Cohort profile:

Norwegian Epidemiologic Osteoporosis Studies (NOREPOS)

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Abstract

Aims

This paper describes the history, purpose, data collection and contributions in the research collaboration Norwegian Osteoporosis Epidemiologic Studies (NOREPOS).

Methods

NOREPOS encompasses almost 85,000 bone mineral density measurements within Cohort of Norway and data on almost 140,000 hip fractures in Norway 1994-2008. Included are anthropometric measurements, blood pressure, lipids and glucose, and 50 standard questions on sociodemographic factors, diseases and risk factors. Blood samples/ DNA are stored.

The main research question posed in NOREPOS is why hip fracture rates in Norway are the highest in the world. Data on hip fractures 2009-2013 will be added in 2014.

Results

Main findings include: Every hour a Norwegian suffers a hip fracture; hip fracture incidence rates declined after 1999; only 16% of patients used anti-osteoporosis drugs one year after hip fracture; 25% of patients died within one year after the fracture; 12% suffered a new hip fracture within 10 years; rural dwellers had lower hip- and forearm fracture incidence than city dwellers; magnesium in tap water may be protective whereas bacterial contamination, cadmium and lead may be harmful to bone health; low serum vitamin D and E levels were associated with higher hip fracture risk; vitamin A was *not* associated with fracture risk; and abdominal obesity increased the risk of hip fracture when BMI was accounted for.

Conclusion

NOREPOS encompasses a unique source of information for aetiologic research, genetic studies as well as for biomarkers of osteoporosis and fractures. Because of the increasing number of elderly in Europe, hip fractures will continue to pose an international public health and health care challenge.

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Why did the study come about?

The research collaboration the "Norwegian Epidemiologic Osteoporosis Studies" (NOREPOS) was established in 1997. Before the research network started, it had been estimated that around 9,000 persons suffered a hip fracture annually in Norway [1] – that means a new hip fracture every hour. The highest incidence of hip fractures ever reported worldwide, was from Oslo [2,3], the capital city of Norway, with rates twice as high as in Amsterdam [4,5]. Within Norway considerable geographic differences was also reported, and in 1989 the incidence was 50% higher in Oslo compared to the rural county of Sogn and Fjordane on the western coast [6]. Based on data from Oslo, it has been estimated that Norwegians suffer about 15,000 forearm fractures annually, an incidence rate which is also among the highest worldwide [7].

Among osteoporotic fractures, hip fracture is the most serious, strongly associated with pain, suffering, reduced functional ability and excess mortality. A meta-analysis indicated that patients with hip fracture may have up to 8-fold increased risk of all-cause mortality during the first 3 months after the fracture [8]. 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 [9].

In addition to dramatic consequences for the individual patient, hip fractures have substantial economic consequences for our societies [10-11] and are one of the most expensive single diagnoses in Norwegian hospitals. Based on figures in a report carried out on assignment from the Norwegian Directorate of Health, expenses for hip fractures in Norway for patients aged 70 and above, were calculated to be about 4.5 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) [12]. In Denmark, the economic burden of *all osteoporotic fractures* was estimated at 1.56 billion Euros for the population 50 years and above (2011), of which more than half will lie with the municipalities [11]. If we apply these figures on the Norwegian population and anticipate the same fracture incidence, the economic burden calculated in Norwegian currency would be almost 10 billion NOK (1.2 billion Euros). The economic burden of fractures are expected to increase due to the

increasing number of elderly [13]. In Norway the number of residents 70 years and above will double during the next 30 years (Statistics Norway).

The purpose of NOREPOS

Information on fracture incidence is of fundamental importance because it lays the foundation for etiologic research on trends and geographical differences. Ultimately such information is an important premise for future preventive strategies and planning of health care services. With this background, 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 [2,5] and to unravel the causes for the substantial geographic variation in the incidence of hip fracture - both within Norway and between Norway and other countries.

How did the study come about?

NOREPOS is a research collaboration on osteoporosis and fractures combining data from four large community-based epidemiologic studies: The Tromsø Study [14-16], the Nord-Trøndelag Health Study (HUNT) [17-19], The Hordaland Health Study (HUSK) [20,21] and the Oslo Health Study (HUBRO) [22,23] (www.norepos.no). See Figure 1.

(Figure 1 in here)

These studies, covering different regions of Norway, were also part of the research collaboration Cohort of Norway (CONOR), described previously (www.fhi.no/conor) [24-26]. Briefly, CONOR includes ten community-based epidemiologic studies and is a collaborative project between epidemiology departments at the universities in Tromsø, Trondheim, Bergen and Oslo, and the Norwegian Institute of Public Health. During the period 1994-2003, around 310,000 individuals were invited of whom nearly 182,000 participated (www.fhi.no/conor). At four of the CONOR study sites, ancillary studies of osteoporosis (bone mineral density [BMD]

measurements), with subsequent follow-up for fractures, were conducted, constituting the NOREPOS collaboration. Later this collaboration has expanded to also include collection of data on hip fractures from all Norwegian hospitals (NORHip - see later).

The history of NOREPOS

At each study-site there are local osteoporosis research groups including 5-15 researchers. Two representatives from each study site constitute the NOREPOS Steering Group. Collectively the Steering Group covers a broad range of scientific fields related to osteoporosis – including epidemiology, endocrinology, gynaecology, rheumatology, physiotherapy, nutrition, health behaviour sciences and general practice. The members are listed her at this web site: http://www.norepos.no/contact.

We have successfully worked together since 1997 and have received grants from The Research Council of Norway (RCN) three times. The first was for network-building, the second grant was for a common PhD candidate who finished her dissertation at the end of 2009, as well as funding to maintain the network. Our third RCN-grant covered the period 2009- 2013, with one PhD and two post doc candidates. Members from the study sites are advisors and co-authors.

In addition to the meetings and research collaboration in NOREPOS, we have for the last 8 years annually arranged a 2-day NOREPOS workshop, attended by 25-35 researchers from around the country, with the following disciplines represented: general practice, epidemiology, statistics, endocrinology, rheumatology, orthopaedics, genetics, pharmacology, gynaecology, nutrition, physiotherapy and biochemistry. Every year we have invited national and international speakers and we have had presentations of results from ongoing research and plans for future studies.

Studies collaborating in NOREPOS

The location of the study sites are presented in Figure 1. The different studies constituting NOREPOS are described in table 1 – i.e. time of study, invited age-groups, participation rate and number of NOREPOS participants with bone density measurement. At each study site, the appropriate Regional Committee for Medical and Health Research Ethics and the Data Protection Authority of Norway reviewed and approved the study protocols. Each participant signed an informed consent. The studies have been conducted in accordance with the World Medical Association Declaration of Helsinki.

(Table 1 here)

Osteoporosis in the Tromsø Study 1994-95, 2001-02, 2007-08

This was the first large population-based epidemiologic study on osteoporosis in Norway. It started in 1994-95 as an ancillary study to the TROMSØ IV, a cohort study of the adult population of Tromsø, Northern Norway [16]. Since 1974, population-based samples have been invited a total of six times to comprehensive health surveys, conducted as collaborations between several teams of scientists. Forearm BMD was measured by single energy x-ray absorptiometry (SXA) in 7,809 participants in Tromsø IV (1994-95) and repeated in the same individuals attending Tromsø V (2001-02). At this survey the same participants were also measured with dual energy x-ray absorptiometry (DXA) (total hip), whereas total body BMD was measured in 1,726 participants. Repeated forearm (SXA), hip and total body BMD (both by DXA) have also been measured in Tromsø VI (2007-08) (http://tromsostudy.com) (Table 1).

The HUNT Osteoporosis Study 1995-97, 2001, 2006-08

This study includes collaborators working on BMD projects and fracture assessment as part of the large North Trøndelag Health Study (HUNT2) [19]. Forearm BMD was measured in 18,265 subjects in 1995-97 [18,27] with the same type of apparatus and protocol as in Tromsø. In 2001, after an average period of 4.6 years a subsample attended a follow-up study with forearm

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densitometry. HUNT3 (2006-2008) was designed as a follow-up of the cohorts measured with densitometry in HUNT2, among whom 12,100 participants had BMD measured at the hip and lumbar spine (DXA), and almost 15,000 had their forearm measured with either DTX 200 (N=9,333) or DTX 100 (N=5,640). The latter group were examined according to previous protocols (SXA) from HUNT2 (http://www.ntnu.edu/hunt).

Osteoporosis in the Hordaland Health Study (HUSK) 1997-99, 1999-2001

In an ancillary study to HUSK, hip and total body BMD was measured in 5,348 participants using DXA methodology [20]. Participants were middle aged (46-49 years) and elderly (71-74 years) previous participants of the Hordaland Homocysteine Study [21]. In addition, forearm BMD was measured in some of the participants on the same SXA machine as in Tromsø. Of the perimenopausal women in the cohort, 73% were re-examined with DXA after two years (http://husk-en.b.uib.no/).

Osteoporosis in the Oslo Health Study (HUBRO) 2000-01

Forearm BMD was measured with SXA in 2,648 participants using the same machine as in Tromsø [22,23]. In addition, hip- and total body BMD were measured by DXA in 703 older men, (http://www.fhi.no/hubro-en), of which the majority previously had participated in the Oslo Study in 1972-73 [28].

What has been collected and measured?

Health behaviours, health status

All the surveys followed a standard data collection procedure including 1) measurements of height, weight, hip/waist circumferences, heart rate, blood pressure; 2) 50 standard questions on sociodemographic factors, health behaviours, general health and disease; 3) a non-fasting blood

sample drawn for analyses of lipids and glucose and 4) an EDTA blood sample/extracted DNA stored at -80°C (see description of CONOR in [25] or at CONOR's web site www.fhi.no/conor). In addition, all the four study sites collected and froze serum samples (-80°C) for later analyses. These serum samples are, however, not part of CONOR, but belong to the individual health study.

Bone mineral density

BMD was measured at each study site, either at the distal forearm with SXA or DXA - and/or at the hip or total body with DXA. All BMD measurements followed a similar protocol. A large amount of work has been undertaken to pool BMD data from all the study sites. For assessment of regional differences in BMD, the measurement levels of the densitometers had to be comparable. Hence, validation, precision and calibration studies, as well as inter-study comparisons, have been conducted [29-32]. We designed and carried out a methodological study comparing the performance of densitometers used in Tromsø, Bergen and Oslo. A total of 16 subjects had three repeated measurements on each of the three machines. We found that the DXA machines in Tromsø and Bergen had excellent agreement for total hip BMD, whereas the results from measurements in Tromsø and Oslo required adjustments before BMD could be compared across these study sites [30].

We have also examined differences in precision of BMD measured by SXA and DXA [32]. SXA showed better precision than DXA in the forearm, and in order to detect a 3% change in BMD one would need two repeated measurements by DXA in the distal forearm at each of two consultations, but only one measurement by SXA at the same site.

Fracture registers

Whereas the first sub-studies mainly were dealing with analyses of BMD, we have later focused on the more important endpoint, namely fractures. HUNT has established a hip- and forearm

fracture register, and in Tromsø all non-vertebral fractures sustained among participants in the Tromsø Study have been registered from 1988 through 2009. In addition, all participants in CONOR were asked about previous hip- and forearm fracture and age at last fracture. Most study sites have collected data on hip fractures from discharge registers at their local hospitals by comparing these data with data from medical records and x-ray registries for participants who have been admitted to a hospital with a hip fracture diagnosis or surgical procedures indicating hip fracture. Researchers from the Tromsø Study have reported that 93% of all hip fractures and 97% of all wrist fractures in the entire study population were found by computer linkage to the radiographic archives, whereas the discharge register detected 87% of all the hip fractures – with no over-reporting [33]. The NOREPOS group has published papers both based on self-reported and registered forearm fractures [24,34] and registered hip fractures [35-38].

NOREPOS has used data from all these local hip fracture registers in a case-cohort study of vitamin concentrations in serum and risk of future hip fracture. Vitamins A (retinol), D (25-hydroxyvitamin D), E (alpha-tocopherol) and K1 (phylloquinone) have been analyzed in stored serum samples from the baseline studies in Tromsø IV, HUNT2, HUSK and HUBRO. In addition, the bone formation marker procollagen 1 aminoterminal propeptide (P1NP) in serum has been determined in a subsample of this same case-cohort, including data from HUSK and HUBRO.

The NOREPOS Hip Fracture Database (NORHip)

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 [5]. Because 1994 was the first year all somatic hospitals in Norway used electronic patient

administrative systems, it was not possible to go further back in time covering the whole country. There are almost 140,000 hip fractures in this historic data base, and the fracture data have being linked to other databases, described below. Hip fractures are defined as the first fracture of the proximal femur that occurred during the observation period, including fractures of femoral neck, per- and sub-trochanteric regions of the hip. Subsequent fractures have also been assessed. 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 (http://norepos.b.uib.no/files/2012/08/Metodebeskrivelse_NORHIP.pdf). Corresponding information about hip fractures sustained 2009-2013 from the Norwegian Patient Register will be added in 2014.

Linkages to other computerized data sources/ registries

Data from CONOR and NOREPOS have been linked to data from several national registers and health surveys:

Statistics Norway, Cause of Death Registry, National Population Register (www.ssb.no/english). From Statistics Norway we have information about marital status, income, education, occupation and place of residence. This information is from official registers or from mandatory censuses, and is considered to be as valid and complete as possible. The Cause of Death Registry contains the cause of death with primary and secondary diagnoses, as well as time and place of death. The National Population Register contains information on country of birth, date of death and date of emigration. This register provides updates of the population at risk of having hip fractures, i.e. the denominator for the incidence studies.

The Norwegian Prescription Database (NorPD) (www.norpd.no) contains all dispensing of prescribed medicines from pharmacies to patients. Established in 2004, the NorPD includes over

34 millions prescriptions dispensed per year. Individual prescriptions (by pseudonym), including time of prescription and dose of specific formulations, have been linked to NORHip [39].

The Norwegian Waterworks Register (VREG) (www.fhi.no/vreg) is a national register of waterworks supplying more than 50 persons or 20 households. The water quality of 87% (approximately 4 million inhabitants) of the population is included. The database, established electronically in 1994, contains administrative conditions, e.g. size, transport system (pipelines), treatment of the water and quality for a large set of components, e.g. pH [40], calcium, bacterial indicators and certain metals. In addition to VREG we also have access to data from an in-depth survey of trace metals in drinking water. This survey was undertaken in 1986-1991 and covers 64 % of the Norwegian population. Thirty parameters were measured, including calcium, magnesium, toxic metals (cadmium, lead, aluminium), iron, zinc, copper and others [41, 42].

Other health surveys

During the years 1972-1988 several health surveys were carried out in Oslo (1972/73) and in three Norwegian counties (Oppland, Sogn og fjordane and Finnmark - 3 times in each county (http://www.fhi.no/artikler/?id=104563).

School-based youth health studies (15-16 years) based on questionnaires in 6 counties, were carried out in 2000-2004 (http://www.fhi.no/artikler/?id=102938), and were linked to the other data-sources.

In addition, we have linked data on previous height and weight measurements from tuberculosis screenings carried out in Norway during 1963-1975 [43] to NORHip. Figure 2 illustrates the different linkages.

All personal identifications are deleted from the files which have the same encrypted project specific number enabling linkages.

 (Figure 2 in here)

What has been found?

The definition of a NOREPOS study is one that includes data from more than one of our study sites. In the early years, NOREPOS focused on methodological issues, quality assessments and analyses comparing BMD levels between the study sites in order to explain regional differences by measured potential explanatory variables. Thus, one of the initial goals of NOREPOS was to compare BMD levels in different regions in Norway, adjusted for important confounders. Later we have mainly published results using fracture as our outcome.

Bone mineral density

In a sub-cohort of middle-aged men measured in the 1970ies, low baseline BMI and weight loss during the following three decades were both strongly and negatively related to total hip BMD [44]. We found higher forearm BMD levels in rural compared to urban areas [29], and hypothesized that these findings may help explain previously found regional differences in fracture rates. Women 60 years and older in Tromsø had higher age-adjusted BMD in the hip than women in Bergen, whereas BMD among women younger than 60 years was similar. Men in Tromsø had higher total hip BMD levels than men in Bergen, at all examined ages [31]. Thus, no apparent north-south gradient was found [31]. The differences could to some extent, but not fully, be explained by higher BMI in Tromsø. Using data from the Tromsø Study, we have discussed the challenges of using various fixed diagnostic levels of BMD in defining osteoporosis [45].

Forearm fracture

Based on CONOR-data, also including information on health status, diseases, lifestyle and demographic factors, we found that the prevalence of self-reported forearm fractures increased with increasing degree of urbanization for both genders [24]. To verify whether lower BMD

and/or different lifestyle could explain the higher proportion of forearm fractures found in urban compared to rural areas, we used data from Tromsø (1994-1995) and Nord-Trøndelag (1995-1997). All women with SXA measurement were followed with respect to hospital-verified forearm fractures (median follow-up 6.3 years). Thirty percent higher rates of forearm fractures were found in urban compared to rural postmenopausal women [34]. These results indicate that 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.

In a collaborative study using data from the HUNT study, we have reported that among women 65 years and older followed for an average of 5.8 years, a weight loss of 5% or more was associated with a 33% increased risk of distal forearm fractures [46].

In the study of drinking water quality based on the linkage between the Norwegian Waterworks Register and CONOR, the prevalence of forearm fracture was found to be higher in areas with acidic water, which could mainly be explained by a higher microbial content in acidic water [40].

Hip fracture

While the hip fracture incidence increased from the 1970ies to the 1990ies [2], rates have declined during the last decade [5]. However, Norway still has among the highest hip fracture incidences in the world [5]. The previously estimated number of hip fractures among adults in Norway, i.e. 9,000) [1], has been verified using data from NORHip [5], and the previously reported differences in hip fracture rates between Norwegian counties [6,47], are still present.

The mean age of the hip fracture patient is 80 years, and women comprise 70% of the fractures. About one in eight hip fracture patients suffer a new hip fracture [48], and one in four hip fracture patients have a second fracture of *any kind* [49]. However, only 16% of female hip fracture patients above 50 years used anti-osteoporosis drugs one year after the fracture [39].

More than one in four hip fracture patients above 50 years die within a year after the fracture [50], and five percent of the total mortality in the population above 50 years can be attributed to hip fractures [50]. 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. During 1999-2008, 23,353 patients above 50 years of age died within a year after the fracture, constituting 29% of all hip fracture patients [50]. The excess mortality was highest during the first two weeks, but was still present more than 10 years after the fracture [50]. One-year absolute mortality rates post hip fracture declined significantly between 1999 and 2008 in men, but increased significantly in women relative to the population mortality [50].

Based on the case-cohort study previously presented, we found that low serum 25(OH)D increased the risk of a subsequent hip fracture [38]. However, we could not confirm [51] the previously reported increased hip fracture risk with increasing serum retinol [52,53]. Further, a high level of vitamin E in serum was associated with reduced risk of hip fracture [54]. No significant association between serum PINP and risk of hip fracture was found [55].

Studies of the association between tap water and hip fractures suggest that magnesium are protective, whereas cadmium and lead are harmful to bone health and increase the risk of hip fracture [41,42].

Based on a total of 136,140 hip fractures, we found a higher hip fracture incidence during the winter compared to the summer months. The distinct seasonal variation was most pronounced in men, the youngest and the healthiest patients [56].

In CONOR, the incidence of hip fracture decreased with increasing Body Mass Index (BMI) in both genders, whereas abdominal obesity *increased* the risk when BMI was adjusted for [57]. After dividing waist hip ratio into tertiles, women had a more than two-fold risk of hip fracture at the combination of high waist-hip ratio and BMI=23 compared to the combination of low waist-hip ratio and BMI=30. In men there was a corresponding four-fold risk. In all the sub-studies of hip fracture, adjustments have been made for important and relevant confounders.

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BMD is not adjusted for, because only a limited number of the hip fracture patients had BMD measurements.

What are the main strengths and weaknesses?

Over the past few decades, the Norwegian scientific community has invested a very large amount of money and effort in establishing some of the largest and well characterized population-based cohorts in the world. Using the 11-digit personal identification number, we have the possibility to link these cohorts with hospitalizations and deaths due to hip fractures in the whole population, enabling large scale etiologic studies of hip fractures. In addition, near 100% complete follow-up of participants through linkages to the Cause of Death Registry and population registries provide the opportunity to answer research question we otherwise would not be able to examine in Norway. Linkage to the Norwegian Waterworks Register is novel and unique. Further we have more than 56 000 forearm BMD measures and more than 28 000 hip BMD measures, in addition to information on risk factor and stored blood samples/DNA from about 180 000 participants in CONOR. Few international research groups are able to conduct studies of this dimension. The large number of participants indicates ample statistical power for a wide range of analyses.

One of the major strengths of NOREPOS is that the health survey data are community based and that information on the major outcome - osteoporotic fractures, covers the whole population. The cohorts have been recruited from different regions of Norway covering a large geographic area stretching from 59 to 69 degrees latitude, areas which previously have been found to vary in hip fracture rates. Another advantage is the large sample size, inclusion of both genders, and a relatively wide age range. We have information on a large number of descriptive variables on the health survey participants, including socio-demographic factors, health behaviours, current and previous disease status, anthropometric measures and blood pressure. The data on socio-demographic factors, cause of death, prescriptions and water quality factors are from the whole population.

All BMD measurements followed a similar protocol and have been analyzed with regard to validation, precision and artefacts, as well as inter-study comparisons [14,32,58,59]. Regarding use of data from CONOR and the BMD measurements, potential weaknesses include different age groups at the various study sites. This, however, may also be considered to be strengths, as mentioned above. The fact that different DXA instruments were used at the various sites may be considered a weakness. While this may restrict direct comparisons of BMD levels between the study sites, it should not impact longitudinal associations between BMD levels and subsequent fracture. As mentioned, we have conducted studies to compare measurements from the various instruments [30] and as before, we will take these differences into account in future analyses. On a large number of participants we do not have densitometry measurements of the hip, only forearm. However, while BMD measured at the hip has the strongest ability to predict and explain hip fractures [60], forearm BMD has an overall ability to predict all osteoporotic fractures, comparable to any other BMD measurement [60,61].

Participation rates varied between study sites ranging from about 50% in HUBRO to 78% in Tromsø. Although one should be cautious in generalizing prevalence estimates, findings of associations between exposures and outcome are expected to be less influenced even at relatively low participation rates [22]. A description of the generalizability of CONOR data is published online in Norwegian [62].

The number of BMD measurements in NOREPOS is one of the largest in the world, including a substantial proportion of men. In Tromsø, Nord-Trøndelag and Hordaland some or almost all participants have had BMD measured twice, and several individuals in Tromsø and HUNT have been measured three times (Table 1).

The limitations described above regarding possible selection bias do not apply when NORHip is linked to national registers – such as Statistics Norway, Norwegian Prescription Database, Norwegian Person Registry, Cause of Death Registry and Norwegian Water Works Register). In these analyses we have information from almost all Norwegians.

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Future plans

NOREPOS contains information on BMD, fractures, anthropometric measurements, blood pressure, heart rate and results from serum analyses. Among those with BMD measurements we have stored whole blood and serum in about 50,000 individuals. CONOR, of which NOREPOS is a part, have frozen whole blood or extracted DNA in about 180,000 individuals. Altogether, these data constitute a unique source of information for aetiologic research, genetic studies as well as for biomarkers of osteoporosis and fractures. Data 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 will perform cross-country comparisons to find possible explanations for the higher hip fracture incidence in Norway.

Because of the increasing number of elderly in the European countries during the years to come, hip fractures will continue to pose a national and international public health challenge and a considerable health care problem.

How do I find out more about NOREPOS?   www.norepos.no

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Contribution

All authors have contributed to conception and collection of data, design, analyses and interpretation of data in NOREPOS papers, revision of content of this paper and approval of last version. Grethe S. Tell and Anne Johanne Søgaard have in addition drafted this paper.

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Table 1. Description of the NOREPOS study population.

Study	Time of study (year)	Invited age-groups (years)	Participation rate (%)	Number of participants with			
				Stored serum	Stored whole blood/DNA	SXA*	DXA**
Tromsø							
Tromsø IV	1994-1995	25-84	77		7620	7809	
Tromsø V	2001-2002	$\geq$ 30	79	5718	900***	5718	5224
Tromsø VI	2007-2008	$\geq$ 30	66	3727	3727	3727	3727
North Trøndelag							
HUNT2	1995-1997	$\geq$ 20	70	18265	18265	18265	
Follow-up	2001	$\geq$ 20	68			6656	
HUNT3	2006-2008	$\geq$ 20	56	11530	11530	5640[#]	12100
Bergen							
HUSK	1997-1999	46-49 71-74	77	5513	5513	208	5348
Follow-up	1999-2001	49-52	68				1371
Oslo							
HUBRO	2000-2001	30-76[¤]	46	3551	3551	2648	703[&]
Total no. of blood samples/BMD measurements				48304	51106	56561	28473

*   Bone mineral density measurements of distal and ultra-distal forearm

**   Bone mineral density measurements of the hip and/or total body

***   New individuals not participating in Tromsø IV

[#]   In addition 9,333 forearms were measured by DXA (DTX 200)

[¤]   Age groups 30, 40, 45, 56/60 and 75/76

[&]   Men age 75-76 yrs.

Figure legends

Figure 1. Map of Norway with the study sites of Norwegian Epidemiologic Osteoporosis Studies (NOREPOS).

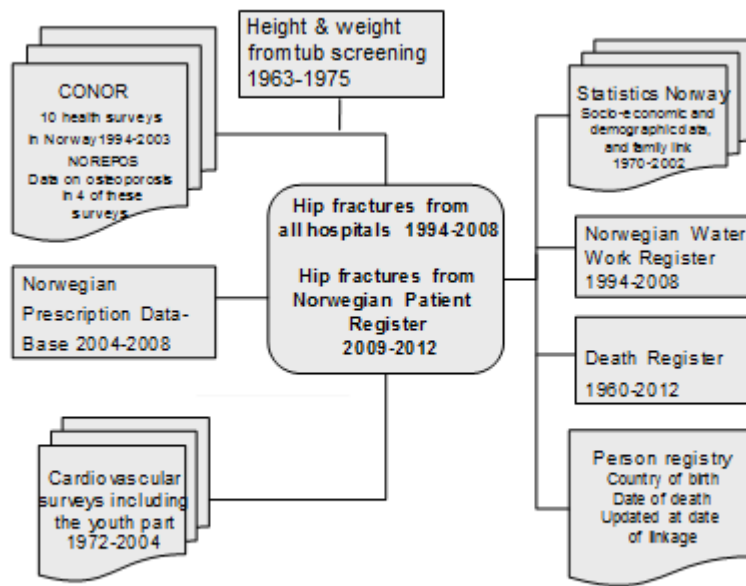**Figure 2.** The linkage of NOREPOS Hip Fracture Database (NORHip) with all data sources.

Fig 1

Fig 2