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RESEARCH

Pre-eclampsia, soluble fms-like tyrosine kinase 1, and the risk of reduced thyroid function: nested case-control and population based study

Richard J Levine,[1] Lars J Vatten,[2] Gary L Horowitz,[3] Cong Qian,[4] Pal R Romundstad,[2] Kai F Yu,[1] Anthony N Hollenberg,[5] Alf I Hellevik,[2] Bjorn O Asvold,[2] S Ananth Karumanchi[5 6 7]

EDITORIAL by North and Taylor

[1]Department of Health and Human Services, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Division of Epidemiology, Statistics, and Prevention Research, Bethesda, MD 20892, USA
[2]Department of Public Health, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[3]Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
[4]Glotech, Rockville, MD, USA
[5]Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
[6]Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
[7]Howard Hughes Medical Institute, Boston, MA, USA
Correspondence to: R J Levine LevineRJ@mail.nih.gov or S A Karumanchi sananth@bidmc.harvard.edu

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ABSTRACT

Objective To determine if pre-eclampsia is associated with reduced thyroid function during and after pregnancy.
Design Nested case-control study during pregnancy and population based follow-up study after pregnancy.
Setting Calcium for Pre-eclampsia Prevention (CPEP) trial of healthy pregnant nulliparous women in the United States during 1992-5, and a Norwegian population based study (Nord-Trondelag Health Study) during 1995-7 with linkage to the medical birth registry of Norway.
Participants All 141 women (cases) in the CPEP trial with serum measurements before 21 weeks' gestation (baseline) and after onset of pre-eclampsia (before delivery), 141 normotensive controls with serum measurements at similar gestational ages, and 7121 women in the Nord-Trondelag Health Study whose first birth had occurred in 1967 or later and in whom serum levels of thyroid stimulating hormone (TSH) had been subsequently measured.
Main outcome measures Thyroid function tests and human chorionic gonadotrophin and soluble fms-like tyrosine kinase 1 (sFlt-1) concentrations in the CPEP cohort and odds ratios for levels of TSH above the reference range, according to pre-eclampsia status in singleton pregnancies before the Nord-Trondelag Health Study.
Results In predelivery specimens of the CPEP cohort after the onset of pre-eclampsia, TSH levels increased 2.42 times above baseline compared with a 1.48 times increase in controls. The ratio of the predelivery to baseline ratio of cases to that of the controls was 1.64 (95% confidence interval 1.29 to 2.08). Free triiodothyronine decreased more in the women with pre-eclampsia than in the controls (case ratio to control ratio 0.96, 95% confidence interval 0.92 to 0.99). The predelivery specimens but not baseline samples from women with pre-eclampsia were significantly more likely than those from controls to have concentrations of TSH above the reference range (adjusted odds ratio 2.2, 95% confidence interval 1.1 to 4.4). Both in women who developed pre-eclampsia and in normotensive controls the increase in TSH concentration between baseline and predelivery specimens was strongly associated with increasing quarters of predelivery sFlt-1 (P for trend 0.002 and <0.001, respectively). In the Nord-Trondelag Health Study, women with a history of pre-eclampsia in their first pregnancy were more likely than other women (adjusted odds ratio 1.7, 95% confidence interval 1.1 to 2.5) to have concentrations of TSH above the reference range (>3.5 mIU/l). In particular, they were more likely to have high concentrations of TSH without thyroid peroxidase antibodies (adjusted odds ratio 2.6, 95% confidence interval 1.3 to 5.0), suggesting hypothyroid function in the absence of an autoimmune process. This association was especially strong (5.8, 1.3 to 25.5) if pre-eclampsia had occurred in both the first and the second pregnancies.
Conclusion Increased serum concentration of sFlt-1 during pre-eclampsia is associated with subclinical hypothyroidism during pregnancy. Pre-eclampsia may also predispose to reduced thyroid function in later years.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Limited data suggest that pre-eclampsia may be associated with hypothyroid function during pregnancy

Women with a history of pre-eclampsia are at increased risk of future cardiovascular and renal disease

WHAT THIS STUDY ADDS

Hypothyroid function during pre-eclampsia may result from the antiangiogenic state

Women with a history of pre-eclampsia may be at increased risk of future hypothyroid function

INTRODUCTION

Although the cause of pre-eclampsia—a pregnancy specific syndrome of new onset hypertension and proteinuria—is still unclear, studies suggest that excess antiangiogenic factors such as soluble fms-like tyrosine kinase 1 (sFlt-1) may be responsible for the clinical phenotype of pre-eclampsia.[1-3] Blood concentrations of sFlt-1increase during the last two months of normal pregnancy and increase to much greater levels in women with pre-eclampsia. sFlt-1 acts by inhibiting vascular endothelial growth factor and placental growth factor signalling. Indeed, the use of vascular

endothelial growth factor inhibitors for the treatment of cancer related angiogenesis has been associated with hypertension, proteinuria, and other conditions resembling those associated with pre-eclampsia.[4 5]

More recently, patients with cancer who had received prolonged therapy with vascular endothelial growth factor inhibitors were found to be at greater risk of hypothyroidism.[6-8] We hypothesised that the excess sFlt-1 accompanying pre-eclampsia might be associated with reduced thyroid function during pregnancy and that women who have had pre-eclampsia would have an increased risk of hypothyroid function later in life.

We carried out a nested case-control study within the Calcium for Pre-eclampsia Prevention (CPEP) trial cohort. We hypothesised that women with pre-eclampsia would experience a greater increase in thyroid stimulating hormone (TSH) concentration during pregnancy than normotensive controls and that the extent of the increase would correlate with the magnitude of the sFlt-1 concentration during pre-eclampsia. We also used a Norwegian population based cohort study (Nord-Trondelag Health Study) to test whether pre-eclampsia in a previous pregnancy is associated with risk of reduced thyroid function in later life.

The CPEP trial

The CPEP trial was a randomised, double blind trial (1992-5) in healthy nulliparous women with singleton pregnancies.[9 10] Of the 4589 women in the trial we excluded 300 (see bmj.com). Of 326 women who developed pre-eclampsia, 141 had at least one serum specimen collected before 21 weeks' gestation (baseline specimen) and one collected after the onset of pre-eclampsia (predelivery specimen). sFlt-1 had been analysed in specimens of a random sample of 2200 women and in all women with pre-eclampsia.[11] After exclusions, 1649 women remained who had been normotensive and without proteinuria during their pregnancies (controls). Each case of pre-eclampsia was matched to the control with two serum specimens closest in gestation to the two case specimens. One baseline and one predelivery specimen were not located. Pre-eclampsia was defined as hypertension (diastolic blood pressure of at least 90 mm Hg on two occasions four to 168 hours apart) and proteinuria (see bmj.com).

Enzyme linked immunosorbent assays for human sFlt-1 had previously been done in duplicate.[11] Thyroid function tests (TSH, free thyroxine, free triiodothyronine, thyroid peroxidase antibodies) were carried out and human chorionic gonadotrophin measured as it is known to stimulate the thyroid gland and decrease TSH concentrations.[12] Reference ranges for TSH (mIU/l) from the manufacturer were 0.33-4.60, 0.35-4.10, and 0.21-3.15 in sera from the first, second, and third trimester. The upper limits of the reference ranges for thyroid peroxidase antibodies (IU/ml) from the manufacturer were 119, 91, and 171 in sera from the first, second, and third trimester.[13]

Statistical analysis—We compared categorical variables using the χ^2 test and continuous variables using *t* tests. The geometric means of TSH, free thyroxine, free triiodothyronine, and human chorionic gonadotrophin and their standard deviations are reported for baseline and predelivery specimens for both cases and controls. Comparisons of cases and controls are presented as two tailed P values. Statistical comparisons of specimens from cases and controls were carried out using linear models, adjusting for age, body mass index, race or ethnicity (black people *v* others), smoking status (current smoker or quit during pregnancy *v* never smoker or quit before pregnancy), human chorionic gonadotrophin concentration, and presence of thyroid peroxidase antibodies above the reference range. The levels of change from baseline to predelivery are presented as ratios. Geometric means of the ratios and their standard deviations are given. We present the comparison statistic between case and control, which is the ratio of their geometric means, with its 95% confidence interval.

RESULTS

Of the 141 women with pre-eclampsia, 63 (42%) had severe pre-eclampsia and in 47 (33%) pre-eclampsia began before 37 weeks' gestation (see bmj.com). The difference in gestational age between baseline and predelivery specimens in cases and controls did not differ significantly (154 *v* 148 days, P=0.08).

Thyroid function tests and pre-eclampsia

The mean values of thyroid function tests at baseline were not significantly different (see bmj.com). However, after the onset of pre-eclampsia, concentrations of TSH and human chorionic gonadotrophin were higher in cases than in controls. The magnitude of the increase in TSH concentration from baseline to predelivery (predelivery to baseline ratio) was greater in cases than in controls (see bmj.com); case ratio to control ratio 1.64 (95% confidence interval 1.29 to 2.08). Compared with baseline specimens, levels of free triiodothyronine were lower in predelivery specimens, and the magnitude of the decrease was significantly greater in cases than in controls (predelivery to baseline ratio 0.85 *v* 0.89, case ratio to control ratio 0.96, 0.92 to 0.99). Although free thyroxine concentrations were also lower in predelivery specimens than in baseline specimens, the decrease was similar between cases and controls.

The distribution of test results for thyroid function among cases and controls at baseline and before delivery was examined in relation to the gestational age specific reference ranges for pregnant women. This was done to determine whether subgroups of the women who developed pre-eclampsia might have concentrations of thyroid hormones indicating the potential for clinically significant thyroid malfunction. Only the distributions of TSH concentration were significantly different between cases and controls. At baseline the proportion of women with concentrations above the reference range did not differ between women who would later develop pre-eclampsia and controls (2% and 3%, P=0.28 after adjustment for age, body mass index, race, smoking, logarithmically transformed human chorionic gonadotrophin concentration, and the presence or absence of thyroid peroxidise antibodies). However,

before delivery the proportion with TSH concentrations above the reference range was greater in cases than in controls: 24% and 14% (arithmetic means 4.47 mIU/l and 4.26 mIU/l) had TSH concentrations above the reference range (adjusted P=0.03). In predelivery, but not baseline, specimens, cases were significantly more likely than controls to have TSH concentrations above the reference range (adjusted odds ratio 2.2, 95% confidence interval 1.1 to 4.4).

Of the 140 women with subsequent pre-eclampsia and 140 controls tested for thyroid peroxidase antibodies at baseline, six (4%) in each group had levels above the reference range (positive result). In predelivery specimens, seven (5%) cases and four (3%) controls had positive results. The distributions of women with positive results did not differ significantly between cases and controls.

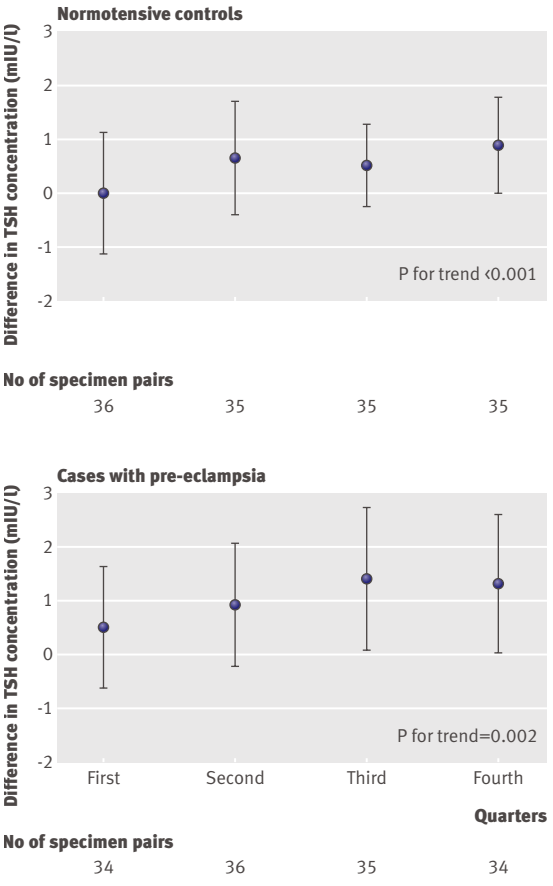
At baseline none of the women had clinical hypothyroidism (TSH concentration above the reference range and free thyroxine below). However, in predelivery specimens two women had developed clinical hypothyroidism (TSH 5.46 and 7.33 mIU/l and free thyroxine 8.0 and 8.2 pmol/l), both after the onset of pre-eclampsia.

Differences in TSH concentrations across quarters of sFlt-1 concentrations

To investigate mechanisms by which pre-eclampsia may be associated with the development of hypothyroidism, the differences between predelivery and baseline values of thyroid function tests were examined according to quarters of sFlt-1 concentrations in the predelivery specimens. Among controls the increase in TSH concentration between baseline and predelivery specimens was strongly associated (P for trend <0.001) with increasing quarters of predelivery sFlt-1 concentration: arithmetic means 0.01 (SD 1.14) mIU/l, 0.66 (1.04), 0.52 (0.75), and 0.92 (0.91) (figure). The arithmetic mean of the difference in free thyroxine concentration between predelivery and baseline specimens was greater in the fourth quarter than in the first quarter (−2.70 *v* −1.67 pmol/l, P=0.03); but the test for trend was not significant.

sFlt-1 concentrations (pg/ml) in normotensive controls for the first to fourth quarters were 1710-5620, 5620-7554, 7554-10 789, and 10 789-34 907. Differences in the arithmetic mean TSH concentrations (mIU/l) for the first to fourth quarters were 0.01, 0.66 (P=0.006), 0.52 (P=0.03), and 0.92 (P<0.001), with P values indicated for comparisons with the first quarter. sFlt-1 concentrations (pg/ml) in the cases for the first to fourth quarters were 6620-13 772, 13 772-21 282, 21 282-30 740, and 30 740-82 739. Differences in the arithmetic mean TSH concentration (mIU/l) for the first to fourth quarters were 0.51, 0.94, 1.41 (P=0.003), and 1.33 (P=0.006), with significant P values indicated for comparisons with the first quarter.

Among the cases with pre-eclampsia, the increase in TSH concentration between baseline and predelivery specimens was also strongly associated (P for trend 0.002) with increasing quarters of predelivery sFlt-1: arithmetic means 0.51 (SD 1.12) mIU/l, 0.94 (1.13), 1.41 (1.32), and 1.33 (1.29). Compared with controls, the increase in cases was consistently greater in each corresponding quarter.



Comparisons of differences in thyroid stimulating hormone (TSH) concentration between predelivery and baseline specimens across quarters of predelivery sFlt-1 concentrations in normotensive controls and cases with pre-eclampsia

Nord-Trondelag Health Study

Between 1995 and 1997 all inhabitants 20 years and older in Nord-Trondelag county in Norway were invited to participate in the Nord-Trondelag Health Study.[14] Overall, 66 140 (71.2%) of 92 936 eligible adults participated. TSH concentrations were determined in samples of the study population and included all women older than 40 years and a 5% random sample of women aged 20-40.

Linkage to medical birth registry of Norway

We restricted the analysis to women who had had their first birth registered with Norway's medical birth registry during the period from 1967 (the start of records) until participation in the Nord-Trondelag Health Study. Among women with a TSH measurement, 7933 had had their first birth in 1967 or later. After exclusions, 7121 women were included in the analysis. Thyroid peroxidase antibodies were measured in women with a TSH concentration greater than 4 mIU/l.

Criteria for pre-eclampsia used by the reporting midwives and obstetricians were an increased blood pressure after 20 weeks' gestation (≥140/90 mm Hg, or an

increase in systolic blood pressure ≥30 mm Hg or in diastolic blood pressure ≥15 mm Hg), from measurements made before 20 weeks' gestation, and proteinuria (≥0.3 g in a 24 hour urine specimen or a urine dipstick result of ≥+).

Procedures

Serum concentrations of TSH were measured at Aker University Hospital, Oslo. The clinical reference range for TSH in this population was defined as 0.50-3.50 mIU/l.[15] Thyroid peroxidase antibodies were also measured in people with TSH concentrations greater than 4 mIU/l (see bmj.com). Those with levels greater than 200 IU/ml were considered to have tested positive for thyroid peroxidase antibodies.

Statistical analysis

We used multiple logistic regression analysis to determine odds ratios and 95% confidence intervals. All analyses were adjusted for age and smoking status (current, former, or never).

Results

Analyses were carried out among 7121 women with TSH measurements who had delivered their first child during or after 1967 (see bmj.com). Among women who had pre-eclampsia in their first pregnancy the probability of having serum TSH concentrations greater than the clinical reference range (>3.5 mIU/l) was higher than for those who did not develop pre-eclampsia in their first pregnancy (adjusted odds ratio 1.7, 95% confidence interval 1.1 to 2.5). The mean number of years elapsed from delivery of the first pregnancy to the date of the TSH measurement was 20.4 among the women with pre-eclampsia in that pregnancy and 21.8 years among the women without pre-eclampsia in that pregnancy.

The association of pre-eclampsia with subsequent hypothyroid function (TSH >4.0 mIU/l) was slightly stronger in the absence of thyroid peroxidase antibodies (adjusted odds ratio 2.6, 95% confidence interval 1.3 to 5.0) than for hypothyroid function with thyroid peroxidase antibodies (1.8, 1.0 to 3.1; see bmj.com). Among women who had pre-eclampsia in two pregnancies, the association with hypothyroid function in the absence of thyroid peroxidase antibodies was particularly strong (5.8, 1.3 to 25.5).

DISCUSSION

This study found that pre-eclampsia among nulliparous women is associated with a greater subsequent risk of subclinical hypothyroidism in pregnancy and that women with a history of pre-eclampsia are at greater risk of hypothyroid function in later life.

The findings during pregnancy are consistent with the results of previous studies[16-18] and indicate that the increases in TSH concentration during pre-eclampsia are not related to changes in circulating human chorionic gonadotrophin concentrations, a protein that stimulates the thyroid gland and suppresses TSH.[12] In women with pre-eclampsia, but also in normotensive controls, the extent of increase in TSH during pregnancy was directly related to the magnitude of circulating sFlt-1 concentrations before delivery. This increase was substantially greater in the pre-eclampsia group, consistent with the suggestion that the effect of pre-eclampsia on thyroid function may be mediated by sFlt-1.

Norwegian women who had pre-eclampsia in their first pregnancy were more likely than other women to have concentrations of TSH above the reference range many years after the pregnancy. The association was stronger if the high concentration of TSH was combined with absence of thyroid peroxidase antibodies, and particularly strong if pre-eclampsia had occurred in two pregnancies. This suggests that the hypothyroid function associated with increased circulating concentrations of TSH in pre-eclampsia may occur independent of the autoimmune mechanisms that are generally accepted as the most likely cause of subclinical and overt hypothyroidism in iodine replete women.[19 20]

The clinical syndrome of pre-eclampsia has been hypothesised to result from excessive release of antiangiogenic proteins—most notably sFlt-1—from the placenta into maternal blood, resulting in an antiangiogenic state with low levels of free placental growth factor and free vascular endothelial growth factor.[2 21] Together with reports of hypothyroidism in patients with cancer treated with vascular endothelial growth factor receptor inhibitors,[5-8 22] the evidence suggests that high levels of exposure to sFlt-1 as in pre-eclampsia may be associated with increased risk for reduced thyroid function during and after pregnancy.

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Competing interests: SAK has served as a consultant to Abbott, Beckman Coulter, Roche, and Johnson & Johnson and has been named coinventor on multiple provisional patents filed by Beth Israel Deaconess Medical Center for the use of angiogenesis related proteins for the diagnosis and treatment of

pre-eclampsia. These patents have been non-exclusively licensed to several companies.

Ethical approval: Because the study used specimens that had been collected as part of the Calcium for Pre-eclampsia trial and could not be linked to identifiable women, the Office of Human Subjects Research of the National Institutes of Health granted an exemption from the requirement for review and approval by the institutional review board. Use of the Nord-Trondelag Health Study and Norwegian birth registry was approved by the Norwegian regional committee for medical research ethics and by the Norwegian Data Inspectorate.

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Multiple sclerosis risk sharing scheme: two year results of clinical cohort study with historical comparator

Mike Boggild,[1] Jackie Palace,[2] Pelham Barton,[3] Yoav Ben-Shlomo,[4] Thomas Bregenzer,[5] Charles Dobson,[6] Richard Gray[7]

[1]The Walton Centre, Liverpool L9 7LJ
[2]John Radcliffe Hospital, Oxford OX3 9DU
[3]Health Economics Unit, University of Birmingham, Birmingham B15 2TT
[4]Department of Social Medicine, Canynge Hall, Bristol BS8 2PS
[5]Biostatistics Unit, PAREXEL International, 14050 Berlin, Germany
[6]Department of Health, Quarry House, Leeds LS2 7UE
[7]University of Birmingham Clinical Trials Unit, Birmingham B15 2TT

Correspondence to: M Boggild mike.boggild@thewaltoncentre.nhs.uk

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ABSTRACT

Objective To generate evidence on the longer term cost effectiveness of disease modifying treatments in patients with relapsing-remitting multiple sclerosis.

Design Prospective cohort study with historical comparator.

Setting Specialist multiple sclerosis clinics in 70 centres in the United Kingdom.

Participants Patients with relapsing-remitting multiple sclerosis who started treatment from May 2002 to April 2005 under the UK risk sharing scheme.

Interventions Treatment with interferon beta or glatiramer acetate in accordance with guidelines of the UK Association of British Neurologists.

Main outcome measures Observed utility weighted progression in disability at two years' follow-up assessed on the expanded disability status scale (EDSS) compared with that expected by applying the progression rates in a comparator dataset, modified for patients receiving treatment by multiplying by the hazard ratio derived separately for each disease modifying treatment from the randomised trials.

Results In the primary per protocol analysis, progression in disability was worse than that predicted and worse than that in the untreated comparator dataset ("deviation score" of 113%; excess in mean disability status scale 0.28). In sensitivity analyses, however, the deviation score varied from −72% (using raw baseline disability status scale scores, rather than applying a "no improvement" algorithm) to 156% (imputing missing data for year two from progression rates for year one).

Conclusions It is too early to reach any conclusion about the cost effectiveness of disease modifying treatments from this first interim analysis. Important methodological issues, including the need for additional comparator datasets, the potential bias from missing data, and the impact of the "no improvement" rule, will need to be addressed and long term follow-up of all patients is essential to secure meaningful results. Future analyses of the cohort are likely to be more informative, not least because they will be less sensitive to short term fluctuations in disability.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Randomised controlled trials have shown that disease modifying treatments can slow the progression of relapsing-remitting multiple sclerosis over a two to three year period

It is not known whether these benefits persist over the longer term or whether patients who stop treatment retain the benefit they have received up to that point

For these reasons, it is not clear whether disease modifying treatments represent a cost effective use of NHS resources

WHAT THIS STUDY ADDS

This two year interim analysis of the UK risk sharing scheme does not provide reliable evidence on cost effectiveness of disease modifying treatments

Results are highly sensitive to how the baseline score and missing follow-up data are handled

Longer more complete follow-up with additional reference datasets will be more informative and less sensitive to short term fluctuations in disability

INTRODUCTION

In 2002, the National Institute for Health and Clinical Excellence (NICE) published appraisal guidance on the use of disease modifying treatments for multiple sclerosis.[1] Randomised placebo controlled trials had shown the short term clinical effectiveness of each drug. To determine the cost utility of the long term effects of treatments ScHARR (Sheffield School of Health and Related Research) created an economic model[2] using data on quality of life collected by the MS Trust from patients in the United Kingdom,[3] cost data,[4] a natural history dataset from London, Ontario,[5] and estimates of delay in disease progression derived from randomised controlled trials. This model suggested that disease modifying treatments were not cost effective over a 10 or 15 year horizon but became more cost effective over 20 years. It was uncertain whether the results of randomised controlled trials lasting no more than three years could be extrapolated over a longer period and whether patients who stopped treatment retained any benefits beyond that point, with disease progressing in line with that expected for untreated patients, or whether there was a rebound effect after cessation of treatment.

Given the above uncertainties, NICE was unable to recommend the treatments for use in the NHS at current prices but instead wanted to consider how they could be made available to patients in a cost effective manner.[1] In February 2002 the UK health departments set out the agreed basis of a "risk sharing scheme," which would allow the prescribing of Avonex, Betaferon, Copaxone, and Rebif 22 and 44 according to the Association of British Neurologists' 2001 guidelines,[6] conditional on the development of a 10 year monitoring study that would collect data on the progression of disease in treated patients and thus help to assess the two critical uncertainties emphasised by NICE. We report the results and implications of the first planned interim analysis, carried out when all patients had been in the scheme for at least two years.

METHODS

The principles for the establishment and conduct of the risk sharing scheme were set out in an NHS circular.[7] It suggested that 5000-7000 patients should be recruited to a monitoring cohort to allow about 1000 patients taking each treatment, large enough to reduce sampling errors to an acceptable level.

Data collection

As this was a pragmatic study, it was designed to collect minimum basic information through clinical assessments with expanded disability status scale (EDSS) scores[8] performed annually within a three month window of entry into the study. Patients were to be followed even if treatment was stopped or altered to minimise "dropout bias" and to test the ScHARR model assumptions that benefit up to that point is maintained over the longer term.

Outcome measures

With no randomised control group, we had to compare the disease progression for the risk sharing cohort with a cohort of patients who were recruited and followed up before the routine use of disease modifying treatments. We used the London, Ontario, dataset,[5] which consists of 1043 Canadian patients, recruited in 1972-84, whose disability was assessed about annually for a median of 25 years from onset of disease with the disability status scale. The dataset derived from this cohort seems to have been collated retrospectively with the disability status scores smoothed to eliminate short term fluctuations. As a result there are no "regressions" in EDSS in the Ontario dataset; disability scores for individual patients can only worsen over time and the ScHARR model had to reflect this.

For each treatment separately we used the ScHARR model to predict the expected movement of patients between the EDSS states both "on" and "off" treatment. See bmj.com.

Our primary outcome measure was a deviation score of the average observed loss of utility (average utility weighted disease progression; see bmj.com) for patients in the risk sharing scheme compared with the expected loss calculated by the ScHARR model for patients "on" treatment.

The "expected benefit" of treatment is the "hypothetical" difference between the expected outcome without and with treatment, as calculated in each case from the ScHARR model. The "actual benefit" of treatment is the "observed" difference between the expected outcome without treatment and the actual outcome with treatment. The "deviation" of the actual benefit from the expected is calculated as a percentage of the expected benefit. This measure can have negative or positive values so that a negative deviation implies that the observed benefit was greater than predicted, a positive deviation implies that it was worse than predicted, and a value of 0 indicates that it was exactly as predicted. This deviation measure is calculated every two years and used as the basis of possible price adjustments under the agreed rules of the scheme.

Statistical methods

One major assumption of the ScHARR model is that EDSS scores are constrained to remain stable or worsen

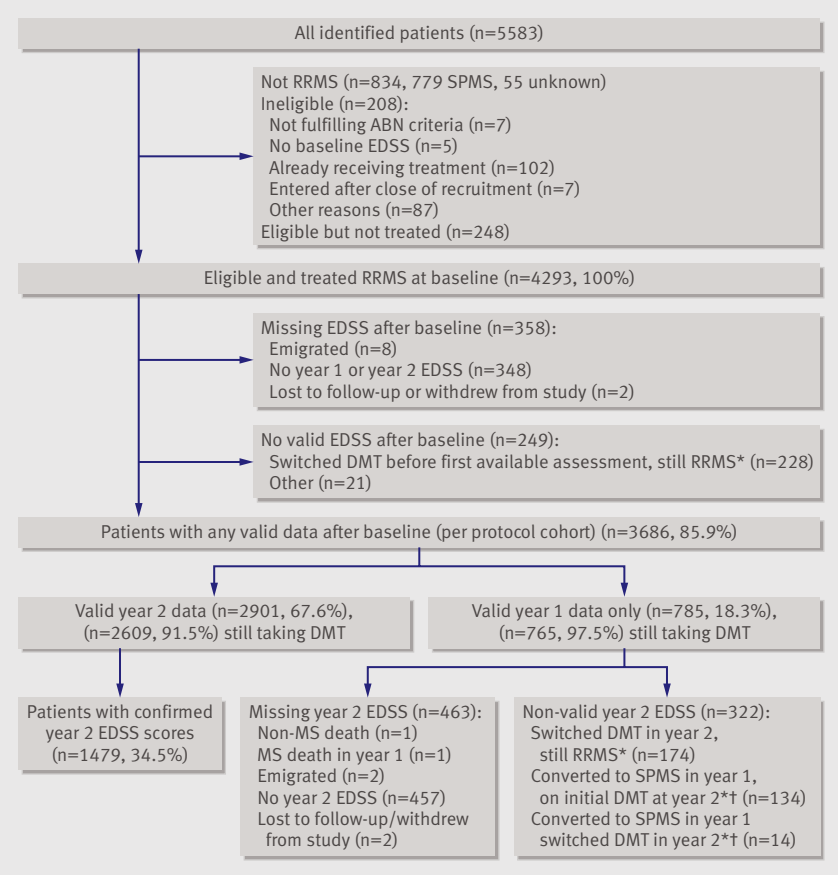

Fig 1 | **Participants with relapsing-remitting multiple sclerosis (RRMS) taking disease modifying treatments (DMT) in multiple sclerosis risk sharing scheme. *Data used for supplementary analyses. †Patients assessed as secondary progressive multiple sclerosis (SPMS) at year 1 follow-up; their EDSS scores for year 1 (but not for later years) retained in primary analysis**

and improvements are not possible. We therefore had to apply an algorithm to the risk sharing scheme cohort to model the way in which we understand the Ontario dataset to have been compiled (we did not have access to the raw Ontario data). See bmj.com.

The primary (per protocol) analysis censored patients who died from causes other than multiple sclerosis, emigrated, were lost to follow-up, or switched treatments. Patients who died from a cause related to multiple sclerosis had their subsequent missing EDSS score altered to a value of 10. The ScHARR model assumed that all those who progressed to secondary progressive multiple sclerosis would stop treatment and could be treated in the same way as other patients who stopped treatment. Patients who moved from relapsing-remitting multiple sclerosis to secondary progressive multiple sclerosis but who still took treatment were censored after the first assessment after conversion and were then treated as "lost to follow-up." We have also carried out a sensitivity analysis to include these patients. The scientific advisory group has also suggested several supplementary sensitivity analyses. See bmj.com.

RESULTS

Participants

Out of 5583 patients registered into the monitoring scheme, 4749 (85%) had relapsing-remitting multiple sclerosis, (fig 1). The baseline data characteristics of all the 4293 eligible patients with relapsing-remitting multiple sclerosis at baseline and the subset of 3686 used in the primary analysis were almost identical.

Over the two year period 1403 (38%) patients in the per protocol analysis set showed an improvement in EDSS scores, and for 591 patients (16%) this was confirmed. These proportions are in contrast with the assumption in the ScHARR model that improvements in annual scores are unlikely. Over the same period 1803 (49%) patients had deterioration in EDSS, and in 834 (23%) this was confirmed. At year two, 2629 patients (71.3% of patients in the per protocol analysis cohort) were still taking their initial treatment, but 272 (7.4%) had stopped all treatment, 214 (5.8%) had switched to a different disease modifying treatment, and 571 (15.5%) had become lost to follow-up, died, or had missing EDSS data at year two.

The mean annual rate of change in the EDSS score in the per protocol analysis cohort was 0.35 after application of the "no improvement" rules and 0.16 with the "raw" data. As a result of the no improvement rules, of the 3686 patients in the per protocol analysis cohort, we modified EDSS scores of 989 (26.8%) patients at baseline and 715 patients (19.4%) for at least one follow-up visit.

Mean EDSS for the 2901 patients in the per protocol analysis with valid EDSS data at year two was 2.68 at baseline, 2.90 after one year, and 3.24 after two years. Patients who had only one year of valid data (n=785) had mean EDSS of 3.14 at baseline and 3.77 after one year ($P<0.001$ for comparison of baseline and of rate of change, Mann-Whitney-Wilcoxon test).

Primary analysis

The primary analysis shows a positive deviation score of 113% for the weighted utility score, the primary outcome measure. See bmj.com. At face value this indicates that cost effectiveness of disease modifying treatments was worse than that expected from the ScHARR model as applied to the Ontario dataset and also worse than that predicted with no treatment from the same model. In absolute terms the EDSS score was 0.10 units worse than the control data and 0.28 units worse than predicted on the assumption that the disease modifying treatments delay progression of the disease.

Sensitivity analyses

Retaining all patients in the analysis regardless of any switching between treatments, and retaining patients who moved from relapsing-remitting to secondary progressive multiple sclerosis but remained taking treatment, made virtually no difference to the deviation measure. The difference between observed and expected EDSS progression was less marked when we restricted the analysis to the subgroup of patients with the year two EDSS score confirmed by valid year three data (0.14 *v* 0.28) or when we adjusted the results to take account of the expected proportion of apparent progressions at year two that were not subsequently

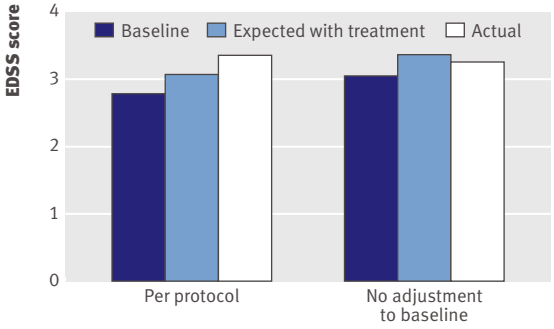

Fig 2 | **Effect of baseline adjustment of EDSS**

confirmed at year three (0.19 *v* 0.28). Imputation of data for year two in patients with only year one values gave results marginally more favourable to the disease modifying treatments in the "best case" scenario (0.27) but distinctly worse in the "worst case" scenario (0.33) compared with the primary analysis (0.28). When we used the unadjusted EDSS scores at baseline (thereby allowing improvement from baseline to year one) while continuing to apply the "no improvement" algorithm to subsequent data points, however, there was a negative deviation measure (−84)—that is, patients progressed less rapidly than predicted from the ScHARR model (−0.11 EDSS points compared with 0.28 in the per protocol analysis) (fig 2).

DISCUSSION

The outcomes so far obtained in the pre-specified primary analysis of the risk sharing scheme suggest a lack of delay in disease progression for all disease modifying treatments combined. Some of the sensitivity analyses performed were more favourable to the drugs.

Factors to consider

Our use of the no improvement "rules" might have underestimated the effects of treatment. The data from the risk sharing scheme had to be modified to allow comparison with the predicted disease progression. EDSS scores for patients with multiple sclerosis, however, do spontaneously improve. In addition, it is clear that the disease modifying treatments do reduce relapses[9] and might allow improved recovery from relapse early in treatment. In the risk sharing cohort, 32% of patients show some improvement in disability scores and for 14% this improvement is sustained for a second year.

The Ontario comparator dataset might therefore not be appropriate and makes reliable interpretation of the short term results problematic. The scientific advisory group considered that it was premature, at this stage, to reach any decision about re-pricing the drugs without further follow-up and analyses.

Limitations and future plans

Estimating cost effectiveness from an observational cohort study with a historical comparator dataset has inherent problems. We appreciated from the outset that a major limitation was the validity and generalisability of the comparison dataset.

Some of the patients who entered the risk sharing scheme at the outset will have had disease for a longer duration than is current clinical practice, as access to treatment in the UK was fairly restricted before the introduction of the scheme. This would potentially bias the results to underestimate the effects of treatment if such patients show less benefit than those treated earlier in the natural course.[10] Another potential bias, which would overestimate the benefits of treatment, is incomplete follow-up. See bmj.com. One of the uncertainties in the original SCHARR model was the estimate of costs and utilities. An additional study to capture cost and utility data has therefore been undertaken.

The original analysis plan wrongly assumed that patients who developed secondary progressive multiple sclerosis would stop treatment and would thus be modelled using the untreated transition probabilities. Most such patients in the scheme, however, continued treatments. Our secondary analysis showed that including patients who developed secondary progressive multiple sclerosis while taking treatment did not have a significant impact on the results, presumably because to date they represent a relatively small proportion of the cohort at this stage.

Since the onset of the risk sharing scheme, there have been changes in the guidelines and management of patients with multiple sclerosis and there are now wider potential eligibility criteria for disease modifying treatments. This might make it difficult to generalise the findings to current practice.

Risk sharing schemes

The risk sharing scheme was a response to a familiar dilemma in health technology assessment—the problem of assessing the longer term benefits of treatments for progressive diseases when, because of cost considerations and the difficulties in maintaining large populations in prolonged placebo controlled studies, pivotal clinical trials maintain randomisation for only a relatively short period compared with the natural course of the disease.

The establishment of the risk sharing scheme has allowed thousands of patients to have access to certain multiple sclerosis drugs and has been the catalyst for major changes in the management of multiple sclerosis, including substantial increases in the number of centres with specialist multi-disciplinary teams. From the perspective of patients with MS, these are all positive developments. This has, however, been achieved by use of NHS resources, which would otherwise have been available for the treatment of other patients. Whether the gain to patients with MS exceeds the loss to those unidentifiable other individuals remains unresolved.

The MS risk sharing scheme could be better termed as "coverage with evidence development" (CED), which has been used in the past few years in the US, Australia, Canada, and Europe. This provides interim approval for reimbursement of a treatment, conditional on the collection of further evidence and review after a specified period.[11] This process allows patient

access to promising new treatments but manages that access in a coordinated way, generating additional evidence that is targeted to reduce uncertainties in a much more structured way than a traditional post-marketing study. While this sounds an attractive option, the comparison of contemporary observational data with historical cohorts is notoriously problematic.

Summary

The UK MS-RSS was an innovative approach to collect new cost effectiveness data as part of an observational clinical cohort study. The two year results highlight many of the methodological difficulties of such an approach, including the inherent difficulty in using historical comparators and the major uncertainties around the interpretation of the current results. The primary analysis did not meet the pre-defined level for cost effectiveness, but, at this stage, it is not possible to determine reliably whether the current pricing of these drugs represent value for money for the NHS. Longer term follow-up will reduce some of the uncertainties arising from short term fluctuations in EDSS score and will provide new empirical evidence to confirm or refute some of the assumptions made by the NICE committee when considering the cost effectiveness of disease modifying treatments.

We acknowledge the contribution of Cindy Cooper and Mark Pickin in relation to patient recruitment to the scheme.

Contributors: See bmj.com.

Funding: The central costs of data collection and analysis were shared in five equal amounts between the Department of Health and the four pharmaceutical companies (Bayer Schering Pharma, Biogen, Merck Serono, Teva). Treatment costs (drug and staff) were largely met by local commissioners, with financial support for nursing and other staff from the companies and the MS Society. Analysis and interpretation of results and drafting of the manuscript were undertaken by a group independent of the study sponsors.

Competing interests: MB and JP have received support for attending international congresses from each of the four pharmaceutical companies funding the study. CD is an employee of the Department of Health and was involved in the negotiation of the original risk sharing scheme.

Ethical approval: This study was approved by the South East multicentre research ethics committee (02/10/78).

Data sharing: Data from the scheme may be available for collaborative studies, applications should be made to the scientific advisory group via the clinical leads (JP, MB).

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From our archive

The late Matron Wardroper (1892)

I saw her first in October, 1854, when the expedition of nurses was sent to the Crimean war. She had been then nine months matron of the great hospital in London, of which for thirty-three years she remained head and reformer of the nursing. Training was then unknown. The only nurse worthy of the name that could be given to that expedition, though several were supplied, was a "sister" who had been pensioned some time before, and who proved invaluable. I saw her next after the conclusion of the Crimean war. She had already made her mark. She had weeded out the inefficient, morally and technically; she had obtained better women as nurses; she had put her finger on some of the most flagrant blots, such as the night nursing, and where she laid her finger the blot was diminished as far as possible, but no training had yet been thought of.

Her force of character was extraordinary; her word was law. For her thoughts, words, and actions were all the same. She moved in one piece. She talked a great deal, but she never wasted herself in talking; she did what she said. Some people substitute words for actions; she never. She knew what she wanted, and she did it. She was a strict disciplinarian; very kind, often affectionate, rather than loving. She took such intense interest in everything, even in things matrons do not generally consider their business, that she never tired. She would be quite late in decorating the chapel at Christmas and Easter with her own hands. She had great taste, and spent her own money. She was a thorough gentlewoman, nothing mean or low about her; magnanimous and generous, rather than courteous.

And all this was done quietly. Of late years the great nursing work has been scarred by fashion on one side, and by mere money-getting on the other—two catastrophes sure to happen when noise is substituted for silent work. Few remember her in these express-train days, dashing along at 60 years in a day.

Florence Nightingale. The reform of sick nursing and the late Mrs Wardroper. *BMJ* 1892;2:1448.

The entire archive of the *BMJ*, going back to 1840, is now available at www.bmj.com/archive.

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Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis

Tom Jefferson,[1] Mark Jones,[2] Peter Doshi,[3] Chris Del Mar[4]

EDITORIAL by Godlee and Clarke
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ANALYSIS, p 1348

[1]Acute Respiratory Infections Group, Cochrane Collaboration, Rome, Italy
[2]University of Queensland, School of Population Health, Brisbane, Australia
[3]Program in History, Anthropology, Science, Technology and Society, Massachusetts Institute of Technology, Cambridge, MA, USA
[4]Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia
Correspondence to: C Del Mar
cdelmar@bond.edu.au

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STUDY QUESTION Do neuraminidase inhibitors prevent or ameliorate seasonal influenza's transmission, symptoms, or complications, and how safe are they?

SUMMARY ANSWER Neuraminidase inhibitors reduce the transmission of seasonal influenza and reduce the duration of symptoms by about half to one day, but published data are insufficient to know if they reduce complications or are safe. Independent randomised trials to resolve these uncertainties are needed.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS This update of a Cochrane review confirms previous findings of neuraminidase inhibitors on the amelioration of seasonal influenza symptoms and transmission. It found unexpected uncertainty about the previous result that oseltamivir reduces the complications of lower respiratory tract infections.

Selection criteria for studies

We searched the Cochrane central register of controlled trials (*Cochrane Library* 2009, issue 2), which contains the Acute Respiratory Infections Group's specialised register, Medline (1950-Aug 2009), and Embase (1980-Aug 2009). We also searched for post-marketing pharmacovigilance data and comparative safety cohorts.

EFFECT OF NEURAMINIDASE INHIBITORS ON INFLUENZA RELATED OUTCOMES

Outcomes	Effect
Prevention of symptoms	Prevent symptoms of influenza but not of influenza-like illness
Duration of symptoms	Shorten duration of symptoms provided they are taken within 48 hours of onset
Transmission	Prevent transmission in households
Complications	Unknown effect; zanamivir might reduce complications, but evidence for oseltamivir is lacking
Harms	Mainly cause gastrointestinal harms
Nasal shedding of virus	Significance on reduction of nasal shedding is unknown

Primary outcome(s)

The main outcomes were the duration and incidence of symptoms; the incidence of lower respiratory tract infections or their proxies (antibiotics prescribed, admissions to hospital); and adverse events.

Main results and role of chance

The efficacy of oral oseltamivir 75 mg daily against symptomatic laboratory confirmed influenza was 61% (risk ratio 0.39, 95% confidence interval 0.18 to 0.85). Inhaled zanamivir 10 mg daily was 62% efficacious (0.38, 0.17 to 0.85). Oseltamivir for postexposure prophylaxis within households had an efficacy of 58% (95% confidence interval 15% to 79%) in one trial and 84% (49% to 95%) in another. Zanamivir performed similarly. Both alleviated the symptoms of influenza-like illness: hazard ratios were 1.20 (95% confidence interval 1.06 to 1.35) for oseltamivir and 1.24 (1.13 to 1.36) for zanamivir. Oseltamivir did not reduce influenza related lower respiratory tract complications (risk ratio 0.55, 95% confidence interval 0.22 to 1.35). There is little generalisable information on zanamivir. From trial evidence, oseltamivir induced nausea (odds ratio 1.79, 95% confidence interval 1.10 to 2.93). Evidence from pharmacovigilance of rarer adverse events was of poor quality or possibly under-reported.

Bias, confounding, and other reasons for caution

Generalising some of the findings to influenza-like illness is uncertain because some trials were carried out in settings with very high proportions of laboratory confirmed influenza.

Study funding/Potential competing interests

This study was supported by the National Health and Medical Research Council (Australia) and the National Institute for Health Research (UK). CDM has provided expert advice to GlaxoSmithKline about vaccination in an unrelated area. TJ was a paid ad hoc consultant to Roche from 1998-9.

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Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: a randomised controlled trial

Kari Johansson,[1] Martin Neovius,[1 2] Ylva Trolle Lagerros,[1 2] Richard Harlid,[3] Stephan Rössner,[1] Fredrik Granath,[2] Erik Hemmingsson[1]

EDITORIAL by Marshall and Grunstein

[1]Obesity Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden
[2]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet
[3]Aleris Fysiologlab, Stockholm
Correspondence to: K Johansson, Obesity Unit, M73, Karolinska Institutet, Department of Medicine, SE-141 86 Stockholm, Sweden
kari.johansson@ki.se

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STUDY QUESTION Does weight loss induced by a very low energy diet (2.3 MJ/day for seven weeks followed by two weeks' gradual increase to 6.3 MJ/day) reduce moderate and severe obstructive sleep apnoea in obese men?

SUMMARY ANSWER After nine weeks, the study showed a 67% reduction in apnoea hypopnoea index (AHI) in the group allocated to very low energy diet, with the greatest effect seen in patients with severe disease, whereas no change occurred in the weight stable control group.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS One randomised controlled trial that assessed the effect of weight loss on mild obstructive sleep apnoea in obese men showed reduced AHI after weight loss. This study shows that obese men with moderate, and particularly with severe sleep apnoea, also benefit from weight loss.

This is a summary of a paper that was published on bmj.com as *BMJ* 2009;339:b4609

Design
Single centre, two arm, parallel, randomised, controlled, open label trial. A blocked randomisation procedure was used for treatment allocation.

Participants and setting
Sixty-three obese men (body mass index 30-40 kg/m^2; age 30-65 years) with moderate to severe obstructive sleep apnoea (AHI ≥15) treated with continuous positive airway pressure.

Primary outcome
AHI, the major disease severity index for obstructive sleep apnoea. AHI was derived from two consecutive nocturnal sleep studies in the home at baseline and after nine weeks.

Main results and the role of chance
Of 63 eligible patients, 30 were randomised to intervention and 33 to control. Two patients in the control group were dissatisfied with allocation and immediately discontinued. All other patients completed the trial. Data from all randomised patients were included in an intention to treat analysis (baseline carried forward for missing data). Both groups had a mean AHI of 37 events/hour at baseline. At week nine, the difference between groups in AHI was 23 events/hour (95% CI 15 to 30) and 20 kg (95% CI 18 to 21) in body weight, favouring the intervention group. In the intervention group, five patients (17%) were disease free after the energy restricted diet (AHI <5) and 15 (50%) had mild disease (AHI 5-14.9), whereas AHI remained at 15 or greater in all controls. In the intervention group, patients who had severe (AHI >30) sleep apnoea at baseline showed a greater reduction in AHI than those who had moderate (AHI 15-30) sleep apnoea at baseline (AHI -38 *v* -12, P<0.001), despite the groups having similar weight loss (-19 kg *v* -18 kg, P=0.55).

CHANGES IN ADIPOSITY AND OBSTRUCTIVE SLEEP APNOEA MEASURES BETWEEN BASELINE AND WEEK NINE

	Intervention (n=30)	Control (n=33)	Mean difference	P
AHI (events/h)	-25 (17)	-2 (11)	-23 (-30 to -15)	<0.001
Weight (kg)	-18.7 (4.1)	1.1 (1.9)	-19.8 (-21.4 to -18.2)	<0.001
Waist circumference (cm)	-18.7 (3.0)	-1.0 (2.4)	-17.7 (-19.1 to-16.3)	<0.001
Neck circumference (cm)	-3.8 (1.2)	0.4 (1.1)	-4.2 (-4.8 to -3.6)	<0.001

Data are mean (SD) or mean (95% CI); P values from independent samples t tests

Harms
Eight adverse events were classified by the study physician as likely to be causally linked with the very low energy diet. These were constipation (n=3), raised alanine aminotransferase levels (n=2), dizziness (n=1), gout (n=1), and dry lips (n=1). All noted adverse events were transient and not present at week nine.

Bias, confounding, and other reasons for caution
The study duration was short. The long term impact of weight loss by a very low energy diet on moderate to severe obstructive sleep apnoea needs further investigation.

Generalisability to other populations
These findings are valid for middle aged, obese men with moderate and severe obstructive sleep apnoea. Further studies are needed to assess whether weight loss by a very low energy diet has the same effect in women and in other age groups.

Study funding/Potential competing interests
This study was partly supported by a grant from Cambridge Manufacturing Company Limited and Novo Nordisk Scandinavia AB. None of the authors reports any competing interest.

Trial registration number
Current Controlled Trials ISRCTN70090382