

The relationship between intact parathyroid hormone and 25-hydroxyvitamin D in United Kingdom resident south asians and whites: A comparative, cross-sectional observational study

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4 **Title:** The relationship between intact parathyroid hormone and 25 hydroxyvitamin D in United
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6 Kingdom resident South Asians and Whites: a comparative, cross-sectional observational study.
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8 **Running Title:** Ethnic differences in iPTH and 25(OH)D
9

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4 **Abstract**
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6 **Introduction:** Ethnic differences in intact parathyroid hormone (iPTH) at similar total 25
7 hydroxyvitamin D (25(OH)D) concentrations have been reported between US resident Whites,
8 Blacks and Hispanics, but this has not been studied between South Asians and Whites. We,
9 therefore, compared the iPTH relationship to 25(OH)D in UK resident South Asians and Whites.
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15 **Methods:** A comparative, cross-sectional observational study in which demographic and
16 laboratory data on South Asian and White residents of Wolverhampton, UK were analyzed. Log-
17 log models measured the association between 25(OH)D and the interaction term of ethnicity and
18 iPTH.
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25 **Results:** Seven hundred and seventy-two patients consisting of 315 white subjects (208 women)
26 and 457 South Asian subjects (331 women) were studied. Compared to South Asians, White
27 subjects were older, had higher serum concentrations of 25(OH)D, creatinine (lower eGFR),
28 adjusted calcium and magnesium, but similar concentrations of iPTH and phosphate. In an
29 adjusted model, variables significantly associated with 25(OH)D included age, creatinine,
30 adjusted calcium and ethnicity; but not iPTH and the interaction term of ethnicity and iPTH (beta
31 coefficient -0.071, 95% CI -0.209, 0.067, p=0.32).
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41 **Conclusion:** In our study cohort, iPTH was not, per se, influenced by 25 (OH)D. We found
42 no ethnic differences in the association between iPTH and 25(OH)D between South Asians
43 and White UK residents
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50 **Keywords:** Vitamin D, Parathyroid hormone, South Asians, White, ethnicity
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4 **Introduction**
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7 Differences in iPTH at similar 25(OH)D levels have been reported between US resident Whites,
8 Blacks and Hispanics [1] and serum PTH rises at a lower 25(OH)D threshold in black women
9 compared to white women [2] but this is controversial [3]. It is, therefore, possible that there are
10 ethnic differences between South Asians and Whites in their iPTH relationship to 25(OH)D but
11 this has not been studied.
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21 New Cross Hospital serves the multi-ethnic population of Wolverhampton (United Kingdom) and
22 its environs. Vitamin D deficiency is common in Wolverhampton [4]. This may be related to
23 limited sunlight (latitude 52.6° N) but also in part to its relatively large local South Asian
24 population, since South Asians in the UK have a higher prevalence of vitamin D deficiency
25 compared to the general population [5, 6]. We present data on iPTH and 25(OH)D investigating
26 possible South Asian-White differences in the association between iPTH and 25(OH)D.
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37 **Materials and Methods**
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39 **Subjects**
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41 In a six month period between April and September, surplus serum from patient samples in which
42 vitamin D had been requested, were identified as part of a service evaluation to assess the local
43 need for ethnic derived iPTH reference intervals. Permission to publish hospital data of the
44 service evaluation has been granted by the Caldicott guardian.
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52 Demographic data on ethnicity, sex, age and medical history were collected from the clinical
53 request form, laboratory computer system and hospital electronic medical records. Test results
54 were obtained from the laboratory computer system. Samples from patients with bone disease,
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4 renal disease, bowel disease, hepatic disease, cancer and electrolyte abnormalities were
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6 excluded. Other exclusion criteria included subjects aged less than 18 years, pregnancy,
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8 supplemental calcium and/or vitamin D, and those whose ethnicity was unknown. Samples and
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10 demographic data were then anonymised.
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15 Blood samples had been collected into Sarstedt serum gel Z/4.7 mL tubes (Sarstedt, Numbrecht,
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17 Germany), centrifuged at 3000g for five minutes and serum separated within 8 hours of collection.
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19 The separated serum was stored frozen -80°C until analysis. Prior to analysis, samples were
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21 thawed, centrifuged at 3000g for five minutes and batched for analysis of serum iPTH, calcium,
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23 magnesium, phosphate, albumin and creatinine.
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29 **Laboratory Methods**

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31 Serum 25(OH)D2 and 25(OH)D3 were measured by the reversed phase LC-MS/MS ⁷ with five
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33 levels of IQC to assure assay performance. The lower limit of quantitation was 5 nmol/L for both
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35 25(OH)D2 and 25(OH)D3. The inter-assay coefficients of variation (CV) were <12% for
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37 25(OH)D2 and 25(OH)D3 over the range 18 – 200 nmol/l.
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43 Serum iPTH was measured using Roche's electrochemiluminescence immunoassay on a Roche
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45 MODULAR ANALYTICS E170 platform (Roche Diagnostics, Mannheim, Germany GmbH). Inter-
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47 assay CVs were < 5% in the range 5.45 - 77.6 pmol/l.
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52 Serum calcium, magnesium, phosphate, albumin and creatinine were analysed on Roche P
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54 modular platform using reagents and methodology supplied by Roche Diagnostics (Roche
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56 Diagnostics, GmbH Mannheim, Germany). The eGFR was calculated according to the simplified
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4 Modification of Diet in Renal Disease Study (MDRD) equation [8]. Calcium was adjusted for
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6 albumin using a locally derived equation [9].
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11 All analytical methods were enrolled in appropriate external quality assurance schemes and
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13 performed within acceptable limits throughout the study and were performed in a fully accredited
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15 laboratory
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20 **Statistical Analysis**

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22 Frequency counts and percentages were used to describe categorical data (sex and ethnicity).
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24 The Kolmogorov and Smirnov method was used to assess normality of data. Mean with standard
25
26 deviation was used to describe continuous parametric data. Non-parametric variables were
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28 transformed logarithmically; for these geometric means were presented with 95% confidence
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30 intervals (95% CIs).
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34 Differences in ethnicity, age, sex, and other biochemical variables were tested using either chi
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36 squared or independent sample t tests. A log-log model was constructed to test the association
37
38 between 25(OH)D (dependent variable) and iPTH. This model was first run unadjusted, then
39
40 secondly adjusted for age, sex, ethnicity, magnesium, adjusted calcium, and creatinine. An
41
42 interaction term between ethnicity and iPTH was included in the model to see whether the
43
44 relationship between iPTH and 25(OH)D was modified by ethnicity.
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49 For the regression models, beta coefficients (B) with 95% CIs are presented. All statistical
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51 analyses were conducted in Stata 14.0 (StataCorp) and Analyse –IT (Analyse-it Software, Ltd,
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53 Leeds, UK)
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4 **Results**
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6 Demographic and biochemical data of 772 patients studied and stratified by ethnicity are shown
7 in Table 1. All patients had concentrations of 25(OH)D2 below the detection limit of the assay and
8 therefore in this evaluation total 25(OH)D corresponds to 25(OH)D3. The data distribution of
9 iPTH and total 25(OH)D in Whites and South Asians is shown in Figure 1.
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18 The white cohort was older and had lower eGFR but higher serum concentrations of 25(OH)D,
19 creatinine, adjusted calcium and magnesium than South Asian patients. Serum iPTH and
20 phosphate concentrations were similar in White and South Asian patients.
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27 The results of the log-log model are shown in Table 2. In the unadjusted model, all variables
28 except the interaction term were associated with 25(OH)D. In the adjusted model, the only
29 variables that remained significantly associated with 25(OH)D were age, creatinine, adjusted
30 calcium, and ethnicity. The interaction term of ethnicity remained and iPTH became not-
31 significantly associated with 25(OH)D.
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39 **Discussion**
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41 Although our patient cohort consisted of those in whom vitamin D had been requested, our data
42 are consistent with those reporting lower serum vitamin D levels in South Asians compared to
43 Whites [5,6].
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50 The weak inverse unadjusted association between iPTH and 25(OH)D became non-significant
51 after adjustment for sociodemographic and biochemical factors. These results are consistent with
52 studies which similarly have failed to confirm an association between iPTH and 25(OH)D [10, 11]
53 but at variance with those reporting an inverse relationship between serum iPTH and serum
54 25(OH)D [12, 13]. Differences between these studies may reflect differences in study populations
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4 and analytical methods. It is worth noting that the first generation competitive PTH immunoassays
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6 used a single polyclonal antibody directed against C-terminal epitopes and measured not only
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8 biologically active intact PTH (iPTH) but also many biologically inactive PTH fragments. These
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10 were replaced by the currently widely used two site immunometric PTH assays which use one
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12 antibody directed at the C-terminal sequence and another at N-terminal sequence and therefore
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14 are more specific iPTH measurement.
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19 This study found no differences between UK resident South Asian and White patients in their
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21 iPTH relationship with 25(OH)D, even after adjusting for variables associated with 25(OH)D.
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23 Furthermore, the interaction term (ethnicity and iPTH) was not significantly associated with
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25 25(OH)D indicating that the relationship between iPTH and vitamin D was similar in South Asians
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27 and Whites. Our data are consistent with a large USA study, reporting no differences in PTH
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29 concentrations in black, Hispanic and white men despite lower 25(OH)D in the black and Hispanic
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31 men [2]. In contrast, the National Health and Nutrition Examination Survey (NHANES) reported
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33 25(OH)D to be significantly lower but PTH significantly higher in Blacks and Mexican-Americans
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35 compared to Whites [3]. Differences between these studies may reflect differences in study
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37 populations, particularly ethnic mix, and analytical methods.
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43 A strength of our study was a large sample of an ethnic minority group allowing use of a range of
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45 statistical tests analyses without risk of type 2 statistical errors. We were also able to adjust for a
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47 range of variables associated with 25(OH)D, thereby minimising the risk of residual confounding.
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49 Our sample, however, may be susceptible to selection bias as the patient cohort encompassed
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51 those in whom vitamin D had been requested; how this sample differs from a general population
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53 sample remains unclear. Vitamin D, however, was lower in South Asians than Whites suggesting
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55 that our sample characteristics were not different compared to other published studies [5,6].
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57 Another limitation was magnesium not corrected for albumin but this is generally not
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4 recommended when serum magnesium and albumin are in the reference range as in this study.
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6 Data on fasting status and diet were not collected and since protein meals increase serum
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8 creatinine it is possible this may have affected the serum creatinine and eGFR results.
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11 **Conclusion**

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14 Our data indicates that 25 (OH)D, per se, does not have an effect on circulating iPTH after
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16 adjusting for sociodemographic and biochemical factors associated with 25 (OH)D . We have
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18 found no evidence to support the notion of ethnic differences between UK resident South Asians
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20 and Whites in their iPTH relationship with total 25(OH)D and therefore there is no need for ethnic
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22 derived iPTH reference intervals.
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Table Legends

Table 1: Demographic and biochemical data in White and South Asian patients

Results are means (SD)

*Geometric means presented with 95% CIs

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7 **Table 2:** Log-log model to test the association between total 25(OH)D against ethnicity and iPTH
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9 before and after adjustment for age, sex, ethnicity, magnesium, adjusted calcium, and creatinine

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12 Data expressed as coefficients (95% confidence intervals)

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16 **Figure Legends**

17 **Figure 1:** Distribution of iPTH and total 25(OH)D in Whites and South Asians
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7 **Figure 1.** Distribution of iPTH and total 25(OH)D in Whites and South Asians
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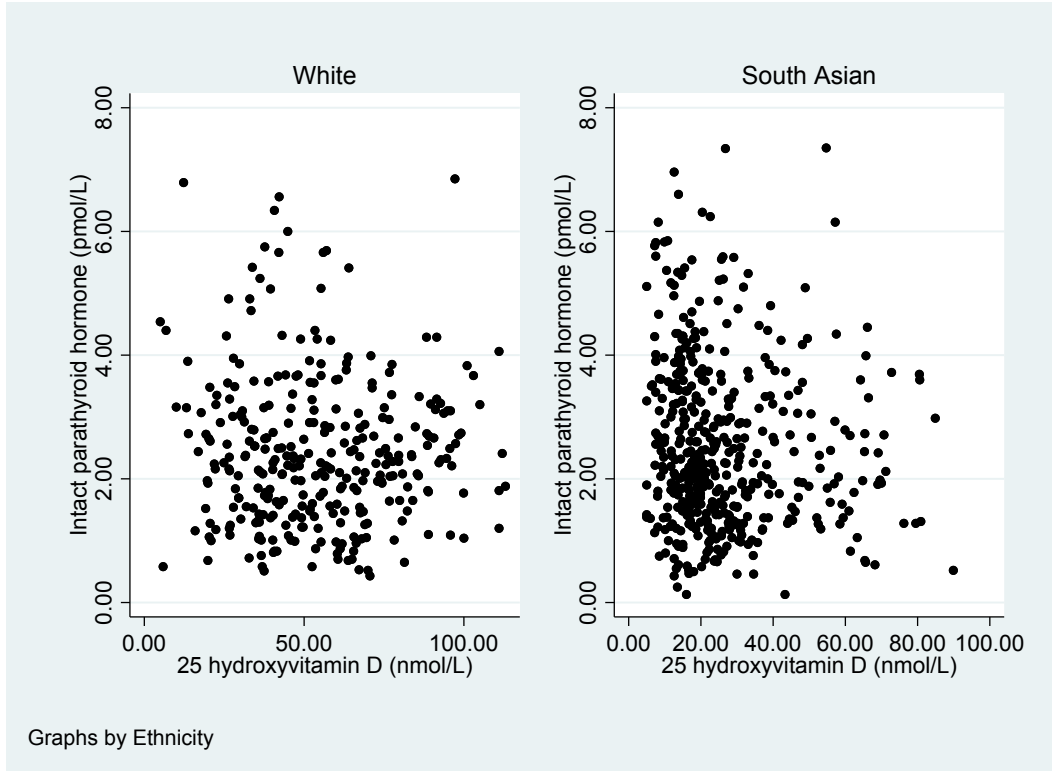


Table 1: Demographic and biochemical data in White and South Asian patients

	Reference Intervals	Overall n = 772	White n = 315	South Asian n = 457	p value White v South Asian
Age (years)		49.5 (13.9)	52.4 (13.5)	47.6 (13.8)	<0.001
Sex (% male)		30.2	34.0	27.6	0.06
iPTH (pmol/l)	1.9 – 6.9	2.49 (1.30)	2.43 (1.21)	2.53 (1.36)	0.29
*25(OH)D (nmol/l)	Adequate: 51 - 250 Insufficiency: 31-50	30.5 (29.1-32.0)	48.5 (45.8-51.3)	22.2 (21.0-23.4)	<0.001
eGFR (ml/min/1.73m ²)		92.7 (21.5)	86.9 (18.3)	96.7 (22.6)	<0.001
Creatinine (umol/l)	50 - 111	71.1 (14.0)	74.6 (13.7)	68.6 (13.7)	<0.001
Adjusted calcium (mmol/l)	2.2 -2.6	2.20 (0.09)	2.22 (0.09)	2.19 (0.08)	<0.001
Phosphate (mmol/l)	0.8 – 1.5	1.19 (0.18)	1.18 (0.19)	1.19 (0.18)	0.45
Magnesium (mmol/l)	0.7 – 1.0	0.85 (0.07)	0.86 (0.07)	0.84 (0.07)	0.001

Results are means (SD)

*Geometric means presented with 95%CIs

Table 2: Log-log model to test the association between total 25(OH)D against ethnicity and iPTH before and after adjustment for age, sex, ethnicity, magnesium, adjusted calcium, and creatinine

Variable	Unadjusted		Adjusted	
	B coefficients (95% CI)	p	B coefficients (95% CI)	p
Age	0.01 (0.01, 0.01)	<0.001	0.01 (0.00, 0.01)	0.001
Male (Ref: female)	0.23 (0.12, 0.33)	<0.001	0.01 (-0.09, 0.11)	0.810
South Asian (Ref: White)	-0.78 (-0.86, -0.70)	<0.001	-0.65 (-0.73, -0.57)	<0.001
iPTH (pmol/l)	-0.08 (-0.17, 0.00)	0.049	-0.10 (-0.17, -0.04)	0.300
Interaction term (ethnicity and iPTH)	-0.09 (-0.23, 0.06)	0.25	-0.07 (-0.21, 0.07)	0.320
Creatinine (umol/l)	0.01 (0.01, 0.02)	<0.001	0.01 (0.00, 0.01)	<0.001
Adjusted calcium (mmol/l)	1.13 (0.59, 1.67)	<0.001	-1.01 (-1.67, -0.34)	0.003
Magnesium (mmol/l)	0.90 (0.22, 1.58)	0.01	-0.23 (-0.79, 0.34)	0.430

Data expressed as coefficients (95% confidence intervals)