# TSH and free-T3 correlate negatively and independently with bone mineral density in adults with subclinical hypothyroidism

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## Introduction

The role of the thyrotropin receptor (TSHR) in bone is unclear. TSHR-deficient mice have low bone mineral density (BMD) and focal osteosclerosis despite normal thyroid hormones (suggesting TSHR function, in bone, is important) (Abe *et al* 2003). Subclinical Hypothyroidism (SH) has various aetiologies including thyroid autoimmunity and inactivating TSHR mutations (TSHR-M). In TSHR-deficiency & TSHR-M elevated TSH compensates for reduced TSHR function (Camilot *et al* 2005), whereas in thyroid autoimmunity it compensates for reduced thyroid synthetic responsiveness (inflammation mediated). We hypothesised differential bone effects in SH relating to these causes.

## Aims of the study

- To explore whether TSH associates with BMD and bone turnover (BT) in an SH cohort.
- To explore whether aetiology of SH influences BMD and BT.

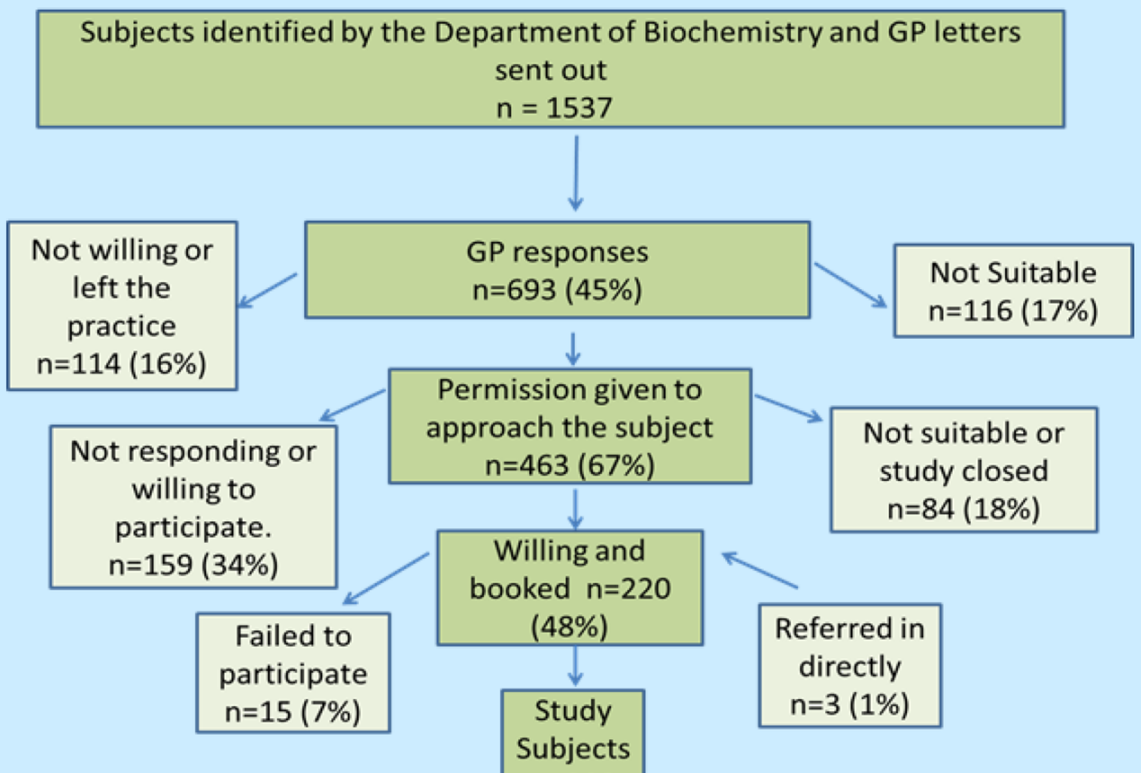
## Methods

208 adults (18-70 years of age) with primary untreated SH (TSH ≥5mU/L) and free of known bone disease were recruited.

A medical/lifestyle history, anthropometric data and blood samples were collected (free-T3, free-T4, TSH, anti-TPO antibodies (categorised as positive (+ve) or negative (-ve)), BT markers [CTX, P1NP]). Mutational screening of the entire TSHR coding region was undertaken by dHPLC and confirmed by direct sequencing.

A DXA bone scan (Lumbar Spine (LS) and hip) generated Z-scores (relative to age/sex-matched normals (BMD-Z)). These are expressed as a number of standard deviations (SD) the subjects value lies above or below the mean. The relationship between parameters of interest were explored using stepwise multivariate regression analyses using Excel and Minitab software.

The subject recruitment process is summarised in the flow diagram below.

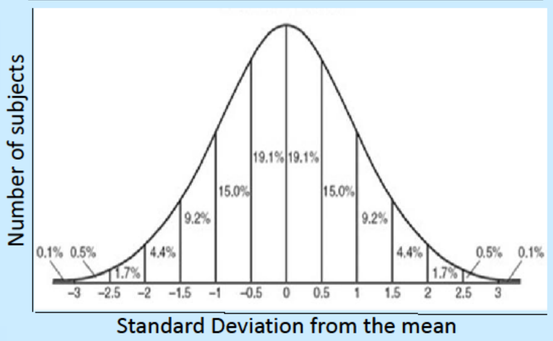



## Results

Cohort characteristics; 75% female (consistent with the epidemiology of SH), 90% Caucasian (reflecting local ethnic makeup) and the median age of participants was 51 years. 50% were TPO antibody +ve (indicating an autoimmune aetiology rather than 'other' causes that include genetic variation) and 6% (n=12) had loss of function mutations.

Total cohort data revealed a higher than expected rate of low BMD at LS (27% with Z-score <1 SD (vs 16% expected); 2.5% with Z score more than 2.5 SDs below the mean (vs 0.6% expected according to a perfect 'Normal' distribution).

Illustration of a perfect Normal Distribution

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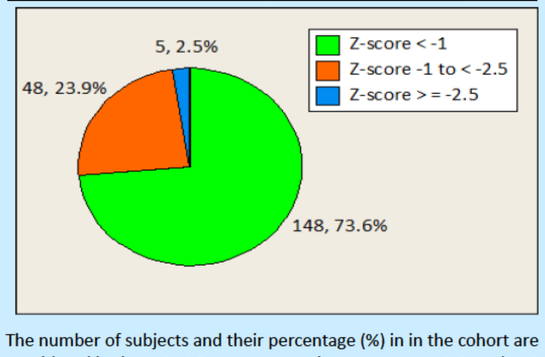
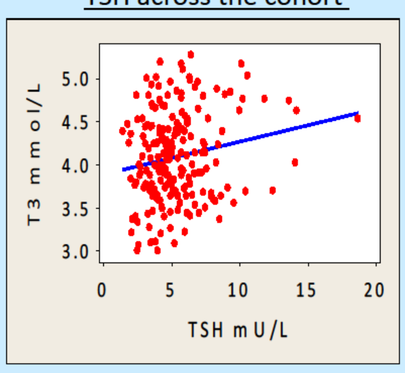
Pie Chart of Lumbar Spine Z-score categories



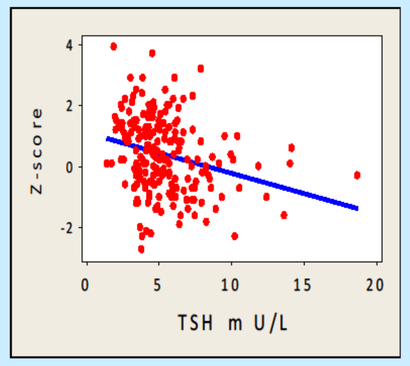

The number of subjects and their percentage (%) in in the cohort are considered in three DXA Z-score categories; <-1, -1 to <-2.5, and > -2.5. The lowest Z-score at any site determines the Z-score category.

An unexpected positive association between TSH and free-T3 was apparent across the cohort (R +0.04, p-value 0.009) as quantified by the correlation coefficient 'R'. After adjustment for potential confounders TSH associated negatively with BMD-Z at LS (R= -1.7, p<0.001) whereas free-T3 associated negatively with BMD-Z (but to a much smaller extent) at hip and LS (hip: R = -0.35, p=0.005; LS: R= -0.5, p=0.002). Free-T4 showed no independent associations. The figures below illustrate the crude, unadjusted associations.

Relationship between free-T3 and TSH across the cohort




Total Lumbar Spine Z-score vs TSH across the cohort

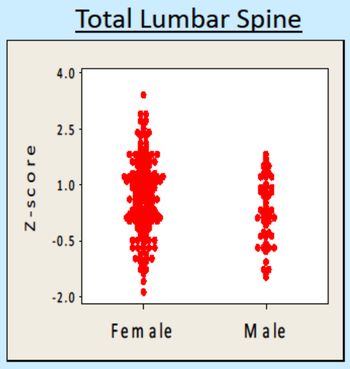



In these regression scattergraphs red dots indicate individual subject values and the blue line indicates the best linear relationship between parameters.

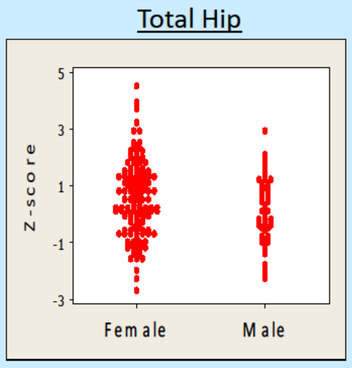
Stratification by SH aetiology showed no influence of TSHR-M on BMD-Z (despite lower free-T3 relative to TSH (R= -0.34, p=0.01) but TPO +ve associated negatively with BMD-Z at LS (R= -0.65, p<0.001). Male gender associated negatively with BMD-Z at all sites (R= -0.8, p=0.001). The BT markers did not associate with either thyroid function or BMD.

DXA Z-score according to Gender

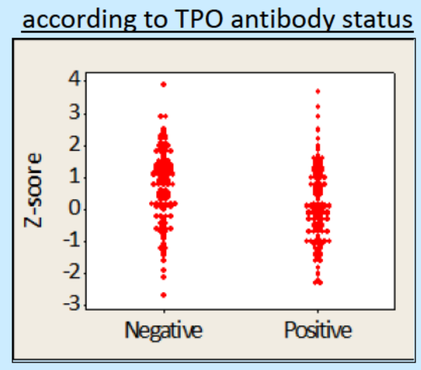
Total Lumbar Spine




Total Hip




Total Lumbar Spine Z-score according to TPO antibody status




In these individual value plots red dots indicate subject Z-scores which collectively depict the category distribution (Female vs Male, or TPO positive vs negative).

## Conclusions

SH appears to have a negative effect on BMD in adults. Negative associations between BMD and free-T3, TSH, male gender and TPO antibody positivity are revealed. If these associations reflect causation it indicates that bone health should be actively evaluated in SH, particularly in those who are male, have thyroid autoimmunity, and in those with any additional risk factors for Osteoporosis.

## References

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- Camilot M, Teofoli F, Gandini A, Franceschi R, Rapa A, Corrias A, Bona G, Radetti G, Tatò L. Thyrotropin receptor gene mutations and TSH resistance: variable expressivity in the heterozygotes. Clin Endocrinol (Oxf) 2005; 63:146–151.

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