Country of birth and recurrent fracture risk in forearm fracture patients living in Norway

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ABSTRACT

Introduction Bone fractures are a major global health concern. Osteoporotic fractures affect the elderly, and high-energy fractures are common among children and young adults. Europe and the USA have higher fracture rates than Latin America, Africa, and Asia. Norway has one of the highest rates of fractures. Country of origin and an initial fracture are known factors that could lead to subsequent fractures. It is unclear whether individuals from non-Norwegian backgrounds face the same risk of recurring fractures as Norwegians. This study aimed to assess the risk of subsequent fractures in patients with an index forearm fracture by country of birth.

Methods Data on forearm fractures treated in Norwegian hospitals from 2008 to 2019 were collected from the Norwegian Patient Register. Index forearm fractures were identified by the ICD-10, S52, whereas subsequent fractures included any ICD-10 fracture codes. Information about the country of birth was obtained from Statistics Norway. Age-standardized incidence rates were calculated by dividing the number of fractures by the years at risk after the initial fracture using direct standardization. The data underwent analysis through Cox proportional hazard regression. From the models, age-adjusted hazard ratios and corresponding 95% confidence intervals (CIs) were determined.

Results Out of 143,476 forearm fracture patients, 35,361 experienced a second fracture of any type. The entire cohort of patients with forearm fractures encompassed a total of 767,531 person-years. Within this population, the overall incidence rate (IR) of subsequent fractures was 461 per 10,000 person-years. Women born in Norway had a high IR of recurrent fracture (IR 516 per 10,000 person-years). Norwegian-born individuals had a higher risk of subsequent fracture than most other regions of birth. However, the reported IRs of subsequent fractures were high compared to previously reported overall fracture rates, irrespective of birth category. Among individuals aged 18–44, there was no significant difference in the risk of subsequent fractures across various categories based on the country of birth. Forearm fractures were the most common type of fracture in all ethnic groups.

Conclusion Individuals born outside Norway had a 0–37% lower risk of a recurrent fracture than Norwegian-born patients. The risk of subsequent fractures increased with age in all groups. The observed rate of recurrent fractures surpasses the general fracture rate for people of the same age in Norway. This indicates that patients with an index forearm fracture face a higher risk of sustaining new fractures compared to those without prior fractures. This study suggests providing secondary fracture prevention strategies to all patients with forearm fractures, regardless of their place of birth.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
NoFRACT	Norwegian Capture the Fracture Initiative
WHO	World Health Organization
DXA	Dual-energy X-ray absorptiometry
BMD	Bone mineral density
EVOS	European Vertebral Osteoporosis Study
ICD-10	The International Classification of Diseases, 10th Revision
FLS	Fracture Liaison Services
OUS	Oslo University Hospital
REC	Regional Committee for Medical and Health Research Ethics
NPR	Norwegian Patient Registry
IR	Incidence rate
HR	Hazard ratio
CI	Confidence interval
Health ABC	Health, Aging and Body Composition
CaMoS	Canadian Multicentre Osteoporosis Study
MrOS	Osteoporotic Fractures in Men
WHI	Women's Health Initiative
SOF	Study of Osteoporotic Fractures

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BACKGROUND

In my capacity as a member of the medical community, I have always entertained the idea of helping people live freely and healthfully. To consider this long-term ambition, I decided to do research on common and important health complications. During my master's degree, I realized that bone fractures represent a critical global health issue and they are more common in Europe and the USA than in other parts of the world, with Norway experiencing significantly high rates (1, 2). Also, recent reports show an increase in fracture risk in Asian countries, including my country of birth (3, 4). However, the reasons behind this increase remain unclear.

This encouraged me to focus my master's thesis on fracture risk. Specifically, I got motivated to study the subsequent fracture risks among individuals residing in Norway and investigate whether individuals with non-Norwegian backgrounds have the same risk of subsequent fractures as the general Norwegian population.

This thesis is part of a larger project, the NoFRACT project: Norwegian Capture the Fracture Initiative. The NoFRACT project is a multi-center study concentrated on preventing secondary fractures. In the NoFRACT study, many dedicated nurses, physicians, and scientists worked, registered, and followed the fracture patients. The primary goal of the NoFRACT study is to assess the effectiveness of an intervention involving the implementation of a standardized program for evaluating and treating bone fragility in patients who have fractured and received fracture liaison services (FLS). The FLS are strategically designed to prevent subsequent fractures and enhance the overall scope of preventive interventions (5, 6).

In this cohort study, data from the Norwegian Patient Registry, the National Population Registry, and Statistics Norway were combined. I have accessed the data used in this thesis project via the TSD system and through working with my supervisors, who are members of the NoFRACT study.

With the guidance of my supervisors, we devised a research focus on forearm fracture patients from different ethnic backgrounds, examining their recurrent fracture risk. This choice was informed by the fact that forearm fractures rank among the most common types of fractures observed in Norway. This thesis aims to investigate the association between country of birth and recurrent fracture risk in forearm fracture patients living in Norway. It also aims to calculate the incidence rates of subsequent fractures among individuals from different countries of origin. The thesis consists of a paper that is to be submitted to Osteoporosis International, a level 2 journal with a relatively high impact factor.

CHAPTER 1: INTRODUCTION

Scandinavian countries are considered to have high rates of bone fragility, osteoporosis, and osteoporotic fractures. Norway also has the highest rates of bone fractures in the world (7, 8). Fractures are a global health problem that leads to a variety of clinical, social, and economic complications and affects populations and societies (9, 10). As the population ages and the number of older people increases in the future, the risk and rate of fractures and their associated health and socioeconomic burdens will increase (11). Fractures are associated with a significant burden of complications, including pain, loss of function, hospitalization, and long-term care (12, 13). Research into the epidemiology of osteoporosis and fractures is critical for targeting those at risk and improving treatment.

1.1 Osteoporosis

1.1.1 Osteoporosis definition

Osteoporosis is one of the most common metabolic and systemic skeletal diseases. It is caused by an imbalance of bone resorption and bone remodeling (14) and is characterized by decreased bone quality and a lower density of mineralized bone, leading to bone fragility and low bone strength. This in turn leads to chronic pain and a high risk of osteoporotic and low-energy fractures (15, 16). Osteoporosis is becoming an increasing burden on healthcare and healthcare systems around the world (17).

1.1.2 Epidemiology of Osteoporosis

According to global studies, over 200 million people have osteoporosis, and almost 70% of people over 80 years old are affected. Globally, approximately 16% of young women have low bone mass and 0.6% have osteoporosis, while in developed areas, 2% to 8% of men and 9% to 38% of women experience osteoporosis (18-20). According to estimates, 10 million Americans over the age of 50 have osteoporosis, and an additional 34 million are at risk for the condition (21).

1.1.3 Diagnosis of Osteoporosis

The diagnostic criteria for osteoporosis are based on the measurement of bone mineral density, known as dual-energy X-ray absorptiometry (DXA), established by the WHO (22, 23). Low bone mineral density (BMD) can lead to bone fragility and osteoporosis (24). A dual-energy x-ray absorptiometry scan measures BMD, which is expressed as the t-score and the z-score (25). The t-score is the difference

between the patient's bone mineral density and the mean bone mineral density in young adults. It is measured in standard deviations. According to the WHO, normal bone mineral density in women is defined as a t-score that is within one standard deviation of the young adult mean. Values between minus 1 and minus 2.5 can be defined as osteopenia, while values below minus 2.5 indicate a diagnosis of osteoporosis (25, 26).

1.1.4 Primary osteoporosis

There are two different categories of osteoporosis: primary and secondary osteoporosis. Primary osteoporosis is the most common form of the disease and includes postmenopausal osteoporosis and senile osteoporosis (27). Postmenopausal osteoporosis, which is common in women, is associated with a physiological process in bone in which the loss of estrogens and androgens leads to increased bone turnover, with more bone resorption than bone formation and a predominance of loss of trabecular bone compared with cortical bone (16, 27, 28). Senile osteoporosis, which occurs in both men and women, is a result of age-related bone loss. It is caused by the loss of stem cell precursors, with the loss of cortical bone predominating (16, 28).

1.1.5 Secondary osteoporosis

Secondary osteoporosis is more common in men and may occur after medical problems such as hyperparathyroidism, anorexia, and malabsorption or medications such as corticosteroids and antiepileptic drugs. These causes negatively affect the achievement of maximum bone mass and bone health and also contribute to bone remodeling and bone fragility (25, 29).

1.2 Fractures

1.2.1 Fractures definition

A bone fracture is a break or crack in a bone caused by a direct or indirect force when the force applied to the bone is greater than the stress that the bone can structurally withstand (30).

1.2.2 Osteoporotic fractures

Osteoporotic fractures are fractures caused by osteoporosis in which the bone structure is damaged to such an extent that the bone becomes fragile and prone to fracture. Fragility fractures, often resulting from low-energy trauma, constitute an important public health problem, especially among the elderly, and lead to substantial pain and suffering for patients and substantial costs to society (1, 31).

Low-energy fractures occur after falling from a non-elevated standing or sitting position or from natural or physiological pressure on weakened bones, and they are more common among the very active young and the elderly (29, 32). Other causes of low-energy fractures are malignancy, inflammation, overexposure to vitamin A, Brucellosis, and osteodystrophy due to chronic renal failure (32). The most common osteoporotic fractures include fractures of the forearm, hip, and spine (33, 34).

1.2.3 Epidemiology of Osteoporotic Fractures

It is documented that the risk of osteoporotic fractures is generally higher in women than men and increases with age (35). Worldwide, approximately 9 million osteoporotic fractures happen per year (19). The prevalence of fractures is higher in high-income countries than in low- and middle-income countries. A total of 50% of women and 20% of men in high-income countries experience osteoporotic fractures in their lifetimes (1, 36). It is estimated that approximately 2.7 million fragility fractures occur annually in Europe, resulting in direct costs of 36 billion euros (37).

1.2.4 High-trauma fractures

High-trauma fractures, as opposed to fragility fractures or low-trauma fractures, are brought on by car accidents and falls that are higher than standing height (38). Also, high-energy trauma from sports and incidents involving vehicles is more likely to cause fractures in children, adolescents, and young adults, mainly men (39-41). Some studies also reported that high-trauma fractures are associated with low BMD, thereby increasing the risk of skeletal fragility and recurrent fractures in later life (38, 42, 43).

1.2.5 Epidemiology of high-trauma fractures

In contrast to osteoporotic fractures, the risk of high-energy fractures is higher in men than women. According to an American study, high-trauma fractures accounted for more than twice as many fractures overall in men 65 or older (21%), compared to older women (9%) (38). It is also documented that almost one-third of children sustain at least one fracture before 17 years of age (41, 44).

1.2.6 Diagnosis of fractures

A fracture is identified through a physical examination and imaging studies; such as X-rays or CT scans. Using imaging testing, the doctor can precisely identify the fracture's site and nature (45). The use of ultrasound for the detection of fractures, particularly pediatric fractures, has grown recently because of the advantages of reducing radiation and also because of the diagnostic difficulties for plain X-rays generated by the cartilaginous elements of the immature pediatric skeleton (46).

1.2.7 Distal forearm fractures

One of the most common fractures, both in children and adults, is a forearm fracture, also known as a wrist fracture. The spectrum of forearm fractures includes isolated radius and ulna fractures, combined fractures, Galeazzi fractures, and Monteggia fractures (47). Among all types of forearm fractures, the most common one is a fracture at the distal radius, or ulna (32.9%), and the least common site is the proximal region (2.8%) (48, 49).

Forearm fractures have a higher incidence rate in the pediatric population than adults, and in the USA, the annual incidence rate is around 1 in 100 children (48, 49). The rates of forearm fractures are high in Scandinavian areas compared to other countries, with about 15,000 occurrences of wrist fractures in Norway (8).

Forearm fractures may occur after low-energy or high-energy trauma, and falling on an outstretched hand is considered the most common cause of forearm fractures (50). Also, motor vehicle accidents, falls from a height, and sports injuries are other causes of this type of fracture (51). Studies show that people who have had a distal forearm fracture are more vulnerable to a subsequent forearm fracture or any other type of fracture (52).

1.2.8 Other types of fracture

Hip and vertebral fractures are also common types of fractures in society, which require emergency and orthopedic teams (33, 53). Hip fractures are more common among the elderly population as a result of a fall. Elderlies are exposed to multiple risk factors for fractures, such as age-associated reduced bone quality. Hip fractures that occur among younger adults are often caused by high-energy trauma or accidents (53, 54).

It is estimated that the global number of hip fractures will increase from 1.26 million in 1990 to 4.5 million by the year 2050 (34). The Centers for Disease Control and Prevention of the USA have published that over 300,000 elderly people in the USA, over the age of 65, are hospitalized for hip fractures annually (55). Additionally, the number of osteoporosis-related fractures in the United States is expected to triple as the population ages (56, 57). Scandinavian countries are also among the high-risk areas for hip fractures. Norway has the highest rates of hip fractures worldwide, and about 9,000 hip fractures occur each year in Norway (58).

Vertebral fractures can occur in the mid-thoracic or thoracolumbar sections of the spine after falling, lifting heavy things, or, in 50% of cases, without a traumatic event (59). Rest and medication can

help mend minor spine fractures, but surgery to straighten the bones may be necessary for more serious fractures. Untreated spinal fractures can result in irreversible spinal cord injury, nerve damage, paralysis, and an increased mortality risk. Vertebral fractures can have a catastrophic impact on a patient's health and quality of life (60).

More than 1.5 million Americans are affected by vertebral fractures each year, with 10.7 per 1000 women and 5.7 per 1000 men (61, 62). Scandinavian regions seem to have higher rates of vertebral fractures than other nations (63). The frequency of vertebral deformities in Oslo residents aged 50 to 80 years was 19.2% in women and 15.7% in men, according to the European Vertebral Osteoporosis Study (EVOS) (64).

1.3 Consequences of fractures

Fractures negatively affect the quality of life and health of individuals and the economic costs of society (65, 66). Decreased mobility, facing difficulties in working life and social activities, long-term performance decline, and increased mortality risk are important consequences of fractures in general (67-70). Disability and comorbidity caused by fractures increase the need for nursing homes and the burden of healthcare costs (70, 71).

Studies have shown that osteoporotic hip fractures are linked to a higher risk of coronary heart disease and are associated with 10–20% mortality during the first year after the fracture (72). A research conducted in Norway, involving nearly 80,000 patients who experienced their first hip fractures, found that the greatest increase in mortality rates happened within the initial two weeks following the fracture. While the excess mortality decreased over time, it remained higher than normal for more than a decade after the fracture. The study revealed that within the first year after a hip fracture, the mortality rate was approximately five times higher for men and three times higher for women compared to the general Norwegian population. Additionally, regardless of the time interval after the incidents, men consistently had a higher excess mortality rate than women (69). Almost half of the patients sustaining hip fractures experience physical difficulties and disabilities (73).

A meta-analysis in 2010 reported that women and men with a hip fracture may have a 5- and 8-fold increased risk of dying from any cause within the first 3 months after the fracture, respectively (74). It is estimated that only 33% of old women who sustain a hip fracture can return to independence (25), and nearly one-third need nursing at home after hospital discharge (75). Furthermore, the economic

burden of fractures is high, as osteoporotic fractures cost the US healthcare system approximately $17 billion each year, and it is predicted that the cost will rise to $50 billion by the year 2040 (76).

1.4 Risk factors for fractures

1.4.1 General risk factors for osteoporosis and fractures

There are a wide range of risk factors contributing to fractures. The most important ones are sex, age, nutritional status, genetics, obesity, family history of fracture, physical activity, calcium and vitamin D deficiencies, bone fragility, osteopenia, menopause, smoking, some medications such as corticosteroids, antiepileptic medicines, and cancer medications, and some diseases, like rheumatoid arthritis (7, 77-79).

The risk of fracture is high in the following groups: elderlies, women, smokers, individuals with a prior history of a fracture, those who use corticosteroids, people with a high intake of alcohol, and those with low BMD and symptoms of secondary osteoporosis. Factors affecting the risk of falls are also contributing to fractures (14, 25, 80).

Contingent to normal bone structure, BMD predicts bone strength; a low BMD level contributes to bone fragility and defines osteopenia and osteoporosis. Therefore, there is a strong association between the probability of fracture and the BMD level (23, 24, 77, 79). Moreover, some studies indicate that country of birth and/or ethnicity can also represent a risk factor for fracture (81). Bone mineral density, bone microarchitecture, bone strength, and factors related to the risk of falling vary in populations in different geographical areas, probably due to both genetic and environmental causes (82, 83).

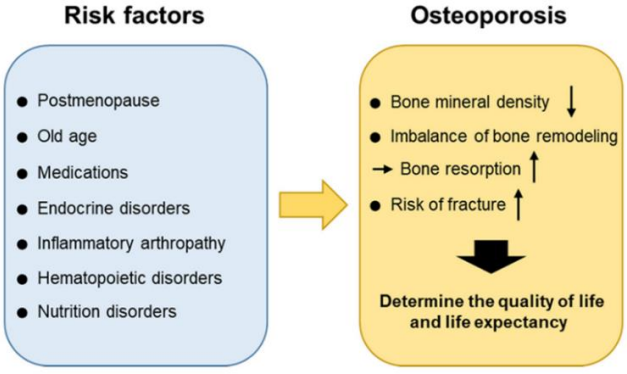

Figure 1.1 Risk factors for osteoporosis and associated fractures. Certain risk factors can disrupt the natural remodeling process, potentially leading to the development of osteoporosis (84)

1.4.2 Geographic and ethnic differences in fracture risk

Some studies have been carried out to measure the risk of fractures among people of different ethnicities, which have revealed that the incidence rate and risk of fractures vary considerably between people in different regions in the world, with higher occurrences in developed countries such as Northern America and Northern Europe compared to developing countries like Asia, Latin America, and Africa (1-3). In comparison to other Asian nations, Taiwan, Japan, Singapore, Kuwait, Iran, and Oman are categorized as high-risk countries for fractures (3, 4).

The low incidence rate of fracture in Africa and most of Asia might be explained by several reasons, including genetic and biologic variation in the skeleton, shorter life expectancies, and physical activity levels (2, 85). According to studies, people of different ethnicities have diverse bone macro- and microstructures; Chinese and Africans have more strong bone architecture (85), and different bone geometry (86).

However, the world's population demographics are changing, with more adults residing in Asia, which results in an increase in fractures in this area, and it is predicted that by 2050, half of all hip fractures will be sustained in Asia (2). Furthermore, population growth is high in the Middle East, Central and East Asia, and Latin America. These countries are anticipated to account for more than 70% of the 6.26 million hip fractures predicted by 2050 (87).

People of different genetic backgrounds living in the USA also have different risks of osteoporosis, as black men and women have less osteoporosis compared to white residents, but those diagnosed with osteoporosis have similar fracture risks (57, 88, 89).

In Europe, there is a north-south gradient in the risk of fracture; prevalence and incidence rates of fractures are higher in North and Nordic countries than in other parts of Europe (2, 35). A study in Sweden reported that the average fracture incidence in this country was 1,229 per 100,000 individuals per year (90).

In Norway, between 1999 and 2008, there were a total of 93,123 hip fractures reported in individuals aged 50 years and above. Among these hip fracture patients, 71% were women (91). According to a Norwegian research, there were 9182 hip fractures on average annually in Norway between 2002 and 2013. The age-standardized rate of hip fractures per 10,000 person-years varied throughout counties, ranging from 34 to 41 for men and from 69 to 84 for women. Women living in Oslo had the greatest rate of hip fractures (92).

It is documented that latitude, sun exposure, and vitamin D play a role in fracture risk (93, 94). Also, research conducted in Sweden found that areas located at higher latitudes experienced higher incidence rates of hip fractures (95), but some studies in Norway reported an opposite trend in fracture risk within the country, as higher incidence rates of hip fractures have been observed in residents in Oslo compared to other parts of the country with a higher latitude (92, 96, 97).

The reasons are not completely understood, but genetic and environmental differences are likely to influence the risk of fractures since these two causes can affect BMD, bone strength, the rate of bone loss, and factors related to the risk of falling, but none of these factors can explain the differences in fracture risk alone (82).

1.4.3 Migration and fracture risk

Migration may have an influence on health in many ways, and the effect of migration varies among different immigrant groups. Generally, over time, it is seen that the risk of disease among immigrants assimilates to the population that they immigrate to. Swedish studies reported that immigrants typically experience a lower risk of fractures compared to the native population (98-100), but second-generation immigrants in Sweden were shown to have a comparable incidence of osteoporotic fractures (first fractures) as Swedish natives did, suggesting that lifestyle and environmental variables may be the main contributors to the risk of fractures in Nordic countries (101).

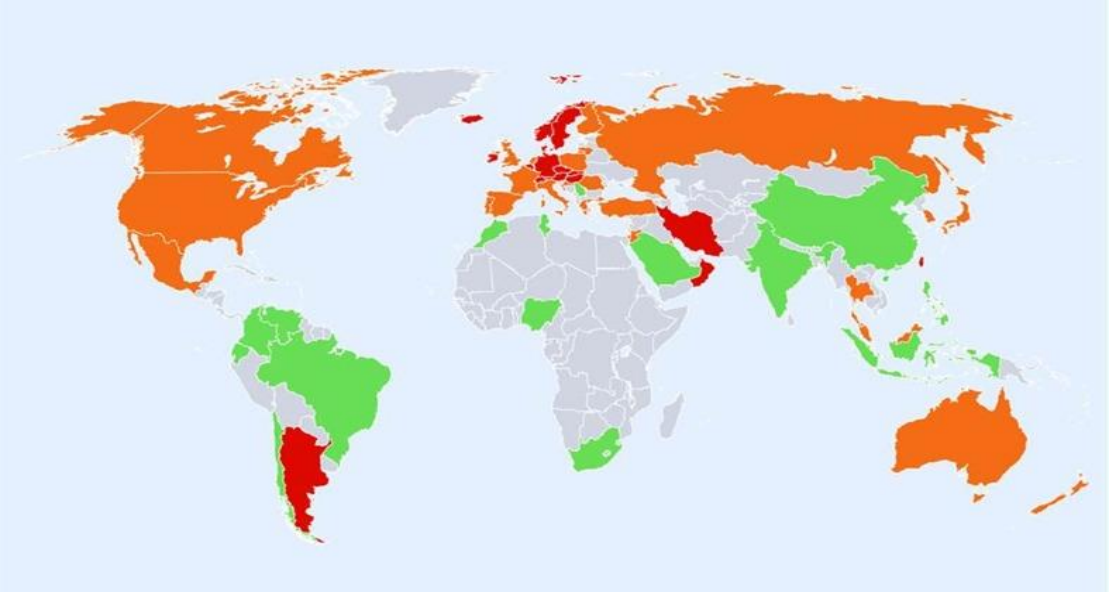

Figure 1.2 Hip fracture rates for men and women in different countries of the world categorized by risk. Countries are color-coded red (annual incidence >250/100,000), orange (150–250/100,000), or green (<150/100,000) (3)

1.5 Recurrent fracture risk

Studies show that the risk of recurrent fractures after any previous fractures is high among both men and women and increases with age (102-105). The skeletal site of the initial fracture may also affect the risk of a subsequent fracture (106, 107). The negative consequences of recurrent fractures are even more than an initial fracture; for instance, the Framingham Heart Study in the USA studied the mortality risk after fractures, demonstrating that the mortality rate after one year of the first hip fracture was 15.9%, while the mortality rate after one year of the second hip fracture was 24.1%; the results were not adjusted for age (108).

The risk of experiencing a recurrent hip fracture varies from 2% to 20% in different studies (102, 109, 110). The Tromsø study in Norway included 3108 individuals with a first fracture after the age of 49. The outcome showed that the risk of sustaining a recurrent fracture increased with age, from 9% to 30% for women and 10% to 26% for men. The findings also showed that 26% of women and 18% of men over the age of 80 with any prior fractures sustain a subsequent fracture, regardless of their high mortality risk (104).

An Australian study examined the risk of a second fracture following a low-energy fracture with The International Classification of Diseases, 10th Revision (ICD-10) codes S22-S82—fractures of the rib(s), lumbar spine, shoulder, and upper arm, forearm, wrist, femur, hip, and lower leg—and found a cumulative incidence of 7.1% at one year and 13.7% at five years for women, and 6.2% at one year and 11.3% at five years for men (111). Furthermore, a study conducted in Canada found that children aged 0 to 15 who experienced a fracture as youngsters had a higher probability of experiencing a recurrent one in the future than those who did not sustain a fracture (42).

The risk of subsequent fractures following the initial fracture decreases over time (112, 113). A retrospective cohort study in the USA studied women over 65 with a fracture, regardless of fracture site except the skull, face, fingers, toes, patella, sternum, scapula, or ribs, in order to examine the risk of recurrent fractures. The study indicated that 10%, 18%, and 31% of women fractured again within 1, 2, and 5 years of the first fracture, respectively. 35% of second fractures occurred in the first year after the previous one. Also, among all subsequent fractures, the risk of hip fracture within 1, 2, and 5 years following any initial fracture was 2.4%, 4.8%, and 10.2%, respectively (112). Additionally, a study conducted in Sweden revealed that women who have experienced an osteoporotic fracture in the past face a higher risk of suffering another fracture, especially within the initial 24 months after the initial fracture (114).

A meta-analysis conducted in 2004, involving 15,259 men and 44,902 women from 11 cohorts, found that individuals with a history of previous fractures had a significantly higher risk of any fracture compared to those without prior fractures (Relative Risk = 1.86; 95% Confidence Interval = 1.75–1.98) (102). A recent meta-analysis of 46 cohorts in 32 countries also found that a previous fracture significantly increased the risk of sustaining a subsequent fracture but that the risk decreased slowly over time. The study also reported that a prior fracture was linked to a significant increase in the risk of mortality in both women and men (113).

1.6 Rationale for the project

Forearm fractures are the most common type of fracture in Norway, and the overall incidence of forearm fractures in Norway is higher than in other countries (8). Several prior studies have concentrated on hip fractures since these fractures are easier to study in register-based data, as hip fractures are surgically treated in hospitals and are more likely to be registered, at least in Western Europe (115). In contrast, forearm fractures can be treated in both primary and specialist care and, depending on severity, can be treated either conservatively (often in emergency units) or surgically in hospitals. Forearm fractures are therefore more difficult to investigate due to the variety of treatments available.

Any form of prior fracture at any age is linked to a significant risk of recurrence. Previous studies highlighted the need for timely management to control and reduce the risk of subsequent fractures (102-104). Compared to studies of first fractures, there is less research focusing on subsequent fractures among immigrant populations.

The population of immigrants in Norway is growing continuously (116). The total and first fracture risk have been found to be lower in immigrants (8, 117), but it is not known whether recurrent forearm fracture risk varies by country of birth in a high-risk population like Norway. Although it is well documented that a previous fracture increases future fracture risk (102), it is important to know to what extent this applies to all groups, irrespective of country of birth. Therefore, it is significant to study the role of ethnicity and country of birth on recurrent fracture risk among people residing in Norway.

1.7 Aim and Objectives of the study

1.7.1 Aim

The overall aim of this project was to study the association between country of birth and the risk of recurrent fractures in individuals living in Norway with a first forearm fracture. This might contribute to targeting at-risk residents and providing better preventive, diagnostic, and therapeutic interventions, as well as decreasing the clinical and socio-economic inequalities of recurrent fractures.

1.7.2 Primary objectives of this study

The primary objectives of this cohort study were to:

1. Estimate the incidence of recurrent fractures in the Norwegian general population over 18 years of age.
2. Estimate the incidence of recurrent fractures among individuals living in Norway aged over 18 and born in other European countries and North America.
3. Estimate the incidence of recurrent fractures among citizens living in Norway aged over 18 born in other countries in the world in the four subgroups of Africa, Central and South America, the Middle East, and Central and Southeast Asia.
4. Compare the age-adjusted incidence rates of recurrent fractures in the mentioned populations.
5. Estimate the incidence of recurrent fractures among the individuals grouped into three different groups by age, namely 18–44, 45–59, and 60 and above.

CHAPTER 2: MATERIALS AND METHODS

2.1 Project organization

This study population consisted of all Norwegian citizens above 18 years of age seeking public health care for treatment of a fracture between 2008 and 2019. This project used data from the Norwegian Patient Registry and Statistics Norway through the Norwegian Capture the Fracture Initiative (NoFRACT) study.

2.1.1 The Norwegian Capture the Fracture Initiative (NoFRACT)

The NoFRACT study is a large cross-regional study on prevention of recurrent fractures introduced to seven Norwegian hospitals, namely Trondheim, Ullevål, Tromsø, Bergen, Molde, Drammen and Bærum. Several nurses, orthopedic surgeons, endocrinologists, rheumatologists, scientists and researchers from hospitals and universities in four health regions in southeastern, western, central, and northern Norway collaborated in this patient-oriented clinical research project.

The NoFRACT study is the first fracture liaison services (FLS) study in Norway with a stepped wedge cluster randomized clinical trial design and a unique project to investigate and evaluate the impact of establishing a standardized intervention program on fracture rates and associated comorbidities. Osteoporosis drugs, fall prevention strategies, and lifestyle recommendations are all part of the interventions, which also entail thorough follow-up (5, 6).

2.1.2 Fracture Liaison Services

A fracture liaison services model of care with a specialized coordinator and a systematic method to detect, evaluate, and treat patients with osteoporosis-related fragility fractures has been implemented in various locations (118, 119). It has been demonstrated that FLS programs boost referrals to bone mineral density (BMD) assessments utilizing dual-energy x-ray absorptiometry for osteoporosis screening (119). In a Swedish minimal FLS, the proportion of individuals who received osteoporosis assessments rose from 8% to 40%, and the treatment rate rose from 13% to 32%. Additionally, compared to individuals who did not receive therapy, those who did had a 51% lower chance of recurrence of fractures (120).

2.1.3 Reference group in the NoFRACT study

Reference group in the NoFRACT study are Åshild Bjørnerem (project chair), Lene B Solberg (project coordinator), May-Britt Stenbro (coordinator of the project nurses), Lars Nordsletten

(responsible for the budget which is located at OUS, Oslo), Tone K Omsland (responsible for register data), Cecilie Dahl (responsible for data management), Trude Basso (responsible for the project web site), Frede Frihagen, Tove T. Borgen, Wender Figved, Erik F. Eriksen, Unni Syversen, Ellen Apalset, Ida Lund.

2.2 Study setting

Norway is a country in Northern Europe with borders with Sweden, Finland, and Russia. It has about 5.5 million inhabitants and is expected to exceed 5.7 million by 2030. Also, life expectancy in Norway is among the highest in the world, at about 83 years (81.7 years for men and 84.7 years for women) (121).

2.3 Definition of the outcome - incident fractures

All types of fractures were defined through standardized ICD-10 codes for diagnosis in the Norwegian health care system: The International Classification of Diseases, Tenth Revision (ICD-10): S22, S32, S42, S52, S62, S72, S82, and S92, including all subcategories (Table 2.1). Registrations with ICD-10 codes for follow-up visits were excluded, except for first-time registrations with a code for follow-up examination, as some patients with fractures receive initial treatment in primary care (without reporting to the NPR) before being referred to a hospital, and consequently, incident fractures are sometimes coded as a follow-up visit (122).

Table 2.1 The International Classification of Diseases, 10th Revision (ICD-10) for fractures

No.	ICD-10	Type of fracture
1	S22.x	Fracture of rib(s), sternum and thoracic spine
2	S32.x	Fracture of lumbar spine and pelvis
3	S42.x	Fracture of shoulder and upper arm
4	S52.x	Fracture of forearm
5	S62.x	Fracture at wrist and hand level
6	S72.x	Fracture of femur and hip
7	S82.x	Fracture of lower leg, including ankle
8	S92.x	Fracture of foot, except ankle

2.4 Data management

A thorough data cleaning process was carried out, focusing on rectifying erroneous coding and ensuring accurate coding of fracture follow-ups or sequelae. Without this cleaning, these issues could have been misinterpreted as multiple fractures. To accommodate multiple registrations for the same fracture, a wash-out time of 6 months (within each fracture category) was implemented. The surgical code for reoperation was also excluded from records. The algorithm used for defining forearm fractures was recently validated and is reported to have a sensitivity of approximately 90% and a positive predictive value of 90% (123).

2.5 Observation time

The maximum observation time for the study was 12 years, from January 1, 2008, to December 31, 2019. All individuals who sustained an index fracture of the forearm (any S52 fracture) were included in the study and observed for any type of subsequent fracture. Person-time in the analyses was calculated as the time from the index forearm fracture to the subsequent fracture or censoring (emigration, death, or end of study).

2.6 Main exposure categories

Individuals were categorized into six different groups based on assumed geographic similarities: Norway, other European countries and North America, Central and Southeast Asia, Africa, the Middle East, and Central and South America. Due to relatively few subsequent fractures among populations in some areas, individuals were also classified into three main groups, namely Norway, European countries and North America, and Other countries. We excluded 990 individuals (0.69% of the total population) without information about their country of origin.

2.7 Sub-group analyses

The patients were divided into three groups based on age: 18–44, 45–59, and 60 and above, to evaluate the risk and incidence rates in different age groups.

2.8 Statistical analyses

Descriptive analyses and survival analyses were performed by STATA 16. Age-standardized incidence rates (IRs) were computed by dividing the number of fractures by the number of years at risk

following the first fracture, using a direct standardization method. This method is employed to compare groups with varying characteristics, ensuring adjustments for the differences between the groups and enabling a more accurate comparison (124). The figures were reported as the number of fractures per 10,000 person-years. Cox proportional hazard models were used to calculate the risk of a recurrent fracture as a function of country of birth, categorized into the six geographical groups, adjusted for differences in age, and stratified by sex. Log minus log curves were evaluated regarding the assumption of proportional hazards, and the assumptions were considered fulfilled. The Kaplan-Meier curve is used for estimating the survival function based on the time to the occurrence of the fracture. Age-adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were obtained from the models. Two-sided p-values <0.05 were deemed significant.

2.9 Ethics

The present study and the linkage of data from the Norwegian Patient Registry (NPR) were approved by the Regional Committee for Medical and Health Research Ethics (REC), with application number 2015/334 and reference number 26953, and the Directorate of Health, with reference number 17/25552-37. The University of Oslo performed a Data Protection Impact Assessment (DPIA) in accordance with the General Data Protection Regulation.

CHAPTER 3: RESULTS

3.1 Descriptive analyses

Among the 143,476 individuals with a forearm fracture included in the study, 100,553 were women, with a mean age at first forearm fracture of 61 years, and 42,923 were men, with a mean age at first forearm fracture of 49.7 years. The age distributions were examined, and no significant differences were found between the median and mean age of the forearm fracture. Consequently, the mean age was reported (data not shown).

A total of 127,431, 10,537, and 5,508 people were born in Norway, other European countries or North America and Other countries, respectively, with a mean age of 59, 48.6, and 44.3 years at the time of the first forearm fracture. Among the individuals born in Other countries, 2,017 were from Central and Southeast Asia, 1,514 from Africa, 1,397 from the Middle East, and 580 from Central and South America, with a mean age at first forearm fracture of 46.4 years, 41.5 years, 43.5 years, and 45.8 years, respectively.

The total number of person-years for the whole cohort of forearm fracture patients was 767,531, and the total incidence rate (IR) of a subsequent fracture in the included population was 461 (95% CI 456-466) per 10,000 person-years. Of the included individuals, 35,361 (24.6%) experienced a subsequent fracture of any type, of which 75.4% were women and 24.6% were men. Among persons with a second fracture, 32,664 were Norwegian-born, 1,899 were from other European nations or North America, and 798 were from Other countries (Table 3.1).

Table 3.1 Number of individuals aged +18 years in 2008–2019 with first forearm fracture and any types of second fractures categorized by country of birth (six groups), mean age of first forearm fracture with 95% confidence interval

Country of Birth[1]	First forearm fracture (*N*)	Mean age (SD)	95% Conf. Interval	A second fracture (*N*)
Norway	127,431	59.0	58.9 – 59.1	32,664
Europe and North America	10,537	48.6	48.3 – 48.9	1,899
Central and Southeast Asia	2,017	46.4	45.8 – 47.1	275
Africa	1,514	41.5	40.1 – 42.1	229
Middle-East	1,397	43.5	42.7 – 44.2	189
Central and South America	580	45.8	44.6 – 47.0	105
Total	143,476	57.7	57.6 – 57.8	35,361

[1] Obtained from Statistics Norway

3.2 Survival analyses

3.2.1 Subsequent fracture risk according to country of birth

The IR of subsequent fractures in Norwegian-born women was 516 per 10,000 person-years, which was higher than the IRs of most, but not all, other regions of birth categories. Women from other European countries or North America had an IR of 406, which was significantly lower than the rate in Norwegian-born women. IRs for women born in other countries than Europe and North America ranged from 230 per 10,000 person-years in the Middle East to 373 per 10,000 person-years in Central and South America (Table 3.2). Subsequent fracture risk expressed as HRs in women born in Central and South America and Africa was not significantly different from Norwegian-born women.

Norwegian-born men had an IR of subsequent fractures at 380 per 10,000 person-years, whereas the IR for men born in other European countries or North America was 303 per 10,000 person-years. The IR for men born in other countries than Europe and North America ranged from 259 per 10,000 person-years in Africa to 356 per 10,000 person-years in men born in Central and South America (Table 3.2). Rates in men from the Middle East and Central and South America were not significantly different from the rates in Norwegian-born men.

The Kaplan-Meier survival curve demonstrated that the highest proportion of recurrent fractures was found among Norwegian-born individuals, where about 40% of patients with an index forearm fracture sustained a subsequent fracture of any type during the 12 years of follow-up. The lowest proportions of subsequent fractures (25%) were observed among people born in Africa, the Middle East, and Central and Southeast Asia, whereas the proportions of subsequent fractures in individuals from Europe and North America, and Central and South America were medium-high (Figure 3.1).

Table 3.2 Number of individuals aged +18 years in 2008–2019 (*N*), number of second fractures, age-standardized incidence rates (IR) per 10,000 person-years, and age-adjusted hazard ratios (HR) of recurrent fracture with 95% confidence interval (CI) for the different countries of birth (six groups)–stratified on sex

	N	**No. second fracture**	**IR**	**95% CI**	**HR**	**95% CI**
Women	**100,553**	**26,654**				
Norway	91,409	24,979	516	509-522	1	(Reference)
Europe and North America	6,007	1,215	406	384-429	0.93	0.88-0.98
Central and Southeast Asia	1,297	177	249	215-289	0.66	0.57-0.77
Africa	828	139	320	271-378	0.96	0.81-1.13

Middle-East	641	75	230	183-288	0.63	0.5-0.79
Central and South America	371	69	373	295-472	0.98	0.77-1.23
Men	**42,923**	**8,707**				
Norway	36,022	7,685	380	372-389	1	(Reference)
Europe and North America	4,530	684	303	281-326	0.85	0.79-0.92
Central and Southeast Asia	720	98	271	222-330	0.77	0.63-0.94
Africa	686	90	259	211-319	0.76	0.62-0.94
Middle-East	756	114	307	255-369	0.88	0.73-1.06
Central and South America	209	36	356	257-494	1.03	0.74-1.43

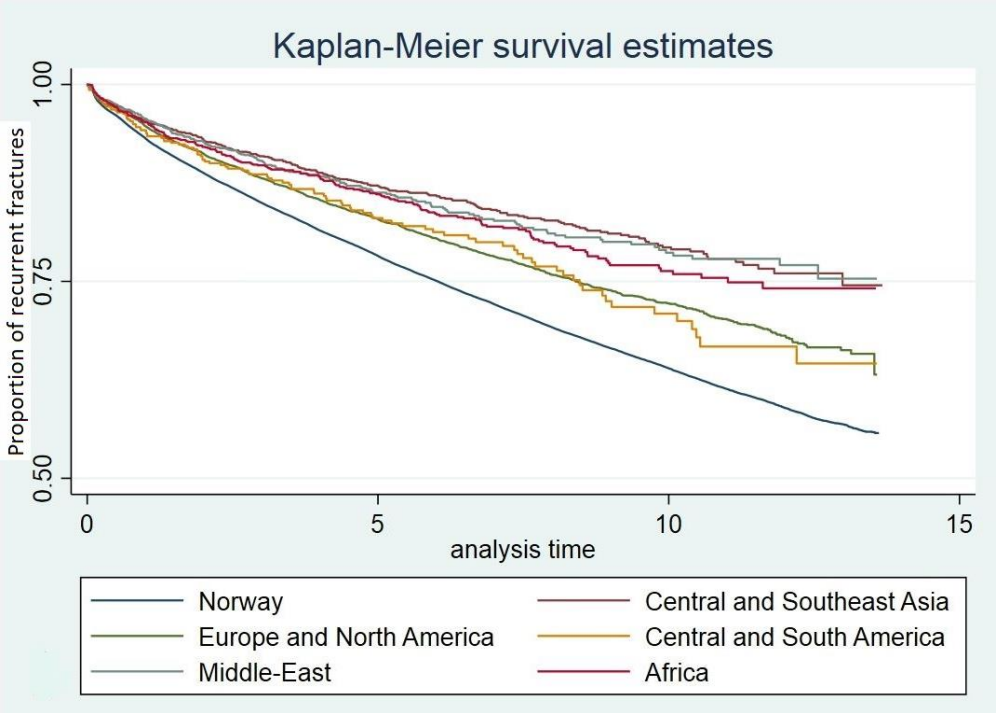

Figure 3.1 Kaplan-Meier survival estimates for the different countries of birth (six groups)

3.2.2 Subsequent fractures according to age

The incidence rates increased from 280 per 10,000 person-years among Norwegian-born individuals aged 18–44 years to 616 per 10,000 person-years among Norwegian-born individuals aged over 60 years. Although not significant in all subgroups, subsequent fracture risk tended to increase in

most regions of the birth category (Table 3.3). In people aged 18–44, the risk of subsequent fracture did not differ significantly between the regions of birth. On the other hand, in people aged 45–59 years, HRs were significantly lower than Norwegian figures in all other categories, except for those born in Central and South America and Africa. With an IR of 616 per 10,000 person-years, Norwegian-born people over 60 had a higher IR compared to all other categories, except for those born in the Middle East (Table 3.3).

Table 3.3 Number of participants aged +18 years in 2008–2019, divided into three age groups (*N*), number of second fractures, age-standardized incidence rates (IR) per 10,000 person-years, and age-adjusted hazard ratio (HR) of recurrent fracture with 95% confidence interval (CI) for the different countries of birth (six groups)

	N	No. second fracture	IR	95% CI	HR	95% CI
Age 18-44	**35,547**	**5,666**				
Norway	26,970	4,635	280	271-287	1	(Reference)
Europe and North America	4,662	644	273	253-295	0.91	0.84-0.99
Central and Southeast Asia	924	118	238	199-285	0.83	0.69-1.00
Africa	945	130	260	220-310	0.89	0.75-1.06
Middle-East	768	94	246	201-301	0.82	0.66-1.00
Central and South America	278	45	330	246-441	1.13	0.85-1.52
Age 45-59	**37,712**	**8,688**				
Norway	32,795	7,866	407	398-416	1	(Reference)
Europe and North America	3,115	536	343	315-373	0.85	0.78-0.93
Central and Southeast Asia	701	95	246	201-301	0.59	0.49-0.73
Africa	437	79	370	296-461	0.93	0.75-1.16
Middle-East	465	67	280	220-355	0.71	0.56-0.91
Central and South America	199	45	447	334-599	1.08	0.81-1.45
Age +60	**71,217**	**21,007**				
Norway	67,666	20,163	616	608-625	1	(Reference)
Europe and North America	2,760	719	539	501-580	0.92	0.85-0.99
Central and Southeast Asia	392	62	327	255-420	0.65	0.51-0.84
Africa	132	20	288	186-446	0.53	0.34-0.82
Middle-East	164	28	365	252-530	0.71	0.49-1.02
Central and South America	103	15	309	187-512	0.58	0.35-0.82

3.2.3 Types of subsequent fractures

Forearm fractures were common subsequent fractures in all ethnic groups, whereas fractures of the rib(s), sternum, spine, and pelvis were less common. The proportion of hip and femur fractures as subsequent fractures varied between 2% in people from Central and South America to 17% in the Norwegian-born population (Figure 3.2).

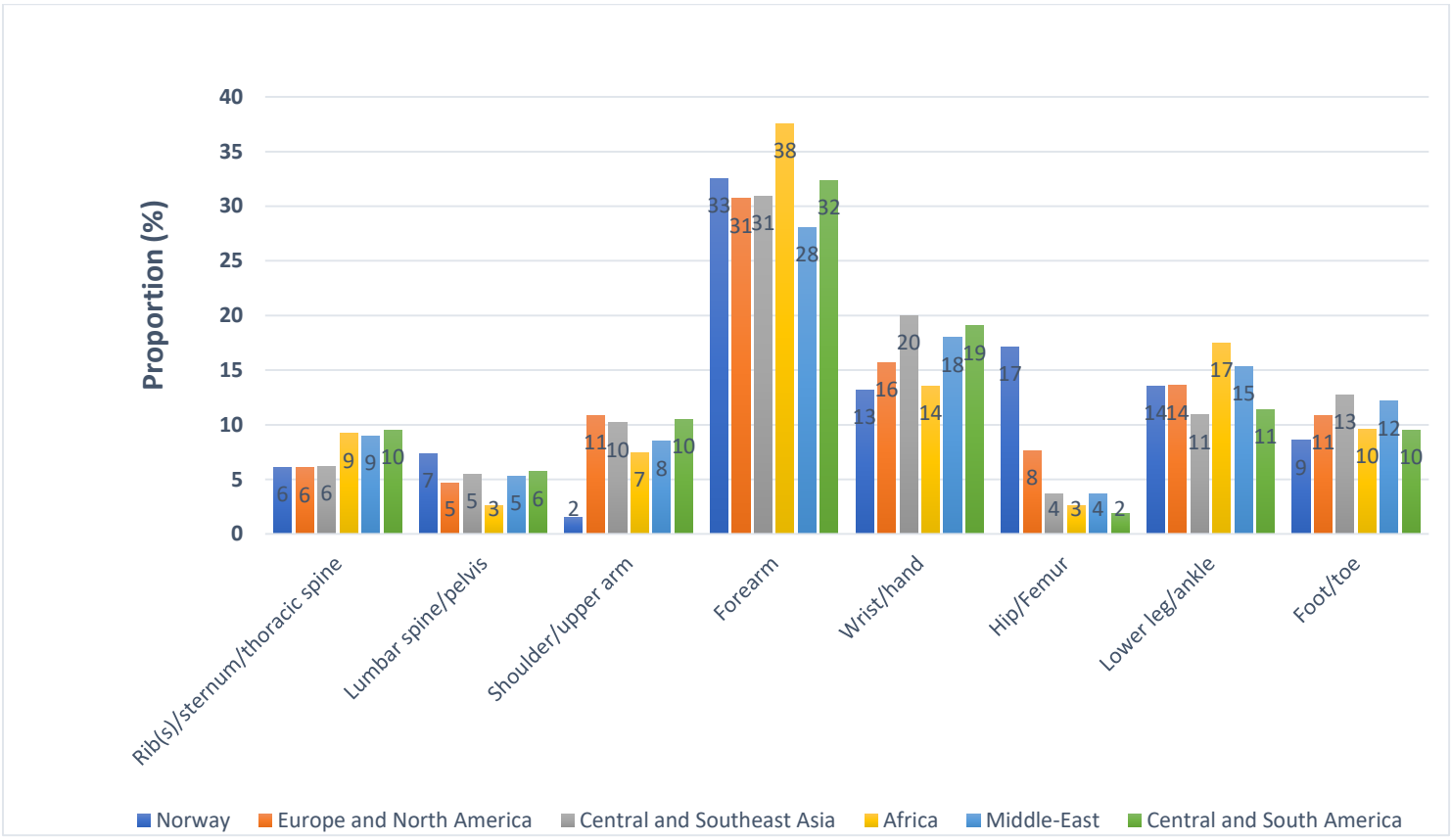

Figure 3.2 Proportions of recurrent fractures in patients with an index forearm fracture 2008–2019 by country of birth (six groups)

CHAPTER 4: DISCUSSION

4.1 Discussion of the main findings

This study found that Norwegian-born individuals had a higher subsequent fracture risk than most patients born outside of Norway. People born outside Europe and North America had either a similar risk or a 2-37% lower risk of subsequent fractures compared to those born in Norway. Across all ethnic groups, the rates of recurrent fractures increased with age. Among individuals aged 18–44, there were no significant differences in the risk of recurrent fractures based on their countries of birth, and no statistically significant distinctions were observed. These variations could potentially be attributed to limited statistical power.

Numerous surveys have investigated the global incidence of fractures, particularly among elderly people (1, 2, 65, 102, 104). Previous studies have shown that European and North American residents have higher incidence rates of fractures compared to individuals from Central and Southeast Asia, Africa and Latin America (2, 117, 125). Also, some studies found that the lowest risk of fracture was among immigrants from countries in Central and Southeast Asia (117, 125). The present study identified a consistent pattern in the subsequent risk of fractures across populations with different countries of birth.

A study in Sweden found that the rate of hip fractures among Swedish-born citizens was about two times higher than among immigrants. The research also showed that while the incidence of hip fractures increased over time among immigrants, it still remained significantly lower than in the native population (99). A Norwegian study, NOREPOS (the Norwegian Epidemiologic Osteoporosis Studies), revealed that in individuals with a previous hip fracture, the age-standardized risk of sustaining another hip fracture was 2.5 times higher in women and 4.6 times higher in men (126).

A recent meta-analysis investigated recurrent fracture risk according to race and ethnicity (113). The following study included cohorts with more than one race or ethnic group, including: Health ABC (Health, Aging and Body Composition) (127), CaMoS (Canadian Multicentre Osteoporosis Study) (128), MrOS USA (Osteoporotic Fractures in Men) (129), WHI (Women's Health Initiative) (130), SOF (Study of Osteoporotic Fractures) (131), Manitoba (132), and UK Biobank (133). The study concluded that, except in one study, the recurrent fracture risk did not differ significantly by race or ethnicity (113). However, in the studies including race and ethnicity, the person-years of follow-up were limited, and the power to

detect differences was therefore not optimal. Using register data from an entire country over many years, like in the current study, gives an excellent opportunity to investigate differences in recurrent fracture risk. Our findings show different recurrent fracture risks among people of different ethnicities, despite adjusting for age.

In a Norwegian study, the overall incidence of distal forearm fractures was reported as 244 per 100,000 person-years, and these fractures constituted 20% of all fractures (134, 135). If making an estimate of the total fracture incidence in Norway based on these figures, it gives a rate of 122 per 10,000 person-years. The subsequent fracture incidence of 461 per 10,000 person-years observed in the current study is 3.8 times higher than the overall fracture estimate, indicating that subsequent fracture risk is considerably increased in patients with a first forearm fracture compared to the general population without previous fractures. Incidence rates and risk of subsequent fracture after a forearm fracture in people from other countries in Europe and North America were lower compared to the Norwegian-born population within similar age groups, but the incidence rates among this population were considerably higher than the overall fracture estimate.

4.2 Explanatory factors for differences in fracture risk by country background

The interactions of factors and mediators contributing to the different risks of subsequent fractures among different ethnicities remain not fully understood. Some prior studies have reported that there is a connection between high fracture rates and countries experiencing better socio-economic advancements, potentially linked to lifestyles characterized by sedentary lifestyles, smoking, and alcohol consumption (1).

Social inequalities might also contribute to increased recurrent fracture risk (136). In immigrants in Canada, a higher risk of a subsequent fracture was reported in Afro-Americans compared to Caucasians (Afro-Americans: HR=2.43, 95% CI 1.37–3.78 vs. Caucasians: HR=1.57, 95% CI 1.32–1.87) (113), possibly due to social inequalities, even though fracture risk is usually lower in Afro-Americans compared to Caucasians (89). However, this is a topic which is very complex and needs further investigations before any conclusions can be drawn.

Another possible explanation for the decreased risk of fractures among immigrants is the phenomenon known as the "Healthy Migrant Effect." This term describes that migrants from certain countries of origin have lower mortality rates compared to the native population in the host countries, especially in industrialized areas (117, 137). According to this theory, individuals in optimal health within

a population are more likely to migrate, potentially resulting in a better overall health status among immigrants when compared to both their country of origin's population and the host population (117, 137, 138).

Research indicates that, on the whole, immigrants in Norway exhibit an 11% survival advantage. However, specific immigrant groups, such as refugees, may experience higher mortality rates than the broader Norwegian population (139).

Additional factors influencing the variation in the risk of recurrent fractures among different ethnic groups are genetic factors and biological differences in skeletal structures (79, 85). Studies have shown differences in macro- and microstructures of bones across various races; for example, Chinese and African populations tend to have a more robust bone architecture. Chinese women, for instance, exhibit a lower risk of hip and distal forearm fractures compared to Caucasians, partly attributed to thicker cortices with reduced porosity and smaller but denser and more interconnected trabeculae in their bones (85).

The origins of these bone structural variances are likely associated with the per pubertal period (140, 141). Research indicates that peak bone mineral accumulation appears earlier in Asians compared to individuals from other regions (142). Additionally, evidence suggests that the onset of puberty, the timing of peak height velocity, and the age at menarche occur earlier in Chinese girls compared to their white counterparts (83, 143, 144). Estrogen has impact on inhibiting periosteal apposition and facilitating epiphyseal closure (145); earlier exposure to estrogen may partially contribute to the narrower and shorter appendicular bones with fewer but thicker trabeculae and a thicker cortex observed in Chinese women compared to Caucasian women (83, 146, 147). Studies show that circulating levels of estrogen, as well as markers of bone formation and resorption, are lower in Chinese compared to white women (83, 146, 147).

Moreover, Caucasians generally have lower bone mineral density (BMD) compared to Africans, Hispanics, and Latin-Americans, and the heritability of BMD is estimated to range from 50% to 85%, indicating a significant genetic influence on bone density (83, 85, 148). The importance of BMD as a risk factor has been frequently debated, and the same is true when it comes to the importance of BMD in explaining differences in fracture risk (83).

Population demographics play a significant role in fracture rates; European and North American countries, with larger elderly populations, tend to have higher fracture rates (2). In geographic

comparisons of fracture rates, adjustments for age are performed but this does not fully solve the problem of differences in life expectancy. However, this trend is more likely to change in the future since life expectancy is increasing in Asia and Latin America, leading to a higher fracture risk among these populations (149).

In addition, latitude and environmental conditions can contribute to regional differences in fracture incidence (2, 93). Early-life environmental influences have a direct impact on peak bone mass, a critical risk factor for childhood bone fractures, osteoporosis, and fracture risk later in life (150, 151). Early environmental factors, such as calcium intake and physical activity, have been demonstrated to significantly affect peak bone mass development by modulating bone accrual during childhood and adolescence (150, 152, 153). Furthermore, environmental influences during intrauterine life may also exert a lasting effect on peak bone mass. Some factors such as infant body weight and overall body size are likely to have association with bone mineral content in young adults (154, 155).

Furthermore, it is likely that certain regional disparities can be attributed to variations in the proportion of cases that are diagnosed and accurately documented. Another potentially crucial factor is the duration of residency in Norway. Unfortunately, our study lacked detailed information regarding the length of time individuals had lived in Norway.

4.3 Significance of studying recurrent fracture risk by country background

Studying subsequent fracture risks is vital for heightening healthcare by improving treatments, targeted interventions, and public health planning (118, 119, 156). Understanding the recurrent fracture risks can help healthcare professionals improve treatment methods. Appropriate treatments based on the specific risk factors that are prevalent in different populations can better outcomes and reduce the risk of future fractures and the associated health problems (156, 157).

Furthermore, identifying populations with a higher risk of recurrent fractures allows for targeted interventions. Healthcare providers can concentrate on prophylactic measures, such as change in lifestyle or pharmacological interventions (118, 119). In addition, knowledge about recurrent fracture risk in different populations contributes to public health planning. It helps develop policies and programs that meet the specific needs of at-risk residents. This can include potential actions on falls prevention, osteoporosis management, and access to healthcare services (14, 57, 156).

Research on recurrent fracture risk can lead to discoveries of genetic factors, lifestyle choices, and medical conditions that can influence recurrent fractures. This knowledge can guide further research and lead to the development of new treatments and preventive measures (1, 156). Also, studying subsequent fracture risk among different populations can help identify and eradicate inequities in the health care system, by ensuring equal and fair access to medical care and support services for all citizens, regardless of their backgrounds or demographic characteristics (158).

4.4 Methodological considerations

4.4.1 Strengths of the study

The study's significant strengths are its substantial sample size and the high quality of the used data. The research included almost all Norwegian residents who experienced a forearm fracture at the age of 18 years or older between 2008 and 2019, excluding only those fully treated in primary care or abroad for travel. These participants were monitored for a maximum duration of 12 years. To our knowledge, this study marks the first of its kind conducted on such a large scale within the population. The data obtained from patient registries contained reliable diagnostic codes and can be linked to other data sets through unique and identifiable numbers. This linkage presented a distinctive opportunity for comprehensive research analysis. Conducting validation studies is also crucial prior to using register data for research purposes. A validation study assessing the accuracy of ICD-10 data and the fracture-defining algorithm revealed a positive predictive value and sensitivity of approximately 90% (123).

4.4.2 Limitation of the study

Information bias

It is important to acknowledge that registry data has its limitations. Essential information may be lost due to misclassification, missed coding, or changes in coding methods over time (159, 160). Nonetheless, data obtained from registries proves highly reliable when standardized algorithms are used for quality assurance. Conducting validation studies is crucial prior to using register data for research purposes. Forearm fractures in this study were validated before the start of the study (123).

Selection bias

However, the number of foreign-born patients was much lower than Norwegian born, leading to uncertainties in the estimates. To mitigate this issue, we grouped individuals from Central and Southeast Asia, Central and South America, the Middle East, and Africa together and made one group named

Other countries, but the overall number in this combined category remained relatively small. Moreover, combining people-groups of distinct genetic makeups and environmental influences may mask the effects of factors that would otherwise be apparent.

The study was limited to individuals who sought diagnosis and treatment for a fracture in hospitals. It is probable that we may have missed a portion of patients who were only treated by primary care providers, which constitutes approximately 5–7% of all forearm fracture patients (122). However, according to Statistics Norway, immigrants are more inclined to live in urban areas where fractures are typically reported to the National Patient Registry (NPR) than in rural areas. In rural regions, patients are more likely to receive treatment from primary care providers without the need for hospital referral and fracture code recording, potentially resulting in unrecorded fractures. Consequently, there was likely a higher likelihood of missing patients among Norwegian-born individuals compared to immigrant patients in this study (122).

It is possible that certain immigrant groups were not included in the study due to various social, political, and cultural obstacles, including language barriers. Additionally, immigrants without a Norwegian identification number may have been automatically excluded from the registry.

It is also possible that we overlooked individuals with fractures sustained abroad. However, even these fractures could potentially have been included and recorded if they required follow-up treatment in Norway, as we incorporated records with follow-up codes that were unique occurrences in the dataset. Consequently, we might have missed more fractures during travel among immigrants, as their higher likelihood of traveling compared to the Norwegian-born population. Importantly, these two potential biases might counterbalance each other somewhat with regards to the hazard ratio. However, it is likely that the rates of recurrent fractures are underestimated in the immigrant population and that a proportion of the reported difference is explained by fractures during travel.

4.4.3 Confounding

In the current study, we have compared incidences of recurrent fracture, and there were no additional confounding factors that we could adjust for. We adjusted for age in our analyses. But age might, in addition, be considered a selection bias as there were large differences in the age distribution of the countries of birth. This complicated the comparison of fracture risk. Consequently, we conducted age-specific analyses within 15-year age brackets to address these complexities.

4.5 Generalizability

This study concentrated on the population living in Norway with different countries of origin. The findings are valid in this study setting, which might restrict their generalizability to other immigrants residing in other countries. Hence, the conclusions are valid for individuals living in Scandinavian countries but might not be directly transferable to other immigrant groups in other countries.

CHAPTER 5: CONCLUSION

In summary, the findings show a variation in the risk of subsequent fractures depending on the individual's country of birth. Individuals born outside Norway had a 0–37% lower risk of a recurrent fracture than Norwegian-born patients. The risk of recurrent fractures escalated with age across all groups, and there was a substantial risk of subsequent fractures within the elderly immigrant populations as well as in the Norwegian-born population.

The observed rate of subsequent fractures in the current study, of 461 per 10,000 person-years, is dramatically higher than the general fracture rate in Norway of the same age. This suggests that individuals who have experienced a first forearm fracture face a significantly higher risk of subsequent fractures when compared to the general population with no history of prior fractures. Understanding recurrent fracture risk among diverse populations is vital for improving healthcare services, enhancing quality of life, and promoting health equity within communities.

CHAPTER 6: IMPLICATIONS FOR FURTHER RESEARCH

Based on this study, it is not possible to conclude whether the risk of subsequent fractures should receive further attention. An important question is whether these differences in recurrent fracture risk are clinically relevant, and also whether immigrant patients with a forearm fracture should be offered fracture liaison services based on similar criteria that are used for Norwegian-born patients. However, there might be subgroups of immigrants who might require special attention, and the focus on secondary fracture prevention in all ethnicities is warranted.

Hence, future studies are needed to investigate any high-risk immigrant subgroups according to length of stay in Norway and also determine to what extent the implementation of preventive measures such as blood tests and measurements of bone mineral density is useful for estimating the risk of osteoporosis and recurrent fracture risk and decreasing the clinical consequences of recurrent fractures.

In addition, further research should focus on: Does time spent in Norway affect fracture risk? How much, if any, of the differences reported can be explained by traveling to the home country? Immigrants seem to have a higher future risk of fracture if they have sustained a previous fracture. Should fracture prevention programs be the same for immigrants as for Norwegians? Do they need special attention because of language barriers, culture, etc.?

Also, further research is required to investigate second-generation immigrants. Studying this group could provide valuable insights into whether environmental factors or genetics play a more significant role in fracture risk. Understanding this distinction can greatly contribute to the development of effective preventive measures against fractures.

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APPENDICES

Appendix 1: REC approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst A	Elin Evju Sagbakken	22845502	18.02.2022	26953

Åshild Bjørnerem

Prosjektsøknad: Behandlingsprogram for å forebygge nye beinbrudd - bruk av registerdata
Søknadsnummer: 2015/334
Forskningsansvarlig institusjon: Universitetet i Oslo
Samarbeidende forskningsansvarlige institusjoner: Oslo universitetssykehus HF

Prosjektsøknad: Endring godkjennes

Søkers beskrivelse

Bruddpasienter har økt risiko for nye brudd og denne gruppen har også økt dødelighet. Prosjektet vil gi ny kunnskap om forebygging av brudd og dødelighet hos bruddpasienter. Hensikten er å måle effekten av et standardisert intervensjonsprogram for bruddpasienter på risiko for nye brudd og dødelighet. Intervensjonen vil trinnvis bli introdusert på 7 norske sykehus og foregå i perioden 2015-2018. Intervensjonen innebærer estimering av individuell bruddrisiko, medikamentell behandling ved behov og veiledning for å forebygge nye brudd. Bruddata 2008-2018 fra hele landet vil bli hentet inn fra Norsk pasientregister og koblet til data fra Folkeregisteret og Statistisk sentralbyrå. For pasienter med hoftebrudd ønsker vi også data fra Nasjonalt hoftebruddregister og Dødsårsaksregisteret. Forekomst av brudd før intervensjon, samt effekt av intervensjonen vil bli analysert (alle typer brudd samlet, samt spesifikke bruddtyper). Det vil bli gjort kost- og nytteberegninger av intervensjonen.

Vi viser til søknad om prosjektendring mottatt 18.02.2022 for ovennevnte forskningsprosjekt.

Søknaden er behandlet av sekretariatet i Regional komité for medisinsk og helsefaglig forskningsetikk (REK) på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

REKs vurdering

REK har vurdert følgende endringer:

- To nye medarbeidere inngår i prosjektgruppen: Sepideh Semsarian og Reyhaneh Lashkari, begge Masterstudenter ved UiO.

Sekretariatet har vurdert søknaden og godkjenner endringene slik de er beskrevet.

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

Vedtak

REK 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.

Prosjektet er godkjent frem til sluttdato 31.03.2025.

Etter prosjektslutt skal opplysningene oppbevares i fem år for dokumentasjonshensyn. Enhver tilgang til prosjektdataene skal da være knyttet til behovet for etterkontroll. Prosjektdata skal således ikke være tilgjengelig for prosjektet. Prosjektleder og forskningsansvarlig institusjon er ansvarlig for at opplysningene oppbevares indirekte personidentifiserbart i denne perioden, dvs. atskilt i en nøkkel- og en datafil. Etter disse fem årene skal data slettes eller anonymiseres.

Vi gjør oppmerksom på at anonymisering kan være mer omfattende enn å kun slette koblingsnøkkelen, jf. Datatilsynets veileder om anonymiserings-teknikker. Vi gjør samtidig oppmerksom på at det også må foreligge et behandlingsgrunnlag etter personvernforordningen. Dette må forankres i egen institusjon.

Sluttmelding
Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest 6 måneder etter sluttdato 31.03.2025, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring
Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen

Jacob C. Hølen

Sekretariatsleder REK sør-øst

Elin Evju Sagbakken

Seniorrådgiver, REK sør-øst A

Kopi til:

Universitetet i Oslo
Oslo universitetssykehus HF
Cecilie Dahl

Appendix 2: Letter of the Directorate of Health

Helsedirektoratet

Returadresse: Helsedirektoratet, Postboks 220 Skøyen, 0213 Oslo, Norge

Universitetet i Oslo - Institutt for helse og samfunn
Cecilie Dahl
Postboks 1130 Blindern
0318 OSLO

Deres ref.:
Vår ref.: 17/25552-37
Saksbehandler: Torstein Otterlei Fjørtoft
Dato: 01.04.2022

Følgebrev og endringsvedtak - Utlevering av data fra Norsk pasientregister (NPR) - Norwegian Capture the Fracture Initiative (NoFRACT) - 2020-2021

Det vises til endringssøknad om tilgjengeliggjøring av opplysninger fra Norsk pasientregister (NPR) av 23.8.2021, vårt vedtak av 13.2.2018 (vår ref. 17/25552-4) og endringsvedtak av 15.12.2021 (vår ref. 17/25552-35).

Det vises også til tidligere leveranser på saken (vår ref. 17/25552-8 og 17/25552-28). Søker ønsker i endringssøknaden av 23.08.2021 opplysninger for en ny periode, 1.1.2020 – 31.7.2021.

Endringsvedtak
Dette følgebrevet er også å anse som et endringsvedtak. Det vises til to mindre endringssøknader (vår ref. 17/2552-41) som søker har sendt inn etter vårt endringsvedtak av 15.12.2021.

- I endringssøknad av 18.02.2022 søkes det om to nye medarbeidere til prosjektet.
- I endringssøknad av 22.02.2022 søkes det om presisering av REKs vedtak datert 30.06.2021, knyttet til utvidet oppfølgingstid. Prosjektet ønsker at utvidet oppfølgingstid også omfatter nye bruddpasienter i perioden 31.12.2019-31.07.2021, og ikke bare det allerede etablerte utvalget (definert fram til 31.12.2019). Søker har behov for informasjon om hele bakgrunnspopulasjonen fram til 31.07.2021, for å beregne total bruddinsidens.

Det er fremlagt

- Endringsvedtak fra REK av 18.02.2022 og 23.02.2022 (REK sør-øst A ref. 26953, vår ref. 17/25552-38 og 17/25552-39).

Selv om samtykke fra deltakere, dispensasjon fra taushetsplikt gitt av REK eller Helsedirektoratet er en forutsetning for tilgjengeliggjøring av personidentifiserbare opplysninger er avdeling helseregistre forpliktet til å gjøre en selvstendig vurdering av om formålet med prosjektet er i samsvar med Norsk pasientregisterforskriften.

Helsedirektoratet
Seksjon leveranse
Torstein Otterlei Fjørtoft
Postboks 6173 Torgarden, 7435 TRONDHEIM • Besøksadresse: Holtermanns veg 70, Trondheim • Tlf.: (+47) 47 47 20 20
Org.nr.: 983 544 622 • postmottak@helsedir.no • www.helsedirektoratet.no

Helsedirektoratet ved avdeling helseregistre har vurdert endringssøknadene og finner at registeropplysningene det er søkt om ligger innenfor NPR sitt formål, jamfør Norsk pasientregisterforskriften § 1-2, og at de øvrige vilkårene for tilgjengeliggjøring er oppfylt. Det vises til opprinnelig vedtak av 13.02.2018 og endringsvedtak av 15.12.2021, samt vilkår.

Tilgjengeliggjøring vil skje med hjemmel i Lov om helseregistre og behandling av helseopplysningen § 19 a. Vilkår for tilgjengeliggjøring av opplysninger er gitt i dette enkeltvedtaket.

Endringsvedtaket kan påklages, jf. forvaltningsloven § 28. En eventuell klage sendes avdeling helseregistre innen tre uker etter at vedtaket er mottatt.

Materialet
I samsvar med våre vedtak, og dialog mellom avdeling helseregistre og Universitetet i Oslo ved prosjektarbeider Cecilie Dahl, tilgjengeliggjøres indirekte personidentifiserbare opplysninger fra NPR til prosjektet "*NoFRACT – Norwegian Capture the Fracture Initiative*". Denne leveransen gjelder ny periode med samme variabler og utvalgskriterier som ved forrige leveranse, men kun fra NPR og ikke KUHR og de andre registrene skissert i tidligere søknader.

Populasjonen fra NPR består av pasienter 20 år og eldre registrert med minst én av følgende ICD-10-koder som hoved- eller bitilstand ved somatiske sykehus i perioden 1.1.2008 – 31.7.2021: S22.x, S32.x, S40.x, S42.x, S43.x, S50.x, S52.x, S53.x, S60x, S62.x, S63.x, S72.x, S82.x, S92.x, T02.x, T08.x, T10.x, T12.x, M48.4, M48.5, M80.x, M81.x, M82.x, M83.x, M84.x, M85.x, M86.x, M89.x, eller Z09.4. De aktuelle kodene er relatert til brudd, kontusjon, dislokasjon, forstuing og forstrekking.

I NPR-utvalget ved forrige utlevering (2008-2019) var det 1 082 070 personer. I denne utleveringen er 122 950 nye personer inkludert i utvalget. Totalt er dermed 1 205 020 personer inkludert, og dette definerer studiepopulasjonen.

10 personer har registrert seg mot deltakelse i studien og er ekskludert fra utvalget, slik som ved forrige leveranse.

Det utleveres 3 filer fra avdeling helseregistre til bruk i prosjektet.

1. **Aktivitetsdata**

Datagrunnlaget er avgrenset til perioden 1.1.2020 – 31.7.2021 for helsetjenesteområdet somatiske sykehus (sykehusopphold). De utleverte data består av alle episoder (poliklinisk kontakt, dagbehandling eller innleggelse) der hoved- eller bitilstand er minst én av de overnevnte ICD-10-kodene knyttet til brudd, kontusjon, dislokasjon, forstuing og forstrekking.

Linjeenheten i datasettet er episode. Filen består av 499 279 episoder, fordelt på 230 980 unike personer.

Filen består av samme variabler som forrige utlevering (29.7.2020), med unntak av variablene behandlingssted2 og behandlingssted2_navn, som er byttet ut med behandlingsstedkode og behandlingsstedkode_navn. Variabelen kilde, som i forrige datafil viste om en pasient var

registrert i NPR, KUHR eller begge registre, er heller ikke med, da denne søknaden kun gjelder data fra NPR.

Tilstandskoder utenom utvalgskriteriene eller utenom oppgitte komplikasjonskoder (T81.x, T84.x, T88.8, T88.9, T92.x, T93.x, Z04.8, Z09.0, Z09.7, Z09.8, Z09.9, Z44.8, Z44.9, Z45.8, Z45.9, Z46.7, Z46.8, Z46.9, Z47.x, Z48.x, Z50.x, Z51.8, Z51.9, Z54.x, Z76.8 eller Z76.9) er blanket ut, i likhet med forrige leveranse.

Omsorgsnivå for episoder fra somatiske sykehus er avledet fra variabelen aktivitetskategori3.

2. Komorbiditetsindeks

Det er også beregnet Charlson komorbiditetsindeks per år for alle pasienter som inngår i populasjonen, og som er registrert med sykehusopphold i somatiske sykehus eller avtalespesialister i perioden 2020 til 31.7.2021. Merk at for året 2021 er kun sykehusopphold fram til og med 31.7.2021 brukt i beregningsgrunnlaget.

Følgende informasjon inngår i filen:

- LNr
- År
- Charlson_indeks

Linjeenheten i dette datasettet er pasient, og totalt består filen av 732 924 unike personer. Årsaken til at det er færre individer i filen med komorbiditetsindeks enn i populasjonen som helhet, er at populasjonen som sendes over til SSB består av bruddpasienter tilbake til 2008. Ikke alle disse pasientene er registrerte med sykehusopphold i 2020 og 2021.

Etter avtale oversendes filer med aktivitetsdata og komorbiditetsindeks via TSD til Universitetet i Oslo v/ Cecilie Dahl. Filer som oversendes fra avdelingshelseregistre blir kryptert med passord. Passordet oversendes på SMS.

I tillegg oversendes en nøkkelfil fra avdeling helseregistre som inneholder identiteten til 1 205 010 unike personer. Filen har CSV-format og det er brukt semikolon (;) som delimiter. Rad 1 i filen består av [saksnr;antall rader med fødselsnummer;dato-tid generert]. Rad 2 og til og med siste rad består av [fødselsnummer med 11 siffer;løpenummer]. Nøkkelfilen oversendes til SSB.

Viktige tilleggsopplysninger

Vilkårene for tilgjengeliggjøringen er gitt i vårt vedtaksbrev av 13.2.2018 (vår ref. 17/25552-4), samt endringsvedtak av 15.12.2021 (vår ref. 17/25552-35).

Vi ber deg snarest og *senest innen 3 uker* kontrollere at de mottatte filene er i orden. Ved feil i tilgjengeliggjorte opplysninger som skyldes håndteringen i avdeling helseregistre vil en korrigert leveranse utføres vederlagsfritt. Henvendelser gjort etter 3 uker vil bli behandlet som en ny søknad.

I medhold av Lov om helseregistre og behandling av helseopplysninger § 19 g kan avdeling helseregistre kreve dekket faktiske utgifter som påløper i forbindelse med behandling og tilrettelegging av opplysninger. Til dette oppdraget er det medgått 31 arbeidstimer hos avdeling helseregistre. Faktura på oppdraget lyder på 34 100 NOK eks. mva. Faktura vil bli sendt separat.

Vennlig hilsen

Inger Johanne Bakken e.f.
seniorrådgiver

Torstein Otterlei Fjørtoft
rådgiver

Dokumentet er godkjent elektronisk

Appendix 3: The article

Recurrent fracture risk in Norwegians and immigrants with an index forearm fracture

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Abstract

Background: Fracture risk is higher in patients with a previous fracture, but it is unknown whether recurrent fracture risk differs by country background. The aim of the current study was to investigate subsequent fracture risk in patients with an index forearm fracture according to region of birth.

Methods: Nationwide data on hospital-treated forearm fractures in patients ≥18 years between 2008 and 2019 were obtained from the Norwegian Patient Register. Index forearm fractures were identified by the ICD-10, S52, including all subgroups, whereas subsequent fractures included any ICD-10 fracture codes. Information about the region of birth was obtained from Statistics Norway. Age-standardized incidence rates (IRs) were calculated as the number of fractures divided by the number of years at risk after the first fracture using direct standardization. Age-adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were obtained by Cox proportional hazard regression.

Results: Among the 143,476 individuals with a first forearm fracture, 35,361 sustained a second fracture. The highest subsequent fracture risk was observed in individuals born in Norway (IR 516 per 10,000 person-years in women and 380 per 10,000 person-years in men), whereas the lowest subsequent fracture risk was observed in patients born outside Europe and North America (IR 278 and 286 per 10,000 person-years in women and men, respectively). Norwegian-born women aged > 60 years had the highest IR: 640 per 10,000 person-years, whereas the lowest IR was among women aged 18–44 born in Other countries, including Central and Southeast Asia, Africa, the Middle East, and Central and South America: 226 per 10,000 person-years. Compared to Norwegian-born individuals, the HR of subsequent fracture in people born in other European and North American countries was 0.93 (95% Cl 0.88–0.98) and 0.85 (95% Cl 0.79–0.92) in women and men, respectively. Individuals born in other countries had HRs of subsequent fracture of 0.76 (95% Cl 0.70–0.84) in women and 0.82 (95% CI 0.74-0.92) in men compared to those born in Norway.

Conclusion: Individuals born outside Norway had a 7–24% lower subsequent fracture risk than those born in Norway. The risk of subsequent fracture increased with age in all groups, including the foreign-born individuals. Consequently, implementing secondary fracture prevention strategies for all forearm fracture patients, regardless of their birth country, is advisable.

Keywords: Forearm fracture, subsequent fracture risk, Country of birth, Ethnicity, Norway

Introduction

Osteoporosis is considered the most prevalent bone disorder in the world. It is a condition with reduced bone mass and bone strength and an increased risk of low-energy fractures (e.g., a fracture caused by a slip, trip, or fall from standing height) (1, 2). Osteoporotic fractures constitute an important public health problem, especially among the elderly. It is documented that 50% of women and 20% of men in high-income countries experience one or more osteoporotic fractures during their lifetime (3). The most common osteoporotic fractures occur in the forearm, hip, and spine (4). Fractures are also common among children, adolescents, and young adults (5). Young adults, usually men, are more likely to fracture due to high-energy trauma such as car accidents and sports activities (6, 7).

Decreased mobility, difficulties in working life and social activities, and increased mortality risk are important consequences of fractures in general, and even more so after subsequent fractures (8-10). The risk of sustaining a subsequent fracture after any type of previous fracture is high among individuals with an initial fracture and increases with age (11-13).

A previous study from Tromsø, Norway, involving 3108 individuals with an initial fracture after the age of 49, studied subsequent fracture by four age groups: 50–59, 60–69, 70–79, and 80 years and older, and found that the risk of sustaining a second fracture of any type rose with age. For women, the risk rose from 9% to 30% between the age groups of 50–59 and 80+, while for men, it increased from 10% to 26% during the same age range. Notably, 26% of women and 18% of men over 80 years old sustained subsequent fractures, regardless of their increased risk of death (13).

The increased risk of sustaining a subsequent hip fracture, the most serious type of osteoporotic fracture, varies from 2% to 20% in different studies (11, 14, 15). A study conducted in Sydney, Australia, examined the risk of subsequent fracture after a low-energy fracture with The International Classification of Diseases, 10th Revision (ICD-10) codes S22-S82; fracture of rib(s), lumbar spine, shoulder and upper arm, forearm, wrist, femur and hip, and lower leg (16). They found a cumulative incidence of 7.1% at one year and 13.7% at five years for women, and 6.2% at one year and 11.3% at five years for men (16).

There are a wide range of risk factors contributing to fractures. The most important ones are age, sex, a prior fracture, low bone mineral density (BMD), smoking, nutritional status, and family history (17). Studies have shown that childhood fractures are associated with low bone mineral density

(i.e., possibly reduced peak bone mass), the risk of skeletal fragility, and future fractures in adulthood (18-20).

Some studies indicate that the country of origin or ethnicity may represent a risk factor for fracture (21, 22), but the reasons are not fully elucidated. Bone mineral density, bone microarchitecture, bone strength, and factors related to the risk of falling vary in populations in different geographical areas, probably due to both genetic and environmental causes, but none of these factors alone can explain the differences in fracture risk (23, 24).

The incidence rates and risk of sustaining fractures vary in different parts of the world, with a higher occurrence in developed areas such as Northern Europe and Northern America compared to Latin America, Africa, and Asia (25, 26). Among Asian countries, Taiwan, Japan, Singapore, Kuwait, Iran, and Oman are classified as high-risk nations for fractures (27, 28). The global demographic landscape is undergoing significant changes, particularly in Asia, where the aging population has led to a notable increase in the incidence of fractures. Projections indicate that by the year 2050, half of all hip fractures globally will be concentrated in Asia (26).

In Europe, there exists a discernible north-south disparity in fracture risk, with northern and Scandinavian countries reporting higher prevalence and incidence rates compared to other regions on the continent (26, 29). Previous studies have shown that the incidence rates of forearm and hip fractures in Norwegian citizens are among the highest worldwide (25, 30, 31).

To our knowledge, recurrent fracture risk according to country of origin has not previously been studied. The aim of this study was to estimate the association between country of birth and the risk of any recurrent fracture in patients with an index forearm fracture in Norway.

Materials and methods

Study population and data sources

This cohort study included all Norwegian residents above 18 years seeking health care for treatment of a fracture in the period 2008–2019. Data were obtained from the Norwegian Patient Registry (NPR) and Statistics Norway through the Norwegian Capture the Fracture Initiative (NoFRACT) study. NoFRACT is a large multi-center study on the prevention of recurrent fractures that uses register data to measure the effect of a secondary fracture prevention program (32, 33).

Definition of the outcome: incident fractures

All types of fractures were defined through standardized ICD-10 codes for diagnosis in the Norwegian health care system: fracture of rib(s), sternum and thoracic spine (S22), lumbar spine and pelvis (S32), shoulder and upper arm (S42), forearm (S52), wrist and hand (S62), hip and femur (S72), lower leg, including ankle (S82), and foot except ankle (S92), including all subcategories. We excluded registrations of follow-up visits, except for first-time registrations with a code for follow-up examination, as some patients with fractures receive initial treatment in primary care (not reporting to the NPR) before being referred to the hospital, and consequently, incident fractures are sometimes coded as a follow-up visit (34). A wash-out period of 6 months (within each fracture type) was applied to handle multiple registrations regarding the same fracture. Records with surgical coding for reoperation were also omitted. Our algorithm for identifying forearm fractures was recently validated it has a sensitivity of approximately 90% and a positive predictive value of 90% (35).

Observation time

The maximum observation time in the study was 12 years, from January 1, 2008, through December 31, 2019. All individuals experiencing an index forearm fracture (any S52 fracture) were included in the study and followed with respect to any type of subsequent fracture. Person time in the analyses was calculated as the time from index forearm fracture to the subsequent fracture or censoring (emigration, death, or end of study).

Main exposures categories

Individuals were categorized into three main groups of countries of birth: (1) Norway; (2) other European countries and North America; and (3) Other countries, including Central and Southeast Asia, Africa, the Middle East, and Central and South America. We excluded 990 individuals with missing information about their country of origin. The remaining population included in the study was 143,476 individuals with an index forearm fracture (S52) followed for up to 12 years. The patients were stratified according to age: 18–44 years, 45–59 years, and 60 years and older, to study the risk in different age groups.

Statistical analyses

Descriptive analyses and survival analyses were performed in STATA 16. Age-standardized incidence rates (IRs) were calculated as the number of fractures divided by the number of years at risk

after the first fracture using a direct standardization method. The figures were reported as the number of fractures per 10,000 person-years. Cox proportional hazard models were used to calculate the risk of subsequent fracture as a function of country of birth, categorized into the three main geographical groups or sub-groups, adjusted for differences in age, and stratified by sex. Log minus log curves were evaluated regarding the assumption of proportional hazards, and the assumptions were considered fulfilled. Age-adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were obtained from the models. Two-sided p-values <0.05 were deemed significant.

Ethics

The study and the linkage of data from the Norwegian Patient Registry were approved by the Regional Committee for Medical and Health Research Ethics (REC), with application number 2015/334 and reference number 26953, and the Directorate of Health, with reference number 17/25552-37. The University of Oslo performed a Data Protection Impact Assessment (DPIA) in accordance with the General Data Protection Regulation.

Results

Among the 143,476 individuals with a forearm fracture who were included in the study, 42,923 were men and 100,553 were women. Of the total, 127,431 individuals were born in Norway, 10,537 in other European countries or North America, and 5,508 in other countries, with a mean age at first forearm fracture of 59 years, 48.6 years, and 44.3 years, respectively (Table 1). Among the included individuals, 35,361 (24.6%) sustained a subsequent fracture of any type. The number of person-years for the whole cohort of forearm fracture patients was 767,531, with a total IR of 461 (95% CI 456-466) per 10,000 person-years.

Subsequent fractures according to country of birth

Norwegian-born women had the highest IR of a subsequent fracture (516 per 10,000 person-years), whereas incidence rates among women born in other European countries or North America and from Other countries were 406 and 278 per 10,000 person-years, respectively (Table 2). Norwegian-born men had the highest subsequent fracture IR (380 per 10,000 person-years), while the IR for men born in other European countries or North America and Other countries was 303 and 286 per 10,000 person-years, respectively (Table 2).

Compared to Norwegian-born women, the age-adjusted HR for any type of subsequent fracture was 0.93 (95% Cl 0.88–0.98) in women from other European and North American countries. The HR of any second fracture among women born in Other countries was 0.76 (95% Cl 0.70–0.84) compared to Norwegian-born women (Table 2). The HR of subsequent fractures was 0.85 (95% Cl 0.79–0.92) in men born in European and North American countries compared to Norwegian-born men. The risk of any second fracture among men born in Other countries was 0.82 (95% CI 0.74-0.92) compared to Norwegian-born men (Table 2).

Subsequent fractures according to age

The risk of subsequent fractures rose with age, irrespective of the region of birth. Incidence rates increased from 280 per 10,000 person-years among Norwegian-born individuals aged 18–44 years to 616 per 10,000 person-years among Norwegian-born individuals aged over 60 years (Table 3). Norwegian-born women aged over 60 years had the highest IR: 640 per 10,000 person-years, while the lowest IR was among women from Other countries aged 18–44: 226 per 10,000 person-years (Table 4).

Incidence rates among Norwegian-born men and men from other European countries and North America also increased with age, while incidence rates among men from Other countries showed less variation with age. Among all men, Norwegian-born men aged over 60 years had the highest IR: 510 per 10,000 person-years (Table 4, Figure 1). Recurrent fracture risk in immigrants from Other countries was significantly lower in all age groups compared to Norwegian-born patients (Table 3).

Types of subsequent fractures

Forearm fractures were the most common type of subsequent fracture in all ethnic groups (n = 10,165), whereas fractures of the rib(s), sternum, spine, and pelvis were the least common subsequent fractures. Compared to Norwegian patients, femoral fracture was less common as a recurrent fracture among people from Other countries, whereas fractures of the shoulder and upper arm were more common (Figure 2).

Discussion

We included almost 150,000 individuals with a first forearm fracture between 2008 and 2019 and found a higher subsequent risk of any type of fracture in Norwegian-born individuals compared to individuals born outside of Norway. The lowest subsequent fracture risk was observed in patients born outside Europe and North America. Incidence rates of subsequent fractures increased with age,

regardless of country background. Among all ethnic groups, forearm fractures were the prevailing type of subsequent fracture.

A Norwegian study found an overall incidence of distal forearm fractures of 244 per 100,000 person-years (36), and these fractures account for 20% of all fractures in the studied population. Hence, the total fracture incidence in the Norwegian population older than 18 years was approximately 122 per 10,000 person-years during 2009–2014 (37). This study's finding of a subsequent fracture incidence of 461 per 10,000 person-years significantly surpasses the overall fracture estimate. This suggests a markedly elevated subsequent fracture risk in individuals with an initial forearm fracture, contrasting sharply with the general population that has not experienced previous fractures. Although individuals from other European and North American countries had lower incidence rates and subsequent fracture risks after a forearm fracture compared to those born in Norway within the same age groups, their rates and risks remained high across all age brackets.

Several surveys have studied the worldwide risk of fracture, especially among elderly populations (11, 13, 38). According to previous studies, Europe, particularly the Scandinavian countries, and North America have been considered high-risk regions for fractures (30, 39). In contrast, countries in Latin America and Central and Southeast Asia have been considered low-risk areas (30, 39, 40). Some studies have revealed statistically different incidence rates of fracture in populations with different ethnicities. It has been reported that European and North American citizens have higher incidence rates compared to individuals from Africa, Latin America, and Central and Southeast Asia (39, 41). The current study found a similar pattern in subsequent fracture risk among populations with different country backgrounds.

A Swedish study found that the incidence rate of hip fracture among Swedish-born citizens was approximately doubled compared to the corresponding rate among immigrants. It also reported that the incidence increased over time among immigrants but remained significantly lower than in the native population (40). A Norwegian study showed that women and men with earlier hip fractures have a 2.5-time and 5-time higher risk of experiencing a new hip fracture, respectively (42).

However, a recent meta-analysis focusing on subsequent fracture risk reported that the risk remained consistent across individuals from different countries of birth (43). Nevertheless, the studies incorporating race and ethnicity had restricted person-years of follow-up, affecting the ability to detect

differences effectively. Still, studies focusing on subsequent fractures among immigrants are limited, and no study has, to our knowledge, considered subsequent fracture risk after a first forearm fracture.

Utilizing comprehensive register data from an entire country over several years, as done in our current study, provides an exceptional opportunity to explore variations in recurrent fracture risk. Our findings highlight distinct recurrent fracture risks among individuals of diverse ethnic backgrounds. We found a lower risk of subsequent fractures of any type in all foreign-born groups compared to Norwegian-born patients. The causes of the different risks of subsequent fractures are unclear. Some previous studies have suggested that countries with higher socio-economic growth have higher fracture rates, which can have a correlation with lifestyles such as sedentary lifestyles, smoking, and alcohol consumption (25).

Migration also has an impact on health; however, the effect of migration varies among different immigrant groups (44). Over time, the risk of disease has been found to equalize with the population that they immigrate to. In Sweden, a similar risk of first osteoporotic fracture was found among second-generation immigrants and Swedish natives, probably due to environmental factors (45). In addition, it is likely that at least some of the regional differences can be explained by differences in the proportion of cases that are diagnosed and properly recorded.

Another possible explanation for the lower risk of fractures in immigrants living in Norway compared to Norwegian-born people is the healthy migrant effect. This claims that it is the healthiest people in a population that is most likely to migrate, initially resulting in a better overall health condition in immigrants compared to the population of origin and the host population (39, 46). It has been found that, overall, immigrants in Norway have a 11% survival advantage. However, some immigrant subgroups, such as refugees, might have higher mortality rates than the general Norwegian population (47).

Other factors contributing to differences in the risk of recurrent fractures in different ethnicities can be genetics and biological variation in the skeleton. Studies reported differences in the macro- and microstructure of bones in people from different ethnicities; Chinese and Africans have a more robust bone architecture. Chinese women have a lower fracture risk of hip and distal forearm than Caucasians, partly due to thicker cortices and smaller but denser trabeculae (48). Caucasians also have a lower BMD than Africans, Hispanics, and Latin Americans, and the heritability of BMD is estimated between 50% and 85% (24, 48, 49).

Population demographics are also contributing factors to fracture risk; there are more elderly people in European and North American countries, leading to more fractures in these areas. In addition, latitude and environmental factors can play a role (26). Variation in the early environment influences peak bone mass, which is considered an important risk factor for childhood bone fractures, osteoporosis, and fracture risk in later life (22, 50). Another possibly important factor is time spent in Norway. In this study, we lacked detailed information about the duration of residency.

Strengths and limitations

The large size of the study sample (almost 150,000 first forearm fractures) and quality of the data are strengths of the study. Almost all Norwegian residents who sustained a forearm fracture aged +18 years in 2008–2019 were included in the study and were followed for up to 12 years. Several previous studies have focused on hip fractures since these fractures are easier to study in register-based data as surgical hospital admissions, at least in high-income countries (51). Forearm fractures, on the other hand, can be treated both in primary and specialist care and, depending on severity, can be treated either conservatively, often in emergency units, or surgically in hospitals.

To the best of our knowledge, this is the first study conducted on subsequent fractures according to country of background in a large population. The data used in the study were from patient registries with relatively reliable diagnosis codes and further linked to other data sources by a person-identifiable number.

Registry data nevertheless has its drawbacks, as some essential information may be lost due to misclassification or changes in coding methods (52, 53). Still, the current registry-based data was found to have high validity when using standardized algorithms for quality assurance (35).

The Norwegian-born population significantly outnumbered individuals from other ethnic backgrounds, which introduced greater uncertainty in incidence rates and hazard ratios, particularly for the patients from Other countries. To address this problem, the populations from these countries were categorized into one group, but still, the total numbers were relatively low. Moreover, the different age distributions in the Norwegian versus immigrant populations also complicated the comparisons of fracture risk, and therefore, we performed age-specific analyses in 15-year age groups.

The study included only individuals seeking hospitalization for the diagnosis and treatment of a fracture. We might have missed those treated only by primary care (about 5–7% of all forearm fracture patients) (34). However, according to Statistics Norway, immigrants are more likely to live in urban areas

(where fractures are reported to NPR) than in rural areas. In rural areas, although rare, patients are more likely to be exclusively treated in primary care without a referral to a hospital; consequently, the fractures might not be captured by the registry. Thus, there was probably a relatively greater probability of missing Norwegian-born than immigrant patients in this study (34).

We might also have missed individuals with fractures sustained abroad. However, these fractures would have been captured if they had been followed up in Norway, as we included records with follow-up codes that occurred only once in the data set. Still, we might have missed more fractures during travel among immigrants because they are more likely to travel and stay abroad for a longer time than the Norwegian-born population. These two biases work in opposite directions on the HR and may, therefore, have limited effect on the findings of lower risk in the immigrant population. Nevertheless, the proportion of fractures missed due to travel is unknown, and we cannot rule out the possibility that some of the difference is explained by this.

In conclusion, we found that the risk of subsequent fracture varied by country background. In both men and women, there was a higher risk of subsequent fractures among the Norwegian-born population compared to individuals born in countries outside of Norway. The risk of subsequent fracture increased with age in all groups, and there was a high rate of subsequent fractures also in the immigrant populations, which warrants a focus on prevention of subsequent fractures in all ethnicities regardless of the country of birth. The Norwegian-born population has among the highest risks of fracture in the world. Future studies should further focus on recurrent fracture risk in immigrants according to length of stay in Norway to elucidate whether a different early environment could be the reason why immigrant populations have a lower risk of subsequent fractures compared to the Norwegian population.

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Table 1 Number of individuals aged +18 years in 2008–2019 with first forearm fracture and any type of second fracture categorized by country of birth (three main groups)

Country of Birth	First forearm fracture (N)	Mean age (SD)	95% Conf. Interval	Second fractures (N)
Norway	127,431	59.0	58.9 – 59.1	32,664
Europe and North America	10,537	48.6	48.3 – 48.9	1,899
Other countries	5,508	44.3	43.9 – 44.7	798
Total	**143,476**	**57.7**	**57.6 – 57.8**	**35,361**

Table 2 Number of participants aged +18 years in 2008–2019 with a first forearm fracture, number of second fractures of any type, age-standardized incidence rates (IR) per 10,000 person-years, and age-adjusted hazard ratio (HR) of recurrent fracture with 95% confidence interval (CI) for the different countries of birth (three main groups)–stratified on sex

	No. first forearm fracture	No. recurrent fracture	IR	95% CI	HR	95% CI
Women	**100,553**	**26,654**				
Norway	91,409	24,979	516	509-522	1	(Reference)
Europe and North America	6,007	1,215	406	384-429	0.93	0.88–0.98
Other countries	3,137	460	278	254-304	0.76	0.70 – 0.84
Men	**42,923**	**8,707**				
Norway	36,022	7,685	380	372-389	1	(Reference)
Europe and North America	4,530	684	303	281-326	0.85	0.79-0.92
Other countries	2,371	338	286	257-318	0.82	0.74-0.92

Table 3 Number of participants aged +18 years in 2008–2019 divided into three age groups (*N*), number of subsequent fractures, age-standardized incidence rates (IR) per 10,000 person-years, and age-adjusted hazard ratio (HR) of subsequent fracture with 95% confidence interval (CI) for the different countries of birth (three main groups)

	N	No. second fracture	IR	95% CI	HR	95% CI
Age 18-44	**35,547**	**5,666**				
Norway	26,970	4,635	280	271-287	1	(Reference)
Europe and North America	4,662	644	273	253-295	0.91	0.84-0.99
Other countries	2,915	387	256	232-283	0.88	0.79-0.97
Age 45-59	**37,712**	**8,688**				
Norway	32,795	7,866	407	398-416	1	(Reference)
Europe and North America	3,115	536	343	315-373	0.85	0.78-0.93
Other countries	1,802	286	304	271-342	0.75	0.69-0.85
Age +60	**71,217**	**21,007**				
Norway	67,666	20,163	616	608-625	1	(Reference)
Europe and North America	2,760	719	539	501-580	0.92	0.85-0.99
Other countries	791	125	325	273-388	0.63	0.53-0.75

Table 4 Number of participants aged +18 years in 2008–2019 divided into the three geographic groups by age, number of second fracture of any type, age-standardized incidence rates (IR) per 10,000 person-years and age-adjusted hazard ratio (HR) of subsequent fracture with 95% confidence interval (CI)–stratified on sex

	No. first forearm fracture	No. second fracture	IR	95% CI	HR	95% CI
Women						
Age 18-44	**16,882**	**2,483**				
Norway	13,645	2,074	246	236-257	1	(Reference)
Europe and North America	1,872	242	255	225-289	1	0.88-1.14
Other countries	1,365	167	226	194-263	0.88	0.76-1.04
Age 45-59	**25,930**	**6,386**				
Norway	22,865	5,850	438	427-449	1	(Reference)
Europe and North America	1,876	342	358	322-398	0.82	0.74-0.92
Other countries	1,189	194	311	270-358	0.72	0.62-0.83
Age +60	**57,741**	**17,785**				
Norway	54,899	17,055	640	631-650	1	(Reference)
Europe and North America	2,259	631	580	536-627	0.95	0.88-1.03
Other countries	583	99	339	279-413	0.63	0.52-0.77
Men						
Age 18-44	**17,665**	**3,183**				
Norway	13,325	2,561	314	302-326	1	(Reference)
Europe and North America	2,790	402	286	259-315	0.86	0.78-0.96
Other countries	1,550	220	284	249-325	0.86	0.75-0.99
Age 45-59	**11,782**	**2,302**				
Norway	9,930	2,016	338	323-353	1	(Reference)
Europe and North America	1,239	194	318	277-367	0.89	0.77-1.04
Other countries	613	92	292	238-358	0.83	0.67-1.02
Age +60	**13,476**	**3,222**				
Norway	12,767	3,108	510	492-528	1	(Reference)
Europe and North America	501	88	357	289-440	0.77	0.62-0.95
Other countries	208	26	281	191-413	0.63	0.43-0.93

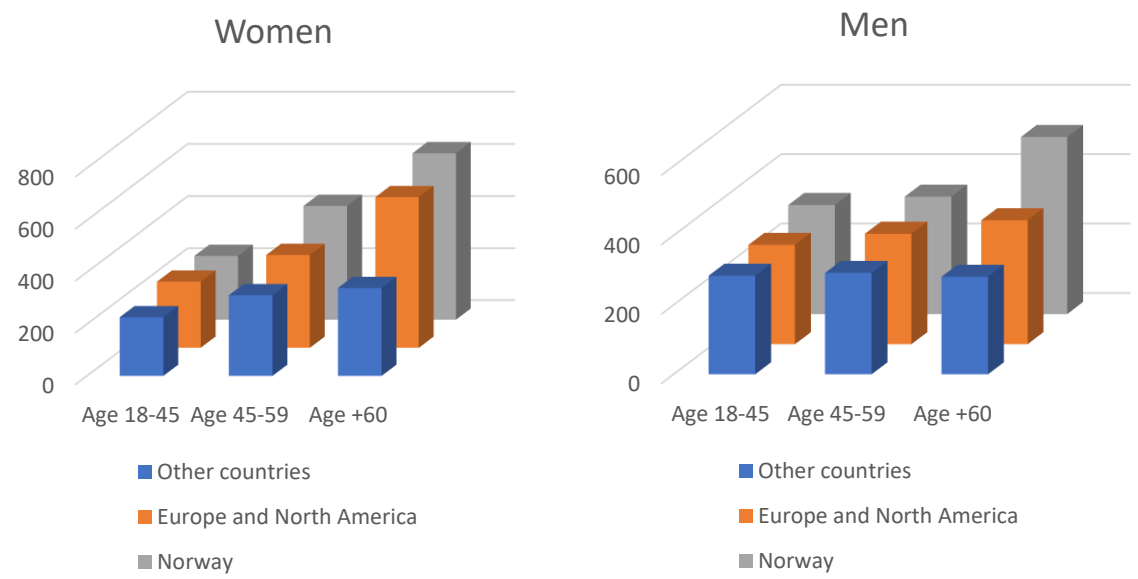

Figure 1 Age-standardized incidence rates (IR) per 10,000 person-years for individuals by age and country of birth (three main groups), stratified on sex

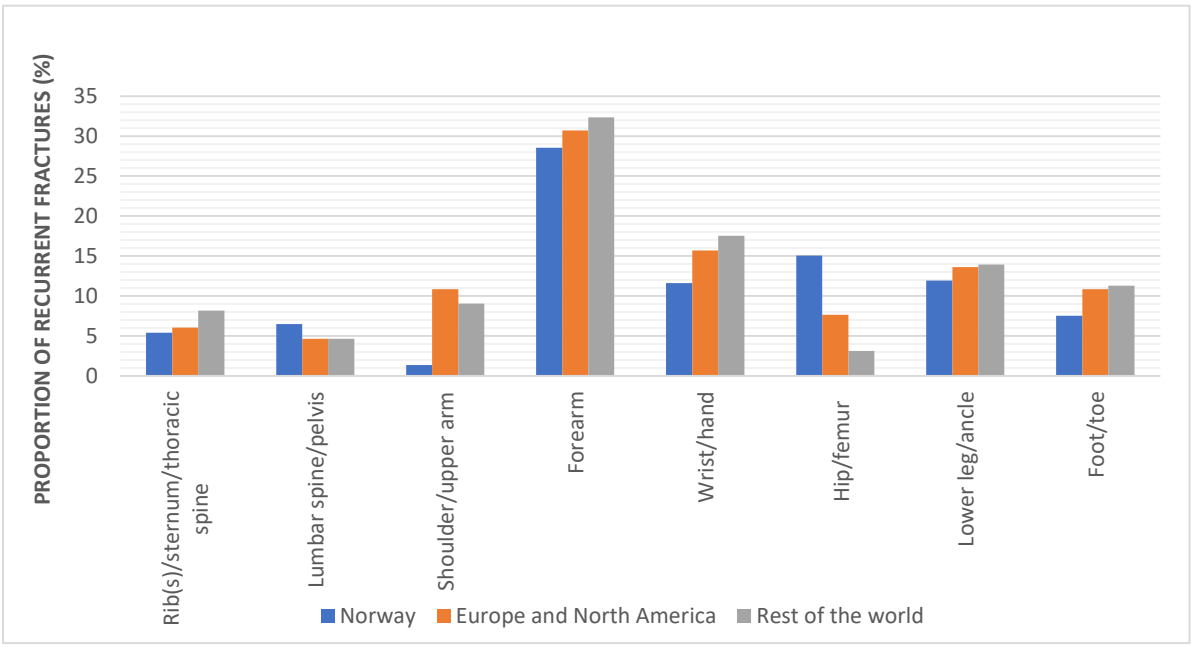

Figure 2 Distribution of subsequent fractures in patients with an index forearm fracture 2008–2019 by country of birth (three main groups)