

Clinical reviews

Our panel of GPs review recent research papers in their specialist areas that may influence the way you practise

Reviewers

Addiction

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substance misuse
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Cardiovascular disease

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Diabetes

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Paediatrics

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Sexual health

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Diabetes

Incretin-based diabetes therapy not associated with increased mortality

A recent meta-analysis, published in the *BMJ*, has shown no increase in all cause mortality in patients with type 2 diabetes using incretin-based treatments i.e. GLP-1 agonists and DPP-4 inhibitors.

The systematic review and meta-analysis reviewed randomised controlled trials that compared GLP-1 agonists or DPP-4 inhibitors with placebo, lifestyle modification, or active antihyperglycaemic drugs in patients with type 2 diabetes. The investigators searched Medline, Embase and the Cochrane Central Register of Controlled Trials, up to February 2017, for eligible studies.

Of 1,187 potentially eligible studies, 189 covering 155,145 participants met all eligibility criteria.

These included several large cardiovascular outcome trials where patients had, or were at high risk of, cardiovascular disease.

Of 189 trials reviewed, 77 reported no deaths at all. The other 112 reported 3,888 deaths among 151,614 patients,

of which 3,592 (92%) were reported from the six large cardiovascular outcome trials.

Meta-analysis of the 189 trials showed no difference in all cause mortality between incretin drugs and controls (1,925/84,136 vs 1,963/67,478). Odds ratio 0.96 (95% CI: 0.90-1.02; $I^2 = 0\%$). The authors state this as moderate quality evidence.

The results suggest the possibility of a mortality benefit with GLP-1 agonists, but not with DPP-4 inhibitors, but the sub group analysis was not sufficiently robust to be certain of this.

All the included trials were funded by the pharmaceutical industry. However, the investigators state that their 'funnel plot and statistical test showed no evidence of publication bias'. Another limitation was that many of the trials had shorter follow-up periods than might be needed to detect mortality differences.

The authors conclude: 'Our results provide no support for the hypothesis that incretin-based treatments are associated with increased all cause mortality in patients with type 2 diabetes.'

'Additional large well designed randomised trials with adequate follow-up will be necessary to definitively establish or refute possible differences in the effect of GLP-1 agonists and DPP-4 inhibitors on all cause mortality,' they add.

The potential associated risks of diabetes drugs, which have been widely reported in the lay press and other media, have made it even harder for diabetologists and GPs to persuade patients of the need to comply with treatments for their condition. It is useful for us to be able to see meta-analyses such as this one.

DR MATTHEW LOCKYER

Liu J, Li L, Deng K et al. Incretin based treatments and mortality in patients with type 2 diabetes: systematic review and meta-analysis. *BMJ* 2017;357:2499



Obstetrics and gynaecology

High maternal BMI linked to increasing risk of congenital abnormalities

The risk of major congenital malformations in infants rises with maternal overweight and degree of obesity, a large study from Sweden has shown.

Sweden has comprehensive national registers that record data on prenatal, birth and fetal outcomes. From 2001 to 2014 prospectively obtained data were collected on around 1.5 million pregnancies.

After exclusions for incomplete data, twin pregnancy, chromosomal abnormality and known genetic

syndromes, 1,243,957 remained for analysis. BMI was recorded at booking.

All women were offered a fetal anomaly ultrasound scan at 18 weeks' gestation. Data on the numbers of pregnancy terminations following this were not presented.

Fetal abnormalities were formally classified as: cardiac, urinary system, genital organs, CNS, digestive system, limb, orofacial clefts, for example.

The overall fetal anomaly rate was 3.5% (n = 43,550). The rate was higher in male than female babies; 4.1% versus 2.8%.

Adjusted risk ratios (RR) were significantly higher (P < 0.001) in: nulliparous women RR 1.07 (95% CI: 1.05-1.09); women >35 years compared with 30-34 years RR 1.06 (95% CI: 1.03-1.09); women without partners RR 1.10 (95% CI: 1.06-1.15); women with fewer years of education; and in smokers.

Significantly higher fetal anomaly rates with higher maternal BMI, after adjustment, were seen for digestive system, genital organ, CNS, cardiac and orofacial cleft defects, see table 1, below.

The highest fetal anomaly rates related to BMI were seen in CNS defects, with infants born to mothers with obesity class III having almost double the risk of those born to normal weight women.

The sex difference for genital organ abnormality was striking; 0.9% of all male versus 0.04% of female babies having an anomaly.

A sub-analysis excluding women

with pre-pregnancy and gestational diabetes made no difference to the significance of the associations.

Maternal country of birth (Nordic versus non-Nordic ethnicity) did not affect the results. The fetal anomaly rates did not vary significantly with BMI for eye, urinary system or limb defects.

Several small studies have shown an association between maternal overweight and obesity and fetal congenital abnormality. This large study from Sweden, where obesity rates have doubled in the past 20 years, has confirmed these findings.

This is an important and worrying study given the rising rates of obesity in general, and obesity during pregnancy in particular.

Observational studies can only suggest association. Nevertheless, the number of women studied was huge, the link to high BMI plausible, and the rise for several specific categories of fetal anomaly with BMI compelling.

The authors speculate on the possible mechanisms linking obesity with fetal anomaly and, not surprisingly, conclude it is multifactorial. They did identify metabolic syndrome as a possible significant factor.

We as GPs can help by advising on effective weight loss strategies prior to pregnancy.

DR CHRIS BARCLAY

Persson M, Cnattingius S, Villamor E et al. Risk of major congenital malformations in relation to maternal overweight and obesity severity: cohort study of 1.2 million singletons. *BMJ* 2017;357:j2563

Table 1

Adjusted risk ratios (RR) of major congenital malformations

	Underweight BMI < 18.5		Normal weight* BMI 18.5-24.9		Overweight BMI 25.0- 29.9		Obesity class I BMI 30.0-34.9		Obesity class II BMI 35.0-39.9		Obesity class III BMI ≥ 40	
	RR	(95% CI)	RR		RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Overall	1.01	(0.95-1.08)	1.00		1.05	(1.02-1.07)	1.12	(1.08-1.15)	1.23	(1.17-1.30)	1.37	(1.26-1.49)
Digestive	0.98	(0.72-1.33)	1.00		0.97	(0.87-1.09)	1.41	(1.21-1.63)	1.33	(1.03-1.72)	1.54	(1.05-2.28)
Genital	1.03	(0.87-1.22)	1.00		1.04	(0.98-1.11)	1.12	(1.02-1.23)	1.27	(1.09-1.47)	1.43	(1.13-1.80)
CNS	1.28	(0.91-1.79)	1.00		1.15	(1.00-1.31)	1.44	(1.20-1.73)	1.65	(1.23-2.21)	1.88	(1.20-2.94)
Cardiac	0.99	(0.90-1.09)	1.00		1.05	(1.01-1.08)	1.15	(1.09-1.20)	1.26	(1.16-1.37)	1.44	(1.27-1.63)
Orofacial clefts	1.20	(0.90-1.60)	1.00		1.09	(0.98-1.22)	1.11	(0.94-1.31)	1.52	(1.19-1.95)	1.44	(0.96-2.16)

*Reference

Mental health

Should lithium treatment be continued during pregnancy?

Women who take lithium during early pregnancy have a slightly increased risk of giving birth to a child with a cardiac malformation, a large retrospective cohort study from the USA has found.

Demographic, healthcare and prescription data were obtained from the Medicaid Analytic eXtract (MAX). The cohort comprised a total of 1,325,563 pregnancies resulting in a live birth between 2000 and 2010.

Lithium and lamotrigine use was defined as the redemption of at least one prescription during the first trimester. Lamotrigine was chosen as a comparator because it is also used in the treatment of bipolar disorder but has not been associated with a raised risk of congenital malformations. Women who were exposed to both drugs were excluded.

Stratified propensity score analysis was used to adjust for a wide range of potential confounders such as age, ethnicity, smoking and comorbidity.

Cardiac malformations occurred in:

- 16 out of 663 infants exposed to lithium (2.41%)
- 15,251 out of 1,322,955 unexposed infants (1.15%)
- 27 out of 1,945 infants exposed to lamotrigine (1.39%)

Compared with unexposed infants, infants exposed to lithium were significantly more likely to have a cardiac malformation; adjusted risk ratio (RR) 1.65 (95% CI: 1.02-2.68).

The results suggest a dose-risk

relationship, with the RR increasing from 1.11 (95% CI: 0.46-2.64) for a daily dose ≤ 600 mg to 3.22 (95% CI: 1.47-7.02) for a daily dose > 900 mg.

Compared with unexposed infants, those exposed to lithium were more likely to have a right ventricular outflow tract obstruction defect RR 2.66 (95% CI: 1.00-7.06). Similar results were obtained when lamotrigine-exposed infants were used as the reference group.

Pregnant women enrolled in Medicaid are young, racially diverse and on low incomes,¹ but there is no good reason why these results should not apply to more affluent populations.

Propensity score analysis does not eliminate the possibility of confounding by indication, but the similar results obtained when lithium was compared with lamotrigine suggest this was not a significant problem. The wide confidence intervals despite the large sample size reflect the difficulty of studying an uncommon side effect of an uncommonly prescribed drug.

NICE recommends that lithium should not be offered to women who are planning a pregnancy or pregnant, unless antipsychotic medication has not been effective. Where lithium is offered it is essential to discuss the risk of cardiac malformations 'but the size of the risk is uncertain'.²

This study now provides clarification: there is a risk but this is smaller than was previously thought: approximately one additional case per 100 exposed infants.

GPs should review their lithium registers and ensure that any women of childbearing age are aware of the risk and of the importance of seeking specialist preconception advice.

When a woman presents with an unplanned pregnancy, NICE recommends that we consider stopping the lithium gradually over a four-week period if she is well.²

This is a difficult decision that should only be made under specialist guidance. There is a need to balance the small risk of harm against the substantially increased risk of relapse, particularly during the postpartum period, if lithium is stopped.

A recent meta-analysis found that in women with bipolar disorder, continuation of prophylactic treatment during pregnancy (lithium in most studies) was 'critically important for maintaining mood stability after delivery'.³

When discussing whether or not to stop lithium, it is essential to discuss absolute, not relative risks. The evidence suggests that, out of 100 women with bipolar disorder who choose to stop their lithium for the duration of their pregnancy, one will thereby prevent their child from being born with a cardiac defect but 43 will suffer a postpartum relapse that they could otherwise have prevented.³

For those who are unwell or at high risk of relapse, NICE recommends either switching gradually to an antipsychotic, stopping lithium and restarting it in the second trimester, or continuing lithium if an antipsychotic is unlikely to be effective.²

However, the authors of the meta-analysis recommend that all women with bipolar disorder should continue their prophylactic medication.³

DR PHILLIP BLAND

Paterno E, Huybrechts KF, Bateman BT et al. Lithium use in pregnancy and the risk of cardiac malformations. *N Engl J Med* 2017;376:2245-54

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- 2 National Institute for Health and Care Excellence. CG192. Antenatal and postnatal mental health: clinical management and service guidance. NICE. London. 2014
- 3 Wesseloo R, Kamperman AM, Munk-Olsen T et al. Risk of postpartum relapse in bipolar disorder and postpartum psychosis: a systematic review and meta-analysis. *Am J Psychiatry* 2016;173:117-27

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Addiction

Risk algorithm could help predict onset of hazardous drinking

A simple risk algorithm may aid GPs in assessing patients' risk of progression to hazardous drinking over 12 months.

The investigators conducted a prospective cohort study involving 174 GPs, from 32 primary care health centres, in six Spanish provinces. Random samples of four to six attendees from GP appointment lists were taken for each day of recruitment. A total of 3,954 abstinent or low-risk drinkers were recruited to the study between October 2005 and February 2006. Participants were evaluated at baseline, and at 6 and 12 months.

Of the 3,954 patients assessed at baseline, 2,667 (67.5%) were interviewed at 6 months and 2,301 (58.2%) at 12 months.

Overall, 41 risk factors were measured and multilevel logistic regression and inverse probability weighting were used to develop the algorithm predictAL-10. The algorithm included nine variables that covered ten questions: province, sex, age, cigarette consumption, perception of financial strain, having ever received treatment for an alcohol problem, childhood sexual abuse, AUDIT-C, and interaction AUDIT-C*Age.

When used to predict development of hazardous drinking the sensitivity and specificity of the predictAL-10 algorithm were 0.83 and 0.80, respectively.

The authors also examined the algorithm without the question on childhood sexual abuse (predictAL-9) obtaining similar outcomes.

Alcohol misuse is responsible for very significant preventable morbidity and mortality in the UK and is associated with high social and economic costs. Medical conditions related to alcohol use include suicide, accidents and injuries, cancers, hypertension, dementia and liver disease. Currently 31% of men and 16% of women in the UK drink more than recommended guideline amounts.¹

Much has been published on screening for alcohol misuse and on brief interventions for those found to be drinking at at-risk levels. However, much less is known about the risk factors for progression to hazardous or harmful use in those who are currently abstinent or low-risk drinkers. Although a risk assessment tool exists, it is complex to deliver and is not easily applicable to the primary care environment.

The study authors conclude: 'The predictAL-10/9 algorithm is a simple, brief, and internally valid risk algorithm to predict the onset of hazardous drinking over 12 months in primary care attendees who are abstinent or low-risk drinkers.'

Because predictAL-10/9 incorporates the AUDIT-C test it allows for simultaneous assessment of current hazardous drinking and the risk of progressing to hazardous drinking, providing opportunities for both primary and secondary prevention of hazardous drinking.

DR JEZ THOMPSON

Bellón JA, de Lios Luna J, King M et al. Predicting the onset of hazardous alcohol drinking in primary care: development and validation of a simple risk algorithm. *Br J Gen Pract* 2017; DOI: <https://doi.org/10.3399/bjgp17X690245>

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1 NHS Digital. Statistics on Alcohol. England 2017 www.gov.uk/government/statistics/statistics-on-alcohol-england-2017

Sexual health

Not all patients with chlamydia are being tested for HIV

Most chlamydia testing now takes place outside genitourinary medicine (GUM) clinics. Although the majority of those tested in other settings are less likely to report risky sexual behaviour, a substantial minority do and some patients with chlamydia infection are missing out on HIV tests, NATSAL-3 has shown.

The investigators compared characteristics of those tested for chlamydia in GUM, general practice and other settings using data from NATSAL-3, a British probability sample survey carried out in 2010-2012.

Survey participants were aged 16-44 years with at least one sexual partner in the past year. Of a total of 8,397 participants (4,992 women) 27% of women and 17% of men reported having a chlamydia test in the past year. This was more common in those aged 16-24 (55% of women and 36% of men) which is the age group eligible for the national chlamydia screening programme in England.

Of those who had been tested, 28% of women and 41% of men had been tested in GUM clinics; 41% and 27% of women and men respectively in general practice, and 31% and 38% in other non-GUM settings including: university, schools, family planning clinics, antenatal clinics and termination of pregnancy services.

Women who tested for chlamydia in general practice tended to be older, living with a partner, and living in rural areas compared with those tested in GUM clinics. Men were just as likely to test in general practice and in GUM clinics for chlamydia.

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People tested in general practice or other settings were generally less likely to report risk behaviours for STIs than those tested in GUM clinics. However, 11% of women tested in general practice and 13% in other non-GUM settings reported unsafe sex i.e. at least two partners in the past year and with no condom use. For men, the figures were 7% of those tested in general practice and 10% of those tested in other settings.

Of the women reporting unsafe sex, 85% of those tested in general practice and 73% tested in other settings had not attended a GUM clinic in the past year. For men, the figures were 80% who were tested in general practice or non-GUM settings.

Of the participants with at least one sexual partner in the past year, 4% of women (n = 285) and 4% of men (n = 178) reported a diagnosis of chlamydia in the past five years. Of these, 58% of women and 77% of men were treated in GUM; 27% of women and 18% of men were treated in general practice.

Of those who were treated for chlamydia in the past five years, 66% of women and 56% of men reported being tested for HIV at the same time; this was less common in those treated in general practice and other locations compared with GUM clinics (55% vs 74%). Of those women tested for chlamydia in non-GUM settings, around half had tested for HIV in a sexual health check and 29% because of pregnancy, very few because they were advised to by a doctor.

Most chlamydia testing occurred in non-GUM settings, in particular general practice, where people tended to have fewer risk behaviours. However, general practice was a setting for at least a quarter of men and women for chlamydia treatment, some of whom were not tested for HIV even though they reported sexual risk behaviour.

There is a clear contribution to STI control from general practice, we need to ensure that we use opportunities to test for STIs including HIV, and treat where appropriate.

DR RICHARD MA

Clifton S, Mercer CH, Woodhall SC et al. Patterns of chlamydia testing in different settings and implications for wider STI diagnosis and care: a probability sample survey of the British population. *Sex Transm Infect* 2017;93:276-83

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