

Diabetes & Obesity Research Review™

Making Education Easy

Issue 81 – 2014

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Abbreviations used in this issue

- BMI** = body mass index
BP = blood pressure
CHD = coronary heart disease
CV = cardiovascular
ER = extended-release
HR = hazard ratio

Welcome to issue 81 of Diabetes and Obesity Research Review.

Two papers address issues related to fast-food/takeaways, with one showing consumption of these foods is greater (and leads to BMI increases) when exposure to outlets is greater, particularly in the workplace environment, while the second reported greater price sensitivity on consumption and insulin resistance among sociodemographic groups in the US with disproportionate burden of chronic disease. Authors from the UK have conducted a systematic review and meta-analysis of trials that have investigated real-world interventional diabetes prevention programmes translated from evidence from efficacy trials. We begin this issue with research investigating outcomes associated with antenatal dietary and lifestyle interventions in overweight/obese pregnant women.

Thank you for your continued interest in Diabetes and Obesity Research Review. Please keep your comments, feedback and suggestions coming.

Best regards,

Dr Jeremy Krebs

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Antenatal lifestyle advice for women who are overweight or obese

Authors: Dodd JM et al., for the LIMIT Randomised Trial Group

Summary: The LIMIT trial researchers randomised women with a singleton pregnancy of 10–20 weeks' gestation and BMI ≥ 25 kg/m² to a comprehensive dietary and lifestyle intervention (n=1108) or standard care according to local guidelines (n=1104); the analyses included 2152 women and 2142 live-born infants. No significant difference was seen between the intervention and control groups for risk of the infant being large for gestational age (19% vs. 21%; p=0.24), although infants born to women in the intervention group were significantly less likely to deliver a baby with a birthweight >4000g (15% vs. 19%; adjusted relative risk 0.82 [95% CI 0.68, 0.99; p=0.04]). No significant between-group differences were seen for maternal pregnancy and birth outcomes.

Comment: It is well recognised that maternal weight is a risk factor for gestational diabetes and associated increased birthweight and adverse pregnancy outcomes for the baby. Therefore it makes good sense that effective weight management during pregnancy might reduce these. This large randomised controlled diet and lifestyle intervention study of overweight women in the second trimester of pregnancy tested this hypothesis. Unfortunately, despite an intensive intervention, there was no difference in gestational birthweight, or rates of pre-eclampsia, hypertension or gestational diabetes. However, there was no difference in weight gain during pregnancy between groups. Therefore it cannot be determined from this study whether effective weight management would have improved these outcomes.

Reference: *BMJ* 2014;348:g1285

[Abstract](#)

Associations between exposure to takeaway food outlets, takeaway food consumption, and body weight in Cambridgeshire, UK

Authors: Burgoine T et al.

Summary: This population-based, cross-sectional study explored the relationships between environmental exposure to takeaway food outlets, takeaway food consumption and bodyweight in 5442 working adults in the UK. Multiple linear regression models showed a positive association between exposure to takeaway food outlets and consumption of takeaway food. The strongest association was seen in work environments (β coefficient, for the most versus least exposed quartile, 5.3 g/day [1.6, 8.7; $p < 0.05$]), although the associations between exposure in home, commuting route and work domains combined and takeaway food consumption were greater in magnitude across exposure quartiles (5.7 g/day [2.6, 8.8; $p < 0.001$]), and the associations between combined exposure and increased BMI and odds ratio of obesity were especially strong (1.21 kg/m² [0.68, 1.74; $p < 0.001$] and 1.80 [1.28, 2.53; $p < 0.05$], respectively). There was evidence of dose-response effects in the associations of takeaway food consumption, but no evidence of effect modification by sex.

Comment: It is increasingly clear that there is great complexity in the causes of obesity, with inter-relationships between genetic predisposition, individual behaviour and the built and regulatory environments. Consumption of energy-dense high-fat foods, such as most forms of takeaway food, is associated with obesity. This cross-sectional study looked at the association between exposure to takeaway outlets and obesity, and extended this further to compare locations of home, commuting route and work. The findings were perhaps predictable that greater exposure was linked to more obesity, although the effect size was still rather modest. The authors concluded that as the association was greatest for exposure around the workplace, this may provide a target for regulatory approaches to restrict this. However, this would be unlikely to be effective in achieving major effects at a population level on its own, and would need to be part of a broader strategy.

Reference: *BMJ* 2014;348:g1464

[Abstract](#)

Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke

Authors: The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects)

Summary: This meta-analysis evaluated the impact of BMI on CHD and stroke, and how much of the impact is mediated by BP, cholesterol and glucose. Data from 97 prospective cohort studies that enrolled a total of 1.8 million participants were pooled. Overall, 57,161 CHD and 31,093 stroke events were reported. The HR of BMI on CHD and stroke was estimated with and without adjustment for all possible combinations of BP and cholesterol and glucose levels. The HR for each 5 kg/m² increase in BMI was 1.27 for CHD and 1.18 for stroke after adjustment for confounders. Forty-six percent of the excess risk of BMI for CHD and 76% for stroke were mediated by the three metabolic risk factors. BP was the most important mediator, accounting for 31% of the excess risk for CHD and 65% for stroke. Both overweight and obesity were associated with a significantly increased risk of CHD and stroke compared with normal bodyweight. Fifty percent and 44% of the excess risk of overweight and obesity for CHD and 98% and 69% of the excess risk of overweight and obesity for stroke, respectively, were mediated by the three metabolic risk factors.

Comment: Prospective cohort studies provide a great opportunity to study the natural history of a disease or to look for potential contributors to development of disease or complications. Obesity has been repeatedly shown to be associated with CV disease. This impressive study of pooled data from a very large number (1.8 million) of individuals with many CV endpoints showed that the majority of the excess risk conferred by obesity for stroke and a third for coronary events is mediated by hypertension, cholesterol and glucose. However, there is still a significant excess risk that remains unexplained. The authors concluded that interventions to reduce these factors may reduce this excess risk, but many randomised controlled trials have failed to demonstrate this with regards to weight loss and glucose lowering, although the evidence is better for cholesterol and hypertension.

Reference: *Lancet* 2014;383(9921):970-83

[Abstract](#)

Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial)

Authors: Yates T et al.

Summary: This prospective assessment of 9306 NAVIGATOR trial participants with impaired glucose tolerance and high CV disease risk explored the association between ambulatory activity and CV event risk; 531 CV events were reported during follow-up of 45,211 person-years. Significant inverse associations were seen between both baseline and change in ambulatory activity and CV event risk (respective adjusted HRs, per 2000 steps per day, 0.90 [95% CI 0.84, 0.96] and 0.92 [0.86, 0.99]).

Comment: There is a bit of a theme of prediabetes to this month's review. Primary-care teams are grappling with what to do with the increasing numbers of individuals identified with prediabetes now that HbA_{1c} (glycosylated haemoglobin) level is part of the CV risk assessment. This analysis of data from the NAVIGATOR trial assessed the impact of background and increased physical activity in those with prediabetes on CV events. Whilst the reduction was modest (~10%), given that this was an event study and not a risk-factor study, it is compelling evidence to support physical activity as part of the management of prediabetes.

Reference: *Lancet* 2014;383(9922):1059–66

[Abstract](#)

Sociodemographic differences in fast food price sensitivity

Authors: Meyer KA et al.

Summary: This paper reported 20-year follow-up of participants from the US CARDIA (Coronary Artery Risk Development in Young Adults; baseline n=5115) study with respect to the effects of 'fast-food' price changes and consumption on cardiometabolic outcomes. Nonlinear multivariable-adjusted associations were seen between fast-food price and consumption ($p < 0.001$), with significant inverse estimated effects on consumption as price increased, which varied by race, income and education ($p \leq 0.07$). The mean frequencies of fast-food consumption were 2.20 and 1.55 times per week for the tenth price percentile among blacks and whites, respectively, and the respective frequencies for the ninetieth price percentile were 1.86 and 1.50 times per week. Differential price effects were seen on homeostatic model assessment of insulin resistance and BMI.

Comment: The role for price regulation on food and the potential for this to have a beneficial effect on rates of obesity and its comorbidities is a hot area, and it is likely to become an election issue in NZ this year. An important consideration is the issue of disparities between ethnicities in obesity, health consequences and engagement with health services. Fast food is generally high in fat, energy dense and high salt, all of which promote obesity and hypertension. This prospective cohort study in the US showed that price of fast food was an important mediating factor in the frequency of consumption. Perhaps more importantly, this effect varied across ethnic groups, suggesting that price strategies through manipulation of taxation may have greater benefits for ethnic groups with greater burden of disease. I hope the Minister is reading this month's review!

Reference: *JAMA Intern Med* 2014;174(3):434–42

[Abstract](#)

Metformin usage in type 2 diabetes mellitus: are safety guidelines adhered to?

Authors: Huang W et al.

Summary: This retrospective review of 301 metformin recipients with type 2 diabetes admitted to a teaching hospital over an 8-month period found that metformin administration was not consistent with guidelines in 31% and 21% at admission and discharge, respectively. Contraindications to metformin were present in 21.6% and 14.3% of patients at admission and discharge, respectively, and the respective proportions of patients receiving an excessive dosage of the agent according to their renal function were 16.5% and 11%. Evidence of lactic acidosis without a clinical diagnosis was present in four patients.

Comment: I know this is a hobbyhorse of mine that the risk of lactic acidosis associated with metformin is overstated. Hence my eye caught this paper from Australia reviewing the usage of metformin according to the Australian medicines handbook guidelines. These suggest contraindication to metformin use in a wide variety of situations. In this review of patients admitted to hospital who were taking metformin, the findings suggest a high rate of poor adherence to these recommendations. However, there were very few episodes of lactic acidosis in these patients. I take this to support my impression that the risk has been overstated and the recommendations should be reviewed.

Reference: *Intern Med J* 2014;44(3):266–72

[Abstract](#)

Hospital admissions in relation to body mass index in UK women

Authors: Reeves GK et al., and the Million Women Study Collaborators

Summary: This prospective cohort study explored the relationship between BMI and hospitalisation rates among 1251,619 Million Women Study participants aged 50–64 years at enrolment, among who 2834,016 incident hospital admissions were recorded during an average of 9.2 years of follow-up. Standardised 10-year admission rates were 2.4, 2.4, 2.6, 3.0 and 3.5 per woman for BMIs of <22.5, 22.5–<25, 25–<30, 30–<35 and ≥ 35 kg/m², respectively ($p < 0.001$ for heterogeneity), and the respective lengths of stay per hospitalisation were 3.1, 2.8, 2.9, 3.2 and 3.8 days ($p < 0.001$). Admission rates increased by a factor of 1.12 for each 5 kg/m² increase in BMI. The risk of admission increased significantly with increasing BMI for 19 of the 25 types of hospital admissions assessed, particularly those associated with diabetes, knee-replacement, gallbladder disease and venous thromboembolism, but also many other common categories, including cataracts, carpal tunnel syndrome and diverticulitis.

Comment: There are plenty of data that show a relationship between obesity and comorbidities such as type 2 diabetes, CV disease, joint damage and some cancers. However, there are less data to show excess use of healthcare resources associated with obesity. This study reports data from the UK from a very large number of middle-aged women showing clear, albeit relatively small, increases in hospital admission and length of stay with increasing obesity. This confirms again the importance of obesity in influencing health status. Of course these data cannot be taken to mean that weight loss will necessarily reduce this, but they do highlight that collection of such data in long-term weight loss studies would be valuable.

Reference: *BMC Med* 2014;12:45

[Abstract](#)



Diabetes prevention in the real world: effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes and of the impact of adherence to guideline recommendations

Authors: Dunkley AJ et al.

Summary: A total of 25 trials of lifestyle interventions, aimed at translating evidence from efficacy trials into real-world intervention programmes, were included in this systematic review and meta-analysis. A primary, direct pairwise meta-analysis of bodyweight loss outcomes, which included 22 trials with 24 study groups, found a mean 2.12kg bodyweight loss over 12 months with lifestyle interventions. Furthermore, each point increase on a 12-point adherence scale was associated with 0.3kg greater bodyweight loss.

Comment: Continuing the theme of diabetes prevention, this study is a meta-analysis of translational studies utilising evidence from efficacy trials into real-world settings. Not all of the studies included were conducted in participants with prediabetes, but also included those at high risk of diabetes. The summary of these data is that translating these interventions into clinical practice is effective in facilitating modest weight loss, which not surprisingly is enhanced by greater adherence to the guidelines. What is missing from this study is the real question of how effective this is in preventing diabetes. It is possible that despite weight loss, diabetes ensues anyway, or conversely that even without significant weight loss, progression to diabetes can be delayed or prevented. This is the question that needs urgent attention.

Reference: *Diabetes Care* 2014;37(4):922–33

[Abstract](#)

Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release

Authors: Garvey WT et al.

Summary: This was a subgroup analysis of 475 phase 3 trial participants with prediabetes or metabolic syndrome at baseline, BMI 27–45 kg/m² and ≥2 comorbidities who had been randomised to receive ER phentermine/topiramate 7.5mg/46mg or 15mg/92mg or placebo, along with a lifestyle intervention, for 108 weeks. Compared with placebo, ER phentermine/topiramate at doses of 7.5mg/46mg and 15mg/92mg was associated with significantly greater bodyweight loss at 108 weeks (10.9% and 12.1%, respectively, vs. 2.5%; $p < 0.0001$), and these reductions were associated with decreases in the annualised incident type 2 diabetes rate of 70.5% and 78.7% for each dose, respectively ($p < 0.05$). A relationship was seen between the ability of ER phentermine/topiramate to prevent progression to diabetes and the degree of bodyweight loss, and significant cardiometabolic parameter improvements accompanied these changes. ER phentermine/topiramate was well tolerated.

Comment: On the same lines, this report is a substudy of a bigger randomised controlled trial, reporting the incidence of diabetes in those with either prediabetes or metabolic syndrome when phentermine and topiramate are added to lifestyle advice. The reduction in both weight and progression to diabetes are impressive. Importantly, the benefit was directly related to the degree of weight lost, implying that the benefit may be seen no matter how the weight loss is achieved. That would be supported by the results from the DPS (Diabetes Prevention Study) and DPP (Diabetes Prevention Program) with intensive lifestyle intervention alone. A very important question is whether there are any long-term side effects of this drug combination, as we have seen virtually all weight loss agents come and go due to adverse effects. It is particularly important when such a large proportion of the population could be eligible for treatment, and we have evidence that nonpharmacological interventions are equally effective when adhered to.

Reference: *Diabetes Care* 2014;37(4):912–21

[Abstract](#)

Working-age adults with diabetes experience greater susceptibility to seasonal influenza

Authors: Lau D et al.

Summary: This population-based study of working-age adults with diabetes each matched with ≤2 nondiabetic controls compared incidences of influenza-related illness between these cohorts over 745,777 person-years of follow-up; the study population consisted of 166,715 individuals, with more comorbidities and greater influenza vaccination rates seen among those with diabetes. The participants with diabetes had more influenza-related hospitalisations than the nondiabetics (rate ratio 1.06 [95% CI 1.02, 1.10]), but no significant between-group difference was seen for influenza-attributable rates of influenza-like illness ($p = 0.06$) or pneumonia and influenza ($p = 0.11$).

Comment: Flu vaccination has been shown to be effective in reducing the incidence and severity of infection in a range of patient groups, and underpins the public health advice for vaccination programmes. This study examines whether those with diabetes are more susceptible to the flu and its complications than those without diabetes. The results support the advice to recommend flu vaccination to adults with diabetes. It doesn't address whether this is also appropriate for children and adolescents, which is likely to be the case, but requires specific study.

Reference: *Diabetologia* 2014;57(4):690–8

[Abstract](#)

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