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Vadiveloo, Thenmalar; Donnan, Peter T.; Leese, Callum J.; Abraham, Kirstin J.; Leese, Graham P.

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DR THENMALAR VADIVELOO (Orcid ID : 0000-0001-5531-6289)

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Increased Mortality and Morbidity in Patients with Chronic Hypoparathyroidism: A population based study

Short Title: Morbidity & Mortality of Hypoparathyroidism

Thenmalar Vadiveloo[1]

Peter T. Donnan[1]

Callum J. Leese[2]

Kirstin J Abraham[2]

Graham P Leese[3]

[1]Dundee Epidemiology and Biostatistics Unit, Division of Clinical and Population Sciences and Education, [2]Royal Devon and Exeter Hospital, Exeter, Devon, [3]Department of Medicine, University of Dundee, Dundee, Scotland, UK

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Corresponding author

Dr. Thenmalar Vadiveloo

Dundee Epidemiology and Biostatistics Unit

University of Dundee, The Mackenzie Building

Kirsty Semple Way, Dundee DD2 4BF

Tel +44 1382 383715

Email: t.vadiveloo@dundee.ac.uk

SUMMARY

Objectives

A population based study was undertaken to determine the mortality and morbidity for people with hypoparathyroidism compared to the general population.

Methods

In this study, patients identified with chronic hypoparathyroidism using data-linkage from regional datasets were compared to five age and gender matched controls from the general population. Data from biochemistry, hospital admissions, prescribing and the demographic dataset were linked. Outcomes for mortality and specified conditions were examined for all patients and sub-divided into post-surgical and non-surgical cases of hypoparathyroidism.

Results

All patients had an increased risk of epilepsy (HR 1.65 (95% CI 1.12-2.44)) and cataracts (HR 2.10 (1.30-3.39)) but no increased fracture risk. Only non-surgical hypoparathyroid

patients also had increased mortality (HR 2.11 (1.49-2.98), cardiovascular disease (HR 2.18 (1.41-3.39), cerebrovascular disease (HR 2.95 (1.46-5.97), infection (HR 1.87 (1.2-2.92) and mental illness (HR 1.59 (1.21-2.11). There was an increased risk of renal failure (HR 10.05 (95% CI 4.71-21.43)) during the first 2000 days (5.5 years) of follow up. Renal failure and death was associated with increasing serum calcium concentrations.

Conclusion

Patients with hypoparathyroidism have an increased risk of cataract and epilepsy. Non-surgical hypoparathyroidism is associated with increased mortality and additional morbidities.

Key words: Calcium, Parathyroid-related disorders, Health Services Research, Statistical Methods, Epidemiology, Hypoparathyroidism, Morbidity

INTRODUCTION

Hypoparathyroidism is a rare disorder characterised by low serum calcium and abnormally low concentration of parathyroid hormone (PTH) (1,2). Hypoparathyroidism may be transient, such as after neck surgery, or may be chronic due to accidental removal of, or permanent damage to the parathyroid glands from surgery (3). Post-surgical hypoparathyroidism is the commonest cause of hypoparathyroidism, occurring in 2-5% long-term surgical neck explorations (4-6). We have recently reported a prevalence of primary hypoparathyroidism in Tayside, Scotland of 40 per 100,000 (7) similar to the rate observed in the US at 37 per 100,000 (8) but greater than that seen in other European studies at 10-24 per 100,000 (9, 10, 11). The rate was 23 and 17 per 100,000 respectively for post-surgical and non-surgical (7). The rate of post-surgical cases is similar across studies from 22 to 29 per 100,000 (7, 8, 10) although lower in Norway at 10 per 100,000 (11). The rate of non-

surgical cases was more variable from 2.3 (9) to 8 (8) to 17 (7) per 100,000. Our methodology however is likely to be more sensitive at identifying patients with milder hypoparathyroidism who may be missed using methods depending on hospital referral and patient registries.

Morbidities associated with hypoparathyroidism are either related directly to low calcium or raised phosphate concentrations or indirectly via treatment for the disorder which comprise oral calcium and vitamin D analogue supplements (4, 12). In addition, some of the non-surgical cases are likely to be due to genetic mutations e.g DiGeorge syndrome, which are known to be associated with congenital heart defects and urogenital abnormalities (13). Other autoimmune aetiologies e.g. autoimmune polyglandular syndrome are associated with Addisons disease and thyroid disease potentially placing patients at risk (14,15). Conventionally, the aim of treatment has been to maintain the serum calcium concentration around the lower limit of the reference range. This limits the risks of hypercalciuria and hypercalcaemia with the resultant risks of symptoms, renal stones, and other complications. Previous studies have reported association between renal complications and hypoparathyroidism (10, 16). The Danish national studies reported that patients with hypoparathyroidism had an increased risk of seizure, depression, neuropsychiatric diseases and infections, whereas there was no increased risk of cardiovascular disease, cataract, fracture or death (10, 17).

The aim of this study was to investigate if patients with chronic hypoparathyroidism had an increased risk of incident cataract, cardiovascular disease, cerebrovascular disease, infections of skin and chest, epilepsy, fracture, mental health, renal failure and death.

MATERIALS AND METHODS

Patients and controls

All Tayside residents registered with a general practice in Scotland are assigned to a unique 10-digit health index, known as a Community Health Index (CHI). CHI is used as a patient identifier that facilitates the linkage of all health care-related records. All such records are held and linked at the Health Informatics Centre (http://www.dundee.ac.uk/hic) of the University of Dundee. We have previously identified adult patients (age 18years and over) between January 1988 and August 2016 with hypoparathyroidism using four principle anonymous patient-level datasets, and the patient selection and classification process is described in detail in Vadiveloo et al. (7). In brief, patients were identified from the Tayside population based on at least three out-patient based measurements of serum albumin-corrected calcium below the reference range (<= 2.15mmol/L) with a minimum of a one-month interval between measurements. All calcium measurements taken as an in-patient were excluded, 94% of patients had a serum calcium below 2.10 mmol/L and 83% of patients had low serum calcium at least 6 months apart. In addition, patients have had one of the following 1) neck surgery or irradiation prior to hypocalcaemia or admission with hypoparathyroidism, 2) low or inappropriately normal plasma parathyroid hormone (PTH) while having low calcium (<5pmol/L) or 3) on three or more prescriptions per year treatment with Calcium and/or cholecalciferol or activated Vitamin D. Exclusion criteria included 1) patients with high PTH while having low calcium; 2) patients with serum 25-OH Vitamin D less than 50 nmol/L while having low calcium; 3) patients who had less than three low calcium concentration after excluding calcium measurements taken during admission; 4) patients who had low calcium concentrations, all within 1 month; 5) patients who had either serum creatinine > 200µmol/L or eGFR < 20 prior to the first recording of a low serum calcium. Using an electronic-based algorithm to identify patients across the community is different to

previous approaches, but arguably identifies patients missed when depending on referrals to a specialist and registration on specific databases, especially non-surgical cases. These issues have been discussed elsewhere (7). Our patients were sub-categorised as having post-surgical hypoparathyroidism, or having non-surgical hypoparathyroidism (7) or having hypoparathyroidism associated with hypomagnesaemia (<0.5mmol/l: lower limit of local reference range is 0.69mmol/l). This last group was assessed separately as some of these patients will have had hypomagnesaemia due to hypoparathyroidism, but some will have had hypomagnesaemia causing the hypocalcaemia, and may not truly have hypoparathyroidism. Drugs which can cause hypomagnesaemia and lower serum calcium include diuretics and proton pump inhibitors, which are markers of confounding co-morbidities such as heart failure and may have influence the outcomes.

In this study, a group of controls from the general Tayside population who had serum calcium concentration within the laboratory reference range were identified and were matched to cases with hypoparathyroidism. For each patient with hypoparathyroidism, five controls were randomly selected, matched by gender, age (± 5 years) and diabetes status. Each comparator was assigned an index date (start of follow-up) identical to the date of diagnosis for hypoparathyroidism of the case. Date of diagnosis was defined as the first low calcium measurement.

Databases and data validity

Tayside population demographic database

This served as a master index to provide information on gender, date of birth, date of death, and dates registered with general practitioner. This information was obtained from the

National CHI register and contained 99% of the population. This was validated by the external systems before it reached the Health Informatics Centre.

Scottish morbidity record 1 (SMR01)

The SMR01 dataset was used to obtain information on morbidity. This dataset consisted of hospital admission data routinely validated and collated by the Information and Statistics Division of the National Health Service in Scotland (http://www.isdscotland.org/isd/2737.html). The International Classification of Diseases (ICD) ninth and 10th revision codes are used in the SMR01 to classify all hospital inpatient episodes.

Tayside prescription database

This contained all prescriptions dispensed from all community pharmacies in Tayside. Each entry comprised the patient's anonymized CHI, prescription date, drug name, formulation, dosage, frequency, and duration. These data were received from Practitioner Services Divisions and we were given access to all prescriptions for anti-epileptic, ant-depressant and anti-psychotic medications.

Biochemistry database

The biochemistry database contained information on serum calcium, parathyroid hormone concentrations and vitamin D concentrations which were used to define the cohort as described previously (7). eGFR measurements were also available to define renal failure.

Each entry comprised the patient's anonymized CHI, the test performed, date, and the results. These data were received directly from the lab systems and were validated routinely.

Statistical methods

The following outcomes of all patients with hypoparathyroidism were identified: cataract, cardiovascular disease, cerebrovascular disease, infections of skin and chest (e.g cellulitis and pneumonia), epilepsy, fracture, mental health, renal failure and death. SMR01, the admission database was used to identify all the above outcomes. Patients who had epilepsy and mental health problem were also identified using the prescribing database. Patients who had renal failure were identified using the eGFR measurements in the biochemistry database. Renal failure was defined as eGFR below 30ml/min. Survival analysis was used to follow up patients until an event occurred, they were censored or the end of the study. Cox proportional hazards model was used to model the data, and the assumption of proportional hazards was assessed using the graphical and numerical methods of Lin, Wei and Ying (1993). These methods are derived from cumulative sums of martingale residuals over follow-up times or covariate values. Non-proportional hazard model was used if there was a violation in the proportional hazard assumption. The outcomes of hypoparathyroid patients were compared with five matched controls (age and gender) from the Tayside population. The association between mean calcium concentration after diagnosis and all the outcomes were also investigated. All analyses were performed on anonymized datasets using IBM SPSS Statistics 22 and SAS 9.4.

Other confounders

Apart from gender and age, other covariates adjusted for in the survival analysis were socioeconomic deprivation and previous history of the disease studied.

Ethical approval

The study was approved by the Tayside Medical Ethics Committee and data protection by the Tayside Caldicott Guardians.

RESULTS

There were a total of 280 patients with chronic hypoparathyroidism, of which 116 cases were post-surgical, 58 cases had hypomagnesaemia and 106 cases were non-surgical (7). The total follow-up period was 2587 years with a median of 9 years. Overall, 30.7% of the cases were male, and the mean age was 51.6 years (SD 19). The baseline characteristics of hypoparathyroid cases and reference population are shown in Table 1. At baseline, significantly higher percentages of hypoparathyroid cases had pre-existing infections ($p<0.001$), cardiovascular disease ($p=0.001$), fractures ($p=0.004$), mental health conditions ($p<0.001$) and renal failure ($p<0.001$) compared to the reference population.

There was no violation of the assumption of proportional hazards in all outcomes except for renal failure. A proportional hazards model was used to assess all outcomes except for renal failure when a non proportional hazard model was used. Table 2 shows the unadjusted and adjusted hazard ratios (HR) for inpatient admissions due to cataract, cardiovascular disease, cerebrovascular disease, infection, epilepsy, fracture, mental health and death. The total number of events for each disease studied were; cardiovascular disease (n=251),

cerebrovascular disease (n=84), cataract (n=137), epilepsy (n=163), infection (n=263), fracture (n=191), mental health (n=619), renal failure (n=149) and death (n=375). Of patients who had an epileptic fit, only two had a serum calcium less than 2mmol/L within one month of the fit. Compared with the reference population, patients with chronic hypoparathyroidism were associated with an increased risk of cardiovascular disease, cerebrovascular disease, cataract, epilepsy, infection, mental health and death. As a sensitivity analysis, when all patients with a serum albumin less than 30 g/L, were excluded, which is a marker of chronic ill health, the adjusted mortality rate remained significant with a hazards ratio of 1.44 (1.02-2.02; p=0.037). There were no significant differences in the risk of fracture between hypoparathyroid patients and the matched reference population. When the hypoparathyroid patients were grouped into two categories, patients in the post-surgical group had a significantly increased risk of cataract and epilepsy compared with the reference population.

However, those in non-surgical group had increased risk of cardiovascular disease, cerebrovascular disease, epilepsy, infection, mental health and death compared with the reference population. Those with hypomagnesaemia associated hypoparathyroidism had increased risk of cardiovascular disease, cataracts, infection, fractures mental health and death. This risk profile is similar, but not identical to those with non-surgical hypoparathyroidism, but the hazards ratios seem to be greater for the hypomagnesaemia group.

The cumulative martingale residuals plots showed that the proportional hazard assumption was violated for all cases and non-surgical cases whereby, the true hazard ratio for renal failure was changing over time. The hazard ratio was found changing at 2000 days after baseline for the non-surgical group, therefore the follow-up time from baseline was split for the overall group and this sub-group ; ≤2000 days and > 2000 days. The Table 3 shows the unadjusted and adjusted hazard ratios (HR) for renal failure. Compared to the reference

population, hypoparathyroid patients had significantly higher risk of renal failure within the first 2000 days from their first low calcium (baseline). The risk of renal failure was no longer significant in patient with hypoparathyroidism after 2000 days from baseline. The risks of renal failure in post-surgical and hypomagnesaemia patients were significantly higher throughout the study period. However, the risk in non-surgical patient were only significantly higher within the first 2000 days from baseline.

Table 4 show that serum calcium concentration was positively associated with renal failure and death, but otherwise mean serum calcium was not associated with any of the outcomes.

DISCUSSION

In this study, we demonstrated an increased death rate with increased risk of cardiovascular disease, cerebrovascular disease, cataract, epilepsy, infection, mental illness, renal failure in all patients with hypoparathyroidism when compared to the matched controls. For patients with post-surgical hypoparathyroidism we demonstrated an increased risk of cataract, epilepsy and renal failure only and no increased mortality. However, patients with non-surgical hypoparathyroidism had an increased risk of death, cardiovascular disease, cerebrovascular disease, epilepsy, infection, mental illness and renal failure. There was no increased risk of fractures in either group. The hypomagnesaemia group should similar risks, but lacking the risks of cerebrovascular disease and epilepsy but additional risk of fracture. The increased risk of fracture is notable given no trends for this in the other two sub-groups and is likely to represent a confounding variable relating to the increased age, existence of diabetes and likely increased frailty of this sub-group. The higher hazards ratios for those with hypomagnesaemia may reflect the lower numbers in this group or may also reflect increased frailty. Our results are remarkably similar to those observed from Denmark, where

there was an increased risk of all the same outcomes with no risk of fractures in non-surgical hypoparathyroidism (9). The Danish study showed a borderline increased risk mortality in non-surgical hypoparathyroidism which did not quite reach statistical significance (HR 1.25, p=0.06) (9) but no increased mortality for post-surgical cases (10). In addition to an increased risk of renal failure and seizures for patients with post-surgical hypoparathyroidism, the Danish study also showed a risk for mental illness and infection (10, 17), although they did not demonstrate any risk for cataracts unlike our study. They had a greater number of patients and may have been better powered to demonstrate these end points which showed a non-significant trend in our study.

Our Scottish cohort and the Danish cohort are the only two reported population-based case controlled follow up studies in hypoparathyroidism that we are aware of. It is an important finding that our data confirmed the previous findings, but also showed a two-fold increased death rate in patients with non-surgical hypoparathyroidism, a finding which did not quite reach significance in the previous study. In addition our study was able to provide a simultaneous comparison between post-surgical and non-surgical cases and hypomagnesaemia cases. It is likely that the vast majority of the group with hypomagnesaemia are non-surgical cases, and they demonstrated greatest risk for death and most (but not all) outcomes measured, although they may be confounded by co-existing co-morbidities. There was also a greater risk for people with non-surgical hypoparathyroidism (normal magnesium concentrations) compared to those with post-surgical hypoparathyroidism. As post-surgical cases occur acutely and not insidiously they are more likely to be recognised early and referred to a specialist clinic where they may get better long-term care. Non-surgical cases may be linked with other co-existing conditions such as Addison's disease and other autoimmune disease or genetic disorders which may add to their

risk. We should be encouraging all cases of persistent hypocalcaemia to be referred to a specialist clinic so that all these issues can be addressed.

Others have shown increased morbidity with high rates of renal failure, renal and basal ganglia calcification (16), along with poor quality of life and heightened anxiety scores (11), mental illness (18) and reduced employability (19). These outcomes have been highlighted in reviews on the outcomes of hypoparathyroidism (4, 20).

We have previously described a high prevalence of hypoparathyroidism in a population based study at 40-47 per 100,000 (7) with a particularly high rate of non-surgical hypoparathyroidism at 17 per 100,000 (7). It is thus important to note the high levels of morbidity especially in the non-surgical cases, if the prevalence of this condition is higher than previously thought. This may not be a surprise as many patients with non-surgical hypoparathyroidism will have had auto-immune causes or genetic causes with associated additional morbidities sometimes requiring additional medications such as corticosteroids. Our results highlight the long-term morbidity associated with hypoparathyroidism which is often unrecognised by clinical staff, as well as short term complications of managing the hypocalcaemia (12, 16, 19).

Serum calcium concentrations were directly associated with renal failure and death as was observed by Mitchell et al (16). Mean serum calcium concentration was not associated with any of the other outcomes, and neither was calcium/phosphate product (data not shown). Mean serum calcium or phosphate concentration from six months after diagnosis is a fairly crude measure of biochemical control, and may not reflect subtle changes in calcium concentration, which may be important in determining the outcomes assessed, and our study may be underpowered. Unfortunately, reliable data on urinary calcium excretion was not

available in this population-based study. Variability in serum calcium or phosphate concentration may also be a factor in determining outcomes that we have not measured.

The mechanisms causing the adverse outcomes are not well studied. Due to a high calcium/phosphate product associated with hyperphosphataemia it is thought that calcium phosphate crystals get deposited in the lens of the eye causing cataract (21) and this may also contribute to arteriosclerosis precipitating cardiovascular and cerebrovascular disease, although chronic hypocalcaemia may also contribute to cardiomyopathy (22) and arrhythmias. Increased renal failure is also likely to be due to deposition of calcium phosphate. Although hypoparathyroidism is a state of low bone turnover with increased bone density (23), this study and previous study (9) did not show an overall increased risk of any fractures. However, an increased risk of forearm fractures has been reported (9). It is difficult to explain the reason for increased neuropsychiatric disease, epilepsy and infection, although the ubiquitous effect of intracellular calcium stabilising cell membranes may be relevant.

Limitations of the study include small numbers of patients (n=280) due to the rarity of the condition, but some end points may be under powered. In addition we did not have data on cancer outcomes or forearm fractures, which may be at increased risk in parathyroid disease. It is possible that we may have missed some well controlled patients who had normal serum calcium throughout. However, our prevalence rates were greater than those previously reported in the literature which is reassuring that it is unlikely that we missed large numbers of patients. We also excluded patients with low serum Vitamin D concentrations to avoid being criticised for inappropriate inclusion, but this also creates a potential weakness, which may have resulted in an under-estimate of the morbidity recorded. Unfortunately we did not have detail on the causes of non-surgical hypoparathyroidism and could not distinguish between genetic, autoimmune and other causes. Additionally we could not be sure whether the group with hypomagnesaemia had low serum magnesium due to the hypoparathyroidism

or whether the hypomagnesaemia was the driving cause of the hypocalcaemia. This is the reason this group was analysed separately, as the latter group would include patients on medications e.g. diuretics and proton pump inhibitors which are markers of other confounding co-morbidities such as cardiac failure. It is possible to purchase calcium and non-activated Vitamin D over the counter and we were unable to account for such prescriptions. As all prescriptions in Scotland are free this may be less of an issue compared to some countries. A further limitation is that the date of inclusion into our study may not be the actual date of diagnosis, if diagnosis occurred some before the start of the study. Conversely however, if there were delays in referral to a specialist, our study would identify the true date of the first low serum calcium which may be years before a specialist makes a formal diagnosis. The strength of this study include that it is a true population based study where patients in both primary and secondary care settings were identified (7). Our study will include patients potentially missed using registry based studies as discussed in detail elsewhere (7), especially patients with milder hypocalcaemia. Patients with vitamin D deficiency were excluded, but if we have erroneously included some patients with milder hypocalcaemia it is likely to have reduced the likelihood of any positive findings. However the outcomes for non-surgical hypoparathyroidism were worse than those for post-surgical cases. The use of prescribing data has helped identify patients with mental illness and epilepsy.

The results from our study and others indicate that the outcomes for hypoparathyroidism are not ideal. Some complications may be related to chronic hypocalcaemia, whilst others may relate to relative overtreatment and chronic hypercalcaemia. All patients with persistent hypocalcaemia should get referred to a specialist clinic where they should be fully evaluated and may get better long-term care, and hopefully improved outcomes. The outcomes of death

and renal failure seem to be associated with higher concentrations of serum calcium, suggesting the latter as a more significant issue for chronic complications. .

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Table 1: Baseline characteristics of people with chronic hypoparathyroidism and comparators. Cases and comparators were matched for age, gender and diabetes status

Variables		Controls[a]	Cases	Cases			p-value[b]
				Surgical	Hypo-magnesaemia	Non-surgical	
N		1301	280	116	58	106	-
Age, mean (SD)		49.6 (18.4)	51.6 (19.3)	47.1 (19.9)	62.8 (16.1)	50.5 (17.9)	p=0.12
Male, n (%)		375 (28.8)	86 (30.7)	23 (19.8)	25 (43.1)	38 (35.8)	p=0.53
Diabetes, n (%)		147 (11.3)	31 (11.1)	12(10.3)	12 (20.7)	7 (6.6)	p=0.91
Deprivation status, n (%)	Affluent	426 (32.7)	74 (26.4)	28 (24.1)	18 (31.0)	28 (26.4)	
	Middle	531 (40.8)	122 (43.6)	51 (44.0)	22 (37.9)	49 (46.2)	p=0.11
	Deprived	304 (23.4)	75 (26.8)	33 (28.4)	16 (27.6)	26 (24.5)	
Previous history, n (%)	Cataract	38 (2.9)	7 (2.5)	2 (1.7)	3 (5.2)	2 (1.9)	p=0.70
	Cardiovascular disease	80 (6.1)	33 (11.8)	8 (6.9)	15 (25.9)	10 (9.4)	***p=0.001***
	Cerebrovascular disease	21 (1.6)	4 (1.4)	0	1 (1.7)	3 (2.8)	p=0.82
	Epilepsy	48 (3.7)	17 (6.1)	4 (3.4)	3 (5.2)	10 (9.4)	p=0.07
	Infection	85 (6.5)	45 (16.1)	15 (12.9)	17 (29.3)	13 (12.3)	***p<0.001***
	Fracture	71 (5.5)	28 (10.0)	10 (8.6)	9 (15.5)	9 (8.5)	***p=0.004***
	Mental Health	226 (17.4)	102 (36.4)	39 (33.6)	27 (46.6)	36 (34.0)	***p<0.001***
	Renal Failure	10 (0.8)	10 (3.6)	4 (3.4)	3 (5.2)	3 (2.8)	***p<0.001***

[a] All cases are matched with controls based on age, gender and diabetes status.

[b] ANOVA for age, chi-square test for the other categorical variables. Differences between the cases and controls were classified as significant if P value ≤0.05.

Table 2: Hazard ratios for in-patient admissions and death for hypoparathyroid patients. Data is subdivided by those with post-surgical hypoparathyroidism, those with non-surgical hypoparathyroidism and those with hypoparathyroidism associated with hypomagnesaemia

	Population	Events	(%)	Unadjusted HR (95% CI)		Adjusted HR (95% CI)	
Cardiovascular							
All hypoparathyroid	280	72	25.7	2.21*	(1.68, 2.90)	2.24*	(1.69, 2.97)
Surgical	116	15	12.9	0.99	(0.59, 1.68)	1.26	(0.74, 2.15)
Hypomagnesaemia	58	31	53.4	7.29*	(4.97, 10.71)	4.06*	(2.72, 6.08)
Non-surgical	106	26	24.5	1.98*	(1.31, 2.99)	2.10*	(1.37, 3.23)
Comparators	1301	179	13.8	1.00		1.00	
Cerebrovascular							
All hypoparathyroid	280	20	7.1	1.70*	(1.03, 2.81)	2.00*	(1.18, 3.38)
Surgical	116	6	5.2	1.17	(0.51, 2.70)	2.06	(0.87, 4.86)
Hypomagnesaemia	58	3	5.2	1.58	(0.50, 5.05)	1.02	(0.32, 3.27)
Non-surgical	106	11	10.4	2.32*	(1.22, 4.41)	2.76*	(1.40, 5.44)
Comparators	1301	64	4.9				
Cataract							
All hypoparathyroid	280	34	12.1	1.84*	(1.25, 2.71)	1.92*	(1.29, 2.85)
Surgical	116	11	9.5	1.31	(0.70, 2.43)	1.87*	(1.00, 3.52)
Hypomagnesaemia	58	11	19.0	3.98*	(2.13, 7.43)	2.14*	(1.10, 4.15)
Non-surgical	106	12	11.3	1.65	(0.91, 3.00)	1.81	(0.99, 3.29)
Comparators	1301	103	7.9	1.00		1.00	
Epilepsy							
All hypoparathyroid	280	43	15.4	1.93*	(1.36, 2.74)	1.56*	(1.08, 2.24)
Surgical	116	17	14.7	1.75*	(1.05, 2.91)	1.74*	(1.02, 2.94)
Hypomagnesaemia	58	5	8.6	1.30	(0.53, 3.18)	0.93	(0.34, 2.54)
Non-surgical	106	21	19.8	2.41*	(1.52, 3.83)	1.63*	(1.01, 2.63)
Comparators	1301	120	9.2	1.00		1.00	
Infection							
All hypoparathyroid	280	75	26.8	2.24*	(1.71, 2.92)	2.30*	(1.75, 3.02)
Surgical	116	17	14.7	1.11	(0.67, 1.82)	1.45	(0.88, 2.40)
Hypomagnesaemia	58	34	58.6	7.91*	(5.47, 11.45)	4.57*	(3.11, 6.71)
Non-surgical	106	24	22.6	1.74*	(1.14, 2.67)	1.79*	(1.16, 2.77)
Comparators	1301	188	14.5	1.00		1.00	
Fracture							
All hypoparathyroid	280	38	13.6	1.34	(0.94, 1.91)	1.05	(0.72, 1.52)
Surgical	116	10	8.6	0.79	(0.42, 1.49)	0.71	(0.37, 1.37)
Hypomagnesaemia	58	17	29.3	4.34*	(2.62, 7.18)	3.48*	(2.09, 5.78)
Non-surgical	106	11	10.4	0.94	(0.51, 1.73)	0.56	(0.29, 1.09)
Comparators	1301	153	11.8	1.00		1.00	
Mental Health							
All hypoparathyroid	280	153	54.6	2.01*	(1.67, 2.42)	1.33*	(1.10, 1.61)
Surgical	116	53	45.7	1.52*	(1.15, 2.02)	0.94	(0.70, 1.26)
Hypomagnesaemia	58	38	65.5	3.36*	(2.40, 4.68)	1.92*	(1.36, 2.71)
Non-surgical	106	62	58.5	2.08*	(1.60, 2.71)	1.58*	(1.20, 2.08)
Comparators	1301	466	35.8	1.00		1.00	
Death							
All hypoparathyroid	280	104	37.1	2.07*	(1.65, 2.60)	2.15*	(1.71, 2.71)
Surgical	116	22	19.0	1.00	(0.65, 1.55)	1.48	(0.96, 2.31)
Hypomagnesaemia	58	41	70.7	5.26*	(3.78, 7.32)	2.84*	(2.01, 4.01)
Non-surgical	106	41	38.7	2.01*	(1.45, 2.80)	2.18*	(1.55, 3.05)
Comparators	1301	271	20.8	1.00		1.00	

Table 3: Unadjusted and adjusted hazard ratios for renal complications for all chronic hypoparathyroid patients.

		Population	Events	(%)	Unadjusted HR (95% CI)		Adjusted HR (95% CI)	
All cases	≤2000 days	280	63	22.5	10.14*	(6.07,16.96)	9.39*	(5.58,15.78)
	>2000 days				1.98*	(1.20, 3.28)	2.47*	(1.47,4.14)
Surgical		116	10	8.6	1.47	(0.76, 2.83)	2.18*	(1.11, 4.25)
Hypomagnesia		58	30	51.7	16.37*	(10.75,24.93)	10.32*	(6.63,16.06)
Non-surgical	≤2000 days	106	23	21.7	7.59*	(4.28, 13.45)	9.94*	(5.53, 17.85)
	>2000 days				1.63	(0.71, 3.76)	1.50	(0.60, 3.73)
Comparators		1031	86	6.6	1.00		1.00	

Table 4. Association between mean serum calcium concentration and outcomes.

Event	Exp (β) (95% CI)	Significance
Cataract	1.977 (0.13, 29.95)	0.623
Cardiovascular disease	0.655 (0.02, 8.36)	0.745
Cerebrovascular disease	3.300 (0.20, 54.59)	0.404
Epilepsy	3.340 (0.39, 30.31)	0.284
Infection	4.975 (0.56, 44.22)	0.150
Fracture	5.732 (0.48, 69.05)	0.169
Mental Health	4.366 (0.53, 35.84)	0.170
Renal Failure	16.605 (1.35, 204.73)	***0.028***
Death	15.584 (1.45, 168.11)	***0.024***