

THIS WEEK'S RESEARCH QUESTIONS

- 906** What is the safety and efficacy of overnight closed loop delivery of insulin (artificial pancreas) compared with conventional insulin pump therapy in adults with type 1 diabetes?
- 907** What effects do coadministration of oxandrolone with growth hormone and timing of pubertal induction have on final height of girls with Turner's syndrome?
- 908** Is prostate cancer screening in general practice feasible and does it reduce cancer specific mortality?
- 909** Are clinical risk factors able to predict pre-eclampsia in nulliparous women and so identify those who require specialist referral?

The artificial pancreas in adults with type 1 diabetes



Roman Hovorka and colleagues' report of two small crossover trials is an unusual *BMJ* paper (p 906). It's about overnight closed loop delivery of insulin using the "artificial pancreas," a system

comprising a subcutaneous insulin infusion pump controlled by a mathematical algorithm that handles data from a continuous glucose monitor. The trials compared the efficacy of this device with a standard insulin pump in two groups of 12 selected adults.

This work is obviously some way from showing effectiveness in a wider sample in regular clinical practice, which is the kind of evidence the *BMJ* usually publishes. However, editors, and reviewers, were intrigued and impressed by the research questions and liked the pragmatism of testing the relative efficacy of the artificial pancreas versus an insulin pump in conditions that mimicked eating dinner in or eating out with wine. The study was funded by public organisations and charities.

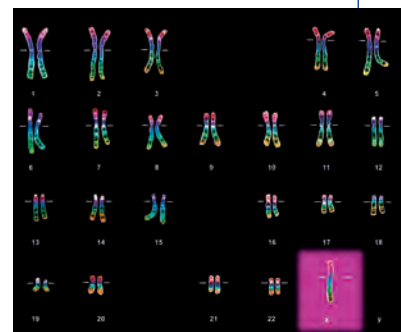
Editorialist Boris Kovatchev says that this research is an important advance for using a randomised crossover design, a particularly good algorithm, and two meal challenges that reflect patients' real lives (p 883).

Optimising growth of girls with Turner's syndrome

Girls with Turner's syndrome (caused by absence or abnormality of one X chromosome) have various physical abnormalities, including short stature and gonadal dysgenesis. These are treated with growth hormone and with oestrogen during adolescence, but uncertainties remain over whether giving the anabolic steroid oxandrolone in combination with growth hormone improves final height and whether pubertal induction should be delayed (risking psychological problems) to extend the growth period and increase final height.

To answer these questions, Emma Gault and colleagues (p 907) conducted a randomised trial of 106 girls with Turner's syndrome, allocating the girls to oxandrolone or placebo from age 9 years.

The girls with evidence of ovarian failure at 12 years old were then randomised to ethinylestradiol or placebo until 14 years old, when all girls with ovarian failure received ethinylestradiol. Oxandrolone treatment improved final height, as did delaying pubertal induction to age 14 years, but doing both offered no added benefit. The authors recommend (in the full paper) that "when growth promotion is being considered in girls with Turner's syndrome, families are offered oxandrolone as an alternative to late pubertal induction."



SOVEREIGN, ISM/SPL



Doing an intention to treat analysis when data are missing

The *BMJ* section on Research Methods and Reporting is flourishing (http://www.bmj.com/search?submit=yes&tocsectionid=Research%20Methods* or hover over the Research tab on bmj.com). The latest article is by Ian White and colleagues on how to conduct and understand intention to treat analyses when a randomised controlled trial has generated an incomplete dataset (p 910).

They start with the helpful reminder that the principle "requires all participants in a clinical trial to be included in the analysis in the groups to which they were randomised, regardless of any departures from randomised treatment... since participants who depart from randomised treatment are usually a non-random subset whose exclusion can lead to serious selection bias."

Such analyses get tricky when there are a lot of missing data, however, and the two commonest fixes are to use the "last observation carried forward" method or multiple imputation. Both rely on making assumptions (informed guesses) and doing sensitivity analyses, and the authors provide a framework using real examples to argue that these should be as plausible as possible.

LATEST RESEARCH: For these and other new research articles see www.bmj.com/research

Risk of venous thromboembolism with oral contraceptives containing drospirenone

Two related studies, by Lianne Parkin and colleagues based on UK data (doi:10.1136/bmj.d2139) and Susan Jick and Rohini Hernandez using US data (doi:10.1136/bmj.d2151), confirm earlier reports that use of oral contraceptives containing the new progestogen drospirenone are associated with a higher risk of non-fatal venous thromboembolism compared with current use of levonorgestrel pills, though the absolute risk remains low.

Calcium supplements with or without vitamin D and risk of cardiovascular events

Mark Bolland and colleagues reanalysed data from the Women's Health Initiative study of calcium and vitamin D supplementation and found that calcium supplements, with or without vitamin D, modestly increased the risk of cardiovascular events, especially myocardial infarction (doi:10.1136/bmj.d2040). This finding was obscured in the WHI study by the widespread use of personal (non-protocol) calcium supplements.

Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies

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Cite this as: *BMJ* 2011;342:d1855
doi: 10.1136/bmj.d1855

This is a summary of a paper that was published on *bmj.com* as *BMJ* 2011;342:d1855

STUDY QUESTION

What is the safety and efficacy of overnight closed loop delivery of insulin (artificial pancreas) compared with conventional insulin pump therapy in adults with type 1 diabetes?

SUMMARY ANSWER

Closed loop delivery of insulin may significantly improve overnight glucose control and reduce the risk of nocturnal hypoglycaemia in adults with type 1 diabetes. The closed loop system has the potential to improve the safety and efficacy of overnight delivery of insulin.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Overnight closed loop delivery of insulin improves control of plasma glucose levels in children and adolescents after large meals and exercise, but efficacy in adults is unknown. In these two small crossover trials overnight closed loop delivery of insulin in adults with type 1 diabetes improved glucose control and reduced exposure to low plasma glucose levels, with no overnight values below 3.0 mmol/L.

Participants and setting

Twenty four adults (10 men, 14 women) aged 18-65 with type 1 diabetes were tested at a research clinic: 12 consumed a medium sized meal ("eating in" scenario) and the other 12 consumed a larger meal accompanied by alcohol ("eating out" scenario).

Design

Two sequential, open label randomised controlled crossover, single centre studies with block randomisation com-

paring closed loop delivery of insulin with conventional insulin pump therapy. During overnight closed loop delivery, glucose sensor measurements were fed into a computer algorithm, which advised on insulin pump infusion rates at 15 minute intervals. During control nights, conventional insulin pump settings were applied. The eating in scenario compared closed loop delivery and insulin pump therapy after a medium sized evening meal (60 g carbohydrates). The eating out scenario comprised a large evening meal (100 g carbohydrates) accompanied by white wine (0.75 g/kg ethanol).

Primary outcome

The primary outcome was the time plasma glucose level was in target (3.91-8.0 mmol/L) during closed loop delivery and a comparable control period.

Main results

In the eating in scenario, overnight closed loop delivery increased the time plasma glucose was in target by a median 15% (interquartile range 3-35%), $P=0.002$. In the eating out scenario, closed loop delivery increased the time plasma glucose was in target by a median 28% (2-39%), $P=0.01$. Analysis of pooled data showed that closed loop delivery overall increased the time plasma glucose was spent in target by a median 22% (3-37%), $P<0.001$. Closed loop delivery reduced overnight time spent hypoglycaemic (plasma glucose concentration ≤ 3.9 mmol/L) by 3% (0-20%), $P=0.04$, and eliminated plasma glucose concentrations below 3.0 mmol/L after midnight.

Limitations

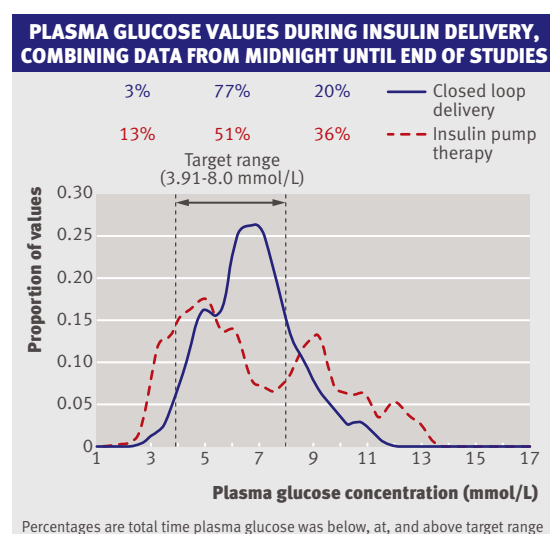
These studies were carried out in a research clinic, using volunteers who were comfortable with pump therapy. The general acceptability of this approach is yet to be determined. The lack of full automation, as the research nurse entered data and adjusted pump settings, is a limitation that is being tackled through the next generation of automated systems.

Study funding/potential competing interests

RH, CK, SAA, SRH, MLE, HRM, DBD, and MEW report competing interests (see *bmj.com*). All researchers are independent of the funding bodies: Diabetes UK, Juvenile Diabetes Research Foundation, Medical Research Council, and National Institute for Health Research.

Trial registration number

ClinicalTrials.gov NCT00910767 and NCT00944619.



Effect of oxandrolone and timing of pubertal induction on final height in Turner's syndrome: randomised, double blind, placebo controlled trial

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Cite this as: *BMJ* 2011;342:d1980
doi: 10.1136/bmj.d1980

This is a summary of a paper that was published on bmj.com as *BMJ* 2011;340:d1980

STUDY QUESTION What is the effect on final height of oxandrolone from age 9 years and of delaying pubertal induction from age 12 to age 14 years with Turner's syndrome receiving a standard dose of growth hormone treatment?

SUMMARY ANSWER Oxandrolone, in combination with growth hormone treatment, has a positive effect on final height in Turner's syndrome, as does pubertal induction at 14 years, but these effects are not additive.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Growth hormone treatment improves growth and adult height in Turner's syndrome, but adding oxandrolone and the optimal age for pubertal induction remain controversial. This study found improved height outcomes with oxandrolone treatment or delaying pubertal induction until age 14.

Design

We devised a randomised, double blind, placebo controlled trial, including two randomisations in a two by two factorial design. Firstly, participants receiving a standard dose of growth hormone (10 mg/m²/week in daily subcutaneous injections) were randomised to oral oxandrolone (0.05 mg/kg/day, maximum 2.5 mg/day) or placebo at age 9 years (or at enrolment, if older). Those with evidence of ovarian failure at age 12 were further randomised to oral ethinylestradiol (year 1, 2 µg daily; year 2, 4 µg daily; year 3, four months each of 6, 8, and 10 µg daily) or placebo; those receiving placebo and those recruited after age 12.25 years started ethinylestradiol at 14 years.

Participants and setting

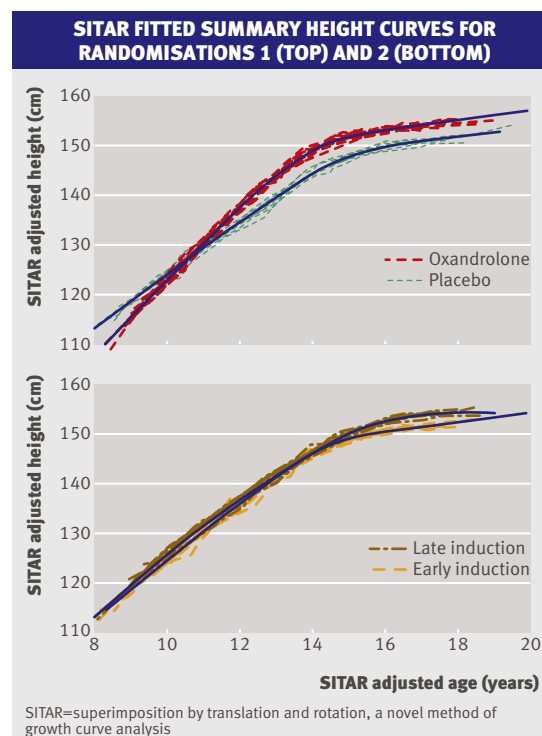
Paediatric endocrinology departments in 36 UK hospitals recruited 106 girls with Turner's syndrome. Fourteen withdrew, 82/92 have now reached final height.

Primary outcome(s)

This was final height, defined by height velocity less than 1 cm/year and bone age at least 15.5 years.

Main results and the role of chance

Oxandrolone increased final height by 4.6 (95% confidence interval 1.9 to 7.2) cm ($P=0.001$, $n=82$), and late pubertal induction (14 years) increased it by 3.8 (0.0 to 7.5) cm ($P=0.05$, $n=48$). By twice randomised group, mean final heights were 147.0 cm for placebo/early induction, 153.1 cm for placebo/late induction, 154.4 cm for oxandrolone/early induction, and 155.1 cm for oxandrolone/late induction. The effects on final height (compared with placebo/early induction) of oxandrolone alone, late induction alone, and oxandrolone plus late



induction were similar, averaging +7.1 (3.4 to 10.8) cm ($P<0.001$).

Harms

No adverse events directly attributable to study drugs were reported. Acne, hypertension, and abnormal liver function did occur but are common in Turner's syndrome.

Bias, confounding, and other reasons for caution

Inclusion of mosaic karyotypes and interrupted or terminated oxandrolone treatment may have reduced the effects of treatment. Only 92/106 girls will be followed to final height. However, the 82 already at final height provide robust efficacy data.

Generalisability to other populations

Karyotype distribution in this group is consistent with previously reported populations, and we have no grounds for believing that this cohort is not representative.

Study funding/potential competing interests

Funding was provided by the Scottish Executive Chief Scientist Office (1999-2004), the British Society for Paediatric Endocrinology and Diabetes, and the Child Growth Foundation.

Trial registration number

Current Controlled Trials ISRCTN50343149.

Randomised prostate cancer screening trial: 20 year follow-up

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Cite this as: *BMJ* 2011;342:d1539
doi: 10.1136/bmj.d1539

This is a summary of a paper that was published on bmj.com as *BMJ* 2011;342:d1539

STUDY QUESTION

What is the feasibility of prostate cancer screening in general practice and does screening reduce cancer specific mortality after 20 years?

SUMMARY ANSWER

Though screening can help to detect prostate cancer while it is localised, the rate of death from prostate cancer was not reduced significantly in the screening group after 20 years.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The benefit of prostate cancer screening is not unequivocal. In this 20 year follow-up, there was a stage shift towards localised disease among men who underwent screening, but the rate of death from prostate cancer did not differ significantly.

Design

The study was a population based randomised controlled trial.

Participants and setting

All 9026 men aged 50-69 in the city of Norrköping, Sweden, were included. General practitioners, department of Urology Norrköping, and the South-East Region Prostate Cancer Register provided data.

Primary outcomes

Tumour stage, grade, and treatment in the screening and control group were recorded, and the rate of death

from prostate cancer after 20 years of follow-up was assessed.

Main results and the role of chance

There were 85 cases (5.7%) of prostate cancer diagnosed in the screening group and 292 (3.9%) in the control group. The risk ratio for death from prostate cancer in the screening group was 1.16 (95% confidence interval 0.78 to 1.73). In a Cox proportional hazard analysis comparing prostate cancer specific survival in the control group with that in the screening group, the hazard ratio for death from prostate cancer was 1.23 (0.94 to 1.62; $P=0.13$). After adjustment for age at the start of the study, the hazard ratio was 1.59 (1.06 to 2.36; $P=0.024$). The log rank test did not show significantly longer overall survival or prostate cancer specific survival for men with prostate cancer diagnosed in the screening group.

Harms

We found no harms associated with screening per se. Overtreatment could be associated with side effects from the treatment given but should be attributed to the treatment rather than the screening procedure.

Bias, confounding, and other reasons for caution

The study was started in 1987 with digital rectal examination performed by a general practitioner and urologist at primary healthcare centres. The diagnosis was obtained by fine needle aspiration biopsy. In the third screening round in 1993 prostate specific antigen, used in prostate cancer screening today, was added as a screening test. Even if there could have been some opportunistic screening in the control group, the relatively low level of prostate specific antigen testing in the background population reduced the chance of contamination.

Generalisability to other populations

The question of generalisability depends on age of the population, the compliance with the screening intervention, the screening test, the cut-off concentration of serum prostate specific antigen, and the screening interval. The outcomes can be generalised to any population resembling that of Norrköping.

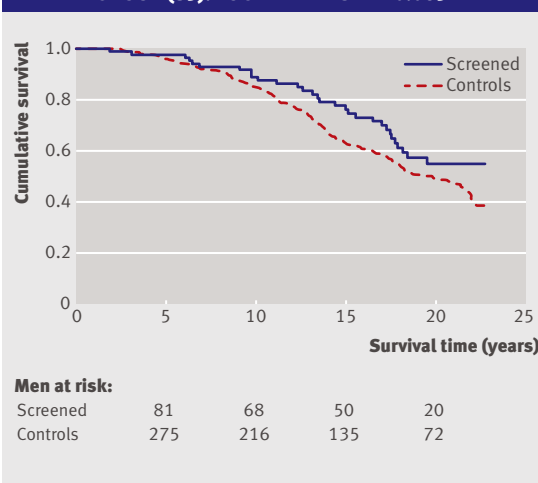
Study funding/potential competing interests

This study was funded by the Research Council of the South-East Region of Sweden, the Swedish Cancer Foundation, and the County Council of Östergötland.

Trial registration number

Current Controlled Trials ISRCTN0634231.

KAPLAN-MEIER CURVES OF PROSTATE CANCER SPECIFIC SURVIVAL FOR MEN DIAGNOSED WITH PROSTATE CANCER IN CONTROL GROUP (292) AND SCREENED GROUP (85). LOG RANK TEST $P=0.065$



bmj.com/podcasts

Gabriel Sandblom talks about the paper's findings at bmj.com/podcasts

Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort

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Cite this as: *BMJ* 2011;342:d1875
doi: 10.1136/bmj.d1875

This is a summary of a paper that was published on bmj.com as *BMJ* 2011;342:d1875

STUDY QUESTION

Are clinical risk factors able to predict pre-eclampsia in nulliparous women and identify a subgroup of women at risk who require specialist referral?

SUMMARY ANSWER

The ability of clinical phenotype to predict pre-eclampsia in healthy nulliparous women is modest and requires external validation, though it could identify a subgroup at high risk in whom specialist referral might be indicated.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The risk of pre-eclampsia associated with combinations of clinical risk factors is largely unknown. Though a prototype algorithm using specific combinations of clinical risk factors for predicting pre-eclampsia in "healthy" nulliparous women has modest prediction, it is a considerable improvement on risk prediction in current practice.

Participants and setting

Between November 2004 and August 2008, "healthy" nulliparous women with a singleton pregnancy were recruited to the Screening for Pregnancy Endpoints (SCOPE) study in five centres in New Zealand, Australia, the United Kingdom, and Ireland.

Design, size, and duration

Of the 3572 women recruited to this prospective cohort study, pregnancy outcomes were available for 3529 (99%). At 14-16 weeks' gestation, the women were interviewed and clinical information on risk factors for pre-eclampsia

collected. Fetal biometry and Doppler studies of the umbilical and uterine arteries were performed at 19-21 weeks. The primary outcome was pre-eclampsia defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, or both, on at least two occasions four hours apart after 20 weeks' gestation but before the onset of labour, or postpartum, with either proteinuria or any multisystem complication of pre-eclampsia. Predictive models for pre-eclampsia were constructed with stepwise logistic regression. The reference group was women who did not develop pre-eclampsia. For internal validation, the calibration and discrimination (10-fold cross validation) of the model was evaluated.

Main results and the role of chance

Pre-eclampsia developed in 186 (5.3%) women, including 47 (1.3%) with preterm pre-eclampsia. The algorithm to predict pre-eclampsia included well recognised risk factors, along with less established factors. The area under the receiver operating characteristics curve (AUC), under internal validation, was 0.71. Addition of uterine artery Doppler indices did not improve performance (internal validation AUC 0.71). A framework for specialist referral based on pre-eclampsia risk assessment was proposed and 21% of those selected for referral developed pre-eclampsia. The relative risk for pre-eclampsia and preterm pre-eclampsia in the specialist referred group compared with standard care was 5.5 and 12.2, respectively.

Bias, confounding, and other reasons for caution

The model will be over-fitted. The AUC for the model based on the observations used to create the model was 0.76, indicating a bias in the C statistic of about 5%. The model has reasonable calibration, but underestimates cases at higher probabilities for pre-eclampsia.

Generalisability to other populations

The prototype algorithm requires external validation in other populations. We expect the screening performance in other cohorts to approximate our internal validation result (AUC 0.71). To considerably improve prediction performance will require the development of specific clinical risk algorithms for disease subtypes, such as preterm and term pre-eclampsia, or the addition of biomarkers.

Study funding/potential competing interests

The SCOPE study was supported by government bodies, charities, and research institutions from New Zealand, Australia, UK, and Ireland (see full paper). RAN and PNB have consultancy relationships with Pronota, RAN and JJW have a consultancy relationship with Alere. LCK, PNB, RAN, MAB, JJW, and LP declare interests in certain patents (see full paper).

CLINICAL RISK FACTORS AT 14-16 WEEKS IN LOGISTIC REGRESSION MODEL FOR PRE-ECLAMPSIA

	No pre-eclampsia (n=3343)	Pre-eclampsia (n=186)	Adjusted odds ratio (95%CI)
Risk factors*			
Decrease of 5 years in age†	28.2 (5.8)	27 (5.8)	1.2 (1.1 to 1.4)
Increase of 5 mm Hg in mean arterial pressure†	78 (8)	84 (8)	1.4 (1.3 to 1.5)
Increase of 5 in body mass index†	25 (5)	28 (7)	1.3 (1.1 to 1.4)
Family history of pre-eclampsia	309 (9%)	35 (19%)	2.0 (1.3 to 3.0)
Family history of coronary heart disease‡	384 (12%)	35 (19%)	1.9 (1.2 to 2.8)
Decrease of 500 g in woman's birth weight	3293 (552)	3177 (540)	1.2 (1.1 to 1.4)
Vaginal bleeding ≥ 5 days	125 (4%)	13 (7%)	2.0 (1.1 to 3.8)
Protective factors			
One miscarriage ≤ 10 weeks, same partner	301 (9%)	8 (4%)	0.45 (0.22 to 0.93)
≥ 12 months to conceive	384 (12%)	12 (7%)	0.40 (0.22 to 0.75)
High fruit intake (≥ 3 /day)	1347 (40%)	52 (28%)	0.69 (0.49 to 0.98)
Alcohol consumption first trimester	1705 (51%)	69 (37%)	0.60 (0.44 to 0.83)
Increase of 5 cigarettes/day†	0.8 (3.0)	0.6 (2.4)	0.73 (0.53 to 1.0)

*Variable name (unit change for adjusted odds ratio).

†Mean (SD).

‡Woman's father had coronary heart disease.