# Diabetes & Obesity Research Review™

Making Education Easy

Issue 92 – 2015


## In this issue:



**Abbreviations used in this issue**

**BP** = blood pressure
**CV** = cardiovascular
**GI** = gastrointestinal
**$Hb_{A1c}$** = glycosylated haemoglobin
**HR** = hazard ratio
**OR** = odds ratio

# Welcome to issue 92 of Diabetes and Obesity Research Review.

Research selected for this issue includes a paper from Sweden detailing a number of possible impacts of bariatric surgery on subsequent pregnancy outcomes. Research from the US has described how several material need insecurities impact on diabetes control and healthcare resource use. In other important research (also from Sweden), a heightened risk of psychiatric disorders was identified in children with type 1 diabetes, highlighting the need for comprehensive surveillance, especially in recently diagnosed children. This issue concludes with research reporting increased all-cause mortality and vascular event risks in women versus men with type 1 diabetes.

I hope you enjoy the selection for this issue, and I am always happy to respond to your questions and comments.

Best regards,


**Associate Professor Jeremy Krebs**
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## Blood pressure lowering in type 2 diabetes

**Authors**: Emdin CA et al.


**Summary**: This systematic review and meta-analysis of 40 trials with a low risk of bias (n=100,354) found that each 10mm Hg decrease in systolic BP among patients with type 2 diabetes receiving BP-lowering treatment was associated with significantly lower risks of mortality (relative risk 0.87 [95% CI 0.78, 0.96]; absolute risk reduction 3.16 per 1000 patient-years [0.90, 5.22]), CV events (0.89 [0.83, 0.95]; 3.90 [1.57, 6.06]), coronary heart disease (0.88 [0.80, 0.98]; 1.81 [0.35, 3.11]), stroke (0.73 [0.64, 0.83]; 4.06 [2.53, 5.40]), albuminuria (0.83 [0.79, 0.87]; 9.33 [7.13, 11.37]) and retinopathy (0.87 [0.76, 0.99]; 2.23 [0.15, 4.04]). The relative risks for outcomes other than stroke, retinopathy and renal failure were lower in studies with baseline systolic BP of >140mm Hg ($p<0.1$ for interaction). With the exceptions of stroke and heart failure, associations between BP-lowering treatments and outcomes did not differ significantly regardless of drug class.


**Comment**: This is more of the same, but it is still worth noting the findings. A focus on BP management in diabetes is well entrenched in usual practice. Numerous clinical trials over the last 15–20 years have demonstrated benefits in reducing both micro- and macrovascular complications. This meta-analysis reconfirms this conclusion. Notably of the outcomes reviewed, reducing BP resulted in the greatest absolute risk reduction for albuminuria. It is also worth noting that there were no differences observed between classes of antihypertensive drugs and mortality and CV disease, but there were differences in stroke and heart failure. Albuminuria was not examined. There has been debate over the treatment target in recent years. This analysis supports lowering to <130mm Hg for systolic BP for additional risk reduction for stroke, retinopathy and albuminuria. Therefore individualising treatment according to best tolerance and adherence with agents should be the focus of therapy. There is a very good editorial that accompanies this paper.


***Reference: JAMA 2015;313(6):603–15***
Abstract

## Impact of $HbA_{1c}$, followed from onset of type 1 diabetes, on the development of severe retinopathy and nephropathy

**Authors**: Nordwall M et al.

**Summary**: The longitudinal observational VISS (Vascular Diabetic Complications in Southeast Sweden) study included 451 patients with type 1 diabetes diagnosed before 35 years of age. Increases in proliferative retinopathy and persistent macroalbuminuria incidences were seen with increasing long-term mean $Hb_{A1c}$ level, with no cases of either complication seen in participants with long-term (20–24 years) weighted mean $Hb_{A1c}$ level of <60 mmol/mol (<7.6%) and respective rates of 51% and 23% among those with levels >80 mmol/mol (>9.5%).

**Comment**: There is nothing earth shattering about this study, but I included it as it also gives real-world data on the impact of tight glycaemic control and risk of microvascular complications in type 1 diabetes. This Swedish registry study supports the DCCT evidence that an $Hb_{A1c}$ level <60 mmol/mol is protective of proliferative retinopathy and nephropathy over 20 years of follow-up. The risk increases significantly with rising $Hb_{A1c}$ level, particularly for retinopathy. This again supports the findings of DCCT that retinopathy has the strongest relationship with glycaemic control. It is reassuring to know that in clinical practice, the trial evidence holds true across the wider patient group and further underpins our practice goals.

***Reference: Diabetes Care 2015;38(2):308–15***
Abstract

## Outcomes of pregnancy after bariatric surgery

**Authors**: Johansson K et al.

**Summary**: This research included 670 women who had singleton pregnancies (recorded in the Swedish Medical Birth Register) after undergoing bariatric surgery and who had presurgery bodyweight documented, each compared with ≤5 matched control pregnancies. Compared with controls, women with pregnancies after bariatric surgery were less likely to develop gestational diabetes (OR 0.25 [95% CI 0.13, 0.47]) and deliver large-for-gestational-age infants (0.33 [0.24, 0.44]), but were more likely to deliver small-for-gestational-age infants (2.20 [1.64, 2.95]) and have a shorter gestational period (273.0 vs. 277.5 days [p<0.001]). Although there was a trend for a higher risk of stillbirth or neonatal death among women who had undergone bariatric surgery (OR 2.39 [0.98, 5.85]), there was no significant difference in the risk of preterm birth (1.28 [0.92, 1.78]) or the frequency of congenital malformations.

**Comment**: There have always been some concerns expressed about the potential risks for young women of reproductive age having bariatric surgery on subsequent pregnancy outcomes. It is therefore great to see some data to specifically address this issue. This retrospective case-control study compared pregnancies in women who have had previous bariatric surgery with women matched for presurgical age and other factors. There was a 75% reduction in rates of gestational diabetes and a 66% reduction in macrosomia in the women who had undergone bariatric surgery. However, the trade-off was a 2-fold increase in small babies and a possible increase in perinatal mortality. There are many theories and potential positive and negative effects of the physiological changes induced by bariatric surgery on the intrauterine environment. Therefore it would be very interesting to know the outcomes of the children with respect to obesity and metabolic health.

***Reference: N Engl J Med 2015;372(9):814–24***
Abstract

## Material need insecurities, control of diabetes mellitus, and use of health care resources

**Authors**: Berkowitz SA et al.

**Summary**: The Measuring Economic Insecurity in Diabetes cross-sectional study explored associations of material need insecurities with diabetes control and healthcare resource use in 411 randomly selected US adults with diabetes; the response rate was 62.3%. Food insecurity was reported by 19.1% of respondents, cost-related medication underuse by 27.6%, housing instability by 10.7%, energy insecurity by 14.1% and ≥1 material need insecurity by 39.1%, and poor diabetes control was identified in 46.0%. Food insecurity and cost-related medication underuse were respectively associated with poor diabetes control (adjusted ORs 1.97 [95% CI 1.58, 2.47] and 1.91 [1.35, 2.70]) and increased outpatient visits (adjusted incident rate ratios 1.19 [1.05, 1.36] and 1.68 [1.21, 2.34]), whereas housing and energy instability were respectively associated with increased outpatient visits (1.31 [1.14, 1.51] and 1.12 [1.00, 1.25]) but not diabetes control; no associations were seen with emergency department/inpatient visits. Each additional insecurity increased the likelihoods of poor diabetes control (OR 1.39 [95% CI 1.18, 1.63]) and outpatient and emergency department/inpatient visits (respective incident rate ratios 1.09 [1.03, 1.15] and 1.22 [0.99, 1.51]).

**Comment**: Despite abundant evidence that tight glycaemic control and BP control reduce the complications of diabetes, any audit performed of primary or secondary care registers of people with diabetes shows that overall there are still many patients who do not achieve these goals. Furthermore, despite my jibes at PHARMAC, we do have a range of therapeutic options available. Therefore there must be other factors that determine this relative lack of success. This paper looked at the impact of unmet material needs and the effect of this on diabetes control in an American population. The results confirm what we might expect, in that greater unmet basic needs were associated with worse control of diabetes. With increasing attention to the issue of poverty in NZ, it is very likely that these same factors are determinants of diabetes control here too. This may be of particular relevance to Māori and Pacific populations who have disproportionate rates of diabetes complications.

***Reference: JAMA Intern Med 2015;175(2):257–65***
Abstract

## Risks of psychiatric disorders and suicide attempts in children and adolescents with type 1 diabetes

**Authors**: Butwicka A et al.

**Summary**: Swedish children with type 1 diabetes (n=17,122) and their healthy siblings (n=18,847) were followed until their eighteenth birthday for psychiatric disorders in this population-based cohort study. Compared with the general population, children with diabetes were at increased risk of psychiatric morbidity within 6 months of diabetes onset (HR 3.0 [95% CI 2.7, 3.4]) and within the total observation period (2.1 [2.0, 2.2]), including most categories of psychiatric disorders including suicide attempts (1.7 [1.4, 2.0]). The psychiatric disorder risk in probands was higher in those born during 1973–1986 versus 1997–2009 (HR 2.7 vs. 1.9). Siblings of patients with type 1 diabetes had a slightly elevated risk of developing any psychiatric disorder (HR 1.1 [95% CI 1.0, 1.1]), but there was no increased risk in any specific category.

**Comment**: The psychological impact of a diagnosis of type 1 diabetes on a child and their family cannot be underestimated. Type 1 diabetes enforces so many changes for the child with respect to food, activities and general freedom, let alone the impact of need to inject insulin and test blood glucose levels. It is therefore not surprising that this contributes to poorer mental health and increased risk of suicide attempts. This is highlighted in this Swedish registry study of children with diabetes and their healthy siblings where mental health issues were evident within 6 months of diagnosis of type 1 diabetes. Indeed this is a prudent reminder that presentations to hospital with ketoacidosis in young people with diabetes are often examples of self-harm and should always prompt consideration of this in the workup of patients.

***Reference: Diabetes Care 2015;38(3):453–9***
Abstract

## Progression of diabetes retinal status within community screening programs and potential implications for screening intervals

**Authors**: Leese GP et al., on behalf of the Four Nations Diabetic Retinopathy Screening Study Group

**Summary**: This observational analysis of data from seven UK diabetes retinal screening programmes involved 354,549 patients observed for ≤4 years during which time 16,196 progressed to referable retinopathy. Among patients with no retinopathy in either eye and bilateral background retinopathy for two successive screening episodes ≥12 months apart, the respective ranges of rates of progression to referable retinopathy across different programmes were 0.3–1.3% and 13–29%, and the respective rates of treatable eye disease at 2 years were <0.3% and ≤4%.

**Comment**: Retinopathy is one of the unique features of diabetes and has the strongest association with level of glycaemic control. Since the advent of widespread retinal photography as a reliable way of properly screening people with diabetes, this has been incorporated into most standards of care systems. Certainly in NZ there is an expectation that people with diabetes are enrolled in a screening programme. Whilst this has many benefits, it is an expensive system and may still fail to reach some of the most at-risk individuals. One way of reducing the cost is to reduce the frequency of screening. This paper from the UK addressed this issue. It showed that for those at low risk of progression to proliferative retinopathy, increasing the screening interval from 12 to 24 months would only have a very small risk at a population level of missing cases. It is of note that in NZ, many centres have been using a 2-yearly recall for many years already. A review of these criteria has suggested a further extension in very low-risk individuals. What is critical in the implementation of these guidelines is to get the risk stratification for any individual correct, and to ensure that the relevant screening interval for them is then put in place. This is the risk of having a variable interval and requires careful consideration to the best way to implement the policy.

***Reference: Diabetes Care 2015;38(3):488–94***
Abstract

**Independent commentary by Associate Professor Jeremy Krebs,** an endocrinologist with a particular interest in obesity and diabetes. He is an Associate Professor with the University of Otago, and Director of the Clinical Research Diploma at Victoria University. As well as clinical and teaching activities, Assoc Prof Krebs maintains active research interests in the area of obesity and diabetes, with a focus on nutritional aspects, bariatric surgery and diabetes service delivery.

**For full bio CLICK HERE.**

## Serum 25-hydroxyvitamin D: a predictor of macrovascular and microvascular complications in patients with type 2 diabetes

**Authors**: Herrmann M et al., for the FIELD Study Investigators

**Summary**: The relationships between baseline blood 25-hydroxyvitamin D level and the incidences of macrovascular and microvascular diseases were explored using data from participants enrolled in the 5-year FIELD trial. Low vitamin D levels (median blood 25-hydroxyvitamin D level ≤50 nmol/L) were seen in 50% of the participants and were associated with a higher cumulative incidence of macrovascular and microvascular events compared with higher levels. In adjusted multivariable models, a 50 nmol/L difference in blood 25-hydroxyvitamin D level was associated with a 23% change in macrovascular complication risk and a (nonsignificant) 11–14% change in microvascular complication risk.

**Comment**: Over the last 10 years there has been a lot of attention on vitamin D, with low status being associated with a wide range of diseases from multiple sclerosis and type 1 diabetes to eczema, osteoporosis and cancers. The frequent assumption that an association represents causality has prompted a host of variable quality studies of vitamin D supplementation. This analysis of the FIELD study, which many centres in NZ took part in, examined the association between vitamin D status and macrovascular disease in those with type 2 diabetes. It is notable, although not new, that 50% of participants had a low vitamin D status, and that this was associated with increased macrovascular but not microvascular events. The authors stressed that this does not determine causality. However, a well-conducted randomised controlled trial to examine whether supplementation reduces this excess risk could be warranted. Perhaps we need vitamin D in the drinking water after all (well at least in something fatty!).

***Reference: Diabetes Care 2015;38(3):521–8***
Abstract



## *Helicobacter pylori* infection decreases metformin tolerance in patients with type 2 diabetes mellitus

**Authors**: Yuxin H et al.

**Summary**: Patients with diabetes (n=415) underwent *H. pylori* infection assessment and received 4 weeks of metformin 500 mg/day progressively increasing to 1500 mg/day; 195 participants were found to be *H. pylori*-positive. Compared with *H. pylori*-negative participants, those who were *H. pylori* positive had significantly ($p<0.01$) higher rates of abdominal pain (44.6% vs. 21.8%), nausea (20.0% vs. 9.6%), bloating (47.7% vs. 23.2%) and anorexia (32.8% vs. 12.3%), and a significantly lower final metformin dose (951.28 vs. 1209.09mg). A multivariate analysis showed that *H. pylori* infection, along with age, gender, body mass index, triglyceride level and low-density lipoprotein cholesterol level, independently predicted GI symptoms.

**Comment**: We are all very familiar with metformin and the GI side effects that limit its tolerability in many patients despite starting with low doses and slow titration. This paper therefore caught my eye. It was a novel concept to me that *H. pylori* infection could be a determining factor in the likelihood of side effects. *H. pylori* infection is common, and therefore potentially very important to identify. In this study there was a very clear increase in a range of GI side effects in individuals who were *H. pylori* positive and this also translated into a reduced tolerable dose of metformin. This therefore raises the tempting hypothesis that treating *H. pylori* infection could improve this. Although ethically tricky to design, this should be tested in a randomised controlled trial. If correct, this could have significant management implications for treating type 2 diabetes.

***Reference: Diabetes Technol Ther 2015;17(2):128–33***
Abstract

## Self-monitoring of blood glucose versus self-monitoring of urine glucose in adults with newly diagnosed type 2 diabetes receiving structured education

**Authors**: Dallosso HM et al.

**Summary**: Patients with type 2 diabetes (n=292) were randomised by practice site to a structured group education programme of self-monitoring of glucose levels using blood or urine. The respective blood and urine glucose level self-monitoring groups had similar reductions from baseline in mean $Hb_{A1c}$ levels at 18 months (–12 and –13 mmol/mol [–0.2 and –0.2%]) and similar improvements for other biomedical outcomes, treatment satisfaction, generic and diabetes-specific well-being and their view of diabetes. Switching from urine to blood monitoring occurred at a significantly higher rate than switching from blood to urine monitoring (18% vs. 1% [p<0.001]).

**Comment**: Perhaps we have come full circle? The development of accurate blood glucose monitoring devices that could be used by individuals in their everyday life was one of the breakthroughs of diabetes management last century. This is particularly true for those with type 1 diabetes on multiple injections of insulin attempting to get tight glycaemic control. However, whilst this is extrapolated to those with type 2 diabetes, evidence to support the extensive use of self-monitoring of blood glucose in type 2 diabetes has been equivocal at best. This is particularly true in early disease before people require insulin therapy. This study is therefore very intriguing. It shows that in combination with a structured education programme, the use of urine glucose monitoring, which is of course a considerably more crude method and also retrospective, was just as good as blood glucose monitoring in facilitating improved glucose control. Given the relative costs of the two methods, perhaps just because we can test blood glucose doesn't necessarily mean we should!

***Reference: Diabet Med 2015;32(3):414–22***
Abstract



## Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes

**Authors**: Huxley RR et al.

**Summary**: This was a systematic review and meta-analysis of 26 studies (n=214,114) reporting all-cause mortality and cause-specific outcomes in patients with type 1 diabetes; a total of 15,273 events were identified. The respective pooled women-to-men ratios of standardised mortality ratios for all-cause mortality, incident stroke, fatal renal disease and fatal CV disease were 1.37 (95% CI 1.21, 1.56), 1.37 (1.03, 1.81), 1.44 (1.02, 2.05) and 1.86 (1.62, 2.15), and for incident coronary heart disease it was more extreme at 2.54 (1.80, 3.60). There was no evidence to indicate a sex difference for cancer or accident/suicide mortality associated with type 1 diabetes.

**Comment**: Premenopausal women generally have a lower CV risk than men, although this becomes attenuated after the menopause. Having diabetes increases CV risk and this drives our treatment pathways. This meta-analysis examines whether there is a sex difference in this increased risk associated with type 1 diabetes. Compared with other disease states such as renal disease or cancers, there was a clear increased excess risk of CV events and 40% greater total mortality for women compared with men with type 1 diabetes. This is very significant and suggests the need for a careful analysis of individual risk when considering management of lipid levels and BP for women with type 1 diabetes, who using traditional risk assessments will frequently come out below treatment thresholds.

***Reference: Lancet Diabetes Endocrinol 2015;3(3):198–206***
Abstract

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