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Norwegian summary/norsk sammendrag

I denne studien har vi funnet vitamin D mangel hos 71.6 % av eldre som ble henvist til psykiatrisk avdelinger ved Universitetssykehuset Nord-Norge. Til sammenligning fant vi vitamin D mangel hos kun 20 % i en kontrollgruppe av eldre fra Tromsøundersøkelsen.
I pasientgruppen fant vi ikke forskjell i vitamin D mangel mellom ulike diagnosegrupper (for eksempel depresjon og psykose). Videre har vi funnet sinkmangel hos 41% i samme pasientgruppe, sammenlignet med kun 14% i en kontrollgruppe fra Tromsøundersøkelsen. I pasientgruppen fant vi lavere forekomst av sinkmangel i pasientgruppen med depresjon sammenlignet med andre diagnosegrupper. I en undersøkelse av 1521 eldre fra Tromsøundersøkelsen fant vi økt risiko for sinkmangel hvis det var samtidig underernæring. Sammenheng mellom kostfaktorer og psykiatrisk sykdom er fortsatt ikke fullt ut forstått og man kan ikke trekke den slutning fra våre studier at vitamin D mangel eller sinkmangel nødvendigvis er årsak til psykiatrisk sykdom. Flere kontrollerte studier er nødvendig for å finne ut om disse kostfaktorene kan være av betydning i behandling av psykiatrisk sykdom.

English summary

We have investigated a selection of biological factors, which could have an impact on psychiatric disorders, especially in the elderly. The first study (paper I) is a case-report, where we describe a patient with treatment resistant depression. Further investigation revealed primary hyperparathyroidism (pHPT), despite a normal calcium level. The depression was cured after operation for pHPT. Disturbance in calcium metabolism should not be forgotten as a differential diagnosis, even with normal calcium levels, especially in treatment resistant depression. Vitamin D is important in calcium metabolism, but the vitamin can also have non-skeletal effects.

Several observational studies have reported an association between vitamin D deficiency and various psychiatric conditions, including depression and psychosis; while randomized treatment studies have revealed conflicting results. There is little knowledge about the vitamin D status in elderly psychiatric patients. In the second study (paper II) we reported a prevalence of 71.6 % of vitamin D deficiency in a sample of 95 elderly patients (>64 years old) admitted to psychiatric hospital in Tromsø, which was significantly higher compared to a prevalence of 20 % in an elderly control group (n=104) from the Tromsø survey. In the patient group, we did not find any significant difference in prevalence of vitamin D deficiency between patients with different diagnoses (i.e., depression, psychosis, and dementia). In addition to vitamin D, several other nutritional factors have been investigated in the literature with respect of a possible association with psychiatric disorders. In the third study (paper III) we explored the micronutrient zinc and found a prevalence of zinc deficiency of 41.0 % in a sample of 100 elderly patients compared to a prevalence of zinc deficiency of 14.4 % in a control group (n= 882) from the Tromsø survey. Zinc deficiency was more common in patients with psychosis, anxiety and dementia, than in patients with depression. Further

analyses were made in a random sample of 1521 elderly participants from the Tromsø survey. Serum zinc and mental distress were measured and an assessment of malnutrition was made. We did not find any significant differences in mental health distress between participants with or without zinc deficiency, but zinc deficiency was positively associated with the risk of malnutrition.

Even though the role of zinc and vitamin D in psychiatric disorders still is under debate, we have found a high prevalence of both zinc and vitamin D deficiency in elderly psychiatric patients, which is of importance because both zinc and vitamin D deficiency do have an impact on overall health.

List of papers

The thesis is based on the following papers:

Paper I. Grønli O and Wynn R: *Normocalcemic hyperparathyroidism and treatment resistant depression*. Psychosomatics. 2013 Sep-Oct;54(5):493-7. doi: 10.1016/j.psym.2012.10.008. Epub 2013 Jan 23

Paper II. Grønli O, Kvamme JM, Jorde R and Wynn R: *Vitamin D deficiency is common in psychogeriatric patients, independent of diagnosis*. Submitted to BMC Psychiatry

Paper III. Grønli O, Kvamme JM, Friborg O and Wynn R: *Zinc deficiency is common in several psychiatric disorders.* PLoS One. 2013 Dec 19;8(12):e82793. doi: 10.1371/journal.pone.0082793. eCollection 2013

Paper IV. Kvamme JM, Grønli O, Jacobsen BK, Florholmen J: *Risk of malnutrition and zinc deficiency in elderly men and women – a cross sectional study (The Tromsø Study)* Submitted to Public Health Nutrition

Abbreviations

1,25 (OH)2D – 1,25-dihydroxyvitamin D

25(OH)D – 25-hydroxyvitamin D

5-HT1A /2A - 5-hydroxytryptamine 1A /2A (receptor)

AD – Alzheimer's disease

BDNF – Brain Derived Neurothrophic Factor

BMI – Body Mass Index

CI – Confidence Interval

DSM-IV - Diagnostic and Statistical Manual of Mental Disorders - 4th Version

GABA – Gamma Amino Butyric Acid

GP – General Practiotioner

HUNT - The Nord-Trøndelag Health Study

ICD-10 – International Classification of Diseases – 10th Version

IRS – Inflammatory Response System

IZiNCG – International Zinc Nutrition Consultative Group

MADRS – Montgomery-Åsberg Depression Rating Scale

MINI – Mini International Neuropsychiatric Interview

MMSE – Mini Mental State Examination

MUST – Malnutrition Universal Screening Tool

NMDA – N-methyl-D-Aspartic Acid

OR – Odds Ratio

pHPT - Primary Hyperparathyroidism

PTH – Parathyroid Hormone

RCT – Randomized Controlled Trial

SCL-10 – Hopkins Symptom Checklist-10

SF-36 – Short Form-36 General Health Survey

SPSS – Statistical Package for the Social Sciences

TNFα - Tumor Necrose Factor α

1 Introduction

1.1 Geriatric psychiatry

Geriatric psychiatry is a rather novel discipline that started in the United Kingdom in the 1970s. The field is also known as old-age psychiatry or psychogeriatrics. It is a branch of psychiatry dealing with the study, prevention, diagnostics and treatment of mental disorders in humans of old age, usually over the age of 65. Geriatric psychiatry will become increasingly important, due to the rapid growing of the elderly population. In Norway, 13% of the population was over 67 years old in 2010, this number is expected to rise to 22% in 2060 (1). There are 22 departments of geriatric psychiatry in Norway, which typically consist of an out-patient clinic and an inpatient ward. The wards are mostly organised as one ward with a mixture of different patient categories (like at the hospital in this study) or as two separate wards with patients with dementia in one ward and patients with other psychiatric disorders in the other ward. The most common diagnostic categories are depression, dementia related problems, bipolar disorders and psychosis. A typical department of geriatric psychiatry does not perform uncomplicated dementia assessments (while some do), but treats patients with dementia who suffer from psychiatric problems such as psychosis or anxiety or display behavioural problems (i.e., aggression). This is done either through guidance of nursing homes and home-care staff or by hospitalizing the patients. While patients with psychosis often are inpatients, patients with depression are either treated as outpatients or admitted to the ward, depending on the severity of the depression.

Geriatric psychiatry differs from adult non-geriatric psychiatry in many ways. Several factors such as co-existent medical conditions, polypharmacy, cognitive decline, retirement, losses and bereavement complicate the assessment and treatment of patients in this age group (2). Therefore, the average length of hospital stay is usually much longer in Norwegian geriatric

psychiatry wards than in Norwegian adult acute-psychiatry wards (40.2 days vs. 9.5 days) (3,4).

1.2 Prevalence of psychiatric disorders in the elderly

The prevalence is the proportion of people in a population that has a disorder (5). Studies on psychiatric disorders in the elderly have reported large variations in prevalence (6,7). This variation in prevalence could be caused by several factors such as differences in sample populations (i.e., by including only community-living elderly or by including elderly in nursing homes), how psychiatric disorders are defined and what kind of diagnostic instruments have been used (8). *Rosenvinge and Rosenvinge* (6) reported a prevalence of 19% (range 2-62%) of depression and 6% (range 0-26%) of severe depression among elderly over 60 years in a meta-analysis based on 55 studies. *Grav et al.* (9) found a higher frequency of depression among the oldest (20-64y: 8.5%, 65-74y: 10.9%, 75-89y: 16.1%) in the Nord-Trøndelag Health Study 3 (HUNT 3). This increase in prevalence of depression has been supported by several Nordic longitudinal studies (10-12). *Pàlsson et al*. (13) reported an increase in the prevalence of depression (DSM-III criteria) from 5.6 % at 70 years of age to 13.0 % at 85 years of age in the Gøteborg study. Several studies have found a higher prevalence of depression in women (14,15), although some studies have not found a gender difference (16). In Norwegian nursing homes, *Selbæk et al*. (17) have reported a 41% prevalence of depression in persons with dementia.

The findings from studies of prevalence of anxiety in the elderly display a similar pattern of extreme variation. In a review article, *Bryant et al.* (7) found a prevalence of anxiety disorders in the elderly of 1.2%-15% in different studies in community samples, and the prevalence of anxiety symptoms was 15-52.3%. Generalised anxiety is the most common

anxiety disorder among the elderly (7,18). The comorbidity with depression makes prevalence studies on anxiety difficult to interpret.

In a large Swedish population sample (n=894) of non-demented elderly aged 70y, 78y and 82y, a 1-month prevalence of psychotic symptoms of 0.9% (70y) to 1.2% (78y, 82y) was reported (19). *Børjesson-Hanson et al.* (20) found a prevalence of 7% of psychotic symptoms in a population of 95 year old non-demented persons (n=338). Psychotic symptoms may also occur in delirium and complicate the study of prevalence of psychotic disorders.

The higher prevalence of depression in the elderly has been investigated thoroughly, and has been associated with a higher occurrence of chronic physical diseases (21-23). Other factors such as a low educational level, living alone, the presence of functional impairment, stressful life events, low social support and poor social networks have also been associated with an increased risk of depression in the elderly (24,25).

1.3 Biological factors and psychiatric disorders

Patients in geriatric psychiatry departments are either referred due to the severity of the psychiatric disorder or because the disorder did not respond to the treatment initiated by the general practitioner. Factors such as co-morbid psychiatric or medical conditions, incipient dementia and vascular lesions have been associated with poorer response to antidepressant treatment in elderly patients with depression (26-28). As a clinician, I have become increasingly interested in whether other biological factors could have an influence on psychiatric disorders in the elderly. This interest started with a patient who had a treatment resistant depression, but by coincidence was discovered to have primary hyperparathyroidism,

despite normal calcium values. He went in to full remission the day after surgery for his condition.

In the context of biological factors, there has been a growing interest in a potential association between dietary/nutritional factors and psychiatric disorders (29). In the Hordaland Health Study adult subjects with better quality diets were less likely to be depressed and a high intake of processed and "unhealthy" food was associated with an increased level of anxiety (30). The same findings were reported in an adult Australian population (29). Studies on self-reported diets are complex to interpret. Consequently, several studies have focused on psychiatric disorders and deficiency of specific micronutrients. Micronutrients are nutrients required by humans in small quantities and are essential in the human body. The micronutrients include vitamins and minerals such as iron and zinc. Attention has particularly been on vitamin B12, folic acid, vitamin D and fatty acids, but also minerals such as zinc and magnesium (31-36). Several physiological and biological changes involved in ageing affect nutritional status and make deficiencies of macronutrients - and micronutrients more common in elderly individuals (37) .

Vitamin D is of particular interest for elderly patients living at high latitudes, above the Arctic Circle due to limited sun exposure during the winter. There is also limited knowledge about the prevalence of vitamin D deficiency in elderly with psychiatric disorders (38). A number of different micronutrients, such as the minerals zinc and magnesium are important for the human body, including brain function (39,40). Malnutrition is more prevalent in elderly individuals and this age group may consequently be at risk of deficiency of specific micronutrients. In the last years there has been published several interesting studies on zinc deficiency and depression (41-43). However, there is limited knowledge of the zinc status of

elderly patients with psychiatric disorders. Studies have also demonstrated a huge variation in zinc status between different countries (44). Most studies of both zinc and vitamin D have focused on depression, thus there is a need for more studies investigating zinc and vitamin D status in elderly with other diagnoses than depression.

Although observational studies will not provide answer to whether these micronutrients have an influence on psychiatric disorders in elderly patients admitted to psychiatric hospitals, increased knowledge about zinc and vitamin D status in this patient group will be an important foundation for intervention studies.

1.4 Vitamin D

There has been an increasing interest in vitamin D deficiency over the last decade. The vitamin is important for bone health, the prevention of osteoporosis and fractures (45). Vitamin D deficiency has also been linked to several non-skeletal conditions, including cancer, diabetes, higher overall mortality, multiple sclerosis and premature aging (45-48). Vitamin D deficiency can cause proximal muscle weakness and muscle pain (49) and vitamin D supplementation has been reported to increase muscle strength and balance, and to reduce the risk of falling (50,51). There has been some discrepancy between findings from observational studies and intervention studies and several of these associations are still under debate (52,53).

1.4.1 Sources of vitamin D

Vitamin D is a fat-soluble vitamin and is essential for humans. There are two sources of vitamin D, either a production in the skin by sun exposure or via dietary consumption. Only a few types of food naturally contain vitamin D_3, such as salmon, mackerel and cod liver oil. In

addition, dietary vitamin D_3 can be obtained through supplements and fortified foods such as milk and margarine. In Norway, vitamin D is mainly consumed as cholecalciferol (vitamin D_3) from animal sources such as fat fish, cod liver oil and some diary products, which are fortified with vitamin D_3 (54,55). The vitamin can be obtained also in the diet as ergocalciferol (vitamin D_2) from plant sources such as mushrooms and yeast products (56,57). Vitamin D_2 contributes only to a limited extent to the total vitamin D consumption in a normal Norwegian diet and is rarely used in supplements in Norway. In most countries the main source of vitamin D is exposure to sunlight (58). Ultraviolet B (UVB) radiation in the wavelength 290-315 nm converts 7-dehydrocholesterol in the skin to previtamin D_3, which is then converted to vitamin D_3 (59). In the liver, the vitamin is then hydroxylated to 25-hydroxyvitamin D (25(OH)D) and further hydroxylated in the kidneys to its active form, 1,25 dihydroxyvitamin D ($1,25(OH)_2D$) (45). Serum 25(OH)D is used to evaluate vitamin D status. Several variables influence how effective the sunlight-derived UVB is, including season, latitude, time of the day, presence of clothing, sunscreen use, age and pigmentation (60). Latitude and season affect the quantity and quality (wavelength) of solar radiation and thus influence the ability of sunlight to synthesize vitamin D_3 in skin. From October to March, skin exposed to sunlight did not produce previtamin D_3 in Edmonton, Canada (52 ° N) (61). In Northern Norway the sun is below the horizon for up to 2 months during the winter and at 70 degree latitude the synthesis of vitamin D in the skin is reported to be absent for 5 months (62). The population living in this area is therefore likely to be dependent on dietary sources of vitamin D during a considerable part of the year (63). Furthermore, aging is associated with low levels of 7-dehydrocholesterol, the precursor of vitamin D_3 in the skin (58). *Holick et al.* have demonstrated a 75% reduction in the capacity to make previtamin D_3 in 70 years old people as compared to young people (64).

1.4.2 Prevalence of vitamin D deficiency

There has been some debate concerning the optimal range of serum 25(OH)D. Serum levels of 25(OH) D below 50 nmol/L are associated with an increase in serum PTH levels (65) and a decrease in physical performance in older individuals (66). It has been suggested that serum 25(OH)D levels above 50 nmol/L are sufficient to sustain bone density and calcium absorption and to prevent osteomalacia (67). This cut-off level is now widely used in studies of vitamin D deficiency. Low levels of vitamin D have been reported in 40% of the adult population in North Trøndelag, Norway (68), but hypovitaminosis D is not only a problem in countries at higher latitudes. A review by *Mithal et al.* (69) concluded that hypovitaminosis D is common in all parts of the world. Indeed, several studies from different countries in Europe have revealed a very high prevalence of vitamin D deficiency especially among institutionalised elderly persons (70,71).

1.4.3 Vitamin D deficiency and mental health symptoms

An association between vitamin D deficiency and depression or depressive symptoms has been found in several cross-sectional studies (72-75). Only a few randomized controlled trials (RCTs) have been conducted studying the effect of vitamin D treatment on depressive symptoms, but with inconsistent results (76-78). The effects of vitamin D supplement in combination with an antidepressant was recently investigated in a small RCT, with significantly more improvement in patients receiving vitamin D and antidepressant vs. placebo and antidepressant (79). There are also studies reporting an association between vitamin D deficiency and psychosis (80-82). Even cognitive impairment has been associated

with vitamin D deficiency (83,84). However, there is lack of knowledge about vitamin D status in elderly persons with psychiatric disorders.

1.5 Calcium regulation

Vitamin D and parathyroid hormone (PTH) play central roles in calcium regulation. PTH secretion is mainly regulated by calcium. Low levels of ionised calcium increase PTH secretion. PTH regulates the serum calcium level by increasing calcium reabsorption in the kidneys and by increasing the release of calcium from the skeleton (85). The conversion of 25(OH)D to its active form 1,25(OH)$_2$D is also stimulated by PTH. An increase in 1,25(OH)$_2$D leads to increased calcium absorption in the gut, increased calcium resorption from bone and reduced excretion in the kidneys, which results in increased serum calcium (86).

1.5.1 Primary hyperparathyroidism

Primary hyperparathyroidism (pHPT) is caused by a hypersecretory state of one or more of the four parathyroid glands, where the parathyroid glands lose the ability to regulate PTH secretion via a negative feedback mechanism with calcium (87). Patients on litium treatment have an increased risk of developing pHPT (88,89). In the past, the classic presentation of pHPT involved the presence of renal stones, bone loss and gastrointestinal symptoms (90). Today, the majority of patients with pHPT are so-called asymptomatic and often discovered by chance because of elevated calcium and PTH levels (91). However, the term "asymptomatic" is somewhat misleading, and refers mainly to the absence of classical symptoms. The "asymptomatic" symptoms include low energy, weakness and cognitive dysfunction (92-94), but also other neuropsychiatric symptoms, including depression, anxiety and psychosis (95-97). The prevalence of pHPT increases with age (98) and is more common

in women (99). A prevalence of 1.5% has been reported in a US population aged 65 years or older (90). A Swedish study has estimated the prevalence of pHPT at 3.4 % in postmenopausal women (100). *Jorde et al.* (101) reported from the Tromsø survey a prevalence of pHPT in older women (70-75 years old) of 3.6%-13.9%, depending on the criteria used to define pHPT.

1.5.2 Normocalcemic primary hyperparathyroidism

Patients with pHPT will usually have increased albumin-corrected calcium and elevated PTH levels. This is however not always the case. A subgroup of patients with pHPT has elevated PTH and normal calcium levels (102,103). The subgroup of normocalcemic pHPT has been described and officially recognized at the third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism (104). The level of vitamin D may be normal, but vitamin D deficiency is more common in patients with pHPT than in matched controls (105). The serum calcium can fall into the normal range due to co-existing vitamin D deficiency (105). Severe vitamin D deficiency can also cause secondary hyperparathyroidism (106). This complex relationship between calcium, PTH and vitamin D is shown in Table 1. In geriatric psychiatry departments in Norway, it is common to measure serum calcium, but not PTH. There is insufficient knowledge about normocalcemic pHPT and we fear that some patients may have psychiatric symptoms due to this underlying condition without the proper cause being identified.

Table 1 Differential diagnosis of primary hyperparathyroidism, typical laboratory findings.

Differential diagnosis of primary hyperparathyroidism, typical laboratory findings

Disease	Laboratory test				
	Intact PTH	Serum calcium	Urinary calcium (mg/24 hours)	Ca/Cr clearance	25OHD
PHPT	High-normal or elevated	Elevated	Normal or elevated	0.01 to 0.05 (>0.02)	Normal or low-normal
Malignancy	Low (<20 pg/mL)	Elevated	Elevated		Depends on malignancy*
FHH	Normal, mildly elevated in 15 to 20 percent	Elevated	Low (<100)	<0.01	Normal
PHPT with vitamin D deficiency	Elevated	Normal or elevated	Low-normal or low (<200)		Low (<20 ng/mL)
Normocalcemic PHPT	Elevated	Normal	Normal		Normal
Secondary hyperparathyroidism due to vitamin D deficiency	Elevated	Normal or low	Low		Low (<20 ng/mL)

PHPT: primary hyperparathyroidism; FHH: familial hypocalciuric hypercalcemia; 25OHD: 25hydroxyvitamin D; Ca/Cr: calcium/creatinine.
* 25-hydroxyvitamin D is often normal in malignancy. It could be low in cases of concomitant vitamin D deficiency, due to poor dietary intake and little sun exposure. The 1,25-dihydroxyvitamin D may be elevated, depending upon the malignancy.

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*1 ng/ml 25(OH)D = 2.496 nmol/L 25(OH)D
* 1pg/ml PTH = 0.1061 pmol/L PTH

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1.6 Zinc

Zinc is a trace element that is essential in numerous aspects of human metabolism. More than 300 enzymes depend on zinc as a co-factor (107). The trace element is essential in gene regulation (108) and in immunological function (109). Zinc is also important for brain growth and function throughout the lifespan (110,111). Recommended daily dietary zinc requirement according to the US Food and Nutrition Board is 11 mg for men and 8 mg for women (112). The most important source of zinc is red meat, while fish and poultry contain substantially less zinc (112).

1.6.1 Zinc deficiency

A serum zinc value below 10.7 µmol/L has often been used to define zinc deficiency, but the cut-off value is dependent on gender, fasting condition and age (113). In a US National Survey with 29,103 participants, total zinc consumption was assessed. Elderly persons over 70 years old, adolescent females and young children between 1 and 3 years old were at the greatest risk of insufficient zinc intake (114). Several studies have also measured zinc levels in an elderly population, with some conflicting results. A study conducted on 188 healthy middle aged persons (55-70 y) and 199 healthy elderly persons (70-85 y) from Italy, France and UK reported a prevalence of zinc deficiency of <5 % (115) . There was no significant difference in serum zinc levels between middle aged and older participants. In this study, the cut-off level for zinc deficiency was 10.7 µmol/L. However, another large European study of 853 healthy elderly persons found a prevalence of zinc deficiency of 31% (cut-off level: 11.0 µmol/L). This study also demonstrated a surprisingly large difference in zinc levels between countries (44). The French sample had a mean plasma zinc value of 14.2 µmol/L, in contrast to only 11.3 µmol/L in the Greek sample. A detailed food questionnaire revealed that French

participants consumed a wider range of food rich on zinc compared with the Greek participants. In another study of hospitalised elderly patients, a prevalence of 28% of zinc deficiency was reported (116).

One main cause of zinc deficiency is low dietary intake of zinc (114,117), but zinc deficiency can also occur due to diseases that impair intestinal absorption or increase intestinal loss of zinc (112). In older people, poor appetite and difficulties in chewing (meat) could also contribute to low dietary intake of zinc (117). However, the relation between malnutrition and zinc deficiency is still not fully investigated.

Mild and moderate zinc deficiency is known to cause impaired taste and smell, delayed wound healing and dysfunction in cell-mediated immunity (39). A severe zinc deficiency can cause pustular-dermatitis, diarrhea, weight loss and infections due to cell-mediated immunity dysfunction (39).

1.6.2 Zinc deficiency and mental health symptoms

An association between low plasma zinc levels and depressive symptoms has been demonstrated in several studies (43,118). However, only two randomized controlled trials (RCTs) have been conducted in a clinically depressed patient group, using zinc as an augmentation to antidepressant medication (41,42). In one small study a significantly better outcome on depressive symptoms was demonstrated in the zinc group compared to the placebo group (41), whereas another larger study with a similar design did not find a better outcome in the zinc group (42). However, in the last study a significant reduction in depressive symptoms was reported in patients with treatment resistant depression (42). Animal studies appear to support an association between zinc deficiency and depression.

Experimentally-induced zinc deficiency in rodents enhances depression-like behaviour (119,120).

There are several possible biological hypotheses that have been put forward to account for the relationship between zinc deficiency and depression. Several studies indicate that increased glutaminergic neurotransmission is associated with depression (121,122). Zinc may lower the glutamate response by a direct inhibition of post-synaptic N-methyl-D-aspartic acid (NMDA) receptors (123). Brain derived neurothrophic factor (BDNF) has been shown to play an important role in depression and has been widely studied (122,124). Zinc treatment has been shown to increase BDNF mRNA levels in different parts of the brain, and it seems that mechanisms regulating BDNF expression are more sensitive to zinc in the hippocampus, than in the cortex (125). Zinc is also very important for a normal function of cell-mediated immunity (125). Zinc deficiency leads to increased levels of pro-inflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α, MCP-1) (126) and this has been linked to a growing understanding of how a dysfunction in the immune system may contribute to the risk for developing psychiatric disorders, including depression (127). Serotonin may also play an important role in understanding the mechanisms of zinc in depression. It has been demonstrated that a 5-hydroyxtryptamine (5-HT1A) antagonist can block the antidepressant effect induced by zinc in the forced swim test in mice (128). It has also been shown that chronic zinc administration in rats increases the density of 5-HT1A serotonin receptors in the hippocampus and 5-HT2A serotonin receptors in the frontal cortex (129). This increase in density of 5-HT1A receptors in the hippocampus is similar to the effect caused by most antidepressants, while an increase in the density of 5-HT2A receptors in the frontal cortex has been found after electroconvulsive stimulation, but not after antidepressant pharmacotherapy (130).

Most studies on zinc deficiency in relation to psychiatric disorders have focused on a potential role in depression. Only a few studies have investigated zinc deficiency in patients with schizophrenia compared to controls, with conflicting results (131,132). However, one interesting animal study did find anxiolytic, antidepressant and antipsychotic-like effects of zinc (133). We have not found any studies investigating zinc deficiency in older patients with a wider range of psychiatric diagnoses. There is a need for more knowledge about whether zinc deficiency is more common in patients with depression than in patients with other psychiatric disorders. The prevalence of zinc deficiency in a general elderly population appears to differ between countries, probably due to a variation in dietary habits (44). Very few studies have been conducted in northern Europe to establish the prevalence of zinc deficiency in the community living elderly.

2 Aims of the thesis

Based on the knowledge of calcium metabolism, vitamin D and zinc deficiency summarized in the Introduction, this thesis will concentrate on the following aims:

1) To explore the prevalence of vitamin D deficiency in elderly patients referred to a psychiatric hospital compared to a control group of community living elderly.
2) To explore if there is a difference in vitamin D deficiency between patients in different diagnostic groups included in a psychogeriatric sample.
3) To examine the prevalence of zinc deficiency in elderly patients referred to a psychiatric hospital compared to a control group of community living elderly.
4) To examine if there is a difference in zinc deficiency between patients in different diagnostic groups included in a psychogeriatric sample.
5) To explore if there is a correlation between zinc deficiency and risk of malnutrition or depressive symptoms among community living elderly.
6) To explore the topic of normocalemic hyperparathyroidism by reviewing a selection of relevant literature and illustrating the topic by means of a case.

3 Subjects

3.1 Subjects in studies I-IV (papers I-IV)

The participants in the case-control studies (study II and III) were patients over 64 years old, referred to psychiatric treatment at the University Hospital of North Norway during the study period of March 2010 - December 2011. The hospital covers a population of 255,000 and is the only psychiatric hospital in the region of the counties of Troms, Finnmark and the northern part of Nordland (Ofoten). The patients were either hospitalized acutely or referred to a planned stay or outpatient treatment. In study II and III, 5 out of respectively 95 (study II) and 100 (study III) participants were outpatients. The participants represent a patient population who either has become acutely ill, or has some sort of treatment-resistant psychiatric disorder. The patient in the case report (study I) was admitted to the same psychiatric hospital.

The participation rate was high. A total of 107 patients were asked to participate in the study, but 5 refused to participate. Two patients were excluded due to current infection. In the vitamin D study (study II), additionally 5 patients were excluded due to lack of serum in the sample tube. As controls in study II, serum from 104 individuals who had participated in the Tromsø 6 survey, were matched for gender, age, body mass index (BMI) and season. This control group was originally recruited to a diabetic study, and had normal glucose tolerance (134). The controls in study III were selected from participants aged 65 to 87 years in the Tromsø 6 survey. Out of a total of 4017 men and women in this age-group, zinc and albumin were analyzed in a random selection of 1765 individuals. Due to different cut-off values during the day, only 882 individuals who had their blood sampled before noon were selected as controls for study III. The group of 1765 individuals from the Tromsø 6 survey were the same subjects included in study IV. Information about weight/height or weight loss was

missing for 200 subjects, and in addition 44 blood samples were discarded due to lack of serum. Thus a total of 1521 participants were included in the study presented in paper IV. An overview of the participants is displayed in Table 2.

Table 2 Participants included in the studies referred to in this thesis (paper I-IV)

	Patients admitted to psychiatric hospital	**Controls from the Tromsø 6 survey**	**Participants from the Tromsø 6 survey**
Paper I	**1**		
Paper II	**95**	**104**	
Paper III	**100**	**882**	
Paper IV			**1521***

* The controls in paper III are included in the sample studied in paper IV.

3.2 The Tromsø 6 survey

The Tromsø 6 study was conducted between October 2007 and December 2008. An invitation was sent to all community living inhabitants in the Tromsø municipality aged 25 to 87 years. A total of 4017 men and women 65 years and older participated, resulting in an overall participation rate of 66%. Only 8 of 4017 (0.2%) participants were nursing home residents.

3.3 Ethics

All participants in study II and III were provided with oral and written information about the study. Due to medical conditions (i.e., dementia), some patients were unable to provide consent alone. Their next of kin were then provided with similar information. A written consent prior to the inclusion in the study were provided from the patient or, when necessary,

from the next of kin. Competency to provide consent was assessed according to established guidelines (135). The person in the single case report (study I) provided a written consent. The controls in study II and III, and the subjects in study IV participated in the Tromsø 6 survey, and gave a written consent for the use of blood samples and information collected in the survey. All the studies were approved by the Regional Committee for Medical and Health Research Ethics for North Norway (REC North).

4 Methods

4.1 Assessment of mental health

4.1.1 The Mini International Neuropsychiatric Interview (study II and III)

The Mini International Neuropsychiatric Interview (MINI) is a short structured diagnostic interview (136). It was developed for both DSM-IV and ICD-10 psychiatric disorders. The MINI+ is a more comprehensive version including 26 diagnostic items (136). The validity of the MINI in relation to both the Structured Clinical Interview (SCID; DSM-III R) and the Composite International Diagnostic Interview (CIDI; ICD-10) has been reported to be good, with the exceptions of generalized anxiety, agoraphobia and bulimia (CIDI) (136).

4.1.2 Montgomery-Åsberg Depression Rating Scale (study II and III)

The Montgomery-Åsberg Depression Rating Scale (MADRS) was originally developed to monitor changes in depressive symptoms in clinical trials (137). The scale consists of 10 items tapping different symptoms of depression and has very few items that tap symptoms that could be caused by physical disorders or functional impairment (137). Each item can be graded from 0 (no symptoms) to 6 (most severe symptoms). MADRS has been validated as a screening instrument for depression in late life, with a suggested cut-off point of 16/17 (138).

4.1.3 Cornell Scale for Depression in Dementia (study II and III)

Depression rating scales that are based on information provided by the patient either as a questionnaire or interview are problematic in people with dementia due to impairments in concentration, memory and judgement. In this context the Cornell scale was introduced in 1988 and validated for use in the elderly with dementia (139). The assessment of depression in demented patients requires observation over time, thus the Cornell scale is designed to utilize information from the patient's caregiver and from a brief interview with the patient (139). The Cornell scale has also been validated for use in the elderly without dementia (140). The scale consists of 19 items designed for the rating of symptoms of depression in persons with dementia. The severity of each item is rated: absent = 0, mild or intermittent =1 and severe = 2. A cut-off point of 8 and above has been reported to be valid for elderly with and without dementia (138).

4.1.4 Hopkins Symptom Checklist (study IV)

The Hopkins Symptom Checklist (SCL) originally consisted of 90 questions, and has later been shortened to 25-item and 10-items versions. The SCL-10 version has shown a good correlation with the validated SCL-90 version (141). The SCL-10 was a part of the Tromsø 6 survey and consists of 10 questions measuring symptoms relating to depression and anxiety. Each question is rated on a four-point scale ranging from 1 (not at all) to 4 (extremely) and the final score is calculated by dividing the total score by the total number of items. A score of $\geq$ 1.85 has been proposed to represent significant symptoms of mental distress (141,142), and this cut-off score is used in study IV.

4.1.5 Mini Mental State Examination (study II and III)

The Mini Mental State Examination (MMSE) was designed as a short examination that concentrates only on the cognitive aspects of mental functions (143). The reliability and validity are reported to be satisfactory (144), and it has a high level of sensitivity for moderate-to-severe cognitive impairment and lower for mild degrees of impairment (144). The MMSE is divided into seven categories; orientation to time, orientation to place, registration of three words, language and visual construction. The test has a maximum score of 30 points and a score of 23 or less has been reported to indicate the presence of cognitive impairment (144).

4.1.6 Clock-Drawing Test (study II and III)

The Clock-Drawing Test (CDT) was designed as a screening tool for cognitive impairment (145). The CDT is reported to have a high correlation with MMSE and other cognitive tests (145). The test has been validated in hospital settings and in older general population settings (146-148). Several versions of the CDT have been developed. In our study a predrawn circle was used and the participants were told to put the numbers on the clock, then the participants were asked to set the time to ten past eleven. There is a maximum score of 5 in the Norwegian version used in our studies.

4.1.7 Questionnaires (study II, III and IV)

The patients participating in the vitamin D and zinc studies (study II and III) were interviewed within the first 3 days after admission. In this interview data regarding education, physical activity, outdoor activity, smoking, alcohol and dietary supplements were collected. The following variables were constructed from patient records: Marital status, previous admissions, physical disorders and medication. The participants in the Tromsø 6 survey did

fill in a self-administrated questionnaire and this was used to obtain information about marital status and smoking habits.

4.2 Assessment of nutritional status

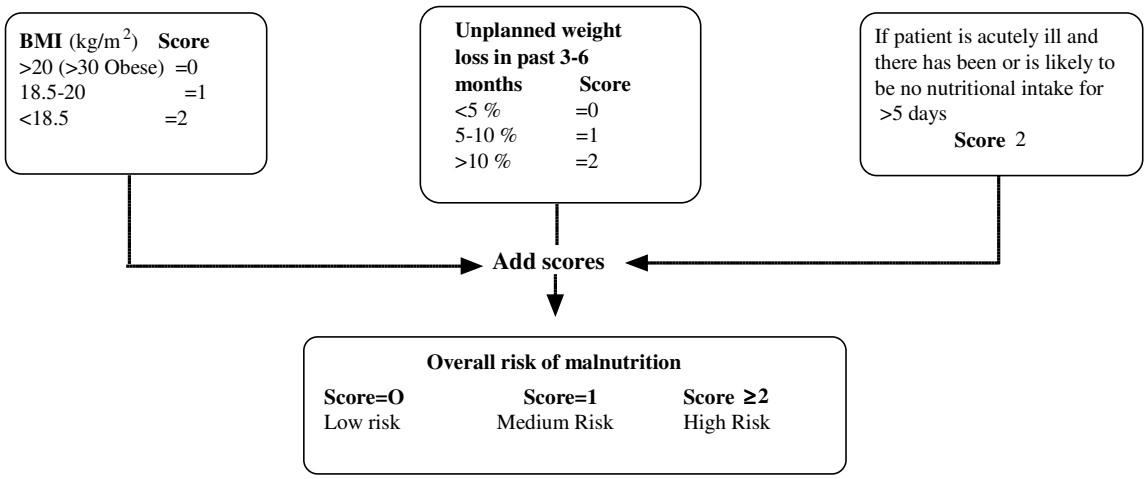
4.2.1 Body Mass Index (study II-IV)

Weight (kg) and height (cm) were measured at the research centres. Participants wore light clothing and no shoes. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared (kg/m²).

4.2.2 Malnutrition Universal Screening Tool (study II and III)

The Malnutrition Universal Screening Tool (MUST) includes a grading of both BMI and weight loss in three categories in addition to an acute disease component (Figure 1) (149). Participants in the Tromsø 6 survey were asked in a questionnaire about any involuntary weight loss during the previous six months (and if so, how many kg). The acute disease component was set to zero, because participation in the Tromsø survey requires the ability to independently visit the research centre.

Figure 1 The Malnutrition Universal Screening Tools (MUST). The risk of malnutrition can be assessed based on the sum of BMI score, a weight-loss score and an acute illness component



The Malnutrition Universal Screening Tool is reproduced here with the kind permission of BAPEN (British Association for Parental and Enteral Nutrition. For further information on MUST and management guidelines, see www.bapen.org.uk.

4.3 Laboratory Analyses

4.3.1 Serum 25(OH)D (study II)

Several methods for quantification of 25(OH)D in serum exist. In study II serum was analyzed for 25(OH)D (sum of 25(OH)D_2 and 25(OH)D_3) at the Hormone Laboratory, Oslo University Hospital and a competitive radioimmunoassay (DiaSorin, Stillwater, MN, USA) method was used. The serum levels of 25(OH)D are expressed as nanomoles per liter. The intra-assay coefficient of variation (CV) is 6%. Total CV is 13% at low levels (38 nmol/l), 16% at middle levels (75 nmol/l) and 14% at high levels (148 nmol/l). Blood samples for 25(OH)D from the patient group were drawn in the morning before 10 AM during the first 3 days of the hospital stay and were stored at -70ºC. The blood samples were analyzed after the

study was completed. The blood samples for 25(OH)D from the control group were drawn when the participants visited the research center and the samples were stored at -70ºC.

4.3.2 Zinc (study III and IV)

For the zinc analyses, trace-metal-free tubes and special gloves were used to avoid contamination. The samples of serum were frozen and stored at -70 C. Serum zinc was later analyzed using a flame atomic absorption at 213.9 nm (Perkin Elmer A-Analyst 800 Atomic Absorption Spectrophotometer) at the Biochemical Department at St.Olavs Hospital, Trondheim. The serum levels of zinc are expressed as micro-mol per liter.

The blood samples for zinc analysis in the patient group were collected before 10 AM, but due to other considerations (laboratory staff logistics), 64% of the samples were collected after patients fasted overnight and 36% of the samples were collected under non-fasting conditions. In the control group, the blood samples were collected under non-fasting conditions between 8 AM and 12 AM. Different cut-off values for serum zinc have been recommended by the International Zinc Nutrition Consultative Group (150) depending on gender, fasting condition and time of blood sampling (i.e., AM or PM). In the studies presented in paper III and IV we have applied the cut-off values for zinc deficiency as defined in the IZiNCG guidelines. For men cut-off values (AM) are 11.3 µmol/L (fasting) and 10.7 µmol/L (non-fasting) and for women (AM) 10.7 µmol/L (fasting) and 10.1 µmol/L (non-fasting). A large proportion of zinc in serum is bound to albumin (108), thus an additional assessment of serum albumin was performed using the brom-cresol green method (Hitachi Modular P, Roche). The lower reference level for serum albumin was 35.0 g/L.

4.4 Statistical analyses

For the statistical analysis, SPSS 20 (SPSS, Inc., Chicago, Illinois, USA) was used. Normal distributions were evaluated using the Kolmogorov-Smirnov test. Baseline differences were analysed using independent samples t-test or Mann-Whitney U test for continuous data, and chi-square tests for dichotomous data. Two sided P-values <0.05 were accepted as statistically significant. In study II, differences in serum 25(OH)D levels between the patient and the control group were analysed using the independent t-test and differences in vitamin D deficiency (yes/no) were analysed using the chi-square test. A logistic regression analysis was performed to assess the association between vitamin D deficiency and the sample variables (patient vs. control), controlling for potential confounders. The result was reported as an odds ratio (OR) with 95% confidence intervals. Due to several small cells (n<5), the Fisher's exact test was used to examine the association between vitamin D deficiency status and psychiatric diagnoses. A one-way analysis of variance (ANOVA) was used to analyse the differences in serum 25(OH)D levels across different diagnostic groups.

In study III, difference in zinc deficiency (yes/no) between the patient group and the control group was analysed using the chi-square test. The association between zinc deficiency and patient/control status was assessed using a logistic regression model, controlling for age, gender, smoking status, living alone, BMI and albumin. The result was reported as an odds ratio (OR) with 95% confidence intervals. Differences in zinc levels between three patient groups were tested using one-way analysis of variance (ANOVA).

In the cross-sectional study (study IV), differences between participants according to zinc status were analyzed using the Chi-square test and the t-test. The association between risk of

malnutrition and zinc deficiency was analyzed in a logistic regression model adjusting for age, gender, albumin and smoking status. The result was reported as an odds ratio with 95% confidence intervals.

5 Summary of results

Paper I

Normocalcemic hyperparathyroidism and treatment resistant depression.
Grønli O, Wynn R.
Psychosomatics. 2013 Sep-Oct;54(5):493-7. doi: 10.1016/j.psym.2012.10.008. Epub 2013 Jan 23

The aim of paper I was to summarize the knowledge of neuropsychiatric symptoms possibly related to primary hyperparathyroidism (pHPT), with a focus on normocalcemic pHPT. This was done using a case report and a discussion in the context of a selection of literature on the topic. Patients suffering from pHPT may display symptoms such as depression, anxiety, psychosis and reduced neurocognitive function. As in our case, the pHPT is not always linked to elevated calcium levels above an upper threshold. A subgroup of pHPT named normocalcemic primary hyperparathyroidism has been officially recognized. Several studies have not found a correlation between serum calcium and the severity of neuropsychiatric symptoms, including depression, although there are some conflicting results. Case-control studies, with few exceptions, have shown an improvement in neuropsychiatric symptoms after surgical parathyroidectomy. Only a few randomized controlled trials on effect of parathyroidectomy have been conducted. Two RCTs found a modest effect on neuropsychiatric symptoms, while one RTC did not find any effect. There is a need of more studies focusing on patients with pHPT with more severe neuropsychiatric symptoms

Paper II

Vitamin D deficiency is common in psychogeriatric patients, independent of diagnosis

Grønli O, Kvamme JM, Jorde R, Wynn R.
Submitted to BMC Psychiatry.

The aim of the study in paper II was to determine the vitamin D status in elderly (> 64y) patients referred to a psychiatric hospital, in comparison to an elderly control group from the general population. Psychiatric and cognitive symptoms were assessed using the MADRS, Cornell, MMSE and Clockdrawing tests. A MINI+ interview, clinical interview, review of medical records and results from tests were used to diagnose the patients. The mean level of 25(OH)D in the patient group (n=95) and the control group (n=104) were 40.5 nmol/L and 65.9 nmol/L, respectively ($p< 0.001$). A high prevalence of vitamin D deficiency was found in the patient group compared with the control group (71.6% vs. 20 %, $p <0.001$). After adjusting for age, gender, season, body mass index and smoking, vitamin D deficiency was still associated with patient status (OR 13.0, CI (95%) 6.0-27.8, $p <0.001$). We found no significant differences in the prevalence of vitamin D deficiency between patients with different categories of psychiatric diagnoses, such as depression, bipolar disorder, psychosis or dementia.

Vitamin D deficiency is very common among psychogeriatric patients, independent of diagnostic category. Even though the role of vitamin D in psychiatric disorders is not established, screening for 25(OH)D in this patient group clearly is important due to the importance of vitamin D for overall health.

Paper III

Zinc deficiency is common in several psychiatric disorders.
Grønli O, Kvamme JM, Friborg O, Wynn R.
PLoS One. 2013 Dec 19;8 (12):e82793. doi: 10.1371/journal.pone.0082793. eCollection 2013

Our aim in paper III was to explore the zinc status of elderly patients referred to a psychiatric hospital in comparison to a control group from the general population. Psychiatric and cognitive symptoms were assessed using the MMSE, Cornell, MMS and Clockdrawing tests. A MINI+ interview, clinical interview, review of medical records and results from tests were used to diagnose the patients.

The prevalence of zinc deficiency in the patient group (n=100) was 41.0% and in the control group (n=882) 14.4 % ($p<0.001$). The association between zinc deficiency and patient /control status was further analysed with logistic regression analyses. In a model adjusting for the fasting condition, gender and age, zinc deficiency was found to be associated with depression/comorbid depression and other psychiatric disorders.

In a model that in addition adjusted for smoking status, living alone, BMI and albumin, only gender and albumin made significant contributions to the model. The relationship between zinc and albumin is complex, and a logistic regression model without albumin might provide the most interesting results. The prevalence of zinc deficiency in the patient group was significantly higher in patients without depression (i.e., with other diagnoses) than in patients with either depression or comorbid depression ($p=0.037$).

Paper IV

Risk of malnutrition and zinc deficiency in elderly men and women – a cross sectional study

Kvamme JM, Grønli O, Jacobsen BK, Florholmen J.

Submitted to Public Health Nutrition

The aim in paper IV was to study a possible association between zinc status and risk of malnutrition and mental health symptoms in a cross-sectional population based survey of community living elderly men and women. Non-fasting zinc was measured in a random sample of 1521 participants. The risk of malnutrition was assessed using the Malnutrition Universal Screening Tool and mental distress was measured with the Hopkins Symptoms Check List-10 (SCL-10).

The prevalence of zinc deficiency in men and women at risk of malnutrition was 31% (men) and 6.7% (women) respectively. In a model adjusted for age, gender, smoking status and serum albumin; zinc deficiency was positively associated with the risk of malnutrition (odds ratio 2.2 (95% CI 1.3-3.6)). We did not find any significant differences in mental distress symptoms between participants with or without zinc deficiency. Our results support the value of assessment of zinc status in elderly people at risk of malnutrition.

6 General discussion - Methodology

6.1 Selection of population and study design

In case-control studies individuals with and without the outcome of interest are studied. Both cases and controls should come from the same population (5). The main studies in this thesis (study II and III) have a *case-control* design. The cases were patients aged over 64 years, admitted to a psychiatric hospital. The patients were either admitted acutely or referred to a planned stay or outpatient treatment. They represented a patient population that either had become acutely very ill, or had some sort of treatment-resistant psychiatric disorder. The controls in study II and III were individuals participating in the Tromsø 6 survey. All community living inhabitants in the age category $\geq$ 64 years were invited. Laboratory analyses of zinc and vitamin D were performed in a random selection of participants. They represented a selection of individuals aged older than 64 years who had been randomly selected for further tests, including blood tests. The study presented in paper IV was population based, drawing participants from the Tromsø 6 survey and had a *cross-sectional* design. The nature of *case-control* studies and *cross-sectional* studies render us unable to draw conclusions concerning causality.

6.2 Validity and Bias

Internal validity concerns the degree to which the results are representative or true for the population that has been studied. The external validity concerns whether it is possible to apply the results to other populations (5). A good internal validity is a precondition for external validity. Bias is systematic errors in estimates that tend to produce results that deviate systematically from the true values (151). Three types of bias can violate the internal validity: selection bias, information bias and confounding (151).

6.3 Selection bias

The patients in the case-control studies (study II and III) were included consecutively in the period from March 2010 until December 2011. Two persons conducted the interviews and it was not possible to include all patients older than 64 years referred to the psychiatric hospital during this period. This was due to travel and vacations, but also due to patient conditions. It is not likely that lack of inclusion in one vacation month (July) has an influence on the main results of the studies.

Patients who were not able to participate in an interview due to medical conditions (i.e., severe dementia) were not included in the study. A few patients (n=5) did not want to participate. The distribution of diagnostic groups in study II and III were typical for patients referred to geriatric psychiatry wards in Norway, an issue that will be discussed in the external validity section. With the exception of patients with severe dementia, the selection bias should be small.

In a case-control design, it is a prerequisite that the controls do not have the disorders of the patients one wants to study. *Hansen et al*. (152) reported that non-attendees in a survey had a 2.5-fold higher prevalence of psychiatric disorders compared with attendees. We did not have access to the mental health status for participants in the control group in study II and III. In the cross-sectional study (study IV) we found a low median SLC-10 score (1.1 in men and 1.2 in women) in 1521 elderly participants representing the same population as the controls in study II and III, and in another study on the same elderly population only 3.9% of men and 9.1 % of women had a SCL score $\geq$ 1.85 (153). Thus it is not likely that elderly patients with significant mental distress to any great extent participated in the population survey. In

comparison to elderly patients admitted to a psychiatric hospital, the control group in study II and III should be regarded as healthy.

The cross-sectional zinc study (study IV) is based on data from the Tromsø 6 study. The attendance rate for participants of 65 years or older was 65.9 % (153). The response rate for the highest age group (over 80 years) was below 50%. Lower mortality rates have been reported in persons who participate in population surveys, compared with those who do not (154). In one study, individuals over 70 years reported immobility due to disease and sufficient follow-up by the family doctor as important reasons for not participating (155). Persons with a reduced cognitive function or dementia are more likely to not participate in surveys. Thus, a certain selection bias is likely. This selection bias could perhaps have influence on the prevalence numbers of zinc deficiency found in the elderly general population. The association between risk of malnutrition and zinc deficiency is less likely to be influenced by a selection bias.

6.4 Information bias

Systematic errors in a study can occur because the information collected about or from participants is incorrect; this is referred to as information bias or misclassification (151). In the case-control studies presented in paper II and III, the classification of patients in the right diagnostic group was of particular importance. The diagnostic procedures included MMSE, MADRS, MINI+ interview, Cornell (when necessary) and access to medical record information. The MINI+ interview has been validated in the English version (136). The Norwegian version was introduced in 1999 and both the MINI and the more extended MINI+ have been used in several Norwegian studies (156,157). However, the Norwegian version of MINI+ has not been validated (158). It was not possible to perform a MINI+ interview on all

the patients due to their mental conditions. However, scores from MMSE, MADRS, Cornell, Clockdrawing Test and the access of medical record information which also could include information from next of kin, made it possible to compare symptoms and signs with diagnostic criteria in the ICD-10 manual. In this way the chance of diagnostic misclassifications is rather small.

In the cross-sectional study presented in paper IV, the SCL-10 instrument was used (see section 4.1.4). The SCL-10 version is reported to correlate highly with the SCL-25 version in a population-based Norwegian study (141). *Sandanger et al.* (159) have demonstrated that SCL-25 only predicted 46% of the diagnoses found by using a structured diagnostic interview (CIDI). Thus a high SCL-10 score ($\geq$1.85) does not necessarily represent or reflect psychiatric disorders of the study subjects and the term *mental distress* is used to describe the score derived from the SCL-10.

Some of the data in study II and III were collected through interviews with patients, when possible. In this interview, data such as time spent outside, exercise and intake of vitamin D supplements were collected. The patients were aware that vitamin D was one of the topics in the study. This kind of interview is vulnerable to recollection bias. In addition, some of the patients had memory problems, which could influence the answers. It is a weakness in the study that we did not confirm data from the interview with data from next of kin. Self-reported information about non-healthy lifestyle habits has also been demonstrated to be underreported (160).

The procedure for blood sampling of vitamin D (paper II) was the same in the patient and the control group. Blood samples from both groups were frozen to -70 and later analysed in the

same batch at Aker Hormonlaboratorium, Oslo. The procedure for blood sampling of zinc was similar in the patient group (study III) and the Tromsø 6 survey. Blood samples were frozen to -70 and later analysed at the Biochemical Department at St. Olavs Hospital, Trondheim. The blood samples from the two groups were not analysed at the same time. This is not ideal, but the measurement method used at the laboratory has an analytic variation of only 4%.

6.5 Confounding

Confounding may be described as a confusion of effects. The effect of the exposure is mixed together with effect of other variables, leading to a bias (5). These extraneous factors are called confounders. A common method to prevent confounding in experimental studies (i.e., treatment studies) is randomisation. In observational studies adjustment for confounders can be done by stratification or by using regression models (5).

Confounding is of particular importance when studying multifactorial psychiatric disorders. Psychiatric disorders could lead to a life-style and diet which can influence levels of serum 25(OH)D and serum zinc. In the vitamin D study (study II) we have statistically adjusted for age, gender, BMI, smoking and blood sampling season. We did not have data for chronic diseases in the control group. Elderly psychiatric inpatients are reported to have higher medical comorbidity than the general population (161). It has been proposed that low 25(OH)D could be a marker for ill health (53). However, in the patient group we did not find any difference in serum 25(OH)D between patients with few (0 or 1) or many (2,3 or 4) chronic diseases (serum 25(OH)D respectively: 38.7 nmol/L and 40.1 nmol/L, p=0.754). In addition we were not able to control for physical activity, educational level or marital status, which have previously been reported to be associated with both serum 25(OH)D and depressive symptoms (75,162,163).

In the case-control zinc study (study III) we were able to control for age, gender, smoking, martial status, BMI, fasting condition and albumin. As for the vitamin D study, we did not have data for chronic diseases in the control group. In a subsequent analysis, we did not find any difference in zinc deficiency in the patient group with 0 or 1 reported chronic diseases or 2,3 or 4 chronic diseases (χ^2 =0.159, p= 0.690). We were not able to control for physical activity, educational level and martial status. However, the information about possible confounding factors that could be associated with both zinc deficiency and psychiatric disorders is limited. Thus it is difficult to predict what influence these possible confounders could have on the results. The same considerations apply to the cross-sectional zinc study (study IV), where the results were adjusted for age, gender, smoking and albumin levels.

The role of serum albumin as a possible confounder is complex. In study III albumin was a predictor for zinc deficiency. There is increasing evidence that depression and other psychiatric disorders are accompanied by an activation of the inflammatory response system (IRS) (124,164). This activation of IRS is known to lower both the zinc level and the albumin level (165). *Maes et al.* (165) have argued that lower zinc levels in depression in part could be explained by lower albumin levels and by other depression-related mechanisms. In an overview article by *King* (108) it was argued that only 1 of every 50 albumin molecules is bound to a zinc atom, and this renders it difficult to ascertain how a reduction in serum albumin could lead to significantly reduced zinc levels. In addition zinc has an influence on albumin synthesis (108,166). The IZiNC group reported that only hypoalbuminemia (<35 g/L) may significantly influence zinc levels (150). We have concluded that a difference in albumin levels between the patient and the control group cannot fully explain the large difference in the prevalence of zinc deficiency.

6.6 External validity

The patient population in study II and III represents a typical sample of psychogeriatric patients, with the exception of patients with severe symptoms of dementia, which were excluded from our studies. In 2012 the Norwegian Board of Health Supervision released a report about the use of geriatric psychiatry wards in Norway (3). The distribution of patients in this report is quite similar to the distribution of patients participating in the studies presented in paper II and III (Table 3), with the exception that there are relatively fewer patients with dementia in our studies. The patients were referred from the entire area of Troms, Finnmark and Ofoten and thus they represent persons from both rural and urban areas. Although we did not have data on mental health in the control group, we have previously argued that the control group should be considered as healthy controls in this context. The findings that indicate a high prevalence of vitamin D and zinc deficiency in a psychogeratric patient population could be generalised to other psychogeriatric populations. There are however several studies on general populations that have demonstrated a rather large variation in zinc levels between countries (44,115), depending on diet habits. Thus, the worldwide generalisability regarding zinc deficiency is more complex. Data on the prevalence of vitamin D deficiency is more robust, indicating that vitamin D deficiency is a global problem (69).

Elderly patients referred to psychiatric services in general have more severe psychiatric disorders than patients treated by a general practitioner (GP). We do not know whether the results from study II and III could be generalised to a GP patient population. In study IV we did not find any association between zinc deficiency and mental distress in elderly persons attending the Tromsø 6 survey. This is in conflict with our findings in study III and implies that the result (i.e., a higher prevalence of zinc deficiency in elderly psychogeriatric patients

compared to a control group) does not necessarily apply to a GP patient population with less severe psychiatric symptomatology.

The study presented in paper IV is based on data from the Tromsø 6 survey. The selection of the study population is important with respect to generalisability. The attendance rate in the age group 60-74 years was high (74%), but only 40% in the age group < 80 years (167). However, 18% of persons over 80 years in Norway live in nursing homes (168). Nursing home residents were also invited, but only 8 of 4017 participants aged 65 years and older were permanent nursing home residents. The attendance rate was actually high for elderly community living persons, and we believe that the results presented in paper IV could be generalised to other populations of community living elderly.

Tabel 3 The distribution of patients in the case-control studies (study II and III) compared to distribution in Norwegian geriatric psychiatry departments (3).

	Norwegian geriatric psychiatry departments	Patients in study II and III
Patients over 80 years old	36%	33%
Women	65%	64%
Affective disorders	43%	42%
Neurocognitiv disorders (i.e., dementia)	53%	36%

7 General discussion - Results

7.1 Introduction

In this thesis we have investigated a selection of biological factors, which could have an impact on psychiatric disorders, especially in the elderly. Hyperparathyroidism is a disease known to cause psychiatric symptoms in some, but not all, patients (169). The condition does not always present with hypercalcemia and could therefore easily be missed. The condition normocalcemic pHPT can occur either as a variation of pHPT (with normal 25(OH)D levels) or as a result of pHPT and vitamin D deficiency. Furthermore, we have studied the prevalence of vitamin D deficiency in elderly with psychiatric disorders. The high prevalence of vitamin D deficiency presented in our study is important because of the impact of vitamin D deficiency on overall health. The condition could also have an impact on psychiatric disorders and low 25(OH)D levels may cause pHPT to be overlooked due to low levels of serum calcium. The last two studies in this thesis focused on another element of nutrition, the micronutrient zinc. We have reported a high prevalence of zinc deficiency in a sample of psychogeriatric patients compared to a control group. However, in a community-living sample of elderly we could not find a significant association between zinc deficiency and mental distress. Malnutrition was associated with zinc deficiency in the community-living sample and could be a cause of zinc deficiency.

Although observational studies do support an association between mental health symptom and both vitamin D deficiency and zinc deficiency, a causal relation between a deficiency state and psychiatric symptoms/disorders has not yet been established. We did not find any correlation between zinc levels and 25(OH)D levels. Whether both zinc and vitamin D deficiency could have an impact on mental health symptoms through common pathways is not known. However, for both conditions an association between low levels and high levels of

proinflammatory cytokines like TNFα has been reported (126,170). Proinflammatory cytokines have been linked to several psychiatric disorders in the advancing field of psychoimmunlogy (164,171). The results in our study are discussed in more detail below.

7.2 Vitamin D deficiency

In study II we found a high prevalence (71.6%) of vitamin D deficiency in elderly patients with psychiatric disorders admitted to psychiatric wards at the University Hospital of North Norway. This was in contrast to a rather low prevalence in a control group (19.2%). Several cross-sectional and cohort studies have found an association between depression and vitamin D deficiency (72-74,172). We have found only one case-control study, comparing young women with depression with healthy controls (173). This study also demonstrated a significant difference in serum 25(OH)D levels between the patient and the control group. An association has also been reported between psychosis and vitamin D deficiency (80,81,174) as well as between cognitive impairment and vitamin D deficiency (84,175,176). To the best of our knowledge, our study (study II) is the first to compare levels of 25(OH)D between a control group and psychogeriatric patients with a wide range of psychiatric disorders.

There are several possible explanations to these findings. We were able to control for some confounding factors, i.e., age, gender, BMI, smoking and blood sampling season. However, it was not possible to control for medical comorbidity. Medical comorbidity in elderly psychiatric inpatients is higher than in the general elderly population (161). In a recently published review article, *Autier et al.* (53) argue that low 25(OH)D levels is a marker for ill health. Older persons with psychiatric disorders could have a diet and outdoor activity pattern that may result in vitamin D deficiency. Healthy controls could be more aware of taking

vitamin D supplements than patients. A total of 39% of the patients reported taking a vitamin D supplement. We do not have the equivalent numbers for the healthy elderly controls.

In our study we did not find any difference in serum 25(OH)D between patients in different diagnostic groups (unipolar depression, bipolar depression, psychosis, dementia and other diagnoses). The number of patients in some of the diagnostic groups was rather small, so we can not rule out the possibility of a type-II error. The main research focus in the relation between vitamin D and psychiatry has previously been on depression. A division of patients into depression as the main diagnosis, depression as part of other diagnoses and other psychiatric diagnoses in our study did not reveal any significant difference in 25(OH)D levels. Even if confounders such as medical comorbidity, diet and outdoor activity can have an impact on both serum 25(OH)D an different psychiatric disorders, it is also possible that vitamin D deficiency can contribute to the development of several psychiatric disorders. Various medical conditions are known to cause a diversity of psychiatric symptoms. In thyrotoxicosis, hyperparathyroidism and vitamin B12 deficiency some persons do not have any neuropsychiatric symptoms, while others have symptoms of anxiety, depression or psychosis (31,169,177). We have also described the same pattern with possible different reactions to zinc deficiency in study III. One hypothesis could be that certain unknown individual factors make some people more vulnerable than others to develop various psychiatric symptoms due to variation in these hormones and micronutrients.

Studies on both humans and animals have proposed possible biological explanations for the impact on vitamin D in psychiatric disorders. Vitamin D receptors have been identified in the human brain (178). Changes in cholinergic, dopaminergic and noradrenergic neurotransmitter systems have been linked to psychiatric disorders (179), and these neurotransmitter systems

can be altered by active vitamin D ($1,25(OH)_2D$) in animal models (180). An alteration in both GABAergic and glutaminergic neurotransmission have been demonstrated in vitamin D deficient mice (181). A dysfunction in both gamma amino butyric acid (GABA) and glutamate neurotransmission has been linked to various psychiatric disorders including depression (182-185).

In study II we found a negative correlation between serum 25(OH)D and PTH, which is in line with other studies (186,187). *Hoogendijk et al.* (187) found an association of depression status and severity with decreased serum 25(OH)D and increased serum PTH levels in older subjects. This study also demonstrated that the PTH level was associated with depression after adjustment for the 25(OH)D level. This could suggest that PTH might have a role in a possible link between vitamin D deficiency and depression. However, PTH stimulates the conversion of 25(OH)D to active vitamin D ($1,25(OH)_2D$). In this study they did not measure serum $1,25(OH)_2D$, thus it is could be that an increased PTH leads to a shift from 25(OH)D to $1,25(OH)_2D$.

Several studies have reported an inverse correlation between 25(OH)D concentrations and serum concentrations of TNFα or C-reactive protein (170,188,189). There is some evidence supporting an association between inflammatory state and psychiatric disorders (164,171). This has led to a postulation that inflammation might be a common factor between non-skeletal health disorders (including psychiatric disorders) and low 25(OH)D levels (53).

A considerable number of observational studies (i.e., case-control, cross-sectional and cohort studies) have been performed focusing on vitamin D deficiency and depression (33). In a meta-analysis by *Anglin et al*. (33) they reported that observational studies provide some

evidence for a relationship between depression and vitamin D deficiency. Only a few well-designed RCTs have been performed. *Dean et al.* (190) did not find any effects of vitamin D supplement on cognitive and emotional functioning on healthy young adults. The same negative finding was reported by *Kjærgaard et al.* (78) in a study on individuals without clinical depression; however post hoc analyses suggested a positive effect in individuals with high depression scores. On the other hand, *Jorde et al.* (77) did find an effect of high dose vitamin D compared with placebo on the cognitive-affective subscale, but not on total Beck Depression Inventory (BDI) score in 334 obese persons. These RCTs do not answer the question whether vitamin D supplementation will be beneficial in patients with clinical depression. Only one study has been published studying effect of vitamin D supplementation on clinically depressed patients (191). In this study an antidepressant (Fluxoetin 20mg) and 1500 IU vitamin D (n=20) had significantly better effect on depressive symptoms than antidepressant and placebo (n=20). We are not aware of any RCT`s investigating the effect of vitamin D supplementation on psychosis (i.e., schizophrenia) or Alzheimer's dementia. Observational studies are not sufficient to answer the question whether psychiatric or cognitive symptoms would improve by an increase in 25(OH)D concentration. More RCTs are needed on patient groups with both low 25(OH)D and clinical depression or other psychiatric disorders.

7.3 Calcium regulation and depression

In study I our aim was to explore the topic of normocalemic hyperparathyroidism by reviewing a selection of relevant literature and illustrating the topic by means of a case. The case was a 70-year-old man admitted to psychiatric hospital because of severe depression. This was his fourth admission due to depression. He did not respond to antidepressant treatment or electroconvulsive treatment. At the time of admission he had a normal level of

albumin-corrected calcium (2.48 mmol/L, normal range 2.15-2.55 mmol/L). During his hospital stay, he was examined by a surgeon because of urinary retention and PTH was measured, which was slightly elevated (9.3 pmol/L, normal range 1.1-7.5 pmol/L). New tests still revealed calcium values in normal range. PTH levels varied from high-normal to elevated. Further investigation with a scintigram revealed two parathyroid adenomas. A surgical parathyroidectomy was performed, and his depressive symptoms disappeared within a few days after the operation. He was without depressive symptoms the following 3 years. A more detailed description of the case can be found in paper I.

The case illustrates some important clinical points. Depression has been described as a symptom of pHPT in several studies (192-194). Interestingly, symptoms of severe depression caused by pHPT were first reported as a case report in 1961 (195). Other neuropsychiatric symptoms including cognitive dysfunction have also been described in studies (93,194,196). Several of the studies investigating neuropsychiatric symptoms have not used control groups, which is a major limitation. A recently published study compared psychiatric symptoms and health-related quality of life in 194 patients with pHPT compared with 186 control subjects undergoing surgery for benign euthyroid nodular goiter. Preoperatively, moderate or severe depression was seen in 16.7% of the pHPT group and 6.5% of the control group (200). This is in line with findings in other studies using control groups (197-199).

The mechanisms causing neuropsychiatric symptoms are not known (200). One possible explanation could be biochemical changes (i.e., in calcium and PTH) associated with pHPT. A correlation between high calcium levels and depressive symptoms has been demonstrated in some studies (199-201), while other studies failed to find any correlation (196,202,203). In a study by *Bargren et al*. (204), patients (n=229) with mild hypercalcemia had significantly

more depression and bone and joint pain than patients with more severe hypercalcemia. However, in this study they found no correlation between baseline PTH values and symptoms, including depression. Despite these findings, other studies have demonstrated a possible correlation between PTH values and neuropsychiatric symptoms. *Roman et al.* (203) examined patients (n=212) who underwent parathyroidectomy and found an association between a reduction in mood and anxiety symptoms and a reduction in PTH levels. In a study of patients with secondary hyperparathyroidism (n=59), the highest levels of PTH was found in the most depressed patients (205). PTH passes the blood-brain barrier (206), and receptors for PTH have been found in the central nervous system (207,208). A study of human brains has demonstrated that parathyroid receptor 2 is expressed in locations that suggest involvement in regulation of anxiety and fear (208).

Changes in cerebral blood flow in the brain may also be an explanatory factor. Reduced regional cerebral blood flow assessed by single-photon emission computer tomography (SPECT) has been demonstrated in patients with depression (209,210). In a prospective study of 16 patients with pHPT, *Mjåland et al.* (211) revealed a reduced regional cerebral blood flow before surgery in 14 patients. After surgery, this reduced blood flow improved to normal values in 13 of the patients, and the MADRS scores normalized in 7 of 8 patients with preoperative high scores.

The patient in our case had normal calcium levels, despite having histology-confirmed hyperparathyroidism. A subgroup of patients with pHPT and normal calcium level has been identified as normocalcemic primary hyperparathyroidism (87,104). To establish the diagnosis, it is important to rule out other causes for an elevated PTH level. Vitamin D deficiency is the most common cause of secondary elevation in PTH (87). In our case, we did

not measure serum 25(OH)D levels. This was due to lack of awareness of this clinical point at that time. There is limited knowledge about the prevalence of normocalcemic pHPT (87) . In a Swedish survey of 5202 postmenopausal women, 30 of 109 persons (28%) with pHPT did exhibit persistent normocalcemia.

As presented in paper II, we have revealed a high prevalence of vitamin D deficiency in a group of psychogeriatric patients. If we only measure serum calcium in a psychogeriatric population, we can easily miss cases of pHPT, either because the patient has normocalcemic pHPT or has a pHPT with vitamin D deficiency, in which case there may be a normal serum calcium level. In addition, there is the possibility of secondary hyperparathyroidism due to vitamin D deficiency. Vitamin D deficiency is associated with a more severe form of pHPT with respect to bone health, although there are some inconsistent findings (212). We are unaware of any studies investigating neuropsychiatric symptoms in vitamin D deficient patients with pHPT. In persons with secondary hyperparathyroidism (n=21), *Jorde et al.* (213) demonstrated that low levels of 25(OH)D was significantly associated with a high depression score.

The impact of surgical parathyroidectomy on neuropsychiatric symptoms has been examined in several studies. With few exceptions, case-control and cohort studies have shown improvements in neuropsychiatric symptoms, including depression (194,199,201,203,214). In trials studying the response of psychiatric symptoms to parathyroidectomy a variety of methods have been used to document psychiatric symptoms, including symptom checklists, self-reporting of psychiatric symptoms and generalized quality-of-life measures (215). *Bollerslev et al*. (197) conducted a RCT on patients with asymptomatic pHPT where the Short Form-36 General Health Survey (SF-36) was used to assess quality of life. This form also

includes some questions about mental health. Patients were randomized to surgery (n=96) or to medical observation (n=95). They found no significant difference in SF-36 scores between the surgery and the observation group (197). The SF-36 was also used in a study by *Ambrogini et al.* (91) where 50 patients with asymptomatic pHPT were randomized to either surgery or observation. They found a modest, but significant effect on several components of the instrument, including mental health (91). In a study by *Rao et al.* (216) patients randomized to surgery (n=25) showed a better social and emotional outcome (measured by the SF-36) than patients randomized to observation (n=28).

It has been argued that the SF-36 is too general for the evaluation of the specific symptoms of pHPT (215). Several large observational studies have been conducted using validated psychometric instruments to observe outcome after parathyroidectomy. In a study by *Roman et al.* (203) 212 patients underwent parathyroidectomy. An improvement in both psychological and neurocognitive measures were demonstrated. Two recently published studies have used the Patient Health Questionaire-9 (PHQ-9), which is a validated instrument designed to measure depression severity and is sensitive to change over time (217). In one study patients with pHPT were either observed (n=81) or underwent surgery (n=88) (not randomized) and compared to a group with benign nontoxic surgical thyroid disease undergoing thyroid surgery (control group) (199). After 1 month and 1 year the PHQ-9 score in the parathyroidectomy group decreased by respectively 63.5% and 65.6% compared to a reduction of 26.3% and 17.9% in the observation group (pHPT without surgery) and a reduction of 30.0% and 49% in the control group (thyroidectomy group). Another study commented on earlier compared 194 patients that underwent parathyroidectomy with 186 patients in a control group who underwent thyroidectomy (200). Moderate or severe depression was observed in 16.7% of the pPHT group and 6.5% in the control group. One

year postoperatively, this proportion declined to 6.6 % in the pPHT group and 3.5 % in the control group. In an invited critique to this article in JAMA Surgery one leading expert argued that last years trials should put to rest the debate on whether parathyroidectomy has a positive impact on neurocognitive dysfunction in these patients (218).

We have not found any studies that systematically examine the effect of parathyroidectomy in patients with more severe symptoms. Several case reports resembling our report have been published, describing patients suffering from long-time depression, with symptom relief almost immediately after parathyroidectomy (219-221). Three very old patients with pHPT underwent parathyroidectomy and a 78% reduction in the Hamilton Depression Rating Scale was demonstrated (214).

There is some evidence that surgery can improve psychiatric symptoms in patients with pHPT. However, it is still not clear whether these results are applicable on patient groups with severe psychiatric symptoms, like patients admitted to psychogeriatric wards. The impact of parathyroidectomy on bone health has been investigated, and there are consistent findings indicating that surgery also can improve bone mineral density in patients with pHPT (215).

In this summary we have not addressed the aspects of cognitive deficits caused by pHPT. There is evidence that pHPT can cause neurocognitive symptoms (92,196) and prospective studies have indicated that parathyroidectomy can reverse cognitive deficits caused by pHPT (194,196). In a review by *Alex et al.* (215) they concluded that more RCTs are needed to validate the results reported in prospective studies.

7.4 Zinc deficiency

In study III we found a significant difference in the prevalence of zinc deficiency between the control group and the patient group. Non-depressed patients (i.e., with other psychiatric diagnoses like dementia or psychosis) had a significantly higher prevalence of zinc deficiency than patients with depression. The finding is interesting, because most previous studies in this field have focused on zinc deficiency and depression. Whether zinc deficiency has any impact on psychotic symptoms is not known. We have not found any studies focusing on zinc deficiency and psychosis among elderly. A few studies have compared zinc levels of patients with schizophrenia with healthy controls, with diverging results (131,132). To the best of our knowledge, the study presented in paper III is the first to report a possible association between zinc deficiency and psychosis among elderly patients.

In our study we also demonstrated a high prevalence of zinc deficiency in patients with dementia, including patients with Alzheimer's disease (AD). Although zinc has been linked to a possible role in the pathogenesis of AD, a causal role in AD has not yet been demonstrated (222). Several studies have failed to reveal a difference in serum zinc levels between controls and patients with AD (223-226). The patients with dementia in our study were admitted to a psychiatric hospital and thus differ from "typical" patients with dementia. They presented psychiatric symptoms (i.e., depression, anxiety or psychosis) or severe behavioural disturbances. Although it is not possible to draw any conclusion on this topic now, one could speculate whether lack of zinc could contribute to behavioural problems and psychiatric symptoms in patients with dementia.

A connection between low zinc levels and depression has been demonstrated in several previous studies (43,44,118,227). Although there are a few negative findings (228,229), a

recently published meta-analysis including 17 case-control and cross-sectional studies concluded that depression was associated with a lower concentration of zinc in peripheral blood (230). Only one study in this meta-analysis included primarily elderly patients and also this study revealed significantly lower zinc levels in depressed patients than in non-depressed participants (231). Only one prospective cohort study has been conducted focusing on the association between the incidence of depression in middle-aged men and zinc intake (not zinc levels) (232). The authors reported that a reduced dietary zinc intake was not associated with an increased risk of severe depression (hospitalization in a 20-year follow-up).

Prospective supplementation trials could be considered to be the most appropriate to establish the direction of causation. Two RCTs have examined antidepressant drug treatment and either zinc or placebo supplementation. On the one hand, a small study of patients with depression (n=14), showed that zinc supplementation significantly reduced depression scores compared to placebo (41). On the other hand, a larger RCT with 60 patients did not find a significant difference in depression scores (42), but in a subgroup of 21 patients with treatment-resistant depression they exhibited a significantly greater reduction in depression scores in the zinc group compared to the placebo group. However, these studies did not include only patients with established zinc deficiency.

The study on zinc deficiency presented in paper III did not include dietary data for the patient or control group. A low intake of zinc could be caused by either a diet low in zinc or by general malnutrition. One study of elderly people revealed a relationship between low dietary zinc intake, plasma zinc status and depressive symptoms (44). Similar findings are reported in a study from Malaysia of postgraduate students (233). Furthermore, one study demonstrated a positive association between depression and low dietary zinc intake in women, but not in men

(234). These three studies used detailed food questionnaires and indicated that low dietary intake of zinc was caused by a diet low on zinc and not due to a low total caloric intake, although this aspect was not discussed in detail. It is not possible to conclude whether these findings represent actual causal relationships, but the results are supported by several animal studies. Rodents on a zinc-deficient diet develop depression-like symptoms, including anhedonia, anorexia, increased anxiety behaviour and increased periods of immobility (119,235,236).

In the study presented in paper IV, we focused on malnutrition and zinc deficiency. Previous studies have reported conflicting results regarding the relationship between malnutrition and zinc deficiency in elderly individuals (116,237). In the study presented in paper IV, the MUST tool was used to assess the risk of malnutrition. An association between zinc deficiency and risk of malnutrition was demonstrated, also after adjusting for age, gender, smoking status and serum albumin in a logistic regression analysis. The most obvious explanation of these findings would be that people at risk for malnutrition eat less food, including less zinc containing food. In a westernized diet meat is the most important zinc source (112). In this population survey, we had some data regarding food intake. There was no difference in meat consumption between individuals with zinc deficiency and those with normal zinc status. Thus, a reduced intake of zinc containing food did not appear to be a major contributor to the findings. However, the population survey did not use a detailed food questionnaire, which would have made it possible to perform a more detailed analysis regarding zinc intake.

In the case-control study (study III) we had BMI as a measure of nutritional status. There was no significant correlation between zinc levels and BMI (data not shown), and in a logistic

regression model, BMI made no significant contribution to the model. However, risk of malnutrition and BMI are not identical parameters. We did not have data to assess the risk of malnutrition in the case-control study (study III). Therefore, we cannot rule out the possibility that some patients could have had a period of malnutrition before inclusion in the study, which could increase the risk of zinc deficiency.

In both the case-control study (study III) and the cross-sectional study (study IV) we found a 6-10 percentage point higher prevalence of zinc deficiency in men, using the recommended cut-off values from the IZiNC group (150). Two other studies on elderly participants have not reported a gender difference in zinc status (44,115), using the same cut-off value for men and women. In a report from the US National Health and Nutrition Examination Survey, *Hotz et al.* (113) demonstrated that the gender difference in serum zinc levels almost disappeared after 60 years of age. This is due to a decline in serum zinc levels in elderly men, while zinc levels in women seem to be rather constant from 20 years of age (113). The decline in serum zinc in elderly men has been commented by the IZiNC group, still recommending same cut-off for younger and elderly men, given the possibility that the decline in serum zinc levels in men over 65 years old could be attributable to declining nutritional status. Thus, a possible explanation for the higher prevalence of zinc deficiency in men could be a poorer nutritional status compared to women. A reduction in cut-off values for zinc deficiency in men in our studies would have further increased the prevalence of zinc deficiency in this group. The serum zinc level was not significantly different between men and women in the case-control study (study III) or in the cross-sectional study (study IV).

In the population study (study IV), we did not find any significant difference in scores of mental distress between participants with and without zinc deficiency. The SCL-10 score used

in the survey is not regarded as a diagnostic instrument, and we do not know how many of the participants with high SCL-10 scores (≥1.85) who had an ongoing depressive or anxiety disorder. This result could be perceived of as in conflict with the result from the case-control study (study III), but it is likely that the patients representing the cases had more severe psychiatric disorders, than participants with high SCL-10 score in the population survey. The results do however imply that our findings in study III (i.e., a higher prevalence of zinc deficiency in patients with psychiatric disorders) not necessarily is valid in a population with less severe psychiatric symptomatology.

8 Implications

8.1 Clinical implications

a) We have reported a very high prevalence of vitamin D deficiency in the elderly with psychiatric disorders. Even if there is an increased focus on vitamin D, there is still a need for more awareness of vitamin D deficiency, especially in psychogeriatric patients. The role of vitamin D in relation to psychiatric disorders is still not clear, but there is mounting evidence that sufficient vitamin D levels are important for general health. We would suggest that vitamin D should be measured routinely in psychogeriatric inpatients and outpatients.

b) The role of zinc in relation to psychiatric disorders is still not clear. However, based on the impact of zinc deficiency on general health and the high prevalence of zinc deficiency in psychogeriatric patients, zinc should probably be measured routinely in this patient group.

c) There should be an increased awareness of normocalcemic hyperparathyroidism, both as an independent condition and as a condition with simultaneously pHPT and vitamin

D deficiency. PTH should be measured in patients who do not respond to antidepressant treatment. If pHPT is diagnosed, surgery should be considered independent of calcium values.

8.2 Research implications

a) The role of vitamin D in psychiatric disorders should be further explored in randomized controlled trials. A first step could be to explore effects of vitamin D as an adjuvant treatment in patients with both vitamin D deficiency and clinical depression.

b) The role of zinc in psychiatric disorders should also be further explored with a RCT. The first step could be to explore the effect of zinc as an adjuvant treatment in patients with zinc deficiency and clinical depression.

c) The prevalence of normocalcemic hyperparathyroidism in patients referred to psychiatric hospitals should be investigated. There is also a need for more knowledge regarding whether patients with severe psychiatric disorders and pHPT would benefit from surgical treatment.

d) The association between pro-inflammatory cytokines and zinc deficiency and vitamin D deficiency should be further explored in patients with psychiatric disorders.

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