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Anti-osteoporotic drug use and quality of life in persons with osteoporosis – The Tromsø Study

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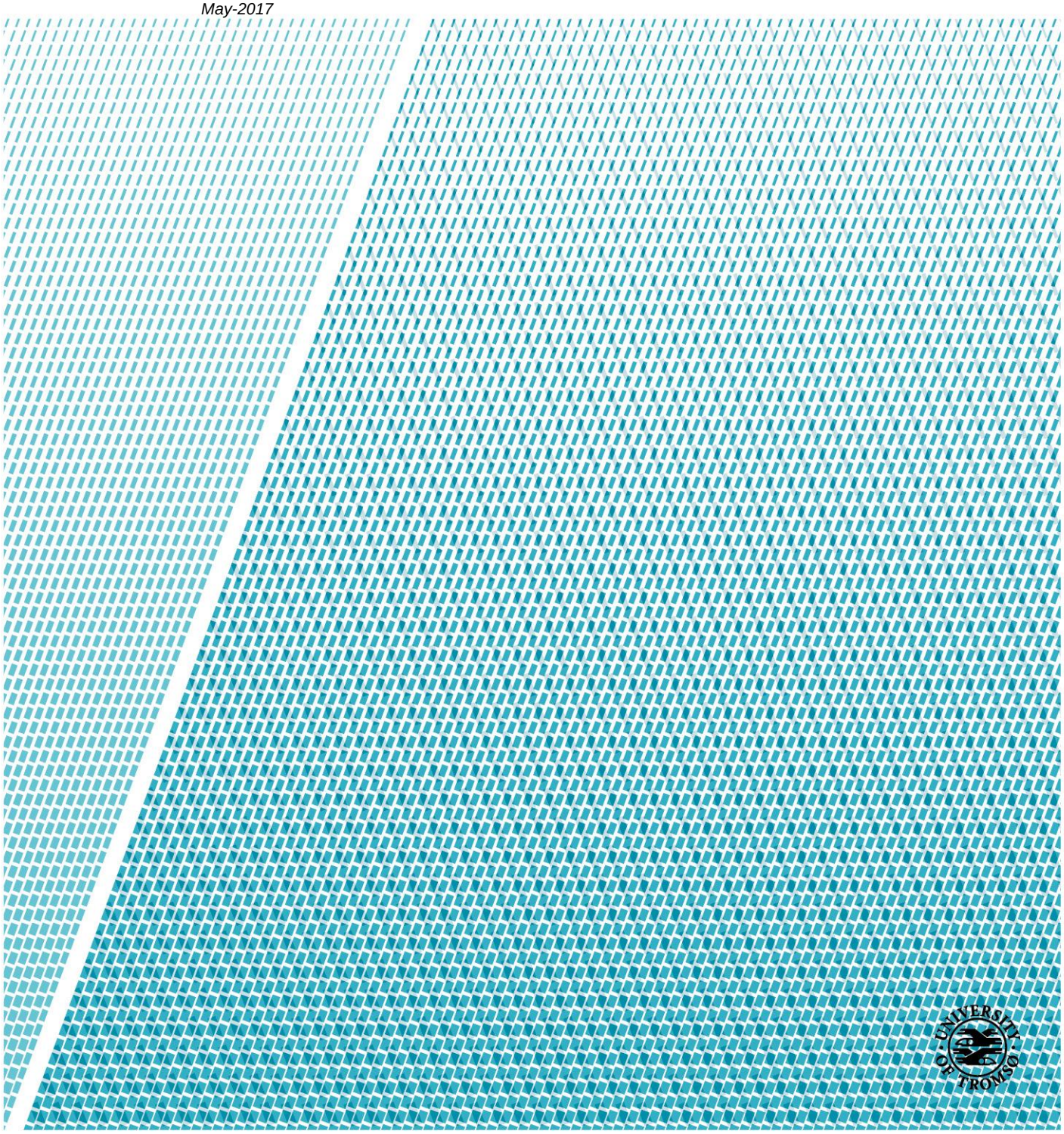

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Abstract

Introduction: Osteoporosis is characterized by decreased bone mineral density (BMD) and is a risk factor for hip, wrist, and vertebral fractures. This is a worldwide public health problem, and causes more than 8.9 million fragility fractures per year. Fragility fractures lead to increased mortality, morbidity, pain, immobility, social isolation and depression, which all may affect the quality of life. Use of anti-osteoporotic drugs (AOD) reduces the risk of fractures and may thus influence the quality of life.

Objective: To investigate a potential association between AOD use and quality of life (QoL) among women and men with osteoporosis.

Methods: This is a cross-sectional study, based on questionnaire data from the sixth wave of The Tromsø Study (Tromsø 6), a population based health survey, which took place in 2007-2008. The 12984 study participants were inhabitants in the municipality of Tromsø aged ≥ 50 years who had osteoporosis in need of treatment, defined by T-score for BMD <-2.5 or from -2.5 to -1.6 combined with prior fracture (n=544). BMD was measured at the non-dominant femoral neck by dual energy X-ray absorptiometry (DXA), fractures were self-reported. AOD use was extracted from the participants' self-reported list of medications (brand names). In multivariable linear regression analysis QoL scores (EQ-5D 3L) was the dependent variable (endpoint), AOD was independent variable (exposure), and adjusted for the covariates age, sex, height, weight, education prior fracture and other diseases. Significance level was set at 5%.

Results: The mean QoL score was 0.68 (SD=0.28) in 54 participants using AOD and 0.82 (SD=0.18) in 424 participants not using AOD. The QoL was inversely associated with use of AOD (B=-0.116, *p*=0.002) after adjusting for covariates. After stratifying the participants into those with prior fracture and not, QoL was inversely associated with use of AOD (B=-0.132, *p*=0.002) among those with prior fracture (n=294). AOD use was not significantly associated with QoL among those not reporting prior fracture (n= 163), (B=-0.086, *p*=0.294).

Discussion and conclusion: Persons with osteoporosis who were using AOD had significantly lower QoL compared to the AOD non-users. This must not be interpreted as AOD use leads to lower QoL. As this is a cross-sectional study, the direction of the association and the causal relationship cannot be established. Confounding by severity or awareness of disease could be a problem, as not all participants knew they had osteoporosis.

Abbreviations

AOD	Anti-osteoporotic drugs
ATC	Anatomical Therapeutic Chemical Classification System
BMD	Bone meniral density
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DAG	Directed Acyclic Graph
DXA	Dual energy X-ray absorptiometry
EQ-5D 3L	EuroQol-5 dimensions 3 levels
HRT	Hormone replacement therapy
MCID	Minimal Clinically Important Difference
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
PTH	Parathyroid hormone
QALY	Quality adjusted life-year
QoL	Quality of life
QUALEFFO	Quality of Life Questionnaires for vertebral and wrist fractures
RANKL	Receptor activator of nuclear factor kappa-B ligand
REK	Regional Committee of Medical and Health Research Ethics
SD	Standard diviation
SERM	Selective estrogen receptor modulators
SPSS	Statistical Package for Social Sciences
SSB	Statistics Norway (Statistikk sentral byrå)
SSRI	Selective serotonin reuptake inhibitors
TTO	Time trade off
VAS	Visual analogue scale
WHO	World Health Organisation

1 Introduction

Bone has three physiological functions. It is a reservoir storage of phosphate and calcium, its mechanical nature supports locomotion and protects internal organs, and it contains bone marrow that produce and develop blood cells (1).

Bone is a living dynamic tissue that has two types of cells, osteoclasts and osteoblasts, that are responsible for the remodeling process of bone regeneration. Osteoclasts break down the bone tissue by releasing collagenase enzymes and acids, while osteoblasts are cells that form bone tissues. They form the hard and very dense bone tissue through deposited calcium and phosphate. Normally, in people who do not have osteoporosis, there is a balance between osteoblast and osteoclast activity. In osteoporosis, the patients have abnormal balance by increased number of osteoclasts and decreased number of osteoblasts. Osteoblast and osteoclast activity can be affected by many factors like age, gender and hormones (2, 3).

Osteoporosis is a common condition characterized by decreased bone mass and microarchitectural deterioration and increased possibility of fractures which may lead to morbidity and mortality (4). The World Health Organization define 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)"* (5).

There are two types of osteoporosis. Primary osteoporosis is caused by postmenopausal status (postmenopausal osteoporosis), old age (senile osteoporosis) or both. The other type is called secondary osteoporosis. This means that osteoporosis is caused by other diseases or disorders, drug use or alcohol intake. Malabsorption and thyrotoxicosis are disorders that may cause osteoporosis through reduction in BMD. Corticosteroid is a drug class that is widely used to treat many diseases and may also cause osteoporosis (6).

There are several clinical complications of osteoporosis like hip, wrist, and vertebral fractures and back pain. The most common complication of osteoporosis is fracture. The vertebral fractures are the most prevalent osteoporosis-related fractures but they are often showing no symptoms before the fracture is happened, and the fact that they are under-diagnosed and under-treated is well documented (7, 8). Fractures will have serious negative impact on quality of life (QoL) and that will trigger accelerated deterioration in quality and length of life, and could lead to death in some cases (9).

Osteoporosis is a major problem in the Norwegian society. Every one hour a Norwegian suffers a hip fracture (10). Among patients who suffer a hip fracture, 12% suffer a new fracture within ten years after the first fracture. QoL will be reduced significantly after fractures, especially hip fractures (11).
Not only the patients' QoL will be affected by fractures, but also the economy of the society. Fractures are one of the most expensive single treatments in Norwegian hospitals. This economic consequence will increase with time because of the increasing proportion of elderly people in Norway, as age is one of the main risk factors of osteoporosis (11).
Despite the availability of good preventive treatment, osteoporosis is still under-diagnosed and under-treated especially among the elderly who are at high risk (9).

1.1 Epidemiology of osteoporosis and fractures

Osteoporosis is one of the ten most common conditions globally (12), nearly 30% of women and 10% of men older than 50 years can have the condition (12). Osteoporosis has no symptoms before the first fracture (13).

Osteoporosis causes many fractures worldwide, more than 8.9 million per year. Only in the USA and Europe there are more than 4.5 million osteoporosis fractures per year. Osteoporosis ranks high among diseases that can lead to patients being confined to bed with severe complications (5).

Osteoporosis and fractures are among the largest health related problems in Europe and worldwide (14). A systematic literature review, that determined country-specific risk of hip fracture and 10-year probability of a major osteoporotic fracture, found a greater than 10-fold variation in hip fracture risk and fracture probability among countries as is shown in figure 1 (14).

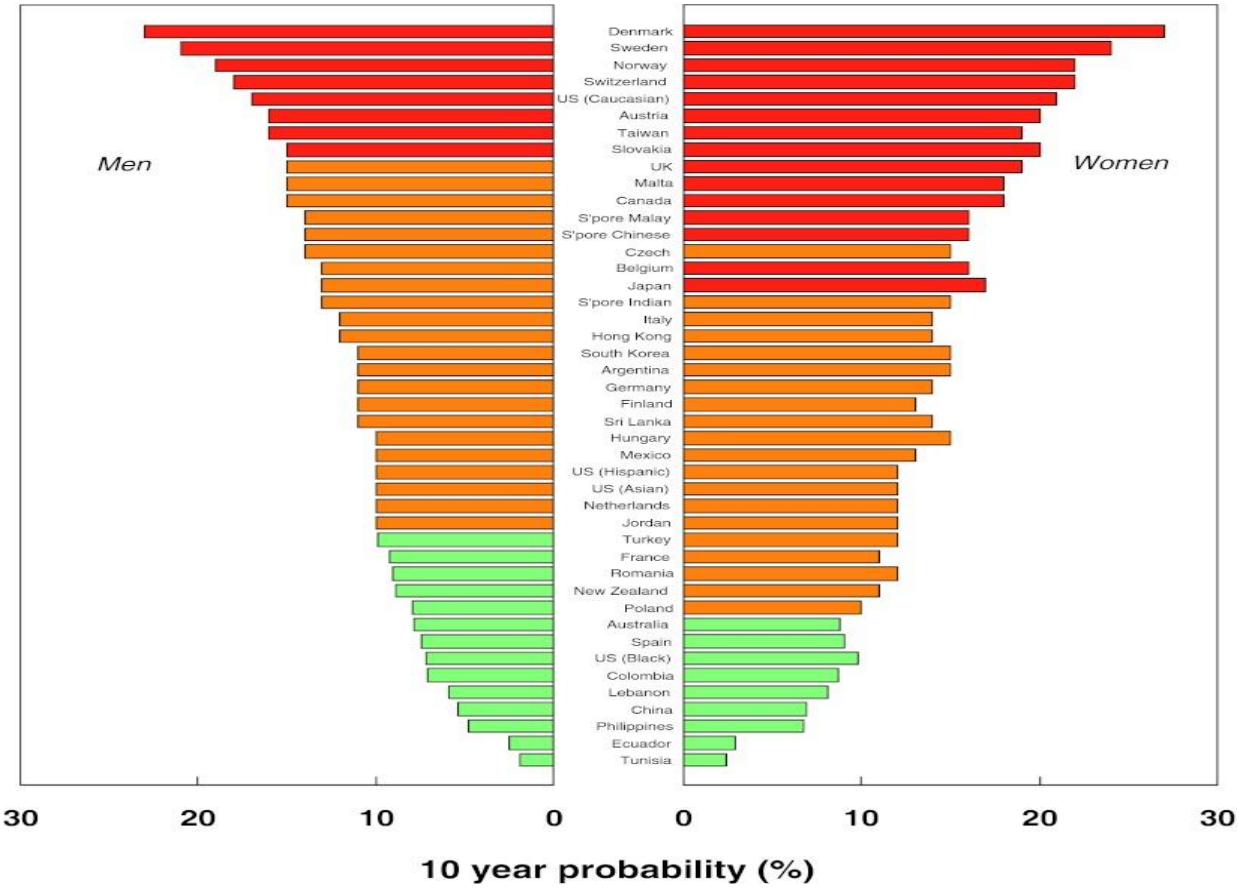

Figure 1 Ten-year probability of osteoporotic fractures in 65 years old men and women with history of fragility fractures, reproduced by permission from Springer (14).

In the European Union (EU), twenty-two million women and 5.5 million men had osteoporosis in 2010. Women had a four times higher incidence than men (15).
The incidence rate of fragility fracture in EU is around 3.5 million fractures per year. These include 610,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1.8 million other types of fractures (like fractures of the sternum, rib, clavicle, pelvis, fibula, scapula, tibia and other femoral fractures) (15), as it shown in figure 2.

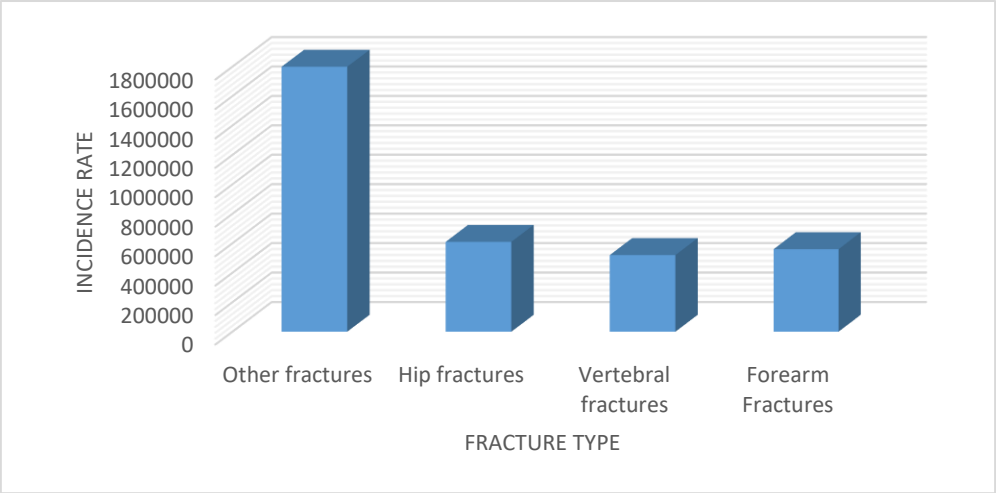

Figure 2 Incidence rate of fractures in EU in 2010 (15).

Over 9000 persons are suffering a hip fracture per year in Norway, which is one of the highest in Europe. This means that there is more than one hip fracture per hour (16). Hip fractures have high mortality rate, and Norway has one of the highest worldwide mortality rate of hip fractures. About 5% of all mortality in patients over 50 years in the Norwegian society is related to hip fractures. About 25% of patients die in the first year after hip fracture (17). A large cohort study from Denmark has shown that the loss of life years after a hip fracture is about 7.5 years, or 18% of their remaining years, in men aged 51-60 years. Older men (over 80 years) loose three years, or 58% of their remaining years. In women the results was 27% loss of remaining years in those aged 50 years or younger, and 38% in women aged over 80 years (18).

Not only hip fractures have very high incidence rate in Norway but also forearm fractures. A study published in 2008 that reported the incidence of distal forearm fractures in Oslo showed that incidence of forearm fractures is higher in Oslo and one of the highest in the world. About 15,000 forearm fractures happen per year in Norway, which means 1.7 forearm fracture per hour (19).

Among all persons with osteoporosis, less than 50% are using AOD, with slightly higher proportion of users among those with prior fractures than those without, as was shown in a master thesis by Ntiamoah in 2016 at UiT (20). Bisphosphonates are the most used drugs (20). It has been shown that only 16% of Norwegian patients who suffer a hip fracture use AOD during the first year after fracture (10). Among all hospitalized old patients with hip fractures,

only 11% in the US, 39% in Korea and 25% in Spain were treated with AOD within three months after hip fractures, as it has been shown in a cross-national study (21).

1.2 Risk factors

Osteoporosis is a disease for which age is the biggest risk factor in both men and women (2, 22). We can divide osteoporosis risk factors into two types: primary, which is the non-drug or non-disease type, and secondary, which is the drug or disease dependent type.

1.2.1 Primary risk factors

Women have higher risk for osteoporosis than men, especially postmenopausal women. This is due to reduced estrogen hormone synthesis in postmenopausal women, and estrogen is the main hormonal regulator for bone metabolism (23). Low body weight is also a risk factor in postmenopausal women (24). Although women have higher risk due to estrogen loss in postmenopausal age, men are also under risk to have osteoporosis, especially elderly men. Men's BMD loss happens gradually and depends upon several factors like ethnicity, diet and overall health. Adult men aged over 60 who have measured BMD and have a T-score that indicate osteopenia, have more than 3% increased 10-year risk of hip fracture and more than 20% increased risk of any fracture type (25).

Prior fractures, especially hip fractures, increase the risk of having a new fracture and is a predictor of incident treatment in both men and women (26). Other types of prior fractures also increase the risk, like low energy fractures in forearm or vertebral, which happen without a big accident, or fractures encountered by regular daily activities at home or after normal falls.

Falling is a particular problem in elderly people, either because of some drugs that can increase the falling probability or because of decreased physical body function. Falling in elderly people is a serious risk factor for fractures in osteoporotic patients. Over 30% of the elderly population aged 65 or older fall at least once per year (27).

There are many other factors that can play a role as risk factor for osteoporosis and fractures. Ethnicity can be a risk factor, in which Scandinavians have higher risk than other ethnicities (28). The height of people is also a risk factor; tall people have higher risk of hip fractures than short people. Family history of osteoporosis, a short fertile period for women, low physical activity, low weight and weight loss (more than 10% weight loss among 25-50 year

olds), can act as risk factors for osteoporosis. Smoking, alcohol intake, reduced exposure to sun light which reduces the vitamin D synthesis, unbalanced diet, inadequate calcium and vitamin D intake, can also increase the risk of osteoporosis (6, 29, 30).

1.2.2 Secondary risk factors

Some drugs that are used routinely to treat other chronic diseases can affect bone and BMD (31). Among these drugs are glucocorticoids, thyroxine, thiazolidinediones, selective serotonin reuptake inhibitors, proton pump inhibitors, loop diuretics and aromatase inhibitors.

Glucocorticoids are used to treat many diseases like autoimmune diseases, inflammation, after organ transplantation, lung diseases and other diseases. These drugs can a weaken the osteoblasts and lead to decrease in bone formation. These effects on bone occur in about 30-50% of patients who use glucocorticoids regardless of dose and length of use (32). Thyroxine is used to treat hypothyroidism in order to stabilize thyroid hormone levels. This drug can lead to osteopenia, bone loss and fractures in postmenopausal women and elderly patients. Thyroxine treatment can lead to osteoporosis through increasing bone resorption directly, but also indirectly by inducing the production of bone-resorbing cytokines (33). Thiazolidinediones are used to treat type II diabetes mellitus. Their side effect on bone are due to decreased osteoblastogenesis and decreased bone formation, because of their action as a selective agonist of peroxisome proliferator-activated receptor-gamma. They also promote osteoclast activity. Risk of fractures in long term treatment with these drugs increases up to 4-fold in men (34) and postmenopausal women (35). Selective serotonin reuptake inhibitors (SSRIs) are used to treat depression. They can lead to bone loss by affecting osteoblast and osteoclast processes in bones, especially among postmenopausal women. The risk of fracture is doubled among postmenopausal women using SSRIs daily for five years at standard doses (36). Proton pump inhibitors are used to treat gastric hyperacidity problems and other gastrointestinal diseases. Long term use of proton pump inhibitors leads to decreased bone resorption through decreasing intestinal calcium absorption, which is important in bone formation. This leads to fractures, especially among postmenopausal women (37). Loop diuretics are used to treat congestive heart failure and to reduce oedema. They have a side effect in association with increased fractures. They inhibit sodium, chloride and calcium reabsorption that lead to decreased BMD and increased fractures rates (38). Aromatase inhibitors like letrozole and anasterozole are used as adjuvant therapy of estrogen-receptor-positive breast cancer in women. By lowering circulating estrogen level in postmenopausal

women can these drugs induce bone loss, decrease BMD and increase possibility of vertebral and non-vertebral fractures, especially wrist fractures, by 40% (39). There are several other drugs that can be risk factors, but in a lower degree, for osteoporosis. Examples are gonadotropin-releasing hormone agonists, medroxyprogesterone acetate, androgen deprivation therapy, anticonvulsants, heparin, oral anticoagulant therapy, calcineurin inhibitors and antiretroviral therapy (31).

Some diseases can be risk factors for osteoporosis. Persons with diabetes mellitus type I have higher risk for osteoporosis than type II (40). Rheumatoid arthritis, especially in women with rheumatoid cachexia which is a condition of increased fat mass and reduced muscle mass with rheumatoid arthritis, can lead to reduced total hip BMD and T-score (41). Chronic obstructive pulmonary disease (COPD) has also a significant association with increased risk of osteoporosis regardless of use of corticosteroids. Patients with COPD have 54% higher risk of developing osteoporosis (42).

1.3 Diagnosis of osteoporosis

The aim of diagnosing osteoporosis is to identify future fractures risk and to monitor the treatment (43). Osteoporosis is diagnosed by measuring bone mineral density (BMD), which is the amount of bone mass per unit volume or per unit area (g/cm^2) (43). There are several techniques that can be used to diagnose osteoporosis, like quantitative ultrasound (QUS), quantitative computed tomography (QCT), radiographic absorptiometry, digital X-ray radiogrammetry and other radiographic techniques. The most commonly used technique is dual energy X-ray absorptiometry (DXA) (43). This technique can be used at hip, forearm or spine to measure the BMD (43).

BMD is usually described by T-score or Z-score, which both are units of standard deviation. T-score refers to number of standard deviations by which BMD differs from the mean value of a reference population (young and healthy individuals). Z-score refers to number of standard deviations by which BMD differs from the mean value expected for a person of the same sex and age as the patient. Z- score is often used in children and teenagers (43).

BMD measuring should be done in the following cases (44): 1) women 65 years or older and men 70 years or older without other risk factors. 2) postmenopausal women, and men older than 50-69 years, who have a risk factor profile or have had a fracture during their adult life.

3) patients who currently or recently have used corticosteroids for a while. And 4) patients who have started AOD treatment within the last two years should have a regular follow-ups every two years by measuring BMD (44).

A DXA-measurement result is usually shown by using T-score. In order to define osteoporosis, the WHO has divided the T-score into four levels using these criteria (45):

> A BMD -1.0 standard deviations or higher indicates normal bone mass. A BMD between -2.5 to -1.0 standard deviations indicates low bone mass or osteopenia. A BMD less than or equal to -2.5 standard deviations below the mean BMD indicates osteoporosis, as shown in figure 3. A BMD less than or equal to -2.5 standard deviations below the mean BMD of young-adult reference group and history of adult fracture indicates severe osteoporosis.

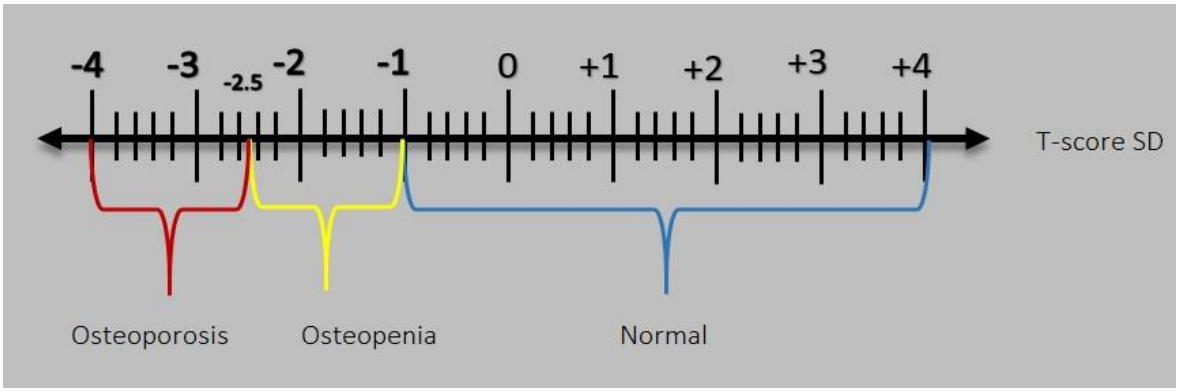

Figure 3 WHO classification for T-score criteria which is the result of DXA (45)

Apart from BMD measurements, there are several other clinical examinations that can be done and disease history that can be registered by the physician. This includes risk factors like age, gender, menopause (women), history of fractures, physical activity, diet (especially vitamin D and calcium), smoking, alcohol intake, hormone levels (for both men and women) and information about use of other drugs e.g. corticosteroids (46). Other laboratory tests can also be used like blood calcium concentration, 24-hour urine calcium level, thyroid gland function test, parathyroid hormone level, testosterone hormone level in men and vitamin D test through 25-hydroxyvitamin D test (46). Norwegian guidelines advises to use these biochemical test only in case of group studying, and not as diagnostic tests.

1.4 Treatment of osteoporosis

There are two ways to treat osteoporosis and thereby prevent its complications. Non-pharmacological treatments are primarily used as prophylaxis against the progression of osteoporosis and its complications. Pharmacological treatment, which is based on treatment with AOD.

1.4.1 Non-pharmacological treatment or prevention

Many non-pharmacological actions can increase BMD and reduce osteoporosis. Increased physical activity, like weight-bearing exercises and general physical activities in young and adult age is effective (47). A healthy nutrition, especially food containing calcium and vitamin D, and weight loss prevention have significant preventive effect. Non-pharmacological treatments also include to reduce or stop smoking tobacco and to reduce or stop drinking alcohol (6).

There are other methods to prevent fractures like reducing the risk of falls, especially in older people that can have osteoporosis (48). This can be done by muscle strengthening, retain balance and withdrawal or reduction of psychotropic drugs. Education programs about the risk of falls and their complications will be effective too (48).

There are other methods to protect the bone from being fractured if the person is falling. These include using a hip protector without increasing fall frequency (49). Another protecting factor, is to simply have sufficient muscles and/or fat around the bone to protect the bone in case of a fall (6, 50).

1.4.2 Pharmacological treatment

In pharmacological intervention there are some drugs or groups of drugs that are commonly used against osteoporosis. These drugs are bisphosphonates, hormone replacement therapy (HRT), denosumab, selective estrogen receptor modulators (SERMs) and parathyroid hormone (PTH). These groups will either slow down bone resorption like bisphosphonates, denosumab and SERM, or induce bone formation like PTH (51).

Bisphosphonates

Bisphosphonates are the main preventive treatment against osteoporosis and its complication, fractures (52). They are the first line therapy against osteoporosis in Norway (51). Bisphosphonates are specific bone resorption inhibitors. Alendronate, the most used

bisphosphonate, localize selectively in active resorption sites in the bone, and especifically inhibit osteoclast activity. This leads to increasing BMD and reduction in fractures (53). Oral bioavailability of this drug group is very low, 1% of the dosage, and it can be affected by food and some minerals like iron and calcium if they are ingested at the same time. Therefore, they should be taken one hour before meal, with only water. Alendronate 70 mg once a week is the most used dosage of bisphosphonates, followed by risedronate 35 mg once a week (43). There are five bisphosphonates on the Norwegian market in 2016. These are alendronate, etidronate, ibandronate, risedronate and zoledronate (51).

A randomized, double-blind study showed a reduction in fracture risk of about 30-50% and increase in BMD after using bisphosphonates by postmenopausal women with a history of vertebral fracture and with low BMD (54). Other studies show bisphosphonates effect on fracture risk and bone loss reduction in postmenopausal women without history of vertebral fractures (55). The effect of bisphosphonates has been shown in men too. A meta-analysis of RCT-studies shows that bisphosphonates reduce the risk of vertebral and non-vertebral fractures and increasing BMD in adult men with osteoporosis (56).

Hormone replacement therapy (HRT)

HRT is a type of therapy used to substitute the loss of hormone in women around menopause. In the treatment of osteoporosis, the important constituent of HRT is estrogen. Estrogens inhibit osteoclasts, which results in increased BMD and decreased fracture risk. HRT can therefore be a treatment alternative in osteoporotic postmenopausal women who also need treatment for vasomotor symptoms of menopause (51). A fairly recent review shows that several observational studies conclude in favor of estrogen treatment, while RCT studies show little benefit of estrogen as an AOD. Additionally, an increased risk of cardiovascular diseases, pulmonary emboli, deep vein thrombosis and breast cancer is shown among postmenopausal women who use HRT. Therefore, it is not recommended as first line treatment of osteoporosis (44).

Denosumab

Denosumab is a fully monoclonal antibody to the receptor activator of nuclear factor-kappaB ligand (RANKL) that blocks its binding to RANK. This will inhibit the activity and number of osteoclasts, increase BMD and decrease fracture risk. Denosumab is given as a subcutaneously injection twice a year for 36 months. This regimen reduces the risk of hip, vertebral and non-vertebral fractures in postmenopausal women (57). Another study shows its

benefit through increased BMD and decreased risk of vertebral fractures in men receiving androgen-deprivation therapy for prostate cancer (58).

Selective estrogen receptor modulators (SERMs)

SERMs, e.g. raloxiphene, are non-hormonal substances that bind to estrogen receptors. They were developed to maintain estrogen effect on cardiac and skeletal tissue without stimulating breast tissue and endometrium. By maintaining the estrogen effect in bone tissues, bone resorption decreases and BMD increases (59). An RCT study shows increasing BMD in femoral neck and spine and reduction in risk of vertebral fractures three years after starting with raloxiphene (60).

Parathyroid hormone (PTH)

As mentioned earlier (1.4.2), the only anabolic AOD is PTH. PTH are recombinant proteins that stimulate positive bone formation balance and remodeling (61). Teriparatid is the PTH used as AOD. It is given subcutaneously once daily in a period of 24 months, and should not be used again in the patient's life time. An RCT study shows increasing BMD in postmenopausal women with osteoporosis after 24 weeks of daily subcutaneous injections of PTH (62).

1.5 Quality of life (QoL) and EQ-5D

All kinds of fractures, both minor and major, may lead to pain, immobility, social isolation, depression and reduced physical activity, which all together will affect QoL (63). Use of AOD decrease the risk of fractures and may increase the QoL.

QoL is a measure of the general well-being and a summary of the positive and negative characteristic of life. There are many ways to calculate QoL, and one of the most frequently used methods in Norway and Europe is the EuroQol-5 dimensions (EQ-5D) questionnaire. The EuroQol Research Foundation's definition of EQ-5D is "*The EQ-5D health questionnaire provides a simple descriptive profile and a single index value for health status"* (64). EQ-5D includes five dimensions and each one of them has either three levels (1-no problem, 2-some problems and 3-extreme problem) in EQ-5D 3L or five levels (1- no problems, 2-slight problems, 3-moderate problems, 4-severe problems and 5-unable to/extreme problems) in EQ-5D 5L. EQ-5D dimensions are: Mobility or movement, self-care (self-dressing or self-washing), usual activities (work, study, housework), pain/discomfort, and anxiety/depression,

as shown in table 1. For children and adolescents aged 7-12 there is a separate type of EQ-5D, the EQ-5D Y (65).

Table 1 EQ-5D 3L dimensions, levels and scores

Dimensions	Levels	Score
Mobility	No problems in walking	1
	Some problems in walking	2
	Extreme problems in walking	3
Self-care	No problems with self-care	1
	Some problems with self-care	2
	Extreme problems with self-care	3
Usual activities	No problems with preforming usual activities	1
	Some problems with preforming usual activities	2
	Extreme problems with preforming usual activities	3
Pain/discomfort	No pain or discomfort	1
	Moderate pain or discomfort	2
	Extreme pain or discomfort	3
Anxiety/depression	No anxiety or depression	1
	Moderate anxiety or depression	2
	Extreme anxiety or depression	3

A total EQ-5D 3L score of for example 11111 indicates no problems at all, while a score of 12321 indicates no problems walking, some problems with self-care, extreme problems with performing usual activities, moderate pain or discomfort and not anxious or depressed.

In order to value EQ-5D (i.e. change it to a numeric score) a method called Visual analogue scale (VAS) or Time trade off (TTO) should be used (66). QoL values vary from 0 (dead) to 1 (best imaginable health), and in some cases it can be in minus (i.e. it is better to die). VAS is a self-reported health scale where the top endpoint *"10"* is called *"Best imaginable health state"* and the bottom endpoint *"0"* is called *"worst imaginable health state"*. The information can be used as a quantitative measure of health made by individuals (67). TTO is based on putting the individual in an imaginary situation and the usual question is "*Imagine that you are told that you have 10 years left to live. In connection with this you are also told*

that you can choose to live these 10 years in your current health state or that you can choose to give up some life years to live for a shorter period in full health. Indicate with a cross on the line the number of years in full health that you think is of equal value to 10 years in your current health state" (68). The Tromsø Study uses TTO, a tariff from UK. Based on this, QoL can be calculated from EQ-5D 3L according to the following equation (69): *"1 + (-0.081 [if there is at least one 2 or 3]) + (-0.269 [if there is at least one 3] + (-0.069[mobility=2] or -0.314[mobility=3]) + (-0.104[self-care=2] or -0.214[self-care=3]) + (-0.036[usual activities=2] or -0.094[usual activities=3]) + (-0.123[pain/discomfort=2] or -0.386[pain/discomfort=3]) + (-0.071[anxiety/depression=2] or -0.236[anxiety/depression =3])"*.

There are several other types of questionnaire that are used to measure QoL for a specific disease, like osteoporosis, chronic obstructive pulmonary disease (COPD) and others. They can be used to measure the burden of this specific diseaseand are called disease specific instruments. The one that are used in osteoporosis is called Quality of Life Questionnaires for vertebral and wrist fractures (QUALEFFO) which was developed by the European Foundation for Osteoporosis in 1992. It is used with patients who have suffered from prior vertebral fractures and have a BMD T-score <-1 SD at lumbar bone. This questionnaire includes questions about pain, physical function, social function, general health perception and mental function. The scale of QUALEFFO is designed to measure The QoL on a scale of 0 to 100, with 0 indicate the best QoL and 100 the worst QoL. The advantages of using QUALEFFO are that it contains more relevant questions, it is more valid and measures accurately QoL in osteoporotic patients. Also, it is less time consuming than general QoL measuring questionnaires (63). QUALEFFO will not be used here in this thesis because The Tromsø Study 6 did not use it.

Quality adjusted life-year (QALY) has been used in many drugs' trials to study the effect of drugs on patients' quality of life (both in quality and quantity) (70), but what we will use here in this thesis is QoL which is the outcome of EQ-5D which constitutes a main part of QALY.

2 Aim

The aim of this master thesis is to investigate a potential association between anti-osteoporotic drug (AOD) use among persons with osteoporosis and their quality of life (QoL).

In persons with osteoporosis, we will compare QoL between those who use AOD and those who do not, while taking into account fractures and other relevant covariates.

The thesis will attempt to answer the following questions:

Is there a difference in QoL between AOD users and non-users?

Does QoL defined by EQ-5D 3L show a different pattern compared with other measurements of QoL, such as various description of pain or of self-reported health status?

How do fractures influence a potential association between QoL and AOD use?

3 Material and method

3.1 The Tromsø Study

The Tromsø Study started in 1974. Only men were incuded and the study aimed at finding reasons for the high death rate of cardiovascular disease in North Norway, and how to prevent cardiovascular diseases (71). A Norwegian man in the 1970s had a 20% risk of dying of heart disease especially myocardial infarction. The purpose of the Tromsø Study was evident from the title of the study as "The Tromsø Heart Study" (71). The seventh wave of the Tromsø Study were completed in October 2016 and included both men and women aged 40 years or more, who are living in the municipality of Tromsø. This latest survey included more than fifty research areas in health and disease. The Tromsø Study has over 45 000 participants in one or more of its surveys, while more than 18 000 participants have attended three or more surveys. The Arctic University of Norway (UiT) funded all the seven surveys (72).

Tromsø is the biggest city in North Norway with more than 74 000 inhabitants (from Statistics Norway SSB-2017). At latitude 69-degree North, Tromsø is located 400 km north of the Arctic Circle. There are two different periods in the year that can affect physical activities for the inhabitants of Tromsø; the "*midnight sun*" which lasts for two months during summer, and the "*polar night*", the dark period during winter, which also lasts for two months. Tromsø has mild climate because of the Gulf Stream. All of these factors have been taken into account in the different Tromsø Study surveys (71). A list of the different surveys of The Tromsø Study is shown in table 2.

Table 2 List of The Tromsø Study surveys (72).

Study survey	Period	Number of participants	Age
Tromsø 1	1974	6595	20-49
Tromsø 2	1979-1980	16651	20-54
Tromsø 3	1986-1987	21826	12-67
Tromsø 4	1994-1995	27158	25-97
Tromsø 5	2001-2002	8130	30-89
Tromsø 6	2007-2008	12984	30-87
Tromsø 7	2015-2016	21083	40+

3.1.1 The sixth wave of the Tromsø Study

The sixth wave of the Tromsø Study (Tromsø 6) was carried out in 2007-2008, and the participants were the residing people of Tromsø with age between 30 to 87 years. The main purpose of the survey was to collect new and repeated measurements of exposure data, in addition to the evaluation of risk factors and treatment. The survey included two screening visits, first visit (all participants, n=12984) and second visit (subgroup, n=7307), and many other follow up studies. In the first visit, a questionnaire was used to collect information about socio-economy, education, family, alcohol and tobacco intake and physical activities. The second visit included clinical examinations on a subgroup, including DXA, visual acuity test, echocardiography and many others. The percentage of attendance rate was 65.7% of all invited subject. The youngest, the oldest and the first time participants had lowest attendance rate, while women showed higher attendance than men (73). The current master thesis will use data from Tromsø 6.

3.2 Study population

The total number of subjects invited to the first visit in Tromsø 6 were 19762 (Figure 4). These included all the subjects that participated in Tromsø 4, all inhabitants aged 40-42 and 60-87 years, a 10% randomly invited sample of subjects aged 30-39 years and a 40% randomly invited sample of subjects aged 43-59 years. The firs visit included 12984 attending subjects. Not all of these subjects were eligible for the second visit, only those who fulfilled one of the following criteria; all subjects aged 50-62 and 75-84 years, randomly sampled 20% of subjects aged 63-74 years and subjects who had participated in the second visit of Tromsø 4 and who were not included through the two first criteria. From the 7958 subjects invited to the second visit, 7307 participated. The total number of participants who had their BMD measured by the DXA method in the second visit was 3663 measured at left femoral neck and 3694 at right femoral neck (73).

The current master thesis include data from the first and the second visit for participants aged 50 years or above, who had measured BMD by DXA at left femoral neck (n=3516), or right femoral neck for those who did not measure BMD at left femoral neck (n=61). Among these

we selected persons with osteoporosis, i.e. those with T-score either <-2.5 SD (n=310) or between -2.5 –and -1.6 SD combined with prior fracture (n=234) (total n=544).

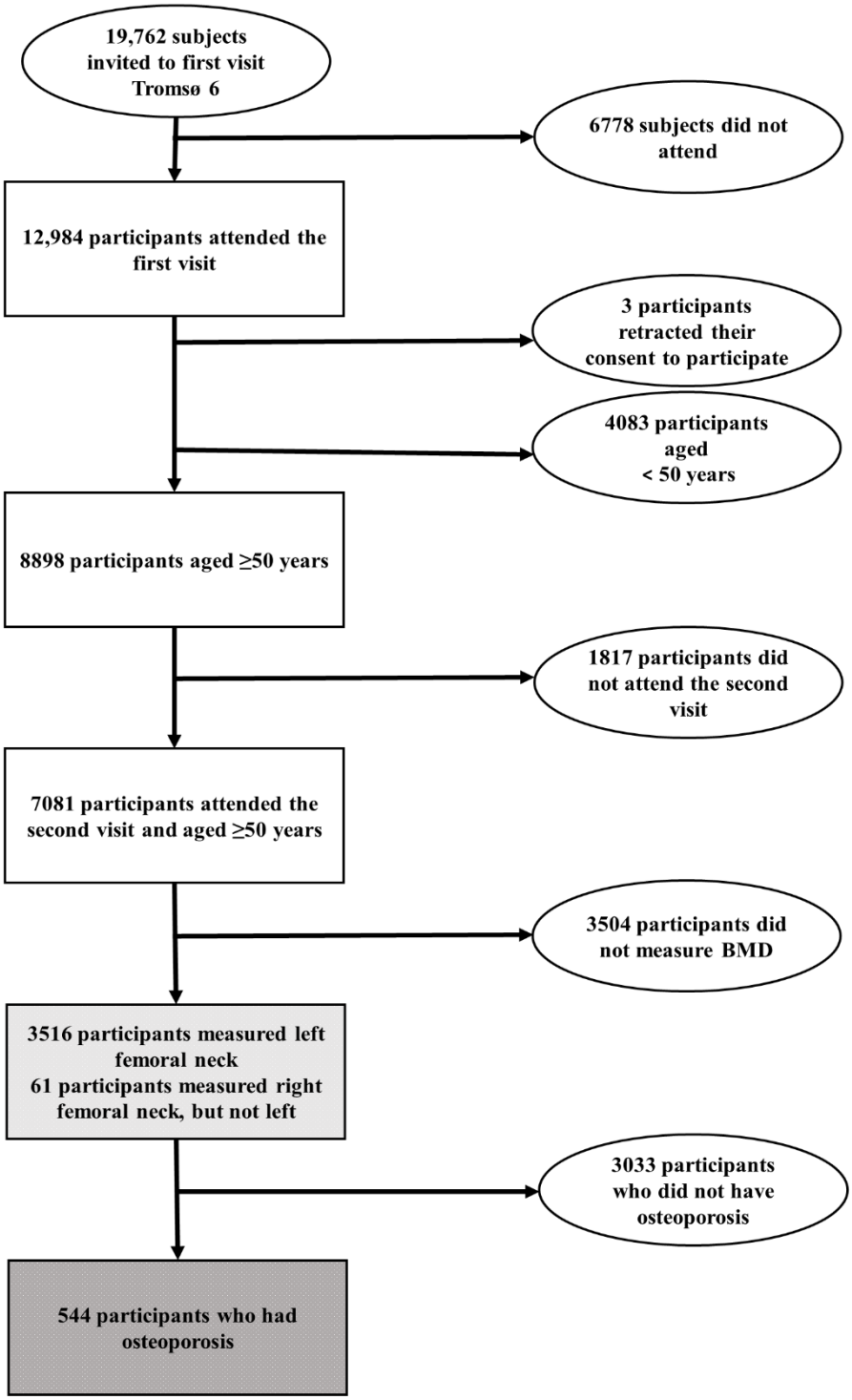

Figure 4 Study population flowchart. The dark grey box is the study population (n=544). The light grey box is the DXA population which is included in some of the descriptive statistics (n=3577)

3.3 Variables

Osteoporosis classification was based on BMD measured at the femoral neck by using DXA. Participants with T-score <-2.5 SD or T-score from -2.5 to -1.6 SD combined with prior self-reported fracture (of the forarm or hip) were considered as osteoporotic (6). T-score was calculated using the National Health and Nutrition Examination Survey (NHANES) III reference and by using Lunar reference, sex specific young adult 20-39 years, (74, 75). The equation used to calculate T-score was:

$$T\ score\ = \frac{patient's\ BMD—population\ peak\ BMD}{standard\ deviation\ (SD)\ of\ population\ peak\ BMD}$$

For young adult female, the reference BMD (population peak BMD) is 0.980 g/cm^2 with 0.12 g/cm^2 standard deviation (SD). For young adult male, the reference BMD is 1.070 g/cm^2 with SD of 0.13 g/cm^2. Osteoporosis fracture information was collected by the question "*Have you ever had a hip fracture?*" or "*Have you ever had a wrist/forearm fracture?*''. The participants who answered "*Yes*'' were considered as having had a prior fracture.

3.3.1 Independent variables

Information on AOD was collected by two questions. First the general question "*Do you take, or have you taken some of the following medications?"* with the sub-point *"Osteoporosis*'', and the response alternatives were "*never used*'', "*Now*'' or "*Earlier*''. This variable was dichotomized into yes ("*Now*") and no ("*Never used"* or *"Earlier*"). The current master thesis also includes information on use of AOD based on the brand names the participants reported in their list of drugs used in the last four weeks. Bisphosphonates have ATC codes M05BA01, M05BA02, M05BA03, M05BA04, M05BA05, M05BA06, M05BA07, M05BA08, M05BB01, M05BC01 and M05BX04. HRT has ATC codes G03CA03, G03CA04, G03CX01, G03FA01, G03FA12 and G03FB05. Denosumab has ATC code M05BX04. SERM has ATC code G03XC01. PTH has ATC code H05AA02 (76).

Kappa statistics was used in order to measure the reliability between these two different AOD questions. The equation used to measure kappa was:

$$\kappa = \frac{p_o - p_e}{1 - p_e} = 1 - \frac{1 - p_o}{1 - p_e},$$

where P_o is the relative observed agreement among raters, P_e is the hypothetical probability of chance agreement and K is Cohen's kappa. The relative agreement between these two

information sources on AOD use was computed and assessed according to the Landis and Koch suggestion (77), as shown in table 3.

Table 3 Agreement measures for categorical data (77)

Kappa result	Strength of agreement
<0.00	Poor
0.00 – 0.20	Slight
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Substantial
0.81 – 1.00	Almost perfect

3.3.2 Covariates

The following covariates were included in the analyses:

- Age (years)
- Gender (male, female)
- Height in centimeter
- Weight in kilogram
- Self-reported prior fractures
- Other diseases that can affect the quality of life like heart attack, angina pectoris, stroke/brain hemorrhage, asthma, chronic bronchitis/ emphysema/ COPD and diabetes mellitus were collected by the question "*Do you have, or have you had …?"*, answer alternative were either "*Yes*" or "*No*".
- Educational level, the question was "*What is the highest levels of education you have completed?*''. There were five answer alternatives for this question, ranging from primary school to university four years or more.
- Physical activity (Exercise and physical exertion in leisure time), the question was *"Exercise and physical exertion in leisure time. If your activity varies much, for example between summer and winter, then give an average. The question refers only to the last twelve months''*. There are four answer categories in this question, varying from low to hard activity.

The categorical independent variables were coded as follows: AOD use (0=not AOD user and 1=AOD user), bisphosphonates use (0=not bisphosphonates use and 1=bisphosphonates use), sex (0=female and 1=male), other diseases (0=no and 1=yes) and prior fractures (0=no and 1=yes).

3.3.3 Dependent variables

We analysed the data using three different dependent variables; EQ-5D 3L, self reported health and muscle and joint pain.

EQ-5D 3L score was used in order to measure QoL. The EQ-5D 3L score is a continuous variable that varies from -0.18 to 1.00, and is measured according to the TTO-tariff from the United Kingdom (72). This variable did not fulfil the assumption of normal distribution. The distribution of the EQ-5D 3L score variable is shown in figure 5.

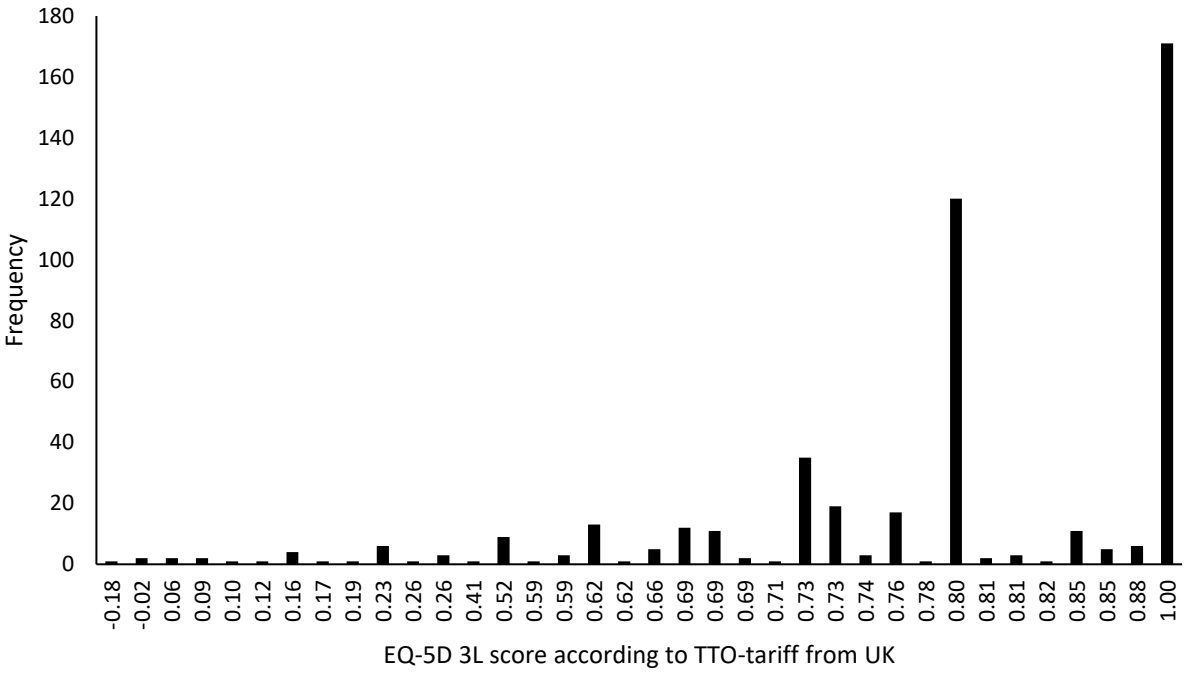

Figure 5 Frequency distribution of the EQ-5D 3L scores

The variable self-reported health was collected from the question "*How do you in general consider your own health to be?*". Answer alternatives were "*Very good*", "*Good*", "*Neither good nor bad*", "*Bad*" or "*Very bad*". we dichotomized this variable into good health (very good, good and neither good or bad) and bad health (bad and very bad).

The variable muscle and joint pain was collected from six questions with the same question frame: "*Have you during the last year suffered from pain and/or stiffness in muscles or joints in your xxx lasting for at least 3 consecutive months?*". The xxx refers to the following six alternatives: neck/shoulder, arms/hands, upper part of the back, the lumbar region, hips/leg/feet, other places). Answer alternatives were *"No", "A little"* or *"A lot".* we dichotomized this variable into pain (A little and A lot) and no pain (No).

The categorical dependent variables were coded as follows: self-reported health (0=bad health and 1=good health), muscle and/or joint pain (coded as 0=no pain and 1=pain).

A complete list of variables used in this thesis is given in table number 4.

Table 4 Complete list of variables

		Variable	Variable type
Population defining variables		T-score from BMD of the femoral neck*	Continuous
		Self-reported prior fractures	Categorical
Independent variables	Exposure of interest	Self-reported AOD use	Categorical
		AOD use extracted from brand name list	Categorical
	Covariates	Age	Continuous
		Gender	Categorical
		Height*	Continuous
		Weight*	Continuous
		Prior fractures	Categorical
		Other diseases	Categorical
		Education	Categorical
		Physical activity	Categorical
Dependent variables		EQ-5D 3L	Continuous
		Self-reported health	Categorical
		Muscle and joint pain	Categorical

Abbreviations: BMD, Bone Mineral Density; AOD, anti-osteoporotic drug; EQ-5D 3L, EuroQol-5 Dimension 3 levels.
*Variables measured at attendence

3.4 Reliability of questions on AOD use

We tested the reliability of the two different questions used to collect information about AOD use. In order to measure inter-rater agreement for categorical items we used kappa statistics, as it takes into account the possibility of agreement occurring by chance. The first question was "*Do you take, or have you taken some of the following medications?"* with the sub point *"Osteoporosis"* and the second one was extracted from the participants' self-reported list of medications (brand names). The results of applying the Kappa equation to test agreement between these two different questions is shown in table 5.

Table 5 Reliability of AOD use questions (Cohen's kappa statistics test).

		Self-reported AOD use		
		Yes	**No**	**Total**
AOD use according to brand names	**Yes**	55	9	64
	No	21	435	456
	Total	76	444	520*

Abbreviations: AOD, anti-osteoporotic drug.
*We excluded missing in self-reported AOD use (n=24)

Kappa calculation: (0.94-0.76) / (1-0.76) = 0.75

A kappa of 0.75 means substantial strength of agreement between these two different AOD questions. A previous master thesis by Ntiamoah showed that the sensitivity of the general AOD use queation versus AOD use according to brand name was 55% and that the dicrepancy between the two sources of AOD-information is mainly due to the inclusion of AODs other than bisphosphonates in the brand name question (20). As we wanted to capture AOD use in general and not merely bisphosphonates use, and as the reliability is fairly good, we chose to use the brand names to define AOD use in our analyses.

3.5 Study design and data analysis

This is a cross-sectional analysis in an observational study. Data analysis was done using the statistical software program Statistical Package for Social Sciences (SPSS) version 24 from IBM for Windows.

In order to compare mean QoL in the study population (AOD users versus non AOD users) with mean QoL in the remaining DXA population (no osteoporosis), we used one way ANOVA test (78).

In order to test the association between AOD use (as well as bisphosphonates alone) and QoL measured by EQ-5D 3L we used linear regression (78). EQ-5D 3L score was a skewed variable and not normally distibuted, therefore we used bootstrapping with both simple and multiple linear regression test. Bootstrapping estimation technique is a technique that is not assuming normally distributed data. Mann-Whitney test was also used with continuous dependent variable, EQ-5D 3L score, in order to check the results from the simple linear regression test. After the multiple linear regression, the Akaike information criterion (AIC) was used to assess the model with and without an interaction term (AOD use * prior fracture). AIC measures the relative quality, model assessment, of these statistical models for a given data set, and compares the two models.

Binary logistic regression test (78) was used with categorical dependent variables to estimate the associations between AOD use and self-reported health and muscle and joint pain, and to adjust for potential confounding factors. Potential confounding factors were chosen based on a Directed Acyclic Graph (DAG) model, as shown in figure 6.

A DAG model gives an entire graphical, and mathematical, model that can help us to minimize bias in the analysis. By adjusting for confounding covariates, and not adjusting for colliders, we can minimize, or eliminate, biased paths and estimate the direct effect from exposure to outcome (the green path in figure 6) (79).

Additionally, the participants were stratified into fracture participants and non-fracture participants, in order to assess the effect of AOD on QoL in both groups. we also tested a potential interaction between AOD use and prior fractures.

Significance level was set at 5%.

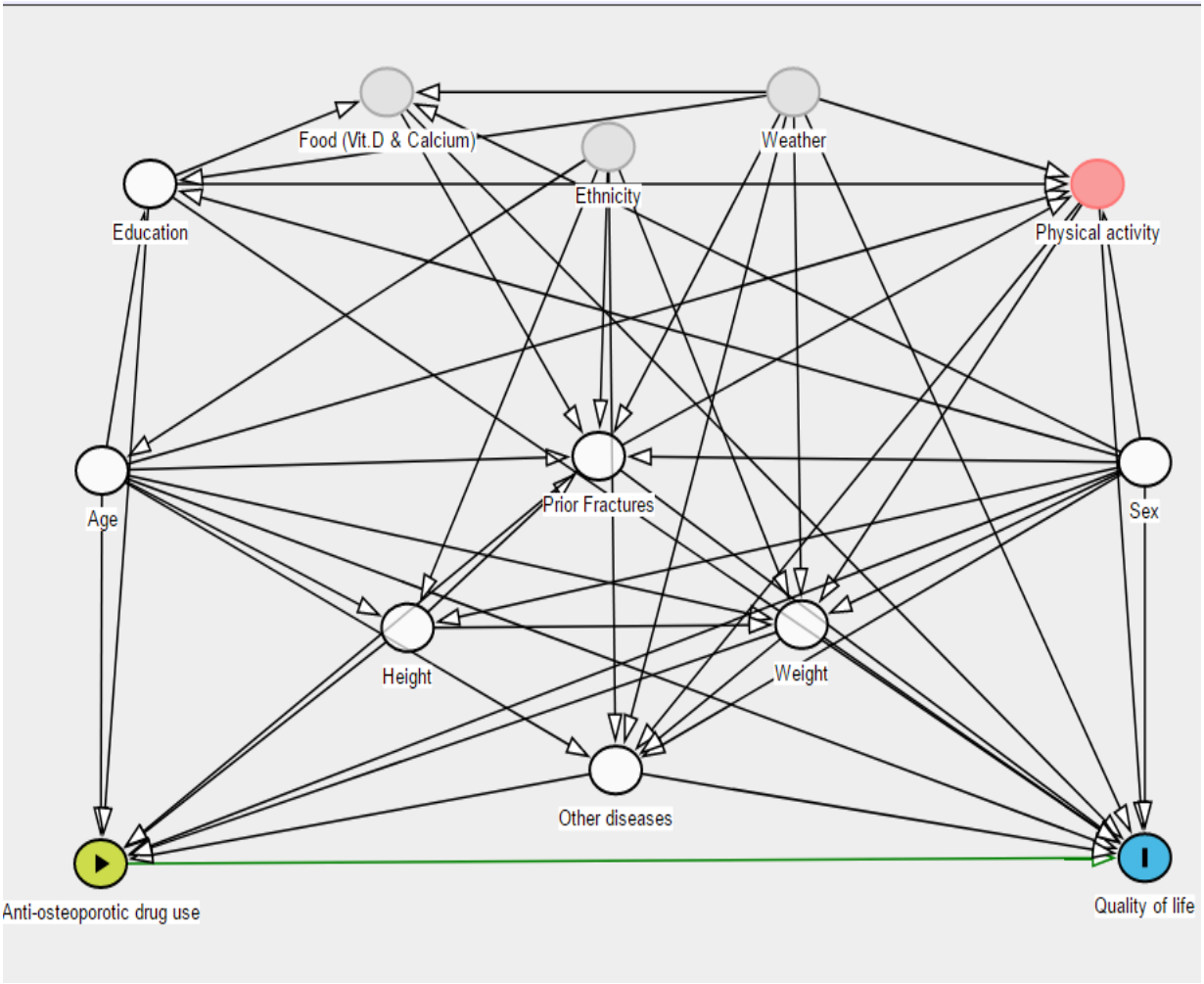

Figure 6 DAG model for independent, covariate and dependent variables. Grey nodes indicate unmeasured variables, white nodes indicate measured variables that we need to adjust for (confounder), red nodes indicate measured variables that we should not adjust for (collider), yellow node indicate independent variable (exposure of interest), and blue node indicate dependent variable (79)

3.6 Ethics

The Tromsø Study was approved by the Regional Committee of Medical and Health Research Ethics (REK) and the Norwegian Data Protection Authority (Datatilsynet). The Tromsø Study complies with International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Guidelines for Ethical Review of Epidemiological Studies 1991 and the Declaration of Helsinki 1964. The participation was voluntary and each participant gave a written informed consent prior to participation (73).

4 Results

4.1 Characteristics of the study population

Table 6 shows the characteristics of the study population according to use and non-use of AOD. The total number of participants who had osteoporosis, and who were eligible for this study, was 544 participants. Among these, 70% (n=380) were women. The average score of EQ-5D 3L was 0.81 (SD=0.2) (n=478). The participants were on average 71.6 years of age (range 50-87). Their average height was 163.8 cm (SD=8.7) (range 139.5 – 187.6), and body weight was 67.8 kg (SD=12.5) (range 33.9 – 120.7). Number of participants who answered "*No*" to the question "*Have you ever had, or do you have osteoporosis?*" were 430, and those who answered "*Yes*" were 95. Number of participants who had prior fracture, wrist and/or hip fracture, was 335 participants and 183 had no prior fracture. The two different questions that were used to collect information about AOD use gave slightly different frequency of use. According to the overall AOD use question, 76 were users and 444 were non users. According to brand names listed by the participants, 65 were users and 479 were non users, and this is the definition of AOD use that were applied in the subsequent analyses. The proportion with lower education was 78.7% (Primary, 1-2 years' secondary school/ Vocational school/ High secondary school (A-level)), while 19.1% had higher education (College, university less than four years/ college, university four years or more). The proportion of participants who had other diseases that can affect QoL (heart attack, angina pectoris, stroke/brain haemorrhage, asthma, chronic bronchitis/ emphysema/ COPD and diabetes mellitus) was 34.9%. According to the question on self-reported health, the proportion of participants who reported good health was 92.6%, while 7% had bad health. Muscle and/or joint pain was reported by 37% of the participants, while 58% reported no muscle and/or joint pain.

After we excluded those who did not answer the EQ-5D 3L questions (n=66) (table 7), the proportion of participants who had BMD <-2.5 SD and were AOD users was 67% of all AOD users according to brand names. Among those who were non AOD users, the proprtion of participants who had BMD <-2.5 SD was 54%.

Table 6 Characteristics of the study population (n=544).

Characteristics	N	%	Non-AOD users*	AOD users*
Age				
50-59	41	7.5	38	3
60-69	172	31.6	159	13
70-79	237	43.6	201	36
80-87	94	17.3	81	13
Sex				
Male	164	30.1	156	8
Female	380	69.9	323	57
Prior fractures (wrist and/or hip)				
Yes	335	61.6	296	39
No	183	33.6	161	22
Missing	26	4.8	-	-
Education level				
Primary/secondary school, modern secondary school	262	48.2	229	33
Technical school, vocational school, 1-2 years senior high school	141	25.9	122	19
High school diploma	25	4.6	20	5
College/university less than 4 years	55	10.1	53	2
College/university 4 years or more	49	9.0	44	5
Missing	12	2.2	-	-
Other diseases that affect QoL				
Yes	190	34.9	169	21
No	354	65.1	310	44
BMD measurement according to DXA method				
BMD <-2.5	310	57.0	265	45
BMD -2.5 – -1.6	234	43.0	214	20
Health status				
Very bad	4	0.7	2	2
Bad	34	6.3	25	9
Neither good nor bad	215	39.5	184	31
Good	251	46.1	232	19
Excellent	38	7.0	35	3
Missing	2	0.4	-	-
Muscle and/or joint pain				
Pain	203	37.3	174	29
No pain	316	58.1	282	34
Missing	25	4.6	-	-

Abbreviations: N, number of participants; %, proportion of participants; AOD, anti-osteoporotic drug; BMD, Bone Mineral density; DXA, dual energy X-ray absorptiometry.
*AOD according to the brand names listed by participants.

Table 7 Bone Mineral Density in AOD users and non-users.

		AOD use according to brand names		
		Yes	**No**	**Total**
BMD measurement T-score according to DXA method	**T-score <-2.5**	36	232	268
	T-score -2.5 – -1.6 with prior fracture	18	192	210
	Total	54	424	478*

Abbreviations: AOD, anti-osteoporotic drug; BMD, Bone Mineral Density; DXA, Deul energy X-ray absorptiometry.
*We excluded those who did not answer EQ-5D 3L questions (n=66).

4.2 EQ-5D 3L score according to degree of osteoporosis and AOD use in the total DXA-populatin (n=3117)

we compared mean EQ-5D 3L score among the following four groups (table 8):

1) Have osteoporosis and are AOD users

2) Have osteoporosis and are not AOD users

3) Prior fracture and DXA >-1.6 SD

4) Not prior fracture and DXA >-2.5 SD

The mean EQ-5D 3L score for AOD users (group 1) was significantly lower compared with the other three groups with p=0.003, 0.002 and 0.002 respectively. There were some missing in this data (range from 6.1% in group number four to 16.9% in group number one), because some participants did not answer the EQ-5D 3L questions.

Table 8 EQ-5D 3L score for the four DXA population

Group number	N*	EQ-5D 3L score mean (SD)	*p*-value
1	54	0.68 (0.28)	Ref.
2	424	0.82 (0.18)	0.003
3	316	0.84 (0.18)	0.002
4	2323	0.83 (0.18)	0.002

Abbreviations: N, number of participants; EQ-5D 3L EuroQol-5 dimensions 3 levels; SD, standard diviation.
*We excluded those who did not answer EQ-5D 3L questions (n=252).

4.3 The association between AOD use and QoL, health and muscle/joint pain

4.3.1 AOD use and QoL

The mean QoL score was 0.68 (SD=0.28) in the 54 participants using AOD and 0.82 (SD=0.18) in the 424 participants not using AOD. The mean QoL score was 0.81 (SD=0.20) for the whole osteoporosis study population (n=478), while the mean QoL was 0.83 (SD=0.20) for the whole population of Tromsø 6, aged ≥ 50 years (n=7848).

In simple linear regression analysis the QoL was inversely associated with the use of AOD (B=-0.145, *p*=0.001, 95% CI -0.227 – -0.072, n=478) (table 9). After adjusting for covariates in a multiple linear regression model, the QoL remained inversely associated with the use of AOD, although the association was slightly weakened (B=-0.114, *p*=0.006, 95% CI -0.199 – -0.033) (n=457). We tested the association between bisphosphonates use only and QoL, with similar result (B=-0.150, *p*=0.002, 95% CI -0.250 – -0.054) after adjusting for covariates(n=457) (data not shown in table 9).

After stratifying the population into prior fracture and no fracture, QoL was inversely associated with use of AOD (B=-0.132, *p*=0.002, 95% CI -0.219 – -0.049) among those with prior fracture (n=294). Among those not reporting prior fracture (n= 163), the association was weaker and not significant (B=-0.086, *p*=0.294, 95% CI -0.259 – 0.084). We also tested a potential interaction between AOD use and prior fractures by including an interaction term in the full model. The interaction term was not significantly associated with QoL (B=-0.029, *p*=0.743, 95% CI -0.188 – 0.139). The result of Akaike Information Criterion (AIC) score for the adjusted model with and without the interaction term was practically the same.

The dependent variable EQ-5D 3L, score was not normally distributed. In order to check the results from the simple linear regression test, we used the Mann-Whitney U-test. This test compare the mean rank of QoL-scores between AOD users and non-users. The Mann-Whitney test confirmed the simple linear regression indicating that QoL was significantly higher among non AOD users (mean rank =247.56, n=424) than AOD users (mean rank =176.22, n=54), U=8031, $p << 0.001$.

Table 9 Simple and multiple linear regression models assessing the association between use of AOD and covariates on QoL as the dependent variable among men and women aged ≥50 with osteoporosis.

Type of analysis	N	Independent variables	B	*P*-value	95% C.I
Not adjusted	478*	**AOD use**	**-0.145**	**0.001**	**(-0.227 – -0.072)**
Adjusted for covariates	457**	**AOD use**	**-0.114**	**0.006**	**(-0.199 – -0.033)**
		Age	**-0.004**	**0.001**	**(-0.007 – -0.002)**
		Sex	0.026	0.287	(-0.022 – 0.075)
		Height	0.001	0.388	(-0.002 – 0.005)
		Weight	0.000	0.741	(-0.003 – 0.002)
		Education	0.008	0.246	(-0.005 – 0.021)
		Other diseases	-0.030	0.137	(-0.069 – 0.007)
		Prior fractures	-0.006	0.768	(-0.045 – 0.033)
Interaction analysis					
Adjusted for covariates	457**	AOD use	-0.067	0.685	(-0.450 – 0.265)
		Age	**-0.004**	**0.001**	**(-0.007 – -0.002)**
		Sex	0.028	0.253	(-0.021 – 0.076)
		Height	0.001	0.415	(-0.002 – 0.005)
		Weight	0.000	0.735	(-0.003 – 0.002)
		Education	0.008	0.244	(-0.005 – 0.022)
		Other diseases	-0.030	0.137	(-0.068 – 0.006)
		Prior fracture	0.026	0.782	(-0.181 – 0.222)
		AOD use vs. prior fracture	-0.029	0.743	(-0.188 – 0.139)
Stratified analysis					
Prior fractures	294	**AOD use**	**-0.132**	**0.002**	**(-0.219 – -0.049)**
		Age	**-0.005**	**0.002**	**(-0.008 – -0.002)**
		Sex	0.037	0.299	(-0.030 – 0.099)
		Height	0.000	0.961	(-0.005 – 0.004)
		Weight	0.000	0.767	(-0.003 – 0.003)
		Education	0.003	0.682	(-0.013 – 0.020)
		Other diseases	-0.047	0.070	(-0.103 – 0.006)
No prior fractures	163	AOD use	-0.086	0.294	(-0.259 – 0.084)
		Age	-0.005	0.065	(-0.009 – 0.000)
		Sex	0.007	0.871	(-0.086 – 0.091)
		Height	0.004	0.157	(-0.002 – 0.009)
		Weight	-0.000	0.974	(-0.004 – 0.004)
		Education	0.019	0.209	(-0.011 – 0.051)
		Other diseases	-0.003	0.938	(-0.069 – 0.072)

Note: Bold variables and values are statically significant.
Abbreviations: QoL, quality of life; N, number of participants; B, beta-coefficients; C.I, confidence interval; AOD, anti-osteoporotic drug.
*Number of missing was 66
**Number of missing was 87

4.3.2 The association between AOD use and self-reported health

Table 10 shows the results from the logistic regression analysis that was conducted to assess whether AOD use were associated with self-reported health. The unadjusted analysis returned an odds ratio (OR) of 0.29 (p= 0.001, 95% CI=0.14 – 0.62) (n=542). This OR value indicates that the AOD users have 71% lower odds to evaluate their health as good with the true population effect lying between 86% and 38%, and this result was statically significant. After adjustment for covariates, including prior fractures, the OR for the association remained significant, OR=0.28 (p=0.004, 95% CI=0.12 – 0.67) (n=505). This means that, as in the unadjusted analysis, AOD users have 72% lower odds to evaluate their health as good with the true population effect lying between 88% and 33.

We also tested a potential interaction between AOD use and prior fracture by including an interaction term in the full model. The interaction term was not significantly associated with self-reported health (OR=0.84, p=0.841, 95% CI=0.14 – 4.87) (n=505).

4.3.3 The association between AOD use and self-reported muscle and/or joint pain

Table 11 shows the results from the logistic regression analysis that was conducted to assess whether AOD use is associated with self-reported muscle and/or joint pain. The unadjusted analysis returned an OR of 1.38 (p= 0.813, 95% CI= 0.81 – 2.35) (n=519). The OR value may indicate that the odds of having muscle and/or joint pain among AOD users is 38% higher than among non-users, but this result was not statically significant. After adjustment for covariates, including prior fractures, the OR for the association was 1.09 (p= 0.757, 95% CI=0.62 – 1.93) (n=501). This means that there was no significant difference in muscle and/or joint pain between AOD users and non AOD users. The inclusion of an interaction term for a potential interaction between AOD use and prior fracture did not change the result, and the interaction term was not significantly associated with muscle and/or joint pain.

Table 10 Logistic regression analyses of association between AOD use and self-reported health among men and women aged ≥50 with osteoporosis.

Type of analysis	N	Independent variables	OR	*P*-value	95% C.I
Unadjusted	542*	**AOD use**	**0.288**	**0.001**	**(0.135 – 0.615)**
Adjusted for covariates	505**	**AOD use**	**0.279**	**0.004**	**(0.116 – 0.668)**
		Age	1.006	0.842	(0.952 – 1.062)
		Sex	1.108	0.871	(0.324 – 3.788)
		Height	1.013	0.705	(0.947 – 1.084)
		Weight	0.996	0.839	(0.961 – 1.033)
		Education	1.449	0.069	(0.971 – 2.163)
		Other diseases	**0.303**	**0.003**	**(0.139 – 0.664)**
		Prior fractures	1.120	0.786	(0.495 – 2.533)
Full model including interaction term	505**	AOD use	0.370	0.505	(0.020 – 6.866)
		Age	1.006	0.837	(0.952 – 1.062)
		Sex	1.133	0.845	(0.326 – 3.940)
		Height	1.012	0.719	(0.946 – 1.083)
		Weight	0.996	0.839	(0.961 – 1.033)
		Education	1.453	0.069	(0.972 – 2.171)
		Other diseases	**0.301**	**0.003**	**(0.137 – 0.662)**
		Prior fractures	1.411	0.779	(0.127 – 15.635)
		AOD use vs. prior fracture	0.835	0.841	(0.143 – 4.874)

Note: Bold variables and values are statically significant.
Abbreviations: N, number of participants; OR, odds ratio; C.I, confidence interval; AOD, anti-osteoporotic drug.
*Number of missing was 2
**Number of missing was 39

Table 11 Logistic regression analyses of association between AOD use and muscle and joint pain among men and women aged ≥50 with osteoporosis.

Type of analysis	N	Independent variables	OR	*P*-value	95% C. I
Unadjusted	519*	AOD use	1.382	0.231	(0.813 – 2.349)
Adjusted for covariates	501**	AOD use	1.093	0.757	(0.621 – 1.925)
		Age	**1.030**	**0.023**	**(1.004 – 1.056)**
		Sex	0.614	0.114	(0.335 – 1.124)
		Height	0.996	0.835	(0.963 – 1.031)
		Weight	1.010	0.280	(0.992 – 1.029)
		Education	0.891	0.117	(0.770 – 1.029)
		Other diseases	1.456	0.062	(0.982 – 2.159)
		Prior fractures	**1.572**	**0.033**	**(1.036 – 2.385)**
Full model including interaction term	501**	AOD use	0.901	0.919	(0.119 – 6.797)
		Age	**1.030**	**0.023**	**(1.004 – 1.056)**
		Sex	0.610	0.111	(0.332 – 1.121)
		Height	0.997	0.845	(0.963 – 1.031)
		Weight	1.010	0.281	(0.992 – 1.029)
		Education	0.890	0.117	(0.770 – 1.029)
		Other diseases	1.459	0.061	(0.983 – 2.164)
		Prior fractures	1.375	0.656	(0.339 – 5.579)
		AOD use vs. prior fracture	1.125	0.844	(0.347 – 3.645)

Note: Bold variables and values are statically significant.

Abbreviations: N, number of participants; OR, odds ratio; C.I, confidence interval; AOD, anti-osteoporotic drug.

*Number of missing was 25

**Number of missing was 43

5 Discussion

5.1 Results

Quality of life is a major issue in the medical and pharmacological field nowadays (80). EQ-5D 3L is a widely-used tool for measuring QoL in Europe and Norway, and it is the one that has been used in the Tromsø Study. It takes only a few minutes to complete these health-related questions, and the results cover a wide array of health-related problems that affect QoL. Osteoporosis gives no or few signs and symptoms, like back pain, but its complications, particularly hip fractures, are painful and may lead to very serious health deterioration, and even precipitate death (80). The use of AOD was low, less than 18% among participants with osteoporosis according to DXA, which was previously shown in master thesis by Ntiamoah at UiT (20). Another study from 2015 also shows low use of AOD after forearm fracture in a survey in central Norway between 2005-2012 (81).

This study shows that in a cross-section of an osteoporotic population, those who use AOD have significantly lower QoL, measured by EQ-5D 3L, than those who do not use AOD. This agrees with the results for the other two outcomes we investigated in this study, self-reported health status and muscle and/or joint pain. Participants who reported AOD use had significantly worse health status than AOD non-users. Likewise, participants who reported AOD use had more muscle and/or joint pain than AOD non-users, although this last result was not statically significant, probably because of the nature of osteoporosis as a condition without sign and symptoms. This can indicate that all these three methods can be used as a measurement method for health status of osteoporotic population, with lesser degree to muscle and/or joint pain. Additionally, this can indicate good capability of using EQ-5D 3L by the participants, and good understanding of its different dimensions and levels.

A randomised controlled study that tested the effect of bisphosphonates on QoL among patients with metastatic bone disease due to breast cancer, showed better QoL after long-term treatment with bisphosphonate because of a reduction in pain among these patients (82). Another randomised control study that tested the effects of nutrition supplementation and bisphosphonates on QoL and some other factors after hip fractures, found that the use of bisphosphonates alone could not stop a drop in QoL. Preservation or less drop in QoL after hip fracture was found when bisphosphonates was combined with high protein nutrition (83). These studies suggest that the effect of bisphosphonates on QoL depends on type of osteoporosis, duration of treatment and type of nutrition. The type of study design of these

two studies, RCTs that included a time dimension, was different from our cross-sectional study design, probably explains the opposite results.

Our result is in agreement with another cross-sectional study that found that AOD users had significantly lower QoL compared to those who had not previously received AOD (84). The authors suggested that a higher knowledge of osteoporosis and their signs and symptoms, risk factors and consequences would give better and earlier osteoporosis prevention behaviours and better QoL. This higher knowledge will require education and courses to improve the awareness of osteoporosis, AOD and other prevention methods. Despite some differences between this study and our study, especially in osteoporosis definition, prevalence of AOD use and fracture sites, we believe that the reason behind this agreement is the same type of study design.

When BMD increases, the fracture risk decreases. The aim of using AOD is to increase BMD and thereby ultimately lower the risk of osteoporotic fractures. As some studies have shown, BMD increases in participants who use AOD and decline in participants who do not use AOD, e.g. those who have had an "AOD holiday" (85-87). QoL will be steeply affected, i.e. decreased (88), when fractures happen, especially hip fractures. So, it would be reasonable to find some results that contrast what we found in this study if we consider the effect of AOD on BMD, osteoporotic fractures and QoL over time.

The Minimal Clinically Important Difference (MCID) for EQ-5D 3L score is the minimum difference in score that is clinically meaningful to patients. Use of MCID enhances the ability to compare between the different EQ-5D 3L measurements for different diseases or populations (89). It is difficult to estimate it exactly, because of the variation between diseases and patients. A comparison of MCID for two health state utility measures, EQ-5D 3L and SF-6D suggested that a MCID for EQ-5D 3L would be in the range of -0.011 to 0.140 (mean 0.074) (90). Our result (B=0.114) lies in the upper part of this range, above mean MCID, and may thus be considered a clinically important difference.

The use of EQ-5D 3L method to calculate QoL is well known and can be used in many health fields. EQ-5D 3L is a general and non-specific measure of QoL, i.e. it is supposed to encompass all sides of health, wellbeing or diseases. On the other hand, the use of a disease specific method to measure QoL, like osteoporosis in this study, could have advantages over this general tool. Besides the specificity of such methods, they also can be less of a burden for the patients, because these methods can be oriented toward the patients' individual problems

(80). One disadvantage with disease specific methods is that a comparison between two different diseases is not possible, in other words these methods are fitting only one disease (80). This means that we would not have been able to compare QoL between our osteoporotic study population and the non-osteoporotic participants in Tromsø 6 using an osteoporosis specific QoL questionnaire like QUALEFFO (as we did in section 4.2) (80). On the other hand, if we used QUALEFFO instead of EQ-5D 3L, the results of a QUALEFFO score would had been more specific for the osteoporosis population than the EQ-5D 3L score, because it contains more relevant questions to osteoporosis signs, symptoms and fractures.

5.2 Methodological considerations

Our data was from Tromsø 6, which is data collected in 2007/2008. The kind of study design that we used here was cross-sectional, and it is the only study design that we could use with this kind of data. If we had data for the same participants from previous waves of the Tromsø Study, Tromsø 4 or Tromsø 5, or even the latest Tromsø 7, then we could have used a longitudinal study design to assess causality between AOD use and QoL.

Our study population was participants with osteoporosis, and the definition of osteoporosis was per the Norwegian guideline for osteoporosis in need of treatment (those who had BMD <-2.5 SD or those who had BMD -2.5 – -1.6 SD with prior forearm/hip fracture). This definition means that we included those who were not aware that they have osteoporosis, and this is not necessarily equally distributed between AOD users and non-users. To maximize the number of participants, i.e. increase the representability of the population and increase the power, we included the BMD measurements for right femoral neck for those who did not measure BMD at left femoral neck.

The classification of prior fractures was based on the participants' answers to the questions on prior wrist/hip fractures. As we do not know the actual fracture date, a "*Yes*" could mean that they had a fracture in childhood, or younger age. This would imply fractures that was a result of an accident, so-called high-energy fractures. Considering these as osteoporotic fractures, like we did in this study, has implications for our study population. This may lead to an artificially high number of participants being classified as osteoporotic participants. Another consideration is that the people who had a recent hip fracture would not be able to participate in this survey, because they have a lot of pain, and may be living in nursing homes at the time of the survey. A third point is that the questionnaire did not have any questions about prior

vertebral fractures, which is one of the most important osteoporotic fracture when it comes to everyday symptoms (pain). We may therefor assume that we do not have the severe osteoporosis cases in this study population. And probably for these reasons, we did not find any significant association between prior fractures and QoL. Neither did we find any clear influence of fractures on the association between AOD use and QoL through interaction and stratified analysis. Use of information on osteoporotic fractures from a register, like the National Hip Fracture Database, is the best way of measuring the influence of osteoporotic fractures on AOD use (26) and QoL.

We chose to use the brand name question as an independent variable, and not the general question on AOD-use. The reason behind this choice was mainly the Kappa statistic results that indicate substantial strength of agreement between the two different sources of information on AOD use. Another reason is that it includes all the types of AOD, not only bisphosphonates. There is no question about bisphosphonates specifically in the questionnaire, but it has been shown that those who answer "*Yes*" to use of AOD is bisphosphonates users rather than users of HRT or other AOD types (20). A master thesis by Ntiamoah from 2016 at UiT showed that the self-reported use of AOD, the first AOD question, was in fact a question about bisphosphonates only, because this question showed high sensitivity and specify with bisphosphonates use from the brand name question (20). So, it is reasonable to include all the type of AOD, by choosing brand name question, in this study to test the association between AOD in general and QoL rather than bisphosphonates only.

We wanted to set up a regression model that adjusted as much as possible for confounding factors and at the same time avoided introducing bias through the variables we included. To avoid biased paths in this analysis, we used a DAG model (79). The DAG model gives us the opportunity to identify the confounding, mediator and collider variables among covariates. We wanted to adjust for confounding and mediator variables, but adjusting for a collider variable would introduce bias. A collider is a variable resulting from the outcome of two or more variables. A collider closes the path between the exposure of interest and the outcome, and does not produce an unconditional association between these variables of interest. So, adjusting for a collider will open this closed path and thereby lead to bias in the model. Physical activity was a collider variable in this DAG model, so adjusting for this variable would have produced a biasing path. Therefore, we chose not to adjust for physical activity. DAG models has some disadvantages. They neither show the direction nor strength of the effect, nor interaction, antagonism or synergism. The researcher decides the direction of the

paths based on previous scientific knowledge. In this case, we mainly used the "*Norwegian guidelines for prevention and treatment of osteoporosis and osteoporotic fractures*", and other reviews and articles. Some of the paths have a logic one way direction, like the path from sex toward education; It is more likely that sex affects education than the opposite. Sex, age, weather and ethnicity are variables that cannot be affected by other variables, but they can themselves affect other variables. Prior fractures, or osteoporosis as a disease, can be affected by many variables (6), for instance sex, age, height, diet, ethnicity and weather. Diseases that we included in the variable "*Other diseases*" are chronic diseases that we believe that they can have some effects on QoL, as explained in the review "*Quality of life in chronic disease patients*" (91). So, the high comorbidity of these participants who have other diseases or their health-consciousness can act as a predictor of AOD use (26). The effect of education level on QoL has been shown in a study where lower educational level was associated with poor QoL among old people (92). A Norwegian study of predictors of AOD use showed that the higher education level, the more awareness of the effect of drug and the more drug use (26). Therefore, we drew a path from education toward AOD use.

We included three unmeasured variables that had shown some effects on osteoporosis, osteoporotic fractures (6) and QoL. These were weather (exposure to sun light), ethnicity and diet rich in vitamin D and calcium. Measuring and controlling for these three variables could give better causality assessment in this study if we disregard the study design problem.

In the main analysis, we used multiple linear regression to assess an association between AOD use and the main outcome EQ-5D 3L score. The reason for using this test was the type of outcome variable (EQ-5D 3L is a continuous variable) and we had more than one predictor in this model (both continuous and categorical variables) (78). The main dependent variable, EQ-5D 3L score, was however a skewed variable and did not follow a normal distribution. To deal with it in a linear regression statistic test we used bootstrapping. With bootstrapping estimation technique, that is not assuming normally distributed data, we can ensure a more reliable regression model that will produce more precise statistical results. Additionally, we used a nonparametric statistic test, Mann-Whitney statistic test, just to check the result of the simple linear regression. We could not use Mann-Whitney as the main analysis because in this test we cannot adjust for covariates.

We chose to use logistic regression to analyse an association between AOD use and the other two end points, self-reported health and muscle and/or joint pain. The reason was that these were dichotomous outcomes, and we had the same type and number of predictors as in the

main analysis (78). Self-reported health was a categorical variable that we dichotomised into good (excellent, good, neither good nor bad) and bad (bad, very bad) health. This cut-off was chosen because we think the participants is more likely to report "*neither good nor bad*" when they have good health but not as good as they want, and those who feel they have bad health will probably not report "*neither good nor bad*" but rather report "*bad*" or "*very bad*". So, this will probably give the clearest separation between good and bad health. We also dichotomised the third dependent variable, muscle and joint pain, into pain (A little, A lot) and no pain (No). This was done to capture as much osteoporosis symptoms as possible, because osteoporosis has no or mild symptoms like back pain. Additionally, dichotomising gives us the opportunity to use binary logistic regression, and gives estimates of the association that are easy to interpret.

Confounding by indication can play a big role in this study, and it is difficult to measure and control for. Participants who use AOD in general had low BMD. A prior osteoporotic fracture and/or used a drug, or have other risk factors, lead to a reduction in BMD. In other words, they recognized the symptoms of osteoporosis, or had been diagnosed by their doctor, and started the treatment after the disease had progressed into a serious stage. This group of participants will thereby probably have worse QoL than non AOD users in this osteoporosis population, as was shown in a cross-sectional study that found lower QoL in osteoporosis participants than in osteopenia and/or normal BMD participants (93). In our study population, we found that two-thirds of AOD users had BMD of <-2.5 SD, while about half of non AOD users had BMD of <-2.5 SD. This indicates that AOD users have more severe degree of osteoporosis. The mean QoL-score in our study population, participants with osteoporosis, was lower than the mean QoL-score of DXA population, i.e. participants without osteoporosis, that indicate and support this confounding type.

Additionally, those who negatively appreciate their QoL or are unsatisfied by their health status are more likely to have more doctor visits. This may cause the AOD use is higher among participants with osteoporosis and with low QoL. From this kind of participants, we can find lower QoL measured by EQ-5D 3L because it is self-reported QoL measurement.

The main strength of this study was the use of DXA measurement of BMD. DXA is a reliable diagnostic tool for classifying our study population as having osteoporosis, namely those who had T-score of <-2.5 SD or T-score of -2.5 – -1.6 with prior fracture. Osteoporosis, QoL of osteoporosis participants and use of AOD are connected to the older aged participants.

Therefore, our study population was restricted to those who aged ≥50 years, which make the results more generalizable to the osteoporotic population.

Our data was from the Tromsø Study which is a population-based survey. The attendance rate was 66%. This is lower than the previous surveys, but still considered as a good attendance rate which contributes to the generalizability of the results. The large number of variables and information collected by the Tromsø 6, gives it an advantage as a data source for studies like ours, making it possible to include almost all the variables that we needed.

Remembering, or recall bias, could be a problem here, especially with the question about prior fractures or with the general AOD use question. Recall problems regarding prior fractures could decrease the number of participants included in this study. However, most of the variables that was used here were variables that are unlikely to give wrong information (e.g. sex, age), measurements done by health personnel (DXA, height and weight), or relatively easy to answer (e.g. current medication use, education, other diseases). The use of brand name of AOD as a variable of AOD use gave an advantage over the self-reported AOD use, because the participants would have access to their drugs while answering at home. A previous study has showed that the agreement between self-report for use of AOD and pharmacy register is high (94). Not only self-reported AOD use has high agreement, but also many other drug types used for chronic diseases (95). We therefore assume that the validity of AOD use in our study is acceptable.

The self-reporting of prior hip and wrist fractures has been shown to be relatively accurate in a Danish study (96). However, in our study population ≥50 years, we do not know when the reported fracture happened. A fracture many years back does probably not refer to an osteoporotic fracture. This could lead to a misclassification of participants, artificially increasing the osteoporosis population, thereby underestimating AOD use and overestimating the effect size.

Another bias that can affect our results is the requirement for the Tromsø Study participants to attend the study site. Selection bias could occur because of the absence of the people who were living at nursing homes, and otherwise weak and sick people. This kind of bias could overestimate the QoL of participants and underestimate the effect size. Additionally, the non-attendance problem can make the results of this study less generalizable.

The problem of missing is another limitation in this study. Participants who did not answer one or more of the questionnaire questions were excluded from the statistic tests. This lead to

a smaller analysis population, which again lead to lower precision and wider confidence intervals. Additionally, missing may increase the possibility of bias in the estimation of parameters because of the possibility of unequal distribution of missing between AOD users and AOD non-users. we could not use an imputation method to control for, or replace, missing data, because of the presence of a not normally distributed variable (EQ-5D 3L) and many dichotomous variables that makes it difficult to replace missing data (97).

The type of the study design that we could use here was cross-sectional. In this type of observational study design, we cannot establish a temporal relationship between exposure (here AOD use) and outcome (here QoL). Because of this, it is impossible to say anything about causality. It could just as well be low QoL that leads to AOD-use than AOD-use leading to low QoL. Therefore, we recommend a future study that consider the time dimension, a longitudinal design like cohort or RCT, to measure the effect of AOD on QoL.

6 Conclusion

Persons with osteoporosis who were using AOD had significantly lower QoL compared to those who did not use AOD at survey time. This must not be interpreted as if AOD use leads to lower QoL. As this is a cross-sectional study, the direction of the association and the causal relationship cannot be established. Confounding by indication, severity or awareness of disease could be a problem as not all participants knew they had osteoporosis.

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8 Appendix

Selected pages from the two questionnaires that were used in the sixth wave of the Tromsø Study. Yellow marks indicate questions used in this master thesis. The full version of the two questionnaires are available from:
https://en.uit.no/forskning/forskningsgrupper/sub?sub_id=453665&p_document_id=453582

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
- ☐ 15-29 minutes
- ☐ 30-60 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
- ☐ 3-4
- ☐ 5-6
- ☐ 7-9
- ☐ 10 or more

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, previously
- ☐ Yes, sometimes
- ☐ Yes, daily

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**

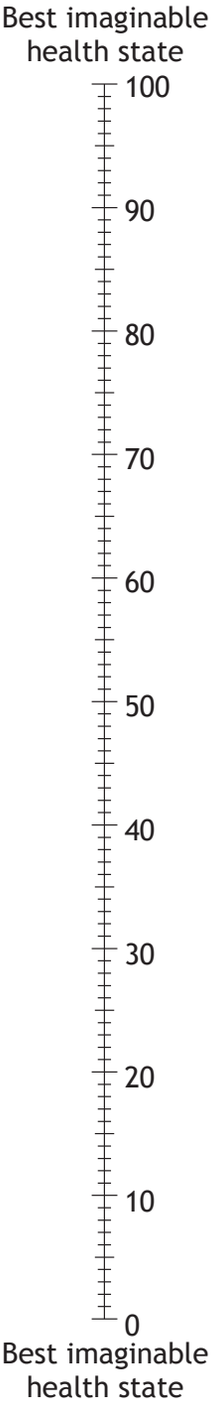
- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

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.

Your own health state today



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