Diabetes & Obesity RESEARCH REVIEW™

Making Education Easy

Issue 156 – 2022

In this issue:

Abbreviations used in this issue

CKD = chronic kidney disease
CV = cardiovascular
GFR = glomerular filtration rate
GLP = glucagon-like peptide
HDL/LDL = high/low-density lipoprotein
HR = hazard ratio
OR = odds ratio
RR = relative risk
SSB = sugar-sweetened beverage

Welcome to issue 156 of Diabetes and Obesity Research Review.

We begin with a systematic review and meta-analysis looking at the impact of various intensities of different statins on non-HDL cholesterol levels in people with diabetes. NZ research is included with a prospective cohort study suggesting that exposure to neonatal hypoglycaemia does not appear to have a detrimental impact on academic performance in mid-childhood. There is also research demonstrating that pictorial warnings about type 2 diabetes and heart damage on SSBs (sugar-sweetened beverages), similar to what we currently have on tobacco products, has the potential to discourage parents from purchasing SSBs for their children. This issue concludes with research reporting that people who experience long-COVID appear to be at increased risk of diabetes.

We hope you enjoy this issue, and we look forward to comments and feedback.

Best regards,

Professor Jeremy Krebs
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Comparative effectiveness of statins on non-high density lipoprotein cholesterol in people with diabetes and at risk of cardiovascular disease

Authors: Hodkinson A et al.

Summary: This systematic review with network meta-analysis of data from 42 randomised controlled trials (11,698 evaluable adult participants with type 1 or 2 diabetes) found that compared with placebo, high-intensity rosuvastatin, moderate-intensity rosuvastatin, high-intensity simvastatin and high-intensity atorvastatin were associated with the greatest reductions in non-HDL-cholesterol levels (–2.31, –2.27, –2.26 and –2.20 mmol/L, respectively); any-intensity atorvastatin and simvastatin and low-intensity pravastatin were also effective for reducing non-HDL-cholesterol levels. Among participants at high risk of a major CV event (n=4670), high-intensity atorvastatin was associated with the greatest reduction in non-HDL-cholesterol level (–1.98 mmol/L). High-intensity simvastatin and high-intensity rosuvastatin were the most effective for reducing LDL-cholesterol levels. Moderate-intensity atorvastatin was associated with a significant reduction in the risk of nonfatal myocardial infarction (RR 0.57 [CI 0.43, 0.76]), but there were no significant differences among the statins for discontinuations, nonfatal stroke or CV-related mortality.

Comment: There is a large body of evidence to support the benefits of statins in reducing CV risk in the general population, for both primary and secondary prevention. This systematic review and meta-analysis looked specifically at those with diabetes, and compared the different statins' abilities to lower non-HDL cholesterol (total cholesterol minus HDL cholesterol). Perhaps not surprisingly, the more potent statins had the greatest effect, with rosuvastatin coming out on top. The key relevance of this to NZ is that we now have funded access to rosuvastatin, albeit on a special authority basis, for those with established or at high risk of CV disease who have not met target LDL levels on other statins.

Reference: BMJ 2022;376:e067731
Abstract

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Preventing type 2 diabetes, overweight and obesity in the Norwegian primary healthcare

Authors: Følling IS et al.

Summary: This cross-sectional longitudinal study with 60 months of follow-up explored changes from baseline in diabetes risk and anthropometrics in 189 adults with a Finnish Diabetes Risk Score ≥12 and/or a BMI ≥25 kg/m² who had been offered attendance at a Norwegian 12-month 'healthy life centre' behavioural programme that includes physical activity and dietary courses as part of primary healthcare. There were significant declines in diabetes risk and anthropometrics after the 60-month follow-up. Among participants classified as high risk for diabetes at baseline (n=65), 42% had converted to moderate risk at 60 months. Six of nine participants with diabetes experienced remission of diabetes. The programme's 60-month dropout rate was 31%, with younger age and higher, BMI, weight and waist circumference significant predictors of dropout.

Comment: I think we would all agree that preventing diabetes is preferable to managing established disease and complications. There have been many studies now showing that diet and lifestyle interventions can work, but have been conducted in research settings and often requiring significant resources. What we need to know is how to translate these findings into real-world settings. That could be primary care, or could be other community-based networks, but needs to be cost effective and sustainable. This study reports a Norwegian experience, and reflects what others have observed in different countries. While some individuals benefit significantly, many are not able to sustain this, or dropout of the programme. Although the problem appears to be universal, the solutions to retaining people and maintaining benefits are likely to require population-specific answers. We need this sort of evidence in NZ, particularly including Māori, Pacific and Indian people for whom diabetes is more prevalent. It is time for a collaborative approach to designing and conducting such a study here in NZ, which has sufficient numbers of participants and duration to meaningfully inform public health policy and implementation. Perhaps this should be part of a new Ministry of Health Diabetes Action Plan.

Reference: BMJ Open 2022;12:e054841
Abstract

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How to identify clinically significant diabetes distress using the Problem Areas in Diabetes (PAID) scale in adults with diabetes treated in primary or secondary care? Evidence for new cut points based on latent class analyses

Authors: de Wit M et al.

Summary: These researchers reported on diabetes distress for adult participants from four studies (43% type 1 diabetes, diabetes duration 0–79 years). They used latent class analyses to identify possible latent groups in the distribution of answers on the individual PAID (Problem Areas of Diabetes) questionnaire items. Three levels of diabetes distress with defined cutoff scores were identified, namely low, moderate and high, although these did not associate with distinct clusters of items. Older people were more likely to be classified as low distress, while women and those with a high HbA_{1c} level were more likely to be classified as high distress. The respective sensitivity and specificity values for the commonly used cutoff of 40 for high distress were 0.95 and 0.97, and for moderate distress, cutoff scores of 17 and 39 were optimal with sensitivity of 0.93 and specificity of 0.94.

Comment: The relentless burden of having a chronic disease, and particularly type 1 diabetes with all the inherent demands of glucose monitoring and insulin treatment, overlaid with the knowledge of how important it is for long-term health, has been well described. Increasingly we understand the impact of diabetes distress on the wellbeing of a person with diabetes and their whānau. However, I'm not sure that we are universally very good at measuring this in day-to-day practice. I guess that is partly driven by the lack of well-defined pathways or tools to address it when we find it! Most secondary-care teams in NZ still do not have easy funded access to psychology services, and the situation is even worse in primary care. This paper describes a tool and scoring system that could be used to identify those at greatest need of help. Now we need the services to be able to provide that.

Reference: BMJ Open 2022;12:e056304
Abstract

Association of neonatal hypoglycemia with academic performance in mid-childhood

Authors: Shah R et al., for the Children With Hypoglycaemia and Their Later Development (CHYLD) Study Team

Summary: This research from Waikato explored the association of neonatal hypoglycaemia with educational performance at age 9–10 years in a prospective cohort of 587 eligible moderate-to-late preterm and term infants who were at risk of hypoglycaemia at birth, 480 of whom were assessed at a mean age of 9.4 years. There was no evidence that children exposed to neonatal hypoglycaemia differed significantly to those who weren't for the primary outcome of low educational achievement (47% vs. 48%; adjusted RR 0.95 [95% CI 0.78, 1.15]), although those exposed to neonatal hypoglycaemia were significantly less likely to be rated by teachers as being below or well below the curriculum level for reading (24% vs. 31%; 0.72 [0.53, 0.99]); there were no between-group differences for other secondary endpoints related to executive function, visual-motor function, psychosocial adaptation and general health.

Comment: Recognising the importance of and appropriate management of neonatal hypoglycaemia is something NZ researchers have led the world in. Here this work is continued by examining the effect of identification and treatment of neonatal hypoglycaemia on subsequent educational outcomes and cognition at age 9 years. It is reassuring to see that when identified and treated, neonatal hypoglycaemia was not associated with any greater risk of poor educational achievement by age 9 years, reinforcing the importance and impact of prior research and changes to clinical practice arising from that.

Reference: JAMA 2022;327:1158–70
Abstract

Association of glucagon-like peptide-1 receptor agonist use with risk of gallbladder and biliary diseases

Authors: He L et al.

Summary: This systematic review and meta-analysis included 76 randomised controlled trials (103,371 participants) reporting data on gallbladder and biliary disease risk associated with GLP-1 receptor agonist use. The analyses revealed that GLP-1 receptor agonist recipients had increased risks of gallbladder or biliary diseases (RR 1.37 [95% CI 1.23, 1.52]), specifically biliary disease (1.55 [1.08, 2.22]), cholecystitis (1.36 [1.14, 1.62]) and cholelithiasis (1.27 [1.10, 1.47]). The association between GLP-1 receptor agonist use and gallbladder or biliary disease risk persisted: i) in 13 weight loss trials (RR 2.29 [95% CI 1.64, 3.18]) and 63 trials in type 2 diabetes or other diseases (1.27 [1.14, 1.43]; p<0.001 for interaction); ii) with higher doses (1.56 [1.36, 1.78]) but not lower doses (0.99 [0.73, 1.33]; p=0.006 for interaction); and iii) with longer duration of use (1.40 [1.26, 1.56]) but not shorter duration (0.79 [0.48, 1.31]; p=0.03 for interaction).

Comment: We are all learning how to best use the GLP-1 agonists in real-world practice outside of the clinical trials now that we have access to dulaglutide. Part of that is to understand the side-effect profile. Whilst we are familiar with nausea, which is predictable, there has been uncertainty in the literature about a possible increase in gallbladder disease. This systematic review and meta-analysis has helped to resolve that uncertainty. Pooled data from 76 studies and more than 100,000 participants showed that pooled biliary tract diseases were almost 40% more likely in those on a GLP-1 agonist than placebo. The observation was that this risk was even greater in trials where weight loss was the primary outcome, and was also higher with longer duration and higher doses. Cholelithiasis and associated cholecystitis are both more common with any weight loss treatment, and therefore this finding is not surprising. It does remind us of the importance of discussing this as we start treating patients with dulaglutide.

Reference: JAMA Intern Med; Published online March 28, 2022
Abstract

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Preconception antidiabetic drugs in men and birth defects in offspring

Authors: Wensink MJ et al.

Summary: The risk for birth defects associated with paternal preconceptional exposure to pharmacological diabetes treatments was explored in a prospective registry-based Danish cohort of 1,116,779 liveborn singletons from mothers with no history of diabetes or essential hypertension. Compared with the reference group (the 3.3% of the offspring who had ≥1 major birth defect), there was no increased risk for offspring of fathers treated preconceptionally with insulin (adjusted OR 0.98 [95% CI 0.85, 1.14]) or sulfonylureas (1.34 [0.94, 1.92]), but there was an increased risk for those of fathers who had received preconceptional metformin (1.40 [1.08, 1.82]), whereas the risk was not increased if metformin had been prescribed the year before or the year after sperm development (0.88 [0.59, 1.31] and 0.92 [0.68, 1.26], respectively), and nor was it increased for unexposed siblings of exposed offspring (1.54 [0.94, 2.53]). Among offspring of fathers with preconceptional metformin exposure, the risk of genital birth defects in boys was particularly high (adjusted OR 3.39 [CI 1.82, 6.30]).

Comment: I am a self-confessed metformin fan and have frequently suggested it be put in the drinking water! Its benefits seem to extend beyond just glucose lowering, with increasing evidence for reduced cancer risk. However, this study suggests my calls for drinking water may be premature. This Danish registry trial looked at rates of birth defects in offspring of fathers who were exposed to metformin at the time of sperm generation and mothers without diabetes. There was an association with increased rates of genital birth defects in boys with fathers taking metformin. Being an observational study, this cannot conclude a causal relationship, but it certainly warrants further investigation and is relevant as the age of diagnosis of type 2 diabetes comes down into more reproductive age groups. These data are not enough to necessarily change prescribing practice in young men, but a discussion with men who are actively trying for pregnancy with their partner, and considering a swap to another agent, would be reasonable.

Reference: Ann Intern Med; Published online March 29, 2022
Abstract

Diabetic kidney disease and risk of incident stroke among adults with type 2 diabetes

Authors: Kaze AD et al.

Summary: These researchers explored associations of kidney function abnormalities and CKD stages with incident stroke in 9170 ACCORD study participants with type 2 diabetes followed for a median 4.9 years. Stroke occurred in 156 participants during a median 4.9 years of follow-up (incidence rate 3.6 per 1000 person-years). Compared with urinary albumin-to-creatinine ratios of <30 mg/g, the risk of stroke was increased by both moderate and severe albuminuria (respective adjusted HRs 1.61 [95% CI 1.12, 2.32] and 2.29 [1.39, 3.80], respectively), and there was a trend for an increased risk with estimated GFRs of <60 vs. ≥60 mL/min/1.73m^2 (1.50 [0.98, 2.29]). The risk of stroke also increased as CKD stage increased (respective adjusted HRs for grades 1–3 versus no CKD, 1.76 [95% CI 1.10, 2.83], 1.77 [1.13, 2.75] and 2.03 [1.27, 3.24]).

Comment: It is well recognised that diabetic kidney disease is associated with an increased risk of cardiac disease and is one of the important risk factors that drives more aggressive glucose level, blood pressure and lipid management. However, less has been reported about risk of stroke. This paper reports a secondary analysis of the ACCORD data from individuals with no baseline history of stroke. Both degree of albuminuria and renal function defined by estimated GFR were strongly related to increasing risk for stroke in the 5-year follow-up period. This was particularly strong with severe albuminuria, where the risk was more than double that of those without microalbuminuria. These data add further strength to the use of GLP-1 agonists, which have been shown to reduce the risk of stroke, in people with type 2 diabetes, particularly when they have a history of renal disease.

Reference: BMC Med 2022;20:127
Abstract

The impact of pictorial health warnings on purchases of sugary drinks for children

Authors: Hall MG et al.

Summary: In this study, parents of children aged 2–12 years (n=325) completed a shopping task in a naturalistic store laboratory with randomisation to SSBs displaying pictorial health warnings about type 2 diabetes and heart damage or displaying a barcode label. The parents were asked to select one beverage and one snack for their child, and one household good, and one of these items was selected for purchase and taking home. Compared with the control arm, pictorial warnings led to a smaller proportion of parents purchasing an SSB (28% vs. 45% [p=0.002], although no significant difference was seen according to any of the 13 participant characteristics examined), fewer calories purchased from SSBs (52 vs. 82 kcal [p=0.003]), reduced intention to serve SSBs to children, a greater feeling of control of healthy eating decisions, increased thinking about SSB-associated harms, stronger negative emotional reactions, greater anticipated social interactions, lower perceived healthfulness of SSBs for children, and greater injunctive norms to limit SSBs for children. No evidence of difference was seen between the two trial arms regarding noticing the labels, appeal of SSBs, perceived amount of added sugar in SSBs, risk perceptions or perceived tastiness of SSBs.

Comment: Given the known associations between SSBs and obesity, diabetes and tooth decay, any mechanism to reduce the consumption of these by children should be considered. Use of negative pictorial images has been shown to be effective in cigarette purchasing and use, which shares many similarities with SSBs. This study explored the use of similar pictorial images on SSBs in a controlled research store environment where parents of children aged 2–12 years were asked to purchase one beverage and one snack for their child. Use of the images on SSB products reduced purchase of these by almost 20% and reduced overall calorie purchase. The images appeared to have induced greater negative feelings about SSBs without necessarily increasing awareness of the images themselves. Introducing a policy to require these negative images on SSBs together with a sugar tax may be a combined package that needs consideration.

Reference: PLoS Med 2022;19:e1003885
Abstract

Independent commentary by Professor Jeremy Krebs MBChB, FRACP, MD

Professor Krebs is an Endocrinologist with a particular interest in obesity and diabetes. He is a Professor with the University of Otago, and former Director of the Clinical Research Diploma at Victoria University - which he established. **FOR FULL BIO CLICK HERE.**

Occupations associated with diabetes complications

Authors: Nakazawa S et al.

Summary: Diabetes complications risks in 39,550 inpatients with diabetes were assessed according to their longest-held and current occupations in this case-control study from Japan. It was found that managers, sales workers, service workers, transportation workers, construction and mining workers, and carrying, cleaning and packing workers more frequently had diabetes complications such as retinopathy, nephropathy, neuropathy and peripheral vascular complications. The risk of all these diabetes complications was particularly increased among service workers (OR 1.36 [CI 1.23, 1.51]), specifically cooks, waiters, building service staff and other service workers (1.30 [1.12, 1.51]), 1.63 [1.36, 1.95], 1.79 [1.21, 2.67] and 2.05 [1.30, 3.22], respectively).

Comment: I thought this was a somewhat quirky but interesting study from Japan. It looks at the association between occupation and risk of diabetes complications. It sourced data from hospital inpatients, which does introduce a bias, but nevertheless is of interest. What emerges is that service and more physical occupations, with the exception of managers, are associated with more microvascular diabetes complications. Since microvascular complications are very closely related to glycaemic control, we could postulate that perhaps people in these occupations have greater difficulty in achieving tight control. However, that is speculative, and more work would be required to tease that out. We also cannot assume that these findings would apply to the NZ population and cultural setting. Furthermore, we would want to use a broader primary-care database to test this out, but it is an interesting study.

Reference: Diabetes Res Clin Pract 2022;186:109809
Abstract

Risks and burdens of incident diabetes in long COVID

Authors: Xie Y & Al-Aly Z

Summary: The risks and burdens of diabetes in the postacute phase of SARS-COV-2 infection were explored in a cohort of 181,280 individuals who had tested positive for COVID-19 in the US. Compared with a contemporary control cohort (n=4,118,441), individuals from the COVID-19 cohort had higher risks of incident diabetes and antihyperglycaemic medication use (respective HRs 1.40 [95% CI 1.36, 1.44] and 1.85 [1.78, 1.92]) and excess burdens of these outcomes (13.46 and 12.35 per 1000 people at 12 months); the risks and burdens of postacute outcomes increased as severity of the acute phase of COVID-19 increased. Similar results were seen when a historical control cohort (n=4,286,911) was used as the reference cohort.

Comment: There are many unknown features of the COVID-19 pandemic, and over the next few years, I'm sure we are going to discover many unexpected sequalae. This study is the first that I am aware of to examine the effect of COVID infection on subsequent risk of developing diabetes. In this study, people who had no prior history of diabetes and who had contracted COVID and survived the first 30 days were compared with two very large control groups of people with no prior diabetes. Over the follow-up of almost 12 months, there was a 40% greater chance of people who had COVID developing diabetes compared with those who hadn't had COVID. If we didn't already have a problem with rising rates of diabetes, then if this finding translates over a longer period of time and across populations, we have a major problem. Once again this could be particularly important for our Māori and Pacific people.

Reference: Lancet Diabetes Endocrinol 2022;10:311–21
Abstract