UiO : Universitetet i Oslo

Combining register information with other data sources

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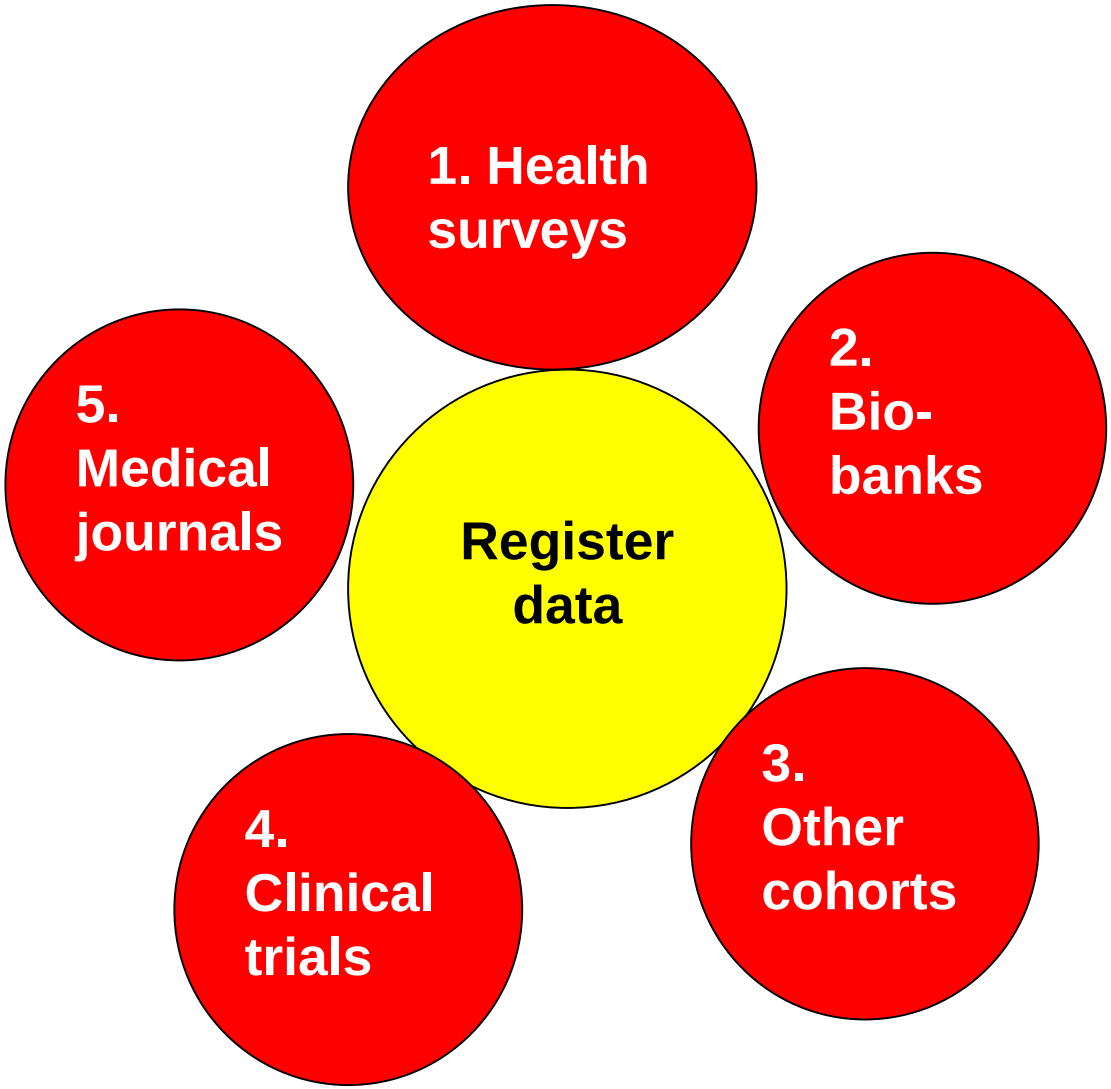
Outline

- Why combine register data with other data?
- Types of possible combinations
- Examples

Why use other data sources than the registers?

- Limited amount and type of variables
- Limited time frame
- Not all types of study questions can be answered by using registers only

- By combining register data with other data sources new exciting possibilities emerge


1. Health surveys
2. Bio-banks
3. Other cohorts
4. Clinical trials
5. Medical journals
Register data

1. Health surveys: CONOR

- CONOR:10 different health surveys during 1994–2003

All surveys comprised:

- a common set of questions
- standardized anthropometric measures
- blood pressure measurements
- non-fasting blood samples

https://academic.oup.com/ije/article/37/3/481/742090

Cohort of Norway

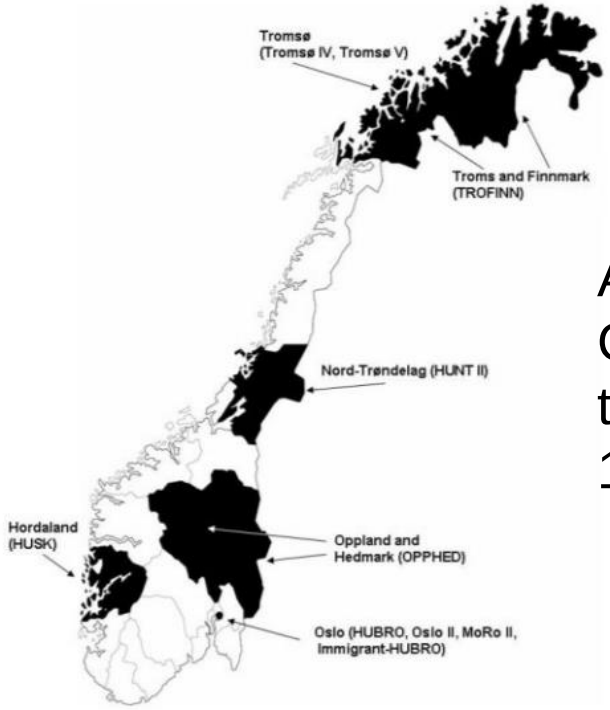


Figure 1 Map of Norwegian counties with location of each sub-study included in cohort of Norway (CONOR)

All surveys used about 50 core CONOR questions agreed upon before the first CONOR survey in Tromsø in 1994

Cohorts: Example

Am J Epidemiol. 2018 May 1;187(5):971-981. doi: 10.1093/aje/kwx339.

Sex Differences in Risk of Smoking-Associated Lung Cancer: Results From a Cohort of 600,000 Norwegians.

Hansen MS[1], Licaj I[1,2], Braaten T[1], Langhammer A[3], Le Marchand L[4], Gram IT[1].

Author information

Abstract

Whether women are more susceptible than men to smoking-related lung cancer has been a topic of controversy. To address this question, we compared risks of lung cancer associated with smoking by sex. Altogether, 585,583 participants from 3 Norwegian cohorts (Norwegian Counties Study, 40 Years Study, and Cohort of Norway (CONOR) Study) were followed until December 31, 2013, through linkage of data to national registries. We used Cox proportional hazards models and 95% confidence intervals to estimate risks. During nearly 12 million person-years of follow-up, 6,534 participants (43% women) were diagnosed with lung cancer. More men than women were heavier smokers. Compared with never smokers, male and female current smokers with ≥16 pack-years of smoking had hazard ratios for lung cancer of 27.24 (95% confidence interval (CI): 22.42, 33.09) and 23.90 (95% CI: 20.57, 27.76), respectively (P for heterogeneity = 0.30). In contrast, for current smokers, in a model with pack-years measured continuously, men had a hazard ratio of 1.43 (95% CI: 1.39, 1.48) and women a hazard ratio of 1.64 (95% CI: 1.57, 1.71) for each 10-pack-year increment of smoking (P for heterogeneity < 0.01). Our results suggest that women have an increased susceptibility to lung cancer compared with men, given the same lifetime smoking exposure.

PMID: 29087432 DOI: 10.1093/aje/kwx339

Cohorts: Example

Smoking status (n=600 000)

- Conor
- 40 years study
- Norwegian counties

Cancer register
Population register

Other data:

Physical activity

BMI

Education

Outcome:
Lung cancer

Table 2. Incidence Rates[a] of Lung Cancer by Subcohort, Sex, and Smoking Status ($n = 585,583$), Norwegian Health Screening Surveys, 1974–2003

Smoking Status	Norwegian Counties Study (1974–1978)		40 Years Study (1985–1989)		CONOR Study (1994–2003)	
	Men	Women	Men	Women	Men	Women
Overall[b]	102.4	59.4	50.4	42.0	83.2	51.5
Never smoker	7.7	7.5	5.7	8.2	4.5	14.0
Former smoker	28.3	25.3	21.5	13.6	76.1	35.1
Current smoker	188.7	135.2	107.0	90.8	189.7	114.4

Abbreviation: CONOR, Cohort of Norway.

[a] Incidence rates per 100,000 person-years.

[b] Never, former, and current smokers combined.

Cohorts - Challenges

- Exposure status may change over time
- Limited amount of confounders available
- Cohorts may be examined at different time points
- Risk of immortal time bias when using cohorts combined with exposure/outcomes in registers!

2. Biobanks

- Types of biobanks

-Research (blood samples, other research collections, gene banks)

-Treatment biobanks (blood, tissue, organs etc)

-Diagnostic biobanks (blood, tissue, autopsy)

https://www.nordforsk.org/en/news/unik-nordisk-studie-av-tarmkreft-ved-hjelp-av-felles-biobankregister

Biobanks

- Different research biobanks exist for different types of research
- Both samples and results from laboratory measurements belong to a biobank
- Biobank data in research is based on informed consent from participants

Am J Clin Nutr. 2015 Nov;102(5):1289-96. doi: 10.3945/ajcn.115.110528. Epub 2015 Sep 16.

No increase in risk of hip fracture at high serum retinol concentrations in community-dwelling older Norwegians: the Norwegian Epidemiologic Osteoporosis Studies.

Holvik K[1], Ahmed LA[2], Forsmo S[3], Gjesdal CG[4], Grimnes G[5], Samuelsen SO[6], Schei B[7], Blomhoff R[8], Tell GS[9], Meyer HE[10].

Author information

Abstract

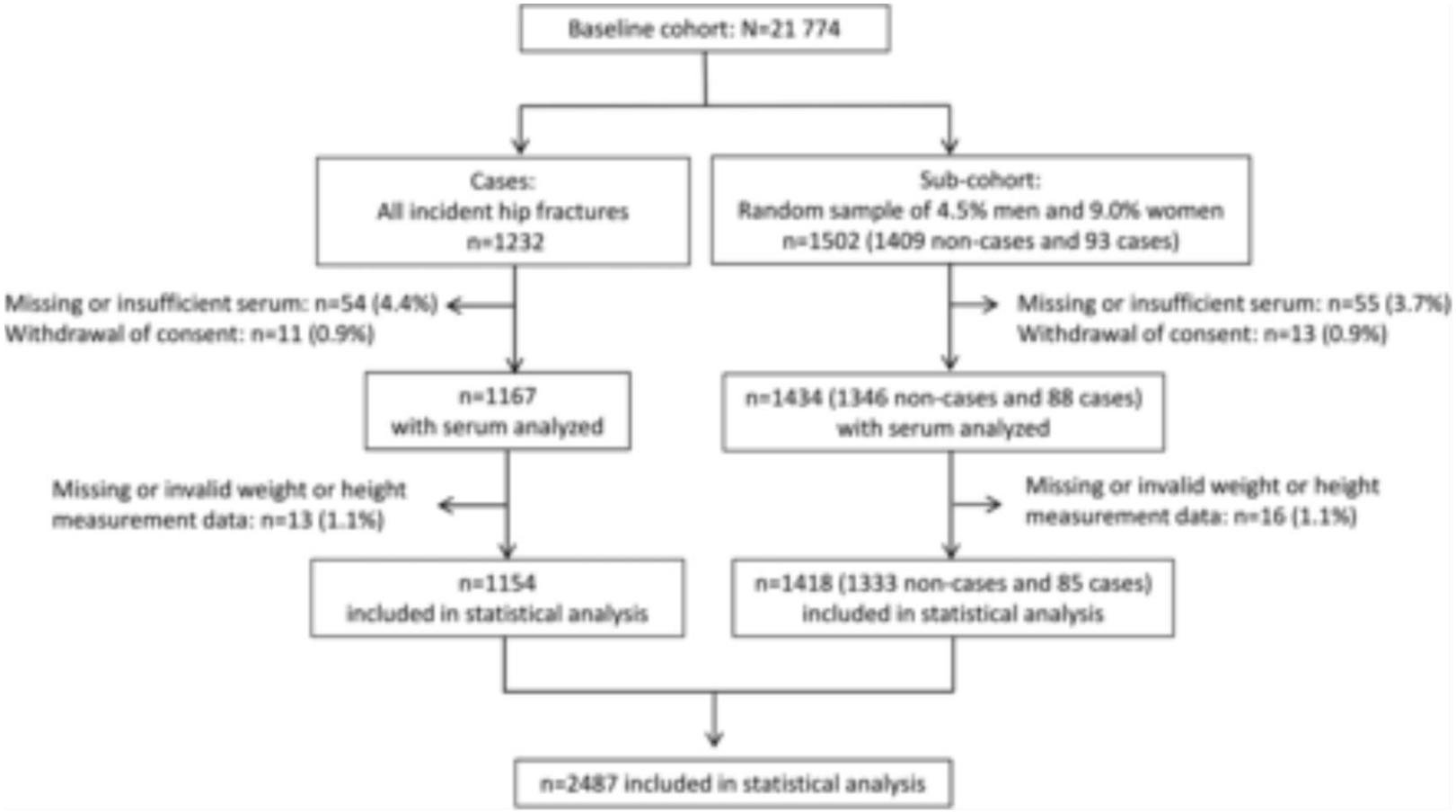
BACKGROUND: Norway has the highest hip fracture rates worldwide and a relatively high vitamin A intake. Increased fracture risk at high intakes and serum concentrations of retinol (s-retinol) have been observed in epidemiologic studies.

OBJECTIVE: We aimed to study the association between s-retinol and hip fracture and whether high s-retinol may counteract a preventive effect of vitamin D.

DESIGN: We conducted the largest prospective analysis of serum retinol and hip fracture to date in 21,774 men and women aged 65-79 y (mean age: 72 y) who attended 4 community-based health studies during 1994-2001. Incident hip fractures occurring up to 10.7 y after baseline were retrieved from electronic hospital discharge registers. Retinol determined by high-pressure liquid chromatography with ultraviolet detection in stored serum was available in 1154 incident hip fracture cases with valid body mass index (BMI) data and in a subcohort defined as a sex-stratified random sample (n = 1418). Cox proportional hazards regression weighted according to the stratified case-cohort design was performed.

RESULTS: There was a modest increased risk of hip fracture in the lowest compared with the middle quintile of s-retinol (HR: 1.41; 95% CI: 1.09, 1.82) adjusted for sex and study center. The association was attenuated after adjustment for BMI and serum concentrations of α-tocopherol (HR: 1.16; 95% CI: 0.88, 1.51). We found no increased risk in the upper compared with the middle quintile. No significant interaction between serum concentrations of 25-hydroxyvitamin D and s-retinol on hip fracture was observed (P = 0.68).

CONCLUSIONS: We found no evidence of an adverse effect of high serum retinol on hip fracture or any interaction between retinol and 25-hydroxyvitamin D. If anything, there tended to be an increased risk at low retinol concentrations, which was attenuated after control for confounders. We propose that cod liver oil, a commonly used food supplement in Norway, should not be discouraged as a natural source of vitamin D for fracture prevention.



From: No increase in risk of hip fracture at high serum retinol concentrations in community-dwelling older Norwegians: the Norwegian Epidemiologic Osteoporosis Studies

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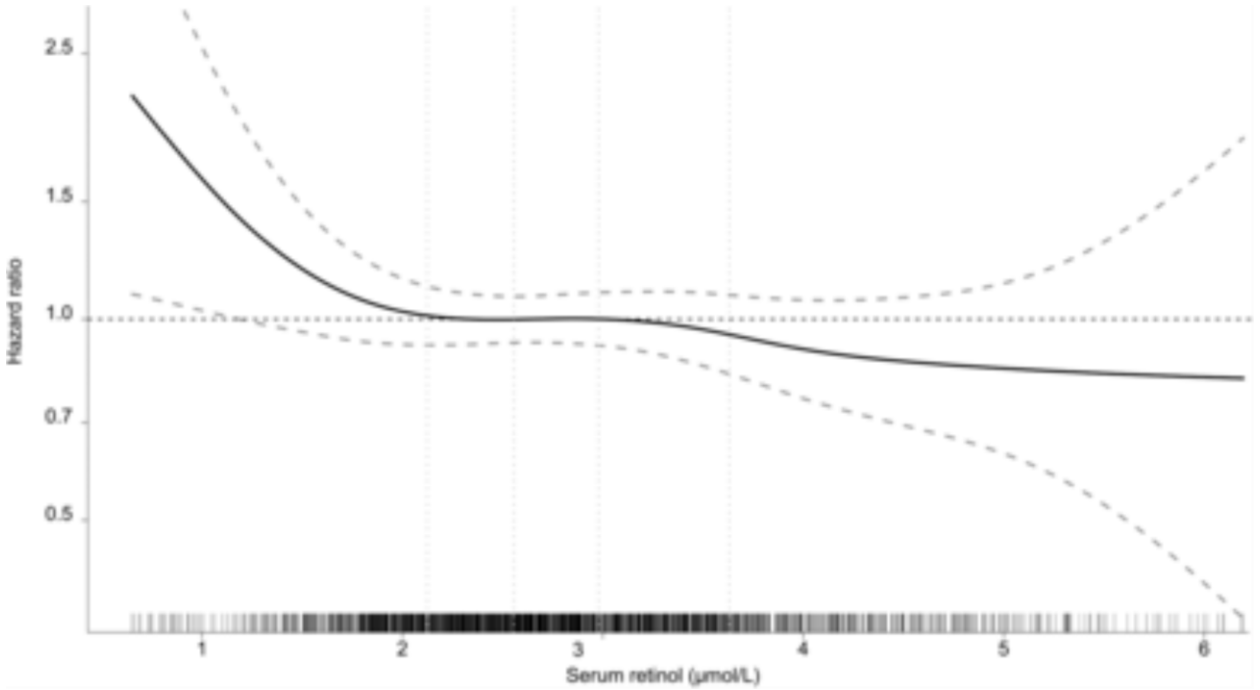

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Am J Clin Nutr. 2015;102(5):1289-1296. doi:10.3945/ajcn.115.110528

Challenges – bio bank samples

- Different stability for molecules

OBS; number of freezing-thawing cycles..

- Storage: Serum, blood, plasma

- Volume required?

Nordic Biobank Network pilot study on colorectal cancer

- In the first phases of the **Nordic Biobank Network pilot study on colorectal cancer 2012–2015**, the formal and practical logistical basis of performing such studies was established.

https://www.nordforsk.org/en/news/unik-nordisk-studie-av-tarmkreft-ved-hjelp-av-felles-biobankregister

Nordic Biobank Network pilot study on colorectal cancer

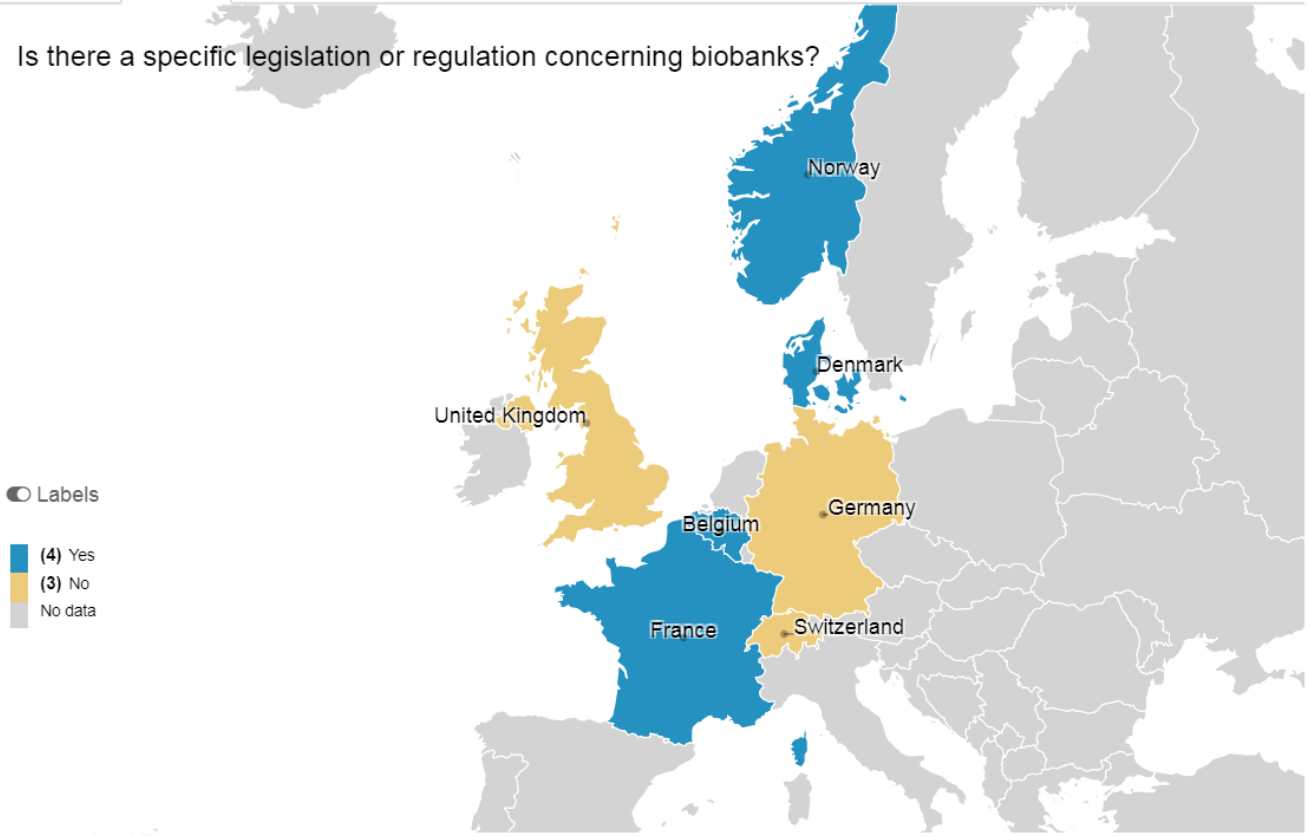
The pilot study encountered complexities and time-consuming processes..

Very few joint Nordic studies that exploit biobanks and registry infrastructures exist, in spite of the potential goldmine these represent for diseases that are not common

Profiles | Map

Help | Share

Is there a specific legislation or regulation concerning biobanks?



Download Table

Search:

Jurisdiction	2. Is there a specific legislation or regulation concerning biobanks?

https://swissbiobanking.ch/regulation-of-biobanks-in-europe/

3.Other cohorts

- Military recruits
- Mandatory tuberculosis screening

BMJ Open. 2017 Oct 27;7(10):e016905. doi: 10.1136/bmjopen-2017-016905.

Cohort profile: a nationwide cohort of Finnish military recruits born in 1958 to study the impact of lifestyle factors in early adulthood on disease outcomes.

Sormunen J[1,2], Arnold M[3], Soerjomataram I[3], Pukkala E[1,4].

Author information

Abstract

PURPOSE: The cohort was set up to study the impact of lifestyle factors in early adulthood on disease outcomes, with a focus on assessing the influence of body composition and physical performance in early adulthood on subsequent cancer risk.

PARTICIPANTS: Men born in 1958 who performed their military service between the ages of 17 and 30 years were included in this study (n=31 158). They were eligible for military service if they were healthy or had only minor health problems diagnosed at the beginning of their service. Men with chronic illnesses requiring regular medication or treatment were not eligible for service. Comprehensive health data including diagnosed illnesses, anthropometric measures and health behaviour were collected at the beginning and at the end of military service, including data from medical check-ups.

FINDINGS TO DATE: During the follow-up, 1124 new cancer cases were diagnosed between baseline (ie, end of the military service for each individual) and end of the year 2014. In the end of the follow-up, 91% of the study participants were still alive. Overweight (body mass index (BMI) ≥25 kg/m^2) and obesity (BMI ≥30 kg/m^2) were associated with an overall increased risk of cancer. A good or excellent physical condition significantly reduced cancer risk.

FUTURE PLANS: The dataset offers the possibility of linkage with other databases, such as the Finnish Cancer Registry (eg, primary site of the tumour, morphology, time of detection, spreading and primary treatment), vital statistics (date of emigration or deaths), censuses (socioeconomic indicators), hospital discharge data (comorbidity) and population surveys (life habits).

KEYWORDS: cancer; cohort; finland; men; population-based; risk factors

Cohort profile: a nationwide cohort of Finnish military recruits born in 1958 to study the impact of lifestyle factors in early adulthood on disease outcomes

Box List of the variables collected at study entry for each member of the cohort

- Personal identity code of the individual
- Professional group
- Marital status
- Beginning of military service (date)
- End of military service (date)
- Reason for preliminary discontinuation of military service (diagnosis)
- Duration of military service
- Military service classifications at different stages of the service
- Classification diagnoses at different stages of the military service
- Self-perceived health status at the beginning and at the end of the service
- Height and weight at different stages of the service
- Blood pressure at different stages of the service
- Physical condition test results at different stages of the service
  - Twelve-minute running test results
  - Muscle strength test results
- Smoking status and amount smoked at different stages of the service
- Use of alcohol and the amount drunken at different stages of the service

Purpose The cohort was set up to study the impact of lifestyle factors in early adulthood on disease outcomes, with a focus on assessing the influence of body composition and physical performance in early adulthood on subsequent cancer risk.

https://bmjopen.bmj.com/content/bmjopen/7/10/e016905.full.pdf

Tuberculosis screening programme

- From 1948 to 1975, Norway had a mandatory tuberculosis screening programme

- Miniature chest X-ray
- Tuberculin test
- BCG-vaccination status
- Measurement of height and weight to the nearest centimetre and half kilogram (not mandatory, from 1963)

Tuberculosis screening programme

- Those infected by TB, had increased all-cause mortality in at least a 20 years period following determination of tuberculin status

- The national population and housing censuses (1960, 1970 and 1980) information on education, employment, marital status and housing

Example: Immune function and hip fracture risk

- Born between 1945-1959
- Attended the screening in 1963-1975 at age 15-30 years
- BCG vaccinated (mandatory BCG vaccination in children at age 14 years in 1949-1994)
- No history of tuberculosis
- Available results from the Pirquet tuberculin test
- Alive and living in Norway at start of follow-up 1 January 1994

4. Clinical trials

JAMA Network | Open

Original Investigation | Orthopedics

Effect of a Fracture Liaison Service on the Rate of Subsequent Fracture Among Patients With a Fragility Fracture in the Norwegian Capture the Fracture Initiative (NoFRACT)

A Trial Protocol

Camilla Andreasen, MD; Lene B. Solberg, PhD; Trude Basso, PhD; Tove T. Borgen, MD; Cecilie Dahl, PhD; Torbjørn Wisløff, PhD; Gunhild Hagen, MPhil; Ellen M. Apalset, PhD; Jan-Erik Gjertsen, PhD; Wender Figved, PhD; Lars M. Hübschle, MD; Jens M. Stutzer, MD; Jan Elvenes, PhD; Ragnar M. Joakimsen, PhD; Unni Syversen, PhD; Erik F. Eriksen, PhD; Lars Nordsletten, PhD; Frede Frihagen, PhD; Tone K. Omsland, PhD; Åshild Bjørnerem, PhD

Recurrent fracture risk

- Prior fragility fracture: 2-fold increased fx risk
- Multiple fractures: 5-fold increased fx risk
- The risk of subsequent fracture is high in all age groups (50+)

Ahmed et al. JBMR. 28 (10)2013, pp 2214– 2221

Recurrent hip fracture risk

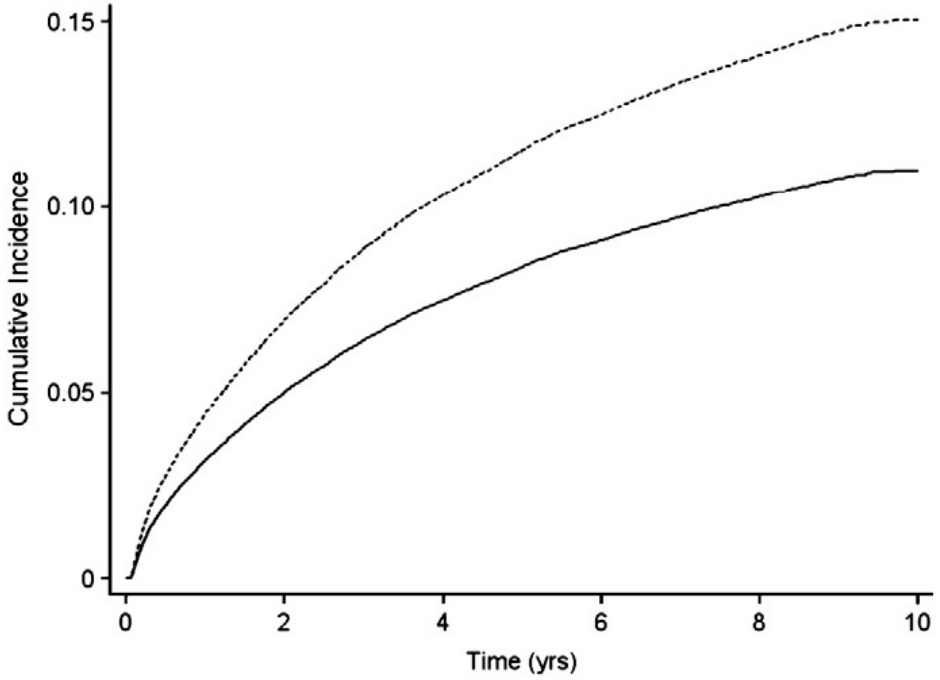


Fig. 1. Cumulative incidence of second hip fracture in women (dashed line) and men (solid line) with a first hip fracture. Results were obtained from competing risk of death regression model with adjustment for age at first hip fracture. The NOREPOS Hip Fracture Database 1999–2008.

A total of
15% of women
11% of men
sustain a second hip fracture within 10 years after a hip fracture

Omsland et al. Bone. 2013;52(1):493-7.

Fracture Liaison Services

- Committed team with dedicated coordinator which acts as the link between the patient and health care system

- Patients are followed up regularly after fracture

- FLS ensures that patients with fragility fractures receive fracture risk assessment and treatment where appropriate

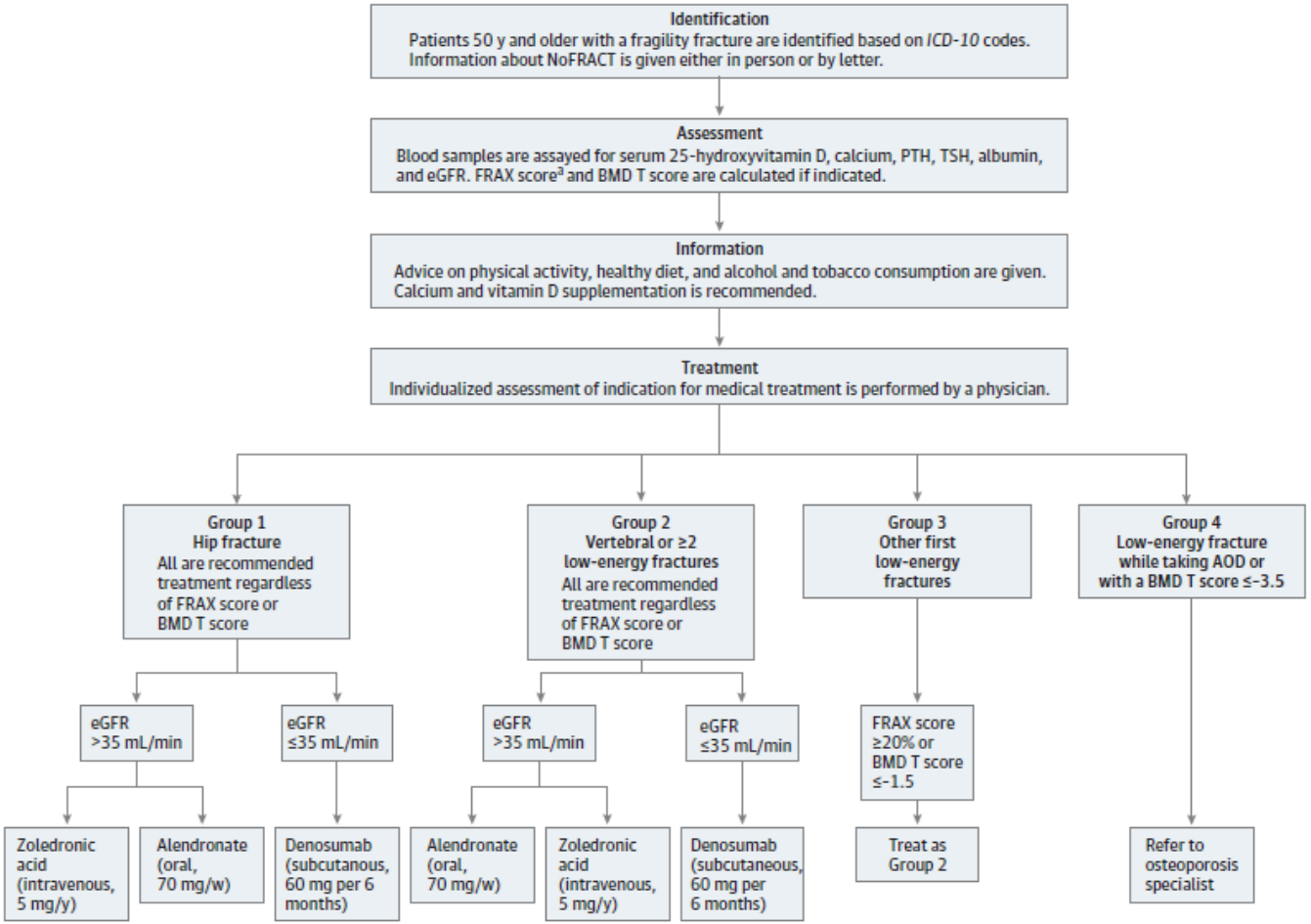
FLS cont.

- Lack of studies of FLS with randomized design

- Axelsson et al 2016: FLS treated patients had a 51 % lower risk of any re-fracture than untreated patients (HR 0.49, 95 % CI 0.37-0.65 $p < 0.001$)

Osteoporos Int. 2016 Nov;27(11):3165-3175.

Figure 2. Application of the Standardized Intervention Program in the Norwegian Capture the Fracture Initiative (NoFRACT) Trial

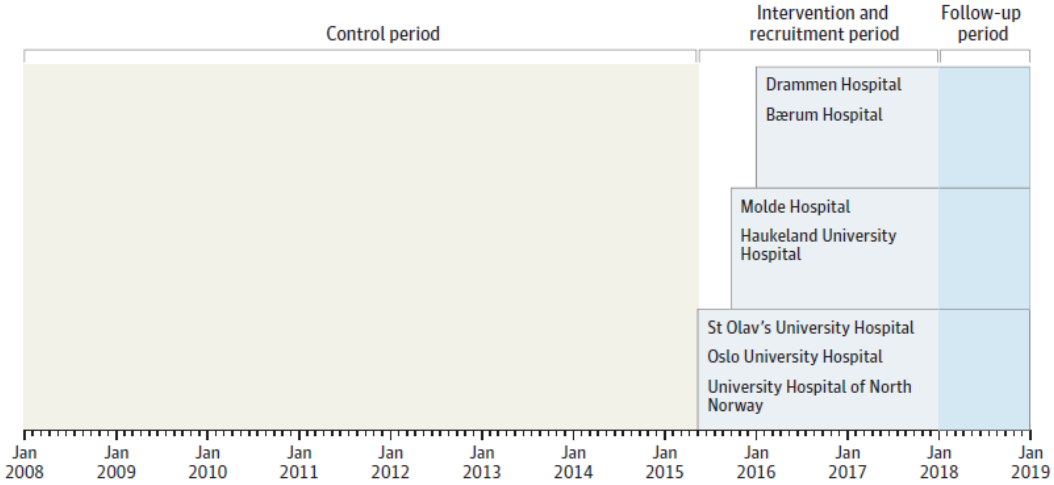


AOD indicates antiosteoporosis drugs; BMD, bone mineral density; eGFR, estimated glomerular filtration rate; *ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision;* PTH, parathyroid hormone; and TSH, thyroid-stimulating hormone.

[a] The Fracture Risk Assessment Tool (FRAX) is used to calculate the 10-year probability of major osteoporotic fracture (score is given as a percentage; a higher percentage indicates higher probability of fracture).

Stepped wedge cluster randomized clinical trial design

Figure 1. Norwegian Capture the Fracture Initiative (NoFRACT) Stepped Wedge Cluster Randomized Clinical Trial Design



The 7 hospitals were randomized for the order of the starting dates and divided into 3 sequences. The intervention was introduced stepwise with 4-month intervals. The intervention period started on May 1, 2015, and will continue through December 31, 2018, with follow-up through December 31, 2019. The University Hospital of North Norway was scheduled to start on May 1, 2015, but was delayed for 5 months and started on October 1, 2015.

Registers

- Norwegian patient register
- Primary health care register (KUHR)
- Population register
- Statistics Norway
- Hip fracture register
- Cause of death register

The Stata Journal
Volume 14 Number 2: pp. 363-380

A menu-driven facility for power and detectable-difference calculations in stepped-wedge cluster-randomized trials

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Abstract. This article introduces the Stata menu-driven program **steppedwedge**, which calculates detectable differences and power for stepped-wedge randomized trials. The command permits continuous, binary, and rate outcomes (with normal approximations) for comparisons using two-sided tests. The command allows specification of the number of clusters randomized at each step, the number of steps and the average cluster (cell) size, or an incomplete design in which the user specifies the design pattern (a matrix with one row per cluster, one column per time point, and entries indicating exposure and observable data). Cluster heterogeneity can be parameterized using either the intracluster correlation or the coefficient of variation (of the outcome). The command is illustrated via examples.

https://www.stata-journal.com/article.html?article=st0341

5.Medical journal information from primary health care

- About 70 % of the population seek their physician every year (Mean: 2,7 consultations per year)

https://tidsskriftet.no/2019/01/kronikk/ny-infrastruktur-allmennmedisinsk-forskning

Snow- a little box

- The physicians get a little box linked to their computer
- Selected data will be transferred to the box
- By connecting the Snow Box server to the electronic medical record (EMR) all personal data remain within the practice
- The program Medrave is installed in the box, and enables searches, including validity studies

Data- The Norwegian Primary Care Research Network

- The data are protected by data privacy regulations

- All researchers who are interested in recruiting GPs, their patients or both to research projects may use The Norwegian Primary Care Research Network. Applicants must apply through the web portal for User Projects

https://www.uib.no/en/globpub/117454/norwegian-primary-care-research-network#costs-involved-in-using-the-network

Examples of use:

- Simple data extraction study:
- How many patients receive treatment x for disease y?

- Complex data extraction study:

Laboratory results, use of medication and symptoms described in the medical records for patients with a specific condition.

Examples of use cont.

- Clinical study:

Patients with diagnosis x are included in a qualitative study (interviews or focus groups).

- Randomised Controlled Trials (RCT):

Patients with disease x are included in a RCT

NORDIC BIOBANKS AND REGISTERS A BASIS FOR INNOVATIVE RESEARCH ON HEALTH AND WELFARE

POLICY PAPER 2/2017

The NOS-M White Paper on Medical Research 2014:

"Nordic registers and biobanks provide a good example and starting point for what can be achieved. The Nordic region can help to solve emerging, complex societal and healthcare issues as well as improve health standards and quality of life across the globe".

Thank you!