Epidemiology and risk factors of hip fractures in Norway

Examples of combining patient administrative systems, regional health studies and national health registries

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26 November 2015
Outline

• Brief presentation of the Norwegian Institute of Public Health (NIPH)
• Tools for research and health surveillance on the population level
• Hip fractures in Norway: Examples from a research area with available high-quality individual-level national data based on large data linkages
The NIPH is one of several agencies of the central health administration of Norway.

Vision: A healthier population
Our tasks are distributed on five main activities

- Health surveillance
- Research
- Advice
- Services
- Preparedness

Domain for Mental and Physical Health in the NIPH
- Health statistics
- Chronic disease epidemiology
- Pharmacoepidemiology
- Mental health
- Alcohol and drug research (from 2016)
Tools and infrastructure for research

- National health registries
- Nationwide and regional population-based health studies
  - Biologic samples, anthropometric measures, clinical examinations, questionnaire data
- Demographic data from Statistics Norway
- Biobanks and laboratory-based methods
- Information technology
National health registries

The NIPH is responsible for 9 of the 16 mandatory national health registries, covering:

• Causes of death
• Births
• Pregnancy termination
• Cardiovascular diseases
• Prescription medications
• Infectious diseases
• Infections in health institutions
• Microbial resistance to antibiotics
• Vaccination
National ID number

• All residents of Norway are allocated a personal national ID number, which they keep for life

• The ID number consists of 11 digits, of which the first six digits indicate the person's date of birth

• The ID number is the key to link individual-level data from different registers and other data sources
Examples from a field where we have high-quality individual-level national data for research and health surveillance based on large data linkages.

Photo: F. Frihagen, Acta Orthop Suppl 2009
Leading causes of disability-adjusted life-years (DALY) in Norway 2013

- Low back & neck pain: 1
- Ischemic heart disease: 2
- Alzheimer disease: 3
- Cerebrovascular disease: 4
- Lung cancer: 5
- Falls: 6
- COPD: 7
- Anxiety disorders: 8
- Depressive disorders: 9
- Skin diseases: 10

http://www.healthdata.org/norway
Bone health through life
Hip fractures

• Proximal femur fractures

• International Classification of Diseases (ICD) codes:
  – ICD-9: 820 with all subgroups
  – ICD-10: S72.0, S72.1 and S72.2
Hip fractures occur from falls combined with bone fragility

A multifactorial health problem

– Ageing
– Fall risk
– Sarcopenia; reduced muscle mass and strength
– Osteoporosis; reduced bone mass and strength
– Poor nutritional status
– Comorbidity
– Use of medications
WELCOME TO NOREPOS

NOREPOS (Norwegian Epidemiologic Osteoporosis Studies) is a national research collaboration network of researchers from five different scientific institutions across Norway. We perform epidemiologic research in the field of osteoporosis. The collaborating institutions in NOREPOS are: University of Bergen (UiB), University of Tromsø (UiT), Norwegian University of Science and Technology (NTNU), University of Oslo (UiO), and the Norwegian Institute of Public Health (FHI). The collaboration has existed since 1997. The project is led by Professor Grethe S. Tell, Department of Public Health and Primary Health Care, University of Bergen. Eight senior researchers, two from each geographical location, constitute the members of the NOREPOS steering committee. NOREPOS received a large grant from the Research Council of Norway in 2008.

We use data sources from large population-based studies in Norway where bone mineral density measurements have been performed. Hip fractures constitute an important endpoint in our research. We have now collected all
Descriptives: Incidence
- Time trends
- Risk of subsequent fractures
- Excess mortality
- Geographic variation
- Seasonal variation

Modifiable risk factors:
- Body composition
- Drinking water quality
- Nutritional factors
Descriptive information:

- Incidence rates
- Time trends
- Geography
- Mortality

Statistics Norway
Socioeconomic, demographic and family data

NOREPOS Hip fracture database
Hip fractures 1994-2013

Person registry
Country of birth, date of death or emigration
Annual number of hip fractures in Norway

Omsland et al., Eur J Epidemiol 2012
Incidence rates of hip fractures in Norway 1999-2008 (NOREPOS), age 50+

Age-standardized rates: New cases per 10,000 persons per year

Women: 13.4%
Men: 4.8%

Omsland et al., Eur J Epidemiol 2012
Incidence rates by age

Mean age at fracture:
- 81.8 years in women
- 78.8 years in men

Note! Women Men

Omsland et al., Eur J Epidemiol 2012
Forecasting the burden of hip fractures
(women 65+)

Omsland & Magnus, *Osteoporos Int* 2014
Cumulative incidence of second hip fracture

15% of the women and 11% of the men who have fractured will suffer another hip fracture within 10 years.
Excess mortality after hip fracture

Standardized mortality ratios (SMR) in Men and Women

Time after first hip fracture (yrs)
Geographic differences within Norway

1988-1989: Incidence rates in the capital Oslo were 50% higher than in the rural county Sogn og Fjordane

Falch JA et al., Bone 1993
Standardized incidence rates of hip fracture according to county, women

Same pattern in men

Inselens per 10 000 personår

- Østfold
- Akershus
- Oslo
- Hedmark
- Oppland
- Buskerud
- Vestfold
- Telemark
- Aust-agder
- Vest-Agder
- Rogaland
- Nordaland
- Søg og Fj
- Møre og Ro
- Sør-Trønde
- Nord-Trønd
- Nordland
- Troms
- Finmark

Omsland TK, unpublished data
## Degree of urbanization

### Women

<table>
<thead>
<tr>
<th>Degree of urbanization</th>
<th>Age adjusted rate ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rural</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Semi-rural</td>
<td>1.05</td>
<td>1.03</td>
</tr>
<tr>
<td>Urban</td>
<td>1.10</td>
<td>1.08</td>
</tr>
</tbody>
</table>

Omsland TK, unpublished data
Seasonal variation: Higher risk in winter than summer

But also summer incidence is very high in Norway

Men

Women

Solbakken SM et al., Arch Osteoporos 2014
Risk factors: Body composition

Two types of anthropometric measures correlated with fat mass

- Body mass index
- Waist hip ratio

“Apple” vs. “Pear”
NOREPOS Hip fracture database
Hip fractures 1994-2013

Statistics Norway
Socioeconomic, demographic and family data

Height and weight
Tub - screenings 1963-1989

Cohort of Norway
10 regional health studies in Norway 1994-2003

Person registry
Country of birth, date of death or emigration
Cohort of Norway linked to hip fractures

- 10 regional health studies 1994-2003
- Standardized anthropometric measurements: Height, weight, waist and hip circumference
- 43,000 men and women aged 60-79
- Followed up to 2008
  - Median 8.2 years
  - 2,400 incident hip fractures
- Cox regression
Higher body mass index is protective
Higher waist-hip ratio is harmful

Søgaard et al., *J Intern Med* 2014
Body mass index and waist-hip ratio combined

Estimated hazard ratios for hip fracture at given levels of BMI and waist-hip ratio

Søgaard et al., J Intern Med 2014
Findings summarized, body composition

• The risk of hip fracture is lower with higher BMI, but this levels off at BMI about 27 kg/m² in men

• Abdominal obesity is independently associated with increased risk of hip fracture, also at lower BMI
Risk factors: Drinking water quality

• Soft surface water >85 %
  – Low pH (rain)
  – Low in minerals

• Groundwater <15 %
  – More minerals, but lower than other European countries, and below recommendations

Groundwater vs. surface water in Norway:
Calcium: 14.5 vs. 3.6 mg/l
Magnesium: 2.5 vs. 0.7 mg/l

WHO:
Ca>20 mg/l
Mg>10 mg/l
Data linkages

NOREPOS Hip fracture database
- Hip fractures 1994-2013
- Cohort of Norway
  - 10 regional health studies in Norway 1994-2003
- Statistics Norway
  - Socioeconomic, demographic and family data
- Norwegian Waterworks Register
- Person registry
  - Country of birth, date of death or emigration
Data sources

- Trace mineral project 1986-1991 (2-4 measurements)
- Population censuses 1960-2001
- NOREPOS Hip fracture database

Water measurements; area levels

Disease outcome; individual level
Geographic information systems (GIS)
Geographic information systems (GIS)
Findings summarized, drinking water quality

- Slightly lower pH in drinking water (pH 6-7) was associated with more self-reported forearm fractures
- **Magnesium** in drinking water was associated with higher risk of hip fracture
- **Cadmium** in drinking water was associated with higher risk for hip fracture (in men)
- **Lead** in drinking water was associated with higher risk of hip fracture in the older (65-85 years)
Risk factors:
Fat-soluble vitamins: A, D, E, K
Vitamin D: Well studied but modest role in fracture prevention

Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis (Review)

Avenell A, Gillespie WJ, Gillespie LD, O'Connell D
Vitamin K: Activation of mineral-carrying proteins in bone

Carboxylation of proteins

Glutamic acid (Glu)

γ-carboxyglutamatic acid (Gla)
(Strong binding affinity with Ca$^{2+}$)
Vitamin E (alpha-tocopherol): Fat soluble plant substance with antioxidant capacity; possible anti-inflammatory actions also in bone.
Preformed retinol (vitamin A): Harmful?

Excessive Dietary Intake of Vitamin A Is Associated with Reduced Bone Mineral Density and Increased Risk for Hip Fracture
Håkan Melhus, MD; Karl Michaélsson, MD; Andreas Kindmark, MD; Reinhold Bergström, PhD; Lars Holmberg, MD; Hans Mallmin, MD; Alicia Wolk, PhD; and Sverker Ljunghall, MD

Vitamin A Intake and Hip Fractures Among Postmenopausal Women

Diane Fuskanch, ScD
Vishwa Singh, PhD
Wallor G. Villott, MD, DrPH
Graham A. Colditz, MD, DrPH

Contact: ingestion of toxic amounts of vitamin A affects bone remodeling and can have adverse skeletal effects in animals. The possibility has been raised that long-term high vitamin A intake could contribute to fracture risk in humans.

Objective: To assess the relationship between high vitamin A intake from foods and supplements and risk of hip fracture among postmenopausal women.

Serum Retinol Levels and the Risk of Fracture
Karl Michaélsson, M.D., Hans Lithell, M.D., Bengt Vessby, M.D., and Håkan Melhus, M.D.

Serum Vitamin A Concentration and the Risk of Hip Fracture among Women 50 to 74 Years Old in the United States: A Prospective Analysis of the NHANES I Follow-up Study
Alexander R. Opotowsky, MD, MPH, John P. Bilezikian, MD

Although retinol has not always been associated with poor skeletal health [75], it is best to avoid cod liver oil and other concentrated fish products as sources of vitamin D due to the higher vitamin A content.
NOREPOS Case-cohort study

1175 hip fractures: Vitamins A, D, E and K in serum samples
Risk of hip fracture across serum 25-hydroxyvitamin D

Justert for alder, kjønn, studiested og BMI

HR 1.38 (95% CI 1.09-1.74) in Q1 (<42 nmol/l) vs. Q4 (>67 nmol/l)
Increased risk at low levels of both vitamins D and K

Table 4: Hazard ratios with 95% confidence intervals for combined groups with s-vitamin K$_1$ ≥ or < the median and 25(OH) D ≥ or < 50 nmol/L.

<table>
<thead>
<tr>
<th>Cases (n)</th>
<th>HR$^a$</th>
<th>95% CI$^a$</th>
<th>p$^a$</th>
<th>HR$^b$</th>
<th>95% CI$^b$</th>
<th>P$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>High K, High D</td>
<td>305</td>
<td>1 (ref)</td>
<td>-</td>
<td>1</td>
<td>(ref)</td>
<td>-</td>
</tr>
<tr>
<td>High K, Low D</td>
<td>201</td>
<td>0.97</td>
<td>0.76 – 1.24</td>
<td>0.80</td>
<td>1.09</td>
<td>0.84 – 1.42</td>
</tr>
<tr>
<td>Low K, High D</td>
<td>304</td>
<td>1.17</td>
<td>0.94 – 1.46</td>
<td>0.16</td>
<td>1.12</td>
<td>0.88 – 1.43</td>
</tr>
<tr>
<td>Low K, Low D</td>
<td>279</td>
<td>1.50</td>
<td>1.18 – 1.90</td>
<td>&lt;0.001</td>
<td>1.41</td>
<td>1.09 – 1.82</td>
</tr>
</tbody>
</table>

$^a$ Base model (adjusted for age, sex and study site)

$^b$ Extended model, a) additionally adjusted for BMI, smoking, triglycerides and α-tocopherol
No increased risk at high retinol

Model includes age, gender, study center, BMI, smoking, physical inactivity, self-rated health, vit. D and E
Independent strong inverse association with vitamin E

Men

\[ p \text{ (linear)} < 0.001 \]

HR 1.20 (95% CI 1.02-1.42)

Women

\[ p \text{ (linear)} = 0.003 \]

HR 1.10 (95% CI 1.02-1.19)

per 10 µmol/L lower serum vitamin E
Findings summarized, vitamins

Middle and high serum concentrations of vitamin D and vitamin E (alpha-tocopherol) is associated with reduced risk of hip fracture compared to low concentrations.

Contrary to expectations, high serum concentrations of vitamin A (retinol) were not associated with increased risk of hip fracture.
Thank you for listening