RESEARCH

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THIS WEEK'S RESEARCH QUESTIONS

Thyroid autoantibodies, normal thyroid function, and risks to the fetus

The suggestion that women with thyroid autoantibodies are at increased risk of having miscarriages and preterm births, even when their thyroids are functioning normally, goes back 20 years. How strong are these associations, and might treatment protect the fetus?

To answer these questions Shakila Thangaratinam and colleagues systematically reviewed and meta-analysed 31 observational studies in more than 12 000 women, plus three randomised trials of levothyroxine in pregnancy (p 1065). They confirmed significant associations between the presence of thyroid autoantibodies and both miscarriage and preterm birth—and, for both outcomes, they found limited evidence from trials that treatment with levothyroxine significantly reduces the risks.

GEOFF KIDD/SPL

This work is a prelude to the same authors' TABLET (Thyroid AntiBodies and LEvoThyroxine) trial, which gets underway this year. This is a randomised, placebo-controlled, double-blind trial in more than 20 British hospitals, testing the hypothesis that in euthyroid women with thyroid peroxidase antibodies, levothyroxine (50 µg orally once daily) started before conception and continued to the end of pregnancy, increases live births beyond 34 completed weeks of gestation by at least 10% compared with placebo (www.eme.ac.uk/projectfiles/0910010info.pdf).

Whether thyroid antibodies directly cause pregnancy loss and preterm delivery or are simply an epiphenomenon remains unanswered, note Roberto Negro and Alex Stagnaro-Green in a linked editorial (p 1035). They see Thangaratinam and colleagues' meta-analyses as a turning point in this story, and say it's now time to do decent benchside studies of the causal mechanisms as well as the TABLET trial.

β blockers in chronic obstructive pulmonary disease

JOHN THYS/REPORTERS/SPL

Many patients with chronic obstructive pulmonary disease (COPD) also have heart disease, and some die of heart failure. Can such patients take β blockers, or do the risks of acute airways obstruction associated with these drugs outweigh the cardiac benefits?

Philip M Short and colleagues tried to answer this question using data from several linked NHS databases in Scotland to conduct a retrospective cohort study with nearly 6000 patients aged over 50 whose COPD met the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. They found that adding β blockers (most of them cardioselective) to standard management of COPD was associated with lower mortality at each treatment step and a 22% overall reduction in mortality over the next four years (p 1068). They minimised the impact of confounding by indication by using a Cox proportional hazard regression model and a matched propensity scoring analysis.

Editorialists Shamsah Kazani and Elliot Israel discuss the limitations of this retrospective analysis but agree that it adds useful evidence (p 1037). They call for prospective studies on this question and give some practical advice: "How should clinicians start a patient with COPD on a β blocker for cardiac indications? It is advisable to use a cardioselective β blocker and to observe the patient during the administration of the first dose. In the rare case that bronchospasm does occur, anticholinergic agents should probably be used first."

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A comparison of clinical officers with medical doctors on outcomes of caesarean section in the developing world Amie Wilson and colleagues' meta-analysis showed no significant difference in outcomes between caesarean sections carried out by medical doctors and those done by trained clinical officers, although the conclusions are tentative because the included studies were non-randomised (doi:10.1136/bmj.d2600).

Proton pump inhibitors and risk of adverse cardiovascular events in aspirin treated patients with first time myocardial infarction In this Danish study, Mette Charlot and colleagues report that treatment with proton pump inhibitors was associated with an increased risk of adverse cardiovascular events for these patients (doi:10.1136/bmj.d2690).

Inadequate reporting of research ethics review and informed consent in cluster randomised trials In a sample of 300 trials published in 150 journals, around a quarter failed to report ethics review, found Monica Taljaard and colleagues (doi:10.1136/bmj.d2496).

MAURO FERMARIELLO/SPL

CME

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Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence

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EDITORIAL by Negro and Stagnaro-Green

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STUDY QUESTION Are thyroid autoantibodies associated with miscarriage and preterm birth in women with normal thyroid function?

SUMMARY ANSWER The presence of maternal thyroid autoantibodies is strongly associated with miscarriage and preterm birth.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Thyroid autoantibodies are thought to be associated with adverse pregnancy outcomes. Our meta-analyses show that the odds of miscarriage are more than tripled and the odds of preterm birth are doubled in the presence of thyroid autoantibodies in women with normal thyroid function.

ASSOCIATION BETWEEN PRESENCE OF THYROID AUTOANTIBODIES AND MISCARRIAGE AND PRETERM BIRTH

Study design	No of studies	Summary odds ratio (95% CI)	P value	Heterogeneity (I^2)
Miscarriage				
Cohort	19	3.90 (2.48 to 6.12)	<0.001	81%
Case control	12	1.80 (1.25 to 2.60)	0.002	56%
Preterm birth				
Cohort	5	2.07 (1.17 to 3.68)	0.01	78%

Selection criteria for studies

We searched Medline (1951-2011), Embase (1974-2011), Cochrane Library (2011), and SCISEARCH (1974-2011) for relevant citations. We generated two subsets of citations, one indexing thyroid autoantibodies and the other indexing the outcomes. These subsets were combined to generate a subset of citations relevant to our research question. We included cohort and case-control studies on women with and without thyroid autoantibodies that evaluated the outcomes of miscarriage and preterm birth.

Primary outcomes

Miscarriage and preterm birth.

Main results and role of chance

We identified 30 articles with 31 studies (19 cohort and 12 case control) involving 12 126 women. Five studies, all of cohort design with 12 566 women, evaluated the association with preterm birth. Of the 31 studies evaluating miscarriage, 28 showed a positive association between thyroid autoantibodies and miscarriage. Meta-analysis showed more than tripling of the odds of miscarriage in the presence of thyroid autoantibodies (odds ratio 3.90, 95% confidence interval 2.48 to 6.12; P<0.001) in the cohort studies and an odds ratio of 1.80 (1.25 to 2.60; P=0.002) in case-control studies. There was a significant doubling in the odds of preterm birth in the presence of thyroid autoantibodies (2.07, 1.17 to 3.68; P=0.01).

Two randomised studies evaluated the effect of treatment with levothyroxine on miscarriage. Both showed a fall in miscarriage rates, and meta-analysis showed a significant 52% reduction in miscarriages with levothyroxine treatment (risk ratio 0.48, 0.25 to 0.92; P=0.03). One study reported on the effect of levothyroxine treatment on the rate of preterm birth and noted a 69% reduction (0.31, 0.11 to 0.90).

Bias, confounding, and other reasons for caution

Although 28 of the 31 miscarriage studies and all five preterm studies showed a positive association, there was still unexplained heterogeneity in the meta-analyses for both outcomes. Reasons could include the variation in study populations, method of testing for thyroid autoantibodies and thresholds used, and the quality features of the studies.

Study funding/potential competing interests

The authors have been funded by the NIHR (National Institute of Health Research, UK) EME Programme (09-100-10) to conduct a multicentre placebo-controlled randomised trial on the pregnancy effects of levothyroxine treatment in thyroid antibody positive women with normal thyroid function (the TABLET trial).

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Outreach education for integration of HIV/AIDS care, antiretroviral treatment, and tuberculosis care in primary care clinics in South Africa: PALSA PLUS pragmatic cluster randomised trial

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STUDY QUESTION Can an educational outreach programme of non-didactic, case based, clinical education of all staff together at their clinic increase access to, and comprehensiveness of, care for ambulatory patients with HIV/AIDS?

SUMMARY ANSWER Outreach education is an effective and feasible strategy for improving comprehensiveness of care of patients with HIV/AIDS, but there is no evidence that it increases access to care.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS HIV/AIDS and antiretroviral care in low and middle income countries is mainly hospital based. With physician shortages this limits access and coverage, necessitating decentralisation to clinics run by nurses. On-site outreach education at such clinics, covering HIV/AIDS and antiretroviral treatment improved the comprehensiveness of care for patients known to have HIV but did not increase the probability that patients in primary care would be screened for HIV and referred for care.

Design

We conducted an unblinded pragmatic cluster randomised trial of the effects of adding outreach education (6-20 visits by trained trainer) to rollout of decentralised nurse run HIV/AIDS/ART services at primary care clinics. Urn randomisation was used to allocate eight clinics to the intervention arm and seven to control. Both arms received usual care (same HIV specialist nurses, same guideline for care of HIV/AIDS/ART) but the intervention arm also received outreach education.

Participants and setting

All patients aged ≥16 enrolling in the HIV/AIDS and antiretroviral treatment programme through any channel (including voluntary counselling and testing) at any of the 15 primary care clinics accredited as HIV treatment sites in Free State Province, South Africa, were included during a one year period and monitored until death or end of the trial.

Primary outcomes

Three primary outcomes: integration of HIV/AIDS and ART care with tuberculosis care (detection of tuberculosis among patients with HIV); quality of pre-ART care provided at the clinic for diagnosed patients with HIV (co-trimoxazole prophylaxis among patients with newly diagnosed HIV); and integration of general primary care provided by nurses with HIV screening (proportion of patients enrolled in the ART programme through newly conducted HIV testing).

Main results and the role of chance

At intervention clinics patients with new HIV diagnosis were more likely to receive co-trimoxazole prophylaxis (41% (2253/5523) *v* 32% (1340/4210), odds ratio 1.95 (95% confidence interval 1.11 to 3.40), tuberculosis was more likely to be detected among HIV/AIDS/ART patients (7% (417/5793) *v* 6% (245/4343); 1.25, 1.01 to 1.55). But enrolment in the HIV/AIDS and ART programme via HIV testing in general primary care was not significantly increased (53% *v* 50%; 1.19, 0.51 to 2.77).

Harms

We did not identify any harms. Despite the added workload, morale improved. New resources were not required as trainers were already in post as supervisors before the study.

Bias, confounding, and other reasons for caution

The trial was successfully completed, with no dropout and low risk of bias. This real world intervention requires decentralising control over detailed clinic level implementation; this might be challenging for centralised organisations to accept.

Generalisability to other populations

The intervention was evaluated under usual care conditions, suggesting that with similar health service organisation and resources, this is a useful supplement to decentralisation of care.

Study funding/potential competing interests

The study was funded by the International Development Research Centre (IDRC) of Canada.

Trial registration number

ISRCTN 24820584.

EFFECT OF ADDITIONAL OUTREACH EDUCATION ON OUTCOME IN PATIENTS WITH HIV/AIDS IN SOUTH AFRICA

Primary outcomes	Outreach education plus nurse training	Nurse training only (control)	Odds ratio (95% CI)	P value	Intracluster correlation coefficient
Enrolment in programme through new HIV testing (1 year)*	3048/5793 (53%)	2187/4343 (50%)	1.19 (0.51 to 2.77)	0.695	0.108
Provision of co-trimoxazole prophylaxis over 12 months	2253/5523 (41%)	1340/4210 (32%)	1.95 (1.11 to 3.40)	0.020	0.034
Tuberculosis case detection*	417/5793 (7%)	245/4343 (6%)	1.25 (1.01 to 1.55)	0.038	0.027

*Denominator includes all patients enrolled in treatment programme, as well as patients who were tested through programme with negative results.

Arsenic exposure from drinking water and mortality from cardiovascular disease in Bangladesh: prospective cohort study

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EDITORIAL by Smith and Steinman

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STUDY QUESTION To evaluate the association between arsenic exposure and mortality from cardiovascular disease.

SUMMARY ANSWER There was a dose-response relation between arsenic exposure (0.1-864.0 µg/L, mean 99 µg/L) and subsequent mortality from cardiovascular disease, especially heart disease. A synergy was observed between cigarette smoking and arsenic exposure in heart disease mortality.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS High levels of arsenic exposure (>500 µg/L) from drinking water have been related to an increased risk of cardiovascular disease. Our findings suggest that smoking enhances the effects of arsenic exposure on mortality from heart disease, even at moderate levels (25.3-114 µg/L) of exposure.

Participants and setting

Participants comprised 11 746 married men and women aged 18-75 in Araihazar, Bangladesh.

Design, size, and duration

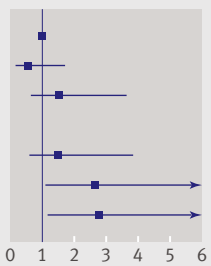
Participants were recruited in 2000, followed up for an average of 6.6 years, and visited every two years. We adapted a validated verbal autopsy procedure to ascertain the causes of deaths. Water samples from all 5966 tube wells in the study area and spot urine samples collected from participants at baseline and at each follow-up visit were tested for arsenic concentration.

Main results and the role of chance

There were 198 deaths from diseases of the circulatory system, accounting for 43% of total mortality in the population. The hazard ratios for mortality from ischaemic heart disease and other heart disease in increasing quarters of well arsenic concentrations (0.1-12.0, 12.1-62.0, 62.1-148.0, and 148.1-864.0 µg/L) were 1.00 (reference), 1.22 (95% confidence interval 0.65 to 2.32), 1.35 (0.71 to 2.57), and 1.92 (1.07 to 3.43), respectively (P=0.0019 for trend). We observed similar associations when we used baseline total urinary arsenic as the exposure variable. The data also show a significant synergistic interaction between arsenic exposure and cigarette smoking in mortality from ischaemic heart disease and other heart disease. In particular, the hazard ratio for the joint effect of moderate level of arsenic exposure (25.3-114.0 µg/L, mean 63.5 µg/L) and cigarette smoking on mortality from heart disease was greater than the sum of the hazard ratios associated with their individual effect (relative excess risk for interaction 1.56, 0.05 to 3.14; P=0.010).

EFFECT OF CIGARETTE SMOKING AND WELL ARSENIC AT BASELINE ON MORTALITY FROM ISCHAEMIC HEART DISEASE AND OTHER HEART DISEASE

Arsenic concentration (µg/L)	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Relative excess risk due to interaction
Never smoked			
0.1-25.2		1 (reference)	
25.3-114.0		0.57 (0.19 to 1.70)	
114-864.0		1.53 (0.65 to 3.59)	
Ever smoked			
0.1-25.2		1.52 (0.58 to 4.02)	
25.3-114.0		2.65 (1.03 to 6.81)	1.56 (0.05 to 3.14), P=0.010
114-864.0		2.76 (1.10 to 6.92)	0.71 (0.02 to 2.40), P=0.052



Bias, confounding, and other reasons for caution

We adjusted analyses for potential confounders including age, sex, smoking status, educational attainment, body mass index (BMI), and changes in urinary arsenic since baseline. We did not adjust our analyses for hyperlipidaemia as it is not thought to be related to arsenic exposures. Adjustments for other established risk factors for cardiovascular disease did not appreciably change results.

Generalisability to other populations

Our results might not be generalisable to other populations with different profiles of risk factors that could interact with arsenic exposure in risk for cardiovascular disease. In particular, we included only married men and women, who tended to have low BMI (mean 18.9). Recruitment of married people helped with retention during follow-up and should therefore enhance internal validity of the findings.

Study funding/potential competing interests

The study was funded by US National Institute of Environmental Health Sciences and the National Cancer Institute through the following grants: P42ES010349, R01ES017541, R01CA102484, R01CA107431, R01ES017541, R01ES011601, P30ES09089, CA016087, ES000260, and CA014599.

CME

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Effect of β blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study

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EDITORIAL by Kazani and Israel

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STUDY QUESTION Do β blockers reduce mortality and exacerbations when added to established pharmacological management for chronic obstructive pulmonary disease (COPD)?

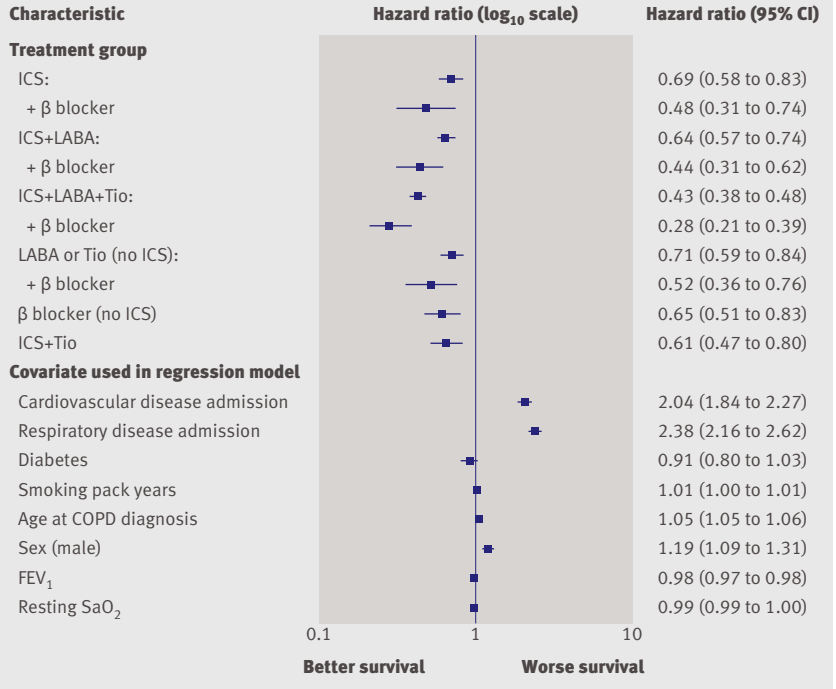
SUMMARY ANSWER Yes, β blockers reduced all cause mortality, emergency oral corticosteroid use, and hospital admissions for respiratory disease when added to established inhaled stepwise therapy for COPD (including long acting β agonists and antimuscarinics).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS β blockers are avoided in patients with COPD because of concerns of bronchospasm and blocking the effects of β agonists. Studies have suggested that β blockers may be beneficial in COPD patients but did not assess these benefits when stratified by concurrent drug treatments. This study assessed the interrelationship of β blockers with β agonists and other concurrent inhaler therapy, and showed that they reduced mortality and exacerbations in COPD patients when added to established inhaled stepwise therapy.

Participants and setting

Patients aged over 50 years with a diagnosis of chronic obstructive pulmonary disease (COPD) based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, from Tayside, Scotland, between 2001 and 2010 were included.

ADJUSTED HAZARD RATIOS FOR ALL CAUSE MORTALITY



ICS=inhaled corticosteroid, LABA=long acting β agonist, Tio=tiotropium, FEV_1=forced expiratory volume in one second, SaO_2=arterial oxygen saturation

Design, size, and duration

In our retrospective cohort study of 5977 patients we used data from our local NHS disease specific COPD database (TARDIS) linked to the Scottish morbidity records providing information on acute hospital admissions, the Tayside community pharmacy prescription records, and the General Register Office for Scotland death registry. Cox proportional hazard regression was used to evaluate the impact of β blocker use in addition to established COPD management for all cause mortality, hospital admissions for respiratory disease, and emergency oral corticosteroid use after correction for influential covariates.

Main results and the role of chance

Our data suggest, through matched propensity scoring analysis, a 22% overall reduction in all cause mortality associated with β blocker use. There were additive benefits of β blockers on all cause mortality at all COPD treatment steps (figure). The adjusted hazard ratio for all cause mortality compared with controls (who received only inhaled therapy with short acting β agonists or antimuscarinics) was 0.43 (95% CI 0.38 to 0.48) for treatment with inhaled corticosteroid, long acting β agonist, plus long acting antimuscarinic, and this declined further to 0.28 (0.21 to 0.39) when a β blocker was added. There were similar trends showing additive benefits of β blockers in reducing emergency oral corticosteroid use and hospital admissions for respiratory disease. β blockers had no deleterious impact on pulmonary function at all treatment steps when given in conjunction with either a long acting β agonist or long acting antimuscarinic.

Bias, confounding, and other reasons for caution

Our study is limited by its retrospective and observational design. Confounding by indication is possible in observational studies, but we used a Cox proportional hazard regression model that corrected for all available influential covariates. Furthermore, when assessing the impact of β blocker use on all cause mortality, we performed a matched propensity scoring analysis suggesting a beneficial effect with β blocker use. Propensity score matched analysis is designed to minimise the effects of confounding by indication.

Generalisability to other populations

This study used a large COPD disease specific database in Tayside. We believe these real life results can be reasonably extrapolated to other similar COPD populations.

Study funding/potential competing interests

This study was funded by the University of Dundee.