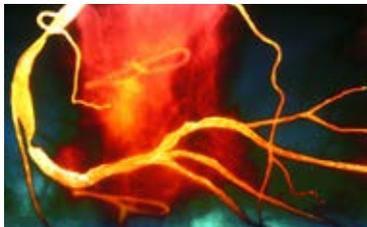


# research



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Renal risks higher with trimethoprim for UTI in older adults compared with other antibiotics PLUS author's perspective p 314

## ORIGINAL RESEARCH Network meta-analysis of diagnostic randomised controlled trials

### Outcomes of non-invasive diagnostic modalities for the detection with coronary artery disease

Siontis GCM, Mavridis D, Greenwood JP, et al

Cite this as: *BMJ* 2018;360:k504

Find this at: <http://dx.doi.org/10.1136/bmj.k504>

**Study question** Which non-invasive anatomical or functional testing strategy provides the most favourable results for subsequent downstream testing and clinical outcomes in patients with suspected coronary artery disease?

**Methods** Available evidence was summarised from diagnostic randomised controlled trials evaluating non-invasive diagnostic modalities to detect clinically relevant coronary artery disease through random effects network meta-analysis. Modalities included exercise electrocardiograms, stress echocardiography, single photon emission computed tomography-myocardial perfusion imaging, real time myocardial contrast echocardiography, coronary computed tomographic angiography, and cardiovascular magnetic resonance imaging. The analysis focused on downstream testing and patient oriented outcomes among individuals with low risk acute coronary syndromes or stable coronary artery disease.

**Study answer and limitations** 18 trials of low risk acute coronary syndrome (n=11 329) and 12 trials of suspected stable coronary artery disease (n=22 062) were included. Among patients with low risk acute coronary syndromes, stress echocardiography and cardiovascular magnetic

resonance imaging were associated with fewer referrals for invasive coronary angiography and revascularisation procedures than anatomical testing (that is, coronary computed tomographic angiography; odds ratio 0.28 (95% confidence interval 0.14 to 0.57) and 0.32 (0.15 to 0.71), respectively), without apparent impact on the future risk of myocardial infarction. For suspected stable coronary artery disease, no individual diagnostic strategy was clearly superior as judged by subsequent need for invasive coronary angiography, although exercise electrocardiograms resulted in the highest overall downstream testing rate. Any potential differences in the risk of future myocardial infarction cannot be ruled out. The low number of clinical outcome events reflects the low risk populations in the included studies. Sparse data for some comparisons might have reduced the power to discriminate clearly between the diagnostic strategies, especially for the group with stable coronary artery disease.

**What this study adds** The study provides direct and indirect evidence about clinically important outcomes for anatomical and functional testing strategies in patients with suspected coronary artery disease. These findings serve as a roadmap for future adequately powered trials that should evaluate more broadly defined clinical outcomes, subsequent use of resources, and cost effectiveness of implemented strategies in current clinical practice.

**Funding, competing interests, data sharing** No specific funding was obtained for this study. The authors have no relevant competing interests. No additional data are available. Systematic review registration PROSPERO registry No CRD42016049442.

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The online version is published along with peer and patient reviews for the paper, and a statement about how the authors will share data from their study. It also includes a description of whether and how patients were included in the design or reporting of the research.

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# Thyroid function in pregnancy and children's cognition

ORIGINAL RESEARCH Prospective cohort study

## Maternal thyroid function and child educational attainment

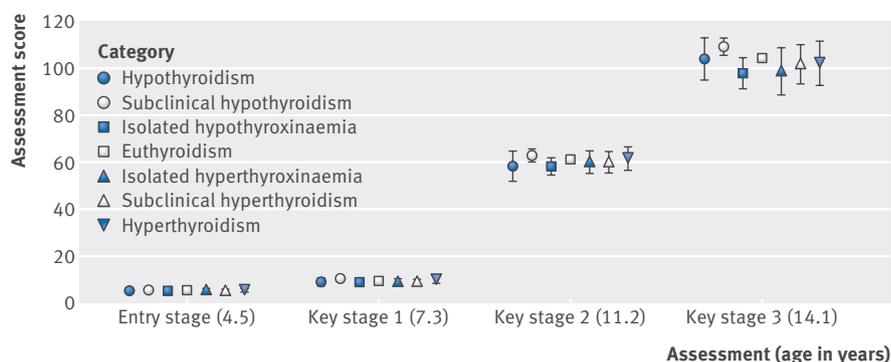
Nelson S, Haig C, McConnachie A, et al

Cite this as: *BMJ* 2018;360:k452

Find this at: <http://dx.doi.org/10.1136/bmj.k452>

**Study question** Does maternal thyroid function in the first trimester influence child scholastic performance and overall educational attainment?

**Methods** 4615 mother-child pairs from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort with a first trimester (median 10 weeks gestation, interquartile range 8-12) sample available for measurement of thyroid stimulating hormone, free thyroxine, and thyroid peroxidase antibodies were analysed. Continuous associations of thyroid stimulating hormone, free thyroxine, and



Mean assessment scores (95% confidence interval) relative to first trimester clinical categories of thyroid function

thyroid peroxidase antibodies and clinical categories of maternal thyroid function with five age specific national curriculum assessments were evaluated. There were between 3580 mother-child pairs at the entry stage assessment (54 months of age) and 4461 pairs at the final school assessment (15 years).

**Study answer and limitations** Maternal thyroid dysfunction in early pregnancy in this unselected population did not have a clinically important association with performance in national curricular assessments. Associations of maternal free thyroxine (rate ratio per pmol/L 1.00, 95% confidence interval 1.00 to 1.01) or

## COMMENTARY No evidence of a link up to age 15

Thyroid dysfunction is a common endocrinological problem during pregnancy, as 0.2% to 0.6% of pregnancies involve overt hypothyroidism and an additional 3.5% to 18.0% of pregnancies are affected by subclinical hypothyroidism (elevated thyroid stimulating hormone concentrations but normal free thyroxine concentrations).<sup>1</sup> Untreated overt hypothyroidism increases the risk of difficulty conceiving and of many adverse obstetrical and child outcomes, including impaired neuropsychological development.<sup>2</sup> The consequences of subclinical thyroid dysfunction, especially with regard to cognitive outcomes for the child, are not that well established.<sup>2</sup>

In this issue, Nelson and colleagues present a study assessing maternal thyroid function tests during early pregnancy and the school attainment of children from 54 months to 15 years of age. Reassuringly, they found no clinically important association between mild maternal hypothyroidism and attainment at school.<sup>3</sup>

### More clinical trials of screening and treatment and prepregnancy cohort studies are now required

This study has many strengths. Thyroid function tests for thyroid stimulating hormone, free thyroxine, and thyroid peroxidase antibodies were assessed mostly during the first trimester, which is the most crucial time for fetal neurodevelopment. Mothers with a known thyroid disease were excluded. Children's school performance data came from the National Pupil Database, which records five age specific assessments, from school entry to the end of secondary school at age 15.

Mild maternal thyroid dysfunction during pregnancy was not associated with children's performance on any of the assessments.<sup>3</sup>

The topic is of international interest because screening for thyroid stimulating hormone in early pregnancy is currently recommended by the American and European thyroid associations only if the mother has risk factors for thyroid disease such as past or current symptoms of thyroid disease, family history, known thyroid antibody positivity, or previous autoimmune disorders.<sup>2,5</sup> So far, the evidence concerning

maternal thyroid dysfunction and cognitive development in offspring has not swayed clinical guidelines towards universal thyroid stimulating hormone screening.<sup>2</sup>

Randomised controlled trials of antenatal screening and treatment of mild maternal thyroid dysfunction have not shown improvements in cognitive function among children of women treated with levothyroxine.<sup>6,7</sup> These studies have been criticised for the late timing of screening and treatment, as studies of pregnant women miss the crucial time of conception and very early fetal development. But we still lack convincing evidence that treating mild maternal thyroid dysfunction in early pregnancy is beneficial for either mother or child.<sup>2</sup>

Further complicating the screening discussion, some studies have suggested that the risk of adverse outcomes for children is not a threshold effect operating only above the upper reference limit for thyroid stimulating hormone, but rather rises continuously as thyroid stimulating hormone increases.<sup>1</sup> Longer follow-up is likely to yield greater insight into how seriously these small statistical increases in risk should be considered.

Fanni Päckilä [fanni.packila@oulu.fi](mailto:fanni.packila@oulu.fi)

See [bmj.com](http://bmj.com) for author details

thyroid stimulating hormone (0.98, 0.94 to 1.02) with the total number of General Certificates of Secondary Education passed (range 0-16) were all close to the null. The study was limited by not having first trimester serum samples or measures of iodine status for all ALSPAC participants. Individual, subtler aspects of cognitive function such as executive functioning, memory, visual attention, and sensorimotor development were not assessed. The study did not address outcomes for very unusual situations such as severe iodine deficiency, or hypothyroidism in both mother and child.

**What this study adds** Children of mothers with hypothyroidism, hyperthyroidism, and subtler forms of thyroid dysfunction in a general population will achieve similar school assessment scores throughout childhood and also the same school leaving exam results as children of women with normal thyroid function.

**Funding, competing interests, data sharing** See [bmj.com](http://bmj.com) for funding. The authors have no competing interests. The technical appendix and statistical code are available from the corresponding author.

Nelson and colleagues analysed their data comprehensively using various thyroid stimulating hormone cut-off values, and they also analysed thyroid stimulating hormone and free thyroxine concentrations as continuous variables without finding any association with educational attainment.<sup>3</sup>

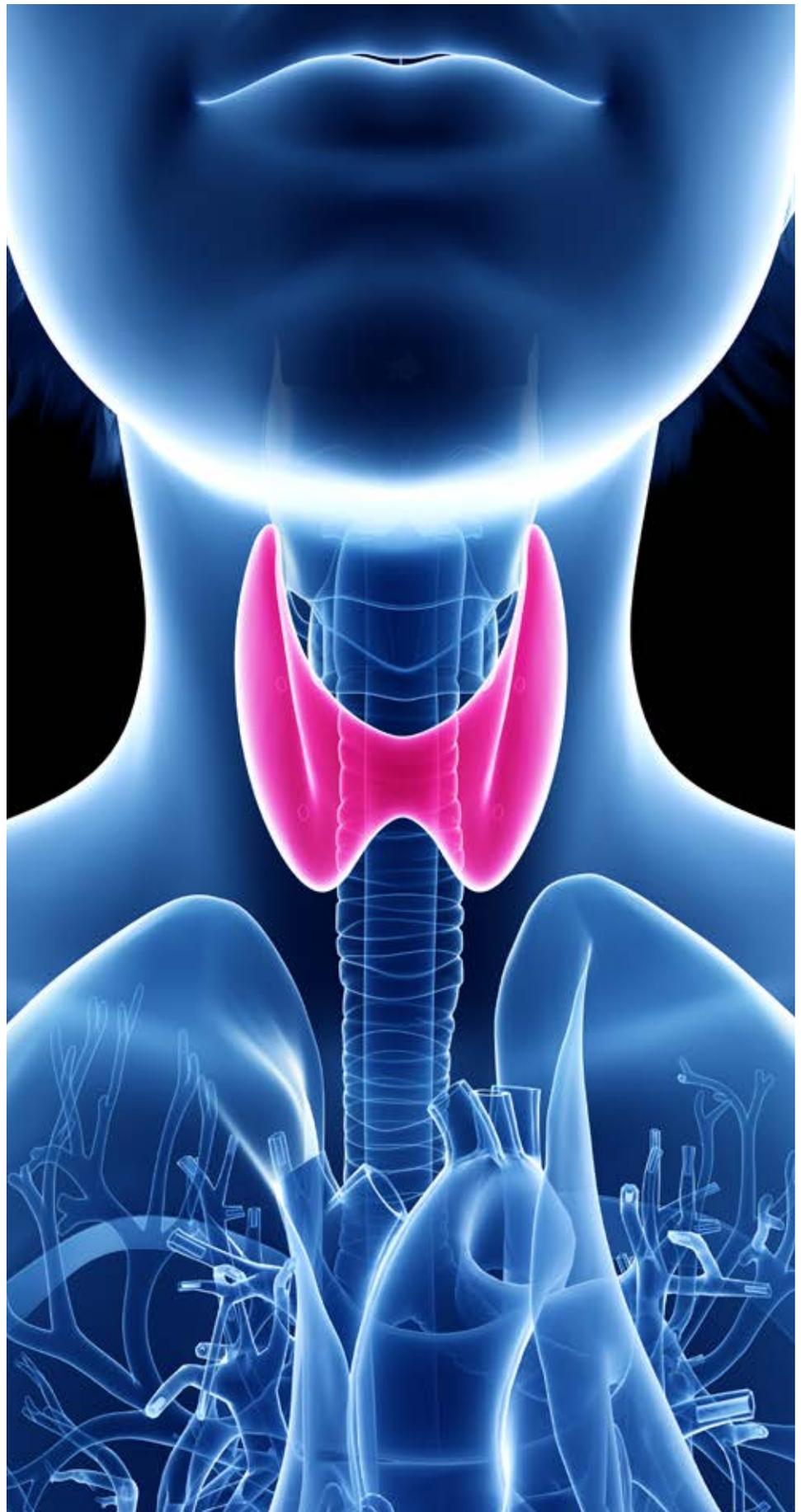
Defining abnormal levels of thyroid stimulating hormone is difficult during pregnancy, and reliable reference ranges are not always available.

Perhaps it's no surprise that the question of universal screening for thyroid stimulating hormone divides professional opinion.

The challenge in prenatal care is to identify women at risk for thyroid diseases as early as possible, even before pregnancy is confirmed. More clinical trials of screening and treatment and especially prepregnancy cohort studies are now required. In the meantime, Nelson and colleagues' study adds important observational evidence that mild maternal thyroid dysfunction during early pregnancy does not seem to affect children's educational attainment adversely.<sup>3</sup>

Cite this as: *BMJ* 2018;360:k636

Find the full version with references at <http://dx.doi.org/10.1136/bmj.k636>



## Trimethoprim use for urinary tract infection and risk of adverse outcomes in older patients

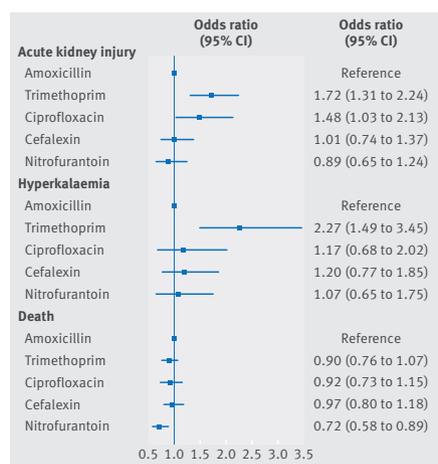
Crellin E, Mansfield K, Leyrat C, Tomlinson LA, et al

Cite this as: *BMJ* 2018;360:k341

Find this at: <http://dx.doi.org/10.1136/bmj.k341>

**Study question** Is trimethoprim treatment for urinary tract infection associated with an increased risk of acute kidney injury, hyperkalaemia, or sudden death?

**Methods** A cohort study that used primary care data from the UK Clinical Practice Research Datalink and linked hospital admissions data from Hospital Episode Statistics. Adults aged 65 and over who had been prescribed trimethoprim, amoxicillin, cefalexin, ciprofloxacin, or nitrofurantoin within three days of a urinary tract infection were identified. Logistic regression was used to calculate odds ratios for acute kidney injury, hyperkalaemia, and death within 14 days of a urinary tract



Odds ratios (95% confidence intervals) comparing the odds of acute kidney injury, hyperkalaemia, and death in the 14 days following initiation of different antibiotic drugs for treatment of urinary tract infection

infection treated with antibiotics. Trimethoprim and the other antibiotic drugs were compared with amoxicillin (reference). The authors adjusted for sex, age, calendar period, chronic comorbidities, baseline renal function, history

of renal or urological disease, and use of renin-angiotensin system blockers or potassium sparing diuretics.

**Study answer and limitations** The risk of acute kidney injury and hyperkalaemia increased in the 14 days following treatment of a urinary tract infection with trimethoprim compared with amoxicillin. A greater risk of death was not found, unlike with previous research. The results, like with most observational studies, may be affected by unmeasured sources of confounding.

**What this study adds** Trimethoprim is associated with a greater risk of acute kidney injury (adjusted odds ratio 1.72, 95% confidence interval 1.31 to 2.24) and hyperkalaemia (2.27, 1.49 to 3.45) compared with other antibiotic drugs in the general population and not just in patients taking renin-angiotensin system blockers.

**Funding, competing interests, data sharing** This study was funded by the Wellcome Trust. The authors have no competing interests. No additional data are available.

## AUTHOR'S PERSPECTIVE Laurie Tomlinson

### How anonymised patient records can improve prescribing guidance

We often hear about the importance of “bench to bedside” medicine, how basic science research is translated into novel treatments. But this paper demonstrates an equally important concept: how anonymised health records provide a rich data source to address clinical questions, which in turn improves patient care. I work as a clinical academic, undertaking outpatient work in nephrology and in my research time, using electronic health records to examine drug effects—often as they relate to kidneys. Over recent years NHS England ran a programme called “Think Kidneys,” aiming to develop resources to improve the detection and treatment of patients with acute kidney injury (AKI). I was lucky enough to be part of the Intervention Workstream, which aimed to develop guidance for clinicians about ways to reduce harm to patients with AKI, particularly related to prescribed medication. There is often very limited research related to drug effects for people with kidney disease as they are frequently excluded from clinical trials owing to concerns about impaired drug excretion or metabolism,



Laurie Tomlinson is an associate professor at the London School of Hygiene and Tropical Medicine, and an honorary consultant nephrologist at Brighton and Sussex University Hospitals NHS Trust

and therefore increased risk of side effects. In addition, the evolving definitions of acute renal failure and subsequently AKI have meant that many older trials recorded limited or inconsistent data about sudden drops in kidney function. Therefore, much prescribing guidance is based on low quality or highly confounded observational studies, often in select patient groups.

The situation when we came to discuss possible guidance about trimethoprim prescribing was slightly different. Here, there were basic science studies of the biochemical effects of trimethoprim, and some high quality observational research using population cohorts. However, these related only to patients taking renin-angiotensin system blockers or spironolactone, and only to use of co-trimoxazole rather than trimethoprim alone. With these uncertainties, the workstream wondered what advice should we

give for the general population? Were the risks for trimethoprim the same as co-trimoxazole? How common was hyperkalaemia among people taking trimethoprim without other risk factors for high potassium levels? It struck me that this was something our research group could look at using UK primary care data.

Availability of large scale anonymised healthcare records and growing skills in conducting such research have enabled increasingly rapid research into drug effects after issues of clinical concern have arisen. This is particularly true for the UK which holds a number of excellent resources such as Hospital Episodes Statistics and databases of anonymised primary care data including the Clinical Practice Research Datalink. However, public confidence in the use of such data may be falling, particularly following the care.data saga. Increasing rates of individuals refusing consent for use of their anonymised data would greatly reduce the generalisability and validity of this type of research. Hopefully, examples of research where careful use of these vitally important resources leads directly to guidance to improve healthcare will maintain the trust of our patients.

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