GP RESEARCH REVIEW™

Making Education Easy

Issue 154 – 2020

In this issue:

Abbreviations used in this issue

BMI = body mass index
CI = confidence interval
COPD = chronic obstructive pulmonary disease
CrI = credible interval
LDL = low density lipoprotein
MI = myocardial infarction
OR = odds ratio
$p_{(OR>1)}$ = posterior probability of OR >1
PSA = prostate-specific antigen
RCT = randomised controlled trial
RR = relative risk
TIA = transient ischaemic attack

Beat Bowel Cancer AOTEAROA

NZMA New Zealand Medical Association

Welcome to issue 154 of GP Research Review.

Following an ischaemic stroke or TIA with evidence of atherosclerosis, patients with a lower target LDL cholesterol had a lower risk of subsequent cardiovascular events than those who had a higher target range, according to the findings of a recent study undertaken in France and South Korea. In this issue, we also discover that sunscreen active ingredients are systemically absorbed after just one application at levels exceeding FDA recommendations. In the Natural Health section, Dr Chris Tofield has reviewed two interesting studies, one investigating vegetable consumption and the risk of early-stage prostate cancer, and the other, healthy lifestyle and life expectancy.

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

Kind regards,
Jim

Assoc Professor Jim Reid
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A comparison of two LDL cholesterol targets after ischemic stroke

Authors: Amarenco P et al.

Summary: This multinational, randomised, parallel-group trial in 2860 patients with ischaemic stroke in the previous 3 months or a transient ischaemic attack (TIA) within the previous 15 days, all with evidence of cerebrovascular or coronary-artery atherosclerosis and receiving statin, ezetimibe or both, tested the use of target LDL cholesterol levels of <1.8 mmol/L or 2.3-2.8 mmol/L. Over a median of 3.5 years, the mean LDL cholesterol level achieved was 1.7 mmol/L in the lower-target group and 2.5 mmol/L in the higher-target group. A composite primary end point (major cardiovascular events including ischaemic stroke, myocardial infarction, new symptoms leading to urgent coronary or carotid revascularisation, or death from cardiovascular causes) occurred in 121 (8.5%) patients in the lower-target group and 156 (10.9%) patients in the higher-target group (adjusted HR 0.78; 95% CI 0.61-0.98; p = 0.04). Intracranial haemorrhage and newly diagnosed diabetes incidence did not differ between groups.

Comment: Prescribing of a statin following a TIA or ischaemic stroke is now considered to be best practice. The object of the study was to look at the outcome of two groups of 1430 study participants each who were treated with a statin over a mean of 3.5 years. The target for one group was a LDL level of 2.5 mmol/L and the other's target was 1.7 mmol/L. There was a lower risk of cardiovascular events in those with the lower level.

Reference: N Engl J Med 2020; 382:9-19
https://www.nejm.org/doi/full/10.1056/NEJMoa1910355

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Effect of sunscreen application on plasma concentration of sunscreen active ingredients: a randomised clinical trial

Authors: Matta MK et al.

Summary: This randomised clinical trial in 48 healthy participants (24 women; 23 white; 23 African American; 1 Asian), examined the systemic absorption and pharmacokinetics of 6 active ingredients (avobenzone, oxybenzone, octocrylene, homosalate, octisalate, and octinoxate) in 4 sunscreen products formulated as lotion (n = 12), aerosol spray (n = 12), non-aerosol spray (n = 12), and pump spray (n = 12). Geometric mean maximum plasma concentrations >0.5 ng/mL were measured for all 6 active ingredients after a single application. These plasma concentrations surpassed the FDA threshold for potentially waiving additional safety studies for sunscreens. The most common adverse event, rash, developed in 14 participants.

Comment: This is a two-edged sword. On one hand we are being sold the "slip, slop, slap" regime for sunscreen to prevent skin damage, and more specifically melanoma prevention, to apply sunscreen 20 minutes before going outside and a further coat 20 minutes later, then every 2 hours subsequently. On the other hand this study demonstrates that systemic absorption of active ingredients surpassed FDA threshold. Can we have our cake and eat it too??

Reference: JAMA. 2020;323(3):256–67
https://jamanetwork.com/journals/jama/article-abstract/2759002

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.

Association of powder use in the genital area with risk of ovarian cancer

Authors: O'Brien KM et al.

Summary: This analysis of pooled prospective observational data from 4 large US cohort studies conducted between 1976 and 2017 (Nurses' Health Study, Nurses' Health Study II, Sister Study, Women's Health Initiative Observational Study; pooled n = 252,745) examined the association between use of powder in the genital area and ovarian cancer. In total, 38% of participants reported use of powder in the genital area, 10% reported long-term use (≥20 years), and 22% reported frequent use (≥1/week). Over a median 11.2 years of follow-up (3.8 million person-years), there was no association between use of powder in the genital area and incident ovarian cancer; ovarian cancer incidence 61 versus 55 per 100,000 person-years among those who had ever used powder versus never users (risk difference 0.09%; 95% CI -0.02-0.19; HR 1.08; 95% CI 0.99-1.17). The estimated HR for frequent versus never use was 1.09 (95% CI 0.97-1.23). For long-term versus never use, the HR was 1.01 (95% CI 0.82-1.25).

Comment: When I was a medical student (more years ago than I wish to recall) it was "recognised" that talcum powder to the female genital region was a no no for a number of reasons, from allergy to ovarian cancer. This is a small study, that has potential for expansion, but it may be that another sacred cow is about to bite the dust.

Reference: JAMA. 2020;323(1):49-59
https://jamanetwork.com/journals/jama/article-abstract/2758452

Association of a workplace sales ban on sugar-sweetened beverages with employee consumption of sugar-sweetened beverages and health

Authors: Epel ES et al.

Summary: This study assessed whether a sugar-sweetened beverages sales ban and a brief motivational intervention at a Northern California university and hospital was associated with changes in sugar-sweetened beverage intake and cardiometabolic health among 214 employees (57.9% women). Baseline mean daily intake of 1050 mL declined to 540 mL at follow-up ($p < 0.001$). Sugar-sweetened beverage intake was correlated with Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) improvements ($r = 0.16$; $p = 0.03$). Those not receiving the brief intervention reduced their sweetened beverage intake by a mean of 246.0 mL versus 762.0 mL in those who received the intervention. Waist circumference declined by 2.1 cm ($p < 0.001$).

Comment: This is yet another paper producing evidence in the fight against obesity. This is another study that demonstrates that restriction on sugar-sweetened beverages results in a significant reduction in waist circumference within 10 months. Imagine what could be done with either a ban, a restriction (either price or physical), or some other constraint of sale to the overall obesity problem, especially (but not only) in children.

Reference: JAMA Intern Med. 2020;180(1):9-16
https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2753425

Comparisons of exacerbations and mortality among regular inhaled therapies for patients with stable chronic obstructive pulmonary disease: systematic review and Bayesian network meta-analysis

Authors: Lee HW et al.

Summary: This Bayesian network meta-analysis was conducted to assess regular inhaler therapies for chronic obstructive pulmonary disease (COPD) patients based on 219 trials (n = 228,710). All drug classes reduced total and moderate to severe exacerbations compared to placebo. A combination therapy containing inhaled corticosteroid (ICS)/long-acting muscarinic antagonist (LAMA)/long-acting beta-agonist (LABA) was the most effect treatment (OR 0.57; 95% CrI 0.50-0.64; $p_{(OR>1)} < 0.001$). The probability of reducing mortality was also higher with ICS/LAMA/LABA (OR 0.74; 95% CrI 0.59-0.93; $p_{(OR>1)} = 0.004$) and ICS/LABA (OR 0.86; 95% CrI 0.76-0.98; $p_{(OR>1)} = 0.015$) than with placebo. Adjusted meta-regression analyses using various sensitivity and covariate only had a minimal effect on these results. ICS/LAMA/LABA did not lower the risk of cardiovascular mortality, but did increase pneumonia probability (OR 1.56; 95% CrI 1.19-2.03; $p_{(OR>1)} = 1.000$).

Comment: Triple therapy (ICS/LABA/LAMA) is the next step in inhaler metered-dose inhaler therapy for COPD. This systematic review and meta-analysis found that in spite of an increased incidence of pneumonia in the ICS containing group, there was no increase in all-cause mortality. The triple therapy group as a whole had fewer exacerbations, and an overall reduced risk of all-cause mortality.

Reference: PLoS Med. 2019;16(11):e1002958
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002958

How reliable is the statistical evidence for limiting saturated fat intake? A fresh look at the influential Hooper meta-analysis

Authors: Thornley S et al.

Summary: This study re-analysed the Hooper meta-analysis (Cochrane Database Syst Rev. 2015 Jun 10;(6):CD011737) to decide whether the study results were sensitive to methodology using inverse-variance heterogeneity analysis. The analysis of the combined cardiovascular disease end point results had a pooled relative risk of 0.93 (95% CI 0.74-1.16), while a traditional random effects analysis had a relative risk of 0.83 (95% CI 0.72-0.96). Furthermore, funnel and Doi plots and Egger test results (and the recent publication of dataset from two large trials of saturated fat replacement on cardiovascular disease that were conducted in the 1970s) suggest publication bias.

Comment: This is a watch this space study. There seems to be emerging evidence in the literature (this is not the first study that I have seen) to question dogma that has now become a sacred cow. The negative effects of saturated fats is now so entrenched that it is almost impossible to question. This paper does just that, and ends in a question. Is it time to reconsider? The jury needs more evidence.

Reference: Intern Med J. 2019;49(11):1418-24
https://onlinelibrary.wiley.com/doi/10.1111/imj.14325

The epidemiological burden of obesity in childhood: a worldwide epidemic requiring urgent action

Authors: Di Cesare M et al.

Summary: Childhood obesity has effects on psychiatric, psychological and psychosocial disorders in childhood and increases the risk of non-communicable diseases in later life. Treatment is difficult and overweight children are likely to become obese adults. The global prevalence of overweight children aged ≤5 years has modestly increased, with heterogeneous trends in low- and middle-income regions, while in children aged 2-4 years the prevalence of obesity has increased moderately. Obesity in those aged 5-19 years was relatively rare in 1975, but was much more common in 2016. The key drivers, which include changing food systems and reduced physical activity, form an obesogenic environment. Effective programmes and policies are needed in multiple sectors to address overnutrition, undernutrition, mobility and physical activity, and the obesity epidemic must be a political priority, with issues addressed locally and globally, by governments, civil society, private corporations and other key stakeholders.

Comment: We are not immune in this country to this onslaught of childhood obesity. As the authors of this very large review note, the key drivers are changing food patterns and reduced exercise. We live in an age of high calorific fast food being cheaper than nutritious food, where sugary fizzy drinks are cheaper than milk, where "screen time" is taking over from play that involves exercise, and where motorised transport has replaced the walk to school. If we collectively do not address these issues the problem will increase.

Reference: BMC Med. 2019;17(1):212
https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-019-1449-8

Aspirin for primary prevention of cardiovascular disease: a meta-analysis with a particular focus on subgroups

Authors: Gelbenegger G et al.

Summary: This meta-analysis, based on 13 RCTs (n = 164,225) examined the risk/benefit ratio of aspirin for primary prevention of cardiovascular disease with a particular focus on subgroups including sex, concomitant statin treatment, diabetes and smoking. Overall, there was no difference between aspirin and control groups for all-cause (RR 0.98; 95% CI 0.93-1.02) and cardiovascular (RR 0.99; 95% CI 0.90-1.08) mortality risks. Compared with controls, aspirin reduced the risk of major adverse cardiovascular events (MACE) by 9% (RR 0.91; 95% CI 0.86-0.95), MI by 14% (RR 0.86; 95% CI 0.77-0.95), and ischaemic stroke by 10% (RR 0.90; 95% CI 0.82-0.99), but increased risk of major bleeding events by 46% (RR 1.46; 95% CI 1.30-1.64). After adjustment for event-associated mortality risk, aspirin use did not translate into a net clinical benefit (mean 0.034%; 95% CI -0.18 to 0.25). In three subgroups there was a small interaction effect for aspirin, reducing risk of MACE by 12% in those receiving statins (RR 0.88; 95% CI 0.80-0.96), by 10% in non-smokers (RR 0.90; 95% CI 0.82-0.99) and by 11% in males (RR 0.89; 95% CI 0.83-0.95).

Comment: Interesting, I know I do go on about risk/benefit ratio, and how this should be a factor in all prescribing. This meta-analysis demonstrates this beautifully. In a nutshell it shows that overall aspirin at the price of increased bleeding risk demonstrates relative reduced risk of MACE in males, those on statins, and in non-smokers. And for the others, there is a 46% relative risk increase of major bleeding versus no benefit at all.

Reference: BMC Med. 2019 Nov 25;17(1):198
https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-019-1428-0

Goodfellow Gems

Great dementia resources on Health Navigator website

Health Navigator NZ is a New Zealand-based website with a lot of very useful clinical information for clinicians, patients and carers. It's up to date and all the information is clinically reviewed. Below are some helpful resources links:

- Assessment of cognition using the MoCA (Montreal cognitive assessment) https://www.mocatest.org/the-moca-test/ or GPCOG http://gpcog.com.au/
- Resources for clinicians include information on driving assessments, clinical pathways, distinguishing depression, from delirium from dementia https://www.healthnavigator.org.nz/health-a-z/d/dementia/#Clinicians
- Caring for a family member with dementia can be very stressful https://www.healthnavigator.org.nz/health-a-z/d/dementia/#Forcarers
- Mate wareware: Understanding 'dementia' from a Māori perspective. NZMJ (2019)

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 a behavioral intervention to increase vegetable consumption on cancer progression among men with early-stage prostate cancer: the MEAL randomized clinical trial

Authors: Kellogg Parsons J et al.

Summary: The US multicentre, Men's Eating and Living (MEAL) RCT examined the use of a behavioural intervention (by telephone promoting consumption of 7 or more daily vegetable servings; n = 237) versus written information on prostate cancer and diet (n = 241) to increase vegetable intake on cancer progression in men with early-stage (stage cT2a or less, PSA <10 ng/mL) prostate cancer. The intervention group reported increased average daily vegetable consumption (2.43 vs 0.45 servings), cruciferous intake (43.1 vs 6.4 g), and total carotenoids (13,839 vs 2,030 µg); all $p < 0.001$. In total, there were 245 progression events (124 vs 121), with no differences in time to progression (unadjusted HR 0.96; 95% CI 0.75-1.24; adjusted HR 0.97; 95% CI 0.76-1.25). 24-month Kaplan-Meier progression-free percentages did not differ between intervention and control groups (difference 2.1%; 95% CI -8.1 to 12.2).

Comment: A cancer diagnosis can lead to a turn-around in people's lifestyle, such as a move towards natural supplements and a healthy way of eating. Unfortunately, in the case of prostate cancer, this study demonstrates no beneficial effect of increased vegetable intake. But surely the answer to cancer doesn't rest with vegetables alone. Possibly a multi-faceted approach to lifestyle change may have yielded better results?

Reference: JAMA. 2020;323(2):140-148
https://jamanetwork.com/journals/jama/article-abstract/2758598

Healthy lifestyle and life expectancy free of cancer, cardiovascular disease, and type 2 diabetes: prospective cohort study

Authors: Li Y et al.

Summary: This analysis of the prospective cohort Nurses' Health Study (1980-2014; n = 73,196) and the Health Professionals Follow-Up Study (1986-2014; n = 38,366) examined how low-risk lifestyle factors (never smoking, BMI 18.5-24.9, moderate to vigorous physical activity ≥30 minutes/day, moderate alcohol intake 5-15 g/day), and an upper 40% diet-quality score) was related to life expectancy free from major chronic diseases. Life expectancy free of diabetes, cardiovascular diseases, and cancer at age 50 was 23.7 years (95% CI 22.6-24.7) among women who did not adopt low-risk lifestyle factors versus 34.4 years (95% CI 33.1-35.5) in those with four or five low-risk factors. In men, life expectancy free of these chronic diseases was 23.5 years (95% CI 22.3-24.7) in men who with no low-risk lifestyle factors versus 31.1 years (95 % CI 29.5-32.5) years in men with four or five low-risk lifestyle factors. Current male heavy smokers (≥15 cigarettes/day) and obese men and women (BMI ≥30) accounted for the lowest proportion (≤75%) of total life expectancy at age 50.

Comment: Another lifestyle study, but this time well powered and with some impressive results. A five-pronged approach to healthy living, consisting of non-smoking, normal BMI, regular physical activity, moderate alcohol and healthier diet, led to 12 years longer disease-free living in healthy women.

Reference: BMJ. 2020 Jan 8;368:l6669
https://www.bmj.com/content/368/bmj.l6669

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.

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