthma incidence was higher in constipated than non-constipated patients (10.4 vs 5.7 per 1000 person-years) with a 1.81-fold greater risk after adjustment for age, gender, urbanisation, comorbidities, and medications (aHR 1.81; 95% CI 1.74-1.88). Subgroup analyses, suggested that patients aged 20-39 years had a 2.01-fold higher risk of asthma in the constipation cohort (95% CI 1.82-2.22). Severity of constipation was associated with increased risk of asthma, with an aHR of 1.92 (95% CI 1.84-2.00) for ≤30 days, 2.07 (95% CI 1.94-2.21) for 31-120 days, and 2.10 (1.96-2.25) for >120 days of laxative prescriptions ($p < 0.001$).

**Comment:** Fascinating. I know a little bit about asthma, and this is the first time that I have seen anything about its relationship with constipation. The asthma rate was doubled in the constipated group which had a 1.81-fold increase in risk as compared with the non-constipated. And the more severe the constipation, the greater the risk of asthma. I must say this is something I have not noticed clinically, but then again, I have never asked!!!!

***Reference: Int J Clin Pract. 2021;75(10):e14540***
Abstract

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## Direct oral anticoagulants versus warfarin in morbidly obese patients with nonvalvular atrial fibrillation: A systematic review and meta-analysis

**Authors:** Mhanna M et al.

**Summary:** This systematic review and meta-analysis examined whether direct oral anticoagulants (DOACs) are effective and safe in morbidly obese patients (BMI >40 or weight >120 kg) with nonvalvular atrial fibrillation (NVAF) based on 10 studies including 89,494 patients on oral anti-coagulation therapy (DOACs n = 45,427; warfarin n = 44,067). The stroke or systemic embolism (SSE) rate was lower in DOAC than warfarin recipients (OR 0.71; 95% CI 0.62-0.81; $p < 0.0001$). The major bleeding rate was also lower with DOACs versus warfarin (OR 0.60; 95% CI 0.46-0.78; $p < 0.0001$). Subgroup analysis suggested that stroke or systemic embolism and major bleeding event rates were lower with rivaroxaban and apixaban than warfarin; however, dabigatran was noninferior to warfarin for stroke or systemic embolism rate but superior for major bleeding.

**Comment:** This meta-analysis of 10 studies including nearly 89,500 subjects looked at the efficacy and safety of DOACs compared to warfarin when used in the morbidly obese. Points of interest were embolic stroke, and major bleeding. DOACs (especially rivaroxaban and apixaban) were clearly superior to warfarin in outcome in both parameters, whereas dabigatran, while similar in embolic occurrence, was also superior in safety.

***Reference: Am J Ther. 2021;28(5):e531-e539***
Abstract



### Independent commentary by Associate Professor Jim Reid

Jim Reid graduated in medicine at the University of Otago Medical School in Dunedin, New Zealand. He had previously trained as a pharmacist. He undertook postgraduate work at the University of Miami in Florida, USA. He headed the Department of General Practice and Rural Health at the Dunedin School of Medicine for over ten years and, following that, was Postgraduate Dean, acting Dean, and then Deputy Dean of the School for several years. Jim also has a private family medicine practice at the Meridian Medical Centre, Dunedin, New Zealand. He is a Life Member and a Distinguished Fellow of the Royal New Zealand College of General Practitioners and a Fellow of the American College of Chest Physicians. He serves on the scientific advisory panel of the NZ Asthma and Respiratory Foundation and is one of the authors of all three of the recently published guidelines - Children's Asthma, Adult and Adolescent Asthma, and COPD. He is also a director for the New Zealand Formulary. **For full bio CLICK HERE.**



## EVIDENCE-BASED NATURAL HEALTH
*by Dr Chris Tofield*

### Use of probiotics in the treatment of functional abdominal pain in children – systematic review and meta-analysis

**Authors:** Trivić I et al.

**Summary:** This systematic review and meta-analysis examined probiotic effects of *Lactobacillus rhamnosus* GG and *Lactobacillus reuteri* DSM 17938 on functional abdominal pain in children based on 9 RCTs (n = 702). Children taking *L. reuteri* had reduction in pain intensity (mean difference -1.24; 95% CI -2.35 to -0.13) and an increase in the number of days without pain (mean difference 26.42 days; 95% CI 22.67-30.17). There were no differences for all other outcomes between probiotics and placebo.

**Comment:** *L. reuteri* has previously been shown to protect against nephropathy in diabetic mice, indicating a possible benefit that is yet to be studied in humans. This review, however, dealt with treatment of abdominal pain in children, for which probiotics are commonly used by parents. Unfortunately, other than achieving some reduction in pain intensity, *L. reuteri* failed to produce a significant impact on this all-too-common symptom in children.

***Reference: Eur J Pediatr. 2021;180(2):339-351***
Abstract

### Potential effects of pomegranate (*Punica granatum*) on rheumatoid arthritis: A systematic review

**Authors:** Malek Mahdavi A et al.

**Summary:** This systematic review of available evidence examined the potential properties of pomegranate (*Punica granatum*) on rheumatoid arthritis based on 12 studies. Human, animal, and *in vitro* studies indicated a potential beneficial effect of pomegranate on clinical symptoms, inflammatory and oxidative factors in rheumatoid arthritis by reducing inflammation and oxidative stress.

**Comment:** Pomegranate has been used for medicinal purposes for thousands of years and is now known as one of the superfoods. The authors' statement here that pomegranate can 'manage rheumatoid arthritis complications' may be a bit bold, but there is certainly merit in using this fruit or its extracts for its known antioxidant properties.

***Reference: Int J Clin Pract. 2021;75(8):e13999***
Abstract


### Dr Christopher Tofield

Dr Tofield completed his medical training at St Bartholomew's and the Royal London Hospital in London. He has extensive experience in general practice, spent several years in clinical research, has published several medical papers, is clinical advisor to Bay of Plenty District Health Board and practices skin cancer medicine and surgery. Chris also has a background in medical writing and editing and while at medical school published a medical textbook on pharmacology. Chris is responsible for sourcing and short-listing national and international studies for GP Research Review. He also selects papers and provides commentary for the Natural Health section in GP Research Review.