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# Are there differences in the prescription of fall risk-increasing drugs between ethnic groups in Norway? A cross-sectional study

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I would like to dedicate this work to the soul of my loved grandfather, Jamal, who was there at the beginning of this journey but did not get the chance to see me come this far.

*List of Abbreviations*

| **Abbreviation** | |
|---|---|
| ATC | Anatomical Therapeutic Chemical |
| BMD | Bone Mineral Density |
| BZD | Benzodiazepines |
| BZD-Z | Benzodiazepines/Z-drugs |
| CNS | Central Nervous System |
| CPES | Collaborative Psychiatric Epidemiology Studies |
| DALY | Disability-Adjusted Life Year |
| DDD | Defined Daily Doses |
| GABA | Gamma-aminobutyric acid |
| GDP | Gross Domestic Product |
| NOREPOS | Norwegian Epidemiologic Osteoporosis Studies |
| NorHip | NOREPOS hip fracture database |
| NorPD | Norwegian prescription database |
| OR | Odds Ratio |
| PR | Prevalence Ratio |
| PTSD | Post-Traumatic Stress Disorder |
| QoL | Quality of Life |
| RCT | Randomized Controlled Trial |

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## Abstract:

Background Benzodiazepines and Z-drugs (BZD-Z) are fall risk-increasing drugs that have been associated with an increased risk of hip fracture (1). Hip fracture is a significant public health issue, with incidence rates varying greatly between ethnicities. Norway has one of the highest incidence rates of hip fractures (2,3). It is unknown if the prescription of BZD-Z differs between ethnic groups in Norway, therefore, this study aims to investigate if there are differences in the prescription of BZD-Z between different ethnic groups in Norway. It is also aimed to describe the rate of hip fractures in BZD-Z users compared to BZD-Z non-users.

Methods The study population comprised all individuals in the Norwegian population who participated in the Population and Housing Census 2001, aged between 50 and 89 during three time-points, 2005, 2010, and 2015. As a rough proxy of ethnicity, background regions were divided into three geographical regions, Norway, South Asia, and the Middle East. Chi-square test ($X^2$) and gender-stratified logistic regression analysis, adjusted for age, were used to assess the relationship between BZD-Z usage and different ethnicities and describe the relationship between BZD-Z usage and hip fractures.

Results In this Norwegian register-based study, it was found that immigrant women were less likely to be prescribed BZD-Z than Norwegian women. In 2015, females from the Middle East had 24% lower BZD-Z prescription prevalence than Norwegian females. While the prevalence of use was 51% lower in females from South Asia than in Norwegian females. However, males from the Middle East had a higher BZD-Z prescription prevalence than males from Norway and South Asia. In 2015, the prevalence of use was 19% higher in males from the Middle East than in Norwegian males. Prevalence of use was 17% lower in males from South Asia than Norwegian males. In addition, it was found that BZD-Z users were more likely to sustain hip fractures compared to non-users (adjusted OR=1.43; 95% CI= 1.36-1.50).

Conclusion Lower rate of prescriptions of BZD-Z was found in immigrant women groups compared to Norwegian women. However, males from the Middle East were prescribed the highest BZD-Z prescriptions compared to males from Norway and South Asia.
Keywords Benzodiazepines. Z-drugs. Ethnicity. Norway. Hip fracture. Fall

## Background:

As a pharmacist, I am interested in studying the effects drugs can cause. After starting this master's degree, I came across the fact that Norway has one of the highest incidences of hip fractures worldwide (3). This motivated me to investigate if a certain class of drugs may play a role in this high incidence of hip fractures. Benzodiazepines and benzodiazepine-related drugs (Z-drugs) are drugs that are known to increase the risk of falling (1).

This led me to ask the questions, are there differences in the prescription prevalence of benzodiazepines and Z-drugs among different ethnic groups in Norway? And if so, does benzodiazepine and Z-drug usage increase the risk of a hip fracture? I have had access to the data used in this thesis project through working with my supervisors, Helena Kames Kjeldgaard and Haakon E. Meyer. Kristin Holvik, senior researcher at the Norwegian Institute of Public Health, has provided us with the datasets.

This thesis is a part of a larger project, the umbrella project PDB 93: The Epidemiology of Prescription Drug Use. The overall aim of the umbrella project is to investigate the link between biological, psychological, socioeconomic, and lifestyle factors and prescription drug usage. This thesis falls within the sub-project PDB 2057: "Osteoporosis and hip fractures - prevalence, drug use, risk factors, and mortality." The aim of PDB 2057 is to study the relationship between various risk factors, social variances, drug use and osteoporosis, hip fractures, and mortality, which includes:

- Gender disparities in comorbidity and survival following hip fractures
- The relationship between several types of osteoporosis therapy and various causes of mortality
- The percentage of people at risk who take antiosteoporosis medication because they have low bone density or have fractures.
- The relationship between the usage of certain drugs, bone mineral density, and the risk of hip fracture.

This thesis aims to investigate the differences in the prescription prevalence of benzodiazepines and Z-drugs among different background regions. It also aims to describe the relationship between their usage and hip fractures.

# 1. Introduction:

For an elderly individual, a hip fracture is often a life-changing event since it typically leads to losing independence, poor quality of life (QoL), and increased susceptibility to higher morbidity and mortality (1,4). Hip fractures vary greatly between nations and ethnic groups, and they continue to be a public concern presented by economic and health burdens globally (3,5). The Norwegian population has among the highest rates of hip fracture worldwide; additionally, it was shown that those born in Norway had double the risk of hip fractures when compared with immigrant groups in Norway born outside Western Europe and North America (3).

Genetics and lifestyle-related factors, including diet, physical activity, and smoking, might all contribute to these variances. Due to increased bone fragility and increased vulnerability towards falling, the risk of hip fracture increases with age (6). Recognizing hip fracture risk factors is the first step toward prevention. Drugs are a modifiable risk factor for falls and their related injuries (7). Currently, there is a great focus on many fall-preventive interventions (8).

Psychotropics usage has been linked to an increased incidence of hip fracture and is now recognized as a risk factor (1). Most hip fractures in the elderly are associated with low bone mineral density (BMD) and osteoporosis, with 90% of them occurring as a consequence of a fall from a standing height or less (6). Antidepressants, hypnotics/sedatives and anxiolytics may increase the risk of falling, and thereby can enhance the risk of hip fractures (9).

Benzodiazepines (BZD) are commonly used to treat a range of conditions affecting the elderly population, such as insomnia and anxiety (7). Numerous studies have investigated the relationship between benzodiazepines and Z-drugs (BZD-Z) and falls, with the majority suggesting an association between BZD-Z use and falls or fractures (1,7,10). The association between BZD-Z and an elevated risk of hip fracture in the elderly is well established (1), but it is unknown if the prescription of BZD-Z differs between ethnic groups in Norway.

## 1.1 Objectives of this study

*Primary objective:*

To study the prescription pattern of BZD-Z in Norway between different background regions using the Norwegian Prescription Database (NorPD).

*Secondary objective:*

To outline the relationship between BZD-Z and hip fractures.

## 1.2 Aims of this study

1. Investigate if there are differences in the prescription of BZD-Z between different ethnic groups aged 50-89 years in Norway, in 2005, 2010 and 2015.
2. Describe the risk of hip fractures in BZD-Z users compared to non-users.

## 1.3 Rationale of the study

Worldwide, Norway has one of the highest hip fracture incidences (11). The elderly are at a greater risk of injuries, even after a relatively minor trauma such as a fall, due to the prevalence and severity of comorbidities, which makes older persons more vulnerable to fractures and injuries (7). Sedative-hypnotic medications are frequently prescribed to the elderly, with BZD-Z being the most used sedative-hypnotic drugs among community-dwelling elders (1,7,10). BZD-Z are commonly used in the elderly Norwegian population (12), but it is unknown if the prescription of BZD-Z differs between ethnic groups in Norway. Therefore, the significance of this study is to explore if prescriptions of BZD-Z differ between ethnic groups and could thus contribute to a higher risk of falling and sustaining a hip fracture in some groups. Findings from this study can aid in the prevention or mitigation of such a potential risk factor.

## 1.4 Fall risk-increasing drugs used in this study

BZD and BZD-related drugs, Z-drugs (also known as Z-hypnotics), are utilized in this study as fall risk-increasing drugs. BZD are sedative-hypnotic prescription drugs that have been used for the treatment of anxiety, epilepsy, insomnia, and other conditions. The Z-drugs were introduced to the market in the 1990s and are solely approved for insomnia (13).

## 2. Literature review:

### 2.1 What are benzodiazepines and Z-drugs?

BZD are a class of prescription drugs classified as sedative-hypnotics that are used for the treatment of anxiety, epilepsy, insomnia, and other conditions. The Z-drugs are not BZD but rather are BZD-related drugs that are only approved for the treatment of insomnia (13,14). According to BZD-Z guidelines, older persons should only use anxiolytic BZD and Z-drugs at modest doses for a limited duration, and hypnotic BZD should be avoided entirely (12).

#### 2.1.1 Pharmacological action and properties of benzodiazepines

BZD are Central Nervous System (CNS) depressants because they induce anxiolysis (minimal sedation), stupor, and sleep. Their mechanism of action is potentiating the binding of the inhibitory gamma-aminobutyric acid (GABA) neurotransmitter on the GABA A receptors in the CNS. Thus they enhance the GABA A receptor activation by lowering the required GABA neurotransmitter concentration needed to activate the receptor (15–17).

The neuron opens a channel that permits chloride ions to flow through after GABA is coupled to the GABA-A receptor. These negative chloride ions make the cell less receptive to other neurotransmitters that would typically stimulate it, such as norepinephrine, serotonin, acetylcholine, and dopamine. BZD bind to their own receptors, benzodiazepine receptors, at the GABA-A receptor as well. When a BZD is combined with GABA, it boosts GABA effects, enabling more chloride ions to enter the cell and making it more resistant to stimulation. This causes anxiolytic, sedative, hypnotic, muscle relaxant, and anticonvulsant properties (15).

Benzodiazepine receptors are further divided into subtypes, each with moderately different functions. Sedative effects are caused by the alpha 1 subtype, anti-anxiety effects are caused by the alpha 2 subtype, and anticonvulsant effects are caused by alpha 1, alpha 2, and alpha 5 subtypes. To a greater or lesser extent, all BZD interact with all these subtypes to cause enhancement in the GABA activity in the brain (15). Therefore, most anxiolytics induce sleep when taken at night, and

most hypnotics sedate when given during the day; thus, there is no definitive division between the two (17).

BZD have varying half-lives and metabolism rates. For example, the half-life of short-acting drugs such as midazolam is less than 24 hours; the half-life of intermediate-acting drugs such as nitrazepam is more than 24 hours, while the half-life of long-acting drugs such as diazepam is more than 48 hours. These half-lives tend to differ among individuals, particularly in the elderly, as they have a slower elimination rate. Therefore, the elderly are at a higher risk of side effects, including impaired cognition, mental confusion, drowsiness, falls, and staggering gait (ataxia) (17).

Most BZD are metabolized by the liver and excreted by the kidneys nearly entirely in the urine. They undergo hepatic phase I metabolism through the cytochrome P450 enzymes, followed by phase II glucuronidation. By producing active metabolites, some BZD exert added action and result in increased duration of action. This is especially seen in long-acting BZD such as diazepam and is a serious consideration in certain patient groups, including the elderly and those with hepatic impairment. Short acing BZD such as midazolam yields no active metabolites (18).

### 2.1.2 Pharmacological action and properties of Z-drugs

Z-drugs include zolpidem, zopiclone, eszopiclone, and zaleplon, are a class of psychoactive drugs very similar to BZD; hence they are sometimes referred to as non-BZD hypnotics (14,15). In addition, their biochemical and physiological actions, known as pharmacodynamical effects, are nearly identical to BZD. Therefore, Z-drugs have similar effects and risks as BZD. However, Z-drugs and BZD do not relate molecularly because they vary in their chemical structures (15).

Similar to BZD, the Z-drugs are GABA-A receptor agonists that exert their pharmacological action through binding to and activating the benzodiazepine site at the GABA-A receptor. However, the main difference is that Z-drugs are relatively subtype-selective, making them novel by providing specific actions and being hypnotics without posing anxiolytic effects. Z-drugs are solely approved for insomnia and sleep disorders also because of their short half-lives ranging from two to six hours (in the non-elderly) (15).

Zopiclone has the longest duration of action, making it more suitable for people suffering from night-time awakening. Zolpidem is effective in decreasing the onset of falling sleep due to its rapid absorption and short duration of action, hence, it is suitable when the primary concern is falling asleep. Zaleplon is ultra-short acting having the shortest half-life and the fastest onset of action, making it suitable for people with intermittent sleep disturbances.  (19).

In the elderly, all Z drugs should be given in lower doses. Hepatic metabolism is primarily responsible for the elimination of Z drugs. Therefore, they should be taken with caution and at a lower dose in patients with hepatic impairment, and they should be avoided in patients with severe hepatic impairment (19). Metabolism of zopiclone yields active metabolites (including eszopiclone) that are renally excreted; thus, it is the only Z-drug that requires dosage adjustments in patients with renal impairment (20).

### 2.2 The rationality of benzodiazepines and Z-drugs usage

While BZD-Z are generally shown to be safe and effective, they can have adverse effects. As mentioned previously, sedation causes decreased psychomotor skills, more significant impairment, an increased risk of traffic accidents, and falls in the elderly. The medications may also decrease cognitive capacities, which can be particularly harmful in older people with limited cognitive abilities (12).

Acording to 2022 updated guidelines, BZD-Z are not indicated for long-term usage, exceeding two weeks, expect in exceptional situation such as in the case of terminally ill patients (21). Nonetheless, a study has shown that BZD usage is continued for more than two years in over 80% of the elderly (7). Long-term use of these drugs is not supported by evidence (21), therefore, both are only suggested for short-term usage, and their discontinuation can result in tolerance, physical dependency, and withdrawal symptoms. Their discontinuation requires a slow gradual tapering over a few weeks or months (14,15).

Because BZD have been shown to be potentially detrimental to the elderly, Z-drugs have previously been suggested as a safer option. In Norway, it has been argued

that the cautious standards for prescribing Z-drugs should be the same as BZD (22). Beers criteria encompass possibly inappropriate use of medications and/or their doses in older adults, as well as medications that are contraindicated for certain illnesses or situations (23). Based on Beers criteria , the American Geriatric Society now advises against giving Z-drugs to the elderly for more than 90 days (22).

BZD-Z are among the most extensively prescribed therapeutic classes worldwide, particularly in developed countries. For example, in France, consumption among individuals over 65 years has reached 30%, more than 20% in Canada and Spain, 15% in Australia, and between 9% and 12% in the United States. A study conducted in Spain reveals a high prevalence of BZD-Z prescriptions. This was exceptionally high in those over 65, regardless of the cognitive deterioration and fall risk (24). In Norway, a study found that prescriptions for Z-drugs among the elderly, particularly women, may suggest that many of them use sleeping medications daily, which is against the guidelines (22).

### 2.3 Indications of benzodiazepines and Z-drugs usage

Indications of BZD-Z are mentioned previously is section 2.1, in this section, the focus will be on discussing the differences between genders and ethnicities in insomnia and anxiety.

#### 2.3.1 Differences between genders and ethnicities in insomnia

Insomnia is defined as difficulty falling asleep, staying asleep or early morning awakenings linked to poor daily functioning, such as decreased cognitive performance, exhaustion, or emotional distress (25,26). Insomnia has been identified as a diagnostic symptom for a variety of mood and anxiety disorders and a variety of medical conditions, such as cardiovascular diseases and cancer (26). Females are more likely than males to have sleep disorders, and both the incidence and gender variances tend to rise as people become older (26,27).

Use of hypnotic drugs is linked to insomnia and is more prevalent in women and the elderly and being linked to physical and mental distress. However, the link between socioeconomic level and hypnotic usage is less clear. Despite these prevalent

insomnia-related variables, the total prevalence of insomnia in Norway reported in various studies ranges from roughly 2 to 48%. Multiple factors might cause this variance. Limitations, such as methodological variability in data collection processes, are the most important ones. These methodological approaches range from personal and telephone interviews to self-reports. Moreover, when comparing studies, the framing of items and criteria may not always look consistent (26).

The drug used as a sleep aid appears to be influenced by sociodemographic factors. Most chronic BZD users are elderly, and males use alcohol for sleep induction more than women (28). According to a study, compared to other European countries, Norway has one of the highest percentages (15.5%) of insomnia diagnosis (25). Rokstad and colleagues investigated the prescribing patterns of hypnotics in Norway in connection to patients' age, gender, and the diagnosis for prescribing and discovered that insomnia was one of the most regularly documented diagnosis for prescribing. Most medications have not been well investigated to find out their principal impacts on sleep and waking behavior. Even though the effects of a medicine are recognized, the action of drugs might differ in individuals who are ill, compared to people without illnesses (28).

### 2.3.2 Differences between genders and ethnicities in anxiety

Anxiety in the elderly, frequently accompanied by depression, can exacerbate physical, cognitive, and functional problems in this vulnerable group (29). Common anxiety disorders include panic disorder, social anxiety disorder, and post-traumatic stress disorder (PTSD) (30). A study that examined ethnic differences in BZD prescriptions revealed that ethnic minority groups are less likely to have BZD dependence diagnosis and receive BZD prescriptions (31). In the Collaborative Psychiatric Epidemiology Studies (CPES), despite the diverse patient pool patterns, it was observed that a lower prevalence of anxiety disorder was recorded in non-white groups. However, when investigated individually, African American groups were more likely to meet the diagnosis of PTSD when compared to both white and other minority groups (30).

Another study utilized the CPES data to look into gender prevalence. It was observed that 33% of women are likely to present with anxiety disorders in their lifetime compared to 22% of men. Generally, women had approximately 1.5-2 times

as common lifetime anxiety rates compared to men, with a number of variations in the rates of prevelance in specified disorders. For example in PTSD patients, the prevalence was 8.5% for women and 3.4% for men, while social anxiety disorders showed no significant difference between the genders (32).

The difference in diagnosis patterns seen in different social groups is impacted by race and gender. Different theories can help clarify the vulnerability of certain groups, unlike the others, for a better diagnosis such as “stress processes”. The theoretical framework considers different exposures to stress, for example, the first line of personal trauma or a second line of stress when a person is exposed to a stressful daily event (33).

Another study shows that psychological distress (that included anxiety) may increase the tendency of perceiving it, as observed in the SAMINOR study of Sami descending Norwegians compared to ethnic Norwegians. Non-ethnic Norwegians reported more stress when compared to ethnic Norwegians when encountering stressful events such as discrimination. However, women from non-ethnic and ethnic Norwegian backgrounds reported a similar stress level (34).

Antidepressants are the first line of therapy for anxiety. In the elderly, both selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors are effective and well-tolerated (35). For clinical situations of anxiety, prescribing restricted quantities of BZD with the lowest attainable dosage of a drug with a short elimination half-life is recommended (29).

### 2.4 Benzodiazepines and Z-drugs and their relation to hip fractures

Several drugs are designated as fall risk-increasing drugs (7), more examples are mentioned in section 1. Substantial evidence suggests an association between psychotropic drugs and falls. Many of the people who awaken at night or in the morning following hypnotic medications report problems with standing steady and maintaining body balance. Consequently, individuals who take hypnotics are more susceptible to experiencing falls and hip fractures (36).

For many years, BZD-Z have been associated with an increased fracture risk (1). Compared to non-BZD users, BZD usage was linked to a 24% higher risk of hip fracture in adjusted models. According to research, the adjusted incidence rate of hip fracture was highest during the first two weeks after taking a BZD, less during the second two weeks, and lowest for long-term users. (37). Single-dose administration of BZD hypnotics severely disrupts bodily equilibrium in a dose-dependent manner (36).

In the Norwegian population, prescriptions of BZD-Z are dispensed to a high number of elderly individuals. The number of prescriptions increases as age advances, increasing the number of prescriptions per recipient (12). The risk of fall increases with increasing number of daily used drugs (7). Therefore, polypharmacy (defined as the usage of five or more drugs) (38), is a prime risk factor for falls among elders, as the number of prescriptions taken each day increases the chance of falling. However, a cross-sectional study showed that polypharmacy is not a risk factor for falls unless a fall risk-increasing drug is involved in the drug regimen (7).

It has been shown that long-acting BZD have been linked to a higher risk of falls and fractures than short-acting BZD (39). Using data from the Norwegian Prescription Database (NorPD), a study in Norway investigated the usage of BZD from 2005 to 2013. According to this Norwegian study, the number of people who take long-acting BZD has decreased by 34%, from 45 per 1000 in 2004 to 30 per 1000 in 2013 (40).

### 2.5 Consequences of a fall, contributing to a hip fracture

Falls among the elderly have far-reaching consequences for society and the individuals involved. Falls are the most common cause of trauma in the elderly. As a result, there is a substantial need for healthcare, which includes prompt medical attention, lengthy rehabilitation, and social repercussions (7). Osteoporosis is a serious condition that particularly affects the elderly, and is linked to fragility and fractures of the hip, spine, and wrist (2). The prevalence of osteoporosis and the rate of fractures are much higher in postmenopausal women than in older men (41). Hip fracture is the most severe consequence of osteoporosis. A combination of decreasing BMD and a fall accounts for most fractures within the elderly population (42).

In addition, women are more prone to falling than men, and are more likely to get injured due to those falls (7). Moreover, the HUNT study conducted in Norway had shown that older women who suffered a hip fracture had higher mortality compared to women who did not experience a hip fracture. The increased mortality was highest shortly after the fracture, but it lasted for several years and was not fully explained by pre-fracture medical issues (43). The increased mortality is seen in both males and females, and males have a higher mortality rate than females (44). Hip fractures were expected to impact 1.25 to 1.66 million people worldwide in 1990, with the number expected to rise to 4.5 to 6.5 million per year by 2050 (45).

Heinrich and colleagues conducted a systematic review that looked at injuries caused by falls in people aged 60 and above in various nations. The authors calculated that healthcare costs related to falls account for 0.85% to 0.5% of overall healthcare costs, which corresponds to 0.07% to 0.20% of Gross Domestic Product (GDP) (7). The expenses of hospitalizations for BZD-related accidental falls are projected to be between €1.5 and €2.2 billion per year in the European Union. The elderly accounted for over 90% of these costs, with hip fractures being the most significant reason (46). Future expenditures will be considerably higher as the world's population ages, and the prevalence of hip fractures rises in some areas (47).

Aside from the considerable financial burden, high cost, and extensive need for healthcare, falls can significantly impact the individual sufferer (7). Even though the age-adjusted rate of hip fractures continues to decline, a recent study indicated that the future burden of hip fractures in terms of expenses and loss of health measured in disability-adjusted life year (DALY) is anticipated to increase (5). Patients examined in the emergency room suffered a decline in their QoL for up to 9 months after a fall. Patients who were not hospitalized faced difficulties with day-to-day activities and taking care of themselves. Furthermore, a fall can trigger a fear of falling. Research has demonstrated that fear of falling has been linked to adverse health effects such as depression and a drop in self-reported QoL, recurrent falls, less physical activity, and limiting or refraining from social activities (7).

### 2.6 What role does ethnicity play in hip fractures?

Several studies suggest a large geographic difference throughout the world, with developed countries reporting a higher hip fracture rate than developing ones (2,47,48). Northern Europe and the United States have the highest incidence of hip fractures; Scandinavian rates are greater than those in Western Europe and Oceania with Norway having the highest rate of fragility hip fractures (2,44). In contrast, Latin America and Africa have the lowest incidence of hip fractures (2).

Hip fractures are substantially less common in African and Asian individuals. These racial and geographical disparities might be explained by Asian nations' shorter life expectancies, genetic background, and high physical activity levels. However, the world's population demographics are changing, with more older adults living in emerging nations, and it's anticipated that by 2050, Asia will account for half of all hip fractures (2). Moreover, Asia, Latin America, the Middle East, and Africa are experiencing the fastest growth in the older population. These regions are anticipated to account for more than 70% of the 6.26 million hip fractures projected by 2050 (47).

In Europe, there is also a north-south gradient in age-adjusted risk, and more fractures are seen in the north than in the south. The effect of ethnicity, latitude, and environmental conditions may be the reasons for this difference, as well as population demography, with more elderly living in areas with higher incidence rates (2). However, a Norwegian study has shown geographical disparities in the frequency of hip fractures that cannot be explained by a north-south gradient (49).

Despite the rate of hip fractures declining in several Western countries (5,50), the number of fractures may potentially rise as the population ages. Age-adjusted hip fracture rates are dropping in Norway, with females experiencing the trend more than males, as detailed national data indicates. Even though the prevalence of hip fractures has decreased, the overall number of hip fractures remains high in both men and women (42,51).

The majority are linked to falls and osteoporosis (discussed in section 2.5), affecting one out of every four postmenopausal white women, but a smaller proportion of men and women of other races. As a result, Europe and North America accounted for

over half of the 1.66 million hip fractures globally in 1990 (47). Understanding how geographic variance is evolving can aid policymakers in formulating methods to mitigate the incidence of hip fractures in emerging nations, which will burden the problem in the future decades (2).

### 2.7 Prevention of benzodiazepine and Z-drug-related falls

Drugs pose as a modifiable risk factor for falls and resulting injuries. Currently, fall prevention is focused chiefly on drugs that increase the risk of falling. In a randomized controlled trial (RCT), the effectiveness of discontinuing psychotropics on avoiding falls in the elderly aged 65 and older was assessed. When psychotropics were gradually removed, there was a 66% reduction in falls compared to those who persisted consuming psychotropic drugs (7). Terminating these drugs may help prevent many of these accidents (46). Notwithstanding, it was concluded that the permanent withdrawal of psychotropics would be challenging. Another study, on the other hand, found that lowering BZD doses is correlated with a high level of success (7).

Although falls are the leading cause of accidents, underlying medical problems such as osteoporosis place the elderly at more risk of dangerous falls. To build an effective fall prevention program, risk factors need to be determined. Several studies on falls and their related risk factors have been undertaken during the last few decades. Although a single factor causes some falls in the elderly population, the majority are caused by a combination of factors. History of previous falls, cognitive and mobility impairments, use of fall risk-increasing drugs, and older age are all substantial risk factors (7).

# 3. Materials and methods:

### 3.1 Project Organization

The project has used existing registry data that is available as part of a larger research project at the Norwegian Institute of Public Health. The name of the project is The Epidemiology of Prescription Drug Use. It is administered by Kristin Holvik, senior researcher in the Norwegian Institute of Public Health.

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### 3.2 Study setting

Norway is a country in Northern Europe with borders with Sweden, Finland, and Russia. It has about 5.3 million people and is expected to exceed 5.5 million by 2024. Norway has one of the world's highest life expectancies, at about 83 years (52).

#### 3.2.1 Migrants in Norway

International migration has grown by almost 272 million individuals, or 3.5% of the world's population, in the previous 15 years. Migrants and their descendants accounted for around 15% of the Norwegian population in 2020, with origins in various countries and regions. The motivations for migration among these varied groups are similarly diverse. Labor migrants make up the highest share of international migrants worldwide and in Norway, followed by persons who travel for a family reunion, asylum, and education (53).

Over the last ten years, the number of individuals migrating to Norway has declined. The maximum number of immigrants was recorded in 2011, with 79,498 persons, and the number of immigrants decreased each year after that. (54). According to Statistics Norway, 53,947 migrants moved to Norway in 2021 (55).

### 3.3 Study design

This is an observational cross-sectional study.

#### 3.3.1 Observation period

This study observed the targeted population starting 2005. BZD-Z users were observed at 3 time-points, 2005, 2010, and 2015. Hip fractures in 2016 were included to describe their association with BZD-Z usage in 2015.

#### 3.3.2 Study population

For the first aim, the study population was inhabitants in Norway who were participants in the Norwegian Population and Housing Census 2001, born 1966 or earlier; it includes all those aged 50 years and older in the last year of currently available NorPD data in the project (2016). The dataset does therefore not include any immigrants who came to Norway after 2001. The years 2005, 2010, and 2015 are three time-points of those who participated in the Population and Housing Census in 2001 and were still alive in the respective years.

The NorPD does not contain all information about prescriptions in nursing homes (56). Therefore, people who moved to a nursing home and received BZD-Z there did not appear as BZD-Z users in the thesis data. In the thesis dataset, each person was counted as a BZD-Z user once within each year, regardless of how many BZD-Z prescriptions they filled. They can be a user in one, two or all the three if they have filled a prescription within each year.

As a rough proxy of ethnicity, background regions were divided into three different geographical regions, Norway, South Asia, and the Middle East. The following countries are included in the Middle East: Bahrain, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates,

Yemen, and Egypt (57). The Indo-Gangetic Plain and peninsular India make up South Asia, a subregion of Asia. Bangladesh, Bhutan, India, Pakistan, Nepal, and Sri Lanka are all regarded part of South Asia; Afghanistan and the Maldives are also included (58). The Middle East and South Asia were chosen due to practicalities, as they are relatively large immigrant groups from different places.

For the second aim, the study population comprised all individuals aged 50 and above who had at least one filled prescription in NorPD in 2015. People who did not have filled a prescription in 2015 were not included. Because the NorPD does not contain all information about prescriptions in nursing homes (56), people who moved to a nursing home did not appear as BZD-Z users in the thesis data. In the thesis dataset, each person was only counted as a BZD-Z user once, regardless of how many BZD-Z prescriptions they filled. In the thesis dataset, information from the Norwegian hip fracture database (NORHip) was restricted to hip fractures occurring in 2016 with up to two hip fractures per person.

### 3.3.3 Exposure variable

Background region was used to approximate ethnicities, which was regarded as the exposure variable for the first aim. BZD-Z users and non-users were further classified into three background regions, Norway, Middle East, and South Asia. The population size was 1,431,609 in the year 2005, 1,524,751 in the year 2010, and 1,629,056 in the year 2015. The total population size of this study is N=2,301,137 because most of the people were participants in all three years.

For the second aim, BZD-Z was regarded as the exposure variable while hip fracture was regarded as the outcome variable. The second aim included 1,531,100 participants who were BZD-Z users and non-users.

### 3.3.4 Covariates

Covariates were gender and age divided into four age groups: 50–59 years, 60–69 years, 70–79 years, and 80–89 years.

### 3.4 Data sources

Data are retrieved from three population wide data sources:

1. The Norwegian Prescription Database (NorPD) that provided the data on all dispensed drugs in outpatient pharmacies. Aggregated data on the use of BZD-Z in different age groups among men and women was studied.
2. Population and Housing Census 2001 from Statistics Norway that provided the population registry status including different immigrant categories in different age groups and gender.
3. NOREPOS hip fracture database (NorHip) that provided data on all hip fractures treated in Norwegian hospitals in 2016.

#### 3.4.1 About The Norwegian Prescription Database (NorPD)

The NorPD includes all prescriptions filled at Norwegian pharmacies since January 1 2004 (56,59,60). All drugs prescribed and dispensed at pharmacies to patients residing outside institutions, meaning outpatient care, are recorded in NorPD. In addition, the NorPD features a website that provides quick access to prescription statistics in Norway. The database includes all patients who received at least one prescription throughout the year (59).

Since NorPD is a database that collects information about drugs that have been delivered in Norway, it can be learned more about the consumers of a specific drug or drug class. This data will be used for statistical analysis, planning, and general scientific study. Individual privacy is secured, and data is kept anonymous (61). It is possible to obtain reports on the number of users of a specific drug or drug category. Searches utilizing the Anatomical Therapeutic Chemical (ATC) code, chemical name, or brand name yields detailed information (59).

NorPD is a valid and reliable data source for analyzing prescription medication use since it covers the whole country. Furthermore, NorPD enables new research fields, in the scope of pharmacoepidemiology, in Norway. It also provides a solid foundation of knowledge for national drug-use decision-making (60).

### 3.4.1.1 Anatomical Therapeutic Chemicals (ATC codes)

The definition of ATC codes is described by the WHO's Collaborating Centre for Drug Statistics Methodology. ATC codes are tools that aid in the study and monitoring of drug use, hence improving the quality of drug usage. This coding has been used to show and compare drug consumptions with great success (62).

The three drug classes used in this study, classified based on ATC codes are:

1. ATC N05BA - BZD derivates (anxiolytics)
2. ATC N05CD - BZD derivates (sedatives and hypnotics)
3. ATC N05CF – Z-drugs

N stands for Nervous System, and N05 represent Psycholeptics, each group is further divided into therapeutic subgroups:

N05A – Antipsychotics (this group is not included in the thesis)

N05B – Anxiolytics

N05C – Hypnotics and sedatives

**N05B - Anxiolytics:** classifies BZD used in the treatment of neuroses and psychosomatic diseases related to anxiety and tension. A few examples of drugs grouped as N05BA, BZD derivates (anxiolytics), are diazepam, lorazepam, and alprazolam (63).

**N05C – Hypnotics:** classifies BZD used mostly to treat sleep disorders. (63)**.** A few examples of drugs grouped as N05CD, BZD derivates (sedatives and hypnotics), are flurazepam, triazolam, and midazolam (64). N05CF, Z-drugs, include zopiclone, zolpidem, zaleplon, and eszopiclone (65).

Active ingredients are subcategorized into five levels (62), Diazepam, Flurazepam, and Zopiclone are utilized as examples to explain the structure of ATC codes:

| | |
|---|---|
| N | Nervous System<br>(1st level, anatomical main group) |
| N05 | Psycholeptics<br>(2nd level, therapeutic subgroup) |
| N05B | Anxiolytics<br>(3rd level, pharmacological subgroup) |
| N05BA | Benzodiazepine derivatives<br>(4th level, chemical subgroup) |
| N05BA01 | Diazepam<br>(5th level, chemical substance) |

| | |
|---|---|
| N | Nervous System<br>(1st level, anatomical main group) |
| N05 | Psycholeptics<br>(2nd level, therapeutic subgroup) |
| N05C | Hypnotics and sedatives<br>(3rd level, pharmacological subgroup) |
| N05CD | Benzodiazepine derivatives<br>(4th level, chemical subgroup) |
| N05CD01 | Flurazepam<br>(5th level, chemical substance) |

| | |
|---|---|
| N | Nervous System<br>(1st level, anatomical main group) |
| N05 | Psycholeptics<br>(2nd level, therapeutic subgroup) |
| N05C | Hypnotics and sedatives<br>(3rd level, pharmacological subgroup) |
| N05CF | Benzodiazepine related drugs<br>(4th level, chemical subgroup) |
| N05CF01 | Zopiclone<br>(5th level, chemical substance) |

### 3.4.2 About The Population and Housing Census 2001

Statistics Norway has developed statistical registers based on official data systems, such as administrative registers kept by other public entities or administrative data collected by Statistics Norway. Data from many sources are combined to create variables not directly present in administrative sources (66). The Population and Housing Census 2001 covered the whole country of Norway. It included all individuals, including foreign nationals, who were residents in Norway under the Central Population Register in November 2001 (67).

The population register provides demographic statistics and information on residence and immigration background. The National Population Register is utilized to obtain birth dates, which are then used to compute a person's age. On December 31, 2001 (age = 2001 minus the year of birth), the age of a person is described as "age at the end of the year" and is the primary age variable in the Census 2001. Personal identification numbers were used to determine a person's sex (66).

Individuals with and without immigrant backgrounds are distinguished. The variable "country of birth" implies the country where an individual was born. The variable "country background" refers to a person's home country when they were born abroad. This is the country of origin for those who were born in Norway. If the mother and father were born in separate countries, the mother's birth country is utilized. Norway is usually the country background for those who are not immigrants. Immigrants are grouped according to their country background. The Nordic countries, Western Europe (except Turkey), North America, and Oceania are all considered Western regions. Eastern Europe, Turkey, Asia, and Africa are examples of non-western regions (66).

### 3.4.3 About NOREPOS

NOREPOS (Norwegian Epidemiologic Osteoporosis Studies) is a nationwide research partnership network of researchers from five distinct Norwegian scientific institutes. On the topic of osteoporosis, NOREPOS conducts epidemiologic research (68). NOREPOS relies on data from extensive population-based studies in Norway that included BMD assessments. Hip fractures are a significant outcome.

The NORHip database contains information on all hip fractures treated in Norwegian hospitals between 1994 and 2019. NOREPOS is interested in investigating population-level risk factors for osteoporosis and fractures, such as nutritional factors, physical activity, weight fluctuations, drug usage, and environmental factors such as drinking water quality (68). This is accomplished by combining data from hip fracture studies and registrations. The aim is to address the question: “Why does Norway have the highest incidence of hip fractures ever reported worldwide?” NOREPOS is a distinctive database for aetiological research and biomarkers of osteoporosis and fractures. (68).

### 3.5 Data access and extraction

***Aim 1:***

The thesis dataset for aim 1 contains information from the Population and Housing Census 2001 and the NorPD. The data were linked using the unique national identity numbers.

The Population and Housing Census 2001 contains data about socio-demographics of the population in 2001 (66,67). For the thesis dataset the variables age, sex and country background were used. The age variable was restricted to those who were 50 years or older or would be 50 by the end of 2016. The country background variable was restricted to those from Norway, South Asia and the Middle East.

The NorPD contains information about all prescriptions filled in Norwegian outpatient pharmacies. It contains information about the ATC-code, DDDs (Defined Daily Doses) and how many prescriptions were filled (60). For the thesis, this information was restricted to persons who had filled at least one prescription with ATC codes N05BA, N05CD or N05CF for each study year.

The data were aggregated on all persons who had the same values of sex (man, woman), age group (50-59, 60-69, 70-79, 80-89), background region (Norway, Middle East, South Asia), user (yes, no), and drug class (nonuser, N05BA, N05CD, N05CF) in each study year (2005, 2010, 2015).

***Aim 2:***

The thesis dataset for aim 2 contains information from the NorPD and the NORHip database and were linked using the unique national identity numbers. The population consisted of everyone who had filled at least one prescription in 2015. In the thesis dataset this information was restricted to yes/no use of prescription with ATC codes N05BA, N05CD and N05CF in 2015.

From 1994 to 2019, NORHip provides data on all inpatient encounters in specialized healthcare in Norway with a hip fracture diagnosis. Patient administrative systems at treating hospitals provided data from 1994 to 2007, whereas the Norwegian Patient Registry provided data from 2008 to 2019. A comprehensive algorithm was used to identify hospitalizations that indicated an incidence of hip fracture using information on co-occurrence of other diagnostic codes, surgical procedure codes, and whether the hip fracture was documented as a primary or secondary diagnosis (69).

In the thesis dataset, this information was restricted to hip fractures occurring in 2016 with up to two hip fractures per person in each year.

The data were aggregated on all persons who had the same values of sex (man, woman), age group (50-59, 60-69, 70-79, 80-89), drug use in 2015 (yes, no), and hip fracture in 2016 (yes, no).

## 3.6 Ethics

This project is a part of the project “The Epidemiology of Prescription Drug Use” that has been approved by the Research Ethics Committee (REC), (REC reference 2009/1521). An amendment about work on this project has been sent to REC and has been approved.

The registry data are pseudonymised and stored at the Norwegian Institute of Public Health’s server in an access restricted research folder. The datasets used in this thesis consisted of aggregated data.

Regarding data handling, data is secured and have been handled in accordance with the regulations of the Norwegian Institute of Public Health, the data analysis was

conducted using the desktop of University of Oslo through VMware Horizon software.

### 3.7 Funding

Data access is covered by the Norwegian Institute of Public Health.

### 3.8 Statistical analysis

STATA software version 17 was used to analyze the data, and p values less than 0.05 were considered of statistical significance. All analyses have been conducted with frequency weights because the thesis datasets were aggregated data. The Pearson's Chi-square test ($X^2$) along with proportions command were used to describe the usage of BZD-Z in each of the three timepoints [Table 1]. The age-adjusted prevalence were calculated by background group and gender using predictive margins based on logistic regression models, and are presented with corresponding 95% confidence intervals (CI) [Tables 2, 3, and 4].

The Norwegian population was utilized as the reference population in the dataset. Odds ratios (ORs) from logistic regression for BZD-Z would overestimate Prevalence Ratio (PR) as BZD-Z use is a frequent endpoint (>>10%), but it should not influence on the significance testing.

The following formula was used to calculate adjusted PR:

$$\text{Adjusted PR} = \frac{\text{adjusted BZD-Z prescription prevalence in other background regions}}{\text{adjusted BZD-Z prescription prevalence in Norwegians}}$$

Proportions command was used for percentage estimation of pattern of usage of BZD-Z based on background regions according to age and gender [Figures 1 and 2]. Proportions were also used for percentage estimation of BZD class and Z-drugs used among users based on background regions according to age [Figure 3].

The Pearson's Chi-square test ($X^2$) was used for assessing the relationship between BZD-Z usage in 2015 and hip fractures in 2016 [Table 5]. Logistic regression was done to calculate the unadjusted and adjusted (for age and gender)

OR to measure the association between BZD-Z usage in 2015 and hip fractures in 2016 [Table 6]. Gender specific logistic regression was further used to calculate the OR based on age groups. The age group 50-59 was used as the reference category because individuals belonging to this age group have the lowest risk of hip fractures [Tables 7 and 8].

### 3.9 Timeline

# 4. Results:

## 4.1 Usage of benzodiazepines and Z-drugs according to background regions and gender

The prevalence of BZD-Z users in the year 2005, 2010 and 2015 was found to be 23.3% (n=334,111), 22.5% (n=342,707) and 20.4% (n=332,035) [Table 1]. Since 2015, is the most recent data, emphasis will be placed on it. Upon adjusting for confounders (age and gender), a comparison of BZD-Z usage between different background regions shows that the difference in 2015 was not statistically different between Norwegian individuals and those from the Middle East (95% CI including 1), but it was statistically significantly different in 2005 and 2010.

In 2015, 20.4% (reference) of individuals from Norway were BZD-Z users, compared to 19.8% (OR for BZD-Z use =0.96; 95% CI= 0.90-1.01) from the Middle East and 13.0% (OR for BZD-Z use =0.57; 95% CI= 0.53-0.60) from South Asia [Table 2]. For individuals from South Asia, PR is 0.64 (13.0/20.4); hence, the prevalence of use was 36% lower in individuals from South Asia compared to Norwegian individuals. While the PR for individuals from the Middle East was 0.97 (19.8/20.4) which suggests that the prevalence of use was only 3% lower than Norwegian individuals, and it was not statistically significant.

Upon running age-adjusted gender-specific analyses, it was shown that in 2015, males from the Middle East had the highest prevalence of prescriptions with 16.4%, (OR for BZD-Z use =1.23; 95% CI= 1.14-1.32), compared to males from Norway with 13.8% (reference) and South Asia with 11.5% (OR for BZD-Z use =0.81; 95% CI= 0.74-0.88) [Table 3]. PR for males from the Middle East is 1.19 (16.4/13.8), therefore, prevalence of use was 19% higher in males from the Middle East compared to Norwegian males. For males from South Asia, PR is 0.83 (11.5/13.8), therefore, prevalence of use was 17% lower in males from South Asia compared to Norwegian males.

Moreover, in 2015, females from Norway had the highest prevalence of prescriptions with 26.7%, compared to females from the Middle East with 20.2% (OR for BZD-Z use =0.69; 95% CI= 0.63-0.75), and South Asia with 13.2% (OR for BZD-Z use =0.41; 95% CI= 0.37-0.45) [Table 4]. PR for females from the Middle East is 0.76 (20.2/26.7), therefore, prevalence of use was 24% lower in females from the Middle

East compared to Norwegian females. For females from South Asia, PR is 0.49 (13.2/26.7), therefore, prevalence of use was 51% lower in females from South Asia compared to Norwegian females.

The difference between background regions in men are relatively small, compared to differences in women where Norwegian women were consistently prescribed more often than women from other background regions. It was also shown that usage was higher in females than males in all three background regions. Individuals from South Asia have been prescribed the least prescriptions in both genders. These patterns were relatively stable through the previous years, 2005 and 2010.

**Table 1: Usage of BZD-Z according to year**

| Year | Total number of individuals | BZD-Z prescriptions | Percentage of users |
|---|---|---|---|
| 2005 | 1,431,609 | 334,111 | 23.3% |
| 2010 | 1,524,751 | 342,707 | 22.5% |
| 2015 | 1,629,056 | 332,035 | 20.4% |

**Table 2: Comparison of BZD-Z usage between different background regions**

| year | Background region | Total number of individuals | BZD-Z users* | 95% CI* | OR (95% CI) for use of BZD-Z* |
|---|---|---|---|---|---|
| 2005 | Norway | 1,421,867 | 23.4% | 23.3-23.5 | 1.00 (reference) |
| | Middle East | 3,934 | 18.2% | 16.9-19.5 | 0.71 (0.65-0.78) |
| | South Asia | 5,808 | 13.1% | 12.1-14.0 | 0.47 (0.43-0.52) |
| 2010 | Norway | 1,510,257 | 22.5%. | 22.5-22.6 | 1.00 (reference) |
| | Middle East | 6,437 | 19.5% | 18.6-20.6 | 0.83 (0.77-0.89) |
| | South Asia | 8,057 | 12.6% | 11.8-13.3 | 0.48 (0.44-0.51) |
| 2015 | Norway | 1,608,051 | 20.4% | 20.4-20.5 | 1.00 (reference) |
| | Middle East | 10,081 | 19.8% | 18.9-20.6 | 0.96 (0.90-1.01) |
| | South Asia | 10,924 | 13.0% | 12.3-13.7 | 0.57 (0.53-0.60) |

*** Adjusted for confounders (age and gender)**

| | Table 3: Comparison of BZD-Z usage between different background regions in males | | | | |
|---|---|---|---|---|---|
| year | Background region | Total number of individuals | BZD-Z users* | 95% CI* | OR (95% CI) for use of BZD-Z* |
| 2005 | Norway | 672,683 | 15.6% | 15.5-15.7 | 1.00 (reference) |
| | Middle East | 2,364 | 15.7% | 14.1-17.2 | 1.00 (0.89.-1.13) |
| | South Asia | 3,382 | 11.6% | 10.5-12.8 | 0.71 (0.63-0.79) |
| 2010 | Norway | 725,147 | 15.1%. | 15.1-15.2 | 1.00 (reference) |
| | Middle East | 4,007 | 16.3% | 15.1-17.5 | 1.09 (1.00-1.20) |
| | South Asia | 4,598 | 11.1% | 10.2-12.1 | 0.70 (0.63-0.77) |
| 2015 | Norway | 780,862 | 13.8% | 13.8-13.9 | 1.00 (reference) |
| | Middle East | 6,431 | 16.4% | 15.5-17.4 | 1.23 (1.14-1.32) |
| | South Asia | 6,186 | 11.5% | 10.7-12.3 | 0.81 (0.74-0.88) |

*** Adjusted for confounder (age)**

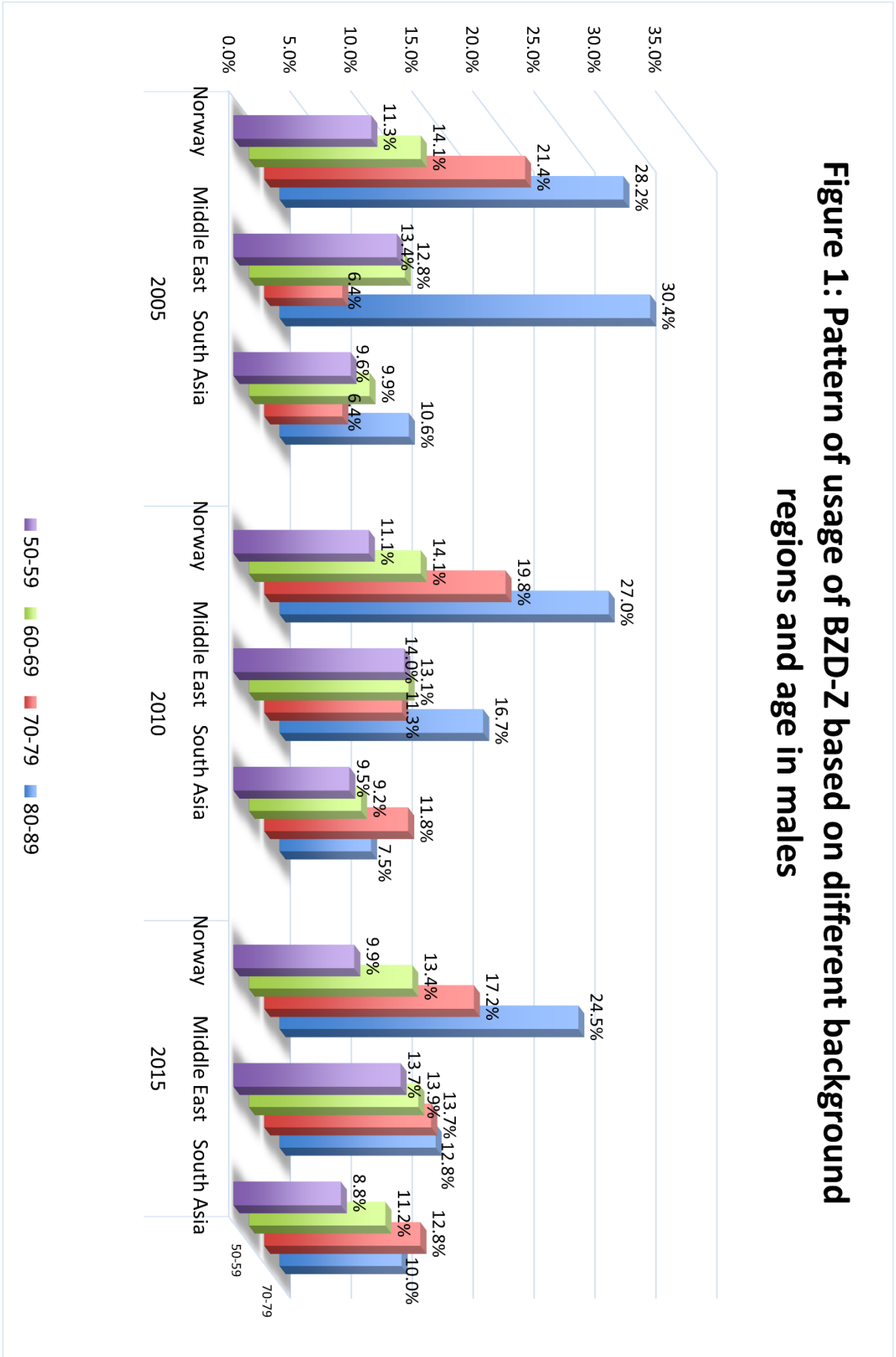
| | Table 4: Comparison of BZD-Z usage between different background regions in females | | | | |
|---|---|---|---|---|---|
| year | Background region | Total number of individuals | BZD-Z users* | 95% CI* | OR (95% CI) for BZD-Z* |
| 2005 | Norway | 749,184 | 30.4% | 30.3 - 30.5 | 1.00 (reference) |
| | Middle East | 1,570 | 18.2% | 16.2-20.2 | 0.50 (0.43-0.57) |
| | South Asia | 2,426 | 12.6% | 11.2-14.1 | 0.32 (0.28-0.37) |
| 2010 | Norway | 785,110 | 29.4% | 29.3-29.5 | 1.00 (reference) |
| | Middle East | 2,430 | 20.0% | 18.4-21.7 | 0.59 (0.53-0.66) |
| | South Asia | 3,459 | 12.4% | 11.2-13.6 | 0.33 (0.30-0.37) |
| 2015 | Norway | 827,189 | 26.7% | 26.6-26.8 | 1.00 (reference) |
| | Middle East | 3,650 | 20.2% | 18.8-21.6 | 0.69 (0.63-0.75) |
| | South Asia | 4,738 | 13.2% | 12.1-14.2 | 0.41 (0.37-0.45) |

*** Adjusted for confounder (age)**

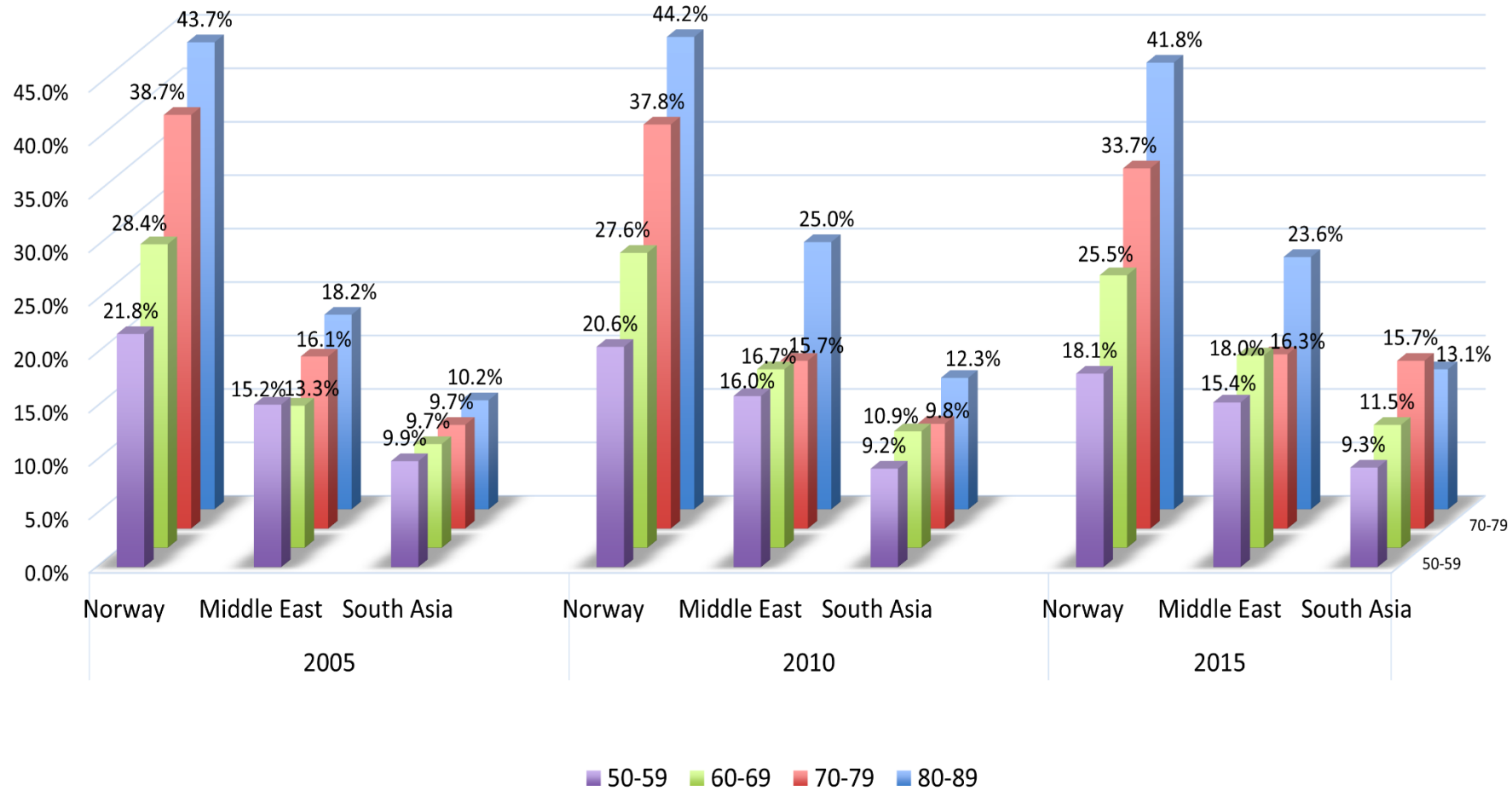
### 4.2 Usage of benzodiazepines and Z-drugs according to background regions and age

Figures 1 and 2 show the usage of BZD-Z according to different background regions and ages in each gender. In both genders and through all three time-points, individuals from Norway had an increasing usage pattern as age groups increased. In contrast, individuals from the Middle East and South Asia had varying patterns [Figures 1 and 2]. In 2005, males from the Middle East aged 80-89 were dispensed the highest prevalence of prescriptions of 30.4%. Male users from the Middle East aged 50-59 also surpassed users from Norway and South Asia in the prevalence of prescriptions in all three time-points. In 2015, the prevalence of prescriptions in males from the Middle East aged 70-79 also exceeded users from Norway and South Asia in as well [Figure 1]. When it comes to females, those from Norway had the highest prevalence of prescriptions in all age groups through all three time-points compared to individuals from the Middle East and South Asia [Figure 2].

**Figure 1: Pattern of usage of BZD-Z based on different background regions and age in males**

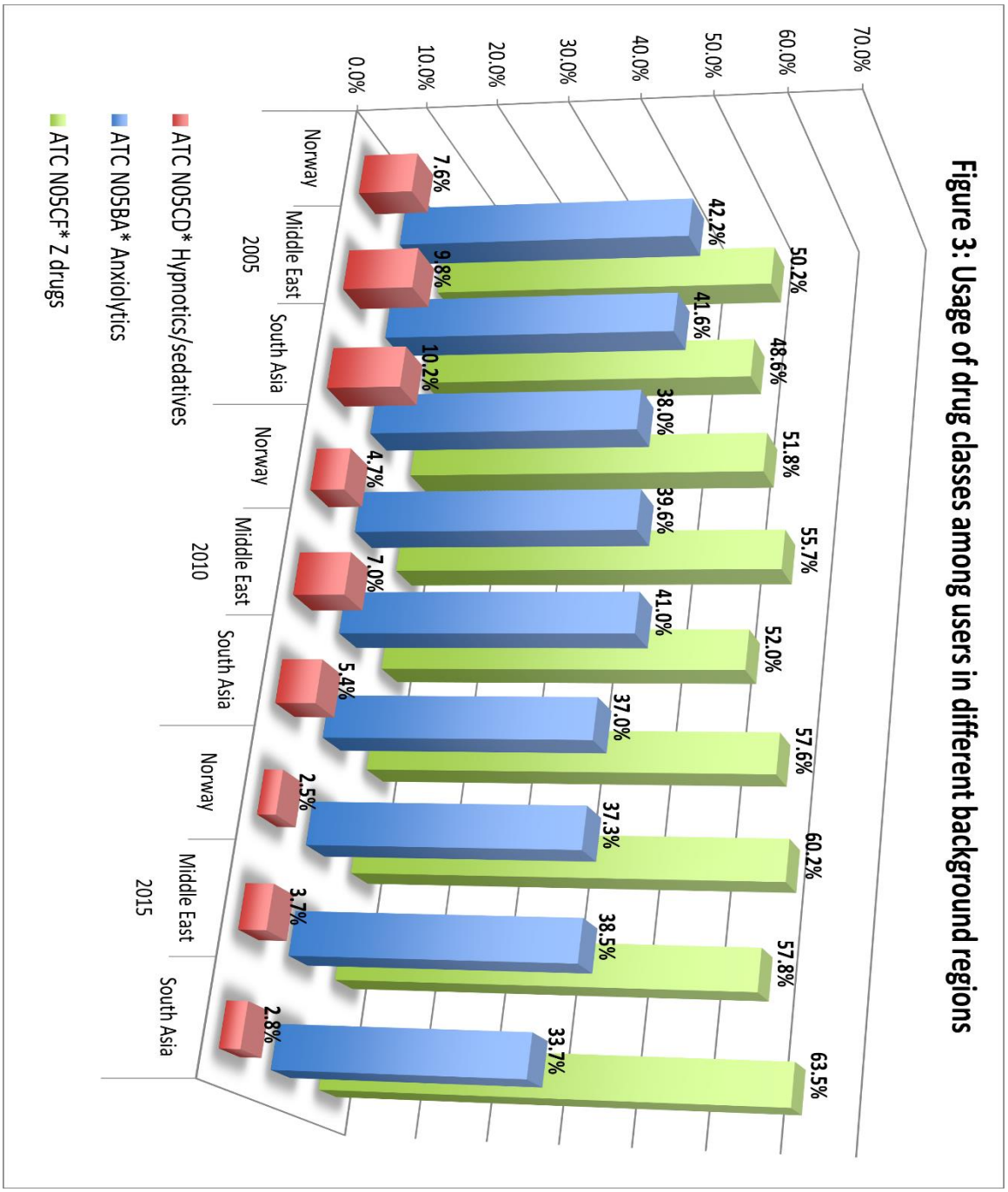


## Figure 2: Pattern of usage of BZD-Z based on different background regions and age in females



### 4.3 Usage of drug classes among users in different background regions

Of the three drug classes, it has been shown that most users were Z-drugs users in all background regions at all three time-points, compared to anxiolytic BZD and hypnotic/sedative BZD. The proportion of Z-drug usage was higher in 2015 compared to 2010, and higher in 2010 compared to 2005. The proportion of usage of anxiolytics was relatively stable, it was lower in 2015 compared to 2010 and 2005, and lower in 2010 compared to 2005. Hypnotics/sedatives BZD were the least used subgroup in all background regions at all three time-points. [Figure 3].



### 4.4 Odds ratios and the association between benzodiazepines and Z-drugs and hip fractures

A total of 6,509 individuals experienced a hip fracture in 2016, of which 2,667 (41.0%) of them were BZD-Z users in 2015, while 3,842 (59%) were non-users [Table 5]. An adjusted OR of 1.43 (95% CI=1.36-1.50) suggests that the odds of hip fracture was significantly higher in BZD-Z users compared to non-users [Table 6]. Upon running gender specific logistic regression based on age groups, results show a higher OR with increased age [Tables 7 and 8]. Males aged 70-79 had 6 times higher odds of hip fracture compared to the youngest age group (50-59), while males aged 80-89 had 21 times higher odds of hip fracture compared to the youngest age group [Table 7]. In females, those aged 70-79 had 11 times higher odds of hip fracture compared to the youngest age group, while females aged 80-89 had 36 times higher odds of hip fracture compared to the youngest age group [Table 8].

**Table 5: BZD-Z user in 2015 v/s hip fracture in 2016**

| | | | Hip fracture in 2016 | | |
|---|---|---|---|---|---|
| | | | Yes | No | Total |
| BZD-Z user in 2015 | Yes | n | 2,667 | 356,628 | 359,295 |
| | | % | 41.0% | 23.4% | |
| | No | n | 3,842 | 1,167,963 | 1,171,805 |
| | | % | 59.0% | 76.6% | |
| | Total | | 6,509 | 1,524,591 | 1,531,100 |

**Table 6: Unadjusted and adjusted OR for the odds of experiencing a hip fracture in 2016 if BZD-Z were used in 2015**

| | Unadjusted OR | 95% CI | Adjusted OR* | 95% CI* |
|---|---|---|---|---|
| Non-users | 1.00 | reference | 1.00 | reference |
| BZD-Z users | 2.27 | 2.16-2.39 | 1.43 | 1.36-1.50 |

*Adjusted for the confounders age and gender.

| Table 7: Logistic regression based on age groups in males | | |
|---|---|---|
| Age group | OR* | 95% CI* |
| 50-59** | 1.00 | reference |
| 60-69 | 2.51 | 2.08-3.03 |
| 70-79 | 6.44 | 5.40-7.68 |
| 80-89 | 21.49 | 18.12-25.50 |

*Odds ratio for hip fracture in different age groups adjusted for BZD-Z use.

**Age group 50-59 was utilized as the reference group, because individuals among this age group have the lowest risk of hip fracture.

| Table 8: Logistic regression based on age groups in females | | |
|---|---|---|
| Age group | OR* | 95% CI* |
| 50-59** | 1.00 | reference |
| 60-69 | 4.07 | 3.42-4.85 |
| 70-79 | 11.62 | 9.85-13.72 |
| 80-89 | 36.69 | 31.19-43.15 |

*Odds ratio for hip fracture in different age groups adjusted for BZD-Z use.

**Age group 50-59 was utilized as the reference group, because individuals among this age group have the lowest risk of hip fracture.

# 5. Discussion:

## 5.1 Findings of the study

Findings from this study show that prescriptions of BZD-Z were lower in female immigrant groups compared to females from Norway; these differences were of statistical significance. Moreover, males from the Middle East had the highest prevalence of prescriptions compared to males from Norway and South Asia. Another study has also shown a significant difference of BZD-Z use prevalence among different countries, it ranged from Israel having the highest prevalence of BZD-Z use with 44.1% to Germany having the lowest prevalence of BZD-Z use with 14.5% (70). Several studies have investigated the role of ethnicities in anxiety, sleeping disorders, and insomnia. It was shown that ethnicity plays a possible role in the incidence and prevalence of these conditions (30,71,72). A study has shown that Norway has one of the highest percentages of insomnia diagnosis compared to other European countries (25).

A possible explanation for the lower use of BZD-Z in other background regions, except for men from the Middle East, may be the healthy migrant effect, which suggests that there is a social selection process concerning migration. It is suggested that the healthiest immigrants choose and are capable of migrating, implying that immigrants are in better health than the general population. This might explain some of the immigrant group's health benefits over the host population (3,73,74). However, it is suggested that the healthy migrant effect may fade over time; many immigrants also report poor health and increasing health-care utilization (73). Their help-seeking behavior may be influenced by cultural factors (75). A study has shown that even after adjusting for socioeconomic factors, ethnicity accounted for a considerable percentage of the variance in most of the help-seeking behaviors studied (76). In addition, ethnic minority groups have been observed to use alternative and diverse help-seeking approaches rather than traditional primary care providers (75).

The immigrant population in Norway is still young, and most people born in other countries who live in Norway have not yet approached higher ages (3). Because the age distribution is different, it is also difficult to compare the proportions of BZD-Z prescriptions among immigrants in Norway to the proportions in their home countries. Therefore, the prevalence estimates were adjusted for age in this

study. Furthermore, this study did not cover the prescriptions of individuals from all countries and all immigrant groups.

Women are more likely than males to have sleep disorders, and both the prevalence and gender differences tend to rise with age. Women and the elderly are more likely to be affected (27). Age was found to be significantly and directly corelated to insomnia prevalence in females but not in males according to The Tromsø study (77). Moreover, another study conducted in Norway has shown that females had higher levels of current and lifetime anxiety than males (78). Such findings may explain the increasing pattern of usage seen with increasing age observed among Norwegians in the results of this thesis. The findings of this thesis also support that females are more likely to suffer from conditions requiring the prescription of BZD-Z.

Numerous studies have investigated the risk of hip fracture (3), as hip fractures are becoming more common worldwide as the world's population ages. The patient's age impacts the outcome of such fractures (79). Compared to non-BZD-Z users, BZD-Z usage was linked to a higher risk of hip fracture (37). Both BZD-Z have been linked to an increased risk of hip fracture in the elderly, and the risks of both drug classes are similar (1). Individuals who have recently been prescribed these drugs are at the highest risk of hip fracture. Clinicians and policymakers are ought to consider the increased risk of falls and hip fractures among new drugs users (1).

According to BZD-Z guidelines, older individuals should only consume anxiolytic BZD and Z-drugs at low doses and for a short period of time, and hypnotic BZD should not be used at all. Because the elderly aged 65-79 are often newly retired but still in good health, they may have different BZD-Z demands than older or younger individuals (12,80). Because BZD have been shown to be potentially detrimental to the elderly, Z-drugs have previously been suggested as a better alternative (22). The findings of this thesis have further confirmed that Z-drugs are the most used drug in all background regions, and hypnotic/sedative BZD were the least used, suggesting adherence to such recommendations.

However, it has been shown that the reduced dose and limited duration recommendations are frequently surpassed; therefore, there is growing concern over the propriety of usage. Nevertheless, in Norway, long-term usage persists despite concerns that BZD advantages diminish over time, while the risk of adverse drug

effects remains high. Greater risk of adverse drug effects, increased risk of accidents such as falling, and increased cognitive decline are the most often reported areas of risk (80). A limitation in this thesis is that duration and doses were not addressed.

The adjusted OR of hip fracture (1.43) for BZD-Z users compared to non-users aligns well with the existing literature (81). Age is a very strong risk factor for hip fracture (69), and women are more likely to experience a hip fracture (7). Thus, the unadjusted OR (2.27) is higher than the adjusted OR (1.43). As increasing age increases the use of BZD-Z and the risk of sustaining a hip fracture, there will be an overestimation of the OR if age and gender were not adjusted.

Moreover, the results suggest that females had higher proportions of BZD-Z usage compared to males. The findings show that the difference between ethnic groups in men are relatively small, while Norwegian women are consistently prescribed much more often. The findings from this study show that BZD-Z usage may act as a modifiable risk factor which can possibly contribute to the high incidence of hip fractures in women and Norwegians.

### 5.2 Strengths of the study

The size of the population, the completeness of the registers encompassing the whole country, and the quality of the prescription database and hip fracture database are the study's strengths. All individuals in all three study years were participants in the 2001 Population and Housing Census. The NorPD and NORHip databases, which contain all dispensed BZD-Z prescriptions in outpatient pharmacies and hip fractures treated in hospitals in Norway throughout the research period, have a high ascertainment.

### 5.3 Limitations of the study

*Aim 1:*

The data is limited to the population participating in the Population and Housing Census in 2001, which means that no registration of immigrants coming to Norway after 2001 is in the data. However, because labor migrants had the highest share of

international migrants (53), the people who came later were probably young. Other causes of immigration include family reunification, education, and asylum (53), which are most probably of younger age groups as well. The difference in age distribution between background regions was mitigated by adjusting for age in the prevalence estimates.

Data on the use of BZD-Z in hospitals and nursing homes was not available in this thesis dataset. The data does not show how many dropped out from 2005 to 2015 due to death, emigration or moving to a nursing home. When participants are assigned to different groups other than the group they should be assigned to, misclassification bias occurs (82). Those who died were removed from the data in the years they were dead, however, the rest appeared as non-users in the years they had emigrated or been in a nursing home. This might have resulted in an overestimation of non-users.

Some of the age groups have small numbers of people leading to greater uncertainty, moreover, immigrant groups had a smaller sample size leading to higher variability than Norwegians, which resulted in a wider confidence intervals. In the thesis dataset, each person was counted as a BZD-Z user once, however, the dataset does not contain information about how many prescriptions an individual filled and DDD. Another general limitation with the NorPD is that it is unknown if people took the medication they were dispensed.

*Aim 2*

The population consists of people with at least one filled prescription in 2015, meaning that people who did not have filled a prescription in 2015 are not included. However, as all types of prescription drugs are registered in the NorPD, this may not be a major issue since most adults over the age of 50 will have probably filled at least one prescription within a year (83).

When the person-time of research participants is misclassified, immortal time bias occurs. Subjects in the exposed group are "immortal" prior to their exposure if exposure is allocated across time but viewed as a binary "ever-exposed" variable (84). It is unknown if the persons were still alive or had emigrated by the end of

2016, meaning that they could have died earlier in the year and therefore not be at risk for hip fracture. Nonetheless, in this study, it was looked at how many of the hip fracture patients in 2016 used BZD-Z restricted only to the previous year (2015) aiming to minimize this bias. Misclassification bias may be also seen because it is unknown who have died, emigrated, or moved to a nursing home, so they could appear as non-users if they had received BZD-Z after moving to a nursing home.

Each person was only counted as a BZD-Z user once meaning that a person might be a user of more than one drug; moreover, the dataset does not contain information about how many prescriptions an individual filled, the duration of usage, and DDD. This is considered a limitation because those taking higher doses, are at the highest risk of hip fracture. Studies have also shown that risk of hip fracture was doubled when two or more BZD were taken concomitantly (4,85). However, according to a Norwegian study, only a small percentage of people are prescribed more than one BZD-Z concomitantly (22).

This study did not consider the usage of long or short-acting BZD as well. It has been shown that long-acting BZD have been linked to a higher risk of falls and fractures than short-acting BZD (39). Underlying medical conditions such as osteoporosis can increase the risk of falls and hip fractures (7), and this was not considered in this study as well. Other fall risk-increasing drugs were not included in this study; a few examples include anti-depressants, anti-hypertensive drugs, neuroleptics and antipsychotics, and nonsteroidal anti-inflammatory drugs (7).

In this thesis dataset, a person could have experienced one or two hip fractures in 2016, this might have overestimated the association between BZD-Z and hip fracture. A possible consideration may be to further study if BZD-Z users were more likely to have two hip fractures compared to non-users. It was also not considered if a person experienced a first, second, or multiple hip fractures. This is because the secondary aim was to “describe” the risk of hip fractures in BZD-Z users compared to BZD-Z non-users, rather than to “investigate”. This thesis does not aim to assess the causal effect of BZD-Z on fractures, and there are numerous confounders not available in the dataset (other than age and gender, as it is aimed to describe only). Because of the small numbers of immigrants, it was not possible to aggregate the

thesis data on background region and explore the association between BZD-Z use and hip fracture stratified on different background regions.

### 5.4 Confounding

In epidemiological research, confounding variables are common and can affect the study's validity. Because of its interaction with both the exposure and the outcome, a confounder will disrupt the association between the exposure and the outcome (86). Age and gender have been regarded as confounders. As mentioned previously, in aim 1, prevalence estimates of BZD-Z usage were adjusted for age to make a fair comparison between background regions. In aim 2, the association between BZD-Z and hip fracture was adjusted for age and gender to minimize confounding.

### 5.5 Validity

#### 5.5.1 Internal Validity (Study Validity)

The degree to which observable findings lead to reliable conclusions about events occurring in the study sample is referred to as internal validity (87). This study has a high internal validity because it is a register-based study. The NorPD and NORHip databases have a high reliability. It has been also aimed to minimize the effect of confounders by using logistic regression and the margins command, to estimate the adjusted prescription prevalence, PR, and OR.

#### 5.5.2 External Validity (Generalizability)

The degree to which findings made from a study can be extrapolated to a larger population than the study group is known as external validity (87). Findings from this study can be generalized to the Norwegian population because this is a nation-wide population study that has represented Norwegians as well as immigrant groups from different places in the world.

# 6. Conclusion:

Higher prevalence of filled prescriptions of BZD-Z were seen in Norwegian females than in female immigrants from outside Norway. However, males from the Middle East had a higher prevalence of BZD-Z use than males from Norway and South Asia. People from South Asia have filled the least prescriptions in both genders. BZD-Z users were found to be more likely to experience hip fractures than non-users. Findings from this study suggest that BZD-Z prescriptions may potentially influence the high prevalence of hip fractures in Norway.

### 6.1 Recommendations

Because of the detrimental consequences of BZD-Z usage, the consideration of non-pharmacological approaches, by practitioners, is recommended for managing insomnia and anxiety in the elderly such as Cognitive Behavioral Therapy. Preventive interventions including drug therapy management, improved nutrition, and elderly-friendly housing arrangements can help to lower the prevalence of falls. Further research compromising other ethnicities, health condition, dosage, and duration of therapy of BZD-Z is encouraged.

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REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

| Region: | Saksbehandler: | Telefon: | Vår dato: | Vår referanse: |
|---|---|---|---|---|
| REK sør-øst A | Hanne Johansen Pekovic | 22845501 | 09.04.2021 | 15538 |
| | | | Deres referanse: | |

Kristin Holvik

**15538 Legemiddelepidemiologi**

**Forskningsansvarlig**: Folkehelseinstituttet

**Søker**: Kristin Holvik

**REKs vurdering**

Komiteen viser til endringsmelding innsendt 26.03.21 for ovennevnte prosjekt (tidligere REK- ref.: 2009/1521). Søknaden er behandlet av sekretariatet i REK sør-øst på delegert fullmakt fra REK sør-øst A, med hjemmel i helseforskningsloven § 11.

Det søkes om å inkludere nye medarbeidere i prosjektet:

- Sonia Rojewski (Stipendiat, FHI).
- Ghazal Almahoud (Masterstudent, FHI)

Følgende medarbeidere har avsluttet sitt arbeid i prosjektet og utgår: Kari Alvær, Lisa Forsén, Ingeborg Hartz, Annette Vogt Hauger, Lena Rogstad Johansen, Annette Løvheim Kleppang, Ida Laake, Katrine Nordby, Bjørn Heine Strand og Margarete Vollrath.

REK har vurdert den omsøkte prosjektendringen og har ingen forskningsetiske innvendinger mot endringen av prosjektet.

**Vedtak**

Godkjent

Komiteen godkjenner med hjemmel i helseforskningsloven § 11 annet ledd at prosjektet videreføres i samsvar med det som fremgår av søknaden om prosjektendring og i samsvar med de bestemmelser som følger av helseforskningsloven med forskrifter.

Vi gjør samtidig oppmerksom på at det etter ny personopplysningslov også må foreligge et behandlingsgrunnlag etter personvernforordningen. Det må forankres i egen institusjon.

Godkjenningen gjelder til 31.12.2030.



**REK sør-øst A**
**Besøksadresse**: Gullhaugveien 1-3, 0484 Oslo
**Telefon**:22 84 55 11 | **E-post**:rek-sorost@medisin.uio.no
**Web**:https://rekportalen.no

Prosjektet skal sende sluttmelding til REK, se helseforskningsloven § 12, senest 6 måneder etter at prosjektet er avsluttet.

Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Opplysningene skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil. Opplysningene skal deretter slettes eller anonymiseres.

Dersom det skal gjøres ytterligere endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende ny endringsmelding til REK.

Vi ber om at alle henvendelser sendes via vår saksportal: https://rekportalen.no

Med vennlig hilsen

Jacob C. Hølen
Sekretariatsleder
REK sør-øst

Hanne Johansen Pekovic
Rådgiver
REK sør-øst

Kopi til: Forskningsansvarlig(e) institusjon(er) og medbruker(e)

**Klageadgang**
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK sør-øst A. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst A, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering.