

our rat models. The ApoE^{-/-} fat-fed mice exhibited a 2-fold increase ($p < 0.001$, $n = 9$), and the ApoE^{-/-}/IL-1R1^{-/-} animals a 4-fold increase ($p < 0.0001$, $n = 5$) in serum OPG compared with chow-fed controls.

Conclusions These studies further implicate IL-1 signalling in PAH; however, the mechanisms remain unclear. The data also support a role for OPG in PAH. Additional studies are underway to examine other key inflammatory pathways to determine whether they compensate for the lack of IL-1 signalling in this model, and so drive disease pathogenesis.

Tuberculosis screening: variations on a theme

S12 SYSTEMS BIOLOGY APPROACHES CHARACTERISE THE HOST RESPONSE TO TUBERCULOSIS

¹MPR Berry, ¹CM Graham, ¹SJ Bloch, ¹T Oni, ¹KA Wilkinson, ³RJ Wilkinson, ²OM Kon, ⁴J Banchereau, ⁴D Chaussabel, ¹A O'Garra. ¹National Institute For Medical Research, London, UK; ²Imperial College Healthcare NHS Trust, London, UK; ³University of Cape Town, Cape Town, Republic of South Africa; ⁴Baylor Institute for Immunology Research, Dallas, Texas, USA

doi:10.1136/thx.2009.127050l

Introduction Tuberculosis (TB) is a major cause of morbidity and mortality worldwide. The immune response during TB is complex and incompletely characterised, hindering the development of new diagnostics, treatments and vaccines. Studies performed in different disease settings (intermediate vs high burden) have sometimes yielded divergent results, limiting advances in our understanding of TB. We used systems biology approaches to obtain an unbiased comprehensive survey of the host response to TB in both the UK and South Africa.

Methods We recruited 214 participants; 153 met the final inclusion criteria. Active TB patients were culture positive. Latent TB patients were positive by both tuberculin skin test (TST) and interferon γ release assay (IGRA), and healthy controls were negative by both TST and IGRA. Whole blood was collected before treatment. RNA was extracted and used for whole genome expression studies using Illumina HT-12 microarrays. This was complemented by multiplexed cytokine analysis using the MILLIPLEX Multi-Analyte Profiling system. Biological data were integrated with comprehensive clinical data including radiology. Data mining was performed using Genespring GX 7.3 and Ingenuity Pathways Analysis software in combination with a novel Genomic Modular Analysis Framework. A subset of patients was assessed at 2 and 12 months post-treatment.

Results 42 participants from London were used as a training set to explore the microarray data, using supervised and unsupervised analyses to define a transcriptional signature. Findings were then tested in an independent set of 53 participants from London, and further validated using an independent cohort of 56 South African patients. We thus identify a robust blood transcriptional signature for active TB in both intermediate and high burden settings. Analysis of blood leucocyte counts and serum cytokines, along with interrogation of gene expression data using Pathway and Modular analysis, suggests that this signature reflects changes in cellular composition and altered cytokine expression. Transcriptional profiles appeared to reflect disease status. Longitudinal analysis revealed that the signature of active TB disappears during successful treatment.

Conclusions This is the first whole-genome expression profiling study in human TB. Our findings have implications for understanding disease pathogenesis, and could yield biomarkers for diagnosis and treatment monitoring.

S13 CONTACT SCREENING WITH SINGLE-STEP TIGRA TESTING AND RISK OF ACTIVE TB INFECTION: THE LEICESTER COHORT ANALYSIS

P Haldar, H Thuraingam, W Hoskyns, G Woltmann. University Hospitals of Leicester, Leicester, UK

doi:10.1136/thx.2009.127050m

Introduction A policy of a systematic single-step T cell-based interferon γ release assay (TIGRA) with QuantiFERON-TB Gold (QTG) has been employed at Leicester to screen for latent tuberculosis infection (LTBI) in close TB contacts since January 2007. Twelve week chemoprophylaxis is offered to all healthy QTG +ve contacts <35 years old. Baseline and longitudinal data have been collected prospectively for all index cases and their associated contacts since the introduction of the policy. Here we present the results of a cohort study examining outcome with QTG testing in all contacts since 2007.

Methods Data from all recorded contacts of patients with active TB diagnosed after 1 January 2007 are included. Contacts that developed active TB during the follow-up period were labelled "converters" if no evidence of active disease was identified at screening. Conversion risk was estimated using Kaplan-Meier plots and compared between defined subgroups using the log-rank test.

Results 2204 contacts (mean age 31.6 years, 51% male) were recorded in 446 notified cases (mean 4.9 contacts per case). 1039 contacts (47.1%) underwent screening with QTG and 204 were QTG +ve (19.6%). The mean follow-up period in QTG screened and unscreened contacts was 435 (± 212) days and 455 (± 235) days, respectively ($p = 0.88$). Chemoprophylaxis was started in 173 contacts (54 QTG untested). No QTG -ve contacts received chemoprophylaxis. Twelve week adherence was achieved in 90 contacts (52%). There were 39 converters (20 in the QTG-screened group). Of these, two had received chemoprophylaxis but only one had completed 12 weeks. All converters in the QTG tested group were QTG +ve. Two-year conversion risk (95% CI) in contacts not receiving chemoprophylaxis was 1.6% (0.8% to 2.4%) in the QTG untested population and 17.2% (9.4–25%) in QTG +ve contacts (hazard ratio (HR) = 10.3 if QTG +ve). Chemoprophylaxis lowered 2-year conversion risk in QTG +ve contacts to 4.7% (2.9% to 6.4%; HR 9 if no chemoprophylaxis).

Conclusion We estimate that 1 in 7.8 contacts testing QTG +ve will develop active TB without prophylaxis. QTG testing is an effective screening tool for identifying contacts at high risk of conversion.

S14 NEW ENTRANT SCREENING FOR LATENT TUBERCULOSIS USING IGRA TESTING ALONE

LP Ormerod. Royal Blackburn Hospital, Blackburn, UK

doi:10.1136/thx.2009.127050n

Background Our Local Government area has predominantly (but not exclusively) immigration from South Asia (India, Pakistan and Bangladesh). Prior to 2006 these were screened for latent tuberculosis infection as per then Joint Tuberculosis Committee 2000 Guidance. Following the National Institute for Health and Clinical Excellence (NICE) Guidelines 2006, new entrant screening for those aged 16–35 from countries with an incidence of under 500/100 000 per annum was limited to a chest x ray only. Data presented in 2007,¹ showed that 10.5% of such individuals without treatment of LTBI developed clinical tuberculosis within 10 years. With these data we obtained funding from the Primary Care Trust (PCT), under Health Improvement initiative money, to screen those aged 16–34 age with interferon γ release assay (IGRA) testing, for a 2 year period from February 2009. Our initial experience is reported.

Methods From 1 February to date (20 July 2009) new entrant TB screening for those aged 16–34 years is by IGRA test alone

Abstract S14 Table

Positive QFT	Negative QFT	Indeterminate QFT
46	100	2

(Quantiferon-in-tube Gold (Cellestis: QFT)). No prior Mantoux test was used (to save staffing costs on testing and reading), and a chest x ray was only performed on those with a positive QFT to exclude active disease, and if there were significant respiratory symptoms. Those with a positive QFT were seen, examined and started on treatment of LTBI with 3 months rifampicin and isoniazid (3RH).

Results Of new entrants (0.90%) from South Asia, 39 (28.9%) were positive, 94 were negative and 2 indeterminate. Of 13 non-African asylum seekers, 6/13 (46.1%) had a positive QFT. Aggregated results are given in the table. No patient with a positive QFT has had clinical disease on x ray and examination. No patient with some symptoms but a negative QFT has had disease (n = 5).

Conclusion The initial 6 months of this 2 year pilot show a 31.1% overall rate of LTBI in our predominantly South Asian 16- to 35-year-old new entrants, who would otherwise have been missed and hence not offered LTBI treatment. This is important as in our locality >90% of cases of TB are in the South Asian population. This strategy will shortly be expanded into the other local PCT with >75% South Asian TB cases. Longer term data on notifications should show whether there has been a fall compared with the non-intervention strategy of 1989–2001.

1. Choudry IW, Ormerod LP. The outcome of a cohort of tuberculin positive, predominantly South Asian, new entrants age 16–34 to the UK: Blackburn 1989–2001; Thorax 2007; S111; page A4.

S15 OUTCOMES AND COST OF MDR-TB IN LEEDS 1996–2009

RY Ahmed, TGD Capstick, JP Watson. *The Leeds Teaching Hospitals, NHS Trust, Leeds, UK*

doi:10.1136/thx.2009.127050p

Background World Health Organization guidelines for managing multidrug-resistant tuberculosis (MDR-TB) are based on expert opinion and a review of retrospective cohort data, but there is no randomised controlled trial evidence. Numbers in the UK remain low (~1% of isolates, 40–55 patients per year).¹ We are aware of no UK published data on MDR-TB outcomes.

Methods We reviewed the case records of all MDR-TB patients treated in Leeds since 1996, looking at their demographic profile, drug resistance, treatment given, the cost and duration of treatment and their outcome.

Results 28 (19 male, 9 female) patients have been treated for MDR-TB in Leeds since 1996, 23 of them since 2003. Ages ranged from 11 months to 71 years (mean 32.8 years). 12 (5 white) were born in the UK. 7 had a previous history of TB. 75% had pulmonary disease. The sensitivity profile is shown in the table. An injectable drug was used in all except one patient who was under 1 year of age. The other commonly used drugs were: fluoroquinolone (25 patients), pyrazinamide (24), ethambutol (22) and prothionamide (20). Side effects were common, requiring a change in treatment in 13 patients. Out of 28 patients, 18 successfully completed their treatment. Five were transferred out, two are still on treatment and three died of their disease. Inpatient stay ranged from 0 to 205 days (mean 66). The mean number of outpatient visits was 31 (range 16–49). The cost of medications ranged from £5893 to £187 000 with a mean of £18 450. Data on length of treatment were available on 15 of the patients who have completed their treatment. 12 received treatment for 18 months and 3 for between 12 and 18 months. Of those completing treatment, there has been

Abstract S15 Table

Drug	No. of patients tested	No. of patients resistant	% of patients resistant
Ethambutol	23	5	21.7
Pyrazinamide	23	4	17.3
Streptomycin	23	20	86.9
Amikacin	19	2	10.5
Capreomycin	15	2	13.3
Ciprofloxacin	18	5	27.8
Moxifloxacin	4	1	25
Ofloxacin	2	1	50
Clarithromycin	16	2	12.5
Azithromycin	9	2	22.2
Prothionamide	1	0	0
Ethionamide	14	3	21.4
p-Aminosalicylic acid (PAS)	19	4	21
Cycloserine	15	2	13.3
Rifabutin	13	12	92.3
Clofazimine	1	1	100
Linezolid	1	0	0
Kanamycin	1	1	100
Roxithromycin	2	1	50
Co-amoxiclav	1	1	100
Meropenem	1	1	100
Tetracycline	1	1	100

no evidence of recurrence to date (range 0–57 months, mean 27 months from completion).

Conclusion Treatment of MDR-TB is costly and side effects common, but good outcomes are possible in a specialist UK centre with current treatment strategy.

1. Tuberculosis in the UK: Annual report on tuberculosis surveillance in the UK 2008. London: Health Protection Agency Centre for Infections, October 2008.

S16 FIVE YEARS OF SUPPORT FOR A TUBERCULOSIS PROGRAMME IN RURAL ZIMBABWE: WHAT HAS BEEN ACHIEVED?

¹KM Scott, ¹FJC Millard, ¹RM Smith, ¹E Manomano, ²M Glenshaw, ¹RD Barker. ¹Department of Respiratory Medicine, Kings College Hospital, London, UK; ²Murambinda Mission Hospital, Buhera, Zimbabwe

doi:10.1136/thx.2009.127050p

Background Zimbabwe has the second highest incidence of tuberculosis (TB) in the world (782/100 000/year). This is largely driven by the HIV epidemic. Furthermore, Zimbabwe has been in financial, economic and political decline for several years. Buhera is a rural district in southern Zimbabwe with a population of ~230 000 people. In 2003 the district medical officer of Buhera requested financial and technical assistance for the TB programme from the British Charity, TB Alert. Here we report outcomes against key performance indicators for the first 5 years of the project.

Methods Site visits were undertaken by British physicians with an interest in TB in Africa. The aims of the project were to improve access to diagnosis of TB, to improve accuracy of diagnosis through increased use of sputum smear microscopy, to improve follow-up and treatment completion and to improve access to HIV care for those co-infected. Performance indicators were agreed and included the number of patients identified in relation to those expected, sputum smear rates, HIV testing and specific anti-HIV treatment administration and treatment outcomes. Some equipment was purchased and key salaries were supported. Approximately £16 000 per annum was contributed by the charity.

Abstract S16 Table Performance indicators for a tuberculosis (TB) programme in Buhera District Zimbabwe

	Year	
	2004	2008
Notifications	1081	1668
Incidence/100 000/year (Buhera residents)	425	570
Proportion of TB patients with sputum smears done	55%	91%
Proportion of TB patients with HIV test done	9%	84%
HIV positive receiving co-trimoxazole	13/97 (13%)	884/1083 (85%)
HIV positive receiving co-trimoxazole receiving antiretroviral therapy	6/97 (6%)	317/1033 (31%)

Results 5989 patients were registered in the 5-year period. 51% were men. The median age was 33 years (range 1–99) and 80.3% had pulmonary tuberculosis (PTB).

In 2008, 47% of patients with PTB were smear positive and 74% of those tested were HIV positive. Of 514 patients with sputum smear-positive PTB diagnosed in 2007, 218 (42.4%) were cured, 139 (27.0%) completed treatment, 3 (0.6%) failed treatment, 45 (8.8%) died, 3 (0.6%) interrupted treatment and 70 (13.6%) transferred out. Outcomes for 36 (7.0%) were not evaluated.

Discussion There has been a significant increase in TB notifications. Despite the increased burden, several aspects of the TB service in Buhera have improved significantly. Factors associated with success include good management, a committed work force, reasonable

financial support and partnership with other non-governmental organisations, especially Médecins sans Frontières. We believe the results represent an outstanding return for the investment.

Acknowledgements We would like to thank TB Alert for financial and moral support.

S17 TUBERCULOSIS AND HIV IN HEALTHCARE WORKERS

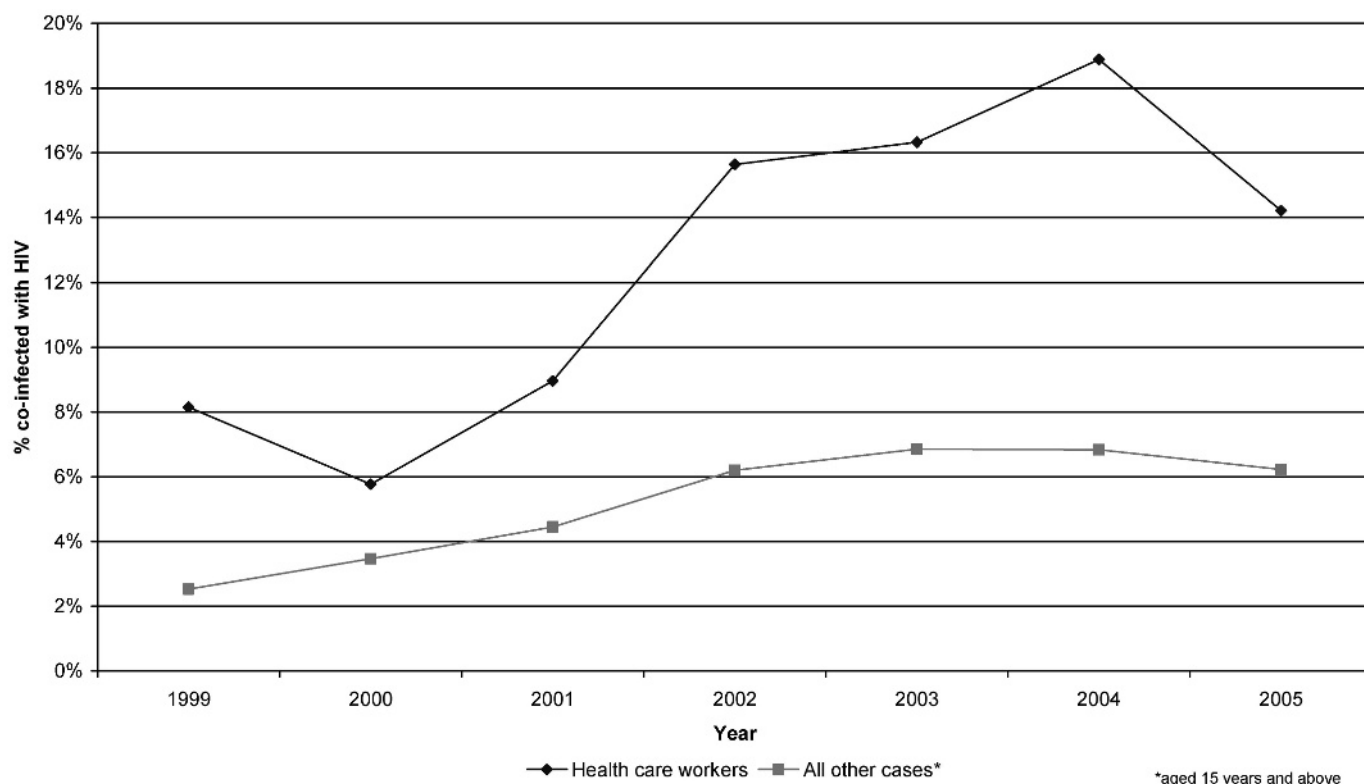
¹JP Crofts, ¹M Kruijshaar, ²V Delphech, ²F Ncube, ¹D Quinn, ¹I Abubakar. ¹Health Protection Agency Centre for Infections, Respiratory & Systemic Infections Department, London, UK; ²Health Protection Agency Centre for Infections, HIV & STI Department, London, UK

doi:10.1136/thx.2009.127050q

Background The National Health Service (NHS) has become increasingly reliant on healthcare workers recruited from overseas. Many of the countries of recruitment have high rates of tuberculosis and HIV. Screening of new healthcare workers (HCWs) for tuberculosis is focused on “one-off” testing. HIV-co-infected individuals often test falsely negative for latent tuberculosis.

Objectives To investigate tuberculosis and HIV co-infection among HCWs.

Methods Enhanced Tuberculosis Surveillance (ETS) collects detailed information, including occupation, on reported tuberculosis cases. To identify cases co-infected with HIV, records in the national ETS database for the years 1999–2005 were matched with records in the national HIV database (1979–2006). Patient confidentiality was protected by unlinked pseudo-anonymised data linkage.



Abstract S17 Figure 1 Prevalence of HIV co-infection in tuberculosis cases, England and Wales, 1999–2005.

Characteristics of HCWs with tuberculosis were compared by HIV status and tested for significance using the χ^2 test or the Fisher exact test where appropriate.

Results Information on occupation was available for 25 696 (54%) cases of which 1627(6%) were HCWs. Compared with all other cases, a higher proportion of HCWs were co-infected with HIV (14.2% vs 5.3%). From 1999 to 2005 the prevalence of HIV among HCWs with tuberculosis almost doubled, with a peak prevalence of 19% in 2004 (fig 1). In total 98% of HCWs with tuberculosis–HIV co-infection were born outside the UK compared with 80% of HCWs with tuberculosis only ($p<0.01$). Co-infected HCWs were more often from sub-Saharan Africa (97%, $p<0.01$); of these, >70% were diagnosed with tuberculosis ≥ 2 years after arrival. HCWs co-infected with HIV were also more likely than HCWs with tuberculosis only to have pulmonary disease (71% vs 52%, $p<0.01$) but had similar levels of multidrug-resistant tuberculosis (2.5% vs 1.4% $p = 0.25$).

Conclusions The burden of tuberculosis and HIV co-infection among HCWs falls mainly upon individuals born in high prevalence countries who often develop tuberculosis some years after arrival in the UK. One-off pre-employment screening for tuberculosis may not be enough to protect patient safety. In those HCWs who are at most risk, the provision of ongoing screening should be considered, and a high index of clinical suspicion for relevant symptoms is important.

Sleep disorders in practice

S18 PREVALENCE OF OBSTRUCTIVE SLEEP APNOEA IN 58 PATIENTS WITH DIABETIC MACULAR OEDEMA

¹RH Mason, ²SD West, ³V Chong, ¹JR Stradling. ¹The Churchill Hospital, Oxford, UK; ²Freeman Hospital, Newcastle upon Tyne, UK; ³The Eye Hospital, Oxford, UK

doi:10.1136/thx.2009.127050r

Introduction and Objectives Diabetic retinopathy is an important cause of visual loss worldwide. We and others recently showed that retinopathy was more common in a group of patients with diabetes if they also had obstructive sleep apnoea (OSA).^{1,2} Although the numbers were small, maculopathy was also related to the presence of OSA.² This study was designed to see if OSA was also related to the presence of diabetic macular oedema (DME), which is at the more severe end of the diabetic retinopathy spectrum, poorly responsive to treatment and the most common cause of blindness in patients with diabetes.

Methods 62 patients who had received laser therapy for DME provided anthropometric data, filled in the Epworth Sleepiness Score (ESS) and were screened with a home sleep study (ApnoeaLink, ResMed) to identify the presence of OSA (oxygen desaturation index (ODI), apnoea–hypopnoea index (AHI) and snoring). These results were compared with available prevalence figures from relevant control populations.

Results 58 patients (27 males) had >2 h of valid overnight data. Average (SD) age 62.9 (10.6), neck circumference 40.6 cm (5.3), body mass index (BMI) 30.9 (6.2), HbA_{1c} 7.7% (1.4), ESS 7.5 (4.7). The prevalence of an ODI ≥ 10 was 53%, that of AHI ≥ 15 was 47%, and 57% had either or both. These prevalences are considerably higher than in any of the control data, 6% in a randomly selected population,³ and 17% in randomly selected patients with type 2 diabetes.⁴ Those with OSA were not significantly sleeper than those without, but they were older and more obese.

Conclusions Individuals with DME show a much higher prevalence of OSA (defined via ODI or AHI) than both the general population and unselected patients with type 2 diabetes. This hypothesis-generating study suggests that OSA might contribute to DME, but

a continuous positive airways pressure (CPAP) intervention study will be required to prove cause and effect.

1. West SD, et al. Prevalence of retinopathy in men with type two diabetes and obstructive sleep apnoea. *Am J Respir. Crit Care Med* 2009;**179**.
2. Merritt SP, et al. Sleep disordered breathing, a causative factor in the development of severe diabetic retinopathy. *Thorax* 2007;**62**(Suppl III):S59.
3. Stradling JR, et al. Which aspects of breathing during sleep influence the overnight fall of blood pressure in a community population? *Thorax* 2000;**55**:393–8.
4. West SD, et al. Prevalence of obstructive sleep apnoea in men with type two diabetes. *Thorax* 2006;**61**:945–50.

S19 IMPACT OF THYROID FUNCTION TESTING IN PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA SYNDROME: A SINGLE-CENTRE EXPERIENCE OVER A DECADE

B Jayaraman, P Farrow. Kent & Canterbury Hospital, Canterbury, UK

doi:10.1136/thx.2009.127050s

Background Abnormal thyroid function is recognised to be associated with obstructive sleep apnoea syndrome (OSAS), but both the SIGN (Scottish Intercollegiate Guidelines Network) guidelines and NICE (National Institute for Health and Clinical Excellence) technical appraisal on OSAS recommend that thyroid function tests (TFTs) may be considered rather than mandatory in such patients. Studies supporting the frequency of abnormal TFTs in patients with OSAS are limited in the literature; therefore, we have performed a review of our experience in investigating OSAS patients from a single institution over a decade.

Method The study was performed in a single sleep-breathing unit, between 1998 and 2008, in investigating patients with OSAS, who were recommended to undergo a trial of continuous positive airways pressure (CPAP) by the multidisciplinary team. A total of 679 patients were found to be eligible and, in addition to their demographics, the presence or absence of normal or abnormal TFTs were collected. 62% of the patients (422/679) included in the study had their TFTs measured and the results were obtained from this cohort of patients.

Results 6.6% (22) were diagnosed to have biochemical hypothyroidism and were already on thyroxine replacement, and 1.4% (6) patients were picked up on screening. 3.1% (13) were diagnosed to have biochemical hyperthyroidism. Male sex (83%; mean age 57 years) was found to be another significant factor in this study with abnormal TFTs.

Discussion Abnormal (hypothyroidism (6.6%) and hyperthyroidism (3.1%)) TFT results were considerably more common (9.7%) in our patients than for reported spontaneous background incidence rates (1–2% and 0.5–2%, respectively) in the UK. The disparity is more marked especially as these overall reported spontaneous background rates are 10 times higher in females, whereas in our study the affected patients were predominantly male. Previous reports have shown the association of abnormal thyroid function and OSAS, but have not led to definitive testing recommendations. We conclude that the substantial excess rates of thyroid disease within our patients with OSAS are sufficient to warrant mandatory thyroid function testing and that it needs to be included in the national guidelines.

Abstract S19 Table

TFTs	Hypothyroidism	Hyperthyroidism
422	28	13

TFT, thyroid function test.