

An example of a successful national research network in epidemiology – The Norwegian Epidemiologic Osteoporosis Studies (NOREPOS)

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WHY EPIDEMIOLOGICAL RESEARCH ON OSTEOPOROSIS AND FRACTURES IN NORWAY?

The pioneers

Knowledge of risk factors and fracture incidence is an important premise for future preventive strategies and planning of health care services. One of the great challenges which have confronted the health services in Norway during the last decades has been the management of and care for patients who have sustained hip fractures. Before 1975, few papers had been published dealing with fracture incidence in Norway. In one article published in “Norsk Magazin for Lægevidenskap” (1939) the author had counted all fract. radii. “typica” treated at “Oslo Legevakt” in 1936 and 1937, examined all x-rays (about 2000-3000), sorted them into 7 sub-groups and made drawings of the different types (1). The author also categorized the fractures after injury mechanism and presented seasonal variation, with the highest incidence during the months November-February, and the lowest in July. The higher incidence during the winter season could not exclusively be explained by snow, ice and sport accidents (1).

As a physician in the 1960s in Finnmark, the northernmost county in Norway, dr. Stadaas was puzzled by the low number of hip fractures. He made a huge effort and collected data on all hip fractures in Finnmark and Hedmark, a county much farther south, and compared this information with published figures from Malmö, Sweden (2). He found that the incidence was lower in Finnmark than in both Hedmark and Malmö, and the lower incidence could not be explained by a somewhat younger population in Finnmark with relatively more men.

Two papers on the epidemiology of hip fractures were published in 1978. The first one was based on a hand-written curve of an increase in number of hip fractures treated at all hospitals in Oslo from 1950 to 1969 made by A. Ilebekk (Figure 1). In addition Falch and Ilebekk retrieved data on hip fractures from “Oslo trygdekontor” 1950-75. They found that the number of hip fractures per year during this period more than tripled in Oslo in persons 50 years and over (3). At that

time, the dimension and seriousness of this problem in Norway was unknown.

The other 1978-paper described incidence, injury mechanism, treatment and length of hospital stay (mean 29 days!), as well as post fracture consequences, rehabilitation and physical functioning among hip fracture patients at “Regionsykehuset i Trondheim” during 1970-74 (4).

In the beginning of the 1980s one fourth of all somatic hospital bed-days for the oldest patients and 46% of the beds for fracture patients of all ages were occupied by hip fracture patients (5). These conclusions were based on data from five Norwegian counties, nationwide data were not available. In the United States the acute care cost of hip fractures almost tripled between 1970 and 1980 (6). Studies from other countries had documented serious consequences of hip fractures for the patients in terms of declined quality of life and physical function, pain, increased dependency of help from others and post fracture mortality (6). However, comparable information from Norway was limited at the time when Jan A. Falch and Vilhjalmur R. Finsen published their first papers included in their doctoral dissertations on fracture epidemiology, osteoporosis and bone loss (6,7).

Falch found that individuals in Oslo had higher incidence of hip fracture than other Norwegian counties (8), and that the age- and sex-specific annual incidence in Oslo was the highest ever reported world wide. Compared to other countries, women in Oslo had a significantly higher incidence of distal forearm fractures (9). Later, results from a large European study on vertebral fractures (EVOS) showed that that women and men in Oslo had the highest prevalence of such fractures in Europe (10).

As shown in Oslo for the decade 1978-88 (11), there was a significant increased hip fracture incidence from 1972/73 to 1983/84 in the Trøndelag counties in Mid-Norway (12). The authors also found an increasing incidence of hip fracture with increasing degree of urbanization – and the difference between people in rural and more urbanized areas was the same in 1983/84 as in 1972/73. The risk of hip fracture increased with number of previous fractures up to age 70 in women and 80 in men, and a second hip fracture

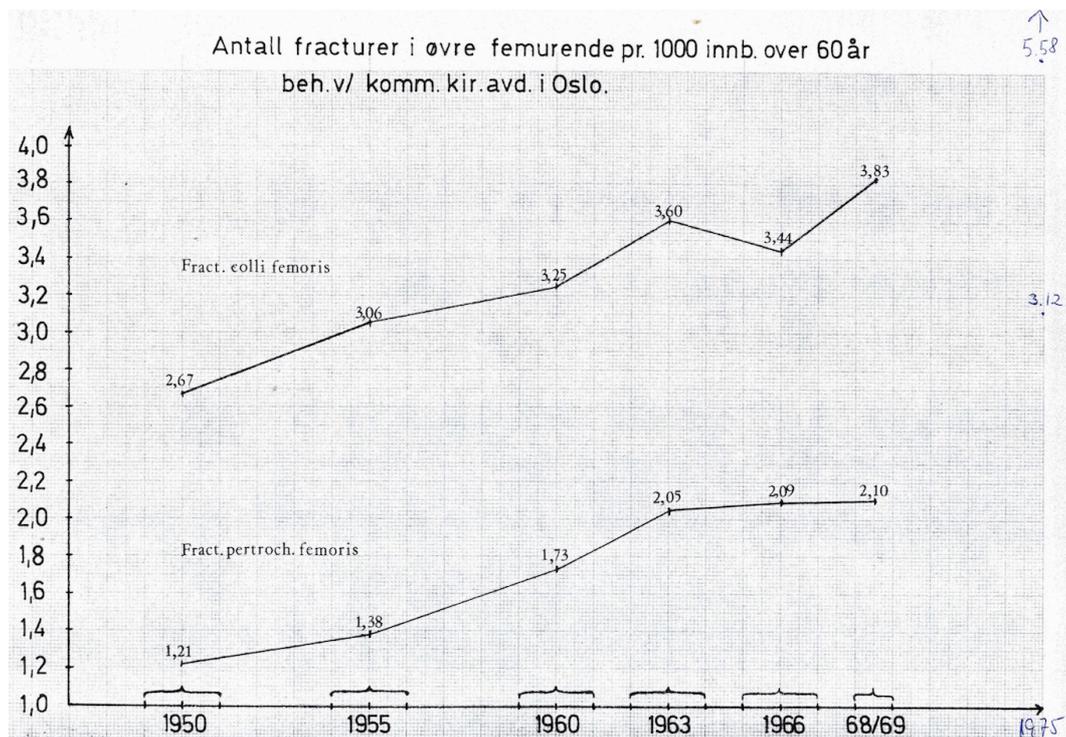


Figure 1. A hand-written curve of the increase in number of hip fractures treated at all hospitals in Oslo from 1950 to 1969 made by A. Ilebekk.

was most often at the same location as the first one and occurred at a mean interval of 7 years after the first (6). Based on a review of many studies, Finsen found a significant association between hip fracture incidence and life expectancy at age 70 in the same country (6).

The increase in hip fracture incidence was also found in the county of Troms, Northern Norway, and the authors reported a much lower incidence in Troms compared to Oslo 1978-1989 (13). In the city of Oslo a higher hip fracture incidence was documented in the east part of the city compared to the west, but even in the west the incidence among women was higher than in the county of Sogn og Fjordane (14). The position of Oslo as the city with the highest hip fracture incidence world-wide has later been verified in several papers – the latest in 2012 (11,15-18).

Other relatively early papers on fracture epidemiology in Norway include Hove's description of the epidemiology of distal forearm fractures based on hospital data from Hordaland (19,20), and Forsén's paper on smoking, physical activity and leanness as predictors of hip fracture – linking data from the first health survey in Nord-Trøndelag (HUNT1) with information from hip fracture patient in local hospitals (21).

Diagnosis and treatment of osteoporosis – introduction of bone mineral density measurements

Before the 1990s, there were no consensus regarding diagnosis and treatment of osteoporosis. X-rays do not reveal osteoporosis before 30-50% of the bone mass is lost. The first machine in Norway (a Studsvik forearm scanner (DPA=dual photon absorptiometry) – see photo Figure 2) measuring bone mineral density (BMD) was

obtained as part of a cancer project at Aker university hospital in 1975. Falch, at that time a young senior resident, was asked to learn how to operate the machine, and to start a research project on calcium and bone metabolism.

The first DXA-machines (Dual-energy X-ray absorptiometry) that can measure the whole body including the hip and vertebrae were acquired in 1991 by two groups of private specialists in Oslo (T. Ruud, gynecology and J. Halse, endocrinology). In 1992 the Aker university hospital received a DXA-machine as a gift



Figure 2. Photo of the first machine in Norway (a Studsvik forearm scanner (DPA=dual photon absorptiometry) measuring bone mineral density (BMD) obtained at Aker University Hospital in 1975.

from “Norske Kvinners Sanitetsforening” (NKS) (The Norwegian Women's Public Health Association). They had paid NOK 850,000 for this Lunar DPX-I machine which was ceremonially presented at a gathering at Aker hospital on May 4th 1992. This machine gave rise to the establishment of the “Laboratorium for Benmetabolisme” at Aker hospital, where Falch was the leader from 1992 to 2008.

Beyond calcium and vitamin D, the only available treatment with documented effect on bone mineral density and fractures before 1995, was oestrogen in women, but such therapy was controversial already at this time (22,23). In addition, calcitonin, sodium fluoride and anabolic steroids were used, but documentation of their effect was limited.

Falch's thesis and later scientific achievements have been of fundamental importance for osteoporosis research and treatment in Norway. Combining the treatment of osteoporotic patients with thorough knowledge of endocrinology, bone metabolism and epidemiology, Falch was a pioneer in osteoporosis epidemiology in Norway. In 1999 he was appointed professor in osteoporosis at the University of Oslo – the first professor in osteoporosis in Norway.

The HEMIL program at the Research Council of Norway

Included in the large HEMIL-program (“Helse, miljø og levekår”) launched by the Research Council of Norway 1987-92, there was a sub-program in Epidemiology, but also one separate sub-program in Health Promotion – with a separate board. The members of this board decided to give priority to research projects in epidemiology and prevention of fractures and injuries in their first call for research proposals. One of the first research fellows to be funded by this program was Haakon E. Meyer. His later thesis “Risk Factors for Hip Fracture – Epidemiological studies in middle-aged and old Norwegian women and men” (1996) (24), took the research on osteoporosis epidemiology a step further – beyond the previous more descriptive studies. Using data from the large population-based Coronary Heart Disease Surveys in three Norwegian counties linked to hip fracture data collected from patient records in local hospitals, he found that low weight, weight loss, high stature and several conditions connected to fragility, e.g. low energy intake, were statistically significant risk factors (24). He also found that the high stature of Norwegians could explain parts of the higher fracture incidence in Norway compared to other regions of Europe (24).

BMD MEASUREMENTS AS PART OF THE POPULATION-BASED HEALTH SURVEYS IN TROMSØ, NORD-TRØNDELAG, HORDALAND AND OSLO (25)

THE TROMSØ STUDY (<http://tromsostudy.com>)

Before the fourth population-based health survey in Tromsø in 1994-95, the Institute of Community Medi-

cine (“ISM”), decided to initiate research on a large public health problem where the scientific evidence was limited. The decision fell on osteoporosis and fractures, based on the reported high hip fracture incidence in Norway (8).

The planning for the fourth Tromsø study and inclusion of measures of bone mineral density started with a “study tour” to experts on osteoporosis epidemiology in Oslo. The “take-home-message” was: “Do not start such a study without physicians with thorough knowledge in bone metabolism and endocrinology.” The group of four who started the osteoporosis project in the Tromsø Study had experience in epidemiology, preventive medicine, rheumatology and gynecology, but also a close contact with bone-specialists at the University hospital in Tromsø. The established Coronary Heart Disease research milieu at “ISM” was sceptic to this new area of commitment, but allowed BMD measurements in a phase 2 – i.e. invitation to a sample of those attending the screening (phase 1) to come to a new appointment.

The Steering Group of the osteoporosis project in Tromsø and the corresponding group in Nord-Trøndelag prepared a joint application to the Ministry of Social Affairs for economic support to the two projects, and were invited to a meeting in the Ministry in October 1993. Both projects got financial contributions – as well as grants from the Research Council of Norway.

Two osteometers (Single X-ray absorptiometry (SXA) – “Adam” and “Eva”) were purchased, operated by two research fellows who later achieved their PhDs on osteoporosis and fractures. One of these fellows even found an error in the software of the machine, an error the manufacturer admitted to, but which resulted in manual corrections of all the scans. About 8,000 subjects were examined in the fourth Tromsø study (1994-95). Since then, BMD measurements (distal forearm, hip, whole body and vertebral scans) have been collected several times – and X-rays from all fractures since 1994 have been registered in a unique database. In addition, a great number of exposure data have been collected in Tromsø since 1974 – six times altogether (26). DXA measurements are included in the seventh Tromsø study in 2015-16.

THE NORD-TRØNDELAG HEALTH STUDY (HUNT) 1995-97 (<http://www.ntnu.edu/hunt>)

In the early 1990s planning of a second population-based health survey in Nord-Trøndelag had started, and measurements of BMD were included (27). A collaboration was established with a planned project on COPD, use of asthma drugs and BMD (28). The fact that Tromsø already was planning a similar osteoporosis project allowed possible comparisons of results and close collaboration.

Two SXA machines like the ones used in Tromsø, were purchased – with extra funding from the Norwegian Women's Public Health Organization (NKS) in Nord-Trøndelag. In total more than 18,000 women and

men in different age-groups were measured. Later, BMD has been measured in a follow-up study in 2001 and in HUNT3 (2006-2008) – both distal forearm, hip and whole body. DXA measurements are planned to be included in the fourth HUNT study in 2017. A local registry of hip- and forearm fractures (1995-2012) has been established in Nord-Trøndelag.

THE HORDALAND HEALTH STUDY (HUSK) 1997-99 (<http://husk.b.uib.no/>)

The Hordaland Health Study was conducted in the county of Hordaland on the west coast of Norway. In an ancillary study on osteoporosis and fractures, BMD of the hip and total body was obtained by one stationary, fan beam dual X-ray densitometer (29). Valid femur scans were obtained for more than 3100 women and men aged 47-50 years and on almost 2250 aged 71-75 years. Total body scans and body composition were also measured. All these participants had also participated in an earlier health study during 1992-93; the Hordaland Homocysteine Study (30).

THE OSLO HEALTH STUDY (HUBRO) 2000-2001 (www.fhi.no/hubro-en)

The National Health Screening Service (NHSS) in Oslo had since the 1970s carried out the practical work regarding collection of data in all regional health screenings in Norway, and before that been responsible for all tuberculosis screenings (31). However, health screening data from both women and men in Oslo were lacking. In collaboration with Professor Dag S. Thelle at the University of Oslo, the NHSS made plans for a Oslo Health Study (HUBRO) starting in 2000, and BMD measurements of a sample of the invited were decided to be included (32,33). The 2 SXA Osteometers from Tromsø were borrowed, and about 2700 individuals in different age groups were measured. In addition, about 700 men who had participated in the first population-based Coronary Heart Disease study in Norway in 1972-73, were invited to a DXA scanning at Aker University hospital.

ESTABLISHMENT OF THE NOREPOS COLLABORATION (WWW.NOREPOS.NO) (25)

Scientists in the osteoporosis studies in Tromsø, HUNT and Hordaland – i.e. Jeanette H. Magnus, Berit Schei and Grethe S. Tell, each applied for funding from the Norwegian Osteoporosis Foundation (NOF) in 1996. Based on the relatedness of the applications, the review board in NOF decided to support the applicants given that they established a research collaboration between the study sites. This was the starting point of the “Norwegian Epidemiologic Osteoporosis Studies” (NOREPOS) research collaboration. Later on, HUBRO was included represented by Haakon E. Meyer – and each of the four partners was subsequently represented with two members each in NOREPOS.

The regional studies were part of the research collaboration Cohort of Norway (CONOR)

(www.fhi.no/conor) (34), and thus include a large number of descriptive variables on the participants, including socio-demographic factors, health behaviours, current and previous disease status, anthropometric measures and blood pressure. In addition, serum has been analysed for blood lipids and glucose, and whole blood samples are stored at -80°C .

The purpose of NOREPOS

The overall purpose of the NOREPOS collaboration was – and still is, to undertake etiologic research in order to shed light on why hip fracture rates in Norway are the highest in the world (11,15) and to unravel potential causes for the substantial geographic variation in the incidence of hip fracture – both within Norway and between Norway and other countries.

At each study site there were established local osteoporosis research groups. Collectively the Steering Committee and the local osteoporosis groups cover a broad range of scientific fields related to osteoporosis, including epidemiology, endocrinology, gynaecology, rheumatology, physiotherapy, nutrition, health behaviour sciences and general practice.

The Steering Committee’s first tasks were, besides applying for funding, to conduct validation, precision and calibration studies, as well as between-study comparisons. Methodological studies comparing the performance of densitometers used in Tromsø, Hordaland, Nord-Trøndelag and Oslo were carried out (35-38). In one of these, a total of 16 participants agreed to travel between study sites and had measurements on each of the DXA machines in Tromsø, Bergen and Oslo. One of the initial goals of NOREPOS was to compare BMD levels in different regions of Norway, adjusted for important confounders (35). Later, the NOREPOS collaboration has been expanded to also include collection and analyses of data on hip fractures from all Norwegian hospitals – i.e. NORHip – see next paragraph.

THE NOREPOS HIP FRACTURE DATABASE (NORHIP) – ONE OF THE WORLD’S LARGEST HIP FRACTURE DATABASES

Among osteoporotic fractures, hip fracture is the most serious, strongly associated with pain, suffering, reduced functional ability and excess mortality. Hip fracture patients may have up to 8-fold increased risk of all-cause mortality during the first 3 months after the fracture (39). One third of those 85 years or older who lived at home when sustaining a hip fracture, lived in a nursing home one year after the fracture (40). In addition to dramatic consequences for the individual patient, hip fractures have substantial economic consequences for society (41,42) and are one of the most expensive single diagnoses in Norwegian hospitals. Based on hip fracture data from 2008-2011, the expenses for hip fractures in Norway for patients aged 70 and above, were calculated to be about 4.5

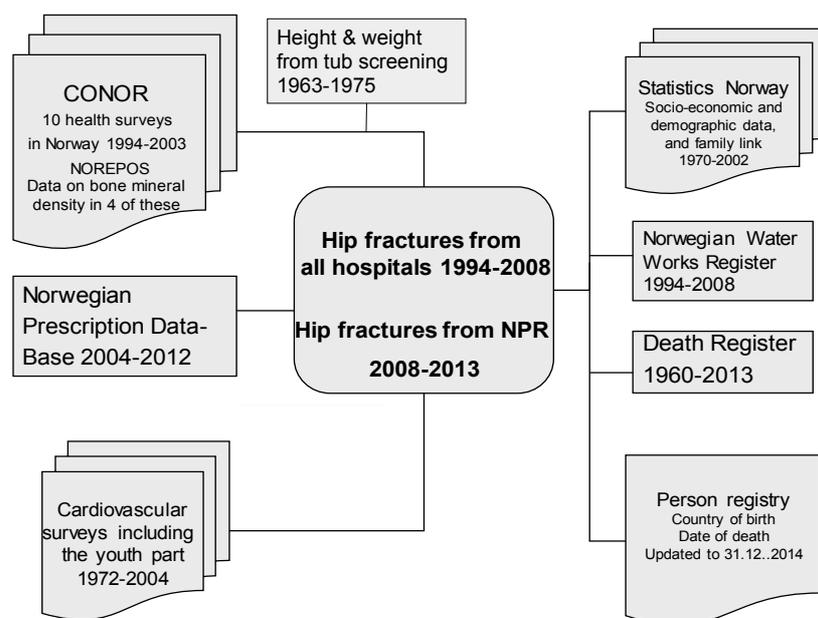


Figure 3. The linkage of the database NORHip with data from other registers and health surveys.

billion NOK the first year (536 mill. Euros) and about 7.5-9.0 billion NOK altogether (i.e. 893 mill.-1.1 billion Euros) (43).

Based on knowledge of the huge consequences of a hip fracture for patient and society, NOREPOS decided to establish a retrospective hip fracture database. The Research Council of Norway awarded in 2008 a four year grant to study predictors, incidence and survival of hip fractures 1994-2008 in the entire country. All hip fractures treated in Norwegian hospitals during this period were retrieved through a system developed by the Norwegian Knowledge Centre for the Health Services, providing a historic database of hip fractures (NORHip) based on computerized records of discharge diagnoses from the hospitals (18). In 2011, after more than 3 years of applications to a countless number of different institutions to be allowed to receive these data, information on almost 140,000 hip fractures was obtained. The fracture data have been linked to other databases and population-based surveys – for example socio-demographic factors, cause of death, prescriptions and water quality factors (Figure 3). To assess the validity of our classification of records, NORHip was compared with local hip fracture registries from Oslo and Tromsø. The combined Cohen's kappa for the comparisons was 0.95. Corresponding information about hip fractures sustained 2009-2013 from the Norwegian Patient Register has been added in 2015. Thus, the NORHip database contains information on about 185,000 hip fractures.

ACCOMPLISHMENTS

NOREPOS investigators have successfully worked together since 1997 and have received grants from The Norwegian Women's Public Health Association, The Norwegian Osteoporosis Foundation and from The Research Council of Norway – for maintaining the

network and for funding of research fellows and post doc positions.

In addition to the meetings and research collaboration within NOREPOS, the network has for the last 10 years annually arranged a 2-day NOREPOS workshop, attended by 25-35 researchers from around the country. Every year national and international speakers have been invited and results from ongoing studies and plans for future studies have been presented.

NOREPOS' website (<http://www.norepos.no>) contains information about workshops, meetings, references to NOREPOS-publications, NOREPOS PhD candidates, names of the members of the steering group and presentations of the activity at all the four study-sites with lists of some of the local publications.

NOREPOS has presented an overview of some important results in a Cohort profile paper published in 2014 (25). Some of the findings are listed below in the form of keywords:

- Low baseline BMI and weight loss during the following three decades were both strongly and inversely related to total hip BMD.
- Higher forearm BMD levels was found in rural compared to urban areas.
- No apparent north-south gradient in BMD was found.
- Self-reported forearm fractures increased with increasing degree of urbanization for both genders. Thirty percent higher rates of forearm fractures were found in urban compared to rural postmenopausal women. BMD is an important explanatory factor for the urban-rural difference, whereas only a small part of the difference may be explained by a higher body mass index in rural women.
- Weight loss of 5% or more was associated with a 33% increased risk of distal forearm fractures.
- The prevalence of forearm fractures was found to be higher in areas with acidic water, which could

mainly be explained by a higher microbial content in acidic water.

- While the hip fracture incidence increased from the 1970s to the 1990s, hip fracture rates have declined during the last decade.
- Norway still has among the highest hip fracture incidences in the world in 2008.
- The previously estimated number of hip fractures among adults in Norway, about 9,000, has been verified using data from NORHip.
- The mean age of hip fracture patients is 80 years, and women comprise 70% of the fractures. About one in eight hip fracture patients suffers a new hip fracture, and one in four hip fracture patients have a second fracture of *any kind*.
- Only 16% of female hip fracture patients above 50 years used anti-osteoporosis drugs one year after the fracture.
- More than one in four hip fracture patients above 50 years die within a year after the fracture.
- One-year mortality in hip fracture patients was almost 5-fold higher in men and 3-fold higher in women compared to the general Norwegian population.
- The excess mortality was highest during the first two weeks, but was still present more than 10 years after the fracture.
- Low serum 25(OH)D was associated with increased risk of hip fracture.
- A high level of vitamin E in serum was associated with reduced risk of hip fracture.
- The content of magnesium seems to be protective, whereas cadmium and lead seems to be harmful to bone health and may possibly increase the risk of hip fracture.
- A higher hip fracture incidence was observed during the winter compared to the summer months.
- The incidence of hip fracture decreased with increasing Body Mass Index (BMI) in both genders, whereas abdominal obesity was associated with *increased* risk when BMI was adjusted for.

CONCLUSIONS

The number of BMD measurements in NOREPOS is one of the largest in the world (more than 56,000

forearm BMD measures and more than 28,000 hip BMD measures), including a substantial proportion of men. In Tromsø, Nord-Trøndelag and Hordaland subgroups of the participants have had BMD measured twice, and several individuals in Tromsø and HUNT have been measured three times. The BMD measurements and the fracture data may be linked to a large number of other risk factor/exposure data from CONOR and other previous population-based health surveys with information from questionnaires, anthropometric measurements, blood pressure, heart rate and results from serum analyses. Few, if any, other research groups are able to conduct studies of this dimension. The large number of participants yields ample statistical power to examine a wide range of research questions.

Altogether, these data constitute a unique source of information for etiologic research, genetic studies as well as for biomarkers of osteoporosis and fractures – and is one example of a successful national research network in epidemiology. In the future, information on hip fractures will be updated with data from the Norwegian Patient Registry, and new deaths will be linked to NORHip from the Cause of Death Registry. Genetic and epigenetic epidemiologic studies are also feasible, as well as studies on gene-environment interactions. Through collaboration with osteoporosis researchers in other countries, we aim to perform cross-country comparisons to find possible explanations for the higher hip fracture incidence in Norway.

The economic burden of fractures are expected to increase due to the increasing number of elderly during the years to come. In Norway the number of residents 70 years and above will double during the next 30 years (Statistics Norway). Thus, hip fractures will continue to pose a national and international public health challenge and a considerable public health and health care problem.

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