GP RESEARCH REVIEW™

Making Education Easy

Issue 1 – 2019

In this issue:

Abbreviations used in this issue

BMI = body mass index
BP = blood pressure
CVD = cardiovascular disease
eGFR = estimated glomerular filtration rate
HbA1c = haemoglobin A1c
HR = hazard ratio
IHD = ischaemic heart disease
LDL = low density lipoprotein
MACE = major adverse cardiovascular events
RR = relative risk

Welcome to the latest issue of GP Research Review.

I know I said this at the time of the 100th issue, but who would have thought that when Shaun Holt asked me to be involved 150 months ago that I would still be doing it – and still enjoying it. A lot of water has passed under the bridge since then, some personal, some professional, some happy, some sad. I have left the employ of the medical school, and have an honorary appointment in the Department of the Dean at the Dunedin School. I am still practising on a 6/10 basis (and enjoying it), and I have been working for BPAC 3/10 helping to produce the material that you get in your inbox (almost) weekly.

I hope you enjoy Research Review as much as I still like cutting to the chase with the papers reviewed. I used to teach Critical Appraisal to my Master's Class and that has placed me in good stead.

Keep the cards and letters coming – I reply to as many as I can.

Kind regards,
Jim

Assoc Professor Jim Reid
jimreid@researchreview.co.nz

…I love receiving these thanks, Jim. Your pithy comments are great!!!! ANON.

…I have been receiving Research Review for years and I find it very useful. GP.

I am a regular reader of the GP Research Review. I am always very appreciative of the succinct summaries and commentaries from Jim - I enjoy his comments and very much appreciate his ability to translate the academic research into pithy practical points and questions for the reality of our NZ general practice world. ASSOCIATE PROFESSOR NIKKI TURNER

Polypill for cardiovascular disease prevention in an underserved population

Authors: Muñoz D et al.

Summary: This US 12-month, randomised controlled trial tested the use of a polypill for the prevention of CVD (atorvastatin 10 mg, amlodipine 2.5 mg, losartan 25 mg, and hydrochlorothiazide 12.5 mg) or the usual-care in low socioeconomic status (75% had annual income <US$15,000) and non-white (96% black) adults (n = 303) in Alabama without CVD. The baseline mean estimated 10-year CVD risk was 12.7%, BP was 140/83 mmHg, and the LDL cholesterol level was 113 mg/dL; monthly polypill cost was US$26. After 12 months, adherence was 86%, mean systolic BP had decreased by 9 mmHg versus 2 mmHg with usual-care (difference -7 mmHg; 95% CI -12 to -2; p = 0.003). Mean LDL cholesterol decreased by 15 mg/dL versus 4 mg/dL (difference -11 mg/dL; 95% CI -18 to -5; p < 0.001).

Comment: This is a point well taken. There is good evidence that the more complex a treatment regime, including increasing the number of medications, the more likely is the risk of non-compliance. With the emergence of blister packing, which is not taken into account in this paper, there is no doubt that with a number of new national CVD prevention guidelines (including NZ) the complexity of the treatments being recommended is escalating. In some, treatment with 2 hypotensive agents at diagnosis of hypertension is being suggested. Add in a statin and then there is 3 to open the batting. The polypill in this study contained 4 agents, and if such treatment were to be accepted as mainstream there will need to be adequate choice of differing combinations and dose. Worth thinking about though!

Reference: N Engl J Med. 2019;381:1114-23
Abstract

Association of treatment with metformin vs sulfonylurea with major adverse cardiovascular events among patients with diabetes and reduced kidney function

Authors: Roumie CL et al.

Summary: This US retrospective cohort analysis compared major adverse cardiovascular events (MACE) among Veterans Health Administration patients with diabetes and reduced kidney function receiving metformin (n = 67,749) or a sulfonylurea (n = 28,976). A propensity score weighted cohort included 24,679 metformin and 24,799 sulfonylurea users (median age 70 years; 98% male, 82% white, median eGFR 55.8 mL/min/1.73 m^2; HbA1c 6.6%). During a median follow-up of 1.0 years for metformin and 1.2 years for sulfonylurea, metformin was associated with 1048 MACE versus 1394 with sulfonylurea (23.0 vs 29.2 per 1000 person-years); the cause-specific adjusted HR for MACE was 0.80 (95% CI 0.75-0.86) for metformin versus sulfonylureas (adjusted rate difference: 5.8 fewer events per 1000 person-years; 95% CI 4.1-7.3).

Comment: This is a large 15-year study that compared outcomes of type 2 diabetics with impaired kidney failure who were treated with either metformin or sulfonylurea. In this country, it is common for these medications to be used together. This paper does not include a combined group, as it was an either/or study. And the result… there was not much in it (only 5.8 fewer MACE per 1000 person years) but metformin won the race!

Reference: JAMA. 2019:322(12):1167-77
Abstract

Association of ideal cardiovascular health at age 50 with incidence of dementia: 25 year follow-up of Whitehall II cohort study

Authors: Sabia S et al.

Summary: This follow-up to the prospective Whitehall II cohort study conducted in 7899 London civil servants, analysed the association between cardiovascular health score (Life Simple 7 metrics: smoking, diet, physical activity, BMI, fasting glucose, blood cholesterol, BP) recorded at age 50 and subsequent incidence of dementia. Over a median follow-up of 24.7 years, 347 incident cases of dementia were recorded. The incidence rate of dementia in those with poor cardiovascular health was 3.2 per 1000 person-years (95% CI 2.5-4.0), the absolute rate difference for intermediate cardiovascular health was -1.5 (95% CI -2.3 to -0.7) and for optimal cardiovascular health it was -1.9 (95% CI -2.8 to -1.1). Higher scores were associated with lower dementia risk per 1 point increment (HR 0.89; 95% CI 0.85-0.95). Similar associations were observed for both behavioural subscales (HR per 1 point 0.87; 95% CI 0.81-0.93) and biological (HR per 1 point 0.91; 95% CI 0.83-1.00). An association between cardiovascular health at age 50 and dementia also occurred in those free of cardiovascular disease during follow-up (HR 0.89 per 1 point; 95% CI 0.84-0.95).

Comment: The Life Simple 7 score is a measure of cardiac health devised by the American Heart Association (healthy weight, healthy diet, physical activity, BP, blood cholesterol, blood sugar, and smoking status). This prospective study basically showed that better cardiovascular health reduced the risk of developing dementia. It looked at the Life Simple 7 score at the age of 50 years, and followed the group for nearly 25 years. In brief, the lower the Life Simple 7 score (low score = worse cardiac health) the greater the chance of developing dementia.

Reference: BMJ. 2019;366:l4414
Abstract

Potential impact on prevalence of obesity in the UK of a 20% price increase in high sugar snacks: modelling study

Authors: Scheelbeek PFD et al.

Summary: These UK authors conducted a modelling study to estimate the impact of a 20% price increase in the cost of high-sugar snacks on BMI and obesity. Data on product level household expenditure from 36,324 households to estimate changes in energy purchase and data on 2544 adults from the National Diet and Nutrition Survey (2012-16) to estimate changes in BMI and prevalence of obesity were used. Across all income groups, the average reduction in energy consumption was estimated to be 8.9 × 10^3 kcal (95% CI -13.1 to 14.2 × 10^3 kcal); BMI was estimated to decrease by 0.53 (95% CI -1.01 to -0.06) and result in a reduction in the UK obesity prevalence after one year by 2.7 % (95% CI -3.7 to -1.7 percentage points). The effect was greatest in low-income households classified as obese and least in high-income households classified as not overweight.

Comment: This is another study that demonstrates the association that pricing of high sugar containing snacks/drinks has on consumption. The impact of increased price was greatest on low-income households, which is where lies the greatest effect of the obesity epidemic. There are now a number of studies demonstrating the same outcome, lower consumption of high sugar containing drinks being related to price, it is becoming a no-brainer. But, who has got the courage with the ballot box looming!

Reference: BMJ. 2019;366:l4786
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. He headed the Department of General Practice and Rural Health at the Dunedin School of Medicine for over 10 years and, following that, was Post-graduate Dean, acting Dean, and then Deputy Dean of the School for a number of years. Jim also has a private family medicine practice at the Caversham 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 a director for both BPAC and the New Zealand Formulary. Jim has a special interest in Respiratory Medicine and has published widely in influenza, asthma and COPD. He is active in research in respiratory medicine and has had considerable international lecturing experience.

Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up: results from the prospective EPIC-Oxford study

Authors: Tong TYN et al.

Summary: Data from the prospective EPIC-Oxford cohort study (n = 48,188) were analysed to assess the association of vegetarianism with risks of ischaemic heart disease and stroke in participants (24,428 meat eaters, 7506 fish eaters, 16,254 vegetarians/vegans) with no history of ischaemic heart disease, stroke or angina. Over a follow-up period of 18.1 years, 2820 ischaemic heart disease cases, 519 ischaemic stroke cases and 300 haemorrhagic stroke cases occurred. After sociodemographic and lifestyle adjustment, lower rates of ischaemic heart disease were observed in fish eaters (HR 0.87; 95% CI 0.77-0.99) and vegetarians (HR 0.78; 95% CI 0.70-0.87) than meat eaters ($p < 0.001$ for heterogeneity), equivalent to 10 fewer cases per 1000 of ischaemic heart disease (95% CI 6.7 to 13.1) over 10 years. Associations for ischaemic heart disease were partly attenuated by adjustment for self-reported high cholesterol, BP, diabetes, and BMI (HR 0.90; 95% CI 0.81-1.00). However, vegetarians had 20% higher rates of total stroke (HR 1.20; 95% CI 1.02-1.40), equivalent to 3 more cases of total stroke per 1000 population (95% CI 0.8-5.4 more) over 10 years, primarily as a result of a higher rate of haemorrhagic stroke.

Comment: This is a large study that demonstrated that over a maximum of 17 years and a minimum of 9 years duration, vegetarians (including vegans) and fish eaters fared better than meat eaters with a 13% reduction in ischaemic heart disease, whereas vegetarians were worse off in the stroke department with a 20% increase over meat eaters. Really out of the frying pan for one and into the fire with the other!!!!

Reference: BMJ. 2019;366:l4897
Abstract

…Just wanted to say I enjoy the GP research articles and use some of the articles to inform my teaching and learning process with students. *RN AND NURSE EDUCATOR.*

…Thanks so much for the GP Research Review. Always interesting and relevant.
PRACTICE NURSE.

…Keep the comments coming please - they condense the articles into logical & easy to understand data that one can relate to [nursing] practice. *CLINIC NURSE.*

Thyroid replacement therapy, thyroid stimulating hormone concentrations, and long term health outcomes in patients with hypothyroidism: longitudinal study

Authors: Thayakaran R et al.

Summary: This retrospective cohort study (1995-2017) using data from a UK electronic patient database (The Health Improvement Network; THIN) examined whether thyroid stimulating hormone (TSH) levels in 162,369 patients with hypothyroidism were associated with all-cause mortality and risk of CVD and fractures. Compared to patients with a reference TSH level category (2-2.5 mIU/L), the risk of ischaemic heart disease increased in patients with a high (>10 mIU/L) TSH level (HR 1.18; 95% CI 1.02-1.38; $p = 0.03$) as did heart failure (HR 1.42; 95% CI 1.21-1.67; $p < 0.001$). A protective effect for heart failure occurred in those with very-low (<0.1 mIU/L) TSH (HR 0.79; 95% CI 0.64-0.99; $p = 0.04$) or low (0.1-0.4 mIU/L) TSH (HR 0.76; 0.62-0.92; $p = 0.006$) levels. Increased mortality occurred in the very-low (TSH <0.1 mIU/L; HR 1.18; 95% CI 1.08-1.28; $p < 0.001$), high (4-10 mIU/L; HR 1.29; 95% CI 1.22-1.36; $p < 0.001$) and highest (>10 mIU/L; HR 2.21; 95% CI 2.07-2.36; $p < 0.001$) TSH levels. Fragility fracture risk increased in patients in the highest TSH category (>10 mIU/L; HR 1.15; 95% CI 1.01-1.31; $p = 0.03$).

Comment: Hypothyroidism is a relatively common condition seen in general practice. This large study (n = 162,396) had a number of outcome measures including ischaemic heart disease, heart failure, stroke/transient ischaemic attack, atrial fibrillation, any fractures, fragility fractures and mortality. The standard lab measurement for determining the correct replacement dose of thyroxine is the level of TSH. The study showed that risk of ischaemic heart disease and heart failure was doubled with high levels (TSH >10 mIU/L; insufficient replacement of thyroxine), but if the TSH was kept within reference levels, there was no difference in other outcome measures.

Reference: BMJ. 2019;366:l4892
Abstract

Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence

Author: Collaborative Group on Hormonal Factors in Breast Cancer

Summary: This review and meta-analysis used individual level data from eligible prospective studies to examine the breast cancer risk associated with different types of menopausal hormone therapy (MHT) based on data for 108,647 postmenopausal women who developed breast cancer at a mean age of 65 years of whom 55,575 (51%) had received MHT. Mean duration of MHT was 10 years in current users and 7 years in past users, mean age at menopause and at starting MHT was 50 years. All MHT types, with the exception of vaginal oestrogens, were associated with an excess breast cancer risk, which increased with duration and were greater for oestrogen-progestagen than oestrogen-only. The excess risks were present during years 1-4 in current users (oestrogen-progestagen RR 1.60; 95% CI 1.52-1.69; oestrogen-only RR 1.17; 95% CI 1.10–1.26), and were 2-fold higher during years 5-14 (oestrogen-progestagen RR 2.08; 95% CI 2.02-2.15; oestrogen-only RR 1.33; 95% CI 1.28-1.37). Oestrogen-progestagen risks between years 5-14 were higher with daily use than with less frequent progestogen use (RR 2.30; 95% CI 2.21-2.40 vs 1.93; 95% CI 1.84-2.01). The RRs during years 5-14 were greater for oestrogen-receptor-positive tumours than for oestrogen-receptor-negative tumours, and were attenuated by starting MHT at >60 years of age or by excess adiposity (low risk for oestrogen-only MHT in obese women). Excess risk persisted for more than 10 years after ceasing MHT, depending on duration of use, with little excess risk after MHT use of <1 year.

Comment: It is interesting how, in medicine, things come the full circle. There have been a number of these in my career, and the acceptance of the place of MHT is one. Ten years ago MHT had a different name (hormone replacement therapy), and following a number of publications had generally become a no no. There is little doubt that some women have significant unpleasant menopausal symptoms, and now MHT, following further publications, has swung back to being an option for women. It is crucial that patients be given full information of the risk involved, especially the relatively low magnitude of risk, but depending on the severity of symptoms, it is an option to be considered.

Reference: Lancet 2019;394(10204):1159-68
Abstract

Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial

Authors: Hardy J et al.

Summary: This 52-week, multicentre, open-label, parallel-group, randomised controlled trial in adult asthma patients examined the combination of budesonide with the fast-onset, long-acting β-agonist (LABA) reliever formoterol (n = 437) versus maintenance budesonide plus as-needed the short-acting β-agonist (SABA) reliever terbutaline (n = 448). Severe exacerbations per patient per year (systemic corticosteroids for ≥3 days, admission to hospital or emergency department) were lower with budesonide-formoterol than with budesonide-terbutaline (RR 0.69; 95% CI 0.48-1.00; p = 0.049; absolute rates 0.119 vs 0.172 per patient per year). The most common adverse event was nasopharyngitis, occurring in 35% of budesonide-formoterol and 32% of budesonide-terbutaline recipients.

Comment: This is a New Zealand-based study with international participation that is in the process of changing the way that asthma is treated. It has already been incorporated into international guideline recommendations. Basically, it showed that the combination budesonide-formoterol used on an as-required rescue medication basis, was more effective in preventing severe exacerbations of asthma than regular budesonide plus as-required SABA. It is important to emphasise that this concept will only work if the long-bronchodilator component has a rapid onset of action as is seen in formoterol, which affects bronchodilatation as rapidly as SABAs.

Reference: Lancet. 2019;394(10202):919-28
Abstract

Goodfellow Gems

Topical and oral treatment can work for fungal nail infection

A recent Alberta Tools for Practice[1] summarises that up to 45-60% of patients on oral treatments for fungal nail infections (terbinafine best; NNT=3 and placebo 6%) will be "cured" after ~1 year with 12 to 16 weeks of treatment.

Re terbinafine versus "azoles" (mostly itraconazole), 58% cure with terbinafine, 46% azole; NNT=9. Risk of terbinafine-induced liver injury: ~1 in 50,000-120,000 prescriptions, and taste loss in 0.6 - 2.8% of those taking the drug.[2] Advise patient to stop taking at first sign of taste loss as it's usually reversible.

Topicals should be reserved for cases with minimal (<40%) nail involvement. Improvement is 6-23% on topicals (efinaconazole best but not available in NZ, ciclopirox is available in NZ; NNT to get cure 15-23 and treat for up to 48 weeks). Amorolfine is available in NZ but no data was presented.

Reference:

1. Putting the FUN in Fungi: Toenail onychomycosis treatments. Alberta Tools for Practice #242. View here
2. Objective assessment of terbinafine-induced taste loss. Laryngoscope (2005). 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

EVIDENCE-BASED NATURAL HEALTH
by Dr Chris Tofield

Effect of Tai Chi versus aerobic exercise for fibromyalgia: comparative effectiveness randomized controlled trial

Authors: Wang C et al.

Summary: The effectiveness of Tai Chi for fibromyalgia was compared with that of aerobic exercise in this prospective, randomised, 52-week, single blind trial. Patients were assigned to either one of four Yang style supervised Tai Chi interventions (12 or 24 weeks, once or twice weekly; n = 151) or to supervised aerobic exercise (24 weeks, twice weekly; n = 75). All 5 treatment groups exhibited improved revised Fibromyalgia Impact Questionnaire (FIQR) scores, but at 24 weeks, the FIQR score improved statistically significantly more in the combined Tai Chi groups than in the aerobic exercise group (difference between groups 5.5 points; 95% CI 0.6-10.4; p = 0.03). When Tai Chi and aerobic exercise were administered with the same intensity and duration (24 weeks, twice weekly), Tai Chi recipients exhibited a greater benefit (between group difference in FIQR scores 16.2 points; 95% CI 8.7-23.6; p < 0.001). Participants undertaking Tai Chi for 24 weeks exhibited greater improvements than those undertaking it for 12 weeks (difference in FIQR scores 9.6 points; 95% CI 2.6-16.6; p = 0.007).

Comment: Tai Chi is pretty ubiquitous now, being used for cardiovascular health, balance, strength, mental health and the list goes on. It would make sense that it has something to offer for fibromyalgia too, and this study from Boston proved just that. They found significantly greater improvements in FIQR scores in the Tai Chi group compared to aerobic exercise. Interestingly, but not surprisingly, the longer the participation in Tai Chi, the greater improvement in score was seen. This is very useful information for GPs, who would normally 'prescribe' general physical exercise. Time to change this advice?

Reference: BMJ. 2018;360:k851
Abstract

Vitamin D supplements and prevention of cancer and cardiovascular disease

Authors: Manson JE et al.

Summary: These US authors conducted a nationwide, randomised, placebo-controlled trial to investigate whether supplementation with vitamin D reduces the risk of cancer or CVD. In their 2-by-2 factorial design, vitamin D3 (cholecalciferol) at a dose of 2000 IU per day and marine n-3 (omega-3) fatty acids at a dose of 1 g per day or placebo were compared in men ≥50 years of age and women ≥55 years of age (n = 25,871). During a median follow-up of 5.3 years, there were no significant differences in the rates of cancer or any type of MACE, with 793 participants in the vitamin D group and 824 in the placebo group diagnosed with cancer (HR 0.96; 95% CI 0.88-1.06; p = 0.47), and 396 and 409, respectively, diagnosed with MACE (HR 0.97; 95% CI 0.85-1.12; p = 0.69).

Comment: It feels like things have quietened down on the vitamin D research front, yet it doesn't feel like we're any clearer on whether it's 'in' or 'out'. In favour of the 'out' lobby, this study didn't show any benefits in terms of cancer or CVD risk reduction. The participants, however, were aged 50-55 and upwards, which one could argue is too late to start prevention. I would feel more comfortable accepting these results if participant age was around 30-40.

Reference: N Engl J Med. 2019;389(1):33-44
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 is clinical advisor to Bay of Plenty District Health Board. Chris also has a background of medical writing and editing and while at medical school published a medical textbook on pharmacology.