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Use of anti-osteoporosis drugs in The Tromsø Study: Is undertreatment a problem?

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Master thesis in Pharmacy

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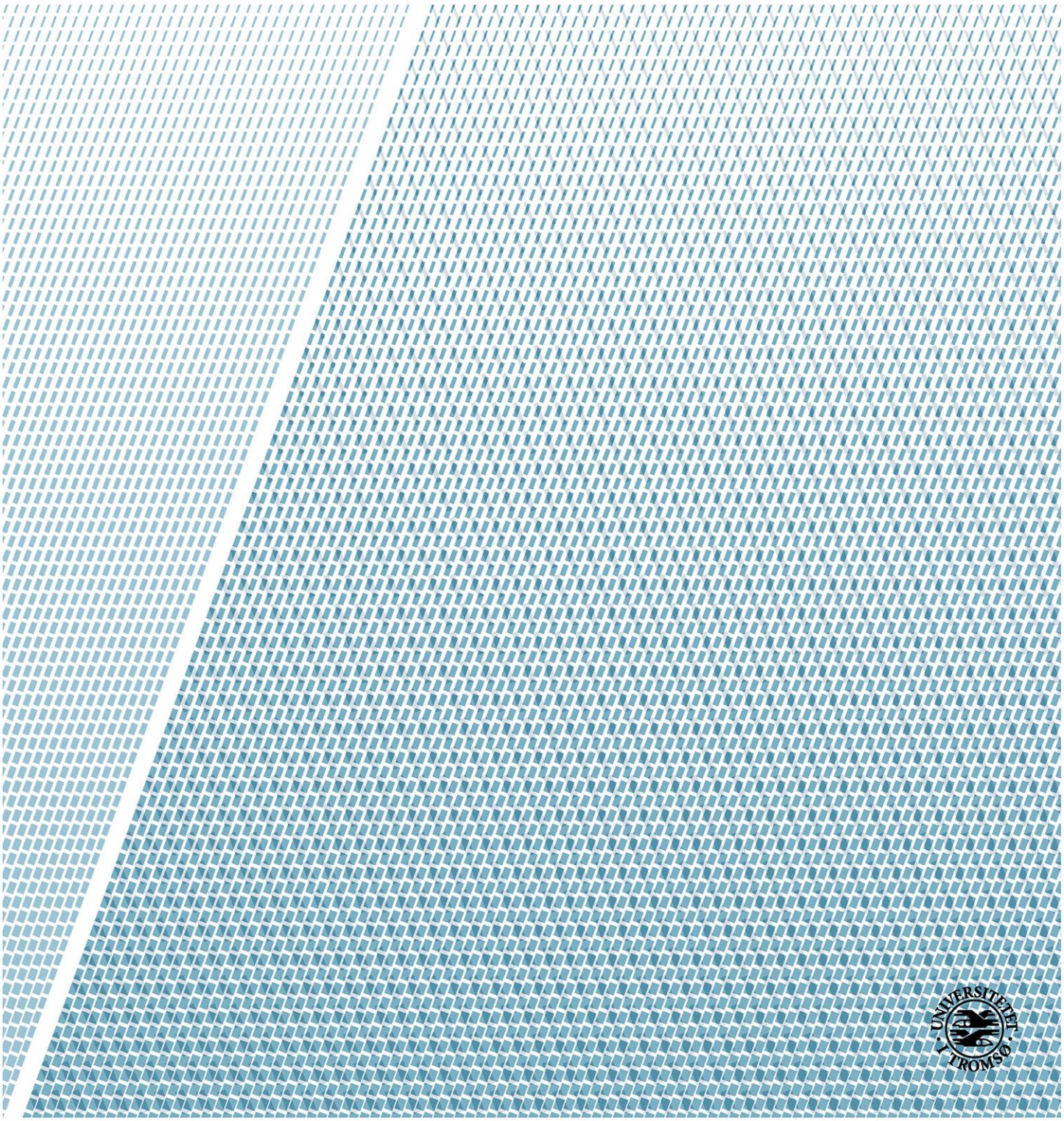

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Summary

Background: Osteoporosis is a major health issue worldwide. Osteoporosis is characterized by the progressive decreasing in bone mass, microarchitecture decline of bone tissue, bone fragility and strength, which leads to an increase in risk of fracture. About a quarter of Norwegian women over 50 years of age were estimated to have the disease in 2010 and Norway has one of the highest reported incidence of hip fractures in the world with over 9000 hip fractures per year. There are numerous effective anti-osteoporosis drugs (AOD) for the prevention and treatment of osteoporosis and fracture. Despite of this, a number of studies have shown that patients are undertreated with AOD after fractures.

The aim of the thesis is to describe the pattern of anti-osteoporosis drug use in a general population among persons with osteoporosis defined by self-report or by bone mineral density measurements, with or without fracture.

Material and Method: A cross-sectional study was conducted based on data from the sixth survey of the Tromsø study (Tromsø 6), which took place in 2007-2008. The data included information from questionnaires and physical examinations of the total study population (n=12981) and additionally bone mineral density measurements from a subpopulation (n=3663).

Results: The prevalence of anti-osteoporosis drug use among participants reporting osteoporosis in the total population was less than 50%. In the subpopulation the prevalence of anti-osteoporosis drug use among participants that are eligible for treatment with anti-osteoporosis drug was under 20%, and only 20% of these participants were aware that they had osteoporosis. Bisphosphonates was the most frequently used anti-osteoporosis drug type. Prevalence of bisphosphonates use among those in need of treatment within the subpopulation was 11%.

Conclusion: This study revealed that the prevalence of anti-osteoporosis drug use among persons eligible for anti-osteoporosis drug treatment is very low, although higher among persons reporting that they had both osteoporosis and fracture. Undertreatment continues to be a problem among persons with osteoporosis and osteoporotic fracture.

Abbreviations

AOD	Anti-osteoporosis drugs
BMD	Bone mineral density
WHO	World Health Organization
DXA	Dual X-ray absorptiometry
HRT	Hormone replacement therapy
SERMs	Selective estrogen receptor modulators
PTH	Parathyroid hormone
SPSS	Statistical Package for the Social sciences
+FX	With fracture
-FX	Without fracture
BMI	Body mass index
RANKL	Receptor activator of nuclear factor kappa-B ligand
HRT	Hormone replacement therapy

1 Introduction

Osteoporosis and osteoporotic fracture is a major health issue worldwide, with an estimated 200 million people having osteoporosis (1). About one out of every two women and one out of five men 50 years and older, will have an osteoporosis-related fracture in their lifetime. Osteoporotic fractures are associated with increased mortality, morbidity, disability and reduced quality of life (2). In Norway, hip fracture accounted for 5% of all deaths among women and men aged 50 years and older, between the years 1999-2008 (3).

In the year 2000, there was a worldwide estimate of 9 million new osteoporotic fractures of which 1.6 million was hip and 1.7 million was forearm fractures (4). Two million fractures are attributed to osteoporosis annually in the US with a nearly cost of $17 billion in 2005 and the cost expected to rise to $25.3 billion by the year 2025 (5).

In the year 2010, approximately 22 million women and 5.5 million men were estimated to have osteoporosis in the European Union (6). Three and a half million new osteoporotic fractures were sustained of which 610 000 and 560 000 comprised of hip and forearm fracture, with a direct cost estimated at £39 billion (6).

The highest incidence of osteoporotic fracture is reported in Scandinavia, and Norway has one of the highest reported incidence of fractures in the world with an estimate of about 9000 hip fractures and 15 000 forearm fracture per year (7). About a quarter of Norwegian women over 50 years of age is estimated to have osteoporosis (7). A recent study reported a decline in hip fracture incidence in Norway, by 20.4% in women and 10.8% in men (8). However the growing number of older persons in the Norwegian population might cause an increase in the future prevalence of osteoporosis and osteoporotic fracture (8, 9).

1.1 What is osteoporosis?

In the body, old bone is constantly being removed by bone-resorbing cells known as osteoclasts and being replaced by new bone by bone-formation cells called osteoblasts (10). Bone loss occurs when there is an imbalance in this process leading to more

bone removal than replacement. Figure 1 shows the changes with bone as a result of bone loss.

Osteoporosis is a disease characterized by the progressive reduction of bone mass, microarchitecture decline of bone tissue, bone fragility and strength, which leads to an increase in the risk of fracture (11, 12). The World Health Organization defines osteoporosis as "a bone mineral density (BMD) that lies 2.5 standard deviations or more below the average value for young healthy women (a T-score of <-2.5 SD)" (13). Osteoporosis does not show any symptoms or pain and is often not diagnosed or treated until a fracture occurs (14). It is therefore regarded more as a risk factor of bone fracture than a disease. Osteoporotic fractures usually occurs in hip, spine or forearms, with hip fractures being the most serious outcome of osteoporosis(15). Hip fracture often occurs late in life and is often associated with acute and chronic pain, disability, high social cost, depression and excess morbidity and mortality (2, 16). It also increases the risk for future fractures by two and a half folds. Wrist fractures are less disabling, but are often precursors of more serious fractures. Therefore the identification and treatment of persons at risk of fracture is important. Persons at high risk for fracture are those with previous fracture, low bone mass and established osteoporosis (12).

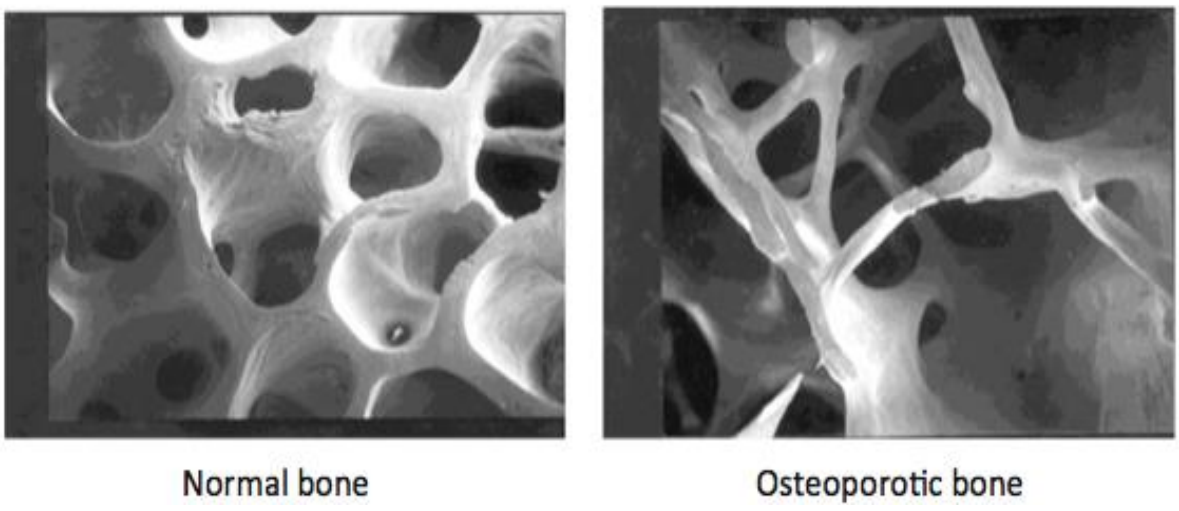


Figure 1 Photomicrographs of normal and osteoporotic bone with permission from Springer (12)

1.2 Risk factors

Osteoporosis is known to be commonly caused by aging (10), with the loss of bone mass in both genders being a result of advancing age and in postmenopausal women being associated with estrogen reduction, particularly with early menopause (17, 18). Diseases like rheumatoid arthritis and the long-term use of drugs like corticosteroids have been shown to also induce what is known as secondary osteoporosis (19).

1.2.1 Age and gender

Osteoporosis affects women more than men, and women have almost twice the risk for hip fracture compared with men (20). This is mainly because of accelerated bone loss in women during the menopausal transition. The decline of estrogen concentration is associated with progressive bone loss with an estimated lifetime risk for fracture of about 50% for women above 50 years. Since men do not undergo a menopausal period, bone loss is therefore sustained later in life (17, 20).

Although osteoporosis mainly affects women, it is also a threat to men. About 20% of men over the age of 60 years will experience an osteoporotic fracture in their lifetime (21). Men over the age of 50 years lose one-half as much bone and have three-fold increase in fracture risk compared to postmenopausal women (22).

The risk of osteoporosis and fracture increases with age, particularly 65 years of age (23), mainly because of an imbalance between bone-resorbing osteoclasts and bone-forming osteoblast. The likeliness of falling is also higher at old age (23, 24). Both men and women with previous fractures, especially hip or spine fracture, have twice the risk of suffering a fracture compared to people of the same age and sex without previous fracture. People with multiple fractures have an eight-fold increase in fracture risk (25).

1.2.2 Secondary causes

Psychotropic medications among other drugs have been shown to increase the incidence of falling among older adult by 47%, which also increases the risk of sustaining a fracture (26). Conditions such as diabetes mellitus, vitamin D deficiency, rheumatoid arthritis and a variety of other conditions can also increase the risk for fracture and osteoporosis (14). Low body weight, having a small body frame, family history of osteoporosis, smoking, high alcohol intake, and medications like

glucocorticoids, have been shown to increase the risk for osteoporosis (27). Glucocorticoid-induced osteoporosis is the most common cause of secondary osteoporosis. It is estimated that 30% of all patients on chronic glucocorticoid therapy will develop osteoporosis, and up to 50% of the patients will experience a fracture (28).

1.3 Diagnosis

Bone mineral density (BMD) measurement is used in the diagnosis of osteoporosis (14). There are a variety of methods to measure bone mineral density including quantitative computed tomography (QCT), quantitative ultrasound (QUS), and X-ray absorptiometry. X-ray based absorptiometry methods are the most used, especially dual energy X-ray absorptiometry (DXA) because of its ability to be used to assess bone mineral of the entire skeleton as well as specific sites. Calcium content in bone tissue is also very sensitive to X-ray absorption, however traditional X-rays cannot measure bone density, but they can identify spine fractures. Measurements are taken at the spine, hip and or forearm. BMD measurement is however, not the only diagnostic criteria of osteoporosis. A number of clinical risk factors including parental history of hip fracture, prior fragility fracture, age, use of systemic corticosteroids, excess alcohol intake, tobacco smoking and having rheumatoid arthritis are also used (14).

1.3.1 Bone mineral density classification

BMD is often classified by T- or Z- score. T-score is the number of standard deviations (SDs) by which BMD of an individual differs from the mean value of a reference population (figure 2). The T-score diagnosis of normal, low bone mass and osteoporosis is based on the WHO diagnostic classification (table 1) (13). This only applies for the diagnostic use in postmenopausal Caucasian women and men aged 50 years or more (29).

The International society for Clinical Densitometry recommends that Z-score instead of a T-score should be used in bone mineral density reporting of women before menopause and men younger than 50 years of age (30). Z-score is a comparison of the patient’s BMD to an age-, sex-, and ethnicity-matched reference population. Z-scores

of −2.0 or lower defined as either “low bone mineral density for chronological age” or “below the expected range for age” and those above −2.0 being “within the expected range for age”(30).

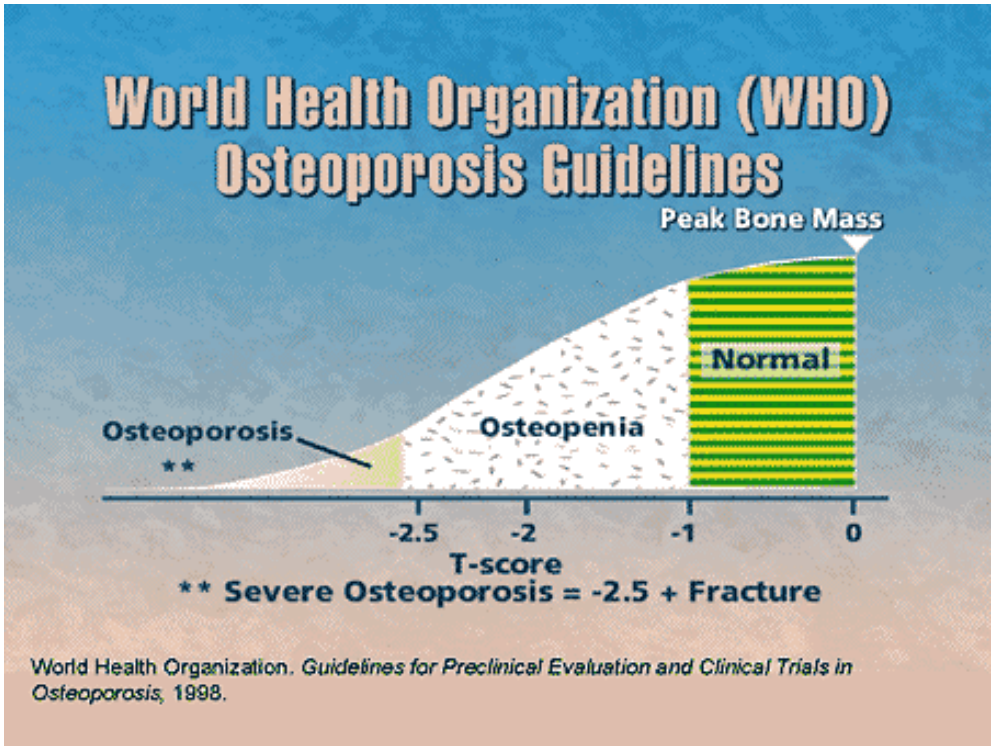


Figure 2 WHO diagnostic T-score classification (13)

Table 1 WHO diagnostic T-score classification

Category	T-score
Normal	-1.0 SD or higher
Osteopenia (low bone mass)	-1.0 ≥ -2.5 SD
Osteoporosis	-2.5 SD or lower

1.4 Treatment

In 2005 the Norwegian Directorate of Health released the Norwegian guidelines for prevention and treatment of osteoporosis and osteoporotic fractures (31). The guidelines recommended preventive measures including adequate calcium and vitamin D inntake, either through food or supplements, lifestyle changes (e.g. exercising, weight reduction, tobacco cessation and moderate alcohol intake), prevention of falls and if possible avoidance of glucocorticoid drugs for postmenopausal women and men age 50 and older (31). Persons that are recommended anti-osteoporosis drug treatment in addition to these preventive measures are postmenupausal women and men age 50 and older with a spine or hip fracture, thoses with a bone mineral density T-score $\leq$ -2.5 standard deviation below the mean value for a reference population (with or without fracture) and postmenupausal women and men age 50 and older with a previous fracture and a bone mineral density T-score ranging from -1.6 to -2.5 (31).

1.4.1 Pharmacological treatment

Pharmacological treatment of osteoporosis can be divided into two groups, antiresorptive drugs, i.e. those that slow down bone resorption like bisphosphonates, raloxifene and denosumab, and anabolic drugs that stimulate bone formation, like parathyroid hormone (PTH).

1.4.2 Bisphosphonates

Bisphosphonates are the main prophylactic treatment against osteoporosis and fracture. They are anti-resorptive agents with high affinity for hydroxyapatite, the mineral component of the bone, and are able to achieve high local concentration within the skeleton (32). This leads to effective limitation of osteoclast-mediated bone resorption, increasing BMD and reduction in fracture risk. Bisphosphonates have been shown to reduce fracture risk about 30%-50% in persons with existing vertebral fracture and also those with low bone mineral density (T-score < -2.5) (33). Bisphosphonates have also been shown to reduce the risk of fracture (34), stop bone loss and improve bone mineral density in men and in both pre- and postmenopausal women (35, 36).

Bisphosphonates are given orally or intravenously and are most widely used because of their ability to be used in the treatment of all osteoporosis types, including osteoporosis in men, postmenopausal women and glucocorticoid-induced osteoporosis. Bisphosphonates have <1% bioavailability when taken orally and it is therefore important to take it correctly. To prevent gastroesophageal side effects and ensure optimum absorption, patients must take the drug with water before meals and in an upright position (37). Randomized controlled trails (RCT) have shown that bisphosphonates have a relatively low risk profile when taken correctly (38). Despite their low risk profile, adverse effects like gastrointestinal upset, muscle pain, dyspepsia, esophagitis and obstipation have been reported in association with oral bisphosphonates (39). Osteonecrosis of the jaw, which is a very rare condition occurring with one out of 100 000 patients, have been reported in association with long-term usage (39, 40). Available bisphosphonates in Norway includes alendronate, risedronate, and ibandronate in oral formulations and zolendronate being used intravenously. Sales of bisphosphonates were at 78 million NOK in 2008 with alendronate constituting 95% of the sales (figure 3). Nearly 57 000 people had at least one bisphosphonate retrieved from pharmacies during 2007-2008 (figure 4), of which 90% were women (41). Bisphosphonates are the first in line anti-osteoporosis drug recommended by the Norwegian health authorities, which is in accordance with international guidelines (31, 42).

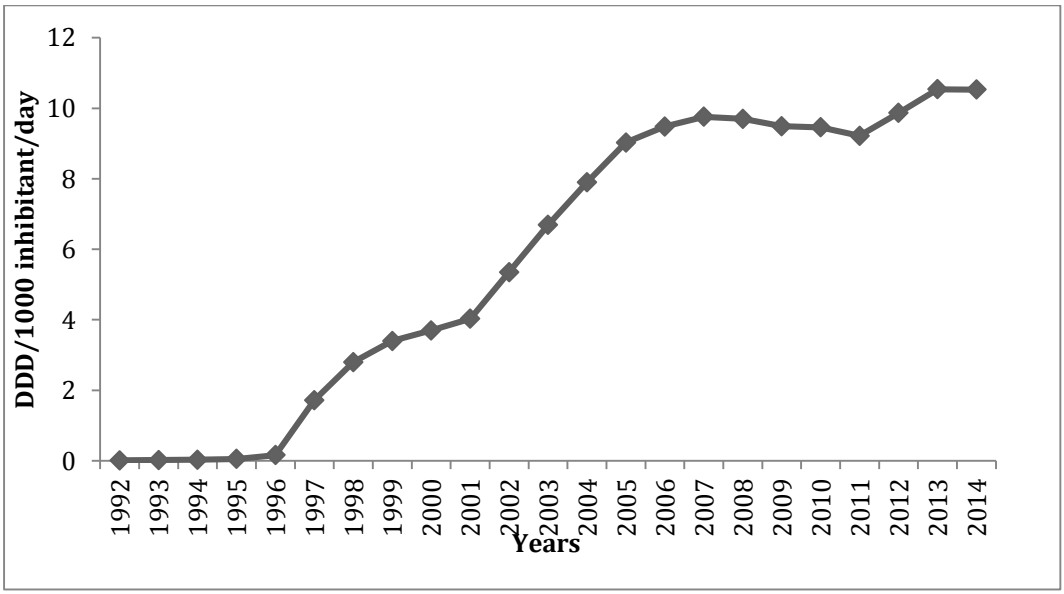


Figure 3 Sales of bisphosphonates (M05) in Norway from 1992 to 2014. Sales are given in defined daily doses (DDD) per 1000 inhabitants per day. Source: Norwegian Drug Wholesaler Database

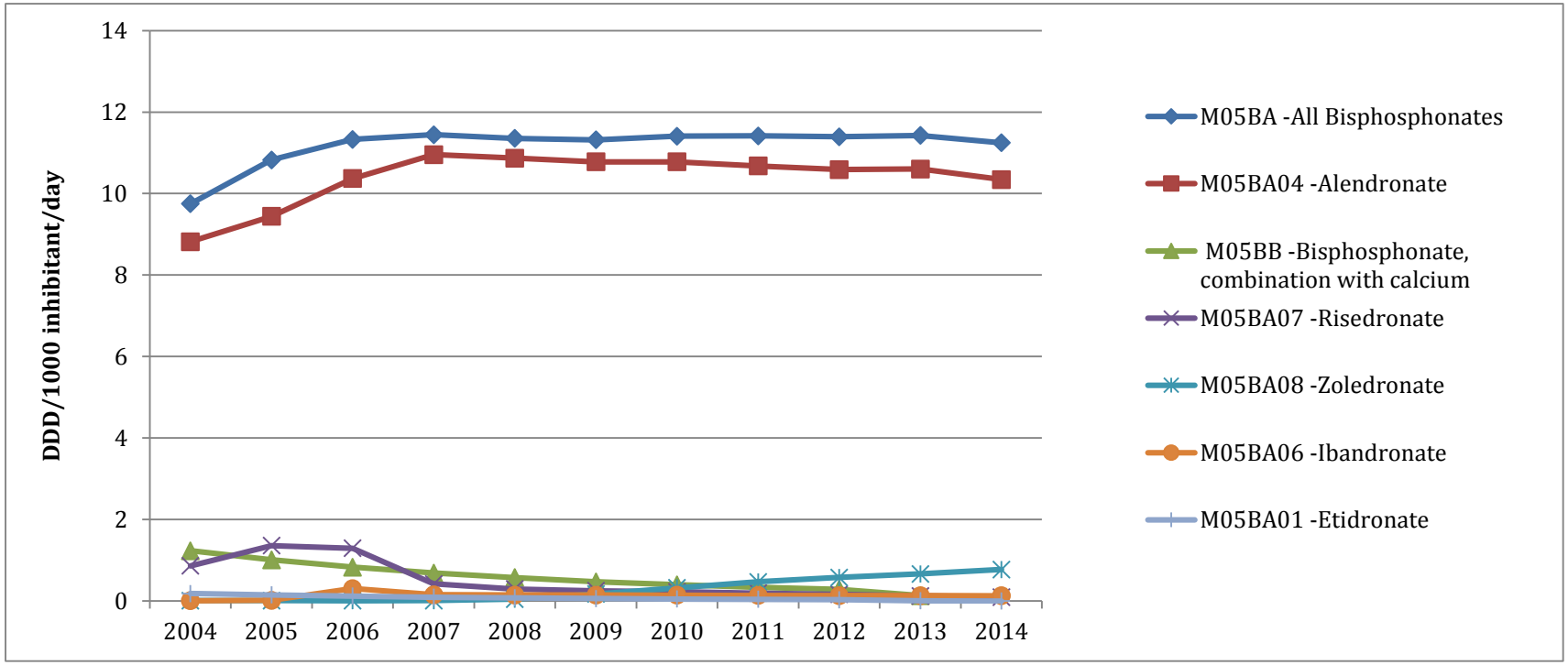


Figure 4 Dispensed bisphosphonates in Norwegian pharmacies from 2004-2014. Only the most dispensed bisphosphonates are presented. Source: The Norwegian Prescription Database (NorPD)

1.4.3 Hormone replacement therapy (HRT)

Estrogen level is the most important factor for bone loss in postmenopausal women (43). Estrogen inhibits bone loss by binding to cellular receptors and suppressing osteoclast activity. Hormone replacement therapy has been shown to have good effect on osteoporosis as well as postmenopausal symptoms like hot flashes. Results from the Women's Health Initiative study state an increase in bone mineral density and also reduction in risk for fracture among postmenopausal women on hormone estrogen (44). It is, however, no longer recommended as the first choice in the treatment and prevention of osteoporosis among postmenopausal women due to increased risk of breast cancer and cardiovascular and venous thromboembolic events. Hormone replacement therapy may be considered appropriate as treatment of osteoporosis for women already on estrogens for the treatment of climacteric syndrome (45).

1.4.4 Denosumab

Denosumab is a fully human monoclonal antibody that binds specifically to Receptor activator of nuclear factor kappa-B ligand (RANKL). RANKL is a regulatory molecule required for the formation and activation of osteoclast. Inhibition of RANKL results in a decrease in bone resorption due to the reduced formation of osteoclast. Denosumab given subcutaneously every six months for 36 months to postmenopausal women with osteoporosis was associated with an increase in bone mineral density and reduced risk of vertebral, hip and non-vertebral fracture (46).

1.4.5 Selective estrogen receptor modulators (SERMs)

SERMs as their name implies are drugs that act on estrogen receptors. Unlike other pure estrogen receptor agonist and antagonist, SERMs have the ability to selectively stimulate or inhibit estrogen-like action in various tissues (47). SERMs stimulate estrogenic action in bone, acting like estrogen to decrease bone resorption and improve bone mineral density, which in turn lead to the decreasing in risk of fracture. Raloxifene is the only SERM approved for the treatment and prevention of osteoporosis in postmenopausal women. Studies have shown significant increase in bone mineral density and risk reduction for vertebral facture in postmenopausal women with osteoporosis when treated with raloxifene (48, 49). However, raloxifene have some of the similar adverse effects as estrogen e.g. increases risk for thrombosis. It can also cause leg cramps and increase hot flashes.

1.4.6 Parathyroid hormone (PTH)

Parathyroid hormone is the only anabolic agent available for the treatment of osteoporosis. Unlike the other anti-osteoporosis drug types that reduce bone resorption, PTH works by stimulating the formation of bone (50). A randomized controlled trial involving over 1600 postmenopausal women with established osteoporosis showed a decrease in the risk of vertebral and non-vertebral fracture by 65% during 18 months of treatment with daily subcutaneous injection of PTH (51). Teriparatide is approved for the treatment of osteoporosis in both women and men with increase risk of fracture. A daily dose of 20 ug is recommend for a maximum treatment time of 24 months. Besides its effectiveness, treatment with PTH is expensive and it is also not directly reimbursed in Norway. The drug is therefore only recommended when other anti-osteoporosis drugs are ineffective or cannot be used by a patient.

1.5 The situation today

Despite the burden on persons affected and the society, and the availability of cost effective drugs, both national and international studies have suggested that osteoporosis is undertreated (25, 52, 53). However, these studies were registry linkage studies and did not include diagnostic information or information on the personal level regarding self-perceived health and reports of adverse effects. It is therefore interesting to investigate the degree of anti-osteoporosis drug use among persons with osteoporosis and/or osteoporotic fractures in a population based health study with information on self-reported health data and diagnostic measures.

2 Aim

The main aim of the study is to describe the pattern of anti-osteoporosis drug use in a general population among persons with osteoporosis, with or without fracture based on questionnaire data and measurement of bone mineral density by dual energy X-ray absorptiometry.

Other specific aims are to figure out whether:

- Prevalence of anti-osteoporosis drug use varies across different diagnosis categories of osteoporosis.
- Users of anti-osteoporosis drugs (i.e. bisphosphonates) have poorer health or experience more adverse effects (gastrointestinal symptoms or muscle/joint pain) than non-users.

3 Material and Method

3.1 The Tromsø study

The Tromsø Study is a population-based, prospective study of various health issues, symptoms and chronic diseases (54). It was initiated in 1974 as a combined population health survey and a research study of cardiovascular diseases. The Tromsø Study has gradually expanded to include several chronic diseases and conditions like diabetes mellitus, atrial fibrillation, venous thromboembolism, osteoporosis and fracture. Six surveys have been carried out 6-7 years apart, referred to as Tromsø 1-6, and a seventh wave of the study is carried out now in 2015-2016. All surveys include questionnaire data, sampling of biological specimens, measurements and clinical examinations. Residents of the municipality of Tromsø are invited to take part in the survey by a personal invitation enclosed with a questionnaire by mail. The invitation includes information about the survey and the examinations. Tromsø 4-7 includes a second examination visit 2-4 weeks later with eligible participants being already identified before their first visit. The questionnaires include questions about disease and symptoms, use of medication, socio-economic status and life style (54). An attachment of the questionnaire used in the sixth survey of the Tromsø Study is at the appendix of this master thesis. Data from the six surveys are currently involved in over 100 different research projects (55, 56).

3.2 Study population and design

This is a cross-sectional study based on data from the sixth survey of the Tromsø Study (Tromsø 6), which took place in 2007-2008. Invited to participate in a two-part examination were all participants from the second visit of the fourth survey of the Tromsø Study who were still residing in Tromsø by September 2007. Additionally, all inhabitants aged 40–42 and 60–87 years, a 10% random sample of individuals aged 30–39 years and a 40% random sample of individuals aged 43-59 were invited to participate (56). The first part of the survey consisted of a 4-page questionnaire covering various health issues that participants filled in at home before attending the study. A second questionnaire covered more details about the topics already covered

by the first questionnaire. The participants could either take it home to fill in or fill in at the study site while they were waiting for various physical examinations. The physical examinations included blood pressure, weight/height and hip/waist measurements, sampling of blood, hair and nose and throat swabs, measurements of pain sensitivity, single energy X-ray absorptiometry (SXA) measurement of forearm bone density and grip strength. The second part of the survey (about 4 weeks later) included dual-energy X-ray absorptiometry (DXA) measurement of BMD at the hip, vertebra and body composition. The study had an attendance rate of 66%, with 12984 out of 19762 invitees attending (figure 5). The study population for this master thesis consists of all participants of Tromsø 6 (n=12981) and a subpopulation (n=3663) with bone mineral density measurements in the second part of the survey (figure 5).

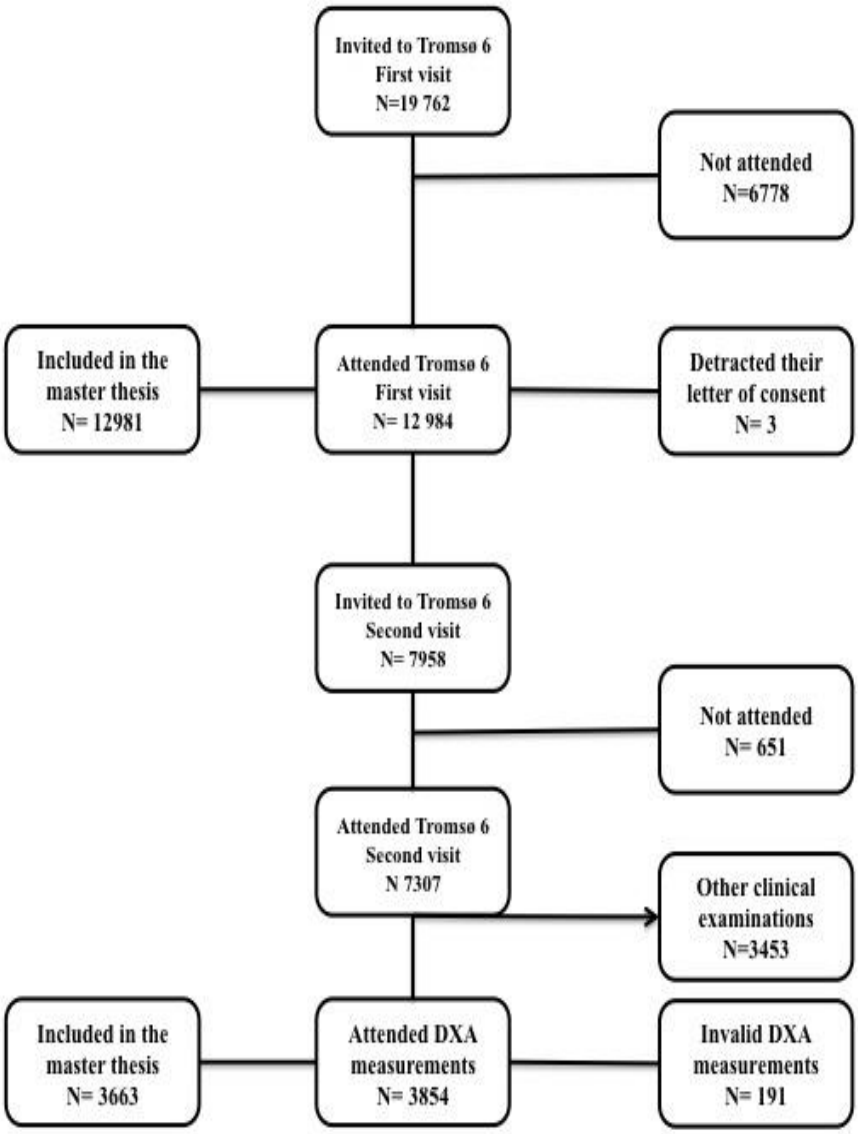


Figure 5 Flowchart of the study population

3.3 Variables

Information about osteoporosis and fracture was collected through self-reports obtained by questionnaires. All participants were considered as having osteoporosis and fracture if they answered, "yes" to the question "Have you ever had, or do you have osteoporosis?" and "yes" to any of the corresponding questions regarding fracture "Have you ever had a hip fracture?" "Have you ever had a wrist/forearm fracture?".

Participants with DXA measurements were classified into different categories of osteoporosis based on their T-score values from their BMD measured by DXA and their answer to the question regarding fracture (see table 2). T-score was calculated from BMD of the left hip by using the National Health and Nutrition Examination Survey (NHANES) III reference (57). The new values were categorized into 3 categories based on the guidelines from The Norwegian Directorate of Health (T-score < -2.5, -2.5 to -1.6 and > -1.6) (31).

Information about drug use was collected through questionnaire that was filled in at home and was checked by trained health personnel at the study site. Anti-osteoporosis drug users were defined as those that answered, "yes" to the question "Do you use, or have you used drugs for osteoporosis?" and also those that listed the brand names of the drugs used.

Based on the Anatomical Therapeutic Chemical (ATC) classification system (58), anti-osteoporosis drugs (AOD) were defined as bisphosphonates (ATC code M05BA), denosumab (M05BX04), PTH (H05AA02), SERM (G03XC01) and HRT (G03CA03, G03CA04, G03CX01, G03FA01, G03FA12 and G03FB05). Calcium supplements with vitamin D (A12A) were not defined as AOD but were included in tabulations because of its positive effect on bone and its recommendation in the prophylaxis and treatment of osteoporosis (31, 42).

Participants from the subpopulation with BMD measurements that were in need of treatment were defined based on their T-score and self-reports about fracture (Table 2).

Table 2 Classification of T-score based on The Norwegian Directorate of Health guidelines (31)*

T-score based on DXA measurements	Fracture (hip or wrist)	No fracture
< -2.5	Established osteoporosis	Osteoporosis
-2.5 to -1.6	Clinical osteoporosis	Osteopenia (in the lower range)
> -1.6	Normal BMD	Osteopenia in the upper range or normal BMD

* Grey areas signifying groups who fulfill the criteria for anti-osteoporosis drug treatment

The validation of the general question "Do you take medication for osteoporosis now" was done by using as the gold standard all self-reported listed brand names of anti-osteoporosis drugs in the same questionnaire.

The question on self-reported health had five response alternatives, but was dichotomized into good (excellent/ good /neither good nor bad) and bad (bad/very bad) for the statistical analyses.

Bisphosphonate use was further studied among the participants who according to their T-score value and self-reported fracture should be recommended AOD treatment (see table 2).

Signs of adverse reactions were defined based on the participant's reports of symptoms such as muscle or joint pain, gastrointestinal symptoms such as heartburn, diarrhea, constipation, bloated stomach and abdominal pains during the last 12 months. The use of drugs for acid related disorders and drugs for peptic ulcer and gastro-esophageal reflux disease were also included.

3.4 Data analysis

Data analysis was performed with the statistical software program IBM SPSS statistics 23 for Mac. Differences between groups were analyzed using X^2-test (categorical variables). Multiple logistic regression was conducted to assess associations while adjusting for potential confounding factors. The significance level was set at 5%.

3.5 Ethics

The Norwegian Data Protection Authority and the Regional Committee of Medical and Health Research Ethics, North Norway approved Tromsø 6. The study complies with the Declaration of Helsinki, International Ethical Guidelines for Biomedical Research Involving Human Subjects and the International Guidelines for Ethical Review of Epidemiological Studies. Participation was voluntary and each subject gave written informed consent prior to participation (55, 56).

4 Results

4.1 Characteristics of the study population

Characteristics of the total population and the subpopulation are presented in table 3. The total population consisted of 6928 women and 6053 men with an overall average age of 57 years. The subpopulation, i.e. the participants with DXA measurements, consisted of 2151 women and 1512 men and had an overall average age of 65 years.

The prevalence of AOD use reported through the general question and according to listed brand name seemed to be slightly higher in the subpopulation (5.2% and 5.5% respectively) compared with the total population (3.4% and 3.6% respectively).

Wrist/forearm fracture was the most reported fracture type overall, and was higher among the subpopulation than among the total population (17.9% vs. 14.9%). Occurrence of hip fracture was higher in the total population than the subpopulation (1.8% vs. 1.4%).

Men seem to have had a slightly higher BMI than women in both populations. Self-reported health seemed to be similar in the two populations, with the majority of the participants (50%) in both groups reporting good health.

Table 3 Characteristics of the study population

	Total population N=12981	**Subpopulation N=3663**
Age, years (mean±SD)	57.5 (12.6)	65.8 (9.4)
Age (n (%))		
30-39 years	509 (3.9)	12 (0.3)
40-49	3574 (27.5)	135 (3.7)
50-59	2436 (18.8)	715 (19.5)
≥60	6462 (49.8)	2801 (76.5)
Self-reported current AOD use (n (%))	440 (3.4)	191 (5.2)
30-39 years	1 (0.2)	0 (0.0)
40-49 years	18 (0.5)	0 (0.0)
50-59 years	36 (1.5)	12 (1.7)
≥60 years	385 (6.2)	179 (6.7)
AOD use according to brand name (n (%)	466 (3.6)	202 (5.5)
30-39 years	1 (0.2)	0 (0.0)
40-49 years	18 (0.5)	1 (0.7)
50-59 years	68 (2.8)	24 (3.4)
≥60 years	379 (5.9)	177 (6.3)
Fracture (%)		
Hip	240 (1.8)	50 (1.4)
Wrist/forearm	1938 (14.9)	655 (17.9)
BMI (mean±SD)		
Women	26.5 (4.6)	26.9 (4.6)
Men	27.2 (3.7)	27.2 (3.4)
Height, cm (mean±SD)		
Women	163 (6.5)	161 (6.3)
Men	177 (6.8)	175 (6.5)
Weight, kg (mean±SD)		
Women	70 (13.0)	70.6 (12.8)
Men	85 (13.3)	83.7 (12.1)
Self-reported health %		
Excellent	1873 (14.4)	380 (10.4)
Good	6592 (50.8)	1835 (50.1)
Neither good nor bad	3699 (28.5)	1235 (33.7)
Bad	651 (5.0)	163 (4.4)
Very bad	48 (0.4)	13 (0.4)

AOD: Anti-osteoporosis drugs

4.2 Validation of the question regarding the use of drugs for anti-osteoporosis drugs (AOD)

When the general question was tested against the first gold standard (total AOD use according to brand name), The general question gave a sensitivity of 55% and a specificity of 98%. About 203 of 455 (45%) were “false negative” and 188 of 12667 (1.5%) were “false positive” (Table 4).

When tested against the second gold standard (bisphosphonates brand name), sensitivity was 99% and specificity was 98%. Three of 241 (1%) were “false negative” and 202 of 12426 (1%) were “false positive”.

Table 4 Validation of the general question regarding the use of drugs for osteoporosis

		AOD brand name reported			**Bisphosphonates brand name**		
		Yes	**No**	**Total**	**Yes**	**No**	**Total**
Self-reported current AOD use	**Yes**	252	188	404	238	202	404
	No	203	12024	12227	3	12224	12227
	Total	455	12212	12667	241	12426	12667

4.3 Prevalence of AOD use in the total population

The prevalence of AOD use among the total population, types of AOD and calcium supplements with vitamin D used are presented separately for women and men in table 5.

Participants are categorized into groups according to their reports of osteoporosis and fracture. Prevalence of AOD use overall was higher (50.9%) among participants reporting osteoporosis and fracture compared with participants reporting osteoporosis without fracture (41.2%). Both groups consisted of mostly women. The group reporting osteoporosis and fracture (n=175) consisted of 166 women and 14 men, the second group (n=262) reporting osteoporosis without fracture, consisted of 231 women and 31 men. Bisphosphonates was the most frequently used anti-osteoporosis drug among both groups and across both gender. Prevalence of bisphosphonates use in the first group was 46.6% for women and 64.3% for the men. For the second group the prevalence was lower in both women (40.3%) and men (35.5%), and the difference most pronounced in men.

PTH use was registered in only one male participant who reported osteoporosis and fracture. SERMs usage was registered among two females with osteoporosis but without fracture (not shown in table).

Table 5 Prevalence of self-reported anti-osteoporosis drug use among the total population (n = 12981) according to self-reported osteoporosis and fracture categorized by gender and anti-osteoporosis drug type

	Total	***Women N=6928***				***Men N=6053***		
Self-reported osteoporosis and fracture	**AOD use**		**Bisphosphonates**	**HRT**	**Calcium + vitamin D***		**Bisphosphonates**	**Calcium + vitamin D***
	n (%)	**N**	n (%)	n (%)	n (%)	**N**	n (%)	n (%)
Osteoporosis +Fx N=175	89(50.9)	**161**	75(46.6)	8(5.0)	39(24.2)	**14**	9(64.3)	5(35.7)
Osteoporosis -Fx N=262	108(41.2)	**231**	93(40.3)	8(3.5)	64(27.7)	**31**	11(35.5)	8(25.8)
Not osteoporosis +Fx N=1826	39(2.1)	**958**	4(0.4)	35(3.7)	11(1.1)	**868**	0(0.0)	3(0.3)
Not osteoporosis -Fx N=9349	165(1.8)	**4793**	13(0.3)	150(3.1)	39(0.8)	**4556**	1(0.0)	6(0.1)
Unanswered N=1369**	65(4.7)	**785**	37(4.7)	28(3.6)	35(4.5)	**584**	1(0.2)	1(0.2)
Total=12981								

*Not included in total AOD use. **Missing information on questions regarding either osteoporosis or previous fracture or both. +FX: With fracture –FX: Without fracture

4.4 Prevalence of AOD use in the subpopulation

Prevalence of AOD use among the different classifications of T-score for participants with DXA measurements, use of bisphosphonates, HRT and calcium supplements with vitamin D is presented in table 6. See table 2 for the classifications of T-score.

Among 85 individuals with osteoporosis and fracture, prevalence of AOD use was 17.6% (Table 6). The prevalence of AOD use was 15.6% for participants with osteoporosis without fracture and 10.2% for participants with clinical osteoporosis, i.e. T-score between -2.5 and -1.6 and with fracture. When AOD was divided into separate drug types, bisphosphonates were the most used drug type. Calcium supplements with vitamin D were also often used. Use of SERMs and PTH are not shown in Table 6. SERMs were registered only in one female participant with osteopenia. PTH was used by only one male participant with osteoporosis and fracture.

Table 6 Prevalence of self-reported AOD use among the subpopulation (n= 3663) according to T-score value and self-reported fracture categorized by gender and anti-osteoporosis drug type

	Total	***Women N=2151***				***Men N=1512***		
T-score with and without fracture	**AOD use**		**Bisphosphonates**	**HRT**	**Calcium + vitamin D***		**Bisphosphonates**	**Calcium + vitamin D***
	N (%)	**N**	**n (%)**	**n (%)**	**n (%)**	**N**	**n (%)**	**n (%)**
< -2.5+Fx N=85	15(17.6)	**73**	12(16.4)	0(0.0)	4(5.5)	**12**	2(16.7)	1(8.3)
< -2.5 -Fx N=128	20(15.6)	**105**	14(13.3)	6(5.7)	10(9.5)	**23**	2(8.7)	1(4.3)
-2.5 − -1.6 +Fx N=196	20(10.2)	**170**	13(7.6)	6(3.5)	6(3.5)	**26**	2(7.7)	0(0.0)
-2.5 − -1.6 -Fx N=508	38(7.5)	**382**	21(5.5)	15(3.9)	24(6.3)	**126**	2(1.6)	0(0.0)
> -1.6 +Fx N=400	27(6.8)	**218**	17(7.8)	8(3.7)	14(6.4)	**182**	2(1.1)	2(1.1)
> -1.6 -Fx N=2109	67(3.2)	**1057**	15(1.4)	50(4.7)	21(2.0)	**1052**	2(0.5)	1(0.1)
Unanswered N=237**	15(6.3)	**146**	11(7.5)	4(2.7)	12(8.2)	**91**	0(0.0)	0(0.0)
Total								

*Not included in total AOD use
**Missing information on question regarding fracture
+Fx: With fracture. -Fx: Without fracture

4.5 Reports of osteoporosis within the subpopulation

Figure 5 shows the classifications of T-score and reports of fracture within the subpopulation and the percentage of participants that reported having osteoporosis in each group. A total of 3546 (96.8%) of the 3663 participants in the subpopulation had answered the question regarding having osteoporosis. Reports of osteoporosis were low among the three groups that are recommended treatment with AOD. Among those with osteoporosis with or without fracture, only 32.9% and 19.2%, respectively, of the participants reported that they had osteoporosis. In the group defined as clinical osteoporosis, 14.8% of the participants reported that they had osteoporosis. In the groups with normal bone mass, the reports of osteoporosis were 7.7% for participants with fracture and 2.2% for those without fracture. Overall, reports of osteoporosis were higher among groups with fracture.

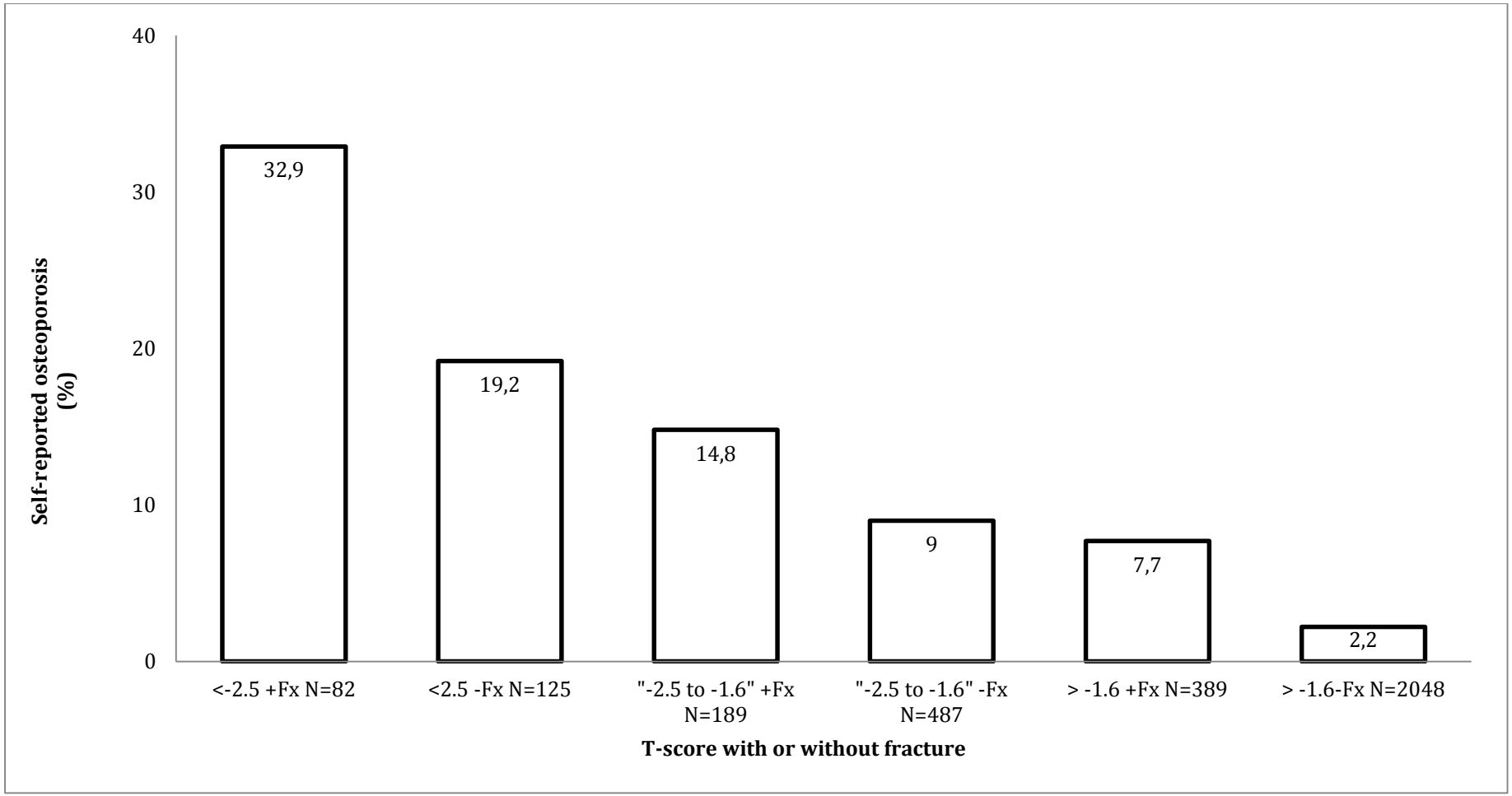


Figure 6 The proportion of participants reporting osteoporosis among the different T-score categories with or without fracture N= 3546. Participants who had missing data regarding reports about fracture (n=226) are not shown in this figure. +Fx/-Fx: With fracture/without fracture

4.6 Factors associated with bisphosphonates use

Based on their T-score and reports on fracture, 409 participants were identified as persons eligible for anti-osteoporosis drug treatment, i.e. bisphosphonates. In this sub group the association between factors like self-reported health, factors indicating gastrointestinal symptoms and muscle and joint pain and bisphosphonate use were analyzed in a binary logistic regression (Table 7).

The regression analysis confirmed the significance of health as a factor associated with bisphosphonate use. Participants that perceived their health as poor had a higher odds of being users of bisphosphonates (OR 3.10, 95% CI 1.23-8.57). There was no statistically significant association between factors indicating gastrointestinal symptoms or muscle and joint pain.

Table 7 Factors influencing prevalent use of bisphosphonates among participants eligible for anti-osteoporosis drug treatment.

	Use of bisphosphonates YES (N=45)	Use of bisphosphonates NO (N=364)	Unadjusted		Adjusted*	
	n (%)	**n (%)**	**OR**	**95% CL**	**OR**	**95% CL**
Self-reported health						
Good	38(86.4)	346(95.3)	1	Reference	1	
Poor	6(13.6)	17(4.7)	3.21	1.20-8.64	3.10	1.23-8.57
Factors indicating gastrointestinal symptoms**						
No	10(22.2)	62(17.6)	1	Reference	1	
Yes	35(77.8)	290(82.4)	0.75	0.35-1.59	0.60	0.27-1.32
Muscle and joint pain**						
No	5(11.1)	71(20.2)	1	Reference	1	
Yes	40(88.9)	281(79.8)	2.02	0.77-5.31	1.88	0.69-5.11

*The association between use of bisphosphonates and self-reported health, factors indicating gastrointestinal symptoms and muscle and joint pain were each adjusted for the other two factors, and for age as a continuous variable. **12 participants with missing data were excluded from the analysis

5 Discussion

Previous history of hip and forearm fracture is associated with low bone mineral density and subsequent fractures (59). Norway has one of the highest rates of hip and forearm fracture in the world (7), and one would expect a high prevalence of anti-osteoporosis drug use among persons that are recommended treatment with AOD. Findings in this study show that this is not the case.

We found that the use of anti-osteoporosis drugs among persons eligible for anti-osteoporosis drug treatment was low. The prevalence was less than 50% among women and men reporting that they had osteoporosis in the total population. The prevalence was slightly higher among participants reporting osteoporosis and fracture. The prevalence of anti-osteoporosis drug use was less than 18% among participants with osteoporosis, as measured by DXA, in the subpopulation. We also found out that among the participants classified as having osteoporosis based on their T-score value, only 20% were aware of their condition. There are several possible reasons for this low usage of anti-osteoporosis drugs found in this study, and one very important factor is adherence to long-term drug therapy.

Low adherence to oral drug therapy in chronic conditions is considered a public health problem (60). Adherence to therapy has become one of the major challenges in the treatment of osteoporosis (61). It is estimated that only half of the patients comply with long-term therapy. Approximately 50% of the women receiving anti-osteoporosis drug treatment for the first time discontinue their treatment within one year (62). In Norway, only 45.5% of osteoporosis patients were adherent of alendronate treatment within five years of treatment (63). Studies show that poor adherence to bisphosphonate therapy is associated with increase in the risk of fracture and smaller gains in bone mineral density (62). Gastrointestinal adverse effects from bisphosphonates given orally as well as the complex intake regime, which requires patients to remain upright and be fasting when administrating the drug, are probably the main reason for patients to discontinue treatment (64, 65). Long-term adherence to anti-osteoporosis drug therapy is needed for optimal therapeutic benefits (33). Patients might also stop treatment because of the benefit not being immediate and they might fail to see the importance of taking the drug.

In this study, the association between gastrointestinal adverse effects and bisphosphonate use was not statistically significant. We found a higher prevalence of gastrointestinal adverse effects among non-users of bisphosphonates. This is surprising because normally, reports of adverse effects are more frequent among users of a drug. However, this can also be interpreted, as non-users having gastrointestinal adverse effects might be the reason why they are not using bisphosphonates.

Some bisphosphonates formulations, especially alendronate and zolendronate have a prolonged dosing interval. Alendronate administrated orally once weekly have been shown to improve patients' adherence (63), but could also potentially have lead participants to forget to report the use of the drug when the survey was conducted. It has been shown that patients recall more often drug that need more refill and drugs that are administrated frequently (66). Participants receiving zolendronate (Aclasta®) injections once a year could forget that they use any anti-osteoporosis drugs if it had been some months in between the time of the dose and the time they answered the survey. But with alendronate consisting of 93% of all bisphosphonates reported, we do not think this is a major problem with our study.

Another explanation for the low prevalence in this study could be misclassification. Some participants could have reported having osteoporosis even though they might not have the disease. Reasons for this could be if the person have sustained a previous fracture, there is a family history of fracture and osteoporosis or they may think they have the disease based on their old age. Thus leading to an artificially low reporting of anti-osteoporosis drug use among participants reporting osteoporosis.

The rules of reimbursement for alendronate in Norway up until 2012 was that one must have suffered a fracture and also had a bone mineral density measurement with a T-score $\leq$ -2.5 before a patient could receive full reimbursement. This could explain the low prevalence in anti-osteoporosis drug use, since Tromsø 6 was carried out during 2007-2008. In 2012 the reimbursement regulations were changed, excluding the requirement of having fracture before patients could get fully reimbursed (67). If lack of reimbursement has influenced our data from Tromsø 6, we might expect a higher prevalence in anti-osteoporosis drug use in Norway after 2012.

Osteoporosis is known as a silent disease as it does not give any symptoms and it is often not diagnosed until the occurrence of fracture. With this in mind, it is not surprising that a considerable proportion of participants were not aware of their condition, although they had DXA measurements that classified them as having osteoporosis. The University Hospital of North Norway is the only place where the DXA station is located in the municipality of Tromsø. Studies have shown that due to the unavailability of diagnostic tools in primary health care, over 75% of osteoporosis patients are not diagnosed and given treatment (68). Distance to DXA facilities has also been shown to influence the persons' attendance to DXA examinations (69). Diagnosis and initiation of treatment could therefore increase with the availability of diagnostics in primary health care, which could also lead to an increased focus on osteoporosis. Reports of osteoporosis was however, high among participants with previous fracture. This could be because of the increase in awareness and concern about their health status after experiencing such a serious outcome as a fracture. A Norwegian study reported that there is a correlation between risk factors such as previous fracture and persons' attendance to DXA examinations (69).

In our study self-reported health was significantly associated with using bisphosphonate, with the odds of being a user of bisphosphonates three times higher among those with poor health compared to those with good health. However, we cannot conclude that users of bisphosphonates had poor health because of bisphosphonate usage and vise versa. One explanation for this finding could be that individuals with poor health maybe more health conscious and are more likely to visit the doctor's office which increases their chances of being prescribed drugs.

Several studies have reported similar low prevalence in anti-osteoporosis drug use. In line with our findings, one study based on a population in central Norway and including data linkage between the fracture registry in Nord-Trøndelag county and the Norwegian Prescription Database (NorPD) examined the use of anti-osteoporosis drugs the first year after fracture in central Norway. The study included 1434 women and 513 men 40-84 years with their first forearm fracture between 2005 and 2012. The prevalence of anti-osteoporosis drugs use after the first year of fracture was 11.2% for women and 2.7% for men (52). Another study involving all Norwegian women and men ≥50 years based on data from the Norwegian Prescription Database, the National Hip Fracture Database, the National Population Register and the

Nationwide Census reported that 16% of women and 4 % of men were treated with anti-osteoporosis drugs within 2 years after a hip fracture (25). In a nationwide survey involving 51,346 patients over age 65 admitted to 318 hospitals in the US for hip fracture, only 7.3% were prescribed anti-osteoporosis drugs (70). In a study from Belgium, just 6% of patients who had sustained a hip fracture received treatment with anti-osteoporosis drugs (53). All these studies show that undertreatment of osteoporosis is not only a problem in Norway, but also worldwide.

5.1 Validity

The general question "Do you take medication for osteoporosis now?" had a sensitivity of 55% and a specificity of 98% when the question regarding use of anti-osteoporosis drugs according to listed brand names was used as a gold standard. This means that the general question regarding use of drugs for osteoporosis have a very good chance of detecting those that actually do not use any anti-osteoporosis drugs (true negatives), but not as good when it comes to detecting those that actually do use anti-osteoporosis drugs (true positives). However, when self-reported use of bisphosphonates was used as the gold standard sensitivity was 99% and specificity 98%. This means that the question regarding use of drugs for osteoporosis have a very good chance of detecting persons that use bisphosphonates (true positives), and it is also just as good to detect persons that are not bisphosphonate users. This high sensitivity probably has to do with how the participants define drugs used for osteoporosis. The first gold standard, which includes all anti-osteoporosis drugs used, is not as specific as the second gold standard because it includes all anti-osteoporosis drug types, including SERMs, PTH and HRT. Among the 203 false negatives, 200 participants were found to be users of HRT and three were bisphosphonate users. Unlike bisphosphonates, HRT is indicated for more than just the treatment of osteoporosis. Participants using HRT for the treatment of menopausal symptoms such as hot flashes may therefore fall in the false negative group since HRT was defined as an AOD in this study. This might also be the case for participants that are receiving glucocorticoid therapy and also using bisphosphonates as a prophylaxis for osteoporosis.

In the cross-tabulation for self-reported current use of anti-osteoporosis drug against the self-reported use of anti-osteoporosis drug according listed brand names, 68 participants among the false positive group were found to be users of calcium

supplement with vitamin D. The calcium supplements with vitamin D in this study are prescription based and it is recommended in the prophylaxis of osteoporosis. This might have confused patients into thinking that it is medical treatment whilst in clinical practice it is considered a supplement.

Overall the general question in the questionnaire regarding the current use of drugs for osteoporosis is very good in identifying participants using bisphosphonates.

5.2 Strengths and limitations

The strength of this study is the use of data from the Tromsø study, a large population-based study with a high attendance rate. Tromsø 6 has an attendance rate of 66%, which is somewhat lower compared to previous waves of the Tromsø study, but it is still considered very good compared to other similar population surveys. Tromsø 6 has good external validity. The majority of the attendees were ≥50 years and with osteoporosis being a disease that normally affects people ≥50 years, we can conclude that the findings in this study is therefore generalizable to the source population.

The availability to DXA measurement of the participants is also a major strength of this study. Diagnostic data interpreted by trained health personnel, makes it possible to correctly classify participants in the different categories of T-score.

Data involved in Tromsø 6 was collected by questionnaire. The advantage with this data collecting method is the ability to easily collect information about a large number of different variables from a large study population. However, the use of questionnaire has it challenges. Researchers must rely on participants remembering and reporting the right information. Studies show that self reports on fracture is very accurate in detecting major fractures such as hip and wrist fractures (71). But it is however often over reported (72). This could lead to a misclassification of participants and an under estimation of the prevalence of anti-osteoporosis drug use.

Several studies have examined self-reported recall accuracy for current or past drug use (66). The majority of people generally remember quite accurately when they have used prescription-based drugs, although they might not remember actual brand names. This may lead to an underreporting of anti-osteoporosis drug used by participants in this study. However, the questionnaire in Tromsø 6 was answered by participants at

the comforts of their homes where they had access to the drugs they take, making it easy to remember and list the brand names of the anti-osteoporosis drugs that they are using.

One requirement for the Tromsø study was the ability of participants to fill in a questionnaire and to visit the study site. This requirement may lead to a selection bias into the population because the oldest people that are weak and frail with potential cognitive issues may fail to attend the study. Information is lost for researchers not being able to include these old persons (56).

In this study the question on self-reported health was dichotomized into good (excellent/ good /neither good nor bad) and bad (bad/very bad) for the statistical analyses. The reason for this is the low number of participants in the different categories (table 3). Participants reporting neither good nor bad health were categorized as good because it was assumed that an individual reporting neither good nor bad health has good health but might think it is not as good. A person with bad health might be less likely to report having neither good nor bad health.

This master thesis is an observational cross-sectional study, a design which is suitable for describing the prevalence of risk factors and outcomes in a population. But it cannot measure disease incidence because of its lack of a time dimension, which makes it unsuitable in concluding about causality of an association.

6 Conclusion

The prevalence of anti-osteoporosis drug use among persons eligible for treatment is very low, although higher among persons reporting osteoporosis and fracture. With the availability of cost effective therapies and with clinical consequences such as fracture-associated morbidity and mortality, as well as the economical burden on society, we can conclude that prevalence of anti-osteoporosis drug use is too low and undertreatment of osteoporosis patient groups continues to be a problem.

7 References

1. Reginster JY, Burlet N. Osteoporosis: a still increasing prevalence. Bone. 2006;38(2 Suppl 1):S4-9.

2. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int. 2009;20(10):1633-50.

3. Omsland TK, Emaus N, Tell GS, Magnus JH, Ahmed LA, Holvik K, et al. Mortality following the first hip fracture in Norwegian women and men (1999-2008). A NOREPOS study. Bone. 2014;63:81-6.

4. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 2006;17(12):1726-33.

5. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007;22(3):465-75.

6. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos. 2013;8:136.

7. Omsland TK, Holvik K, Meyer HE, Center JR, Emaus N, Tell GS, et al. Hip fractures in Norway 1999-2008: time trends in total incidence and second hip fracture rates: a NOREPOS study. Eur J Epidemiol. 2012;27(10):807-14.

8. Sogaard AJ, Holvik K, Meyer HE, Tell GS, Gjesdal CG, Emaus N, et al. Continued decline in hip fracture incidence in Norway: a NOREPOS study. Osteoporos Int. 2016.

9. Strand BH, Eriksen HM, Tambs K, Skirbekk V. Norwegian Institue of Public Health. Health among elderly in Norway. 2014 [cited 03.09.2015]. Available from: http://www.fhi.no/eway/default.aspx?pid=240&trg=MainContent_6898&Main_6664=6898:0:25,7524:1:0:0:::0:0&MainContent_6898=6706:0:25,7893:1:0:0:::0:0.

10. Clarke BL, Khosla S. Physiology of bone loss. Radiol Clin North Am. 2010;48(3):483-95.

11. Licata AA, Williams SE. A DXA Primer for the Practicing Clinician. Springer New York. 2013. p. 5-13.

12. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014;25(10):2359-81.

13. World health Organization. WHO scientific group on the assessment of osteoporosis at primary health care level. 2004.

14. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2013;24(1):23-57.

15. Oden A, McCloskey EV, Johansson H, Kanis JA. Assessing the impact of osteoporosis on the burden of hip fractures. Calcif Tissue Int. 2013;92(1):42-9.

16. Borgstrom F, Kanis JA. Health economics of osteoporosis. Best Pract Res Clin Endocrinol Metab. 2008;22(5):885-900.

17. Sinnesael M, Claessens F, Boonen S, Vanderschueren D. Novel insights in the regulation and mechanism of androgen action on bone. Curr Opin Endocrinol Diabetes Obes. 2013;20(3):240-4.

18. Clarke BL, Khosla S. Female reproductive system and bone. Arch Biochem Biophys. 2010;503(1):118-28.

19. Clarke BL. Corticosteroid-induced osteoporosis: an update for dermatologists. Am J Clin Dermatol. 2012;13(3):167-90.

20. Waugh EJ, Lam MA, Hawker GA, McGowan J, Papaioannou A, Cheung AM, et al. Risk factors for low bone mass in healthy 40-60 year old women: a systematic review of the literature. Osteoporos Int. 2009;20(1):1-21.

21. Korpi-Steiner N, Milhorn D, Hammett-Stabler C. Osteoporosis in men. Clin Biochem. 2014;47(10-11):950-9.

22. Laurent M, Gielen E, Claessens F, Boonen S, Vanderschueren D. Osteoporosis in older men: recent advances in pathophysiology and treatment. Best Pract Res Clin Endocrinol Metab. 2013;27(4):527-39.

23. Drake MT, Clarke BL, Lewiecki EM. The Pathophysiology and Treatment of Osteoporosis. Clin Ther. 2015;37(8):1837-50.

24. Ambrose AF, Cruz L, Paul G. Falls and Fractures: A systematic approach to screening and prevention. Maturitas. 2015;82(1):85-93.

25. Devold HM, Sogaard AJ, Tverdal A, Falch JA, Furu K, Meyer HE. Hip fracture and other predictors of anti-osteoporosis drug use in Norway. Osteoporos Int. 2013;24(4):1225-33.

26. Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med. 2009;169(21):1952-60.

27. Emkey GR, Epstein S. Secondary osteoporosis: pathophysiology & diagnosis. Best Pract Res Clin Endocrinol Metab. 2014;28(6):911-35.

28. Bultink IE, Baden M, Lems WF. Glucocorticoid-induced osteoporosis: an update on current pharmacotherapy and future directions. Expert Opin Pharmacother. 2013;14(2):185-97.

29. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ, 3rd, Khaltaev N. A reference standard for the description of osteoporosis. Bone. 2008;42(3):467-75.

30. Binkley N, Bilezikian JP, Kendler DL, Leib ES, Lewiecki EM, Petak SM. Summary of the International Society For Clinical Densitometry 2005 Position Development Conference. J Bone Miner Res. 2007;22(5):643-5.

31. Norwegian Directorate of Health. National guidelines for prevention and treatment of osteoporosis and osteoporotic fractures 2005. Available from: https://helsedirektoratet.no/.

32. Drake MT, Cremers SC. Bisphosphonate therapeutics in bone disease: the hard and soft data on osteoclast inhibition. Mol Interv. 2010;10(3):141-52.

33. Khan A, Dubois S, Khan AA, Rahman MZ, Khan OA, Syed HT, et al. A randomized, double-blind, placebo-controlled study to evaluate the effects of alendronate on bone mineral density and bone remodelling in perimenopausal women with low bone mineral density. J Obstet Gynaecol Can. 2014;36(11):976-82.

34. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008(1):CD001155.

35. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA. 1998;280(24):2077-82.

36. Boonen S, Reginster JY, Kaufman JM, Lippuner K, Zanchetta J, Langdahl B, et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. N Engl J Med. 2012;367(18):1714-23.

37. Norwegian Medicines Agency. Fosamax 70mg. Drug description 2015 [cited 27.08.2015]. Available from: http://slv.no/_layouts/Preparatomtaler/Spc/2000-09210.pdf.

38. Strampel W, Emkey R, Civitelli R. Safety considerations with bisphosphonates for the treatment of osteoporosis. Drug Saf. 2007;30(9):755-63.

39. Kennel KA, Drake MT. Adverse effects of bisphosphonates: implications for osteoporosis management. Mayo Clin Proc. 2009;84(7):632-7; quiz 8.

40. Watts NB. Long-term risks of bisphosphonate therapy. Arq Bras Endocrinol Metabol. 2014;58(5):523-9.

41. Rønning M, Sakshaug S, Strøm H, Berg CL, Litleskare I, Blix HS, et al. Drug Consumption in Norway 2004-2008. Norwegain Institue of Public Health [cited 29.08.2015]. Available from: http://www.legemiddelforbruk.no/.

42. Scottish Intercollegiate Guidline Network. Management of osteoporosis and the prevetion of fragility fractures 2015. Available from: http://www.sign.ac.uk/.

43. Gambacciani M, Levancini M. Hormone replacement therapy and the prevention of postmenopausal osteoporosis. Prz Menopauzalny. 2014;13(4):213-20.

44. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA. 2003;290(13):1729-38.

45. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-33.

46. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756-65.

47. Maximov PY, Lee TM, Jordan VC. The discovery and development of selective estrogen receptor modulators (SERMs) for clinical practice. Curr Clin Pharmacol. 2013;8(2):135-55.

48. Fujiwara S, Hamaya E, Sato M, Graham-Clarke P, Flynn JA, Burge R. Systematic review of raloxifene in postmenopausal Japanese women with osteoporosis or low bone mass (osteopenia). Clin Interv Aging. 2014;9:1879-93.

49. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA. 1999;282(7):637-45.

50. Adami S. Full length parathyroid hormone, PTH(1-84), for the treatment of severe osteoporosis in postmenopausal women. Curr Med Res Opin. 2008;24(11):3259-74.

51. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344(19):1434-41.

52. Hoff M, Skurtveit S, Meyer HE, Langhammer A, Sogaard AJ, Syversen U, et al. Use of anti-osteoporotic drugs in central Norway after a forearm fracture. Arch Osteoporos. 2015;10:235.

53. Rabenda V, Vanoverloop J, Fabri V, Mertens R, Sumkay F, Vannecke C, et al. Low incidence of anti-osteoporosis treatment after hip fracture. J Bone Joint Surg Am. 2008;90(10):2142-8.

54. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: the Tromso Study. Int J Epidemiol. 2012;41(4):961-7.

55. The Tromsø Study. Available from: http://www.tromsostudy.com [cited 28.08.2015].

56. Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njolstad I. The sixth survey of the Tromso Study (Tromso 6) in 2007-08: collaborative research in the interface between clinical medicine and epidemiology: study objectives, design, data collection procedures, and attendance in a multipurpose population-based health survey. Scand J Public Health. 2013;41(1):65-80.

57. Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, et al. Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int. 1998;8(5):468-89.

58. World health Organization.WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2013. Oslo, 2012.

59. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. JAMA. 2007;297(4):387-94.

60. Thier SL, Yu-Isenberg KS, Leas BF, Cantrell CR, DeBussey S, Goldfarb NI, et al. In chronic disease, nationwide data show poor adherence by patients to medication and by physicians to guidelines. Manag Care. 2008;17(2):48-52, 5-7.

61. Warriner AH, Curtis JR. Adherence to osteoporosis treatments: room for improvement. Curr Opin Rheumatol. 2009;21(4):356-62.

62. Imaz I, Zegarra P, Gonzalez-Enriquez J, Rubio B, Alcazar R, Amate JM. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. Osteoporos Int. 2010;21(11):1943-51.

63. Devold HM, Furu K, Skurtveit S, Tverdal A, Falch JA, Sogaard AJ. Influence of socioeconomic factors on the adherence of alendronate treatment in incident users in Norway. Pharmacoepidemiol Drug Saf. 2012;21(3):297-304.

64. Modi A, Sen S, Adachi JD, Adami S, Cortet B, Cooper AL, et al. Gastrointestinal symptoms and association with medication use patterns, adherence, treatment satisfaction, quality of life, and resource use in osteoporosis: baseline results of the MUSIC-OS study. Osteoporos Int. 2016;27(3):1227-38.

65. Clark EM, Gould VC, Tobias JH, Horne R. Natural history, reasons for, and impact of low/non-adherence to medications for osteoporosis in a cohort of community-dwelling older women already established on medication: a 2-year follow-up study. Osteoporos Int. 2016;27(2):579-90.

66. West SL, Strom BL, Poole C. Validity of Pharmacoepidemiologic Drug and Diagnosis Data. Pharmacoepidemiology: John Wiley & Sons, Ltd; 2007. p. 709-65.

67. Norwegian Medicines Agency. Changes in reimbursement list. 2012. Available from: http://www.legemiddelverket.no/Blaa_resept_og_pris/blaaresept_forhaandsgodkjent_refusjon/endringslogg_refusjon/Documents/Oversikt endringer refusjon 2012.pdf.

68. Nguyen TV, Center JR, Eisman JA. Osteoporosis: underrated, underdiagnosed and undertreated. Med J Aust. 2004;180(5 Suppl):S18-22.

69. Hoiberg MP, Rubin KH, Gram J, Hermann AP, Brixen K, Haugeberg G. Risk factors for osteoporosis and factors related to the use of DXA in Norway. Arch Osteoporos. 2015;10:16.

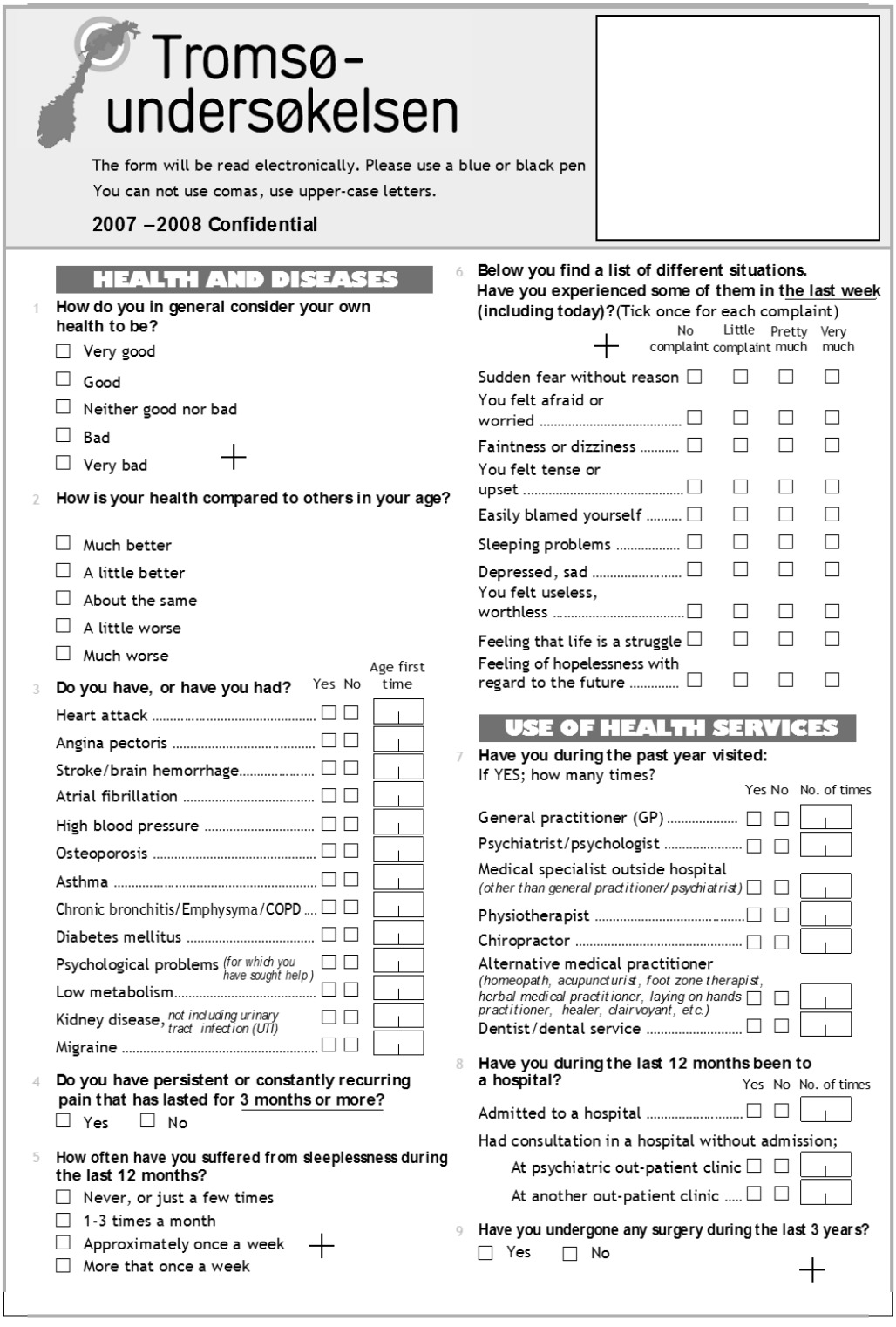
70. Jennings LA, Auerbach AD, Maselli J, Pekow PS, Lindenauer PK, Lee SJ. Missed opportunities for osteoporosis treatment in patients hospitalized for hip fracture. J Am Geriatr Soc. 2010;58(4):650-7.

71. Honkanen K, Honkanen R, Heikkinen L, Kroger H, Saarikoski S. Validity of self-reports of fractures in perimenopausal women. Am J Epidemiol. 1999;150(5):511-6.

72. Joakimsen RM, Fonnebo V, Sogaard AJ, Tollan A, Stormer J, Magnus JH. The Tromso study: registration of fractures, how good are self-reports, a computerized radiographic register and a discharge register? Osteoporos Int. 2001;12(12):1001-5.

8 Appendices

8.1 Questions used in Tromsø 6



Tromsø-undersøkelsen

The form will be read electronically. Please use a blue or black pen
You can not use comas, use upper-case letters.

2007 –2008 Confidential

HEALTH AND DISEASES

1 **How do you in general consider your own health to be?**

- ☐ Very good
- ☐ Good
- ☐ Neither good nor bad
- ☐ Bad
- ☐ Very bad

2 **How is your health compared to others in your age?**

- ☐ Much better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Much worse

3 **Do you have, or have you had?**

	Yes	No	Age first time
Heart attack	☐	☐	
Angina pectoris	☐	☐	
Stroke/brain hemorrhage	☐	☐	
Atrial fibrillation	☐	☐	
High blood pressure	☐	☐	
Osteoporosis	☐	☐	
Asthma	☐	☐	
Chronic bronchitis/Emphysyma/COPD	☐	☐	
Diabetes mellitus	☐	☐	
Psychological problems *(for which you have sought help)*	☐	☐	
Low metabolism	☐	☐	
Kidney disease, *not including urinary tract infection (UTI)*	☐	☐	
Migraine	☐	☐	

4 **Do you have persistent or constantly recurring pain that has lasted for 3 months or more?**

☐ Yes ☐ No

5 **How often have you suffered from sleeplessness during the last 12 months?**

- ☐ Never, or just a few times
- ☐ 1-3 times a month
- ☐ Approximately once a week
- ☐ More that once a week

6 **Below you find a list of different situations. Have you experienced some of them in the last week (including today)?** (Tick once for each complaint)

	No complaint	Little complaint	Pretty much	Very much
Sudden fear without reason	☐	☐	☐	☐
You felt afraid or worried	☐	☐	☐	☐
Faintness or dizziness	☐	☐	☐	☐
You felt tense or upset	☐	☐	☐	☐
Easily blamed yourself	☐	☐	☐	☐
Sleeping problems	☐	☐	☐	☐
Depressed, sad	☐	☐	☐	☐
You felt useless, worthless	☐	☐	☐	☐
Feeling that life is a struggle	☐	☐	☐	☐
Feeling of hopelessness with regard to the future	☐	☐	☐	☐

USE OF HEALTH SERVICES

7 **Have you during the past year visited:** If YES; how many times?

	Yes	No	No. of times
General practitioner (GP)	☐	☐	
Psychiatrist/psychologist	☐	☐	
Medical specialist outside hospital *(other than general practitioner/psychiatrist)*	☐	☐	
Physiotherapist	☐	☐	
Chiropractor	☐	☐	
Alternative medical practitioner *(homeopath, acupuncturist, foot zone therapist, herbal medical practitioner, laying on hands practitioner, healer, clairvoyant, etc.)*	☐	☐	
Dentist/dental service	☐	☐	

8 **Have you during the last 12 months been to a hospital?**

	Yes	No	No. of times
Admitted to a hospital	☐	☐	
Had consultation in a hospital without admission;			
At psychiatric out-patient clinic	☐	☐	
At another out-patient clinic	☐	☐	

9 **Have you undergone any surgery during the last 3 years?**

☐ Yes ☐ No

USE OF MEDICINE

10 **Do you take, or have you taken some of the following medications?** (Tick once for each line)

	Never used	Now	Earlier	Age first time
Drugs for high blood pressure	☐	☐	☐	
Lipid lowering drugs	☐	☐	☐	
Drugs for heart disease	☐	☐	☐	
Diuretics	☐	☐	☐	
Medications for osteoporosis	☐	☐	☐	
Insulin	☐	☐	☐	
Tablets for diabetes	☐	☐	☐	
Drugs for metabolism Thyroxine/levaxin	☐	☐	☐	

11 **How often have you during the last 4 weeks used the following medications?**(Tick once for each line)

	Not used the last 4 weeks	Less than every week	Every week, but not daily	Daily
Painkillers on prescription	☐	☐	☐	☐
Painkillers non-prescription	☐	☐	☐	☐
Sleeping pills	☐	☐	☐	☐
Tranquillizers	☐	☐	☐	☐
Antidepressants	☐	☐	☐	☐

12 **State the names of all medications -both those on prescription and non-prescription drugs- you have used regularly during the last 4 weeks.** Do not include vitamins, minerals, herbs, natural remedies, other nutritional supplements, etc.

_____

_____

_____

_____

_____

_____

If the space is not enough for all medications, use an additional paper of your own.

When attending the survey centre you will be asked whether you have used antibiotics or painkillers the last 24 hours. If you have, you will be asked to provide the name of the drug, strength, dose and time of use.

FAMILY AND FRIENDS

13 **Who do you live with?** (Tick for each question and give the number)

	Yes	No	Number
Spouse/cohabitant	☐	☐	
Other persons older than 18 years	☐	☐	
Persons younger than 18 years	☐	☐	

14 **Tick for relatives who have or have had**

	Parents	Children	Siblings
Myocardial infarction	☐	☐	☐
Myocardial infarction before 60 years	☐	☐	☐
Angina pectoris	☐	☐	☐
Stroke/brain haemorrhage	☐	☐	☐
Osteoporosis	☐	☐	☐
Stomach/duodenal ulcer	☐	☐	☐
Asthma	☐	☐	☐
Diabetes mellitus	☐	☐	☐
Dementia	☐	☐	☐
Psychological problems	☐	☐	☐
Drugs/substance abuse	☐	☐	☐

15 **Do you have enough friends who can give you help when you need it?**

☐ Yes ☐ No

16 **Do you have enough friends whom you can talk confidentially with?**

☐ Yes ☐ No

17 **How often do you normally take part in organised gatherings, e.g. sports clubs, political meetings, religious or other associations?**

☐ Never, or just a few times a year
☐ 1-2 times a month
☐ Approximately once a week
☐ More than once a week

WORK, SOCIAL SECURITY AND INCOME

18 **What is the highest level of education you have completed?** (Tick one)

☐ Primary, 1-2 years secondary school
☐ Vocational school
☐ High secondary school (A-level)
☐ College/university less than 4 years
☐ College/university 4 years or more

19 **What is your main occupation/activity?** (Tick one)

☐ Full time work ☐ Housekeeping
☐ Part time work ☐ Retired/benefit recipient
☐ Unemployed ☐ Student/military service

20 **Do you receive any of the following benefits?**

- ☐ Old-age, early retirement or survivor pension
- ☐ Sickness benefit (are in a sick leave)
- ☐ Rehabilitation benefit
- ☐ Full disability pension
- ☐ Partial disability pension
- ☐ Unemployment benefits
- ☐ Transition benefit for single parents
- ☐ Social welfare benefits

21 **What was the households total taxable income last year?** Include income from work, social benefits and similar

- ☐ Less than 125 000 NOK
- ☐ 125 000-200 000 NOK
- ☐ 201 000-300 000 NOK
- ☐ 301 000-400 000 NOK
- ☐ 401 000-550 000 NOK
- ☐ 551 000-700 000 NOK
- ☐ 701 000 -850 000 NOK
- ☐ More than 850 000 NOK

22 **Do you work outdoors at least 25% of the time, or in cold buildings (e.g. storehouse/industry buildings)?**

☐ Yes ☐ No

PHYSICAL ACTIVITY

23 **If you have paid or unpaid work, which statement describes your work best?**

- ☐ Mostly sedentary work *(e.g. office work, mounting)*
- ☐ Work that requires a lot of walking *(e.g. shop assistant, light industrial work, teaching)*
- ☐ Work that requires a lot of walking and lifting *(e.g. postman, nursing, construction)*
- ☐ Heavy manual labour

24 **Describe your exercise and physical exertion in leisure time. If you activity varies much, for example between summer and winter, then give an average. The question refers only to the last year.** (Tick the one that fits best)

- ☐ Reading, watching TV, or other sedentary activity.
- ☐ Walking, cycling, or other forms of exercise at least 4 hours a week *(here including walking or cycling to place of work, Sunday-walking, etc.)*
- ☐ Participation in recreational sports, heavy gardening, etc. *(note:duration of activity at least 4 hours a week)*
- ☐ Participation in hard training or sports competitions, regularly several times a week.

25 **How often do you exercise?** (With exercise we mean for example walking, skiing, swimming or training/sports)

- ☐ Never
- ☐ Less than once a week
- ☐ Once a week
- ☐ 2-3 times a week
- ☐ Approximately every day

26 **How hard do you exercise on average?**

- ☐ Easy- do not become short-winded or sweaty
- ☐ You become short-winded and sweaty
- ☐ Hard- you become exhausted

27 **For how long time do you exercise every time on average?**

☐ Less than 15 minutes ☐ 30-60 minutes
☐ 15-29 minutes ☐ More than 1 hour

ALCOHOL AND TOBACCO

28 **How often do you drink alcohol?**

- ☐ Never
- ☐ Monthly or more infrequently
- ☐ 2-4 times a month
- ☐ 2-3 times a week
- ☐ 4 or more times a week

29 **How many units of alcohol** (a beer, a glass of wine or a drink) **do you usually drink when you drink alcohol?**

☐ 1-2 ☐ 5-6 ☐ 10 or more
☐ 3-4 ☐ 7-9

30 **How often do you drink 6 units of alcohol or more in one occasion?**

- ☐ Never
- ☐ Less frequently than monthly
- ☐ Monthly
- ☐ Weekly
- ☐ Daily or almost daily

31 **Do you smoke sometimes, but not daily?**

☐ Yes ☐ No

32 **Do you/did you smoke daily?**

☐ Yes, now ☐ Yes, previously ☐ Never

33 **If you previously smoked daily, how long is it since you stopped?**

Number of years ☐

34 **If you currently smoke, or have smoked before: How many cigarettes do you or did you usually smoke per day?**

Number of cigarettes ☐

35 **How old were you when you began smoking daily?**

Number of years ☐

36 **How many years in all have you smoked daily?**

Number of years ☐

37 **Do you use or have you used snuff or chewing tobacco?**

☐ No, never ☐ Yes, sometimes
☐ Yes, previously ☐ Yes, daily

DIET

38 **Do you usually eat breakfast every day?**

☐ Yes ☐ No

39 **How many units of fruits or vegetables do you eat on average per day?** (units means for example a fruit, a cup of juice, potatoes, vegetables)

Number of units ☐☐

40 **How many times per week do you eat hot dinner?**

Number ☐☐

41 **How often do you usually eat these products?** (Tick once for each line)

	0-1 times/ mth	2-3 times/ mth	1-3 times/ week	4-6 times/ week	1-2 times/ day
Potatoes	☐	☐	☐	☐	☐
Pasta/rice	☐	☐	☐	☐	☐
Meat *(not processed)*	☐	☐	☐	☐	☐
Processed meat *(sausages/meatloaf/meatballs)*	☐	☐	☐	☐	☐
Fruits, vegetables, berries	☐	☐	☐	☐	☐
Lean fish	☐	☐	☐	☐	☐
Fat fish *(e.g. salmon, trout, mackerel, herring, halibut, redfish)*	☐	☐	☐	☐	☐

42 **How much do you normally drink the following?** (Tick once for each line)

	Rarely/ never	1-6 glasses /week	1 glass /day	2-3 glasses /day	4 or more glasses /day
Milk, curdled milk, yoghurt	☐	☐	☐	☐	☐
Juice	☐	☐	☐	☐	☐
Soft drinks with sugar	☐	☐	☐	☐	☐

43 **How many cups of coffee and tea do you drink daily?** (Put 0 for the types you do not drink daily)

	Number of cups
Filtered coffee	☐☐
Boiled coffee (coarsely ground coffee for brewing)	☐☐
Other types of coffee	☐☐
Tea	☐☐

44 **How often do you usually eat cod liver and roe?** (i.e. "mølje")

☐ Rarely/never ☐ 1-3 times/year ☐ 4-6 times/year

☐ 7-12 times/year ☐ More than 12 times/year

45 **Do you use the following supplements?**

	Daily	Sometimes	No
Cod liver oil or fish oil capsules	☐	☐	☐
Omega 3 capsules *(fish oil, seal oil)*	☐	☐	☐
Vitamins and/or mineral supplements	☐	☐	☐

QUESTONS FOR WOMEN

46 **Are you currently pregnant?**

☐ Yes ☐ No ☐ Uncertain

47 **How many children have you given birth to?**

Number ☐☐

48 **If you have given birth, fill in for each child: birth year, birth weight and months of breastfeeding** (Fill in the best you can)

Child	Birth year	Birth weight in grams	Months of breastfeeding
1	☐☐☐☐	☐☐☐☐	☐☐
2	☐☐☐☐	☐☐☐☐	☐☐
3	☐☐☐☐	☐☐☐☐	☐☐
4	☐☐☐☐	☐☐☐☐	☐☐
5	☐☐☐☐	☐☐☐☐	☐☐
6	☐☐☐☐	☐☐☐☐	☐☐

49 **During pregnancy, have you had high blood pressure?**

☐ Yes ☐ No

50 **If yes, which pregnancy?**

☐ The first ☐ Second or later

51 **During pregnancy, have you had proteinuria?**

☐ Yes ☐ No

52 **If yes, which pregnancy?**

☐ The first ☐ Second or later

53 **Were any of your children delivered prematurely (a month or more before the due date) because of preeclampsia?**

☐ Yes ☐ No

54 **If yes, which child?**

1st child ☐ 2nd child ☐ 3rd child ☐ 4th child ☐ 5th child ☐ 6th child ☐

55 **How old were you when you started menstruating?**

Age ☐☐

56 **Do you currently use any prescribed drug influencing the menstruation?**

Oral contraceptives, hormonal IUD or similar ☐ Yes ☐ No

Hormone treatment for menopausal problems ☐ Yes ☐ No

When attending the survey centre you will get a questionnaire about menstruation and possible use of hormones. Write down on a paper the names of all the hormones you have used and bring the paper with you. You will also be asked whether your menstruation have ceased and possibly when and why.

Tromsø 6

- part of The Tromsø Study

FILL OUT THE FORM IN THIS WAY:

The form would be read by machine, it is therefore important that you tick appropriately:

☒ Correct

☑ Wrong

☒ Wrong

■ If you tick the wrong box, correct by filling the box like this

Write the numbers clearly 1 2 3 4 5 6 7 8 9 0

7 | 4 Correct

7 | 4 Wrong

Use only black or blue pen, do not use pencil or felt tip pen

1. DESCRIPTION OF YOUR HEALTH STATUS

Mark the statement that best fits your state of health today by ticking once in one of the boxes under each of the five groups below:

1.01 **Mobility**

- ☐ I have no problems in walking about
- ☐ I have little problems in walking about
- ☐ I am confined to bed

1.02 **Self-care**

- ☐ I have no problems with self-care
- ☐ I have some problems washing or dressing myself
- ☐ I am unable to wash or dress myself

1.03 **Usual activities** (e.g. work, study, housework, family or leisure activities)

- ☐ I have no problems with performing my usual activities
- ☐ I have some problems with performing my usual activities
- ☐ I am unable to perform my usual activities

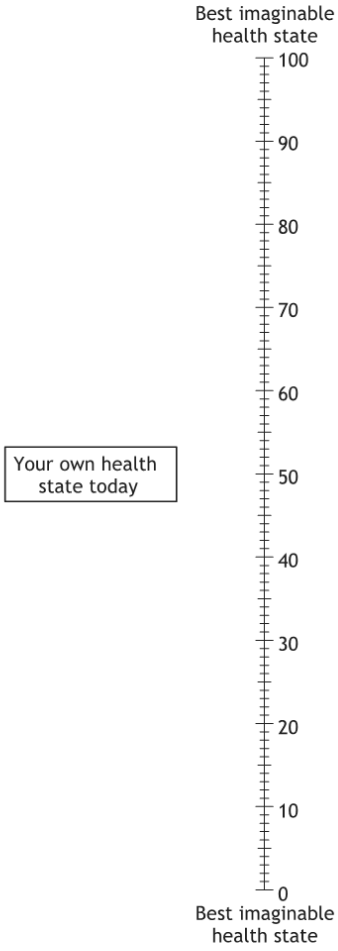
1.04 **Pain and discomfort**

- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

1.05 **Anxiety and depression**

- ☐ I am not anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

1.6 To allow you to show us how good or bad your state of health is we have made a scale (almost like a thermometer) where the best state of health you can imagine is marked 100 and the worst 0. We ask you to show your state of health by drawing a line from the box below to the point on the scale that best fits your state of health.



2. CHILDHOOD/YOUTH AND AFFILIATION

2.01 **Where did you live at the age of 1 year?**

- ☐ In Tromsø *(with present municipal borders)*
- ☐ In Troms, but not Tromsø
- ☐ In Finnmark
- ☐ In Nordland
- ☐ Another place in Norway
- ☐ Abroad

2.02 **How was your family's financial situation during your childhood?**

- ☐ Very good
- ☐ Good
- ☐ Difficult
- ☐ Very difficult

2.03 **What is the importance of religion in your life?**

- ☐ Very important
- ☐ Somewhat important
- ☐ Not important

2.04 **What do you consider yourself as?** (Tick for one or more alternatives)

- ☐ Norwegian
- ☐ Sami ethnicity
- ☐ Kven/Finnish
- ☐ Another ethnicity

2.05 **How many siblings and children do you have/have you had?**

Number of siblings ..... ☐☐

Number of children ..... ☐☐

2.06 **Is your mother alive?**

☐ Yes ☐ No

If NO: her age when she died ..... ☐☐

Is your father alive?

☐ Yes ☐ No

If NO: his age when he died ..... ☐☐

2.07 **What was/is the highest completed education for your parents and your spouse/cohabitant?** (Tick once for each column)

	Mother	Father	Spouse/ cohabitant
Primary 7-10 years, 1-2 years secondary school	☐	☐	☐
Vocational school	☐	☐	☐
High secondary school (A level)	☐	☐	☐
College or university (less than 4 years)	☐	☐	☐
College or university (4 years or more)	☐	☐	☐

3. WELL BEING AND LIVING CONDITIONS

3.01 **Below are three statements about satisfaction with life as a whole. Then there are two statements about views on your own health. Show how you agree or disagree with each of the statements by ticking in the box for the number you think fits best for you.** (tick once for each statement)

	Completely disagree 1	2	3	4	5	6	7 Completely agree
In most ways my life is close to my ideal	☐	☐	☐	☐	☐	☐	☐
My life conditions are excellent	☐	☐	☐	☐	☐	☐	☐
I am satisfied with my life	☐	☐	☐	☐	☐	☐	☐
I have a positive view of my future health	☐	☐	☐	☐	☐	☐	☐
By living healthy, I can prevent serious diseases	☐	☐	☐	☐	☐	☐	☐

3.02 **Below are four statements concerning your current job conditions, or if you are not working now, the last job you had.** (Tick once for each statement)

	Completely disagree 1	2	3	4	5	6	7 Completely agree
My work is tiring, physically or mentally	☐	☐	☐	☐	☐	☐	☐
I have sufficient influence on when and how my work should be done	☐	☐	☐	☐	☐	☐	☐
I am being bullied or harassed at work	☐	☐	☐	☐	☐	☐	☐
I am being treated fairly at work	☐	☐	☐	☐	☐	☐	☐

3.03 **I consider my occupation to have the following social status in the society** (if you are not currently employed, think about your latest occupation)

- ☐ Very high status
- ☐ Fairly high status
- ☐ Middle status
- ☐ Fairly low status
- ☐ Very low status

3.04 **Have you over a long period experienced any of the following?** (Tick one or more for each line)

	No	Yes, as a child	Yes, as adult	Yes, last year
Been tormented, or threatened with violence	☐	☐	☐	☐
Been beaten, kicked at or victim of other types of violence	☐	☐	☐	☐
Someone in your close family have used alcohol or drugs in such a way that it has caused you worry	☐	☐	☐	☐

If you have experienced anything of the above, how much are you affected by that now?

☐ Not affected ☐ Affected to some extent ☐ Affected to a large extent

4. ILLNESS AND WORRIES

4.01 **Have you during the last month experienced any illness or injury?**
☐ Yes ☐ No

If YES: have you during the same period? (Tick once for each line)

	Yes	No
Been to a general practitioner	☐	☐
Been to a medical specialist	☐	☐
Been to emergency department	☐	☐
Been admitted to a hospital	☐	☐
Been to an alternative practitioner *(chiropractor, homeopath or similar)*	☐	☐

4.02 **Have you noticed sudden changes in your pulse or heart rythm in the last year?**
☐ Yes ☐ No

4.03 **Do you become breathless in the following situations?** (tick once for each question)

	Yes	No
When you walk rapidly on level ground or up a moderate slope	☐	☐
When you walk calmly on level ground	☐	☐
While you are washing or dressing	☐	☐
At rest	☐	☐

4.04 **Do you cough about daily for some periods of the year?**
☐ Yes ☐ No

If YES: Is the cough usually productive?

☐ Yes ☐ No

Have you had this kind of cough for as long as 3 months in each of the last two years?
☐ Yes ☐ No

4.05 **How often do you suffer from sleeplessness?** (tick once)
☐ Never, or just a few times a year
☐ 1-3 times a month
☐ Approximately once a week
☐ More than once a week

If you suffer from sleeplessness monthly or more often, what time of the year does it affect you most? (Put one or more ticks)
☐ No special time
☐ Polar night time
☐ Midnight sun time
☐ Spring and autumn

4.06 **Have you had difficulty sleeping during the past couple of weeks?**
☐ Not at all
☐ No more than usual
☐ Rather more than usual
☐ Much more than usual

4.07 **Have you during the last two weeks felt unhappy and depressed?**
☐ Not at all
☐ No more than usual
☐ Rather more than usual
☐ Much more than usual

4.08 **Have you during the last two weeks felt unable to cope with your difficulties?**
☐ Not at all
☐ No more than usual
☐ Rather more than usual
☐ Much more than usual

4.09 **Below, please answer a few questions about your memory:** (tick once for each question)

	Yes	No
Do you think that your memory has declined?	☐	☐
Do you often forget where you have placed your things?	☐	☐
Do you have difficulties finding common words in a conversation?	☐	☐
Have you problems performing daily tasks you used to master?	☐	☐
Have you been examined for memory problems?	☐	☐

If YES to at least one of the first four questions above: Is this a problem in your daily life?
☐ Yes ☐ No

4.10 **Have you during the last last year suffered from pain and/or stiffness in muscles or joints in your neck/shoulders lasting for at least 3 consecutive months?**
(tick once for each line)

	No	A little	A lot
Neck, shoulder	☐	☐	☐
Arms, hands	☐	☐	☐
Upper part of the back	☐	☐	☐
The lumbar region	☐	☐	☐
Hips, leg, feet	☐	☐	☐
Other places	☐	☐	☐

4.11 **Have you suffered from pain and/or stiffness in muscles or joints during the last 4 weeks**

	No	A little	A lot
Neck, shoulder	☐	☐	☐
Arms, hands	☐	☐	☐
Upper part of the back	☐	☐	☐
The lumbar region	☐	☐	☐
Hips, leg, feet	☐	☐	☐
Other places	☐	☐	☐

4.12 **Have you ever had:**

	Yes	No	Age last time
Fracture in the wrist/underarm?	☐	☐	
Hip fracture?	☐	☐	

4.13 **Have you been diagnosed with arthrosis by a doctor?**
☐ Yes ☐ No

4.14 **Do you have or have you ever had some of the following:**

	Never	Little	Much
Nickel allergy	☐	☐	☐
Pollen allergy	☐	☐	☐
Other allergies	☐	☐	☐

4.15 **Have you ever experienced infertility for more than 1 year?**
☐ Yes ☐ No

If Yes: was it due to:

	Yes	No	Do not know
A condition concerning you?	☐	☐	☐
A condition concerning your partner?	☐	☐	☐

4.16 **To which degree have you had the following complaints during the last 12 months?**

	Never	Little	Much
Nausea	☐	☐	☐
Heartburn/regurgitation	☐	☐	☐
Diarrhoea	☐	☐	☐
Constipation	☐	☐	☐
Alternating diarrhoea and constipation	☐	☐	☐
Bloated stomach	☐	☐	☐
Abdominal pain	☐	☐	☐

4.17 **If you have had abdominal pain or discomfort during the last year:**

	Yes	No
Was it located in your upper stomach?	☐	☐
Were you bothered as often as once a week or more during the last 3 months?	☐	☐
Became better after bowel movement?	☐	☐
Are the symptoms related to more frequent or rare bowel movements than normally?	☐	☐
Are the symptoms related to more loose or hard stool than normally?	☐	☐
Do the symptoms appear after a meal?	☐	☐

4.18 **Have you ever had:**

	Yes	No	Age last time
Stomach ulcer	☐	☐	
Duodenal ulcer	☐	☐	
Ulcer surgery	☐	☐	

4.19 **For women: Have you ever had a miscarriage?**
☐ Yes ☐ No ☐ Do not know
If Yes: number of times

4.20 **For men: Have your partner ever had a miscarriage?**
☐ Yes ☐ No ☐ Do not know
If Yes: number of times

4.21 **Is your diet gluten-free?**
☐ Yes ☐ No ☐ Do not know

4.22 **Have you been diagnosed with Dermatitis Herpetiformis (DH)?**
☐ Yes ☐ No ☐ Do not know

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4.23 **Have you been diagnosed with coeliac disease, based on a biopsy from your intestine taken in an endoscopy examination?**
☐ Yes ☐ No ☐ Do not know

4.24 **Do you have your natural teeth?**
☐ Yes ☐ No

4.25 **How many amalgam tooth fillings do you have/have you had?**
☐ 0 ☐ 1-5 ☐ 6-10 ☐ 10+

4.26 **Have you been suffering from headache the last year?**
☐ Yes ☐ No

If No: go to section 5, food habits

4.27 **What kind of headache are you suffering from?**
☐ Migraine ☐ Other headache

4.28 **How many days per month do you suffer from headache?**
☐ Less than one day
☐ 1-6 days
☐ 7-14 days
☐ More than 14 days

4.29 **Is the headache usually:**
(tick one for each line)

	Yes	No
Pounding/pulsatory pain	☐	☐
Pressing/tightening pain	☐	☐
Unilateral pain *(right or left)*	☐	☐

4.30 **What is the intensity of your headache?**
☐ Mild *(do not hinder normal activity)*
☐ Moderate *(decrease normal activity)*
☐ Strong *(block normal activity)*

4.31 **What is the duration of the headache usually?**
☐ Less than 4 hours
☐ 4 hours - 1 day
☐ 1-3 days
☐ More than 3 days

4.32 **If you suffer from headache, when during the year does it affect you most?** (tick one or more)
☐ No special time
☐ Polar night time
☐ Midnight sun time
☐ Spring and/or Autumn

4.33 **Before or during the headache, do you have a transient:**

	Yes	No
Visual disturbances? *(flickering, blurred vision, flashes of light)*	☐	☐
Unilateral numbness in your face or hand?	☐	☐
Deterioration by moderate physical Activity?	☐	☐
Nausea and/or vomiting?	☐	☐

4.34 **Describe how many days you have been away from work or school during the last month due to headache?**
Number of days ☐☐

5. FOOD HABITS

5.01 **How often do you usually eat the following?** (tick once for each line)

	0-1 times per month	2-3 times per month	1-3 times per week	More than 3 times per week
Fresh water fish *(not farmed)*	☐	☐	☐	☐
Salt water fish *(not farmed)*	☐	☐	☐	☐
Farmed fish *(salmon, trout, char)*	☐	☐	☐	☐
Tuna fish *(fresh or canned)*	☐	☐	☐	☐
Fish bread spread	☐	☐	☐	☐
Mussels, shells	☐	☐	☐	☐
The brown content in crabs	☐	☐	☐	☐
Whale or seal meat	☐	☐	☐	☐
Pluck (liver/kidney/heart) from reindeer or elk/moose	☐	☐	☐	☐
Pluck (liver/kidney/heart) from ptarmigan/grouse	☐	☐	☐	☐

5.02 **How many time during the year do/did you usually eat the following?** (number of times)

	In adulthood	In childhood
Mølje (cod or pollack meat, liver, and roe) *(Number of times per year)*	☐☐	☐☐
Gulls egg *(Number of eggs per year)*	☐☐	☐☐
Reindeer meat *(Number of times per year)*	☐☐	☐☐
Local mushroom and wild berries *(blueberries/lingonberries/cloudberries) (Number of times per year)*	☐☐☐	☐☐☐

5.03 **How many times per month do you eat canned (tinned) foods (from metal boxes)?**

Number ☐

5.04 **Do you take vitamins and/or mineral supplements?**

☐ Yes, daily ☐ Sometimes ☐ Never

5.05 **How often do you eat?**

	Never	1-3 times per month	1-3 times per week	4-6 times per week	1-2 times per day	3 times per day or more
Dark chocolate	☐	☐	☐	☐	☐	☐
Light chocolate/milk chocolate	☐	☐	☐	☐	☐	☐
Chocolate cake	☐	☐	☐	☐	☐	☐
Other sweets	☐	☐	☐	☐	☐	☐

5.06 **If you eat chocolate, how much do you usually eat each time?**
Compared with the size of a Kvikk-Lunsj sjokolade *(a chocolate brand in the market)* and describe how much do you eat in relation to it.

¼	½	1	1 ½	2	More than 2
☐	☐	☐	☐	☐	☐

5.07 **How often do you drink cocoa/hot chocolate?**

Never	1-3 times per month	1-3 times per week	4-6 times per week	1-2 times per day	3 times per day or more
☐	☐	☐	☐	☐	☐

6. ALCOHOL

6.01 How often have you in the last year:	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
Not been able to stop drinking alcohol when you have started?	☐	☐	☐	☐	☐
Failed to do what was normally expected of you because of drinking?	☐	☐	☐	☐	☐
Needed a drink in the morning to get yourself going after a heavy drinking session?	☐	☐	☐	☐	☐
Had feeling of guilt or remorse after drinking?	☐	☐	☐	☐	☐
Not been unable to remember what happened the night before because of your drinking?	☐	☐	☐	☐	☐

	Never	Yes, but not in the last year	Yes, during the last year
6.02 **Have you or someone else been injured because of your Drinking?**	☐	☐	☐
Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	☐	☐	☐

7. WEIGHT

7.01 **Have you involuntary lost weight during the last 6 months?**

☐ Yes ☐ No

If Yes: how many kilograms? ☐☐

7.02 **Estimate your body weight when you were 25 years old:**

Number of kilograms ☐☐☐

7.03 **Are you satisfied with your present body weight?**

☐ Yes ☐ No

7.04 **What weight would you be satisfied with (your "ideal" weight)?**

Number of kilograms ☐☐☐

8. SOLVENTS

8.01 **How many hours per week, do you do the following leisure- or professional activities:**

Automobile repair/paint, ceramic work, painting/solvents, hair dressing, glazier, electrician. (Put 0 if you do not engage in such leisure or professional activities)

Number of hours per week on average ☐☐

8.02 **Do you use hair color preparations**

☐ Yes ☐ No

If Yes: How many times per year? ☐☐

9. USE OF HEALTH SERVICES

9.01 **Have you ever experienced that disease has been inadequately examined or treated, and that this had serious consequences?**

- ☐ Yes, this has happened to me
- ☐ Yes, this has happened to a close relative *(child, parents, spouse)*
- ☐ No

If Yes, where do you think the reason of the problem is? (tick once or more):

- ☐ With a general practitioner
- ☐ With an emergency medical doctor
- ☐ With a private practising specialist
- ☐ With a hospital doctor
- ☐ With another health personnel
- ☐ With an alternative practitioner
- ☐ with more than one person due to the failure of procedures and collaboration

9.02 **Have you ever felt persuaded to accept an examination or treatment that you do not want?**

☐ Yes ☐ No

If Yes, do you think this has had unfortunate health-related consequences?

☐ Yes ☐ No

9.03 **Have you ever complained about a treatment you have got?**

- ☐ Have never a reason for complaining
- ☐ Have considered complaining, but did not do that
- ☐ Have complained verbally
- ☐ Have complained in writing

9.04 **How long have you had your current general practitioner/other physician?**

- ☐ Less than 6 months
- ☐ 6 to 12 months
- ☐ 12 to 24 months
- ☐ More than 2 years

9.05 **At the last visit to the general practitioner, did the doctor(s) speak to you in a way so you understand them?** Answers to a scale from 0 to 10, where 0 = they were difficult to understand and 10 = they were always easy to understand

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

9.06 **How would you characterize the treatment or counselling, you got the last time you were with a doctor?** Answer on a scale from 0 to 10, where 0 = very bad treatment, and 10 = very good treatment

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

9.07 **Do you have during the last 12 months experienced that it has been difficult to be referred to special investigations (like X-ray or similar) or to specialized health service (private practising specialist or at hospital)?**

- ☐ Not applicable
- ☐ No problem
- ☐ Some problems
- ☐ Great problems

9.08 **Have you during the last 12 months experienced that it is difficult to be referred to physiotherapist, chiropractor or similar?**

- ☐ Not applicable
- ☐ No problem
- ☐ Some problems
- ☐ Great problems

9.09 **All in all, have you experienced that it is difficult or simply to be referred to specialized health services?**

- ☐ Not applicable
- ☐ Very difficult
- ☐ Somehow difficult
- ☐ Reasonably easy
- ☐ Very easy

10. USE OF ANTIBIOTICS

10.01 **Have you used antibiotics during the last 12 months?** (all penicillin-like medicine in the form of tablets, syrups or injections)

☐ Yes ☐ No ☐ Do not remember

If YES: What did you get the treatment for?
Have you taken many antibiotic treatments, tick for each treatment.

	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	Treatment 6
• Urinary tract infection *(bladder infection, cystitis)*	☐	☐	☐	☐	☐	☐
• Respiratory tract infection *(ear, sinus, throat or lung infection, bronchitis)*	☐	☐	☐	☐	☐	☐
• Other	☐	☐	☐	☐	☐	☐
Treatment duration: number of days	| |	| |	| |	| |	| |	| |

How did you acquire the antibiotics for treatment?
Have you acquired many treatments, tick for each one.

	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	Treatment 6
With prescription from a doctor/dentist	☐	☐	☐	☐	☐	☐
Without contacting a doctor/without prescription:						
· Purchase from a pharmacy abroad	☐	☐	☐	☐	☐	☐
· Purchase over the internet	☐	☐	☐	☐	☐	☐
· Remnants from earlier treatment at home	☐	☐	☐	☐	☐	☐
· From family/friends	☐	☐	☐	☐	☐	☐
· Other ways	☐	☐	☐	☐	☐	☐

10.02 **Do you have antibiotics at home?**

☐ Yes ☐ No

If YES:is this after an agreement with your doctor for treatment of chronic or frequently recurring disease?

☐ Yes ☐ No

If No: how did you acquire this antibiotic?
(Multiple ticks are possible)

Purchased from a pharmacy abroad ☐
Purchased over the internet ☐
Remnants from earlier treatment ☐
From family/friends ☐
Other ways ☐

10.03 **Would you consider using antibiotics without consulting your doctor?**

☐ Yes ☐ No

If YES: which conditions would you treat in such situation? (multiple ticks are possible)

Common cold ☐
Cough ☐
Bronchitis ☐
Sore throat ☐
Sinusitis ☐
Fever ☐
Influenza ☐
Ear infection ☐
Diarrhoea ☐
Urinary tract infection ☐
Other infections ☐

11. YOUR CIRCADIAN RHYTHM

We will ask you some questions about your sleeping habits

11.01 **Have you worked in a shift work schedule during the last 3 months?**

☐ Yes ☐ No

11.02 **Number of days per week which you cannot freely choose when you sleep (e.g. work days)?**

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

Then I go to bed at ..... |_|_|_|

I get ready to fall asleep at ..... |_|_|_|

Number of minutes I need to fall asleep ..... |_|_|

I wake up at ..... |_|_|_|

With help of: ☐ Alarm clock ☐ External stimulus *(noise, family members etc.)* ☐ By myself

Number of minutes I need to get up ..... |_|_|

11.03 **Number of days per week which you can freely choose when you sleep** (e.g. free days or holidays)

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

Then I go to bed at ..... |_|_|_|

I get ready to fall asleep at ..... |_|_|_|

Number of minutes I need to fall asleep ..... |_|_|

I wake up at ..... |_|_|_|

With help of: ☐ Alarm clock ☐ External stimulus *(noise, family members etc.)* ☐ By myself

Number of minutes I need to get up ..... |_|_|

12. SKIN AND DERMATOLOGY

12.01 **How often do you usually take a shower or a bath?** (tick once)

- ☐ 2 or more times daily
- ☐ 1 time daily
- ☐ 4-6 times per week
- ☐ 2-3 times per week
- ☐ Once a week
- ☐ Less than once a week

12.02 **How often do you during a day usually wash your hands with soap?** (tick once)

- ☐ 0 times
- ☐ 1-5 times
- ☐ 6-10 times
- ☐ 11-20 times
- ☐ More than 20 times

12.03 **Have you ever taken any antibiotics (penicillin and similar medicines) because of a skin disease, for example infected eczema, acne, non-healing leg ulcers, recurrent abscess?**

☐ Yes ☐ No

If Yes: How many times in average per year did you take antibiotics during the period you were most affected (tick once)

☐ 1-2 ☐ 3-4 ☐ More than 4 times

12.04 **Have you or have you ever had the following skin disorders?** (tick once for each line)

	Yes	No
Psoriasis	☐	☐
Atopic eczema (children's eczema)	☐	☐
Recurrent hand eczema	☐	☐
Recurrent pimples/spots for several months	☐	☐
Leg or foot ulcer that did not heal for 3-4 weeks	☐	☐

If Yes for the question on leg and/or foot ulcer, do you have the ulcer today?

☐ Yes ☐ No

12.05 **Have you often or always any of the following complaints?** (tick once for each line)

	Yes	No
Swelling in the ankles or legs, particularly in the evenings	☐	☐
Varicose veins	☐	☐
Eczema (red, itchy rash) on your legs	☐	☐
Leg pain when you walk, but is relieved when you stand still	☐	☐

12.06 **Have you ever had the following diagnoses by a physician?** (tick once for each line)

	Yes	No
Psoriasis	☐	☐
Atopic eczema	☐	☐
Rosacea	☐	☐

12.07 **Have you recurring large acne/abscesses that are tender/painful and often form scars in the following places?** (tick once for each line)

	Yes	No
Armpits	☐	☐
Under the breasts	☐	☐
Stomach groove/the navel	☐	☐
Around the genitalia	☐	☐
Around the anus	☐	☐
The groin	☐	☐

If Yes: Have you ever visited a physician because of abscesses?

☐ Yes ☐ No

If Yes, did you get any of the following treatments? (tick once for each line)

	Yes	No
Antibiotic ointment	☐	☐
Antibiotic tablets	☐	☐
Surgical drainage	☐	☐
A larger surgical intervention including skin removal	☐	☐
Surgical laser treatment	☐	☐

Follow-up questions

INFORMATION TO FOLLOW-UP QUESTIONS

The following pages with questions should not be answered by all. If you have answered yes to one or more of questions below, we ask you to move on to the follow-up questions on the topic or topics you have answered yes to. The first four topics are from the first questionnaire and the last question is from this form.

We have for the sake of simplicity highlighted topics with different colors so that you will find the questions that applies to you.

If you answered YES to that you have: long-term or recurrent pain that has lasted for 3 months or more, please answer the questions on page 19 and 20. The margin is marked with green.

If you answered YES to that you have undergone any surgery during the last 3 years, please answer the questions on page 21 and 22. The margin is marked with purple.

If you answered YES to that you're working outdoors at least 25% of the time, or in facilities with low temperature, such as warehouse/industrial halls, please answer the questions on page 23 The margin is marked with red.

If you answered YES to that you have used non-prescription pain relievers, please answer questions on page 24. The margin is marked with orange.

If you answered YES to that you have or have ever had skin problems (such as psoriasis, atopic eczema, non-healing leg or foot ulcerl, recurrent hand eczema, acne or abscesses), please answer the questions on page 25. The margin is marked with yellow.

If you have answered **NO** to these five questions, you are finished with your answers. The questionnaire is to be returned in the reply envelope you were given at the survey. The postage is already paid.

Should you wish to give us written feedback on either the questionnaire or The Tromsø Survey in general, you are welcome to that on page 26.

Do you have any questions, please contact us by phone or by e-mail. You can find the contact information on the back of the form. **THANK YOU** for taking the time to the survey and to answer our questions.

13. FOLLOW-UP QUESTIONS ON PAIN

You answered in the first questionnaire that you have protracted or constantly recurrent pain that has lasted for 3 months or more. Here, we ask you to describe the pain a little closer.

13.01 **How long have you had this pain?**

Number of years ☐☐ months ☐☐

13.02 **How often do you have this pain?**

- ☐ Every day
- ☐ Once a week or more
- ☐ Once a month or more
- ☐ Less than once a month

13.03 **Where does it hurt?** (Tick for all locations where you have protracted or constantly recurrent pain)

- ☐ Head/face
- ☐ Jaw/temporo-mandibular joint
- ☐ Neck
- ☐ Back
- ☐ Shoulder
- ☐ Arm/elbow
- ☐ Hand
- ☐ Hip
- ☐ Thigh/knee/leg
- ☐ Ankle/foot
- ☐ Chest/breast
- ☐ Stomach
- ☐ Genitalia /reproductive organs
- ☐ Skin
- ☐ Other locations

13.04 **What do you believe is the cause of the pain?** (Tick for all known causes)

- ☐ Accident /acute injury
- ☐ Long-term stress
- ☐ Surgical intervention/operation
- ☐ Herniated disk *(prolapse)* /lumbago
- ☐ Whiplash
- ☐ Migraine/headache
- ☐ Osteoarthritis
- ☐ Rheumatoid arthritis
- ☐ Bechterews syndrome
- ☐ Fibromyalgia
- ☐ Angina pectoris
- ☐ Poor blood circulation
- ☐ Cancer
- ☐ Nerve damage/neuropathy
- ☐ Infection
- ☐ Herpes zoster
- ☐ Another cause *(describe below)*
- ☐ Don't know

Describe the other cause:

.....

13.05 **Which kind of treatment have you received for the pain?** (Tick for all types of pain treatments you have received)

- ☐ No treatment
- ☐ Analgesic medications
- ☐ Physiotherapy/chiropractic treatment
- ☐ Treatment at a pain clinic
- ☐ Surgery
- ☐ Psycho-educative/relaxation training/ psychotherapy
- ☐ Acupuncture
- ☐ Complimentary medicine *(homeopathy, healing, aromatherapy, etc.*
- ☐ Another treatment

13.06 **On a scale of 0 to 10, where 0 corresponds to no pain and 10 corresponds to the worst possible pain you can imagine:**

How strong would you say that the pain usually is?	No pain	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable pain
How strong is the pain when it is in its strongest intense?	No pain	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable pain
To what degree does the pain interfere with your sleep?	No effect	0	1	2	3	4	5	6	7	8	9	10	Impossible to sleep
To what degree does the pain interfere with performing common activities at home and at work?	No effect	0	1	2	3	4	5	6	7	8	9	10	Can not do anything

14. FOLLOW-UP QUESTIONS ON SURGERY

In the first questionnaire you answered that you have undergone an operation during the last 3 years.

14.01 **How many times have you undergone surgery during the last 3 years?**

Number ..... ☐

Below, please describe the operation. If you have undergone several operations during the last 3 years, these questions concern the last surgery you underwent.

14.02 **Where in your body did you have surgery?**
(If you were operated simultaneously in several places in the body, tick more than once)

Surgery in the head/neck/back
- Head/face ☐
- Neck/throat ☐
- Back ☐

Surgery in the chest
- Heart ☐
- Lungs ☐
- Breasts ☐
- Another surgery in the chest region ☐

Surgery in the stomach/pelvis
- Stomach/intestines ☐
- Inguinal hernia ☐
- Urinary tract/reproductive organs ☐
- Gall bladder/biliary tract ☐
- Another surgery in the stomach/pelvis ☐

Surgery in the hip/legs
- Hip/thigh ☐
- Knee/leg ☐
- Ankle/foot ☐
- Amputation ☐

Surgery in the shoulder and arm
- Shoulder/overarm ☐
- Elbow/underarm ☐
- Hand ☐
- Amputation ☐

14.03 **Reason for the surgery:**
- Acute illness/trauma ☐
- Planned non-cosmetic operation ☐
- Planned cosmetic operation ☐

14.04 **Where did you have the surgery?**
- Tromsø hospital ☐
- Harstad hospital ☐
- Other public hospital ☐
- Private clinic ☐

14.05 **How long time is it since you had surgery?**

Number of years ..... ☐ Months ..... ☐

14.06 **Do you have reduced sensitivity in an area near the surgical scar?**

☐ Yes ☐ No

14.07 **Are you hypersensitive to touch, heat or cold in an area near the surgical scar?**

☐ Yes ☐ No

14.08 **Does slight touch from clothes, showering or similar cause discomfort/pain?**

☐ Yes ☐ No

14.09 **If you had pain at the site of surgery before you had surgery, do you have the same type of pain now?**

☐ Yes ☐ No

14.10 **The pain at the site of surgery:** Answer on a scale from 0 to 10, where 0=no pain and 10=worst pain you can imagine

	No pain	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable pain
How strong pain did you have at the site of surgery before you had surgery		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
How strong pain do you normally have at the site of surgery now		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
How strong pain do you normally have at the site of surgery when it is most intense		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

15. FOLLOW-UP QUESTIONS ABOUT WORK IN COLD ENVIRONMENT

In the first questionnaire you answered yes to that you work in cold environments. Here are some follow-up questions that we hope you will answer.

15.01 **Do you feel cold at work?**

- ☐ Yes, often
- ☐ Yes, sometimes
- ☐ No, never

15.02 **For how long have you been exposed to cold air below 0°C during the last winter?**

Leisure/hobbies *(hours/week)* ..... |_|

Work *(hours/week)* ..... |_|

Outdoors, with suitable clothing *(hours/week)* ..... |_|

Outdoors, without suitable clothing *(hours/week)* ..... |_|

Indoors, with no heating *(hours/week)* |_|

In cold, with wet clothing *(hours/week)* ..... |_|

Contact with cold objects/tools *(hours/week)* ..... |_|

15.03 **What ambient temperature prevents you from:**

	Under °C
Working outdoors	
Training outdoors	
Performing other activities outdoors	

15.04 **Have you during the last 12 months had a frostbite with blisters, sores or skin injury?**

☐ Yes ☐ No

If Yes, how many times? ..... |_|

15.05 **Have you had itching and/or rash in relation to cold exposure?**

☐ Yes ☐ No

15.06 **Have you during the last 12 months been involved in an accident which required medical treatment where cold was an important factor?**

	Yes	No
At work	☐	☐
In leisure time	☐	☐

15.07 **Do you experience any of the following symptoms while you are in a cold environment? If so, at what temperature do the symptoms occur?**

	Yes	No	Under °C
Breathing problems	☐	☐	
Wheezy breathing	☐	☐	
Mucus secretion from lungs	☐	☐	
Chest pain	☐	☐	
Disturbance in heart rhythm	☐	☐	
Impaired blood circulation in hands/feet	☐	☐	
Visual disturbance *(short term/transient)*	☐	☐	
Migraine *(short term/transient)*	☐	☐	
Fingers turning white *(short term/transient)*	☐	☐	
Fingers turning blue-red *(short term/transient)*	☐	☐	

15.08 **How does a cold environments and cold-related symptoms influence your performance?**

	Decrease	No effect	Improve
Concentration	☐	☐	☐
Memory	☐	☐	☐
Finger sensitivity *(feeling)*	☐	☐	☐
Finger skill *(motor)*	☐	☐	☐
Control of movement *(for example tremor)*	☐	☐	☐
Heavy physical work	☐	☐	☐
Long-lasting physical work	☐	☐	☐

16. USE OF NON-PRESCRIPTION PAINKILLERS MEDICATIONS

In the first questionnaire you answered that you had used non-prescription painkillers (analgesic) medications in the last 4 weeks. Here are some follow-up questions we hope you will answer.

16.01 **What types of non-prescription painkiller medications have you used?**

Paracetamol: *(Pamol, Panodil, Paracet, Paracetamol, Pinex)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ daily

How much you take usually daily when you use the medications? *(number of tablets, suppositories)* ..... ☐☐

Acetylsalicylates: *(Aspirin,Dispril, Globoid)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ Daily

How much you take usually daily when you use the medications? *(number of tablets)* ..... ☐☐

Ibuprofen: *(Ibumetin, Ibuprofen, Ibuprox, Ibux)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ Daily

How much you take usually daily when you use the medications? *(number of tablets, suppositories)* ..... ☐☐

Naproxen: *(Ledox, Naproxen)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ Daily

How much you take usually daily when you use the medications? *(number of tablets)* ..... ☐☐

Phenazone with caffeine: *(Antineuralgica, Fanalgin, Fenazon-koffein, Fenazon-koffein sterke)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ daily

How much you take usually daily when you use the medications? *(number of tablets)* ..... ☐☐

16.02 **For which complains do you use non-prescription painkiller drugs?** (multiple ticks are possible)

- ☐ Headache
- ☐ Menstrual pain
- ☐ Migraine
- ☐ Back pain
- ☐ Muscle/joint pain
- ☐ Tooth pain
- ☐ Other

16.03 **Do you think you have experienced side effects of some of the medications?** (tick once for each line)

	Yes	No
Paracetamol	☐	☐
Acetylsalicylates	☐	☐
Ibuprofen	☐	☐
Naproxen	☐	☐
Phenazone with caffeine	☐	☐

16.04 **Where do you use to buy such medications?**

- ☐ Pharmacy
- ☐ Grocery
- ☐ Patrol stations
- ☐ Abroad
- ☐ Internet

16.05 **Do you combine the treatment with the use of prescribed pain-relief medications?**

☐ Yes ☐ No

17. FOLLOW-UP QUESTIONS ABOUT SKIN DISEASES

On page 15 in this questionnaire you answered that you have or have had a skin disease. Here are some follow-up questions we hope you will answer.

Answer on a scale from 0 to 10, where 0 corresponds to no symptoms and 10 correspond to worst imaginable complaints. If you answered YES to that you have or have had:

	No complaint	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable complaints
17.01 **Psoriasis**													
· How much are you affected by your psoriasis today?		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
· How much are you affected by your psoriasis when it is most severe?		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
17.02 **Atopic eczema**													
· How much are you affected by your atopic eczema today?		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
· How much are you affected by your atopic eczema when it is most severe?		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
17.03 **Hand eczema**													
· How much are you affected by your hand eczema today?		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
· How much are you affected by your hand eczema when it is most severe?		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
17.04 **Acne**													
· How much are you affected by your acne today?		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
· How much are you affected by your acne when it is most severe?		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
17.05 **Abscesses**													
· How much are you affected by your abscesses today?		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
· How much are you affected by your abscesses when it is most severe?		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

17.06 **Here is a list of factors that might trigger or exacerbate abscesses, tick for what you think apply to you:**

	Yes	No
Stress/psychological strain	☐	☐
Narrow/tight clothing	☐	☐
Menstrual periods	☐	☐
Pregnancy	☐	☐
Other	☐	☐

17.07 **How many episodes of abscesses do you usually have per year?** (tick once)

☐ 0-1 ☐ 4-6
☐ 2-3 ☐ More than 6

17.08 **How old were you when you got abscesses for the first time?**

☐ 0-12 years ☐ 26-35 years
☐ 13-19 years ☐ 36-50 years
☐ 20-25 years ☐ Older than 50 years

17.09 **If you no longer have abscesses, how old were you when it disappeared?**

☐ 0-12 years ☐ 26-35 years
☐ 13-19 years ☐ 36-50 years
☐ 20-25 years ☐ Older than 50 years

FEEDBACK

Should you wish to give us a written feedback on either the questionnaire or The Tromsø Study in general, you are welcome to it here:

Thank you for your help