

**RAPID  
COMMUNICATION**

# Normocalcaemic, vitamin D-sufficient hyperparathyroidism – high prevalence and low morbidity in the general population: A long-term follow-up study, the WHO MONICA project, Gothenburg, Sweden

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## Summary

**Objective** There is limited knowledge about the natural history of normocalcaemic, vitamin D-sufficient hyperparathyroidism (nHPT). The aim was to study the prevalence of nHPT and its relation to morbidity.

**Design** Cross-sectional and retrospective study at the Sahlgrenska University Hospital, Gothenburg, Sweden.

**Subjects** A random population of 608 men and women, age 25–64 years, was studied in 1995 as part of the WHO MONICA study and reinvestigated in 2008 ( $n = 410$ , of whom 277 were vitamin D sufficient).

**Measurements** A serum intact parathyroid hormone (S-PTH)  $\geq 60$  ng/l was considered as HPT, S-calcium 2.15–2.49 mmol/l as normocalcaemia and S-25(OH)D  $\geq 50$  nmol/l as vitamin D sufficiency. Data on fractures, stroke and myocardial infarction were retrieved until 2013, that is a 17-year follow-up.

**Results** The prevalence of nHPT was 2.0% in 1995 (age 25–64) and 11.0% in 2008 (age 38–79). S-PTH was positively correlated with age and BMI. After adjustment for these variables, a high S-PTH level ( $\geq 60$  ng/l) at follow-up was associated with previously low S-25(OH)D, high osteocalcin, S-PTH and both past and presently treated hypertension. No relation was seen with creatinine, cystatin C, malabsorption markers, thyroid function, glucose, insulin, lipids, calcaneal quantitative ultrasound, fractures, myocardial infarction, stroke or death at follow-up.

**Conclusions** This small random population study showed that nHPT was common, 11% at follow-up. Only one individual developed mild hypercalcaemia in 13 years. Previous S-PTH was predictive of nHPT and hypertension was prevalent, but no increase in hard end-points was seen over a 17-year period.

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## Introduction

The serum intact parathyroid hormone (S-PTH) assay was introduced in the early 1990s and facilitated the diagnosis of primary hypercalcaemic hyperparathyroidism (pHPT).<sup>1</sup> In the past, patients with pHPT were commonly severely symptomatic at the time of diagnosis due to bone loss and kidney stones. Today the high availability of serum calcium (S-Ca) and S-PTH analyses facilitates earlier diagnosis, and the patients are often asymptomatic at the time of diagnosis.<sup>2</sup> In our clinical experience, the analyses of S-PTH have increased in recent years – irrespective of calcium aberrations – in the evaluation of patients with, for example, metabolic bone disease. A new group of patients has thereby been discovered, characterized by normal S-Ca and elevated S-PTH levels in the absence of vitamin D deficiency, renal disease or medications, which elevate S-PTH. This diagnostic entity has been named normocalcaemic primary HPT (nHPT).<sup>2–4</sup> No official recommendations for the follow-up and treatment of nHPT have been established due to the scarcity of data on the prevalence, natural history and outcome of medical or surgical management. Specialists in the field monitor patients with nHPT similarly as they monitor patients with asymptomatic mild pHPT.<sup>2,3</sup>

The natural history of long-standing nHPT and the rate of progression into pHPT are poorly known.<sup>5</sup> Most studies including S-PTH have been performed on referral groups of patients,

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mostly to bone and metabolic units.<sup>6,7</sup> In addition, it is uncertain which S-Ca level could be considered safe in patients with mild pHPT.<sup>8</sup> pHPT increases both fracture risk through bone loss and cardiovascular morbidity and mortality. There is also an association between higher S-PTH levels (within the normal range) and cardiovascular mortality in the absence of calcium aberrations and vitamin D deficiency.<sup>9,10</sup>

This study evaluates both the progression rate of nHPT into pHPT and the cardiovascular and skeletal morbidity in a random population sample without referral bias. We analyse S-PTH levels in relation to variables of calcium homeostasis, other hormone levels, body composition, medication, bone characteristics and blood pressure, with a follow-up of end-points (fractures, myocardial infarction, stroke and mortality) after 17 years. The hypothesis was that nHPT in vitamin D-sufficient subjects was associated with an increased risk of fractures and/or cardiovascular disease and could progress to pHPT.

## Materials and methods

### Subjects

A random population sample of men and women ( $n = 2400$ , aged 25–64 years) from the city census was investigated in 1995 in Gothenburg, Sweden (latitude 57°N), as part of the World Health Organization MONItoring of trends and determinants for CArdiovascular disease (WHO MONICA) project. Bone and body composition measurements and hormonal blood sampling were performed on a subset of participants ( $n = 608$ ), including all the women in the age group 45–64 years, every fourth woman aged 25–44 and every fourth man in all age groups (25–64, randomly selected). These individuals were invited to a re-investigation in 2008–2009 (participation rate 67%,  $n = 410$ ). Fifty-five subjects could not be reached or were deceased. Non-attendance was due to travelling, living abroad, difficult family circumstances or unwillingness to participate. One subject had been excluded from the study due to renal insufficiency. The study was approved by the Ethics Committee of the University of Gothenburg and the National Data Inspection Board, and all participants gave their written informed consent. The Declaration of Helsinki was followed.

### Anthropometry

Body weight was measured to the nearest 0.1 kg in the fasting state with the subject in underwear only. Body height was measured to the nearest 1 cm. Body mass index (BMI) was calculated as body weight divided by height squared ( $\text{kg}/\text{m}^2$ ). Waist circumference was measured with a soft tape midway between the lowest rib margin and the iliac crest in the standing position. The hip circumference was measured over the widest part of the gluteal region, and the waist/hip circumference ratio was calculated. A single operator performed the measurements on both occasions. Blood pressure is reported as the mean of three consecutive measurements in the sitting position with a random-zero sphygmomanometer (Hawksley & Sons).

### Bioimpedance and bone measurement

Fat-free mass and body fat were estimated using impedance measurements (SEAC Multiple frequency bioimpedance meter, model SFB 2, UniQuest Ltd., Brisbane, Queensland Australia), based on total body resistance and reactance. Calcaneal Quantitative UltraSound (QUS; LUNAR Achilles) was performed as previously described in detail.<sup>11</sup> Speed of sound (SOS) and broadband ultrasound attenuation (BUA) were measured, and stiffness index in relation to young subjects was estimated.

### Blood samples

Fasting venous blood samples were collected in the morning; in menstruating women on cycle day 7–9. Blood samples were obtained from January to June and from September to December in comparable monthly proportions (Table 1), similarly at start and at follow-up. S-25(OH)D was measured with a radioimmunoassay 125I RIA kit (DiaSorin, Stillwater, MN, USA). The total coefficient of variation (CV) was 12.5% for the mean level of 36.2 nmol/l, 15.3% for 57.0 nmol/l and 14.0% for 147.5 nmol/l. S-1,25(OH)<sub>2</sub>D was also determined using the 125I RIA kit (DiaSorin). The total CV was 14.9% for the mean level of 49.9 pmol/l. S-PTH was determined by immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The intra-assay CV was 10% for the interval 4–10 ng/l and 6% for the interval 11–30 ng/l; the total CV was 6%. S-osteocalcin was determined by radioimmunoassay.

Serum-free T4 and TSH were measured with the ECLIA Modular immunometric method (Roche, Mannheim, Germany).

Thyroxine peroxidase antibodies (S-anti-TPO), vitamin B12, S-Ca, creatinine, cystatin C, lipids, alkaline phosphatase (S-ALP), phosphate, iron and cortisol, all from serum, and glucose and homocysteine from plasma were analysed by routine methods. Similar methods were used at start and follow-up. A S-PTH  $\geq 60$  ng/l was considered as HPT and a S-Ca level of 2.15–2.49 mmol/l as normocalcaemia. Vitamin D insufficiency was defined as S-25(OH)D  $< 50$  nmol/l.<sup>4,12</sup> nHPT was defined as normocalcaemia and elevated S-PTH and S-25(OH)D  $\geq 50$  nmol/l. pHPT as hypercalcaemia combined with elevated S-PTH and secondary HPT (sHPT) as hypocalcaemia (S-Ca  $< 2.15$  mmol/l) and elevated S-PTH.

### Pharmacological treatment and nutrition

Ongoing pharmacological treatment was inquired with similar questionnaires in 1995 and 2008 and coded according to the Anatomical Therapeutic Chemical (ATC) Classification System. Similar questionnaires in 1995 and 2008 were used for the assessment of intake of dairy products and degree of physical activity 1–4 (low to high) at work and at leisure time.

### Fractures, myocardial infarction, stroke and other diseases

Records of X-ray-verified fractures deemed to be of osteoporotic origin (upper arm, wrist, ankle, leg, hip, pelvis, rib and vertebra)

**Table 1.** Subjects with nHPT, that is serum intact PTH  $\geq 60$  ng/l compared with subjects with normal S-PTH, both groups with serum 25(OH)D  $\geq 50$  nmol/l, assessed in 2008. Means  $\pm$  SD are given. *P*-value adjusted for age and body mass index (BMI) is given in the far right column. ALP, Alkaline phosphatase; BUA, broadband ultrasound attenuation; CVD, cardiovascular disease

Variable	PTH $\geq 60$ ng/l <i>n</i> = 45	PTH < 60 ng/l <i>n</i> = 232	<i>P</i> -value	<i>P</i> -value adjusted for age and BMI
<b>Clinical features</b>				
Age, years	66.3 $\pm$ 7.2	63.2 $\pm$ 9.2	0.0368	0.0606
Male, <i>n</i> (%)	7 (15.9%)	50 (21.7%)		
Female, <i>n</i> (%)	37 (84.1%)	180 (78.3%)	0.5130	0.5214
Height, cm	165.0 $\pm$ 9.7	166.9 $\pm$ 8.2	0.0800	0.6831
Height change 2008–1995, cm	−1.86 $\pm$ 1.20	−1.64 $\pm$ 1.22	0.1007	0.8424
Weight, kg	76.2 $\pm$ 13.6	72.6 $\pm$ 12.7	0.0442	0.6836
Weight change 2008–1995, kg	1.91 $\pm$ 0.63	1.95 $\pm$ 0.79	0.8451	0.9946
BMI, kg/m <sup>2</sup>	28.0 $\pm$ 4.7	26.0 $\pm$ 3.7	0.0089	0.0059
Waist, cm	93.6 $\pm$ 11.9	88.9 $\pm$ 11.7	0.0054	0.5942
Hip, cm	106.8 $\pm$ 7.8	104.3 $\pm$ 8.1	0.0715	0.6359
Waist/hip ratio	0.875 $\pm$ 0.085	0.852 $\pm$ 0.091	0.0611	0.5132
Syst. blood pressure, mmHg	141.0 $\pm$ 21.3	132.6 $\pm$ 20.9	0.0142	0.1983
Diast. blood pressure, mmHg	82.1 $\pm$ 10.1	89.8 $\pm$ 10.5	0.0414	0.3008
Body fat, kg	28.7 $\pm$ 10.4	24.6 $\pm$ 8.6	0.0098	0.6867
Fat-free mass, kg	48.0 $\pm$ 10.4	48.4 $\pm$ 9.6	0.8110	0.9610
<b>Biochemical analyses</b>				
S-Phosphate mmol/l	1.05 $\pm$ 0.17	1.08 $\pm$ 0.14	0.1996	0.4393
S-PTH, ng/l	73.4 $\pm$ 14.2	40.8 $\pm$ 9.6	<0.0001	<0.0001
S-Calcium, mmol/l	2.34 $\pm$ 0.08	2.36 $\pm$ 0.08	0.4363	0.1411
S-25(OH)D nmol/l	65.8 $\pm$ 13.8	77.7 $\pm$ 23.3	0.0005	0.0022
S-1,25(OH) <sub>2</sub> D, pmol/l	118.5 $\pm$ 42.7	127.2 $\pm$ 45.7	0.2167	0.4954
S-Osteocalcin, nmol/l	3.07 $\pm$ 1.15	2.86 $\pm$ 1.03	0.1477	0.0501
S-ALP, $\mu$ kat/l	1.26 $\pm$ 0.30	1.18 $\pm$ 0.32	0.0369	0.3801
S-Creatinine, $\mu$ mol/l	75.0 $\pm$ 15.9	70.8 $\pm$ 12.4	0.1206	0.0780
S-PTH 1995, ng/l	51.1 $\pm$ 13.7	36.5 $\pm$ 13.1	<0.0001	0.0004
S-Calcium 1995, mmol/l	2.43 $\pm$ 0.15	2.43 $\pm$ 0.12	0.7201	0.9984
S-25(OH)D 1995, nmol/l	53.8 $\pm$ 14.3	50.6 $\pm$ 14.7	0.3555	0.2677
S-25(OH)D < 50 nmol/l 1995, <i>n</i> (%)	22 (48.9%)	121 (52.2%)	0.8110	0.9610
S-Osteocalcin 1995, nmol/l	1.58 $\pm$ 0.42	1.44 $\pm$ 0.38	0.2467	0.0432
<b>Bone characteristics and CVD</b>				
BUA, dB/MHz 2008	105.7 $\pm$ 11.4	107.3 $\pm$ 10.9	0.6934	0.4188
BUA, db/MHz 1995	108.1 $\pm$ 9.8	109.0 $\pm$ 10.1	0.6655	0.8934
Fracture before 1995, <i>n</i> (%)	7 (15.6%)	43 (18.5%)	0.8150	0.8075
Fracture after 1995, <i>n</i> (%)	16 (35.6%)	65 (28.0%)	0.3991	0.8910
Any fracture in life, <i>n</i> (%)	23 (51.1%)	105 (45.3%)	0.5763	0.8099
Myocardial infarction, <i>n</i> (%)	3 (6.7%)	6 (2.6%)	0.1655	0.1577
Stroke, <i>n</i> (%)	4 (8.9%)	15 (6.5%)	0.7478	0.5561
<b>Medications 2008, <i>n</i> (%)</b>				
Calcium/vitamin D supplement	3 (6.7%)	34 (14.7%)	0.2200	0.1056
Anti-hypertensive medication	22 (48.9%)	63 (27.2%)	0.0081	0.0364
Bone-specific treatment*	3 (6.7%)	9 (3.9%)	0.6124	0.3353
Thiazides	3 (6.7%)	8 (3.4%)	0.5152	0.3878
<b>Medication 1995, <i>n</i> (%)</b>				
Calcium/vitamin D supplement	0 (0.0%)	0 (0.0%)		
Anti-hypertensive medication	9 (20.0%)	15 (6.5%)	0.0141	0.0376
Bone-specific treatment	0 (0.0%)	0 (0.0%)		
Thiazides	1 (2.2%)	1 (0.4%)	0.5980	0.4184
<b>Month S-PTH test in 2008, <i>n</i> (%)</b>				
January	4 (8.9%)	18 (7.8%)		
February	3 (6.7%)	27 (11.6%)		
March	10 (22.2%)	32 (13.8%)		
April	3 (6.7%)	35 (15.1%)		
May	6 (13.3%)	21 (9.1%)		

(continued)

Table 1. (continued)

Variable	PTH $\geq$ 60 ng/l <i>n</i> = 45	PTH < 60 ng/l <i>n</i> = 232	<i>P</i> -value	<i>P</i> -value adjusted for age and BMI
June	0 (0.0%)	8 (3.4%)		
July	0 (0.0%)	0 (0.0%)		
August	0 (0.0%)	0 (0.0%)		
September	0 (0.0%)	3 (1.3%)		
October	11 (24.4%)	33 (14.2%)		
November	5 (11.1%)	39 (16.8%)		
December	3 (6.7%)	16 (6.9%)	0.8905	0.8452

\*Mainly bisphosphonates.

according to ICD 10 codes S22, S32, S42, S52, S62, S72, S82, S92, T08, T10, T12, T14 along with records regarding myocardial infarction, haemorrhagic and nonhaemorrhagic stroke and death were retrieved from the Gothenburg hospital records via the National Board of Health and Welfare, Stockholm, Sweden, until 1 January 2013. Low-energy fractures were regarded as possible osteoporotic fractures, whereas other fractures related to accidents were not included. Only the first fracture is included in the analysis. The subjects were also asked about other diseases, neck and other surgery and kidney stones. Hypertension was considered when antihypertensive agents were used.

### Statistical methods

Means, medians and standard deviations (SD) were calculated using conventional methods. For comparison between groups, the Fisher's exact test was used for dichotomous variables, the Mantel-Haenszel chi-square test for ordered categorical variables and the Mann-Whitney *U*-test for continuous variables. Adjustments for age and BMI and logistic regression analyses were performed. Odds ratios (OR) were calculated with the chi-square test. A *P*-value of  $<0.05$  (two-sided test) was considered statistically significant.

## Results

### Prevalence of HPT in 1995 and at follow-up

At first assessment in 1995, 25 subjects had elevated S-PTH and normal S-Ca, of whom 12 of 608 were vitamin D sufficient thereby fulfilling the diagnostic criteria for nHPT, giving a prevalence of 2.0% in the age range 25–64 years (Table 1). At the reassessment of nHPT, 13 years later, five individuals were either deceased or lost to follow-up. Three of the remaining subjects had normalized their S-PTH levels and were vitamin D sufficient. One subject had nHPT both in 1995 and in 2008. Two had vitamin D insufficiency with elevated S-PTH levels. One woman had developed breast cancer, mild hypercalcaemia (2.55 mmol/l), but normal S-PTH (36 ng/l) and high S-25(OH)D (133 nmol/l) with a daily supplementation of 1000 mg Ca and 800 IU Vitamin D<sub>3</sub>; a possible progression to pHPT (Fig. 1). Two of seven had fractured during follow-up.

Of those with normal S-Ca, high S-PTH and vitamin D insufficiency in 1995, *n* = 13, (Fig. 1) four individuals out of the remaining eight were still in the same state and three had normalized at follow-up. One developed sHPT.

pHPT was found in nine of the 608 subjects (1.5%) in 1995 (Fig. 1). Mean S-Ca was  $2.69 \pm 0.16$  mmol/l, mean S-PTH  $71.7 \pm 9.1$  ng/l (range 60–84). Two of the nine subjects in 1995 were lost to follow-up, one of whom passed away and one moved from town. Despite the fact that the subjects with pHPT in 1995 had received no treatment for HPT, all had normal S-Ca levels at follow-up (mean S-Ca  $2.36 \pm 0.07$  mmol/l). Three had nHPT, one had vitamin D insufficiency and elevated S-PTH, and the remaining three had normal S-PTH (Fig. 1).

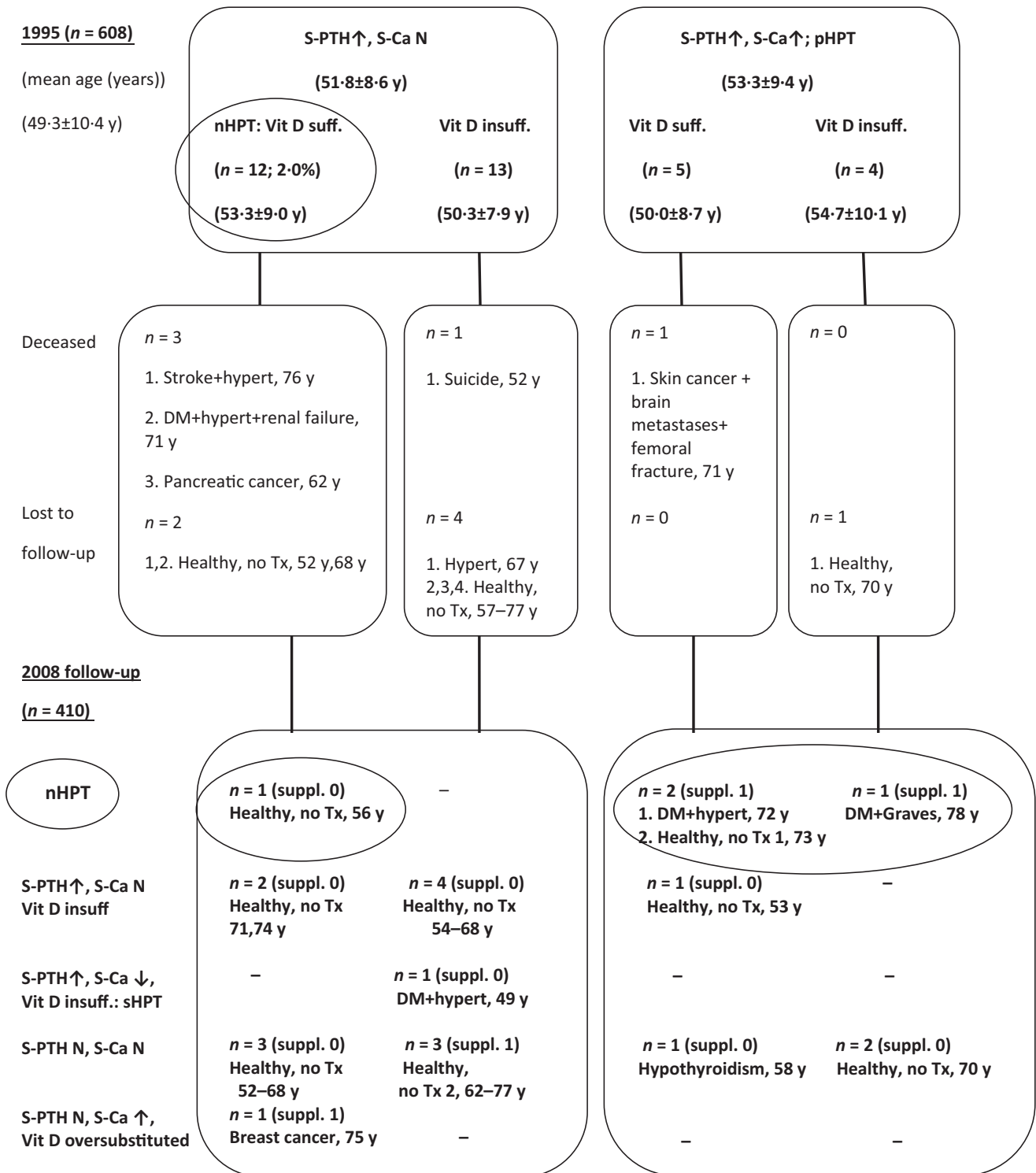
### Cross-sectional comparison of subjects with nHPT and subjects with normal S-PTH in 2008

At the re-examination in 2008, at the age of 38–79, nHPT was prevalent in 45 of 410 subjects (11%) of this random population sample. They were compared with 232 subjects (57%) with S-25(OH)D  $\geq 50$  nmol/l and normal S-PTH (Table 1). Of interest is that 133 of 410 (32%) had vitamin D insufficiency and were not included in the present analyses.

There was no gender or seasonal sampling difference between individuals with nHPT and vitamin D-sufficient individuals with normal S-PTH (Table 1). S-PTH was positively correlated with age and BMI; therefore, all reported statistical comparisons were adjusted for age and BMI in Table 1.

The prevalence of hypertension, determined by the use of antihypertensives, was higher, but S-25(OH)D was lower in nHPT than in subjects with normal S-PTH. There were no differences between groups regarding blood glucose, lipids, thyroid hormones, S-anti-TPO, vitamin B12, folic acid, phosphate, iron, creatinine, cystatin C, glucose, insulin, body height, weight, change in height or body weight or calcaneal QUS during 13 years (Table 1).

The subjects with nHPT had higher weekly intake (adjusted for age and BMI) of fat cheese (*P* = 0.0028) and cream (*P* = 0.0114), but lower intake of fatty fish (*P* = 0.0358) and vitamin D fortified low fat milk (*P* = 0.0154) than subjects with normal S-PTH. The calcium intake/day was above the recommended daily intake of 1000 mg/day in both groups. There were



**Fig. 1** Flow chart for subjects with a serum parathyroid hormone level  $\geq 60$  ng/l in 1995 and at follow-up 13 years later. Left square shows subjects aged 25–64 years with normal S-calcium (S-Ca) and elevated serum parathyroid hormone (S-PTH) levels in 1995 and at the re-examination 13 years later. Left square, left column shows the flow chart for nHPT. Right square shows subjects with pHPT in 1995 and at follow-up 13 years later, the WHO MONICA study, Gothenburg, Sweden. Right square, left panel shows the flow chart for subjects with vitamin D-sufficient pHPT. nHPT, normocalcaemic and vitamin D-sufficient hyperparathyroidism; pHPT, primary hyperparathyroidism; sHPT, secondary hyperparathyroidism; Vit D insuff., vitamin D insufficiency defined as S-25(OH)D < 50 nmol/l; Suppl., daily use of calcium/vitamin D supplementation; y, years; Tx, treatment; DM, diabetes mellitus; hypert, hypertension; N = normal

no significant differences in calcium/vitamin D supplementation (mainly 1000 mg calcium and 800 IU cholecalciferol) or thiazides between the two groups (Table 1). Physical activity at work or leisure time did not differ between groups.

Data from 1995 for the two groups compared in Table 1 showed a higher prevalence of hypertension and higher S-PTH and S-Osteocalcin levels in nHPT than in those with normal S-PTH in 2008. Notable is that the S-Ca and S-25(OH)D levels in 1995 did not differ between groups. The S-Ca levels in 2008 were evenly distributed within the normocalcaemic range in relation to S-PTH (Fig. 2).

No increase in the incidence of kidney stones, fractures, myocardial infarction (OR = 1.99, 95%CI 0.65–11.18;  $P = 0.16$ ) or stroke (OR = 1.41, 95%CI 0.45–4.47;  $P = 0.56$ ) during life or in mortality rates after 2008 was found in subjects with nHPT compared with subjects with normal S-PTH.

### Hypercalcaemia at the cross-sectional analyses in 2008

In 2008, 14 subjects with sufficient vitamin D levels (S-25(OH)D range 56–133; median 85 nmol/l) had elevated S-Ca levels and normal S-PTH. None had thiazide treatment, and four had calcium/vitamin D supplementation. One woman underwent surgery for mammary cancer; otherwise no malignancies were known. One of these individuals had nHPT in 1995 (mentioned above with specification of analysis results), and the others had normal S-PTH and S-Ca levels at that time. Six subjects of the 14 (43%) with hypercalcaemia and normal S-PTH had sustained fractures (ns compared with nHPT). Two subjects with hypercalcaemia had S-PTH 56 and 58 ng/l and should probably be considered as pHPT. The remaining 12 subjects with hypercalcaemia had S-PTH levels between 21 and 43 ng/l. Three subjects, besides the 14, had pHPT (hypercalcaemia and elevated S-PTH). Should the definition of pHPT be hypercalcaemia with measurable S-PTH, then the prevalence would be 4.1% in the age span

of 38–79 years. The linear correlation between S-Ca and S-PTH in subjects with and without vitamin D insufficiency is shown in Fig. 2.

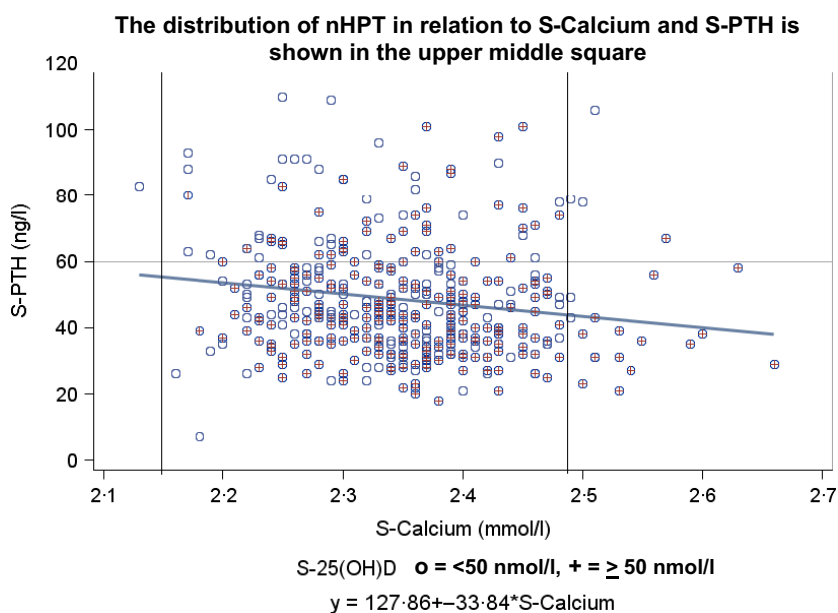
### Different cut-off levels of S-PTH and regression analyses

If the upper serum intact PTH level was set at 60, 65 or 70 ng/l, the prevalence of nHPT in 1995 was 2.0%, 1.0% and 0.5%, respectively, and at the re-examination in 2008, the prevalence was 11.0%, 7.8% and 4.9%, respectively. Factors of significance in a stepwise logistic regression analysis were previous osteocalcin and S-PTH, S-25(OH)D and treated hypertension. The higher the cut-off level for S-PTH, the stronger independent significant association for hypertension was seen (Table 2). Furthermore, a level of S-25(OH)D  $\geq 90$  nmol/l resulted in S-PTH below 60 ng/l in all subjects.

### Discussion

During recent years, there has been extensive discussion regarding the clinical entity of nHPT. It remains unclear whether an isolated elevated S-PTH is pathological *per se*, an early marker of an upcoming pathological state, a marker of a syndrome or just a part of the ageing process. S-PTH levels may rise due to low levels of circulating S-25(OH)D levels, low calcium intake, renal disease and certain medications.<sup>3</sup> It is, however, uncertain to what extent elevated S-PTH, with sustained S-Ca levels and without the factors mentioned above, leads to pHPT or increased morbidity and mortality.<sup>7</sup>

This study provides new data on the prevalence and natural history of nHPT in a nonreferral asymptomatic, random population cohort. After excluding subjects with renal insufficiency and vitamin D insufficiency, the prevalence of nHPT was 2.0% in the initial screening and 11.0% 13 years later. One individual developed mild hypercalcaemia with normal PTH at the age of



**Fig. 2** Distribution of subjects,  $n = 410$ , regarding S-Ca in relation to S-PTH with vitamin D insufficiency (S-25(OH)D < 50 nmol/l: open circles) and sufficiency (cross in circles). Subjects with normocalcaemic, vitamin D-sufficient hyperparathyroidism (nHPT) are evenly distributed in the upper middle section. The straight horizontal line indicates the reference level of S-PTH, 60 ng/l, and the two vertical lines show the reference levels of S-Ca between 2.15 and 2.49 mmol/l. The equation for the regression line estimate is given below the figure.

**Table 2.** Final stepwise logistic regression analysis with different cut-off levels for serum parathyroid hormone (S-PTH) together with S-25(OH)D  $\geq 50$  nmol/l as the dependent variable and all significant variables from Table 1 included as predictors for S-PTH at the 13-year follow-up in 2008

Independent variable	Odds Ratio	Confidence interval	P-value
<b>nHPT cut-off 60 ng/l</b>			
Age	1.033	0.947–1.128	0.4618
BMI	1.063	0.899–1.258	0.4730
S-PTH 1995	1.104	1.038–1.173	0.0016
S-Osteocalcin 1995	1.668	1.144–2.433	0.0079
S-25(OH)D	0.762	0.639–0.909	0.0025
Treated hypertension	5.585	1.217–25.632	0.0269
<b>nHPT cut-off 65 ng/l</b>			
S-PTH 1995	1.078	1.041–1.116	<0.0001
S-Osteocalcin	1.070	1.001–1.145	0.0479
S-25(OH)D	0.934	0.880–0.991	0.0248
Treated hypertension	4.080	1.443–11.534	0.0080
<b>nHPT cut-off 70 ng/l</b>			
BMI	1.120	1.014–1.238	0.0260
S-PTH 1995	1.107	1.052–1.165	<0.0001
S-Osteocalcin	1.098	1.010–1.193	0.0273
S-25(OH)D	0.914	0.843–0.990	0.0281
Treated hypertension	9.954	2.370–41.800	0.0017

75 years. In addition, three of the twelve subjects with nHPT in 1995 had normalized completely in 2008, and subjects with pHPT in 1995 had normalized S-PTH or had nHPT at follow-up without surgical treatment.

Published data regarding progression rates from nHPT to pHPT have hitherto been conflicting. While some groups have reported low progression rates and morbidity,<sup>13,14</sup> others have found high progression rates (19–25%) during much shorter follow-up periods.<sup>6,7</sup> The highest progression rates were seen in studies on referral patients with clinical features of metabolic bone disease.<sup>6,7</sup> The design of our study could explain the conflicting results; selection bias was not an issue in the present study. In otherwise healthy subjects, nHPT might therefore not necessarily be the early stage of pHPT, but a secondary phenomenon strongly associated with age, weight and S-25(OH)D levels. We showed that S-PTH correlated with increasing age, BMI and low S-25(OH)D, which is in accordance with earlier results<sup>15,16</sup> There was also a significant positive correlation with treated hypertension, but not with other cardiovascular outcomes. Our initial hypotheses regarding increased skeletal and cardiovascular morbidity and mortality were therefore rejected. There was no difference between groups in calcaneal QUS outcomes during follow-up, nor was there an increase in fracture rates or nephrolithiasis in individuals with nHPT. Body height decrease during follow-up could be a rough indicator of silent, subclinical vertebral compression fractures, but no difference between the groups could be found in this aspect.

Subjects with nHPT had a higher prevalence of hypertension already at fairly young age, 25–64, irrespective of obesity. A high aldosterone-to-renin ratio has been associated with a high S-PTH in a population aged 25–88 years.<sup>17</sup> Furthermore,

renin–angiotensin–aldosterone inhibitors have been shown to be associated with lower S-PTH.<sup>18</sup> No other correlations between S-PTH, and factors of the metabolic syndrome (glucose, insulin or lipids) could be seen after adjustment for BMI in the present cohort.

The question emerges whether the current reference intervals used for S-PTH in the normal population should be adjusted for BMI, and possibly also for age, to avoid false diagnosis of HPT, especially in the presence of normal S-Ca levels. Regardless of whether the cut-off level of S-PTH was 65 or 70 ng/l, there was a considerable prevalence of nHPT. On the other hand, the cut-off level for vitamin D sufficiency may be too low. Our prevalence of nHPT in 2008 was 11.0%, which is much higher than some previously presented lower estimates in men, 0.4–3.1%,<sup>19</sup> but similar to a Canadian mixed population-based study (CaMos), where the prevalence was 10.7% with the same S-25(OH)D cut-off value as we used: 50 nmol/l.<sup>4,12,20</sup> A higher S-PTH was predictive of nHPT at follow-up. This could reflect either that nHPT is a state that progresses over time, or alternatively a reflection of individual homeostatic levels with regard to sufficient S-25(OH)D levels and S-PTH.

One weakness of our study is that only one sampling at each time-point was assessed for S-Ca without analyses of ionized S-Ca or urinary calcium. In addition, the use of calcium loading tests or vitamin D intervention treatments could add important information regarding the mechanism behind elevated S-PTH in combination with normal S-Ca. However, this is a first attempt to study, in an unbiased random sample, the magnitude of the problem with nHPT due to increasing clinical use of S-PTH analysis for various and sometimes unknown reasons.

## Conclusion

This random population-based study showed that nHPT was common, with a prevalence of 11% at follow-up, and was independently related to obesity and treated hypertension. S-PTH was predictive over time. Only one individual progressed to mild hypercalcaemia. No increase in fractures or cardiovascular disease in subjects with nHPT was seen over a 17-year period. Prospective, larger follow-up studies are warranted to clarify this state in order to establish reliable guidelines and adjust clinical practice accordingly.

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