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Risk factors for fractures in Tromsø

The Tromsø Study

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Contents

List of papers

This thesis is based on the following papers, referred to in the text with their Roman numbers;

I. Luai A. Ahmed, Henrik Schirmer, Gro K. Berntsen, Vinjar Fønnebø, Ragnar M. Joakimsen. *Self-reported diseases and the risk of non-vertebral fracture: The Tromsø Study.* Osteoporos Int. 2005 Apr 19.

II. Luai A. Ahmed, Henrik Schirmer, Gro K. Berntsen, Vinjar Fønnebø, Ragnar M. Joakimsen. *Features of the metabolic syndrome and the risk of non-vertebral fracture: The Tromsø Study.* Osteoporos Int. "in press".

III. Luai A. Ahmed, Ragnar M. Joakimsen, Gro K. Berntsen, Vinjar Fønnebø, Henrik Schirmer. *Diabetes mellitus and the risk of non-vertebral fracture: The Tromsø Study.* Osteoporos Int. 2005 Nov 10.

IV. Luai A. Ahmed, Henrik Schirmer, Ragnar M. Joakimsen, Vinjar Fønnebø, Gro K. Berntsen. *Validation of the Cummings' risk score; how well does it identify women with high risk of hip fracture: The Tromsø Study.* Osteoporos Int. Submitted.

Introduction

Background

A fracture is a break or crack in a bone. Fractures are common and anyone can fracture a bone. They occur when the bone can not withstand the physical force excerpted on it. There are several types or classifications of fracture; simple, stress, comminuted, impact, compound, complete and incomplete. Depending on the type and location of a fracture, the treatment varies from immobilization using cast or splint to surgical intervention. Before the availability of radiographic techniques, surgeons relied on knowledge of dissected specimens and clinical evidence in determining the nature of the injury. Modern treatment of fractures began several years after the discovery of X-rays at the end of the nineteenth century [1].

Epidemiology of non-vertebral fractures

With the explosion of epidemiologic activity just after the Second World War, there was increased awareness of the increasing incidence of fractures especially among the elderly, and several studies about the epidemiology of fractures were published [2-5]. Thereafter studies have shown an increasing incidence of all types of fractures [6-13]. Recently a levelling out or even decreasing trends in hip fracture incidence have been described [14-17].

The seriousness of a fracture depends on the location of the fracture and the age of the individual who suffered the fracture. Although fractures can affect any person worldwide, increasing incidence of fractures among the elderly population constitutes a demanding health problem in the western world during the last decades. Older adults suffer more from fractures as their bones are more likely to be brittle [18] and therefore need less force to fracture. When occurring in the elderly or as a result of minimal trauma (falling from standing height) fractures are considered to be osteoporotic [19].

Osteoporosis, which is one of the most prevalent chronic health conditions among the elderly, is a systemic disorder characterized by low bone mass and micro-architectural deterioration of

bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk [20]. An operational definition of osteoporosis developed by a working group of the World Health Organization (WHO) have related the condition to bone mineral density (BMD); a BMD level more than 2.5 standard deviations (SD) below the young normal mean [21]. Regardless of definition, bone fractures are the major cause of morbidity and mortality associated with osteoporosis [22].

Overall, with the growing proportion of elderly in the population there is an increasing incidence of fractures. This picture held true in the Scandinavian region where the incidence of fractures is among the highest in the world [23-27], even after age-adjustment [7-9, 28-31]. On the other hand studies have reported an increased sex- and age-specific incidence of all fractures among middle-aged and elderly also in other populations [7, 32].

Most studies on fractures have been focusing on vertebral and hip fractures among elderly people. Hip fractures are the fractures most easy to describe with respect to consequences, both in terms of economical and human cost, and information on this single fracture type can illustrate the extensive consequences of fractures in general. The incidence of these fractures varies with geographical region, race, sex and age [33, 34]. Hip fractures are more common in women than men with a high mean age (around 80 years).

More than 10,000 patients are discharged with this diagnosis every year from Norwegian hospitals, and they spend a total of 130,000 days in hospital every year [35, 36]. In comparison, patients with the diagnosis of acute myocardial infarction spend a total of 110,000 days in hospital every year [35]. A hip fracture leads to severe consequences for the victim; quite often it reduces the quality of life drastically for the rest of the patients' life [37]. Approximately one fourth of hip fracture patients must have help in every day life after the fracture, and 60 % will never regain their initial functional level [38, 39]. In addition, hip fracture patients have a substantially increased mortality after the fracture [38, 40-42], with

threefold increase in mortality the first year [43]. Other fractures also have serious consequences, -they occur earlier in life-, so they will often limit an active way of life in shorter or longer periods of time [44]. Based on incidence numbers and cost-calculations from USA [45], hip fractures lead to direct expenses of more than 1.2 billion NKr (1993) every year (10000 fractures x 17500 $ (1993) x 7.0 NKr (≈ exchange rate) = 1.22 billion NKr).

Other non-vertebral fractures than hip fractures are not uncommon [23, 27, 46-49]. However the proportion of people who have already had fractures is only a small fraction of those potentially at risk [38].

Fracture aetiology

Fractures may be subdivided according to their aetiology into; those caused solely due to sudden injury, those due to bone fatigue or repeated stress, or a pathological fracture in a bone weakened by disease [1]. Most models describing fracture aetiology contain the following elements:

1. Factors that increase the risk of a trauma (most often a fall). Examples of such factors may be vertigo, reduced eyesight or agility, reduced balance, engaging in risk sport or slippery surfaces.
2. Factors related to the trauma: Amount of energy involved, direction of forces and location of impact.
3. The skeleton's ability to resist a trauma. This is dependent of factors like bone quality, bone mass and bone size.
4. Protective factors. Examples might be reaction time, thickness of loose tissue covering skeletal structures, and hip protectors (cushions).

These factors constitute some component causes of different causal mechanisms for fracture. For a subject to fracture, only high impact trauma can cause a fracture by itself. Otherwise a complete causal mechanism involving several component causes should be satisfied. This

indicates the need of joint action of several component causes to cause a fracture, and the impossibility of identifying a complete causal mechanism due to the unlimited list of component causes or risk factors. However identifying strong component causes which play major causal role in a high proportion of the fracture cases is possible.

Risk factors for non-vertebral fractures

Substantial numbers of studies have elaborated the associations between several risk factors and the risk of non-vertebral fractures. Race, gender, age, bone mineral density (BMD), type of falls and its risk factors, body weight and height, body mass index (BMI), physical activity, smoking and history of previous fracture(s) are among the most frequently documented risk factors for non-vertebral fractures in review, clinical trail and large follow-up studies [50-56]. They will be discussed briefly in the following paragraphs.

White women and men have higher age-specific incidence rates of hip fractures than black women and men [19, 57]. Fracture incidence differs between men and women with respect to age. Whereas men suffer most from fracture before the age of 45, women fracture after that age [58]. Although the high incidence of fractures among young men probably are attributed to high susceptibility to accidents in sport and at work, even men at higher age fracture some sites more than women; skull, chest, clavicle, scapula, radius/ulna shaft, metacarpals and phalanxes, most probably as a result of the same risk seeking behaviour [59]. Fractures at the ends of radius and ulna, humerus, pelvis, femur, patella, tibia, fibula and ankle are more common in older women [32]. Overall women have two to three times higher age-specific incidence rates of hip fractures and six to eight times higher incidence rates of Colles' and proximal humerus fractures than men [19].

The association between low bone mineral density and fracture risk have been reported in many studies [60-63]. Although increased fracture risk is associated with decreased BMD in both white and black women, white women have a higher fracture risk at every level of BMD

than black women [64]. Although many risk factors other than bone density might increase fracture risk through changes in bone mass, some non-BMD risk factors predispose or constitute independent component causes for fractures.

Falls and their risk factors could be considered as a strong component cause of all fractures apart from some cases of pathological fracture incidents, as a fall will be part of the majority of fracture mechanisms. Several studies have shown that falls, their characteristics and direction independently predict fractures [19, 55, 65-68].

High risk of fractures is associated with low body weight and weight loss [19, 68], and increased body height [57, 69-71]. Accordingly the association between BMI and fracture risk is consistently negative [19, 57, 70, 72-75]. Although higher impact of a trauma is expected with increased body mass, the lower fracture risk among the obese is thought to be associated with protective layers of fat padding around skeletal structures and better bone mass [70, 72].

Although positive association between physical activity and bone mass have been reported [19, 76, 77], physical activity might affect fracture incidence differently at sites. Overall inactive individuals have higher fracture risk than active ones [19, 75, 78, 79].

Despite the huge number of studies showing negative association between smoking and BMD, the importance of this relation and its association with age is still uncertain [80]. Smoking was associated with greater loss of bone in postmenopausal women and had no effect in premenopausal women [80]. This could be due to accelerated natural menopause, modified oestrogen metabolism or decreased body weight in smoking women [57]. Although the risk of hip fractures associated with smoking was higher in both men and women in some studies [69, 80, 81], other studies showed no increased hip or non-vertebral fractures risk among women [57, 59, 75].

Several studies have indicated that previous fracture predict high risk of a subsequent fracture [67, 82-84], and one meta-analysis have shown that previous vertebral fracture carries a high risk of a subsequent hip fracture in both men and women, while the risk of new hip fracture is higher in men with previous Colles' fracture than in postmenopausal women with such history [85].

Despite the thorough investigations with respect to the associations between the previously mentioned risk factors and fracture risk, inadequate information is available concerning other component causes for fractures; diabetes mellitus, stroke, asthma, thyroid diseases, heart diseases, psychiatric disorders, cancer and epilepsy, where most studies have focused only on the effect of these chronic diseases on bone mineral density. Moreover, no attention has been paid to the association between features of the metabolic syndrome which are risk factors for some of these diseases and the risk of non-vertebral fractures.

Diabetes mellitus

Despite the relatively high number of studies on the association between diabetes mellitus and fracture risk compared to other chronic diseases, there is still uncertainty about this relation. Increased fracture risk in patients with diabetes was reported in some but not all studies. Several follow-up studies reported an increased hip fracture risk among diabetics. An increased hip fracture risk was described in men and women aged 35 to 49 years with history of diabetes mellitus [69]. In another study, Forsen et al [86] found an increased risk of hip fracture in women younger than 75 years with type I diabetes and those with type II for more than 5 years, and in men older than 75 years with type II diabetes for less than 5 years. Increased risk of hip and proximal humerus fractures among women 65 years of age and older with type II diabetes was described by Schwartz et al [87]. Diabetic Mexican Americans over 65 years had a increased risk of hip fractures, especially those using insulin [88]. In the Rotterdam Study [89] men and women older than 55 years with already established and

treated type II diabetes had an increased non-vertebral fracture risk. Insulin-treated diabetes was associated with proximal humerus fractures [55] and foot fractures [68] in women 65 years and older. However the latter study found that the risk of ankle fractures was not associated with any type of diabetes in older women [68]. On the other hand, two case-control studies found that hip fracture risk was not significantly increased in diabetics [90], and hip and distal arm fracture rates were not increased in insulin-treated women [91].

Although the risk associated with type I diabetes has been consistent in many earlier studies, whether type II diabetes is a risk factor by itself or whether its associated risk mainly is due to insulin use or its onset late in life is unclear. Most of these studies have focused on fracture risk in specific locations, mainly the hip, and the majority of these studies included only older women. The association between type I diabetes mellitus and fracture risk might act through changes in bone mass, which could be due to the co-morbidities, complications or poor control of type I diabetes [92-94]. Higher risk of falls due to episodes of hypoglycaemia would be expected among type I diabetics leading to increased fracture risk.

Despite the high bone mineral density usually found in type II diabetics [87, 89, 92, 95-97], the co-morbidities associated with diabetes, the visual or neuromuscular functions deficiencies, the effect of medications contribute to the increased fracture risk. In addition, increased risk of falling and its risk factors among diabetics [98], or structurally altered bone in diabetes [99] could also play a major role in increasing fracture risk.

Stroke

Earlier follow-up studies found stroke as a risk factor for hip fracture in men aged 35-49 years [69] and in both men and women with mean age around 73 years [100, 101], while another study described a trend toward an increased risk of hip fracture among women 65 years or older with history of stroke [82]. In addition case-control studies described an increased hip fractures risk associated with history of stroke in women [72, 73] and in both men and women

[102]. Although the increased risk of falls due to balance problems and neuromuscular functions deficiencies might explain the increased fracture risk in stroke patients, reduced bone mass in the paretic extremities -due to immobilization- has also been shown to contribute to an increased fracture risk [103].

Asthma

Asthma and mainly the use of corticosteroids have been described as major determinants of fractures in general and vertebral and rib fractures in particular [104]. The adverse effect on bone density and fracture risk caused by oral corticosteroids [104, 105] in contrast to inhaled steroid therapy [106, 107] could indicate different patterns of association between asthma and fracture risk -even in the same individual- when changing type of medication.

Thyroid diseases

Hyperthyroidism has been the focus of earlier studies of fracture risk associated with thyroid disease. It was described as a risk factor for hip fracture among old women in a longitudinal [82] and a case-control study [108]. However another case-control study found no increased fracture risk in patients with previous thyrotoxicosis [109]. On the other hand there is no information on the association between hypothyroidism and fracture risk.

Psychiatric disorders

Previous studies found that patients with mental distress or using psychotropic drugs have increased risk of fractures [110-113]. The use of psychotropic drugs may increase the risk of fractures by increasing the likelihood of falls [114-116]. Other suggested mechanisms of the increased fracture risk among mentally distressed subjects were health neglecting behaviour and corticosteroid induced osteoporosis [110].

Heart diseases

Low bone mineral density and bone loss were found to be associated with an increased risk of cardiovascular and coronary heart disease mortalities [117]. No information is available

through Medline search to describe the association between heart diseases and fracture risk. However aortic calcification, which is a risk factor for cardiovascular disease and atherosclerosis was associated with low BMD in some [118, 119], but not all [120, 121] studies.

Cancer

Earlier studies found a reduced risk of hip fracture in women with endometrial [122] but not breast cancer [123]. Excessive endogenous estrogens, which can delay the postmenopausal bone loss, might explain the reduced risk of fractures in women with endometrial cancer. The reduced risk might also be confounded by the associated increased weight and change in lifestyle. However the relationship between cancer and fracture risk need more thorough investigation taking into account all possible explanations and confounding factors.

Epilepsy

Previous studies showed a high incidence of fractures among patients with epilepsy or those using anticonvulsants drugs [73, 101, 124, 125]. Apart from fractures sustained during epileptic fits, increasing fracture risk among epileptics is related to a reduced mobility in exhausted patients or the use of antiepileptic drugs.

Features of the metabolic syndrome

Apart from body mass index (BMI), little is known about the relationship between the metabolic disturbances or features of the metabolic syndrome and the risk of non-vertebral fractures. No significant association has been found between diastolic/systolic blood pressure (BP), total cholesterol, triglycerides and glucose and the incidence of hip fracture [69]. Some studies have used the surrogate endpoint bone mass density with conflicting results. Although higher blood pressure (BP) was associated with increased bone loss at the femoral neck in one study [126], another study found hypertension to be associated with higher bone mineral density values in men and women 50 years of age and older [95]. Another study found that

systolic and diastolic blood pressures, serum triglycerides, blood glucose, BMI and waist-to-hip ratio were positively associated with bone density ($p< 0.001$), and high-density lipoprotein (HDL) and serum cholesterol were negatively associated with bone density [127]. A possible explanation for the negative association between HDL and serum cholesterol and bone mineral density in women could be that an unbalanced diet severely limiting calcium intake in order to correct serum levels of cholesterol is a risk factor for postmenopausal osteoporosis and wrist fractures as found by Varenna et al. [128].

Overall these findings indicate a possible protective effect of metabolic syndrome on fracture risk which is supported by one study showing that women with postmenopausal fractures had lower BMI and higher serum levels of HDL than those without fractures [117].

Identification of subjects with high risk of fractures

Although the identification of individuals with high hip fracture risk –who may effectively benefit from pharmaceutical preventive intervention- have relied mainly on BMD measurements [63, 129, 130], the low sensitivity of BMD in the prediction of fractures [131, 132] will result in unnecessary pharmaceutical intervention in many elderly women. On the other hand, non-BMD risk factors independently play a major role in the prediction of hip fracture [82, 133-135]. Combining BMD measurements with non-BMD risk factors allows better assessment of fracture risk [136-140] and help targeting prevention to high risk individuals as shown in earlier studies [134, 141-145]. Although these studies used different risk score definitions, they indicated better identification of high risk women based on non-BMD risk factors. A straightforward comparison between BMD and risk score screening will be meaningful when considering the efforts and cost as well as the total number of women needed to be screened.

Aims of the thesis

The main aim of this thesis was to explore different risk factors for non-vertebral factures among the population of Tromsø, with main focus:

- To examine whether men and women with self-reported chronic diseases like diabetes mellitus, stroke, asthma, thyroid disease, psychiatric disorders, heart disease, epilepsy and cancer have higher risks for non-vertebral fractures than others.
- To elucidate the association between the metabolic syndrome and non-vertebral fractures.
- To investigate whether men and women with validated diabetes mellitus have higher risks of non-vertebral fractures than non-diabetics.
- To validate the Cummings' risk score for hip fracture, and whether the risk score is better than BMD in identifying old women with high risk of hip fracture.

Material and methods

In Tromsø, a large proportion of the populations have been surveyed several times in five large population-surveys since 1974, with a primary aim of earlier population-surveys to map risk factors for cardiovascular disease. In addition, the University Hospital of Tromsø is the only hospital in the vicinity, and the distance to the nearest hospital or radiographic station is above 200 km. Consequently, there is a unique situation with respect to research, with vast amounts of baseline data on a total population, and easy access to a near to complete end-point registry of fractures in the same population. The fracture registration in the archive of the Department of Radiology is of high quality, the sensitivity of this registry is for instance higher than self-report with a questionnaire, and the specificity is close to 100%, as the golden standard for fractures is radiographic verification [146].

Study design

This is a large population-based observational study. With the prospective design of this study, the risk factors included, were measured/classified before the occurrence of fractures.

Study population

The population-survey in Tromsø has comprised the cohorts presented in table 1. The target cohort of the present thesis comprises the 27159 persons who attended the survey in 1994/95 (papers I-III). At that time all residents of the Tromsø municipality born 1969 or earlier were invited to the first phase of the forth survey. Among the 37559 persons invited, 2139 persons died or moved before their scheduled phase I examination. The eligible population was therefore 35420 persons, and 27159 (77%) participants attended the phase I examination of the survey and answered the relevant questionnaires. Among these persons, there is data from 1986/87 (Tromsø III) on 15 952 persons and data from 1979/80 on 11 368 persons.

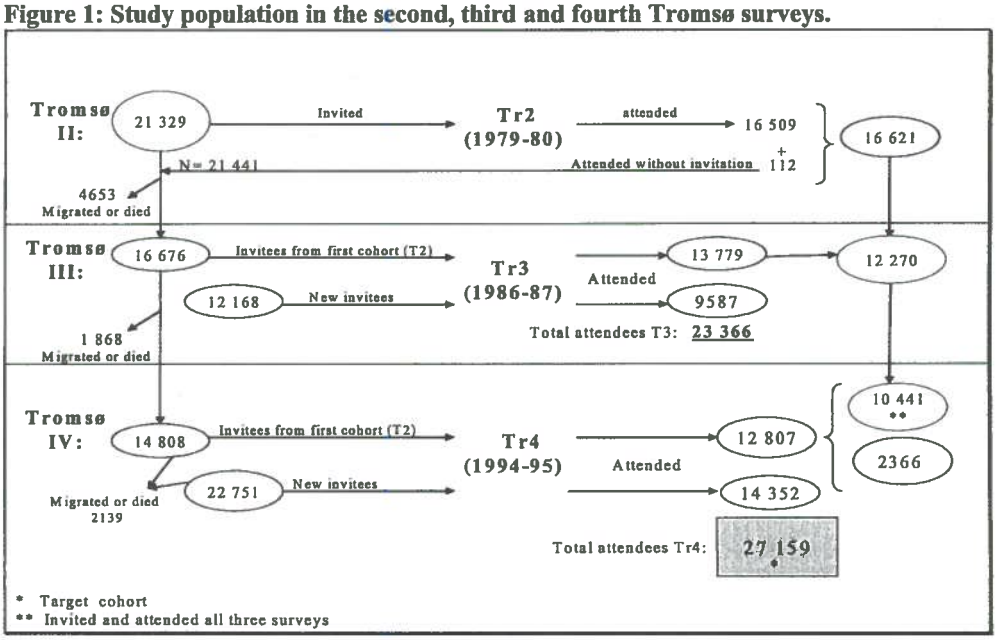
Table 1: Participation in the five Tromsø surveys.

Survey	Point of time	Invited	Attendees*
Tromsø I	1974	All men 20-49 years, a total of 9000	6595
Tromsø II	1979/80	All women 20-49 years, all men 20-45 years, a total of 21329 persons. (112 persons came without an invitation)	88% of invited women. 82% of invited men (16,621 persons)
Tromsø III	1986/87	All women 20-56 years, all men 20-61 years, a total of 28847 persons.	85% of invited women. 76% of invited men. (21826 persons).
Tromsø IV	1994/95	All persons above the age of 25 years. 37559 invited.	74% of invited women. 79% of invited men. (27159 persons).
Tromsø V	2001/02	All persons attended the Tromsø IV phase II survey and residents in certain age strata, total 10353 invited.	81% of invited women. 76% of invited men. (8130 persons).

* Percentage adjusted for those who had died, migrated or who were temporarily absent (travel etc.) on the time of the survey.

Details of the participation in the second, third and forth surveys are presented in figure 1. Upon attendance at phase I, all women aged between 55 and 74 were invited to The Tromsø Osteoporosis Study (TROST) together with a 5-10% random samples of younger and older age groups (n=5936), among them all women aged 65 years and older (n=1410) constitute the population in paper IV.

Figure 1: Study population in the second, third and fourth Tromsø surveys.



Data from questionnaires and examinations

Questionnaires printed on the reverse side of letters of invitation were distributed to the eligible population in each Tromsø survey. In the forth survey (1994/95) two sets of questionnaires were handed out (appendix A-C). The first one was printed on the reverse side of a letter of invitation, while the second one was handed out at the health examination to be returned by mail.

The first questionnaire was checked for inconsistency by a trained nurse at the health examination, and it included questions on diseases and symptoms, habits with respect to physical activity, diet, smoking, coffee-consumption and work-related issues. The second questionnaire differed for those younger or older than 70 years, and included questions on health condition, earlier diseases, diseases in the family, use of medication, use of health service, more on diet, alcohol-consumption, more on physical activity, marital status, educational level, more on symptoms, sleeplessness, mental health and reproductional factors among women (including use of per oral contraceptives and hormones).

At the health examination, body height, weight and blood pressure were measured and blood specimens were obtained (tested for total-cholesterol, HDL-cholesterol, triglycerides, glucose and gammaglutamyltransferase). Height and weight were measured in light clothing without shoes to the nearest centimetres/kilogram. Non-fasting values for serum lipids and glucose were registered.

In addition, all women aged 50-74 and all men aged 55-74 and a 5-10 % sample of other age-categories were invited to an extended examination with measurement of bone mass, 12-channel ECG, ultrasound examination of the abdominal aorta and of the carotid arteries, balance tests, test of muscle-strength in hands and thighs, measurement of fat percentage in the body in addition to extensive blood testing and records of medication. Half of the attendees also received an Echo-Doppler examination of the heart. Forearm bone

densitometry measurement was performed on the non-dominant arm at distal and ultra-distal sites with two single x-ray absorptiometric devices (DTX-100; Osteometer MediTech, Inc., Hawthorne, California) [147]. A total of 7948 persons had their bone mass measured, and 6891 persons completed the extensive examination.

Registration of exposure variables

Data from questionnaires and examinations were used to define exposure variables in each paper depending on the main aim of the corresponding analysis.

Paper I:

The participant was considered to have a disease if he or she answered yes for the disease or its corresponding drug (ex. insulin or anti-diabetic drug for diabetes), or filled out the age at onset of the disease. For thyroid disease, self-reported thyroxin use was used to distinguish between hypothyroidism and hyperthyroidism. For psychiatric disorder, the participant was considered exposed if he or she had sought help for psychological problems or reported use of antidepressants or tranquillisers. Heart disease included those who had self-reported history of angina and/or myocardial infarction. The reference group included those with none of the selected diseases. Other self-reported diseases like rheumatoid arthritis, osteoarthritis and Parkinson disease were not included in the final presentation as data were available only for participants of the second phase and consequently made multivariate analysis dubious due to low power.

Paper II:

Using information collected from questionnaires and examinations, the metabolic syndrome criteria were defined using the National Cholesterol Education Program (NCEP)- Adult Treatment Panel III [148]. Accordingly the criteria are:

1. Hypertension; blood pressure $\geq$ 130/85 and/or medication.
2. Hypertriglyceridemia; triglycerides > 1.695 mmol/l.

3. Low HDL cholesterol; < 1.036 mmol/l (men), < 1.295 mmol/l (women).
4. Central obesity; waist circumference > 102 cm (men), > 88 (women).
5. Fasting plasma glucose ≥ 6.1 mmol/l

Measurements for the last two criteria were available only for participants attending the second phase. BMI was used instead of waist circumference as both were possible alternatives in other studies [149, 150]. In this analysis the cut-off values for BMI were calculated as the mean BMI values in men and women with waist circumference of 102 and 88 centimetres respectively among those who attended the second phase. Accordingly BMI > 28.3 for men and BMI >27 for women will be used. The last criterion was valued positive if non-fasting glucose level was ≥11, ≥10 or ≥6.1 mmol/l and the time since last meal was >1, >2 or >8 hours respectively. Mean BP was calculated using the formula (systolic BP+ diastolic BP*2)/3.

Paper III:

Possible cases of diabetes mellitus were identified as all participants who:

(i) Reported diabetes mellitus or age when diagnosed in the fourth survey.

(ii) Reported use of anti-diabetic drugs in the fourth survey.

(iii) Reported diabetes mellitus in the second, third and fifth surveys.

(iv) Had elevated HbA1c (≥ 6.5) level in the fourth or fifth surveys (only phase II population).

(v) Were registered with a diabetes related diagnosis in the medical records.

According the International Classification of Diseases (ICD) coding, any diabetes related code was validated by check of the medical records. Out of 756 possible cases of diabetes mellitus, 646 subjects were confirmed to have diabetes by review of the medical records, of them 455 subjects had the disease before the start of follow-up and the other 191 subjects (pre-diabetics) developed the disease during the follow up. Information regarding the type of

diabetes and the use of insulin was collected from the medical records. Any patient using anti-diabetes tablets or diet to control diabetes was reported as type II diabetic. For those using insulin, the clinician's classification was used; in addition to WHO diagnostic criteria, usually based on clinical presentation in addition to level of C-peptide

Paper IV:

The risk factors used in this paper were maternal history of osteoporosis, underarm fracture after the age of 50, self-reported poor health, caffeine intake, physical inactivity, height more than 167 cm, weight loss of more than 5 kg or BMI less than 20, use of long-acting benzodiazepines, use of anticonvulsant drugs, self-reported hyperthyroidism, inability to rise up from a chair without help, resting pulse rate more than 80 and being older than 80 years at the time of BMD measurement. Weight measurements from the previous surveys were used to determine weight change. Because of the widespread acceptance of the WHO definition of osteoporosis [151], the population in this paper was divided into both BMD-tertiles and the *T*-score categories.

Fracture registration

The fracture registry is based on the radiographic archives at the University Hospital in Tromsø. The nearest alternative radiographic service or fracture treatment facility is located 250 km from Tromsø. The only fractures that would be missed are fractures occurring while inhabitants were travelling and no control radiographic examination was done after returning home, in addition to fractures not radiographically examined. An earlier registration for participants in the second and third Tromsø surveys was performed, validated and described by Joakimsen et al. [146].

The computerized records in the radiographic archives of the University Hospital contain codes for different information about fractures in addition to the national personal identification number and time of investigation. Any fracture-coded radiographic

examinations on invitees in the fourth survey were reviewed to ascertain the fracture code, identify exact anatomical location of fracture and to distinguish consecutive fracture cases from one another (Appendix D). In addition the discharge records were checked with respect to hip fractures. Although some radiographic examination descriptions included information about the mechanism of fracture, more than 70% of fractures were lacking information about energy and involvement of snow or ice. Therefore the analyses were not classified according to the level of energy and snow or ice involvement. On the other hand, vertebral fractures were not included in this study as their confirmed diagnose needs a series of comparable radiographic examinations starting before the occurrence of the fracture and a standard diagnostic protocol.

The fracture registry covered the period between the 1st of January 1994 and the 31st of December 2000. Table 2 shows the observed numbers of all non-vertebral fractures between 1994 and 2000, among all those attended the survey (N= 27159).

Table 2: Numbers of observed non-vertebral fractures among all those attended the forth survey (N= 27159).

Age-group	Men				Women			
	Observed N of fractures 1994-2000				Observed N of fractures 1994-2000			
	N	All	Hip	Forearm	N	All	Hip	Forearm
25-29	1 515	55	0	10	1 795	21	0	5
30-39	3 205	85	2	11	3 608	59	1	25
40-49	3 288	104	1	23	3 384	83	4	38
50-59	2 222	70	10	14	2 221	155	13	89
60-69	1 488	53	14	17	1 635	199	42	97
70-79	934	49	24	7	1 239	201	74	83
80+	214	30	21	4	411	85	43	30
Total	12 866	446	72	86	14 293	803	177	367

Statistical analysis

Power

The power of a study refers to its ability to demonstrate an association if one exists [152]. Power-calculations were performed in order to estimate whether the cohort is large enough to perform the analyses at all, or whether more follow up time is needed. The calculations were

performed using Epi-Info prior to the fracture registry and start of follow-up, based on the number of expected fractures in the cohort. Assuming alpha= 0.05, beta= 0.20 (i.e. power= 80%), the review of relative risks possible to establish dependent on strata-size and fracture type is given in table 3.

Table 3: Power calculations.

Prevalence of exposure	Among all women (N=14 293)			Among women >50 years (N= 5 507)		
	Any fracture	Hip fracture	Forearm fracture	Any fracture	Hip fracture	Forearm fracture
1 %	1.9	4.3	2.9	2.1	4.5	3.1
2 %	1.6	3.2	2.3	1.8	3.3	2.4
5 %	1.4	2.3	1.8	1.5	2.3	1.9
10 %	1.3	1.9	1.6	1.3	1.9	1.6
30 %	1.2	1.6	1.4	1.2	1.6	1.4
50 %	1.2	1.5	1.3	1.2	1.6	1.4
	Among all men (N=12 866)			Among men >50 years (N= 4 856)		
1 %	5.4	2.1	5.4	2.9	5.8	7.9
2 %	3.8	1.7	3.8	2.3	4.1	5.3
5 %	2.7	1.5	2.7	1.8	2.8	3.5
10 %	2.2	1.3	2.2	1.6	2.3	2.7
30 %	1.7	1.2	1.7	1.3	1.8	2.1
50 %	1.7	1.2	1.7	1.3	1.8	2.0

For an exposure with prevalence of 2% (for example self-reported stroke among men), the study has power of 80% to identify a relative risk of forearm fractures of 3.8 or higher. For an exposure with prevalence of 1% or less, like validated type I diabetes in women the study is powered to identify with 80% chance of success a relative risk of 4.3 or more.

Analyses

With the main aim to determine who is more likely to suffer a fracture faster, relative risks (RR) of fracture were calculated using Cox proportional hazard (PH) model in the SAS statistical package [153]. The Cox model is a robust model that gives good estimates of regression coefficients, hazard ratios and adjusted survival curves which closely approximate the results for the correct parametric model [154]. The proportional hazard model assumes a constant hazard ratio over time, or equivalently, a hazard for one individual that is proportional to the hazard for any other individual, where the proportionality constant is

independent of time. Satisfaction of the PH assumption was assessed for fracture risk predictors using the graphical approach. The log-log survival curves of variables being investigated were compared, where parallel curves indicate a satisfied PH assumption. Confidence intervals (95%) were estimated and the significant level was chosen at 5%.

In papers I-III follow-up time was assigned for each participant from the date of phase I examination to date of first fracture, date of death or emigration or to the 31st of December 2000. The total length of follow-up was 72848.6 person-years for men and 80653.9 person-years for women. As paper IV focused on 5-year fracture risk, the participants were followed for a maximum of 5 years from the date of BMD measurement for each woman with respect to first hip fracture. For these women the total length of follow-up was 6704.1 person-years.

Differences in means between groups were tested using age-adjusted general linear models. Interaction terms of all possible combinations of two or more causes that might modify one another were introduced to the models to determine the necessity for product terms in linear models. All proportional hazard models were adjusted for possible confounders, which might be associated with both the exposure and effect variables. Data are presented stratified by sex.

Paper I: The age adjusted risk of fracture for each of the self-reported diseases were calculated first alone against the reference group, then in a multivariable analysis for all the diseases in the model to check the independent effect of each disease as opposed to a possible increased or decreased risk by increased burden of disease. Disease questions with no answers were treated as missing values. Graphical evaluation of the Proportional Hazards (PH) assumption of the Cox-Model was done for each disease adjusting first for age, and then for other diseases and confounders. In the multivariate models the regression coefficients for chronic diseases were tested as a group to minimize chance findings due to multiple testing.

Furthermore, to check the effect of the burden of disease, subjects with self-reported chronic diseases that had independent fracture risks were given a score of one for each disease and

grouped according to number of chronic diseases. All models were adjusted for age, BMI, smoking and physical activity.

Paper II: All subjects with missing value for any of the criteria of the metabolic syndrome were excluded. Subjects were given a score of one for each feature of the metabolic syndrome (based on the NCEP definition) and grouped according to number of features. All the variables were included in one model to assess their independent effects on fracture risk. First, the variables were entered in continuous forms, then in dichotomous forms based on cut-off points defined by the NCEP definition of the metabolic syndrome to assess linear trends and threshold effects. The metabolic features were ranked in quartiles and linear trends of the risk of fractures assessed. Models were stratified by statistically significant interacting variables. Stratification was based on the cut-off point determined by the NCEP definition of the interacting variable. The risks associated with elevated non-fasting serum glucose adjusted for time since last meal, were measured among those attending the second phase of the survey only. The multivariate models of the continuous and dichotomous forms of the variables were adjusted for age, diabetes mellitus, smoking and physical activity. Each model including quartiles of one metabolic feature was adjusted for the other features in their continuous forms and age and diabetes mellitus.

Paper III: There was one diabetic woman with uncertain type who was excluded from the corresponding analyses. Sex specific models were adjusted for age, Body Mass Index (BMI), smoking, and metabolic syndrome features (mean blood pressure, serum high-density lipoprotein (HDL) and serum triglycerides). In a separate analysis the pre-diabetics were excluded from the non-diabetic population. To evaluate the effect of disease duration, type II diabetics were grouped according to their disease duration (4 years intervals) into 3 groups in addition to 2 groups of the pre-diabetics (those who will develop the disease within 4 years or after more than 4 years from the start of follow-up).

Paper IV: According to the number of risk factors the women were allocated in three groups; low risk: 0-2, medium risk: 3-4 and high risk: 5+ risk factors. Frequency tables were used to estimate crude fracture risks. Dummy variables were created for the risk score levels and the *T*-score categories, and the associated fracture risk ratios (RR) were calculated using the Cox proportional hazard (PH) models. The log-rank statistic was performed to test the overall difference between the survival curves of six subgroups; osteoporotics with high-, medium- or low-risk and non-osteoporotics with high-, medium- or low-risk.

Main results

Paper I: Self-reported chronic diseases and non-vertebral fractures risk.

Self-reported diabetes mellitus, stroke, asthma, hypo- and hyperthyroidism and psychiatric disorders were associated with increased fracture risk. Multivariate analyses showed an independent risk of fractures associated with self-reported diabetes mellitus, hypothyroidism and psychiatric disorders among men. Among women the independent risk was associated with self-reported asthma, hypo- and hyperthyroidism and psychiatric disorders. Self-reported heart disease had a protective effect on wrist fracture, especially in women. Increased burden of chronic diseases increase the risk of all non-vertebral ($p< 0.0001$), wrist ($p= 0.005$), proximal humerus ($p=0.0004$) and hip fracture ($p= 0.0002$) in men, and for proximal humerus ($p= 0,003$) and hip fracture ($p= 0.04$) in women.

Paper II: Features of the metabolic syndrome and non-vertebral fractures risk.

Increasing number of metabolic syndrome features was associated with significantly reduced fracture risk in both men and women, $p= 0.004$ and $p< 0.0001$ respectively. High BP was protective against fracture in men (RR 0.89 (95% CI 0.8-0.99)), while increased body mass index (BMI) was protective in women (RR 0.91 (0.84-0.98)). Increasing non-fasting serum levels of HDL increased fracture risk in women (RR 1.12 (1.05-1.21)). BMI modified the effect of HDL in men. Accordingly high HDL increased fracture risk in men with high BMI (RR 1.51 (1.2-1.9)).

Paper III: Diabetes mellitus and non-vertebral fractures risk.

Men with type I diabetes had an increased risk of all non-vertebral and hip fractures, RR 3.1 (95% CI 1.3-7.4) and RR 17.8 (95% CI 5.6-56.8) respectively. Diabetic women regardless of type of diabetes had significantly increased hip fracture risk, RR 8.9 (95% CI 1.2-64.4) and

RR 2.0 (95% CI 1.2-3.6) for type I and type II diabetes respectively. Diabetic men and women using insulin had increased hip fracture risk. Duration of disease did not alter hip fracture risk.

Paper IV: Validation of the Cummings' risk score.

Among 1410 elderly women 759, 578 and 73 had low, medium and high risk scores respectively. BMD screening applied to these individuals would yield an osteoporotic sub-group demonstrating a 5-year risk of 5% or more: 54 women with a high risk-score of 5+ had a 5-year risk of 13.0%. Thus the original Cummings Risk score was validated in a new population.

By applying the risk score in women aged 65+, it was possible to reduce the number needed to be screened for osteoporosis from 1410 to 73, and treat 54 instead of the 771 women with osteoporosis in this age-group.

General discussion

Methodological considerations

This population-based cohort study included large numbers of both men and women, with a wide age range at base line, who are followed over the period between the date of phase I examination to the 31st of December 2000 with respect to the occurrence of non-vertebral factures. With the prospective design of this study, the risk factors included were measured and/or classified without knowledge of the future risk of fractures. However the study is vulnerable to measurement error in form of random (imprecision) and systematic (bias) sources of error.

Random error

Random error is the chance of non-reproducibility of the study findings. It can result in weakening of a true association or inability of finding an association between exposure and effect variables. Precision (lack of random error) can be improved by increasing the size of the study and the efficiency of the study by modifying its design [155]. The large size of this study reduces sampling error and therefore increases precision. Moreover, the study efficiency is improved with the proper allocation of subjects into study groups using all the available information of the data.

Random error was addressed by the statistical inference. Estimation of the associated relative risk and its confidence interval were calculated. Hypotheses were tested at the 0.05 alpha level with a 95% confidence interval. The null hypothesis was rejected if the 95% confidence interval did not include the null value of one (significant finding). Data that retain the null hypothesis; the 95% confidence interval includes the null value of one, were reported as non-significant. By applying these significance levels of the tests, Type I errors, which represent the possibility of rejecting null hypotheses that are true, are avoided. Although the avoidance of Type I error increases the likelihood of Type II error, which represent the possibility of not

rejecting a null hypothesis when it is false, the large study size and the a priori calculated power indicate an overall good power of the study minimizing the chance of Type II error. However, the wide confidence intervals for the fractures risk estimates associated with self-reported chronic diseases in paper I and diabetes mellitus in paper III are indications of low power due to relatively few numbers of cases and short follow-up time. This problem can be related to underestimation of the real number of cases (exposed) in the cohort rather than to the total sample size, and a longer follow-up time might result in better confidence limits.

Validity and bias

Systematic error (bias) refers to any trend in the way the study population were selected, the data and variables were measured and/or classified, or the confounding factors were controlled for that can lead to conclusions that are non-randomly deviating from the truth. These types of biases can distort the estimation of an epidemiologic measure of interest and retract from the internal validity of study [155].

Internal validity

With the high response rate in the study, and the limited potential biases discussed below, the results of this study are valid for the great majority of the population of Tromsø.

Selection bias:

The potential for selection bias is limited with 77% of the eligible population included in the study. Overall there were no defined criteria for those invited to the fourth survey apart from age (born 1969 or earlier). Figure 2 and 3 show the percentages of attendance by age groups among men and women respectively. The lowest attendance rates were among those less than 45 years and those older than 75 years, with respectively rates 66% and 74% of attendance among men and 73% and 67% among women. We have no possibility to explore differences between responders and non-responders, however in the second and third surveys with attendance rate of 73%, the age-adjusted mortality was higher among non-responders, and the

incidence of fractures were almost similar in the two groups [59]. This indicates a minimized effect of non-respondence on the estimated associations.

Figure 2: Percentages of attendance by age groups among men.

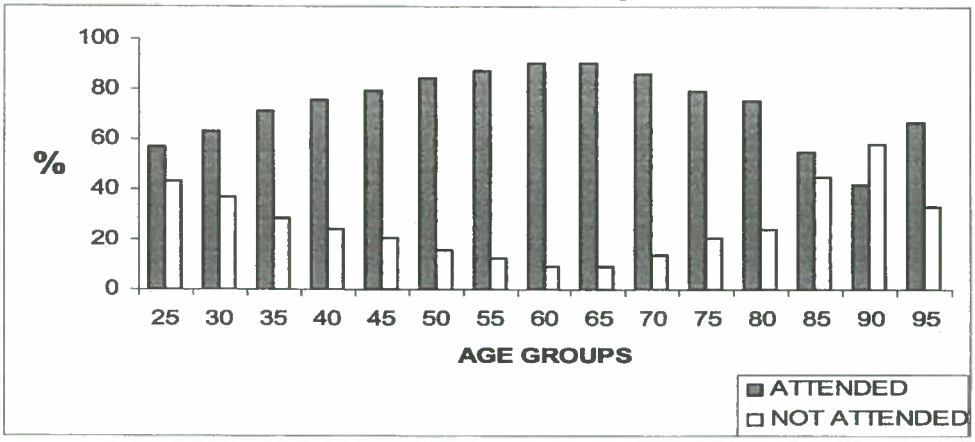
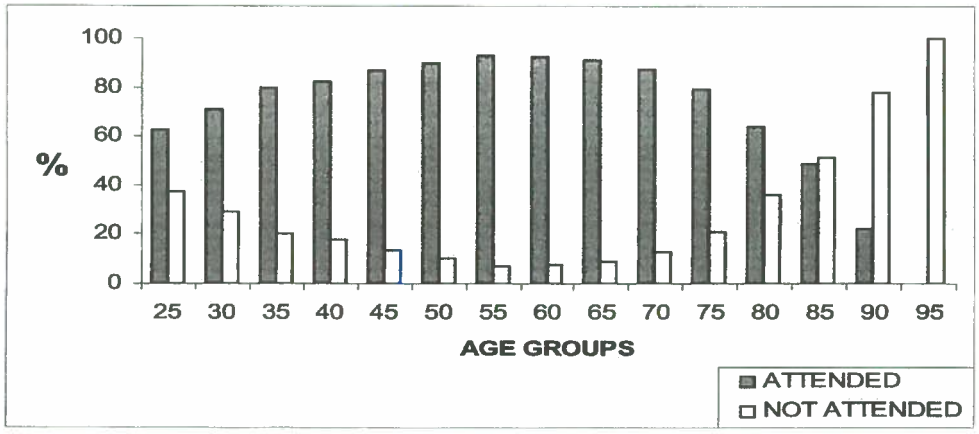


Figure 3: Percentages of attendance by age groups among women.



Information bias:

As most of the exposure variables used in this study were dichotomous, there is the possibility of misclassification of study subjects on one or more factors. This held true especially in paper I where all of the exposure variables were self-reported which could lead to recall bias. However, previous studies have shown that the agreement between self-report of chronic diseases and medical record is excellent or fairly accurate for diabetes mellitus, stroke, cancer,

and heart diseases [156-160]. Moreover the diseases studied were chronic in nature with a higher mortality rate for those affected than for those without the diseases. This suggests that subjects exposed to chronic diseases are more likely to be censored during the follow-up period than non-exposed. In addition there will be a gradually increase in prevalence of unknown exposure to chronic diseases among the control group. Thus the relative risk estimates were prone to be underestimated.

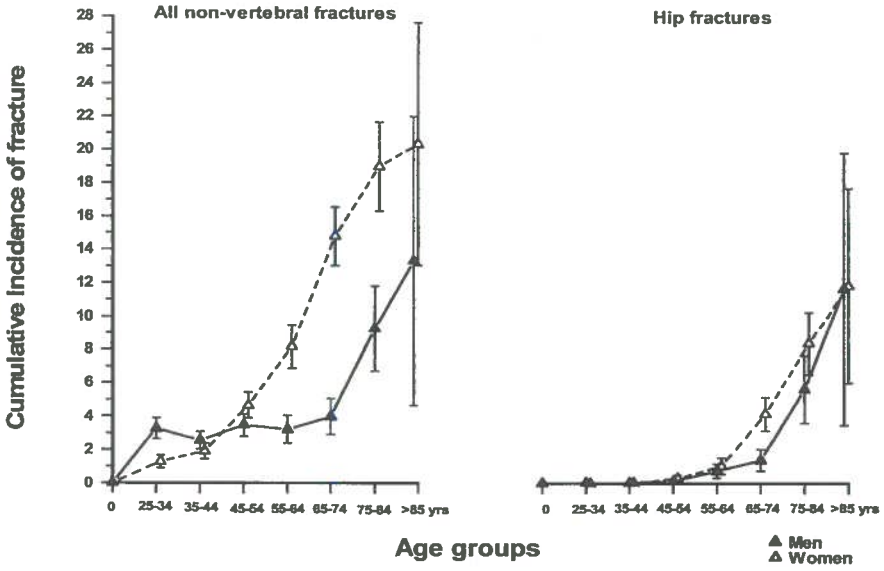
Although the validation of diabetes cases in paper III was based on reviewing the medical records, there is a possibility of underestimation of diabetes in this cohort. This non-differential misclassification will render the results underestimated, as the diagnosed diabetic cases may constitute only 50% of the actual number of diabetics in the population especially among those older than 30 years [161].

Confounding:

With the wide range of independent risk factors for fracture risk, it is certain that some of these independent risk factors will have some degrees of associations. Moreover, other factors with protective effect on fracture risk might be associated with some of the independent risk factors. Therefore the association between the exposure and effect variables might be distorted by an extraneous factor(s) which is/are associated with the effect (fracture risk) in both the exposed and unexposed groups, leading to mixing of effects or confounding.

Age is the most important confounder as it is associated with almost all the exposure variables and the fracture risk. The effect of age on non-vertebral and hip fractures risk among men and women is shown in figure 5. As mentioned before, the risk of non-vertebral fractures is higher in men than women before the age of 45 years, and the risk of hip fractures starts to increase in both men and women after the age of 60 although more consistent in women. By the age of 80 years hip fracture risk is similar in both genders. On the other hand, with the exception of paper IV, all the variables used were affected by age.

Figure 5: Cumulative incidence of non-vertebral and hip fractures among men and women by 10 years age groups.



To counteract any distortions in the association between exposure and effect variables, all the analyses were adjusted for age. The same was done with respect to other important confounders (BMI, smoking, physical activity, previous fracture, self-reported health) whenever they show significant contribution to the undergoing analyses; if the crude and adjusted measures of association are dissimilar. The relevant adjustment in each paper was mentioned above in the statistics and analysis section. Moreover, multivariate models including all the exposure variables under diagnose were conducted to check the independent effect associated with each variable (component cause) as opposed to a possible increased or decreased fracture risk by other exposure variable(s).

Separate from confounding, some extraneous factors can also have modification on the effect of an exposure. This effect modification or interaction; difference in effect of one factor according to the level of another factor, can have direct biological and public health relevance. Therefore interaction terms (exposure variable multiplied by possible effect

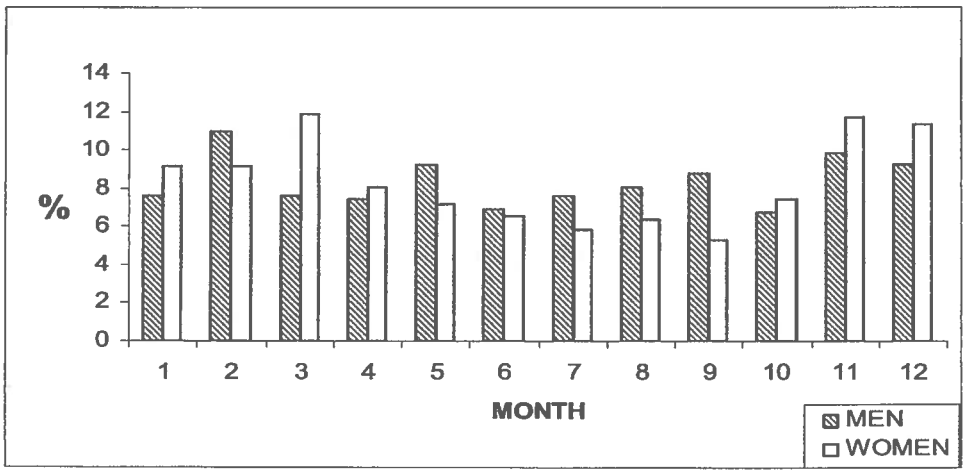
modifier) were introduced to the models to assess any significant differences between models with and without the interaction terms.

External validity

The external validity of the study refers to the generalisation of the internally valid results – for the source population- to other populations. The population in this study is representative of the Norwegian and any Scandinavian population, as it is largely a middle-class Caucasian population. However variations with respect to a rather extreme weather conditions and hilly topography of the city should be considered when comparing the results to populations living in different conditions.

The possibility of seasonal variation effect on fracture risk was tested using Chi square test for one-way frequency table. No differences in fracture frequency through out the year were found in men (p=0.6), but in women there was a significant difference (p>0.0001) (figure 6). However Comparing those without self-reported diseases to those with self-reported diseases –in paper I-, there was no significant general association between disease status and frequency of fracture by months in both men (p= 0.8), and women (p= 0.1).

Figure 6: Monthly variation of non-vertebral fractures risk among men and women.



Causality

Finding and describing relationships between cause and effect is a major concern in modern epidemiologic research. Such relationships will be tested first to search for a statistical association between exposure and effect. Then comes the derivation of biological meaning; causal inference [162]. Although several causes can be determined, the epidemiologic evidence by itself is insufficient to establish causality but it can provide powerful circumstantial evidence [152]. Providing such evidence on some component causes might help identifying strong causes relevant in a large proportion of cases. In this study, however, the majority of associations between risk factors and fracture risk described cannot be described as strong causes. This might be due to the relatively low prevalence of exposure to some chronic diseases, for instance, in the general population compared to other risk factors like smoking or physical inactivity. However, age-specific fracture risk would be strongly affected by some chronic diseases in elder people. The agreement between some of the results in this study and earlier studies gives consistency in the causal relationship for some risk factors, however special consideration should be made to differences between studies in terms of populations investigated and methods used. Overall neither of the chronic diseases associated with high fracture risk is a necessary, sufficient nor specific cause, but a strong epidemiological evidence of relationship with fractures can be demonstrated.

Fracture incidence

The overall incidence (per 10000 person-years) of all non-vertebral fractures in this study was 61.2 and 99.7 for men and women respectively. The age-specific fracture incidences per 10000 person-years are given in table 4. Overall there is gradual increase in the incidence of all non-vertebral fractures and hip fractures for both men and women. Comparing fracture incidence in this cohort with other studies requires consideration of the differences in

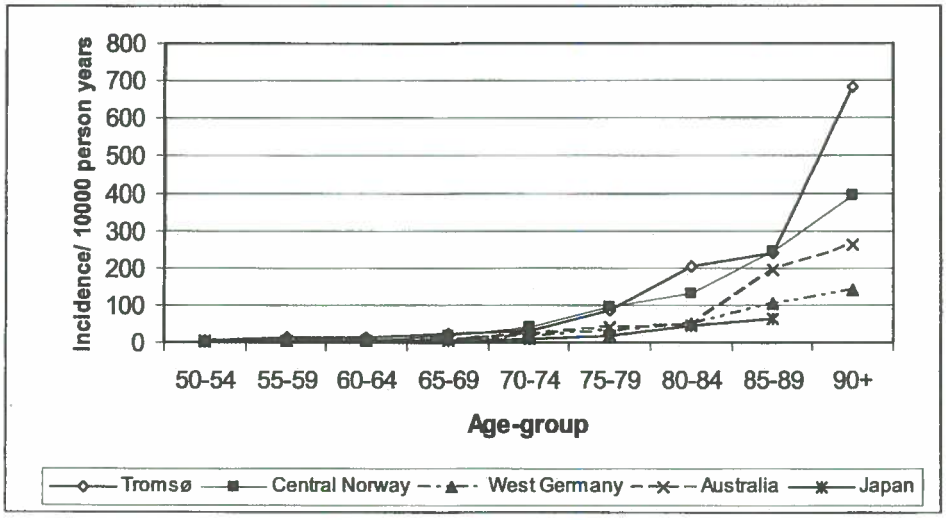
definition of fracture sites, fracture ascertainment methods, distribution of age groups and population characteristics in each study.

Table 4: Incidence of fracture per 10000 person-years in the study population.

	All non-vertebral		Forearm		Proximal humerus		Hip	
	Men	Women	Men	Women	Men	Women	Men	Women
25-29	63.2	20.1	11.3	4.8	1.1	1.0	0	0
30-34	50.0	23.9	11.0	8.6	1.1	0	1.1	0
35-39	41.7	32.1	1.0	15.0	2.1	1.9	1.0	0.9
40-44	45.9	32.7	10.1	17.8	3.0	1.0	0	0
45-49	63.4	51.6	13.8	20.5	3.2	8.2	1.1	4.1
50-54	55.9	120.1	10.5	69.6	0	12.0	3.9	6.7
55-59	53.6	128.3	11.4	70.5	9.5	7.3	13.2	14.6
60-64	60.6	168.1	17.7	89.0	4.4	15.6	13.3	22.4
65-69	70.3	277.8	24.0	122.3	2.7	30.9	21.3	66.1
70-74	81.7	290.8	12.8	117.2	16.1	36.4	32.2	86.7
75-79	147.4	368.5	18.0	139.7	30.0	34.6	84.7	145.1
80-84	331.9	466.1	42.7	155.4	14.1	55.5	204.2	206.3
85-90	307.3	442.4	58.4	103.2	0	83.6	238.4	257.4
90+	682.7	1455.6	0	799.4	0	0	682.7	551.3
Total	***61.2***	***99.6***	***11.6***	***44.8***	***3.9***	***10.0***	***9.7***	***21.4***

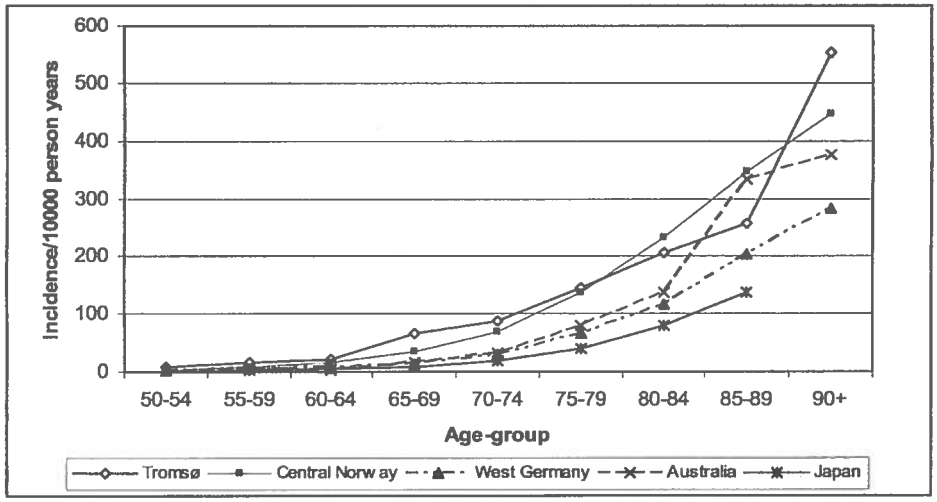
Crude comparisons with studies having the same fracture location and age groups are presented in figure 7 and 8 for men and women respectively. Overall there are similar patterns of increasing hip fracture incidence by age.

Figure 7: Incidence of hip fracture among men in defined populations.



Hip fracture incidences in this cohort (2000) and central Norway (1998) [163] were the highest compared to incidences in Australia (1996) [48], former West Germany (1996) [164] and Japan (1994) [11]. Among men (figure 7), hip fracture incidence in central Norway (1998) [163] was the closest to Tromsø (2000), whereas the lowest incidence was in Japan [11]. Among women (figure 8), the hip fracture incidences were higher in all the studies compared to incidences among men.

Figure 7: Incidence of hip fracture among women in defined populations.



Although hip fracture incidence in Norway among the highest in the world, recent studies have indicated an insignificant change in the incidence during the last decade [14, 163]. Similar patterns were described before. A downturn in hip fracture incidence was reported first in the United States [17, 165], then studies in Scandinavian countries [166-168], England [169], Australia [15] and New Zealand [170] have shown that the incidence is no longer increasing. In Tromsø, interestingly, there is a reduction in the incidence of all non-vertebral fractures between 1988 to 1995 [79] and 1995 to 2000 (present study) by 47% in men aged 28-70 years and 41% in women aged 28-65 years. Exploring differences in risk factor trends and changes in lifestyle between countries and within the same country in different time periods opens the possibility to identify important causal risk factors.

Intervention

Increased intake of calcium and vitamin D, smoking cessation and physical activity are health advice relevant to all to reduce fracture risk. Hip protectors have shown a risk reduction of more than 50% and are a useful prophylactic device [171, 172], but due to low compliance probably only relevant in subjects with high risk due to increased fall tendency. Bisphosphonates offers pharmaceutical prophylaxis, but this has only been shown in those with osteoporosis as defined by the WHO [173, 174]. Whether it has an effect on normal BMD has yet to be shown. In view of the possible side-effects of screening [175], bisphosphonates [176] and hip protectors – impracticalities of their application and cosmetic discomfort-, a 5-year cumulative risk of 5% for hip fracture and the WHO definition of osteoporosis [177] were used as the threshold for pharmaceutical preventive intervention. This corresponds to an absolute number of hip fractures saved due to treatment to be over 1 per 100 treated women with a risk of at least 1% per year, a priori chosen for treatment to be considered. The need to differentiate between intervention and diagnostic thresholds [136], helps in better targeting of high risk individuals. Identified individuals with high hip fracture risk may effectively benefit from pharmaceutical preventive intervention.

Overall using a simple scoring of a given set of risk factors, as suggested by Cummings [82], does identify high-risk subjects well in different populations. However, differences of the significance of non-BMD predictors of hip fracture between different populations [67] should be considered.

Implications

Paper I is the first study to investigate the independent risk associated with more than half a dozen of chronic diseases earlier found to be associated with fracture risk. Although the paper used self-reported exposure data and had limited power making the disease by disease approach vulnerable, especially where it can not support the risk found in other studies, it emphasizes the need to adjust for other co-morbidities when looking at the risk of fracture associated with single chronic diseases. In addition it shows an increased non-vertebral fractures risk with increasing burden of disease in both men and women. It also shows different relationships of self-reported diseases with fractures according to the site of fracture. Such differences have been reported earlier [178]. Even hip, femoral neck and intertrochanteric fractures have different risk factors and therefore different physio-pathologic processes have been suggested [179]. For clinicians, it is important to be aware of the increased fracture risk among subjects with chronic medical conditions. Precautions especially for those with more than one chronic disease could prevent additional increase in the risk of fracture in these patients.

In paper II, the negative associations between some of the features of the metabolic syndrome and non-vertebral fracture risk are in accordance with earlier findings of increased bone density in subjects with high blood pressure, low HDL levels and increased BMI [126, 127]. In addition the paper shows a reduced risk of non-vertebral fractures by increasing number of metabolic syndrome features. Although it is not a recommendation to increase subject's blood pressure, weight or serum lipids, the findings of this paper help in understanding how diseases like diabetes mellitus and heart diseases might affect fracture risk as the metabolic syndrome is an important risk factor for both diseases [180]. Accordingly, the findings show that the risk of fracture associated with type II diabetes is not explained by the metabolic abnormalities preceding the disease, and other factors like glucose intolerance, the effect of medications and

other pathophysiological mechanisms should be considered when investigating the fracture risk associated with type II diabetes. This was supported in paper III, where further adjustment for features of the metabolic syndrome slightly reduced –although still significant- the hip fracture risk associated with type II diabetes especially in women. Moreover, men and women who developed type II diabetes after more than 4 years from the start of follow-up who were in their metabolic syndrome phase at baseline, had the lowest hip fracture risk

On the other hand findings in paper III support associations between types of diabetes mellitus and fracture risk especially hip fractures. They also indicate that the risk associated with insulin is not explained solely by type I diabetes, and the duration of the disease and most probably the duration of insulin use is the main predictor of fracture risk especially in type II diabetic women.

The debating question on how to identify individuals with a high hip fracture risk who may benefit from pharmaceutical preventive intervention was discussed in paper IV. Whereas using a modified version of the simple risk score introduced by Cummings [82] identified a high risk group constituting only 5.2% of the total population of women 65 years and older. This approach identifies and therefore targets the pharmaceutical intervention to where it is most effective, leading to a dramatic reduction in the number needed to treat to prevent one hip fracture in comparison to earlier recommendations [181].

Further research

More attention is needed to investigate further known and possible risk factors for fractures. Focusing on bone mineral density alone would not clarify why certain subjects are more vulnerable to fractures than others, for instance in the case of type II diabetics. New studies are needed to justify the fracture risk associated with chronic diseases when adjusting for other co-morbidities and with features of the metabolic syndrome.

Particularly in Tromsø, the field of fracture risk needs further exploration. The ongoing population surveys with the high attendance rates and the continuous fracture registry provide a unique opportunity for research. Further studies should be performed to examine among other possibilities the following areas:

1. From the results of paper I, a strong effect of burden of disease on fracture risk was found. By applying the same princible on known risk factors for fracture, it might help identifying a threshold number of risk factors or a weighted score that could be used to identify those at risk of fractures. This could be an alternative or even better way to identify subjects in need of prophylactic treatment.
2. The assessment of absolute risk rather that the relative risk permits better selection of individuals or population subgroups either for further risk assessment or for intervention [182]. As in cardiovascular prevention, targeting those with increased absolute risk rather than with identified individual risk factors will increase cost effectiveness of screening and prophylactic treatment. In Tromsø applying this concept by measuring the age specific absolute risk of non-vertebral fractures could help in the management of individuals where long-term gains are likely by proper prophylactic and pharmaceutical interventions.
3. High mortality rate were recorded among hip fracture patients [40, 41, 43]. With the advanced care and rehabilitation of these old patients, one could expect a reduction in

death rate among these patients. With no previous assessment of the case fatality in Tromsø, calculating case fatality ratio of hip fracture in two different periods of time will assess any reduction of hip fracture case fatality ratio.

4. Are those with poor health condition at high risk of fracture? And is psychiatric score a predictor for fracture in addition to self-reported psychiatric illness? Further information is needed with respect to the relation between self-reported health status, psychiatric disorders and the risk of non-vertebral fractures.
5. The relationship between metabolic syndrome and type II diabetes mellitus and osteoporosis. This would explain further the results in the second and third papers and help in understanding the causal relationship between these factors and fractures.
6. Is the age related fall in BMD the cause of the age related increase in fracture incidence? This could be investigated by assessing the relationship between changes in BMD and fracture risk.
7. Assess whether risk scores or equations based on 10-year fracture risk improve the sensitivity and specificity of screening for individuals with high risk of fractures.

General conclusions

- The independent non-vertebral fracture risk associated with self-reported chronic diseases differs between men and women as well as between fracture sites in the same gender. Diabetes mellitus, hypothyroidism and psychiatric disorders were associated independently with increasing risk of fractures among men. Women had an independent increased risk of hip fracture among those with asthma and of proximal humerus fractures among those with hypo- and hyperthyroidism and psychiatric disorders. The independent effect of each chronic disease seems to be additive as increasing burden of chronic disease increases fracture risk regardless of possible differences in causal pathway.
- Increasing burden of metabolic syndrome features significantly protect against non-vertebral fractures. Increasing BP in men and BMI in women and decreasing non-fasting serum levels of HDL in women and obese men reduce the risk of non-vertebral fractures.
- An increased risk of all non-vertebral fractures and especially hip fractures was found in type I diabetic men and men using insulin. Regardless the type, diabetic women had a high risk of hip fractures only.
- The original Cummings' risk score identify well women aged 65+ at high risk of hip fractures and restriction of BMD measurements to this high risk group can safely be done without missing subjects with a five year hip fracture risk of 5% or more. It was possible to reduce the number needed to be screened for osteoporosis from 1410 to 67, and treat 48 instead of the 771 women with osteoporosis in this age-group using 5% 5-year hip fracture risk as treatment threshold.

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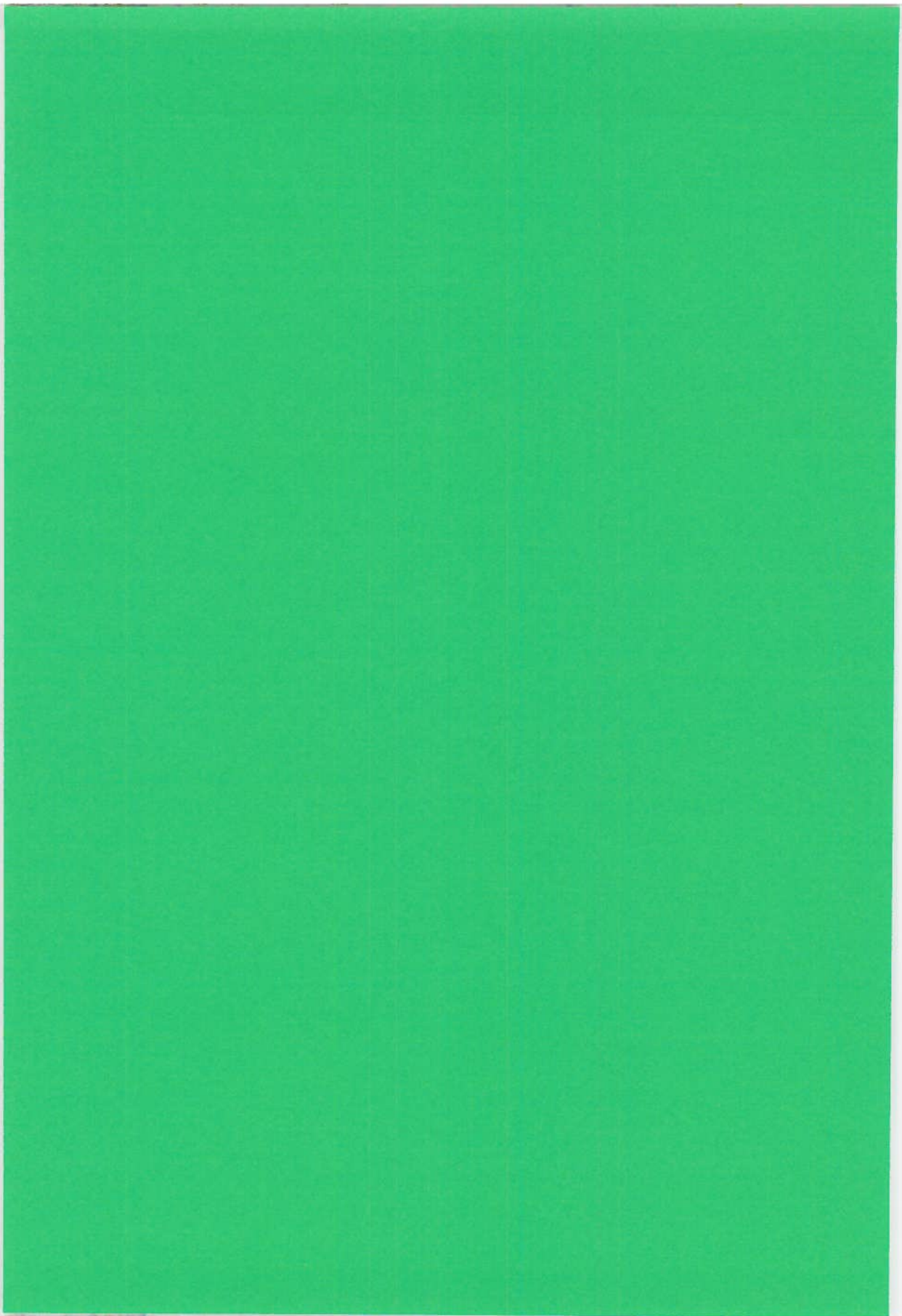
Paper I



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Self-reported diseases and the risk of non-vertebral fractures: The Tromsø Study.

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Abstract

Aim: We wanted to estimate the independent fracture risk associated with chronic diseases for men and women separately, adjusting for other known risk factors.

Methods: This is a population based study of all those who attended the fourth survey (1994/95) in the Tromsø Study (N= 27 159), followed until the 31st of December 2000 with respect to non-vertebral fractures. At baseline the age range was 25-98 years. Chronic disease cases were defined by self-report in questionnaires. All non-vertebral fractures were registered by computerized search in radiographic archives in the sole provider of radiographic service in the area.

Results: A total of 446 and 803 non-vertebral fractures were registered among men and women respectively. Self-reported diabetes mellitus, stroke, asthma, hypo- and hyperthyroidism and psychiatric disorders were associated with increased fracture risk. Multivariate analyses showed an independent risk of fractures associated with self-reported diabetes mellitus, hypothyroidism and psychiatric disorders among men. Among women the independent risk was associated with self-reported asthma, hypo- and hyperthyroidism and psychiatric disorders. Self-reported heart disease had a protective effect on wrist fracture, especially in women. Increased burden of chronic diseases increase the risk of all non-vertebral ($p< 0.0001$), wrist ($p= 0.005$), proximal humerus ($p=0.0004$) and hip fracture ($p= 0.0002$) in men, and for proximal humerus ($p= 0.003$) and hip fracture ($p= 0.04$) in women.

Conclusion: There was an independent fracture risk associated with self-reported diabetes mellitus, asthma, hypo- and hyperthyroidism and psychiatric disorders in men and women. Increasing burden of disease increased fracture risk in both men and women.

Introduction

Osteoporotic fractures are a major health problem in the western world. Fractures are considered to be osteoporotic when they occur in the elderly or as the result of minimal trauma [1, 2]. The proportion of people who have already had fractures is only a small fraction of those potentially at risk [3]. However, many of these fractures are probably preventable. Attempts to disclose important risk factors have focused on studies mainly of the older part of the population. Bone mineral density, low body mass, sedentary life-style, type of fall and its risk factors, the presence of a previous fracture history, smoking, alcohol consumption, and a number of chronic medical disorders are some of the risk factors reported to be associated with fracture incidence [1-4]

Most studies focus on the effect of chronic diseases on bone mineral density. Some studies assess the influence of these diseases on fracture risk. The increased risk of fractures for increased number of chronic diseases has previously only been documented in middle aged women [2, 5].

Increased fracture risk was reported in patients with diabetes [4, 6-8], history of stroke [4, 9-11] asthma or using corticosteroids [12], history of epilepsy or using anticonvulsants drugs [11, 13, 14], hyperthyroidism and excessive doses of thyroid hormone [10, 15] and mental distress or using psychotropic drugs [16-19]. However other studies found no increased risk among patients with diabetes [10, 20], stroke [4, 10], thyrotoxicosis [21] and endometrial and breast cancer [22, 23]

Any relation to fracture risk might act through changes in bone mass, body mass, physical activity, visual function or neuromuscular function, other risk factors for falling or the effect of medications used for these medical disorders. However the effect of each of these chronic diseases has been estimated in studies mainly with women having a high mean age without adjustment for other co-morbidities.

We wanted to estimate the independent non-vertebral fracture risk associated with chronic diseases identified by questionnaire in a large population based follow up of 27159 people aged 25 to 98 years at baseline, adjusting for other known risk factors.

Material and methods

Study population

The Tromsø study is a population based cohort study with five repeated health surveys since 1974. In the fourth Tromsø survey (1994/95), all residents of the Tromsø municipality born 1969 or earlier were invited to the first phase of the survey. Among the 37,559 persons invited, 2139 persons died or moved before their scheduled phase I examination. The eligible population was therefore 35,420 persons, and 27,159 (77%) participants attended the phase I examination of the survey and answered the relevant questionnaires [24].

Registration of exposure variables and confounding factors

The first questionnaire was printed on the reverse side of a letter of invitation. At the health examination, a trained nurse checked the questionnaire for inconsistency and handed out a second questionnaire to be returned by mail.

The first questionnaire included among others questions about having diabetes mellitus, stroke, asthma, myocardial infarction and angina pectoris, in addition to risk factors such as physical activity and smoking habits [25]. The second questionnaire differed for those younger [26], or older [27] than 70 years. There were more questions concerning previous and present diseases and symptoms including thyroid disease, cancer, epilepsy, psychiatric disorder, and the age of first diagnose and use of drugs. The examination included among other; blood pressure measurements, blood samples and weight and height determination. Height and weight were measured in light clothing without shoes to the nearest centimetres/kilogram.

The participants were considered to have a disease if he or she answered yes for the disease or its corresponding drug (ex. insulin or anti-diabetic drug for diabetes), or filled out the age at onset of the disease. For thyroid disease, we used self-reported thyroxin use to distinguish between been hypothyroidism or hyperthyroidism. For psychiatric disorder, the participant was considered exposed if he or she had sought help for psychological problems or reported use of antidepressants or tranquillisers. Heart disease included those who had self-reported history of angina and/or myocardial infarction. The reference group included those with none of the selected diseases.

Fracture registration

Our fracture registry is based on the radiographic archives at the University Hospital in Tromsø. The nearest alternative radiographic service or fracture treatment facility is located 250 km from Tromsø. The only fractures that would be missed are fractures occurring while inhabitants were travelling and no control radiographic examination was done after returning home, in addition to fractures not radiographically examined.

The computerized records in the radiographic archives of the University Hospital contain codes for different information about fractures in addition to the national personal identification number and time of investigation. Any fracture-coded radiographic examinations on participants in the fourth survey were reviewed to ascertain the fracture code, identify exact anatomical location of fracture and to distinguish consecutive fracture cases from one another. Similar registration for participants in the second and third Tromsø surveys was performed, validated and described by Joakimsen et al. [28].

For our target population, the fracture registry covered the period between the 1st of January 1994 and the 31st of December 2000. We measured the risk for all non-vertebral, wrist, proximal humerus and hip fractures. Follow-up time was assigned from the date of phase I examination for each participant to date of first fracture or to 31 December 2000.

Statistics and analysis:

The relative risk (RR) of fracture was calculated using Cox proportional hazard model in the SAS statistical package [29]. First we calculated the age adjusted risk of fracture for each of the self-reported diseases alone against the reference group, then in a multivariable analysis for all the diseases in the model to check the independent effect of each disease as opposed to a possible increased or decreased risk by increased burden of disease. Disease questions with no answers were treated as missed values. Graphical evaluation of the Proportional Hazards (PH) assumption of the Cox-Model was done for each disease adjusting first for age, and then for other diseases and confounders. In the multivariate models the regression coefficients for chronic diseases were tested as a group to minimize chance findings due to multiple testing.

Furthermore, to check the effect of the burden of disease, subjects with self-reported chronic diseases that had independent fracture risks were given a score of one for each disease and grouped according to number of chronic diseases.

All models were adjusted for age, BMI, smoking and physical activity. Interaction terms were introduced into the final model to assess interaction between each disease and BMI, self-reported health status and history of previous wrist or hip fracture.

Results:

A total of 446 and 803 non-vertebral fractures were registered among men and women respectively. Men suffered 86, 29 and 72 wrist, proximal humerus and hip fractures respectively. Where for women the numbers were 367, 83 and 177 in the same order. Table one shows the characteristics of subjects with each self-reported disease and the reference population. Generally there was a significant age adjusted difference, at baseline, between subjects with one or more of the self-reported diseases and the reference population with respect to mean BMI, smoking habit, physical inactivity and self-reported health status.

Subjects with self-reported diseases referred to their health status as poor ($p< 0.0001$). Subjects with self-reported heart diseases differed unfavourably from the reference population for all variables of interest ($p<0.0001$). Apart from self-reported epilepsy, the participants with the other self-reported diseases were older than the reference population ($p<0.0001$).

Figure 1 shows the strong effect of age on all non-vertebral fracture risk, especially among women.

Table two presents the adjusted fracture risk for each of the selected self-reported diseases compared with the reference population. Self-reported diabetes mellitus, stroke, asthma, hypo- and hyperthyroidism and psychiatric disorders had an increased risk of fracture in one or more locations. Self-reported heart disease was associated with 40% reduction in the risk of wrist fracture in women. For women the PH assumption was not satisfied for asthma and risk of all non-vertebral and for epilepsy and risk of wrist.

When we measured the risk associated with each disease against all those without the specific disease i.e. a less strict description of the reference population, as expected, similar significant fracture risks were found with slight reduction of the overall risk estimates among women.

Multivariate risk of fractures:

Table 3 shows the fracture risk in multivariate analyses among men and women. There was a consistent trend of an increased risk of all fractures among men with self-reported diabetes mellitus and psychiatric disorders although not significant at all sites. In men self-reported hypothyroidism had an increased risk of hip fractures.

Among women, self-reported asthma was the only disease associated with increased risk of hip fractures with RR 1.9 (95% CI 1.1-3.3). Increased risks of proximal humerus fracture were associated with self-reported hypo- and hyperthyroidism and psychiatric disorders in women. Self-reported heart disease was associated with low risk of wrist fracture.

Adjusting for history of previous fractures (which included wrist and hip fractures from the questionnaires and any fracture occurred after the 1st of January 1994 and before the examination date) did not affect the risk of fractures associated with self-reported diseases. There were significant interactions between self-reported diabetes mellitus and heart diseases and smoking, and between self-reported psychiatric disorders and physical activity with respect to all non-vertebral fracture risk in women. However stratifying the multivariate analysis on these factors gave a non-significant increase fracture risk among diabetic smoking women (RR 2.0 (95% CI 0.9-4.6)) compared to (RR 0.5 (95% CI 0.3-1.1)) among non-smokers. No differences were reported when stratifying the analyses for the other diseases.

Burden of disease:

The risk of fractures in men and women increased with increasing burden of disease as shown in Figure 2. For men the trend of increasing risk of fractures with increasing burden of disease was significant for all non-vertebral (p= 0.01) and wrist fracture (p= 0.02), whereas for women the trends were significant for proximal humerus fracture (p= 0.001) and hip fracture (p= 0.01).

When restricting the analysis to diseases with independent fracture risk; diabetes mellitus, hypothyroidism and psychiatric disorders for men, and asthma, hypo- and hyperthyroidism, psychiatric disorders for women, the trends of increasing fracture risk with increasing burden of disease were significant among men for all non-vertebral (p< 0.0001), wrist (p= 0.005), proximal humerus (p=0.0004) and hip fracture (p= 0.0002). And for women the trends remained significant for proximal humerus fracture (p= 0.003) and hip fracture (p= 0.04).

Allocating a score of minus one to self-reported heart disease, which showed a protective effect in the multivariate analysis, did not change the risk for increasing burden of disease in both sets of analyses.

Discussion

Among the chronic diseases with a univariate risk of fractures, we found an independent risk most consistently for self-reported diabetes mellitus, hypo- and hyperthyroidism and psychiatric disorders.

To our knowledge this is the first study to investigate the independent risk associated with more than half a dozen of chronic diseases earlier found to be associated with fracture risk.

This study included a large numbers of both men and women, with a wide age range at base line. The external validity refers mainly to a Caucasian population as only 2.5% were of Sami origin. The potential for selection bias is limited with more than 77% of the eligible population included in the analyses. The lowest attendance rates were among those less than 45 years and those older than 75 years, with respectively rates 66% and 74% of attendance among men and 73% and 67% among women. We do not have permission to explore differences between responders and non-responders, however in the second and third surveys with attendance rate of 73%, the age-adjusted mortality was higher among non-responders, and the incidence of fractures was almost similar in the two groups [30]. The responders in the forth survey did not know the study was about fractures. With the prospective design of this study, the diseases and other risk factors included, were classified or measured without knowledge of the future risk of fractures.

The diseases studied were chronic in nature with a higher mortality rate for those affected than for those without the diseases. This suggests that subjects exposed to chronic diseases are more likely to be censored during the follow-up period than non-exposed. In addition there will be a gradually increase in prevalence of unknown exposure to chronic diseases among the control group. Thus the relative risk estimates were prone to be underestimated.

Our analyses did not include bone densitometry, thus we cannot evaluate whether the increased fracture risk was mediated by reduction in bone mass in the diseased group. Studies

with bone mineral density measurements would face a power problem when adjusting for chronic diseases; as such studies usually include fewer participants. However adjusting for self-reported osteoporosis- that reflects the tip of the iceberg of osteoporosis- did not alter the fracture risks in the multivariate analyses. Prevention and treatment of osteoporosis will not affect fracture incidence in this study, as no body used biphosphonate in 1994 and only 2.2% of women and 0.23% of men used it in 2001. In addition these small groups would be included in those with the self-reported osteoporosis. A possible limitation of the study's generalisablity could be introduced by the extreme weather conditions in Tromsø with snow 6 months a year. We did find a seasonal variation in fracture rate but only among women (p<0.0001). There were no association between presence of chronic disease and the seasonal variation in fracture rate. A major limitation of this study is the validity of questionnaire data in defining diseases due to recall bias. However the agreement between self-report of chronic diseases and medical record has been described as excellent to fairly accurate for diabetes mellitus, stroke, cancer, and heart diseases [31-34].

Diabetes mellitus: Previous studies on diabetes mellitus and fracture risk were limited mainly to hip fracture risk and included mostly women. Most of the earlier longitudinal studies described associations between diabetes mellitus and fractures. Despite the non-differentiation of the type of diabetes in this study, the increased risk of hip fractures we found among men and women in the univariate analyses is generally consistent with two earlier Norwegian studies [4, 6]. However a larger study covering four areas in the United States, indicated that type II diabetes is also a risk factor for proximal humerus fractures among women older than 65 years [7]. In this study, we observed no proximal humerus fractures risk among diabetic women. The non-significant risk of hip fracture among women in the multivariate analysis in this study could be an indicator that the overall risk of hip fracture associated with diabetes in earlier studies is explained by other co-morbidities or the increased burden of disease.

Stroke: Earlier studies found stroke as a risk factor for hip fracture in men [4], women [35] and both [9]. A trend toward an increased risk of hip fracture among 65 years or older women with history of stroke, was described [10]. We found a non-significant 80% increased risk of hip fractures in women and a four times increased risk of wrist fractures among men with self-reported stroke in the univariate analyses. When restricting the analysis to those older than 65 years, there was a significant two-fold increase risk of hip fractures among women (data not presented). However, in this study there were no independent fracture risks associated with stroke when controlling for other chronic diseases, even when restricting the analysis for those older than 65 years.

Asthma: Asthma and mainly the use of corticosteroids have been described as a major determinants of fractures in general and vertebral and rib fractures in particular [12]. The results in this study generally supported the first part of the above-mentioned fact concerning wrist fracture risk among men in the univariate analysis and hip fracture risk among women in the multivariate analysis. When testing the satisfaction of the PH assumption, the risk of fracture associated with self-reported asthma changed over time for all non-vertebral fractures among women in univariate analysis, and in both men and women in the multivariate analyses. This could be due to the adverse effect on bone density and fracture risk caused by oral corticosteroids [12, 36] in contrast to inhaled steroid therapy [37, 38].

Thyroid diseases: Hyperthyroidism has been the focus of earlier studies of fracture risk associated with thyroid disease. It was described as a risk factor for hip fracture among old women in a longitudinal [10] and a case-control study [15]. However another case-control study found no increased fracture risk in patients with previous thyrotoxicosis [21]. In this study almost similar patterns of increased fracture risks were found in hypo- and hyperthyroidism among women with respect to proximal humerus fractures. Among men the

risk of all non-vertebral and particularly hip fractures were high in those with hypothyroidism, and reached a significant level for hip fracture in the multivariate analysis.

Psychiatric disorders: we found a consistently elevated risk of fractures at all sites in men in both the uni- and multivariate analyses. For women the independent risk was highest and only significant for proximal humerus fractures. Previous studies found that patients using benzodiazepines or other psychotropic drugs might increase their risk of fractures. Our findings are not comparable with the positive relation between hip fracture and mental distress found by Forsen et al. [16] and Søgaard et al. [19], possibly due to differences in exposure data handling and fracture prevalence .

Heart diseases: to our knowledge no pervious follow up study has examined the association between heart diseases and non-vertebral fracture risk. However low bone mineral density and bone loss were found to be associated with an increased risk of cardiovascular and coronary heart disease mortalities [39]. Thus increased fracture risk should be expected. In contrast, we found that women with heart diseases, tended to have an independent reduction of wrist fracture risk by 50 %, and the risk of hip fracture among men was reduced by 50% although not significantly.

Cancer: earlier studies found a reduced risk of hip fracture in women with endometrial, but not breast cancer [22, 23]. In this study exposure to any type of cancer had an overall independent borderline protective effect mainly due to reduced risk of all non-vertebral fractures (p=0.06) in women. Our non-significant estimate could be due to dilution by types of cancer with neutral or high risk of fracture included in the same group.

Epilepsy: Previous studies showed a high incidence of fractures among patients with epilepsy [13, 14]. The univariate analyses findings indicate that men and women with self-reported epilepsy have increased risk of all non-vertebral fractures although it was not significant. However self-reported epilepsy affected fracture risk differently over time, which might be

related to the different types of drugs used, as shown by Vestergaard et al. who found an increased fracture risk for those using phenytoin [14].

Burden of disease:

The effect of burden of disease has been described as a risk factor for perimenopausal fractures. Where having three or more chronic health disorders was associated with non-osteoporotic (thoracic or lumbar spine, hip, proximal humerus or wrist) fracture risk (RR 1.6 (95% CI 1.1-2.2)) [2], and with fractures other than those of the wrist or ankle (RR 1.6 (95% CI 1.4-2.0)) [5]. No such association has been studied among men. Our study supports an increased risk of proximal humerus and hip fractures with increased burden of chronic disease among women, whereas for men the risk was high for all locations of fractures when restricting the analysis to diseases with independent fracture risk. As these findings support the independent associations in the multivariate analyses, they indicate that just because an individual has many diseases we cannot presume that he/she is frail with respect to bone health. It is the precise nature of the diseases in question and their additive effect which matters.

In our findings, there were different relationships of self-reported diseases with fractures according to the site of fracture. Such differences have been reported before [5]. Even hip, femoral neck and intertrochanteric fractures have different risk factors and therefore different physio-pathologic processes have been suggested [40]. Diabetes mellitus should be considered as a risk factor for particular types of fractures [7], as different studies found different associations between diabetes and types of fractures.

The lowest risks associated with the self-reported diseases among women were of the wrist. As reported before, fractures of the distal forearm tend to occur among women who are relatively healthy and active -which was not the case in our female subjects with the self-reported diseases. That is in contrast to women with poor neuromuscular function who were

less healthy and active than others of their age were at increased risk for fracture of the proximal humerus [41], which was the case in our female patients with self-reported hypo-, hyperthyroidism and psychiatric disorders.

The nature of the exposure data (self-reports) in this study and the limited power make the disease by disease approach vulnerable, especially where we can not support the risk found in other studies due to non significant similar trends. If our non significant findings were due to lack of power, we would expect the burden of disease analysis to come out stronger with all diseases included, which was not the case. However, this paper emphasizes the need to adjust for other co-morbidities when looking at the risk of fracture associated with single chronic diseases.

Conclusion

The independent non-vertebral fracture risk associated with self-reported chronic diseases differs between men and women as well as between fracture sites in the same gender. Diabetes mellitus, hypothyroidism and psychiatric disorders were associated independently with increasing risk of fractures among men. Women had an independent increased risk of hip fracture among those with asthma and of proximal humerus fractures among those with hypo- and hyperthyroidism and psychiatric disorders. The independent effect of each chronic disease seems to be additive as increasing burden of chronic disease increases fracture risk regardless of possible differences in causal pathway.

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TABLE 1: characteristics of the reference population (with none of the selected chronic diseases) and men and women with the selected diseases in the forth survey 1994-95 (The Tromsø Study).

	No.	Number of fractures [§]	Mean age	Mean BMI	Smokers %	Physical inactivity %	Self reported poor health %
Men							
Reference population	9763	308/53/19/37	44.7	25.5	38.6	41.4	18.3
Diabetes	241	16/2/2/8	60.7*	27.1*	24.6**	66.7**	58.8*
Stroke	228	12/7/0/5	64.7*	25.8	36.4	79.8*	62.6*
Asthma	906	34/11/2/7	47.8*	25.6	32.5**	48.0***	38.6*
Hypothyroidism	78	5/0/0/2	55.5*	26.7**	38.5	64.1***	52.6*
Hyperthyroidism	51	1/0/0/0	53.7*	26.4	33.3	47.1	58.8*
Psychiatric dis.	829	45/12/7/8	48.2*	25.6	41.9***	48.3***	48.3*
Heart diseases	878	40/10/2/14	65.4*	26.6*	27.7*	74.5*	70.0*
Cancer	272	13/1/0/6	61.5*	25.2**	30.2***	59.3	47.8*
Epilepsy	125	6/1/0/0	45.1	25.8	34.4	49.6	33.9*
Women							
Reference population	9903	426/211/38/64	44.6	24.4	37.5	53.8	23.8
Diabetes	274	31/11/2/16	64.7*	27.9*	22.3**	77.0	67.9*
Stroke	190	30/12/3/12	65.8*	26.3	29.1	85.1***	76.7*
Asthma	1127	72/31/8/19	49.4*	25.6*	36.6	60.6	51.8*
Hypothyroidism	444	44/16/9/13	58.4*	26.1*	30.9	70.7	55.0*
Hyperthyroidism	276	20/10/5/2	51.7*	25.4	31.5	65.1	48.2*
Psychiatric dis.	1580	99/51/14/19	48.4*	24.9	43.5*	62.2**	52.9*
Heart diseases	611	83/29/10/34	71.4*	27.0*	20.9**	90.4*	84.1*
Cancer	524	43/17/7/11	58.9*	25.6	27.8***	72.5	52.0*
Epilepsy	166	13/5/1/1	46.6	25.0	37.0	63.3***	45.2*

[§] *All non-vertebral/ wrist/ proximal humerus/ hip fractures.*
* *Significantly different from the reference population without chronic diseases after adjustment for age ($p < 0.0001$).*
** *Significantly different from the reference population without chronic diseases after adjustment for age ($p < 0.01$).*
*** *Significantly different from the reference population without chronic diseases after adjustment for age ($p < 0.05$).*

TABLE 2: Relative risk of fracture and 95% CI associated with each self-reported diseases compared to those with none of the selected diseases among men and women, adjusted for age, BMI, smoking and physical activity in the forth survey 1994-95 (The Tromsø Study).

	Men				Women			
	All	Wrist	Proximal humerus	Hip	All	Wrist	Proximal humerus	Hip
Diabetes	1.9 1.1-3.1	1.3 0.3-5.7	1.7 0.4-7.9	2.4 1.1-5.3	1.0 0.7-1.5	0.7 0.4-1.3	0.7 0.2-3.0	2.2 1.3-4.0
Stroke	1.2 0.7-2.2	3.9 1.6-9.3	-	0.8 0.3-2.0	1.3 0.9-1.9	1.0 0.5-1.8	1.2 0.3-3.9	1.8 0.9-3.4
Asthma	1.2 0.8-1.7	2.1 1.1-4.1	0.8 0.2-3.3	1.0 0.4-2.3	N/A*	1.0 0.7-1.4	1.3 0.6-2.8	1.5 0.9-2.6
Hypothyroidism	1.8 0.7-4.3	-	-	3.1 0.7-12.9	1.2 0.9-1.6	0.8 0.5-1.4	2.6 1.2-5.5	1.7 0.9-3.1
Hyperthyroidism	0.6 0.1-4.0	-	-	-	1.2 0.8-1.9	1.2 0.6-2.3	3.2 1.3-8.2	0.7 0.2-2.8
Psychiatric dis.	1.7 1.2-2.3	2.6 1.4-4.9	3.4 1.4-8.3	1.7 0.8-3.7	1.2 1.0-1.5	1.3 0.9-1.7	1.8 1.0-3.3	1.4 0.8-2.3
Heart disease	1.1 0.7-1.5	1.5 0.7-3.3	0.3 0.1-1.5	0.7 0.4-1.4	0.9 0.7-1.2	0.6 0.4-1.0	1.1 0.5-2.3	1.4 0.9-2.1
Cancer	1.2 0.7-2.2	0.5 0.1-3.9	-	1.2 0.5-2.9	0.9 0.7-1.2	0.7 0.4-1.2	1.5 0.7-3.4	1.1 0.6-2.0
Epilepsy	1.7 0.7-3.5	1.5 0.2-10.6	-	-	1.6 0.9-2.8	N/A*	1.4 0.2-10.0	0.8 0.1-5.5

Relative risk with value (-) indicate no fractures in this location and therefore the analysis wasn't performed.
N/A: Disease variable did not satisfy the PH assumption.*

TABLE 3: Independent relative risk of fracture and 95% CI of self-reported diseases adjusted for age, BMI, smoking and physical activity among men and women in the forth survey 1994-95 (The Tromsø Study).

	Men				Women			
	All	Wrist	Proximal humerus	Hip	All	Wrist	Proximal humerus	Hip
Diabetes	2.3 1.3-3.9	1.3 0.3-5.3	3.2 0.7-14.1	4.5 2.0-10.4	0.8 0.4-1.4	0.5 0.2-1.4	0.9 0.2-3.6	1.7 0.9-3.5
Stroke	0.8 0.4-1.8	2.1 0.6-6.8	N/A*	0.9 0.3-3.0	1.3 0.8-2.1	1.3 0.6-2.7	1.9 0.6-6.2	1.3 0.6-2.9
Asthma	N/A*	1.3 0.5-2.9	0.5 0.1-14.1	N/A*	N/A*	N/A*	N/A*	1.9 1.1-3.3
Hypothyroidism	1.5 0.6-4.2	-	-	5.4 1.3-22.6	1.4 1.0-1.9	1.0 0.6-1.8	2.9 1.3-6.2	1.7 0.9-3.3
Hyperthyroidism	0.5 0.1-3.7	-	-	-	1.5 0.9-2.4	1.3 0.7-2.7	4.3 1.7-10.7	0.9 0.2-3.6
Psychiatric dis.	1.7 1.2-2.3	2.6 1.4-4.8	5.2 2.1-12.8	1.6 0.6-4.0	1.1 0.9-1.4	1.2 0.8-1.7	1.8 1.0-3.4	1.1 0.6-1.9
Heart disease	1.0 0.7-1.6	1.5 0.7-3.3	0.5 0.1-2.1	0.5 0.2-1.1	0.8 0.6-1.1	0.5 0.3-0.8	0.9 0.4-2.3	1.3 0.8-2.1
Cancer	1.1 0.6-2.1	0.5 0.1-3.9	-	1.2 0.4-3.8	0.7 0.4-1.0	0.6 0.3-1.2	1.3 0.5-3.4	1.0 0.5-2.1
Epilepsy	1.7 0.8-3.8	1.1 0.2-8.0	-	-	N/A*	N/A*	0.9 0.1-6.8	0.6 0.1-4.0

Relative risk with value (-) indicates no fractures in this location and therefore the disease wasn't included in the model.
N/A: Disease variable did not satisfy the PH assumption.*

Figure 1: The percentages and 95% CI of the mean of all non-vertebral fractures among age groups for men and women in the forth survey 1994/95 (The Tromsø Study).

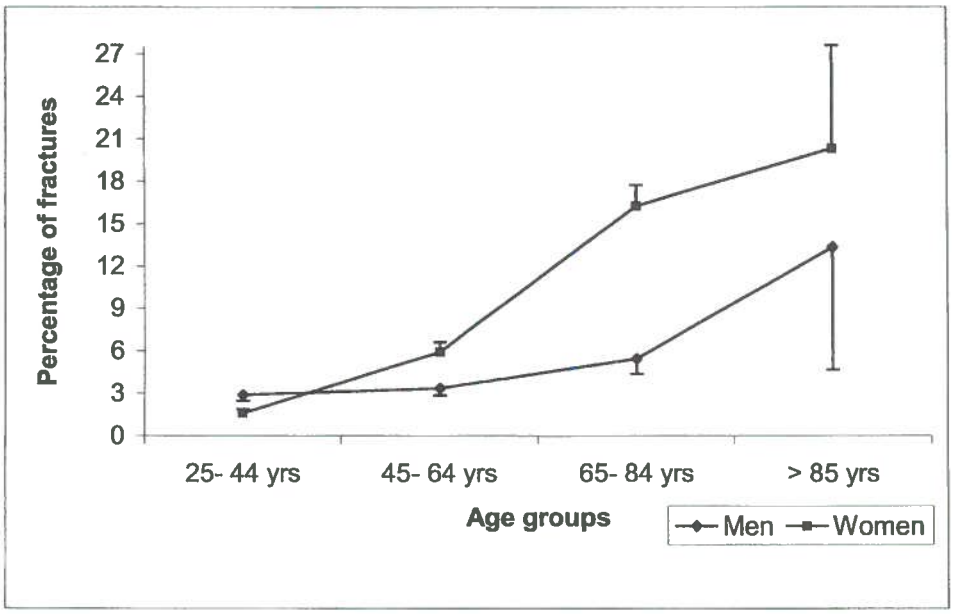
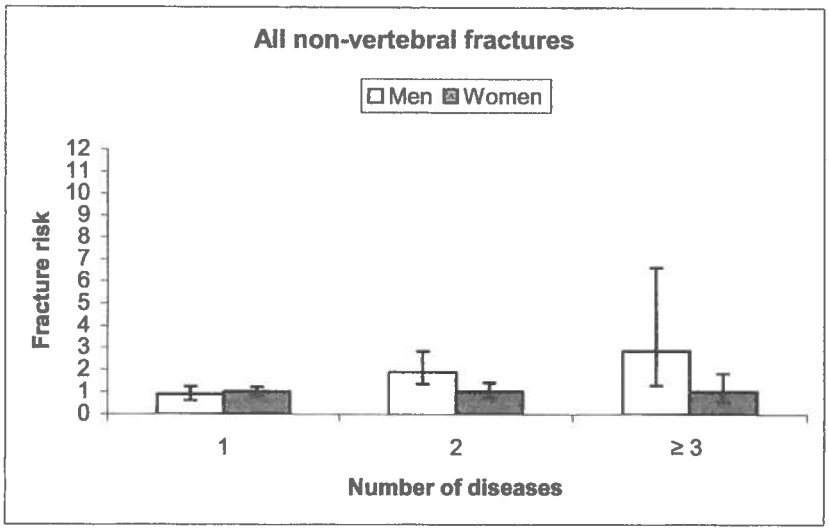
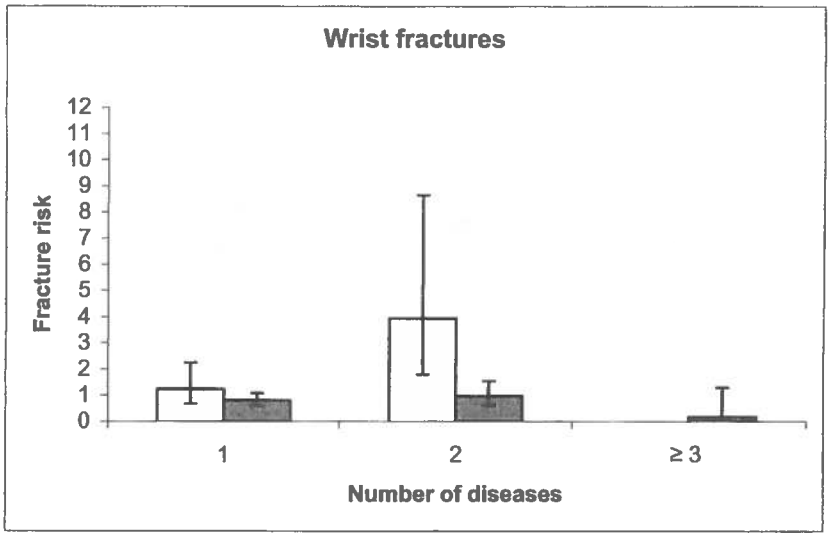


FIGURE 2: The relative risk and 95% CI for all non-vertebral, wrist, proximal humerus and hip fractures by burden of disease among men and women in the forth survey 1994/95 (The Tromsø Study).





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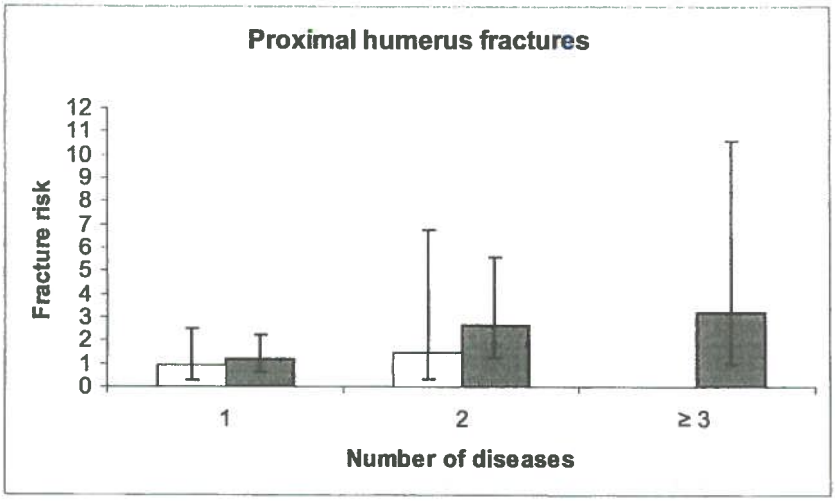
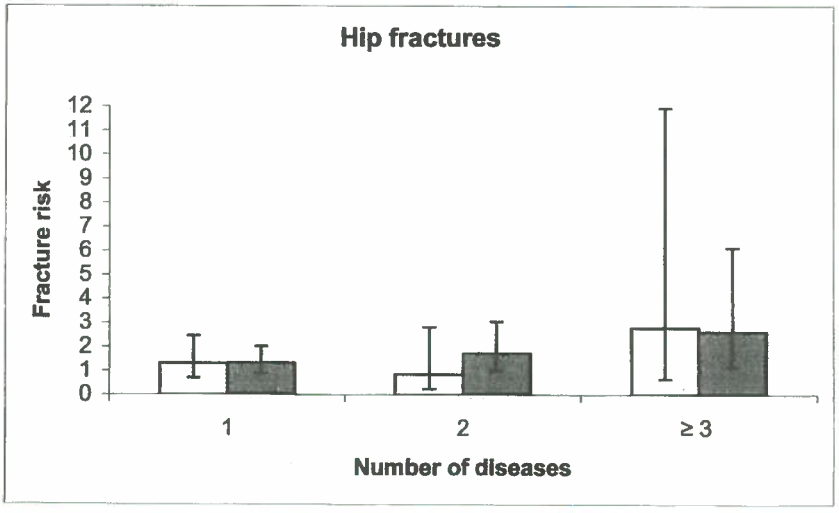
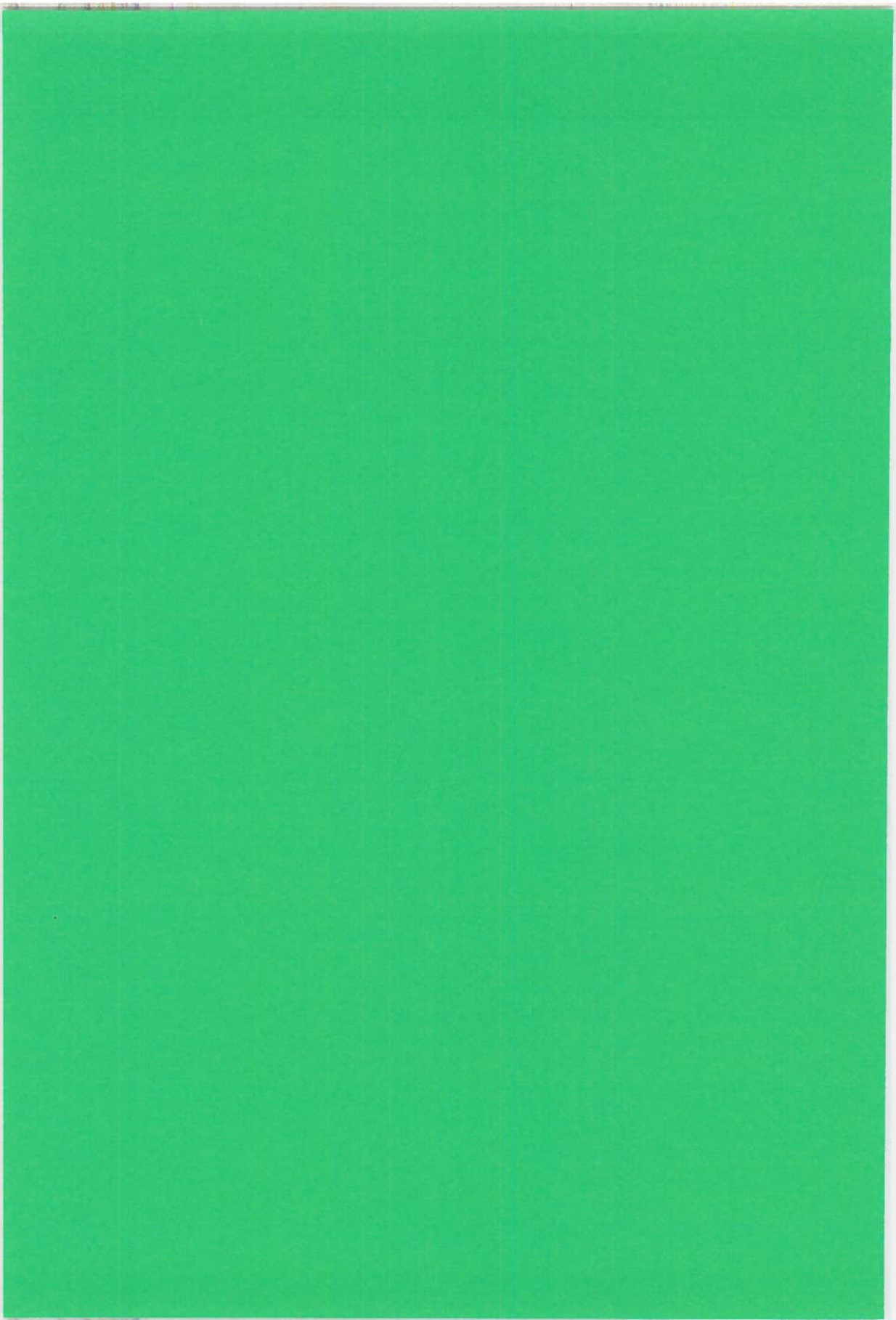




Paper II



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Features of the Metabolic Syndrome and the Risk of Non-vertebral Fractures: The Tromsø Study.

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Abstract

We wanted to examine whether the features of the metabolic syndrome carried an increased risk of non-vertebral fracture.

This is a population-based 6-years follow-up of 27,159 subjects from the municipality of Tromsø, followed from 1994 until 2001. Age range was 25-98 years. Non-fasting serum levels of high-density lipoprotein (HDL), triglycerides and glucose, blood pressure (BP), weight and height were measured at baseline. All non-vertebral fractures were registered by computerized search in radiographic archives.

A total of 1,249 non-vertebral fractures were registered. Increasing number of metabolic syndrome features was associated with significantly reduced fracture risk in both men and women, $p= 0.004$ and $p< 0.0001$, respectively. High BP was protective against fracture in men [relative risk (RR) 0.89; 95% confidence interval (CI) 0.8-0.99], while increased body mass index (BMI) was protective in women (RR 0.91; 95% CI 0.84-0.98). Increasing non-fasting serum levels of HDL increased fracture risk in women (RR 1.12; 95% CI1.05-1.21). BMI modified the effect of HDL in men. Accordingly high HDL increased fracture risk in men with high BMI (RR 1.51; 95% CI 1.2-1.9).

Increasing burden of metabolic syndrome features protects against non-vertebral fractures. Reduced non-vertebral fracture risk was associated with HBP in men and increased body mass in women. Lower non-fasting serum levels of HDL protect against fractures in women and obese men.

Introduction

Apart from body mass index (BMI), little is known about the relationship between metabolic disturbances or features of the metabolic syndrome and the risk of non-vertebral fractures. No significant association has been found between diastolic/systolic blood pressure (BP), total cholesterol, triglycerides and glucose and the incidence of hip fracture [1]. Some studies have used the surrogate endpoint bone mass density with conflicting results. In one study BP was associated with increased bone loss at the femoral neck [2]. Another study found that systolic and diastolic BP, serum triglycerides, blood glucose, BMI and waist-to-hip ratio were positively associated with bone density ($p< 0.001$), and high-density lipoprotein (HDL) and serum cholesterol were negatively associated with bone density [3]. This indicates a possible protective effect of the metabolic syndrome on fracture risk which is supported by one study showing that women with postmenopausal fractures had lower BMI and higher serum levels of HDL than those without fractures [4]. Although the metabolic syndrome is an important risk factor for diabetes [5], increased fracture risk among diabetics has been reported in some [1, 6, 7] but not all studies [8, 9].

We wanted to estimate the risk of non-vertebral fracture associated with the features of the metabolic syndrome in a large population-based follow-up of 27,159 people aged 25- 98 years at baseline, independent of other known risk factors.

Material and methods

Study population

The Tromsø study is a population-based cohort study with five repeated health surveys since 1974. In the fourth Tromsø survey (1994/95), all residents of the Tromsø municipality born 1969 or earlier were invited to the first phase of the survey. Among the 37,559 persons invited, 2,139 persons died or moved before their scheduled phase I examination. The eligible population was therefore 35,420 persons, and 27,159 (77%) participants attended the phase I

examination of the survey and answered the relevant questionnaires. All subjects aged 55-74 and random 5-10 % samples of all other age groups were invited to a second visit for more extensive screening. A total of 7,694 subjects attended the second phase of the survey [10].

Registration of exposure variables and confounding factors

The first questionnaire was printed on the reverse side of a letter of invitation. At the health examination, a trained nurse checked the questionnaire for inconsistency. The questionnaire included, among others, questions about having diabetes mellitus, myocardial infarction, angina pectoris, hypertension and use of drugs such as hypertension medications, lipid lowering drugs (only for those younger than 70 years) and cortisone tablets, in addition to risk factors such as physical activity and smoking habits [11]. The examination included standardized measurements of BP, weight, height and non-fasting serum lipids. Height and weight were measured in light clothing without shoes to the nearest centimetres/kilogram. Among information collected in the second phase, non-fasting serum glucose levels and waist circumference in centimetres were measured and the time since last meal was reported. All levels of serum lipids and glucose were measured in mill moles per litre.

The metabolic syndrome criteria were defined using the National Cholesterol Education Program (NCEP)- Adult Treatment Panel III [12]. Accordingly the criteria are:

1. Hypertension; BP $\geq$ 130/85 and/or medication.
2. Hypertriglyceridemia; triglycerides > 1.695 mmol/l.
3. Low HDL cholesterol; < 1.036 mmol/l (men), < 1.295 mmol/l (women).
4. Central obesity; waist circumference > 102 cm (men), > 88 (women).
5. Fasting plasma glucose $\geq$ 6.1 mmol/l

Measurements for the last two criteria were available only for participants attending the second phase. BMI was used instead of waist circumference as both were possible alternatives in other studies [13, 14]. In this study, the cut-off values for BMI were calculated as the mean

BMI values in men and women with waist circumference of 102 and 88 cm, respectively, among those who attended the second phase. Accordingly, BMI > 28.3 for men and >27 for women was used. The last criterion was valued positive if non-fasting glucose level was ≥11, ≥10 or ≥6.1 mmol/l and the time since last meal was >1, >2 or >8 hours respectively. Mean BP was calculated using the formula (systolic BP+ diastolic BP*2)/3.

A complete validated register of cases of diabetes mellitus was available. Cases of diabetes mellitus were identified by review of medical records of all participants who:

i. Reported diabetes mellitus or age when diagnosed in the fourth survey.

ii. Reported use of anti-diabetic drugs in the fourth survey.

iii. Reported diabetes mellitus in the second, third and fifth surveys.

iv. Had elevated HbA1c (≥ 6.5) level in the fourth or fifth surveys.

v. Were registered with a diabetes related diagnosis in the medical records.

Out of 756 possible cases of diabetes mellitus, 646 subjects were confirmed to have diabetes; of them, 455 subjects had the disease before the start of follow-up and the other 191 subjects developed the disease during the follow up.

Fracture registration

Our fracture registry is based on the radiographic archives at the University Hospital in Tromsø. The nearest alternative radiographic service or fracture treatment facility is located 250 km from Tromsø. The only fractures that would be missed are fractures occurring while inhabitants were travelling and no control radiographic examination was done after returning home as well as fractures not radiographically examined. The computerized records in the radiographic archives of the hospital contain codes for different information about fractures in addition to the national personal identification number and time of investigation. All fracture-coded radiographic examinations performed on participants of the fourth survey were reviewed to ascertain fracture code, identify exact anatomical location of the fracture and to

distinguish consecutive fracture cases from one another. Similar registration for participants in the second and third Tromsø surveys was performed, validated and described by Joakimsen et al. [15].

For our target population, the fracture registry covered the period between 1 January 1994 and 31 December 2000. Follow-up time was assigned for each participant from the date of phase I examination to the date of first fracture or to 31 December 2000.

Statistics and analysis:

The relative risk (RR) of fracture was calculated using Cox proportional hazard model in the SAS statistical package [16]. All subjects with a missed value for any criteria of the metabolic syndrome were excluded (n= 168). Data are presented stratified by gender. Differences in means between groups were tested using age-adjusted general linear models. Subjects were given a score of one for each feature of the metabolic syndrome (based on the NCEP definition) and grouped according to number of features. All variables were included in one model to assess their independent effects on fracture risk. First, the variables were entered in continuous forms, then in dichotomous forms based on cut-off points defined by the NCEP definition of the metabolic syndrome to assess linear trends and threshold effects. The metabolic features were ranked in quartiles and linear trends of the risk of fractures assessed. Interaction terms between variables were tested. Models were stratified by statistically significant ($p< 0.05$) interacting variables. Stratification was based on the cut-off point determined by the NCEP definition of the interacting variable. Risks associated with elevated non-fasting serum glucose adjusted for time since last meal, were measured among those attending the second phase of the survey only. Multi-variate models of the continuous and dichotomous forms of variables were adjusted for age, diabetes mellitus, smoking and physical activity. Each model including quartiles of one metabolic feature was adjusted for the other features in their continuous forms in addition to age and diabetes mellitus.

Results:

A total of 446 and 803 non-vertebral fractures were registered among 12,866 men and 14,293 women respectively. After excluding all subjects with missed measurements of any metabolic syndrome criteria, 438 men out of 12,780 and 789 women out of 14,211 suffered non-vertebral fractures. Among 227 men and 228 women with validated diabetes mellitus, there were 51 and 30 type I diabetics, respectively. Table 1 show the characteristics of the total study population, non-diabetics and type II diabetics stratified by gender. Generally, there were significant age-adjusted differences at baseline between non-diabetics and type II diabetics with respect to BP and non-fasting serum lipids profiles, except for diastolic BP, mean BP and cholesterol in men. There were no significant differences between total population and non-diabetic groups as they were largely overlapping, apart from age in both men and women. Those with non-fasting HDL levels below the gender-specific cut-off points, 1.4% and 0.92% reported using lipid-lowering drugs in men and women, respectively. The same percentages for subjects with non-fasting triglycerides levels above cut-off point were 1.81% and 1.77 for men and women respectively.

Figure 1 shows the adjusted relative risk of non-vertebral fractures by the burden of metabolic syndrome features (BP, HDL, triglycerides and BMI), as defined earlier. Although less linear for men, the trends were significant for both gender; (p= 0.004, men and p< 0.0001, women). Accordingly, men and women with the metabolic syndrome defined by having three or more of these criteria were protected against fractures (RR 0.71; 95% CI 0.51-0.99) and (RR 0.66; 95% CI 0.53-0.82), respectively.

Figure 2 shows the relative risk of non-vertebral fracture by quartiles of mean BP, HDL, triglycerides and BMI in men and women, in multivariate models adjusted for age and diabetes mellitus. Due to a significant interaction between HDL and BMI in men, fracture risk was estimated in stratified models for these variables. There was a trend of significantly

reduced fracture risk by increasing mean BP among men only (p= 0.04). . Increasing levels of HDL increased fracture risk significantly in men with BMI greater than 28.3 kg/m^2 (p= 0.046) whereas among women, increased fracture risk by increasing HDL (p= 0.023), and reduced fracture risk by increasing BMI (p= 0.004) were unaffected by each other.

Accordingly, in women, the independent risk of non-vertebral fractures associated with one standard deviation change in each feature of the metabolic syndrome was significantly increased for increasing level of HDL (RR 1.12; 95% CI 1.05-1.21) and decreased for increasing BMI (RR 0.91; 95% CI 0.84-0.98). In men, the non-vertebral fracture risk was independently decreased for increasing mean BP (RR 0.89; 95% CI 0.8-0.99), and increased for increasing level of HDL in men with high BMI (RR 1.51; 95% CI 1.2-1.9). In men with low levels of HDL increasing BMI decreased fracture risk without reaching statistical significance (RR 0.77; 95% CI 0.6-1.01).

When applying the NCEP definition of the metabolic syndrome on the features in multivariate models, only women had independently reduced fracture risk associated with high triglycerides and BMI as shown in table 2. Among men, although there was interaction between HDL and BMI, stratifying the model by BMI did not show significant association between dichotomized HDL and fracture risk in men with high BMI. Adjusting the models for hypertension treatment did not alter the association between BP and fracture risk in either men or women. Including only those treated for hypertension, the analysis showed non-significant 30% and 18% fracture risk reduction in men and women respectively. Further adjustment for medications such as oral steroids and lipid lowering drugs (only among those younger than 70 years) did not alter the risk estimates, although using lipid lowering drugs independently protects against fractures only in women (RR 0.11; 95% CI 0.01-0.8).

In separate analyses restricted to those attended the second phase of the survey, elevated non-fasting serum levels of glucose in both continuous and dichotomous forms showed no association with non-vertebral fracture risk in both men and women.

Limiting the analysis to type II diabetics, no association was found between features of the metabolic syndrome and non-vertebral fracture risk. However, including those who developed type II diabetes after the start of follow-up (n=191) to the diagnosed type II diabetics showed a borderline significant >50% reduction in fracture risk associated with hypertriglyceridemia (p=0.053) in women.

Discussion

There was a significant protective effect against non-vertebral fractures by increasing burden of metabolic syndrome features. We found reduced risks of non-vertebral fractures with increasing BP in men and for increasing BMI in women, and an increased risk of fractures with increasing levels of HDL among women and obese men.

Bias considerations:

This study included a large numbers of men and women with a wide age range at base line. The external validity refers mainly to a Caucasian population. The potential for selection bias was limited, with 77% of the eligible population included in the analyses. With the prospective design of this study, risk factors included were measured and/or classified without knowledge of the future risk of fractures.

The limited power constitutes a major limitation in this study with respect to the analyses among type II diabetics. Interpretation of results were limited to the effect of non-fasting serum levels of HDL and triglycerides on non-vertebral fracture risk. With respect to non-fasting glucose, interpretation of results was limited mainly to men and women older than 55 years.

Burden of metabolic syndrome features: To our knowledge, our study is the first to report a reduced risk of non-vertebral fractures by increasing number of the metabolic syndrome features. Features of the metabolic syndrome included were BP, HDL, triglycerides and BMI. For those with one feature, men were more protected than women. The high number of hypertensive men and women in this category explains the difference, as hypertension protects significantly against fractures in men only.

Blood pressure: In the study by Cappuccio et al. higher BP in elderly women (66-91 years) was associated with increased bone loss at the femoral neck [2], while Lidfeldt et al. found diastolic and systolic BP to be positively associated with bone density (wrist) among women (50-59 years) [3]. One Canadian study found hypertension to be associated with higher BMD values in men and women 50 years of age and older [17]. As most fractures occur in those aged >65 years and BP increases with age, an increased risk of fractures for increasing BP should be expected. On the contrary, we found no risk associated with increasing BP in women and a protective effect in men. Although higher risk of falls due to episodes of hypotension could be expected among hypertensive-treated patients, adjusting for treatment did not affect the association between hypertension and fracture risk. Moreover, low fracture risk was observed among those using treatment for hypertension although it was not significant.

High-density lipoprotein: HDL has been shown to be negatively associated with bone density [3], and as expected, our results showed a high risk of non-vertebral fractures associated with increasing levels of HDL in women and men with high BMI. One possible explanation for this phenomenon in women could be that an unbalanced diet severely limiting calcium intake in order to correct serum levels of cholesterol is a risk factor for postmenopausal osteoporosis and wrist fractures as found by Varenna et al. [18]. However, the interpretation of our results

should be carefully considered, as only non-fasting levels of HDL were used. Why HDL, in men, is associated with increased fracture risk in the obese only needs further studies.

Triglycerides: Triglycerides have been shown to have a positive association with bone density among women [3], which is in accordance with the protective effect on fracture risk of high triglyceride levels for women in our study. Increasing levels of triglycerides was not associated with fracture risk in men. As non-fasting levels of triglycerides were used in this study, further studies including fasting levels are needed to justify out results.

Body Mass Index: The association between BMI and fracture risk was consistently negative among women, which support earlier findings [19-23]. Among men, there was non-significant association between BMI and fracture risk; but when stratified by HDL levels, risk estimates suggested much lower risk (with borderline significance) in those with low HDL levels only. Although higher impact of a trauma is expected with increased body mass, the lower fracture risk among the obese is thought to be associated with protective layers of fat padding around skeletal structures and better bone mass [19, 21].

Glucose: Previous studies have suggested an effect of glucose on bone metabolism; however, conflicting results were reported [24-27]. Our findings showed no significant association between non-fasting glucose levels and fracture risk; however, the interpretation of such findings will be limited to non-fasting levels in older men and women.

Type II diabetes mellitus: The new knowledge about features of the metabolic syndrome opens up the possibility for solutions to the conflicting results regarding diabetes mellitus, bone mass and fracture risk. Despite the high risk of fractures among type II diabetic women described previously [6, 7], hyperinsulinemia associated with the metabolic syndrome may be responsible for increased bone density [3, 28]. Our findings show that the risk of fracture associated with type II diabetes is not explained by the metabolic abnormalities preceding the disease. As the other metabolic features apart from impaired glucose metabolism are

protective or indifferent with respect to fractures, other factors such as glucose intolerance, effect of medications and other patho-physiological mechanisms should be considered when investigating the fracture risk associated with type II diabetes.

Conclusion

Increasing burden of metabolic syndrome features significantly protect against non-vertebral fractures. Increasing BP in men and BMI in women and decreasing non-fasting serum levels of HDL in women and obese men reduce the risk of non-vertebral fractures.

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Table 1: Baseline characteristics of men and women in the fourth survey 1994-1995 (The Tromsø Study).

	Men			Women		
	Total population	Non-diabetics	Type II diabetics	Total population	Non-diabetics	Type II diabetics
N	12780	12557	172	14211	13985	196
Total number of fracture	438	425	8	789	764	22
Number of fractures by location *	72/84/29/43 /80	65/82/27/42 /79	4/1/1/1/1	175/359/83/ 30/59	162/349/81/ 30/58	12/10/1/0/1
Age	46.7 ± 0.13	46.4 ± 0.13	64.1 ±0.85§*	47.2 ± 0.13	46.9 ± 0.13	68.1 ± 0.81§*
Diastolic blood pressure	80.0 ± 0.1	80.0 ± 0.11	84.8 ± 0.95	76.4 ± 0.11	76.3 ± 0.11	88.0 ± 1.2§
Systolic blood pressure	137.5 ± 0.15	137.3 ± 0.15	150.5 ± 1.7§	132.3 ± 0.19	131.9 ± 0.19	164.9 ± 1.9§
Mean blood pressure	99.2 ± 0.11	99.1 ± 0.11	106.7 ± 1.11	95.1 ± 0.13	94.8 ± 0.13	113.6 ± 1.35§
High-density lipoprotein, HDL	1.34 ± 0.003	1.35 ±0.003	1.23 ± 0.03§	1.64 ± 0.003	1.64 ± 0.003	1.39 ± 0.03§
Cholesterol	6.05 ± 0.01	6.04 ± 0.01	6.47 ± 0.1	6.05 ± 0.01	6.04 ± 0.01	6.75 ± 0.09§
Triglycerides	1.77 ± 0.01	1.76 ± 0.01	2.34 ± 0.1§	1.35 ± 0.01	1.33 ± 0.01	2.44 ± 0.11§
Body Mass Index, BMI	25.6 ± 0.03	25.6 ± 0.03	28.0 ± 0.3§	24.8 ± 0.04	24.7 ± 0.04	29.4 ± 0.42§

Data are means ± standard error.
Blood pressure measured in mmHg. HDL, cholesterol and triglycerides level are measured in mmol/l.
Body Mass Index measured in kg/m^2.
* Hip/ wrist/ proximal humerus/ ankle/ foot fracture.
§* Mean difference between non-diabetics and type II diabetics, p value < 0.0001.
§ Age-adjusted mean difference between non-diabetics and type II diabetics, p value < 0.0001.

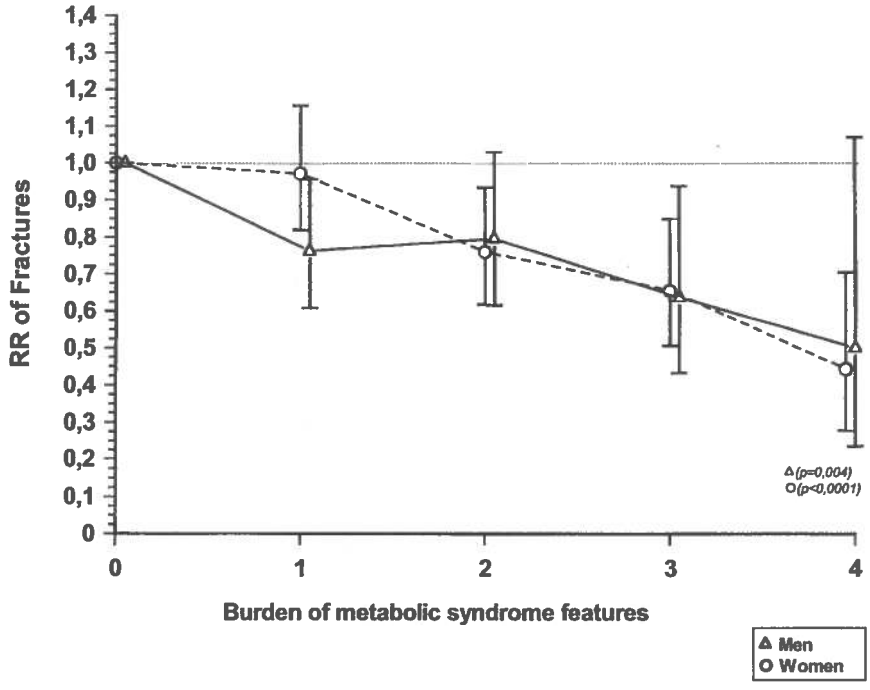
Table 2: Relative risk (RR) and 95% confidence interval (CI) of non-vertebral fractures for abnormal values of features of the metabolic syndrome as defined by the National Cholesterol Education Program (NCEP 2001) in gender-specific multivariate models, adjusted for age, diabetes mellitus, smoking and physical activity (The Tromsø Study).

	Men	Women
Blood pressure ≥ 130/85	0.81	0.95
	0.65-1.01	0.81-1.11
HDL <1.036 mmol/l (men)	0.89	0.83
<1.295 mmol/l (women)	0.68-1.17	0.68-1.01
Hypertriglyceridemia	0.96	0.83
≥1.695 mmol/l	0.78-1.18	0.7-0.99
BMI >28.3 (men)	0.79	0.81
> 27 (women)	0.6-1.03	0.68-0.95

Table 3: Relative risk and 95% CI of non-vertebral fractures for abnormal values of features of the metabolic syndrome as defined by the National Cholesterol Education Program (NCEP 2001) among *type II diabetic* in sex specific multivariate models adjusted for age, smoking and physical activity (The Tromsø Study).

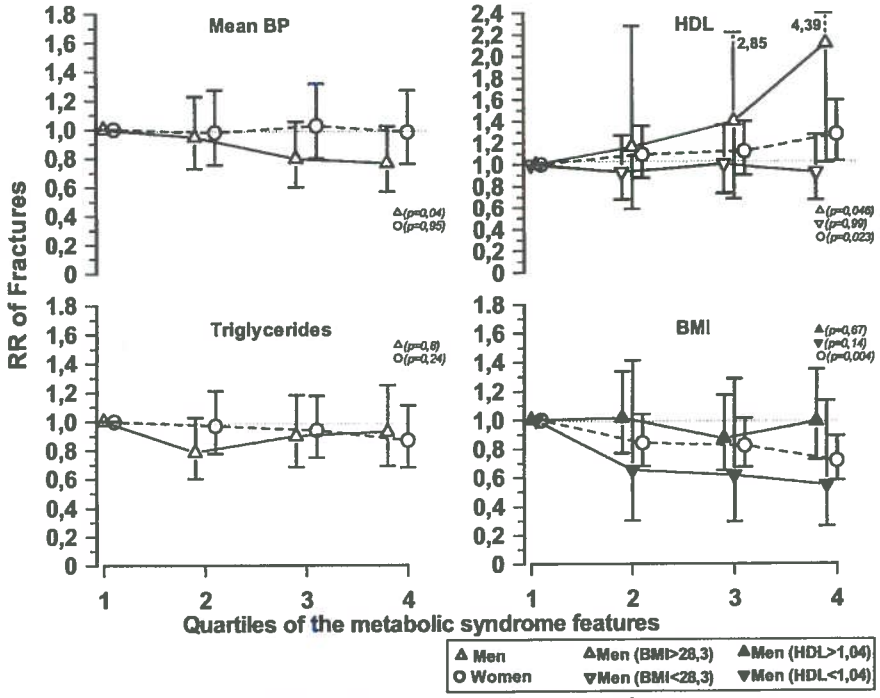
	Men	Women
Blood pressure ≥ 130/85	1.84	1.02
	0.35-9.65	0.39-2.66
HDL <1.036 mmol/l (men)	0.95	0.7
<1.295 mmol/l (women)	0.17-5.43	0.28-1.74
Hypertriglyceridemia	0.92	0.68
≥1.695 mmol/l	0.2-4.27	0.28-1.68
BMI >28.3 (men)	0.37	1.29
> 27 (women)	0.01-2.0	0.5-3.29

Figure 1: Relative risk (RR) of non-vertebral fractures and 95% confidence interval (CI) by burden of metabolic syndrome features* among men and women in the fourth survey 1994-1995 (The Tromsø Study).



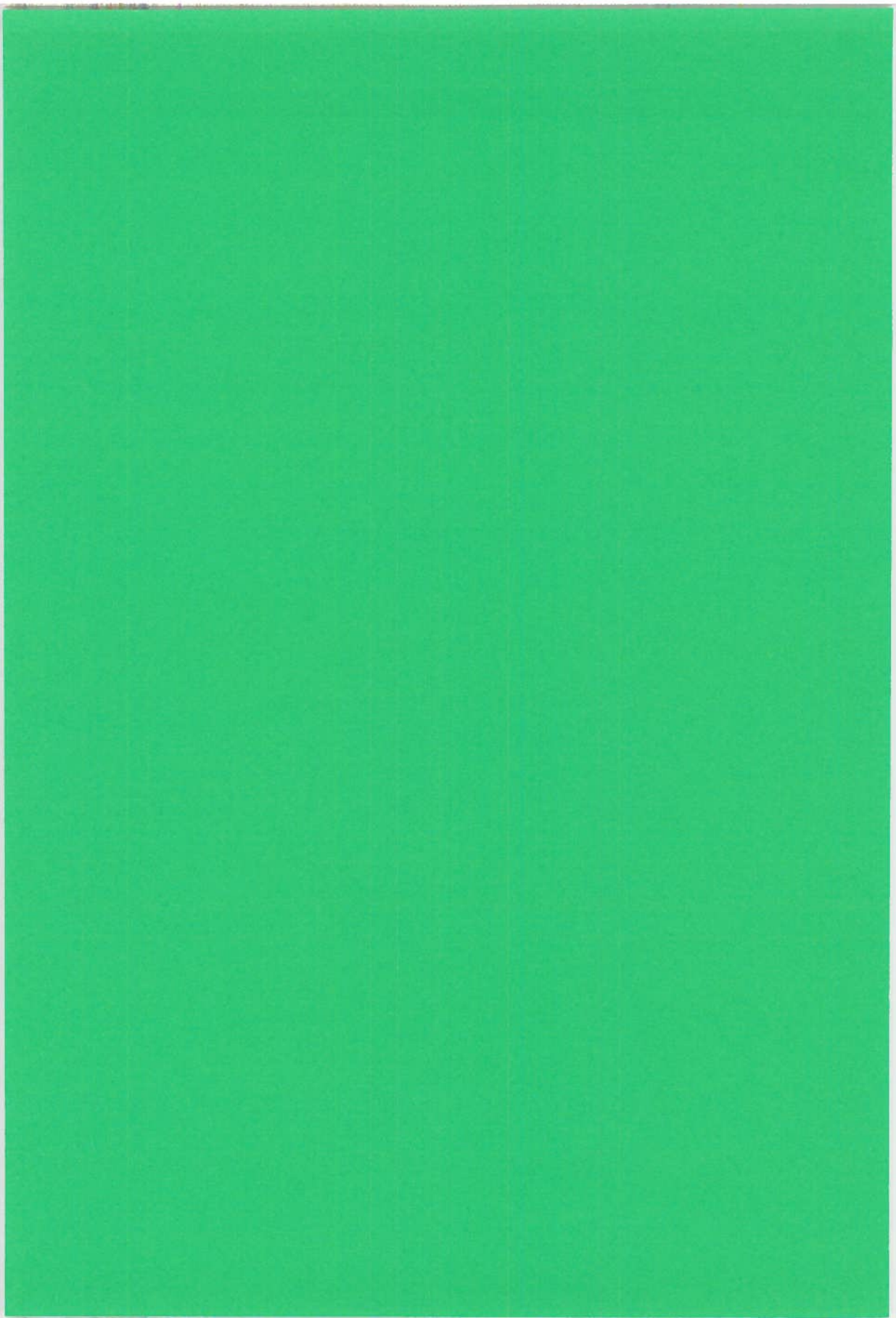
* Blood pressure, High-density Lipoprotein, Triglycerides and Body Mass Index.

Figure 2: Relative risk (RR) of non-vertebral fractures and 95% confidence interval (CI) by quartiles of mean blood pressure (BP), High-density Lipoprotein (HDL), Triglycerides and Body Mass Index (BMI) in multivariate models adjusted for age and diabetes mellitus among men and women in the fourth survey 1994-1995 (The Tromsø Study).



The RR for men is stratified by BMI for HDL quartiles and by HDL for BMI quartiles.

Paper III



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ORIGINAL ARTICLE

Diabetes mellitus and the risk of non-vertebral fractures: the Tromsø study

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Abstract We wanted to determine the risk of non-vertebral fracture associated with type and duration of diabetes mellitus, adjusting for other known risk factors. This is a population-based 6-year follow-up of 27,159 subjects from the municipality of Tromsø, followed from 1994 until 2001. The age range was 25–98 years. Self-reported diabetes cases were validated by review of the medical records. All non-vertebral fractures were registered by computerized search in radiographic archives. A total of 1,249 non-vertebral fractures was registered, and 455 validated cases of diabetes were identified. Men with type I diabetes had an increased risk of all non-vertebral [relative risk (RR) 3.1 (95% CI 1.3–7.4)] and hip fractures [RR 17.8 (95% CI 5.6–56.8)]. Diabetic women, regardless of type of diabetes, had significantly increased hip fracture risk [RR 8.9 (95% CI 1.2–64.4) and RR 2.0 (95% CI 1.2–3.6)] for type I and type II diabetes, respectively. Diabetic men and women using insulin had increased hip fracture risk. Duration of disease did not alter hip fracture risk. An increased risk of all non-vertebral fractures and, especially, hip fractures was associated with diabetes mellitus, especially type I. Type II diabetes was associated with increased hip fracture risk in women only.

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Keywords Diabetes mellitus · Hip fracture · Insulin · Non-vertebral fractures · Type I diabetes · Type II diabetes

Introduction

Osteoporotic fractures are a major health problem in the western world. Bone mineral density, low body mass, sedentary lifestyle, type of fall and its risk factors, the presence of a previous fracture history, smoking, alcohol consumption, and a number of chronic medical disorders, are some of the risk factors reported to be associated with fracture incidence. Poor metabolic control and lifestyle constitute major risks for osteoporosis and fractures in diabetics [1]. Increased fracture risk in diabetic patients have been reported in some [2–6], but not all, follow-up studies [7, 8]. The risk associated with type I diabetes has been consistent in many earlier studies, but whether type II diabetes is a risk factor by itself, or whether its associated risk is mainly due to insulin use or its onset late in life is unclear. Most studies have focused on fracture risk in specific locations, mainly the hip.

We wanted to determine the risk of non-vertebral fracture associated with type and duration of diabetes mellitus in a large population-based follow-up of 27,159 people aged 25 years to 98 years at baseline, adjusting for other known risk factors.

Material and methods

Study population

The Tromsø study is a population-based cohort study with five repeated health surveys since 1974. In the fourth Tromsø survey (1994/1995), all residents of the Tromsø municipality born in 1969 or earlier were invited to the first phase of the survey. Among the 37,559 persons invited, 2,139 persons had died or had moved before their scheduled phase I examination. The eligible population was, therefore, 35,420 persons, and 27,159 (77%) participants

attended the phase I examination in the survey and answered the relevant questionnaires.

Registration of exposure variable and confounding factors

The first questionnaire was printed on the reverse side of a letter of invitation. At the health examination a trained nurse checked the questionnaire for inconsistency and handed out a second questionnaire to be returned by mail. The first questionnaire covered, among other topics, history of diabetes mellitus, age when diagnosed, history of stroke, physical activity, smoking habits and self-rated health status. In the second questionnaire there were questions about the use of insulin and anti-diabetes medication. The examination included, among others, standardized measurements of blood pressure, non-fasting serum lipids and height and weight determination. Height and weight were measured, with the subject wearing light clothing and without shoes, to the nearest centimeter/kilogram.

Validation of diabetes cases

Cases of diabetes were identified by review of the medical records of all participants who:

1. Reported diabetes mellitus or age when diagnosed in the fourth survey.
2. Reported use of anti-diabetes drugs in the fourth survey.
3. Reported diabetes mellitus in the second, third and fifth surveys.
4. Had elevated HbA1c ($\geq$6.5) level in the fourth or fifth surveys.
5. Were registered with a diabetes-related diagnosis in the medical records.

In accordance with the International Classification of Diseases (ICD) coding, we validated any diabetes-related code by checking the medical records. Of 756 possible subjects with diabetes mellitus, 646 were confirmed to have diabetes, and, of them, 455 had had the disease before the start of follow-up and the other 191 subjects (pre-diabetics) developed the disease during the follow-up. Information regarding the type of diabetes and the use of insulin was collected from the medical records. Any patient using anti-diabetes tablets or diet to control diabetes was reported to be a type II diabetic. For those using insulin, the clinician's classification was used, in addition to WHO diagnostic criteria, usually based on clinical presentation in addition to level of C-peptide.

Fracture registration

Our fracture registry is based on the radiographic archives at the University Hospital in Tromsø. The nearest alternative radiographic service or fracture treatment facility is located 250 km from Tromsø. The only fractures that would have been missed were those that had occurred while inhabitants were traveling and had undergone no control radiographic examination when they returned home, in addition to fractures not radiographically examined. An earlier registration for participants in the second and third Tromsø surveys was performed, validated and described by Joakimsen et al. [9]. The computerized records in the radiographic archives of the University Hospital contain codes for different information about fractures in addition to the national personal identification number and time of investigation. Any fracture-coded radiographic examinations of participants in the fourth survey were reviewed to ascertain the fracture code, identify the exact anatomical location of the fracture and to distinguish consecutive fracture cases from one another. In addition, the discharge records were checked with respect to hip fractures.

For our target population, the fracture registry covered the period from the 1st of January 1994 to the 31st of December 2000 with respect to all non-vertebral fractures. Follow-up time was assigned from the date of phase I examination for each participant to date of first fracture, date of death or to the 31st of December 2000.

Statistics and analysis

The relative risk (RR) of fracture was calculated using the Cox proportional hazard model in the SAS statistical package [10]. Data are presented stratified by gender. Differences in means between groups were tested using age-adjusted general linear models. There was one diabetic woman with uncertain type who was excluded from the corresponding analyses. In a separate analysis the pre-diabetics were excluded from the non-diabetic population. To evaluate the effect of disease duration, we grouped type II diabetics into three groups, according to the duration of their disease (4-year intervals). In addition, the pre-diabetics were divided into two groups (those who would develop the disease within 4 years, and those who would develop the disease after more than 4 years, from the start of follow-up).

Interaction terms were introduced to the models to assess interaction between the disease and body mass index (BMI), self-reported health status and history of previous wrist or hip fracture. Physical activity and self-reported stroke/self-reported health status were left out of the final models as they did not contribute significantly to the models. The final gender-specific models were adjusted for age, BMI, smoking, and metabolic syndrome features (mean blood pressure, non-fasting serum high-density lipoprotein (HDL) and triglycerides).

Results

A total of 446 and 803 non-vertebral fractures was registered among 12,866 men and 14,293 women, respectively.

Table 1 Baseline characteristics of diabetic and non-diabetic men and women in the fourth survey, 1994–1995 (the Tromsø Study). Non-fasting values of high-density lipoprotein (HDL) and triglycerides are reported. Smoking, level of physical activity, previous stroke and health status are self-reported

Parameter	Number	No. of fractures	Mean age (years)	Mean BMI	Smokers (%)	Physically inactive (%)	Stroke (%)	Poor health (%)	Mean blood pressure (mmHg)	Mean HDL level (mmol/l)	Mean triglyceride level (mmol/l)
Men											
Non-diabetics	12,639	432	46.4	25.6	37.6	44.5	1.7	25.0	98.9	1.35	1.77
Pre-diabetics[a]	95	2	59.1[b]	29.6[c]	37.9	69.5[c]	3.2	51.6[c]	109.8[d]	1.22[d]	2.69[d]
Diabetics	227	14	59.7[b]	27.0[d]	23.3[c]	67.0[c]	6.6[c]	59.0[d]	104.1	1.27[d]	2.18[d]
Type I	52	5[c]	45.4	25.0	34.6	48.1	3.8	30.8	95.5	1.42	1.67
Type II	175	9	64.0[b]	28.0[d]	20.0[c]	72.6[c]	7.4[c]	67.4[d]	106.6	1.23[d]	2.33[d]
Insulin: yes	86	4	61.2[b]	28.6[d]	19.8[c]	70.9[c]	10.5[d]	62.8[d]	105.8	1.23[d]	2.38[d]
Insulin: no	89	5	66.7[b]	27.3[c]	20.2[c]	74.2	4.5	71.9[d]	107.4	1.23[d]	2.29[d]
Women											
Non-diabetics	14,065	777	46.9	24.7	36.5	57.3	1.2	32.4	94.7	1.64	1.33
Pre-diabetics[a]	96	8	61.1[b]	30.1[d]	21.9	79.2	3.2	59.4[c]	109.5[d]	1.42[d]	2.52[d]
Diabetics	228	26	65.8[b]	28.7[d]	22.4[c]	77.2	7.9[d]	68.9[d]	111.3[d]	1.45[d]	2.36[d]
Type I	29	3	43.5	24.3	41.4	48.3	0	20.7	95.9	1.81[c]	1.02
Type II	198	23	68.2[b]	29.3[d]	19.7[c]	81.3	9.1[d]	75.8[d]	113.5[d]	1.39[d]	2.56[d]
Insulin: yes	78	8	65.7[b]	30.5[d]	19.2	78.2	6.4[c]	74.4[d]	111.8[d]	1.41[d]	2.44[d]
Insulin: no	120	15	69.7[b]	28.6[d]	20.0	83.3	10.8[d]	76.7[d]	114.7[d]	1.38[d]	2.64[d]

[a]Compared with non-diabetics (men n=12,544, women n=13,969)
[b]Mean difference between: (all diabetics, type I, type II insulin yes and insulin no) and non-diabetics, $P<0.0001$
[c]Age-adjusted mean difference between (all diabetics, type I, type II insulin yes and insulin no) and non-diabetics, $P<0.05$
[d]Age-adjusted mean difference between (all diabetics, type I, type II insulin yes and insulin no) and non-diabetics, $P<0.0001$

There were 227 men and 228 women with validated diabetes mellitus (22.9% and 12.7% type I diabetics, for men and women, respectively). Characteristics of the cohort are presented in Table 1. Type I diabetics were not significantly different from the non-diabetics except for higher HDL levels among type I diabetic women. On the other hand, type II diabetics, regardless insulin use, and those who developed type II diabetes after the start of follow-up were significantly different from the non-diabetics in most of the baseline characteristics. More than 62% of men and 72% of women using insulin were type II diabetics, and, of type II

Table 2 All non-vertebral fractures: adjusted relative risks and 95% CI among diabetic men and women in the fourth survey, 1994–1995 (the Tromsø Study)

Parameter	Number	No. of fractures	Age-adjusted RR	RR adjusted for age, BMI, and smoking	RR adjusted for age, BMI, smoking, and metabolic features[a]
Men					
Non-diabetics	12,639	432	1.0	1.0	1.0
Type I	52	5	3.06 (1.27–7.38)	3.08 (1.28–7.44)	3.05 (1.26–7.38)
Type II	175	9	1.19 (0.61–2.31)	1.31 (0.67–2.56)	1.21 (0.6–2.47)
Insulin: yes	86	4	1.1 (0.41–2.95)	1.24 (0.46–3.34)	0.95 (0.3–2.98)
Insulin: no	89	5	1.28 (0.53–3.11)	1.38 (0.57–3.35)	1.45 (0.59–3.52)
Insulin[b]					
Insulin, yes	138	9	1.71 (0.88–3.31)	1.87 (0.96–3.62)	1.68 (0.83–3.39)
Women					
Non–diabetics	14,065	777	1.0	1.0	1.0
Type I	29	3	3.03 (0.98–9.44)	2.97 (0.96–9.24)	2.85 (0.92–8.87)
Type II	198	23	0.89 (0.59–1.35)	0.97 (0.64–1.47)	1.08 (0.7–1.67)
Insulin: yes	78	8	0.87 (0.43–1.74)	0.99 (0.49–1.99)	1.09 (0.54–2.19)
Insulin: no	120	15	0.9 (0.54–1.5)	0.96 (0.57–1.6)	1.07 (0.63–1.83)
Insulin[b]					
Insulin, yes	107	11	1.08 (0.59–1.96)	1.21 (0.67–2.2)	1.31 (0.72–2.38)

[a]Mean blood pressure, HDL and triglycerides
[b]Regardless of type of diabetes

Table 3 Hip fractures: adjusted relative risks and 95% CI among diabetic men and women in the fourth survey, 1994–1995 (the Tromsø Study)

Parameter	Number	No. of fractures	Age-adjusted RR	RR adjusted for age, BMI, and smoking	RR adjusted for age, BMI, smoking, and metabolic features[a]
Men					
Non-diabetics	12,639	65	1.0	1.0	1.0
Type I	52	3	17.79 (5.57–56.75)	17.79 (5.57–56.79)	18.43 (5.72–59.34)
Type II	175	4	1.45 (0.53–3.99)	1.56 (0.57–4.3)	1.63 (0.59–4.5)
Insulin: yes	86	2	1.77 (0.43–7.22)	2.04 (0.49–8.41)	2.12 (0.51–8.76)
Insulin: no	89	2	1.23 (0.3–5.03)	1.25 (0.31–5.13)	1.28 (0.31–5.28)
Insulin[b]					
Insulin. yes	138	5	3.87 (1.56–9.6)	4.44 (1.77–11.15)	4.6 (1.83–11.56)
Women					
Non-diabetics	14,065	163	1.0	1.0	1.0
Type I	29	1	8.55 (1.19–61.49)	8.93 (1.24–64.36)	9.03 (1.25–65.07)
Type II	198	13	1.72 (0.97–3.02)	2.03 (1.15–3.58)	1.9 (1.04–3.49)
Insulin: yes	78	4	1.72 (0.64–4.64)	2.09 (0.77–5.67)	2.06 (0.76–5.62)
Insulin: no	120	9	1.71 (0.87–3.36)	1.99 (1.01–3.9)	1.78 (0.86–3.71)
Insulin[b]					
Insulin, yes	107	5	2.05 (0.84–4.98)	2.48 (1.02—6.06)	12.43 (0.99–5.97)

[a]Mean blood pressure, HDL and triglycerides
[b]Regardless of type of diabetes

diabetics, 50.9% men and 60.6% women were not using insulin.

Tables 2 and 3 show, respectively, non-vertebral and hip fracture risks, adjusted for age, BMI, smoking and metabolic features. Further adjustment for physical activity and self-reported stroke or self-reported health status did not affect the risk estimates.

In Table 2, type I diabetes mellitus was a strong predictor for non-vertebral fractures among men unaffected by the adjustment factors. Among women, only those with type I diabetes had a consistent, increased—although not as strong statistically—risk of non-vertebral fractures.

In Table 3, type I diabetic men and women had a highly significant increased risk of hip fracture. On the other hand, type II diabetic women showed a significantly increased risk of hip fracture when adjustment was made for more factors than age, with the highest risk indicated when adjustment was made for age, BMI and smoking. Although hip fracture risk was consistently not significantly increased among type II diabetic women using insulin, type II diabetic women not using insulin had a significantly increased risk when adjustment was made for age, BMI and smoking. The use of insulin (regardless of type of diabetes) was associated with significantly increased risk of hip fracture in both men and women. The exclusion of subjects who developed diabetes mellitus after the start of follow-up from the non-diabetic population did not affect the results.

We found an increased risk of hip fractures independent of duration of diabetes in female type II diabetics (data not shown). This held true also when we included those who were diagnosed as type II diabetics within 4 years of the start of follow-up. When those who developed type II diabetes later than 4 years after the start of follow-up were included, there was a significant trend of increased risk of hip fractures (P=0.049) for increasing time as diabetics. This finding was mainly due to a lowered risk for those developing diabetes late in the follow-up. For men there was a similar but non-significant trend.

There was no significant interaction between the risk associated with diabetes mellitus and the other possibly confounding variables: BMI, history of previous fracture, smoking, physical activity, self-reported health status or self-reported stroke.

Discussion

We found an increased risk of non-vertebral and hip fractures in men with type I diabetes and those using insulin. Increased risk of hip fracture was found in diabetic women. The risk was consistent for both types of diabetes but higher in those with type I diabetes.

Bias considerations

This study included a large number of both men and women, with a wide age range at baseline. The external validity refers mainly to a Caucasian population. The potential for selection bias is limited with more than 77% of the eligible population included in the study. The lowest attendance rates were among those less than 45 years of age and those older than 75 years, with, respectively, rates of 66% and 74% of attendance among men and 73% and 67% among women. We had no possibility to explore differences between responders and non-responders; however, in

the second and third surveys, with an attendance rate of 73%, the age-adjusted mortality was higher among non-responders, and the incidence of fractures was almost similar in the two groups [11]. With the prospective design of this study, the risk factors included were measured and/or classified without knowledge of the future risk of fractures.

The limited power constitutes a major limitation in this study. Although the validation of diabetes cases was based on reviewing the medical records, there is a possibility of underestimation of diabetes in this cohort. This non-differential misclassification will render our results underestimated, as the diagnosed diabetic cases may constitute nearly 50% of the actual number of diabetics in the population, especially among those older than 30 years [12].

Implications

Earlier studies of fracture risk associated with diabetes mellitus have found conflicting results. Forsen et al. in the HUNT Study [2] found an increased risk of hip fracture in women younger than 75 years with type I diabetes and those with type II for more than 5 years, and in men older than 75 years with type II diabetes for less than 5 years. History of diabetes mellitus was associated with increased hip fracture risk in men and women aged 35 years to 49 years [13]. Increased risk of hip and proximal humerus fractures among women 65 years of age and older with type II diabetes was described by Schwartz et al. [3]. Diabetic Mexican–Americans aged over 65 years had an increased risk of hip fractures, especially those using insulin [4]. In the Rotterdam Study [6] men and women older than 55 years with already established and treated type II diabetes had an increased non-vertebral fracture risk. Insulin-treated diabetes was associated with proximal humerus fractures [14] and foot fractures [7] in women 65 years and older.

On the other hand, increased risk of ankle fractures was not associated with any type of diabetes in older women [7], hip fracture risk was not significantly increased in diabetics [8, 15], and hip and distal arm fracture rates were not increased in insulin-treated women [16]. The majority of these studies included only older women.

Generally, our findings support associations between types of diabetes mellitus and fracture risk, especially hip fractures. The increased fracture risk of the hip but not all non-vertebral fractures among women could suggest a different impact of diabetes on different skeletal locations.

Type I diabetes mellitus

Type I diabetes was associated with high risks of hip fracture in both men and women and a threefold increase in non-vertebral fracture risk, although it was borderline significant in women. Further adjustment for features of the metabolic syndrome increased the risk estimates of hip fracture associated with type I diabetes in both men and women.

The association between type I diabetes mellitus and fracture risk might act through changes in bone mass, which could be due to the co-morbidities, complications or poor control of type I diabetes [1, 17, 18]. Higher risk of falls due to episodes of hypoglycemia would be expected among type I diabetics, leading to increased fracture risk.

Type II diabetes mellitus

Our results showed an increased risk of hip fracture among type II diabetic women only. This risk was mainly affected by BMI in our models, as type II diabetics were generally obese and, therefore, expected to be protected against fracture; when adjusted for BMI and even for smoking habits, the risk increased significantly. The risk estimate did not change when the analysis was restricted to women older than 40 years or even older than 50 years, which supports earlier findings [19]. Despite the high bone mineral density usually found in type II diabetics [3, 6, 17, 20–22], the co-morbidities associated with diabetes, the visual or neuromuscular functions deficiencies, and the effect of medication, contribute to the increased fracture risk. In addition, increased risk of falling and its risk factors among diabetics [23, 24], or structurally altered bone in diabetes [25], could also play a major role in increasing fracture risk. Further adjustment for features of the metabolic syndrome, which is an important risk factor for diabetes [26], reduced the hip fracture risk estimate associated with type II diabetes in women.

Insulin use

We found that the use of insulin is associated with increasing hip fracture risk in both men and women. Among men using insulin who suffered hip fracture, 60% were type I diabetics and had had the disease for at least 32 years before suffering a hip fracture, whereas, among women, only 20% had type I diabetes, with a minimum duration of 13 years. Of type II diabetic women using insulin who had suffered hip fracture, 75% had had the disease for more than 12 years before the fracture.

These findings could indicate the possibility that the risk associated with insulin is not explained solely by type I diabetes, and the duration of the disease and, most probably, the duration of insulin use is the main predictor of fracture risk, especially in type II diabetic women. Moreover, insulin-treated diabetics are prone to suffer more episodes of hypoglycemia and falls than diabetics not using insulin. However, even though women with type II diabetes and women overall using insulin had significantly increased risks of hip fractures, type II diabetic women using insulin as an exposed group did not show a significantly increased risk of hip fracture compared with non-diabetics. Although a slightly higher risk estimate for those on insulin compared with those not using insulin could indicate an increased risk for type II diabetics using insulin,

a cautious interpretation of this finding is required, owing to the low power. Further investigations in populations with a higher prevalence of diabetes would clarify the effect of insulin on fracture risk among type II diabetics.

Disease duration

We found an increased risk of hip fractures, independent of duration of diabetes, among type II diabetic women. However, a significant trend of increasing hip fracture risk by increasing disease duration was shown when we included those who had developed type II diabetes late after the start of follow-up. Men and women who had developed type II diabetes after more than 4 years from the start of follow-up had the lowest mean age and the highest BMI at baseline, compared to the other type II duration categories, and, thus, the lowest hip fracture risk.

On the other hand, all type I diabetics who suffered fractures had had the disease for more than 13 years and were older than 41 years at the time of the fracture. The longer duration before type I diabetics suffered fractures, despite their low bone mass, indicated that other factors were needed, for instance, disease complications, or that certain threshold points of bone mass should be reached to cause a fracture.

Conclusion

In a follow-up of a large population aged 25 years to 99 years at baseline we found an increased risk for all non-vertebral fractures and, especially, hip fractures, in type I diabetic men and men using insulin. Regardless of the type, diabetic women had a high risk of hip fractures only. Further analyses are needed to clarify the associations between type II diabetes and insulin use and fracture risk.

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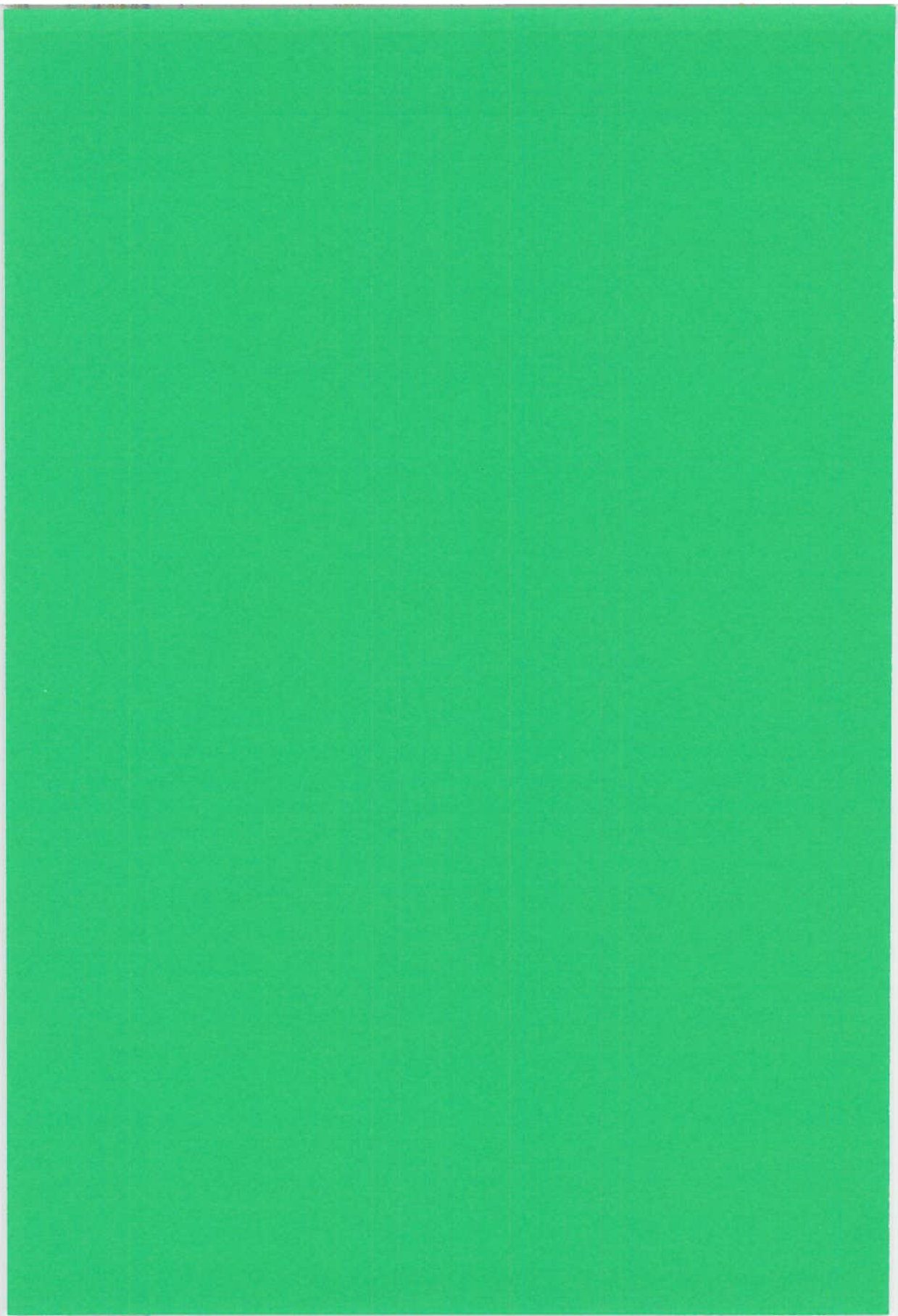
Paper IV



VALIDATION OF THE CUMMINGS' RISK SCORE; HOW WELL DOES IT IDENTIFY WOMEN WITH HIGH RISK OF HIP FRACTURE: THE TROMSØ STUDY.

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Abstract

Identification of individuals with a high hip fracture risk who may benefit from pharmaceutical preventive intervention is presently mainly based on bone mineral density (BMD) measurements. BMD measures have been combined with non-BMD risk factors to better target treatment, but validated risk-scores are lacking. We examined a two-step case-finding strategy where the Cummings' risk score (NEJM 1995) was applied in a population together with BMD screening in order to identify in what subgroups pharmaceutical preventive intervention should be considered. We chose a 5-year cumulative risk (5-year risk) of 5% for hip fracture and the WHO definition of osteoporosis, as the threshold for pharmaceutical preventive intervention.

All Tromsø women aged between 65 and 74 were invited to the Tromsø Osteoporosis Study (TROST) together with a 5% random sample of women aged 75-84 years (n=1410). All had a forearm BMD measurement in 1994/95 and were followed with regard to non-vertebral fracture in the computerized register at the department of radiology in the university hospital, the sole provider of radiological service in the population. A risk score was constructed matching the Cummings score as closely as possible. The population was divided into nine groups according to risk-factor score (low risk: 0-2, medium risk: 3-4, and high risk: 5+) combined with three BMD-categories: normal, osteopenia, and osteoporosis (WHO-definition).

In all 759, 578 and 73 women had low, medium and high risk scores respectively. BMD screening applied to these individuals would yield an osteoporotic sub-group demonstrating a 5-year risk of 5% or more: 54 women with a risk-score of 5+ had a 5-year risk of 13.0%.

By applying the risk score in women aged 65+, it was possible to reduce the number needed to be screened for osteoporosis from 1410 to 73, and treat 54 instead of the 771 women with osteoporosis in this age-group.

Introduction

Hip fractures are an important health problem. With the growing proportion of elderly in the population there is an increasing incidence of hip fractures. Individuals with high hip fracture risk may effectively benefit from pharmaceutical preventive intervention and therefore need to be identified. Although the identification of these individuals have relied mainly on BMD measurements [1-3], the low sensitivity of BMD in the prediction of fractures [4, 5] will result in unnecessary pharmaceutical intervention in many elderly women. On the other hand, non-BMD risk factors independently play a major role in the prediction of hip fracture [6-9]. Combining BMD measurements with non-BMD risk factors allows better assessment of fracture risk [10-14] and help targeting prevention to high risk individuals as shown in earlier studies [8, 15-19]. These studies have developed differently defined risk scores, but validations of these risk-scores in other populations are sorely lacking. A straightforward comparison between BMD and risk score screening will be meaningful when considering the efforts and cost as well as the total number of women needed to be screened.

We examined a two-step case-finding strategy where the Cummings' risk score from the Study of Osteoporotic Fractures (SOF) [6] was applied in a population based setting together with BMD screening in order to validate its ability to identify in what subgroups pharmaceutical preventive intervention should be considered.

Materials and methods

Study population

The Tromsø study is a population based cohort study with five repeated health surveys since 1974. In the fourth Tromsø survey (1994/95), all residents of the Tromsø municipality born 1969 or earlier were invited to the first phase of the survey. Among the 37,559 persons invited, 2139 persons died or moved before their scheduled phase I examination. The eligible

population was therefore 35,420 persons, and 27,159 (77%) participants attended the phase I examination of the survey and answered the relevant questionnaires.

Upon attendance at phase I, all women aged between 55 and 74 together with a 5-10% random samples of younger and older age groups (total=5936) were invited to The Tromsø Osteoporosis Study (TROST) with response rate of 79%. This analysis is based on all women aged 65 years and older (n=1410) who attended the fourth survey; all subjects with history of previous hip fracture were excluded.

Registration of exposure variables

The first questionnaire was printed on the reverse side of a letter of invitation. At the health examination, a trained nurse checked the questionnaire for inconsistency and handed out a second questionnaire to be returned by mail. The questionnaires covered among others, maternal history of osteoporosis, physical activity, coffee and tea consumption, self-rated health status, history of forearm fracture after the age of 50 years, history of hip fracture, history of epilepsy and history of thyroid disease. All medications were registered, among them long-acting benzodiazepines and anticonvulsant drugs.

The examination included among other; standardized measurements of pulse rate, rising from a chair without using one's arms and height and weight determination. Height and weight were measured in light clothing without shoes to the nearest centimetre/kilogram. Weight measurements from the previous surveys were used to determine weight change.

Forearm bone densitometry measurement was performed in 1994/95 on the non-dominant arm at distal and ultra-distal sites with two single x-ray absorptiometric devices (DTX-100; Osteometer MediTech, Inc., Hawthorne, California) [20].

Fracture registration

Our fracture registry is based on the radiographic archives at the University Hospital in Tromsø. The nearest alternative radiographic service or fracture treatment facility is located

250 km from Tromsø. The only fractures that would be missed are fractures occurring while inhabitants were travelling and no control radiographic examination was done after returning home, in addition to fractures not radiographically examined. An earlier registration for participants in the second and third Tromsø surveys was performed, validated and described by Joakimsen et al. [21]. The computerized records in the radiographic archives of the University Hospital contain codes for different information about fractures in addition to the national personal identification number and time of investigation. Any fracture-coded radiographic examinations on participants in the fourth survey were reviewed to ascertain the fracture code, identify exact anatomical location of fracture and to distinguish consecutive fracture cases from one another. In addition the discharge records were checked with respect to hip fractures. For our target population, the hip fracture registry covered the period between the 1st of January 1994 and the 30th of April 2003.

For this study focusing on 5-year fracture risk, the participants were followed for a maximum of 5 years from the date of BMD measurement for each woman with respect to first hip fracture.

Data preparation and analysis:

In view of the possible side-effects of screening [22], bisphosphonates [23] and hip protectors – impracticalities of their application and cosmetic discomfort-, we chose a priori an absolute number of hip fractures saved due to treatment to be over 1 per 100 treated women, and a risk of at least 1% per year for treatment to be considered. This corresponds to a 5-year hip fracture risk of 4.9%. We used a 5-year cumulative risk of 5% for hip fracture and the WHO definition of osteoporosis [24], as the threshold for pharmaceutical preventive intervention.

A risk score was constructed matching the Cummings' score as closely as possible. Most of the risk factors described in the original publication were used (table 1). The risk factors included were maternal history of osteoporosis, forearm fracture after the age of 50, self-

reported poor health, caffeine intake, physical inactivity, height more than 167 cm, weight loss of more than 5 kg or BMI less than 20, use of long-acting benzodiazepines, use of anticonvulsant drugs, self-reported hyperthyroidism, inability to rise up from a chair without help, resting pulse rate more than 80 and been older than 80 years at the time of BMD measurement. Similar to the original study, women were allocated in three groups according to the number of risk factors; low risk: 0-2, medium risk: 3-4 and high risk: 5+ risk factors. Because the WHO definition of osteoporosis has gained widespread acceptance [25], we chose to deviate from Cummings original study and divide the population according to both BMD-tertiles and the *T*-score categories.

Analyses were performed with the use of the SAS statistical package [26]. Frequency tables were used to estimate crude fracture risks. Dummy variables were created for the risk score levels and the *T*-score categories, and the associated fracture risk ratios (RR) were calculated using the Cox proportional hazard (PH) models. The log-rank statistic was performed to test the overall difference between the survival curves of six subgroups; osteoporotics with high-, medium- or low-risk and non-osteoporotics with high-, medium- or low-risk.

Results

A total of 83 hip fractures were registered among 1410 women older than 65 years during the whole follow-up period, with 49 hip fractures occurring in the first 5 years. The total number of all non-vertebral fractures in this cohort was 170 fractures in 5 years. Figure 1 shows the total number of invited and attending women older than 65 years at baseline. The total attendance rate for this age group was 75.9%. Characteristics of the cohort are presented in table 2. Generally the majority referred to their health as poor, and a high proportion consumed more than the equivalent of two cups of coffee per day. Nearly one third of them had a high pulse rate and one fifth was physically inactive. Only age, weight and height were independently significantly different between subjects with and without hip fractures. In all

759, 578 and 73 women had low, medium and high-risk scores respectively. With respect to BMD screening 202, 437 and 771 women were normal, osteopenic and osteoporotic respectively. Figure 2 shows the distribution of the *T*-score categories by risk score groups.

Figure 3 shows the percentage suffering hip fracture by the risk score levels and the *T*-score categories separately. Women with a low risk score suffered 21 hip fractures, while those with high-risk score suffered 8 hip fractures corresponding to 2.8% (95% CI 1.6%-3.9%) and 11.0% (95% CI 3.7%-18.2%) 5-year risk respectively. The osteoporotic group suffered 75.5% of the hip fractures. This corresponds to 4.8% (95% CI 3.3%-6.3%) 5-year risk. The 5-year cumulative risk of hip fracture was significantly increased among women with 5 or more risk factors and among osteoporotic women. The corresponding risk ratios (from the Cox-PH models) were (RR 4.2 (95% CI 1.9-9.5)) in women with 5 or more risk factors compared to women in the lowest risk category, and (RR 9.8 (95% CI 1.4-71.5)) in osteoporotic women compared to women with BMD in the normal range.

To evaluate the combined effect of both risk identification strategies the 5-year cumulative risks of hip fracture among the *T*-score categories were stratified by risk score levels (figure 4). As shown, the crude 5-year fracture risk was above 5% only among the osteopenic and osteoporotic women who had 5 or more risk factors, however only statistically significant in the osteoporotic group (13.0% (95% CI 3.9%-22.0%)). Age adjustment did not alter the risk estimates.

To validate the difference between subgroups, Kaplan-Meier survival curves of six modified subgroups; osteoporotics with high-, medium- or low-risk and non-osteoporotics with high-, medium- or low-risk are shown in figure 5. As expected the osteoporotics high-risk subgroup had the lowest fracture free probability. Interestingly this subgroup shows a lower fracture free probability already after 2 years. The 5-year log-rank test was highly significant (p= <0.0001). The non-osteoporotic high-risk individuals had a probability of fracture not

significantly different from the other subgroups. Extending the follow-up period to 7 years did not alter the differences between the survival curves significantly (data not shown).

Among women younger than 75 years (n=1344) the 5-year hip fracture risk was only significant in the osteoporotic women who had 5 or more risk factors (12.7% (3.1%-22.4%)) (similar to the overall risk). However for those older than 75 years (n=66) the 5-year hip fracture risk was > 5% but not significant among the osteoporotic women regardless their risk score (data not shown).

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the two different types of screening (BMD and risk score) in the total population are shown in table 3. BMD screening has the highest NPV, but only 1% better than risk score screening alone. On the other hand risk score screening has a PPV of 11.0%, more than the double of BMD screening alone. Selective BMD screening in the high-risk group only, identifies 7 of 8 fracture cases as osteoporotic, the last being osteopenic. Overall there was a reduction in the number needed to be screened for osteoporosis from 1410 to 73 women.

Ranking the BMD into tertiles showed an increasing hip fracture risk among women with high and low risk score by decreasing BMD (data not shown).

Discussion

We have validated a non-BMD risk score for hip fractures in a population different from the one the score was generated in, thus validating general use of the score. Given an intervention threshold of 5% 5-year hip fracture risk, it was possible to reduce the number needed to be screened for osteoporosis from 1410 to 73, and treat 54 instead of the 771 women with osteoporosis in this age-group.

Bias considerations:

This study included only women, with an age range at base line from 65 to 84 years. As the sample only constitutes 5% of women aged 75-84 years, our risk estimates refer mainly to

those aged 65-74 years. There was a non-significant indication of BMD being a better screening tool in those older than 74 years, but as there only were 66 subjects in this subgroup, this finding has to be tested in a better powered study. The external validity refers mainly to a Caucasian population. The potential for selection bias is limited with around 77% of the eligible population included in the study. The lowest attendance rate was among those older than 75 years with rate of 46.5%. We have no possibility to explore differences between responders and non-responders, however in the second and third surveys with attendance rate of 73%, the age-adjusted mortality was higher among non-responders, and the incidence of fractures was almost similar in the two groups [27]. In this study the follow up time for each woman started from the BMD measurement date with a maximum value of 8,3 years, we used a 5-year probability of fracture to ensure that all women will have a 5 years follow-up time. Major limitations of this study are the limited power and the use of forearm BMD measurement instead of that of hip BMD to predict hip fracture. However forearm BMD measurement has been described to predict hip fractures well, although not as well as hip BMD [16, 28, 29]. At the time of the forth survey (1994/95) forearm BMD screening was only a practical alternative compared to the long time (15-20 min) of DXA measurement of the hip. On the other hand, compared to forearm BMD, hip BMD identifies few individuals as osteoporotic due to the low population threshold derived from a wider SD in young subjects and thus more individuals with hip fractures would probably be missed. However the results of this study should be validated with hip BMD measurements.

Implications:

Hip fractures are an important health burden with a high case fatality in the elderly. Increased intake of calcium and vitamin D, smoking cessation and physical activity are health advice relevant to all. Hip protectors have shown a risk reduction of more than 50% and are a useful prophylactic device [30, 31], but due to low compliance probably only relevant in subjects

with high risk due to increased fall tendency (i.e. a high non-BMD risk score). Bisphosphonates offers pharmaceutical prophylaxis, but this has only been shown in those with osteoporosis as defined by the WHO [32, 33]. Whether it has an effect on normal BMD has yet to be shown.

Kanis et al. [10] addressed the need to differentiate between intervention and diagnostic thresholds. They recommended a cost-effective intervention threshold as a 10-year hip fracture probability of 4.14% at the age of 65 years [34]. Taking the costs and known side effects into account we chose in this study a (conservative) 5-year hip fracture probability of 5% to warrant treatment intervention with bisphosphonates. Among all osteoporotic women in this study (n=771), with an absolute 5-year risk of 4.8% and around 37% reduction in hip fracture risk and 70% compliance [32, 33, 35], if they were all treated with bisphosphonates around 9 hip fractures would be saved (1 to 2 hip fractures per 100 women, corresponding to a number needed to treat (NNT) over 5 years of 80). Although this is a reasonable NNT, it implies medicalisation of large groups with low absolute risk as shown.

Conflicting results regarding the sole use of BMD in screening for fracture risk have been published [29, 35-37]. However the effectiveness of screening based on BMD measurements alone is questionable, as more than 70% of women 65 years or older are osteoporotic as shown in our study. The low PPV and high NPV indicate that BMD measurements alone are only useful to identify individuals with low hip fracture risk.

Combining BMD measurements with non-BMD risk factors allows better assessment of fracture risk and better targeting of high risk individuals [13, 14, 19, 38]. Risk scores for fracture have been constructed in different ways. Cummings et al. [6] found an additive effect of individual risk factors identifying a subgroup with substantially increased hip fracture risk, where women with multiple risk factors and low BMD were especially at high risk. In comparison to this simple score, other studies have developed different –rather complex- risk

scores. Black et al. [12] have developed and validated a clinical assessment algorithm (the FRACTURE index) based on the SOF data which used to assess the 5-year risk of hip and other osteoporotic fractures. Another study found that women with 5 or more risk factors from the SOF study have high fracture rate compared to a universal group of women with BMD measurement [39]. Moreover, risk points and scores based on regression models parameters [11, 17, 18, 40] with or without BMD measurements help in the identification of high hip fracture risk women. In women with previous BMD measurements, a relative risk derived risk score and an algorithm derived from risk factors increased the number of high risk women identified [15, 16]. Although these studies used different risk score definitions, they indicated better identification of high risk women based on non-BMD risk factors. Kanis et al. [9] recommended a case finding strategy based on assessment of fracture probability using clinical risk factors and where appropriate additional BMD testing.

In this study we applied a two-step case-finding strategy using a modified version of the original simple risk score introduced by Cummings [6] with a main objective to validate its ability to identify women with high risk of hip fracture rather than to develop a new fracture risk score.

We show that forearm BMD measurements can be restricted to those with 5 or more risk factors, as no other subgroups had more than 5% 5-year hip fracture risk even after stratification on osteoporosis. Thus supporting Kanis' recommendation [9]. Our approach identified a high risk group constituting only 5.2% of the total population of women 65 years and older. By applying the diagnostic threshold of osteoporosis as defined by the WHO, screening of this high-risk group identified 74% of them as osteoporotic. Although this osteoporotic subgroup constitutes only around 7% of the total number of osteoporotic women in the population, the effectiveness of this strategy relies on reducing the number of women needed to be screened by 95% i.e. screening 73 women instead of 1410.

Using this approach we are able to identify and therefore target the pharmaceutical intervention to where it is most effective. Treating the identified 54 osteoporotic women with bisphosphonates corresponds to NNT to prevent one hip fracture of 30, in comparison to a NNT of 80 when screening all women for osteoporosis as recommended before [41].

In this study both the osteopenic and the osteoporotic subjects with 5 or more risk factors had a risk greater than 5%, although only with a significantly increased risk in the osteoporotic subgroup. Using hip protectors, calcium and vitamin D will reduce the risk with more than 50% in the osteopenic group. In the osteoporotic group an even larger risk reduction would be expected due to independent effects of hip protectors and bisphosphonates in combination. As suggested by Kanis et al. [42] and supported by the results from Mayo Clinic [43], bisphosphonates might be as useful in osteopenic as osteoporotic subjects. Treating all women in the high risk score group with bisphosphonates could render forearm BMD measurements unnecessary. Further studies looking at the additional effect of hip BMD measurements might restore osteoporosis as a screening tool in high risk subgroups.

When using 4 or more (4+) risk factors as a cut-off point the high-risk group constituted 19.2% of the total population. Screening this high-risk group identified 64.1% as osteoporotics suffering 22.4% of the total number of hip fractures. Only the osteoporotic subjects had 5-year hip fracture risk more than 5% (6.4%) corresponding to a NNT here of 60. Lowering the cut-off of Cummings to 4+ identifies an osteoporotic subgroup with an absolute hip fracture risk high enough to warrant prophylactic treatment, but necessitates BMD screening. As the NNT is well below the suggested threshold of hundred, whether to use 5+ or 4+ as cut-off depends on the availability and cost of BMD screening in these subgroups.

BMD and non-BMD risk factors most likely change differently over time. Accordingly longer follow up could alter the relative importance of these risk factors. Therefore a 10-year probability as suggested by Kanis et al. [10], could yield a more powerful risk score. The

significance of non-BMD predictors of hip fracture differ between different populations [40, 44]. Despite this, the simple scoring of a given set of risk factors, as suggested by Cummings does identify high-risk subjects well in different populations. A score summing up all reported risk factors could perform even better.

Conclusion

The original Cummings' risk score identify well women aged 65+ at high risk of hip fractures and restriction of BMD measurements to this high risk group can safely be done without missing subjects with a five year hip fracture risk of 5% or more.

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Table 1: Risk factors for hip fracture as defined by Cummings et al. (NEJM 1995) and in this study.

Cummings' risk factors*	Our risk factors
Current weight less than at the age of 25	Weight loss (>5 kg) or BMI <20 kg/m^2
Height at age 25 ≥ 168 cm	Height ≥168 cm
Maternal history of hip fracture	Maternal history of hip fracture
Any fracture (except hip fracture) since age of 50	Any fracture (except hip fracture) since age of 50
Self-rated health (fair, poor or very poor health)	Self-reported health (good or poor health)
No walking for exercise	Physically inactive (no activity)
Current using of long-acting benzodiazepines	Using long-acting benzodiazepines
Current using of long-acting anticonvulsant	Using anticonvulsant drugs
Resting pulse rate >80 beats/min	Pulse rate > 80 beats/min
Caffeine intake more than the equivalent of two cups of coffee/day	Caffeine intake more than the equivalent of two cups of coffee/day
Inability to rise from chair without using arms	Unable to rise from chair without help
Pervious hyperthyroidism	Self-reported hyperthyroidism
Age ≥ 80	Age ≥ 80 at the time of BMD measurement
On feet ≤ 4 hr/day	N/A**
Lowest quartile of depth perception	N/A**
Lowest quartile of contrast sensitivity	N/A**
Calcaneal BMD	Forearm BMD

* Risk factors associated with hip fracture risk in multivariable models.
** Not applicable in this study.

Figure 1: Number of invited and attended women older than 65 years by age groups in 94/1995 (The Tromsø Study).

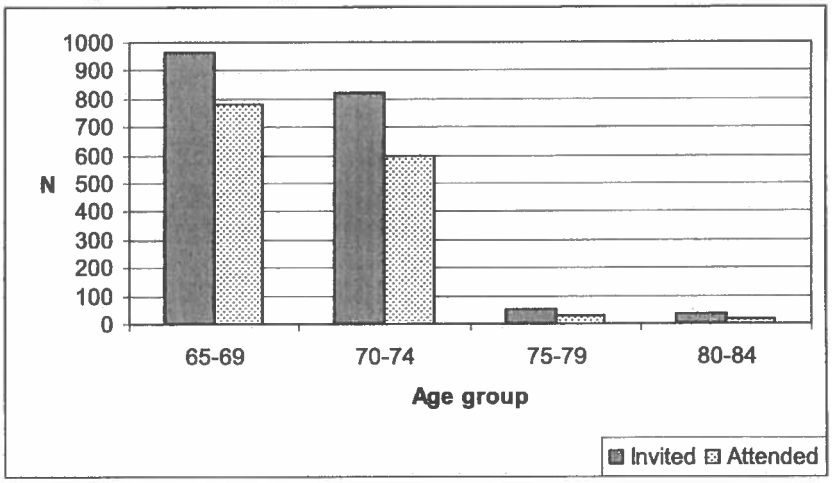


Table 2: Baseline characteristics of 1410 women older than 65 years in 94/1995 (The Tromsø Study).

Characteristic	Subjects with hip fractures	Subjects without hip fractures	Relative risk* RR (95% CI)
Number	49	1361	-
Age (years) (mean ± SD)	70.4 ± 3.4	69.5 ± 3.3	1.1 (1.0-1.2)
Weight (kg) (mean ± SD)	65.7 ± 15.1	68.6 ± 12.3	0.8 (0.6-1.0)
Height (cm) (mean ± SD)	161.3 ± 6.5	159.9 ± 6.0	1.3 (1.0-1.7)
BMI (kg/m^2) (mean ± SD)	25.1 ± 4.7	26.8 ± 4.6	0.6 (0.5-0.9)
Forearm BMD (g/cm^2) (mean ± SD)	0.33 ± 0.06	0.37 ± 0.06	0.6 (0.5-0.8)
Maternal history of hip fracture (%)	2.04	2.65	0.7 (0.1-5.3)
Any fracture (except hip fracture) since age of 50 (%)	20.41	15.28	1.4 (0.7-2.8)
Self-reported hyperthyroidism (%)	0	3.53	-
Self-reported poor health (%)	59.18	57.83	1.1 (0.6-1.9)
Physically inactive (%)	22.45	19.25	1.2 (0.6-2.4)
Using long-acting benzodiazepines (%)	26.53	15.87	1.9 (1.0-3.6)
Using anticonvulsant drugs (%)	2.04	0.66	3.0 (0.4-21.5)
Pulse rate > 80 beats/min (%)	34.69	29.02	1.3 (0.7-2.4)
High caffeine intake** (%)	81.63	86.04	0.7 (0.4-1.5)
Unable to rise from chair without help*** (%)	6.12	2.42	2.7 (0.9-8.8)
Age ≥ 80 at the time of BMD measurement (%)	2.04	0.96	2.3 (0.3-16.7)
Currently a smoker (%)	32.7	23.0	1.7 (0.9-3.0)

* RR given for 5 year change in age and per 1 SD increase in continuous variables.
** consumed more than the equivalent of two cups of coffee per day.
*** rise up from a chair without using own arms for five times.

Figure 2: Distribution of BMD categories by risk score levels for women older than 65 years in 94/1995 (The Tromsø Study).

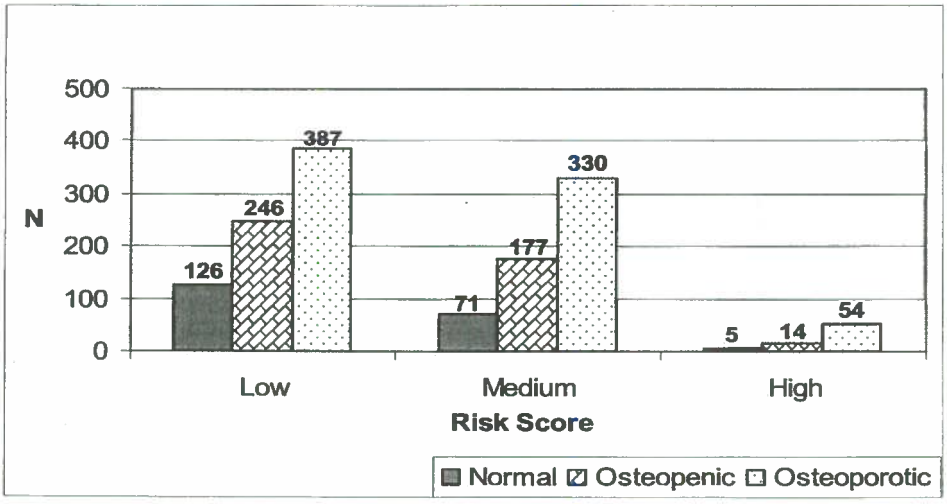
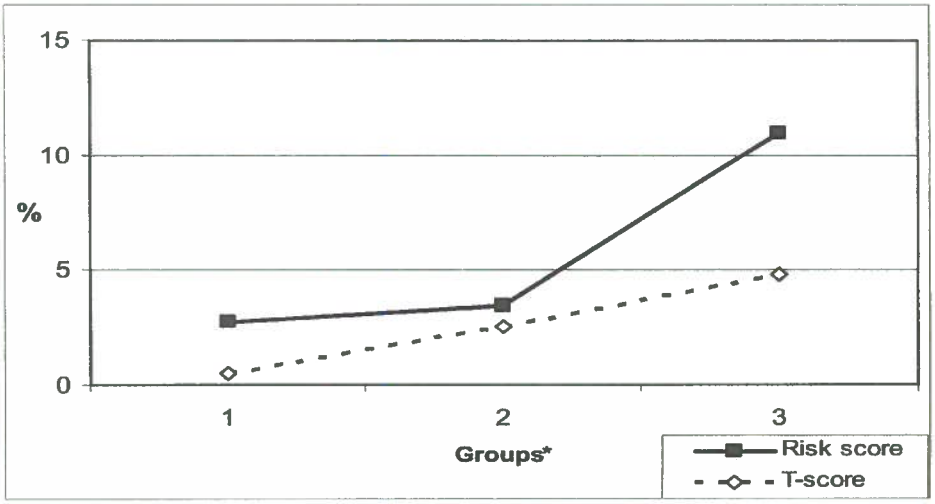


Figure 3: Five years probability of hip fracture by risk score levels and *T*-score categories among women older than 65 years (The Tromsø Study).



* Risk score: 1) Low, 2) Medium, 3) High.
T-score: 1) Normal, 2) osteopenic, 3) Osteoporotic.

Figure 4: Five years probability of hip fracture in *T*-score categories by risk score levels among women older than 65 years (The Tromsø Study).

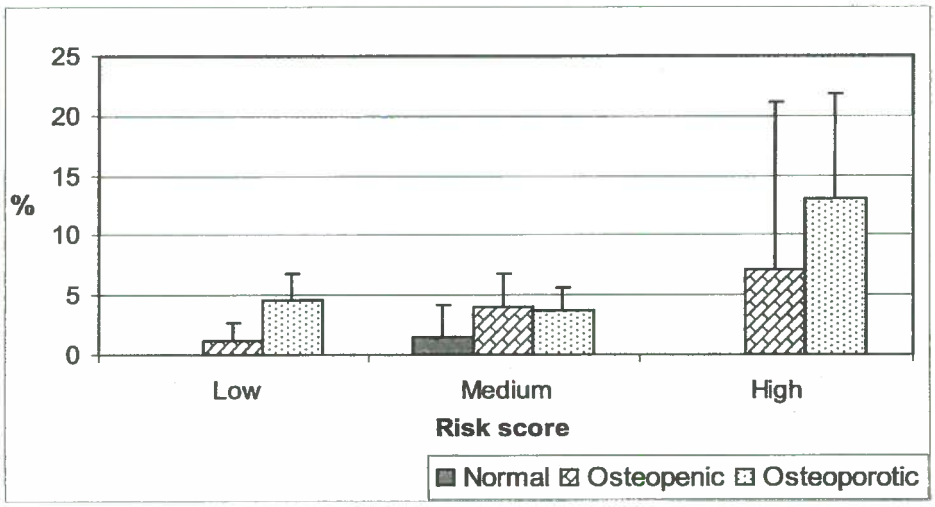


Figure 5: Kaplan-Meier survival curves of subgroups of *T*-score and risk score categories in women older than 65 years (The Tromsø Study).

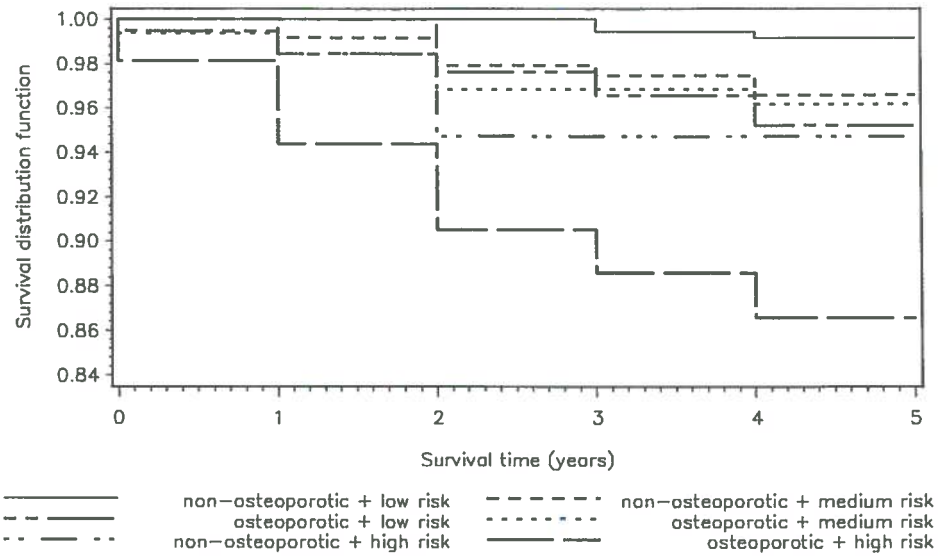
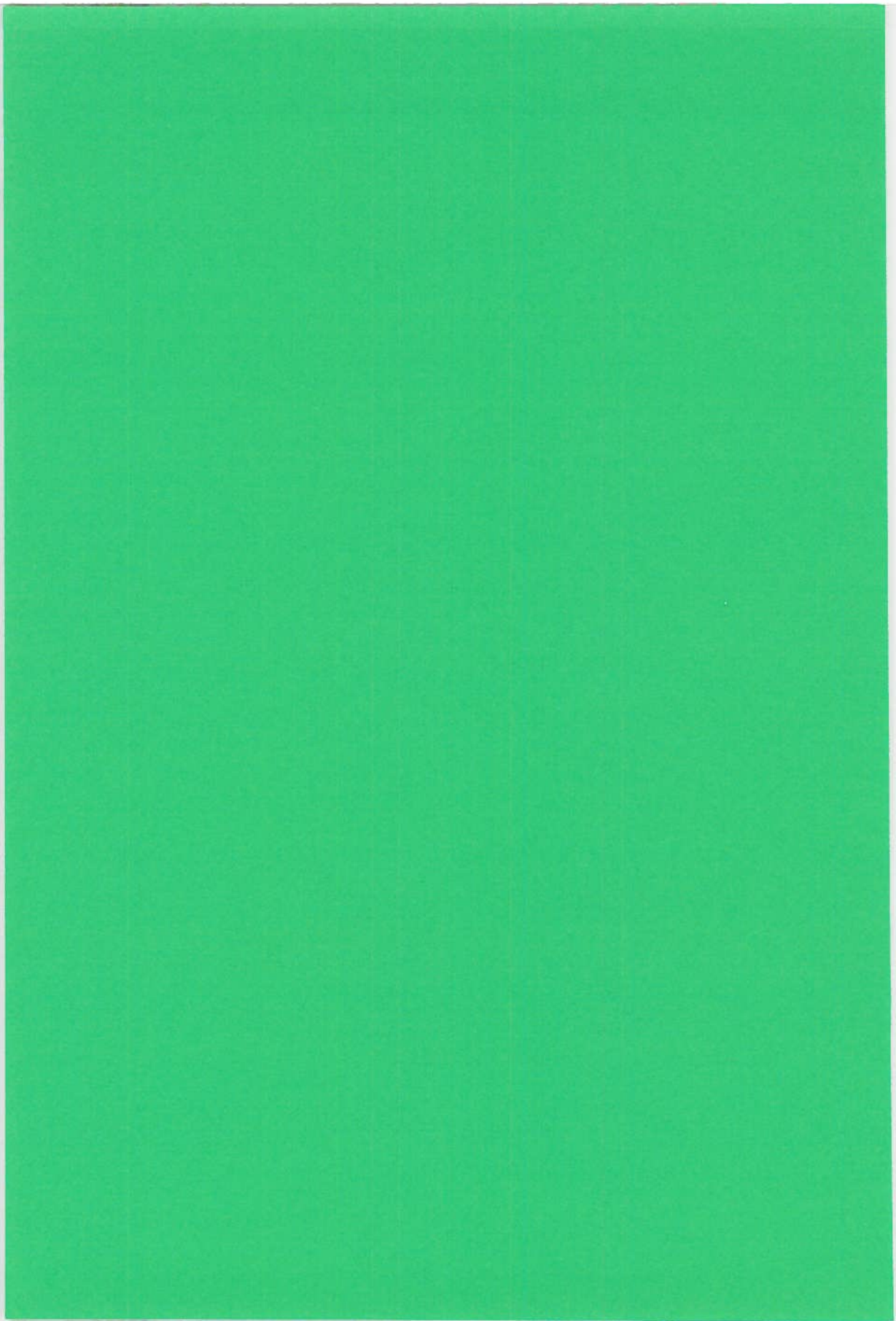


Table 3: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of different types of hip fracture risk screening of women 65 years and older (The Tromsø Study).

	N	No. of fracture	Sensitivity	Specificity	PPV	NPV
Screening all women for osteoporosis	1410	49	75.5	53.9	4.8	98.1
Screening all women for risk score	1410	49	16.3	95.2	11.0	96.9
Selective BMD screening in the high risk score group only	*73*	*8*	*87.5*	*27.7*	*13.0*	*94.7*

Appendix A



English translation of invitation with the first questionnaire used in the health survey in Tromsø 1994/95

Translation based on translations by Kevin McCafferty and Anne Clancy

HEALTH SURVEY
INVITATION

"This is your chance"

Date of birth Social security No.

Municipality Electoral ward No.

Welcome to the Tromsø Health Survey!

The Health Survey is coming to Tromsø. This leaflet will tell you when and where. You will also find information about the survey in the enclosed brochure.

We would like you to fill in the form overleaf and take it with you to the examination.

The more people take part in the survey, the more valuable its results will be. We hope, therefore, that you will be able to come. Come along even if you feel healthy, if you are currently receiving medical treatment, or if you have had your cholesterol and blood pressure levels taken recently.

Yours sincerely,
Municipal Health Authorities
Faculty of Medicine - University of Tromsø
National Health Screening Service

"This is a real opportunity — Take it!"

Your own health

What is your current state of health?
Tick one box only.

- Poor ☐
- Not so good ☐
- Good ☐
- Very good ☐

Do you have, or have you ever had:

	YES	NO	Age first time
Myocardial infarction	☐	☐	_____ years
Angina pectoris	☐	☐	_____ years
Stroke/ brain haemorrhage	☐	☐	_____ years
Asthma	☐	☐	_____ years
Diabetes	☐	☐	_____ years

Do you take medicine for high blood pressure?

- At the moment ☐
- Used to, but not any longer ☐
- Never have ☐

Have you during the last year suffered from pains and/or stiffness in muscles and joints that have lasted continuously for at least 3 months?

YES ☐ NO ☐

Have you in the last two weeks felt:

	No	A little	A lot	Very much
Nervous or worried?	☐	☐	☐	☐
Anxious?	☐	☐	☐	☐
Secure and calm?	☐	☐	☐	☐
Irritable?	☐	☐	☐	☐
Happy and optimistic?	☐	☐	☐	☐
Down/depressed?	☐	☐	☐	☐
Lonely?	☐	☐	☐	☐

Smoking

Did any of the adults at home smoke while you were growing up? YES ☐ NO ☐

Do you now, or have you previously, lived with daily smokers after your 20th birthday?

YES ☐ NO ☐

If "YES", for how many years in all? ____Years

How many hours a day do you normally spend in smoke-filled rooms? _____Hours
Put 0 if you do not spend time in smoke-filled rooms.

Do you yourself smoke:	YES	NO
Cigarettes daily?	☐	☐
Cigars/cigarillos daily?	☐	☐
Pipe daily ?	☐	☐

If you previously smoked daily, how long is it since you stopped? _____ Years

If you smoke daily at the moment, or have smoked before:

How many cigarettes do you smoke/did you smoke per day? _____ Cigarettes

How old were you when you began smoking daily? Age _____ Years

How many years in all have you smoked daily? _____ Years

Exercise

How has your physical activity in leisure time been during this last year? *Think of your weekly average for the year. Time spent going to work counts as leisure time.*

	Hours pr. week None	Less than 1	1-2	3 or more
Light activity (*not sweating or out of breath*)	☐	☐	☐	☐
Hard activity (*sweating/ out of breath*)	☐	☐	☐	☐

Coffee

How many cups of coffee do you drink daily? *Put 0 if you do not drink coffee daily.* Cups ☐☐☐

Boiled coffee (i.e., grind boiled and allowed to draw) ☐☐☐

Other coffee ☐☐☐

Alcohol

Are you a teetotaler? YES ☐ NO ☐

How many times a month do you normally drink alcohol? *Do not count low-alcohol beer. Put 0 if less than once a month.* ____ Times

How many glasses of beer, wine or spirits do you normally drink in a fortnight? *Do not count low-alcohol beer. Put 0 if less than once a month.*

Beer Glasses	Wine Glasses	Spirits Glasses
☐☐	☐☐	☐☐

Fat

What kind of margarine or butter do you normally use on bread? *Tick one box only.*

Don't use butter/margarine	☐
Creamery butter	☐
Hard margarine	☐
Soft margarine	☐
Butter/margarine blend	☐
Light margarine	☐

Education/work

What is the highest level of education you have completed?

7-10 years primary/secondary school, modern secondary school, folk high school	☐
Technical school, middle school, vocational.. school, 1-2 years' senior high school	☐
A-levels/High school diploma, (3-4 years)	☐
College/university, less than 4 years	☐
College/university, 4 or more years	☐

What is your current work situation?

Paid work	☐
Full-time housework	☐
Education, military service	☐
Unemployed, redundant	☐

How many hours of paid work do you have pr. week? _____ Hours

Do you receive any of the following benefits?

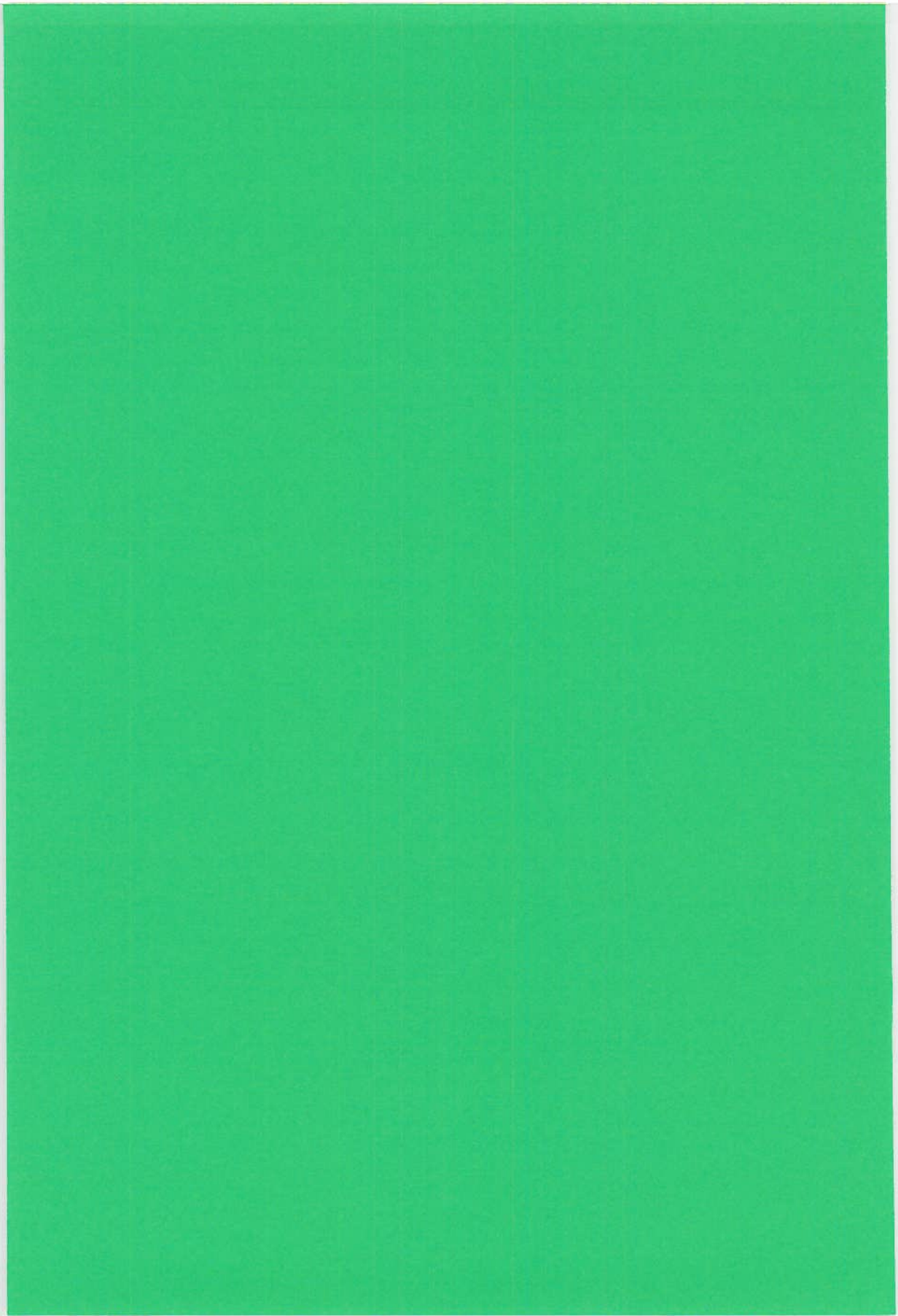
Sickness benefit (sick leave)	☐
Rehabilitation benefit	☐
Disability pension	☐
Old-age pension	☐
Social welfare benefits	☐
Unemployment benefit	☐

Illness in the family

Have one or more of your parents or siblings had a heart attack or had angina (heart cramp)?

YES	NO	DON'T KNOW
☐	☐	☐

Appendix B



English translation of the second questionnaire used in the health survey in Tromsø 1994/95 for subjects younger than 70 years.

Based on translations by K. McCafferty and A. Clancy

TROMSØ HEALTH SURVEY

The main aim of the Tromsø survey is to improve our knowledge of heart and circulatory conditions in order to aid prevention. The survey is also intended to improve our knowledge of cancer and other general conditions, such as allergies, muscle pains and nervous conditions. We would therefore like you to answer some questions about factors that may be relevant for your risk of getting these and other illnesses.

This form is part of the Health Survey, which has been approved by the Norwegian Data Inspectorate and the Regional Board of Research Ethics. The answers will only be used for research purposes and will be treated in strict confidence. The information you give us may later be stored along with information from other public health registers in accordance with the rules laid down by the Data Inspectorate and the Regional Board of Research Ethics.

If you are unsure about what to answer, tick the box that you feel fits best.

The completed form should be sent to us in the enclosed pre-paid envelope.

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

National Health
Screening Service

If you do not wish to answer the questionnaire, tick the box below and return the form. Then you will not receive reminders.

I do not wish to answer the questionnaire. ☐

Date for filling in this form: Day/Month/Year

CHILDHOOD/YOUTH

What Norwegian municipality did you live in at the age of 1 year? _____

If you did not live in Norway, give country of residence instead of municipality.

How was your family's economic situation while you were growing up?

- Very good ☐
- Good ☐
- Difficult ☐
- Very difficult ☐

For how much of the first three years of your life
- did you live in a town/city? ____ Years
- did your family have a cat or dog in the home? ____ Years

For how much of the first 15 years of your life
- did you live in a town/city? ____ Years
- did your family have a cat or dog in the home? ____ Years

HOME

Who do you live with?
Tick once for each item and give the number of persons.

	YES	NO	Number
Spouse/partner	☐	☐	____
Other persons over 18 years	☐	☐	____
Persons under 18 years	☐	☐	____

How many of the children go to day care/kindergarten/ nursery school? ____

What type of home do you live in?

- Villa/ detached house ☐
- Farm ☐
- Flat / Apartment ☐
- Terraced / semi-detached house ☐
- Other ☐

How big is your home? _____ m2

Approximately what year was your home built? _____

	YES	NO
Has your home been insulated after 1970?	☐	☐
Do you live on the bottom floor/cellar level?	☐	☐
If "YES", is the floor laid on concrete?	☐	☐

What is the main source of heat in your home?

- Electric heating ☐
- Wood-burning stove ☐
- Central heating system using:
  - Paraffin ☐
  - Electricity ☐

	YES	NO
Do you have fitted carpets in the living-room?	☐	☐
Is there a cat in your home?	☐	☐
Is there a dog in your home?	☐	☐

WORK

If you are in paid or unpaid work, which statement describes your work best?

- I am mainly seated while working (*e.g., at a desk/assembly work*) ☐
- My work requires a lot of walking (*e.g., shop assistant, light industrial work, teaching*) ☐
- My work entails a lot of walking and lifting (*e.g., postman/woman, nurse, building work*) ☐
- I do heavy physical work (*e.g., forestry, heavy agricultural/construction work*) ☐

Do you have any influence on how your work is organised?

- No, not at all ☐
- To a small extent ☐
- Yes, to a large extent ☐
- Yes, I decide myself ☐

	YES	NO
Are you on call; do you work shifts or nights?	☐	☐

Do you do any of the following jobs (full- or part-time)?

Tick one box only for each item.	YES	NO
Driver	☐	☐
Farmer	☐	☐
Fisherman	☐	☐

YOUR OWN ILLNESSES

Have you ever had:

Tick one box only for each item. Give your age at the time. If you have had the condition several times, how old were you last time?

	YES	NO	AGE
Hip fracture	☐	☐	____
Wrist/forearm fracture	☐	☐	____
Whiplash	☐	☐	____
Injury requiring hospital admission	☐	☐	____
Stomach ulcer	☐	☐	____
Duodenal ulcer	☐	☐	____
An operation for stomach/ duodenal ulcer	☐	☐	____
Throat/ neck operation	☐	☐	____

Have you you ever had, or do you still have:

Tick one box only for each item.	YES	NO
Cancer	☐	☐
Epilepsy	☐	☐
Migraine	☐	☐
Chronic bronchitis	☐	☐
Psoriasis	☐	☐
Osteoporosis	☐	☐
Fibromyalgia/fibrositis/ chronic pain syndrome	☐	☐
Psychological problems for which you have sought help	☐	☐
Thyroid disease	☐	☐
Liver disease	☐	☐
Kidney stone	☐	☐
Appendectomy	☐	☐
Allergy and hypersensitivity:		
Atopic eczema (e.g., childhood eczema)	☐	☐
Hand eczema	☐	☐
Hay fever	☐	☐
Food allergy	☐	☐
Other hypersensitivity (not allergy)	☐	☐

How many times have you had a cold, influenza (flue), vomiting/diarrhoea, or similar in the last six months?

_____ times

Have you had any of these in the last two weeks?

YES	NO
☐	☐

ILLNESS IN THE FAMILY

Tick the appropriate box for relatives that have, or have ever had the following illnesses: *Tick "None" if none of your relatives have had the condition.*

	Mother	Father	Brother	Sister	Child	None
Stroke or brain haemorrhage	☐	☐	☐	☐	☐	☐
Myocardial infarction before age 60	☐	☐	☐	☐	☐	☐
Cancer	☐	☐	☐	☐	☐	☐
Asthma	☐	☐	☐	☐	☐	☐
Stomach/ duodenal ulcer	☐	☐	☐	☐	☐	☐
Osteoporosis	☐	☐	☐	☐	☐	☐
Psychological problems	☐	☐	☐	☐	☐	☐
Allergy	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐	☐	☐
-age when they got diabetes	___	___	___	___	___	___

SYMPTOMS

	YES	NO
Do you cough approximately every day of the year?	☐	☐
If "Yes": Is your cough productive ?	☐	☐
Have you had this kind of cough for as long as 3 months in each of the last two years?	☐	☐
Have you had periods of wheezing in your chest?	☐	☐
If "Yes", has this occurred: *Tick one box only for each item.*		
At night	☐	☐
In connection with respiratory infections	☐	☐
In connection with physical exertion	☐	☐
In connection with very cold weather	☐	☐
Have you noticed sudden changes in your pulse or heart rhythm in the last year?	☐	☐

How often do you suffer from sleeplessness?

- Never, or just a few times a year ☐
- 1-2 times a month ☐
- Approximately once a week ☐
- More than once a week ☐

If you suffer from periods of sleeplessness, what times of the year does it affect you most?

- No particular time of year ☐
- Especially during the dark winter months ☐
- Especially during the midnight sun period ☐
- Especially in spring and autumn ☐

Have you in the last twelve months suffered from sleeplessness to the extent that it has affected your ability to work? YES ☐ NO ☐

How often do you suffer from headaches?

- Seldom/Never ☐
- Once a month or more ☐
- Once a week or more ☐
- Every day ☐

Does the thought of getting a serious illness ever worry you?

- Not at all ☐
- Only a little ☐
- Some ☐
- Very much ☐

USE OF HEALTH SERVICES

How many visits have you made during the past year due to your own health or illness? *Tick 0 if you have not had such contact*

	Number of times the past year
To a general practitioner (GP)/ Emergency GP	____
Psychologist or psychiatrist	____
Other medical specialist (not at a hospital)	____
Hospital out-patient clinic	____
Hospital admission	____
Medical officer at work	____
Physiotherapist	____
Chiropractor	____
Acupuncturist	____
Dentist	____
Alternative medical practitioner (homoeopath, foot zone therapist, etc.)	____
Healer, Faith healer, clairvoyant	____

MEDICATION AND DIETARY SUPPLEMENTS

Have you for any length of time in the past year used any of the following medicines every day or almost daily? Indicate how many months you used them for. *Write 0 for items you have not used.*

Medication:	
Painkillers	____ mths
Sleeping pills	____ mths
Tranquilizers	____ mths
Antidepressants	____ mths
Allergy drugs	____ mths
Asthma drugs	____ mths
Dietary supplements	
Iron tablets	____ mths
Calcium tablets or bonemeal	____ mths
Vitamin D supplement	____ mths
Other vitamin supplements	____ mths
Cod liver oil or fish oil capsules	____ mths

Have you in the last 14 days used the following medicines or dietary supplements? *Tick one box only for each item.*

Medicines	YES	NO
Painkillers	☐	☐
Antipyretic drugs (to reduce fever)	☐	☐
Migraine drugs	☐	☐
Eczema cream/ointment	☐	☐
Heart medicine (not blood pressure)	☐	☐
Lipid lowering drugs	☐	☐
Sleeping pills	☐	☐
Tranquilizers	☐	☐
Antidepressants	☐	☐
Other drugs for nervous conditions	☐	☐
Antacids	☐	☐
Gastric ulcer drugs	☐	☐
Insulin	☐	☐
Diabetes tablets	☐	☐
Thyroxin tablets (for metabolic disorder)	☐	☐
Cortisone tablets	☐	☐
Other medicine(s)	☐	☐

Dietary supplements	YES	NO
Iron tablets	☐	☐
Calcium tablets or bonemeal	☐	☐
Vitamin D supplement	☐	☐
Other vitamin supplements	☐	☐
Cod liver oil or fish oil capsules	☐	☐

FRIENDS

How many good friends do you have whom you can talk confidentially with and who give you help when you need it? _____ good friends

Do not count people you live with, but do include other relatives!

How many of these good friends do you have contact with at least once a month? _____

Do you feel you have enough good friends? YES ☐ NO ☐

How often do you normally take part in organised gatherings, e.g., sewing circles, sports clubs, political meetings, religious or other associations?

- Never, or just a few times a year ☐
- 1-2 times a month ☐
- Approximately once a week ☐
- More than once a week ☐

DIET

If you use butter or margarine on your bread, how many slices does a small catering portion normally cover? By this, we mean the portion packs served on planes, in cafés, etc. (i.e., 10-12g)

A catering portion is enough for about ____ slices.

What kind of fat is normally used in **cooking** (not on the bread) in your home?

- Creamery butter ☐
- Hard margarine ☐
- Soft margarine ☐
- Butter/margarine blend ☐
- Oils ☐

What kind of bread (bought or home-made) do you usually eat? *Tick one or two boxes!*

The bread I eat is most similar to

- White bread ☐
- Light textured brown bread ☐
- Ordinary brown bread ☐
- Coarse brown bread ☐
- Crisp bread ☐

How much (in **number** of glasses, cups, potatoes or slices) do you usually eat or drink **daily** of the following foodstuffs? *Tick one box for each foodstuff.*

	0	Less than 1	1-2	3-4	5-6	More than 6
Full cream milk (fresh or soured) (glasses)	☐	☐	☐	☐	☐	☐
Semi-skimmed milk (low-fat) (fresh or soured) (glasses)	☐	☐	☐	☐	☐	☐
Skimmed milk (fresh or soured) (glasses)	☐	☐	☐	☐	☐	☐
Tea (cups)	☐	☐	☐	☐	☐	☐
Orange juice (glasses)	☐	☐	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐	☐	☐
Slices of bread in total (incl. crispbread)	☐	☐	☐	☐	☐	☐
Slices of bread with fish (e.g., mackerel in tomato sauce	☐	☐	☐	☐	☐	☐
- lean meat (e.g., ham)	☐	☐	☐	☐	☐	☐
- fat meat (e.g., salami)	☐	☐	☐	☐	☐	☐
- cheese (e.g. Gouda/ Norvegia)	☐	☐	☐	☐	☐	☐
- brown cheese	☐	☐	☐	☐	☐	☐
- smoked cod caviar	☐	☐	☐	☐	☐	☐
- jam and other sweet spreads	☐	☐	☐	☐	☐	☐

How many **times per week** do you normally eat the following foodstuffs? *Tick a box for all foodstuffs listed.*

	Never	Less than 1	1	2-3	4-5	Roughly every day
Yoghurt	☐	☐	☐	☐	☐	☐
Boiled or fried egg	☐	☐	☐	☐	☐	☐
Breakfast cereal/ oat meal, etc.	☐	☐	☐	☐	☐	☐
For dinner						
- meat	☐	☐	☐	☐	☐	☐
- sausage/meatloaf/ meatballs	☐	☐	☐	☐	☐	☐
- fat fish (e.g., salmon/ redfish)	☐	☐	☐	☐	☐	☐
- lean fish (e.g., cod)						
- fishballs/fishpudding/ fishcakes	☐	☐	☐	☐	☐	☐
- vegetables	☐	☐	☐	☐	☐	☐
Mayonnaise, remoulade	☐	☐	☐	☐	☐	☐
Carrots	☐	☐	☐	☐	☐	☐
Cauliflower/cabbage/ broccoli	☐	☐	☐	☐	☐	☐
Apples/pears	☐	☐	☐	☐	☐	☐
Oranges, mandarines	☐	☐	☐	☐	☐	☐
Sweetened soft drinks	☐	☐	☐	☐	☐	☐
Sugarfree ("Light") soft drinks	☐	☐	☐	☐	☐	☐
Chocolate	☐	☐	☐	☐	☐	☐
Waffles, cakes, etc.	☐	☐	☐	☐	☐	☐

ALCOHOL

How often do you usually drink	beer?	wine?	spirits?
Never, or just a few times a year	☐	☐	☐
1-2 times a month	☐	☐	☐
Roughly once a week	☐	☐	☐
2-3 times a week	☐	☐	☐
Roughly every day	☐	☐	☐

Approximately how often in the last year have you drunk alcohol that equals at least 5 small bottles of beer, a bottle of wine, or 1/4 bottle of spirits?

- Not in the last year ☐
- Just a few times ☐
- 1-2 times a month ☐
- 1-2 times a week ☐
- 3 or more times a week ☐

For approximately how many years has your alcohol comsumption been as you described above? _____ years

WEIGHT REDUCTION

About how many times have you deliberately tried to lose weight? *Write 0 if you never have.*

- before age 20 _____ times
- after age 20 _____ times

If you have lost weight, about how many kilos have you ever lost at the most?

- before age 20 _____ times _____ kg
- after age 20 _____ times _____ kg

What weight would you be satisfied with (your "ideal weight")? _____ kg

URINARY INCONTINENCE

How often do you suffer from urinary incontinence?

Never	☐
Not more than once a month	☐
Two or more times a month	☐
Once a week or more	☐

Your comments:

Thank you for helping us! Remember to post the form today!
Tromsø Health Survey

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

How old were you when you had your first menstruation? _____ years

If you no longer menstruate, how old were you when you stopped having menstruation? _____ years

Apart from pregnancy and after giving birth, have you ever stopped having menstruation for 6 months or more?

YES ☐ NO ☐

If "Yes", how many times? _____ times

If you still menstruate or are pregnant:

What date did your last menstruation begin?

day/month/year ___ / ___ / ___

Do you normally use painkillers to relieve period pains?

YES ☐ NO ☐

PREGNANCY

How many children have you given birth to? _____ children

Are you pregnant at the moment? YES ☐ NO ☐ Don't know ☐

During pregnancy, have you had high blood pressure and/or proteinuria? YES ☐ NO ☐

If "Yes", during which pregnancy?

	Pregnancy: First	Later
High blood pressure	☐	☐
Proteinuria	☐	☐

If you have given birth, fill out for each child the year of birth and approximately how many months you breastfed the child.

Child:	Year of birth:	Number of months breastfed:
1	_____	_____ months
2	_____	_____ months
3	_____	_____ months
4	_____	_____ months
5	_____	_____ months
6	_____	_____ months

CONTRACEPTION AND OESTROGEN

Do you, or have you ever, used:	Now	Used to	Never:
Contraceptive pills (incl.minipill)	☐	☐	☐
A hormonal intrauterine device	☐	☐	☐
Oestrogen (tablets or patches)	☐	☐	☐
Oestrogen (cream or suppositories)	☐	☐	☐

If you use contraceptive pills, hormonal intrauterine device, or oestrogen, what brand do you currently use?

_____

If you use, or have ever used, contraceptive pills:

Age when you began taking the pill? _____years

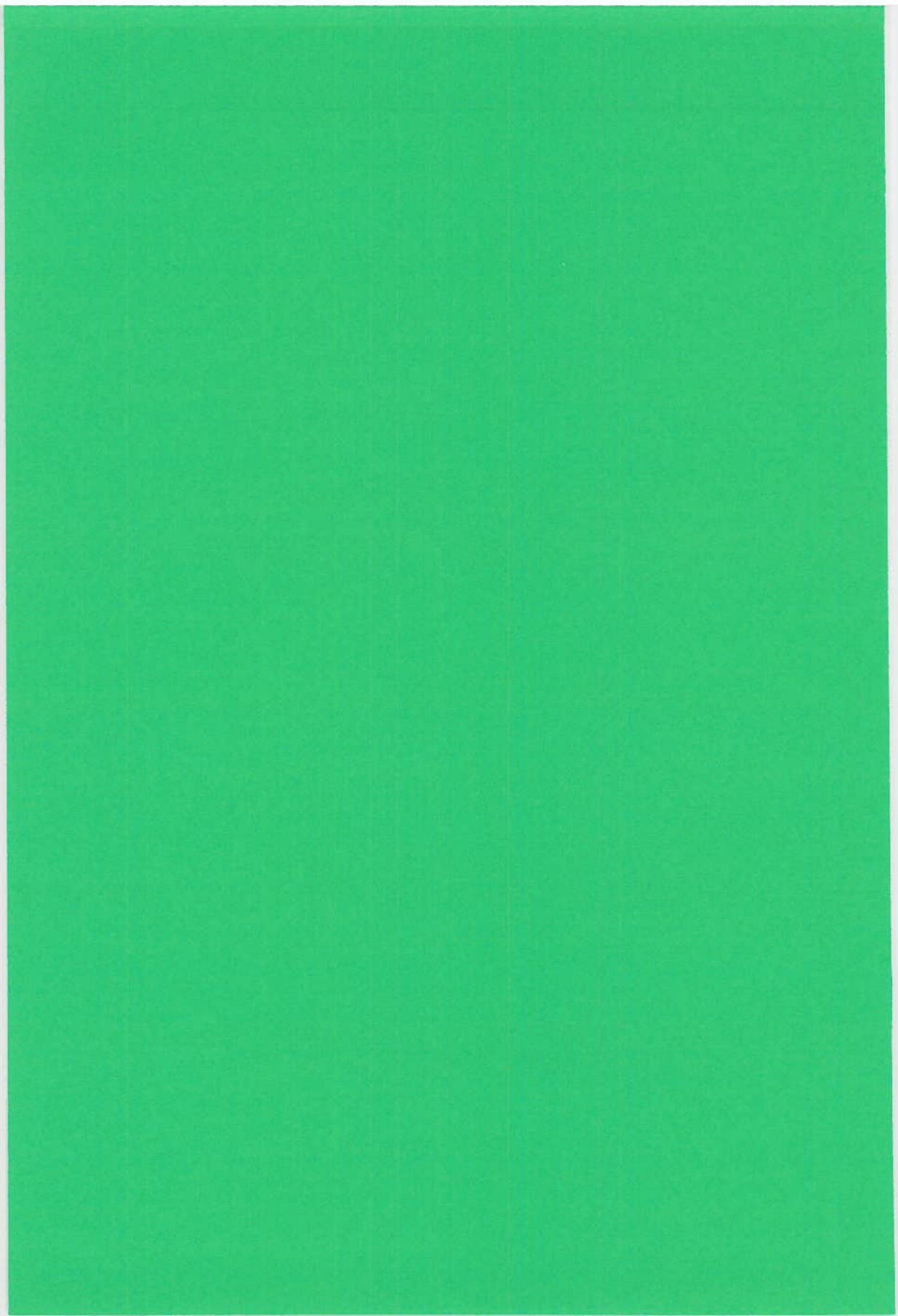
How many years in total have you taken the pill? _____years

If you have given birth, how many years did you take the pill before your first child? _____years

If you have stopped taking the pill:

Age when you stopped? _____years

Appendix C



English translation of the second questionnaire used in the health survey in Tromsø 1994/95 for subjects 70 years or older.

Based on translations by Kevin McCafferty and Anne Clancy.

TROMSØ HEALTH SURVEY
for the over 70s

The main aim of the Tromsø survey is to improve our knowledge of heart and circulatory conditions in order to aid prevention. The survey is also intended to improve our knowledge of cancer and other general conditions, such as allergies, muscle pains and nervous conditions. The ultimate aim is to gain an overview of the general health of the elderly population. We would therefore like you to answer the questions below.

This form is part of the Health Survey, which has been approved by the Norwegian Data Inspectorate and the Regional Board of Research Ethics. The answers will only be used for research purposes and will be treated in strict confidence. The information you give us may later be stored along with information from other public health registers in accordance with the rules laid down by the Data Inspectorate and the Regional Board of Research Ethics.

If you are unsure about what to answer, tick the box that you feel fits best.

The completed form should be sent to us in the enclosed pre-paid envelope.

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

National Health
Screening Service

If you do not wish to answer the questionnaire, tick the box below and return the form. Then you will not receive reminders.

I do not wish to answer the questionnaire. ☐

Date for filling in this form: Day/Month/Year

CHILDHOOD/YOUTH

What Norwegian municipality did you live in at the age of 1 year?

If you did not live in Norway, give country instead of municipality.

How was your family's financial situation while you were growing up?

- Very good ☐
- Good ☐
- Difficult ☐
- Very difficult ☐

How old were your parents when they died?

- Mother _____ years
- Father _____ years

HOME

Who do you live with?
Tick one box for each item and give the number of persons.

	YES	NO	Number
Spouse/partner	☐	☐	_____
Other persons over 18 years	☐	☐	_____
Persons under 18 years	☐	☐	_____

What type of home do you live in?

- Villa/detached house ☐
- Farm ☐
- Apartment/flat in block/terrace ☐
- Terraced/semi-detached house ☐
- Other ☐

How long have you lived in your present home? ____years

Is your home adapted to your needs? YES ☐ NO ☐
If "No", do you have problems with:

- Space ☐
- Variable temperature/too cold/too warm ☐
- Stairs ☐
- Toilet ☐
- Bath/shower ☐
- Maintenance ☐
- Other (please specify) ☐

Would you like to move into a retirement home?
YES ☐ NO ☐

PREVIOUS WORK AND FINANCIAL SITUATION

Which statement best describes the type of work you did for the last 5-10 years before you retired?

- I was mainly seated while working (*e.g., desk/assembly work*) ☐
- My work required a lot of walking (*e.g., shop assistant, housewife, teaching*) ☐
- My work required a lot of walking and lifting (*e.g., postman, nurse, construction work*) ☐
- I did heavy physical work (*e.g., forestry, heavy agricultural work, heavy construction work*) ☐

Did you do any of the following jobs (full- or part-time)?
Tick one box only for each item.

	YES	NO
Driver	☐	☐
Farmer	☐	☐
Fisherman	☐	☐

How old were you when you retired? _____ years

What kind of pension do you have?

- Basic state pension ☐
- Additional pension ☐

How is your current financial situation?

- Very good ☐
- Good ☐
- Difficult ☐
- Very difficult ☐

HEALTH AND ILLNESS

Has your state of health changed in the last year?

- Yes, it has got worse ☐
- No, unchanged ☐
- Yes, it has got better ☐

How do you feel your health is now compared to others of your age?

- Much worse ☐
- A little worse ☐
- About the same ☐
- A little better ☐
- Much better ☐

YOUR OWN ILLNESSES

Have you ever had:
Tick one box only for each item. Give your age at the time. If you have had the condition several times, how old were you last time?

	YES	NO	AGE
Hip fracture	☐	☐	_____
Wrist /forearm fracture	☐	☐	_____
Whiplash	☐	☐	_____
Injury requiring hospital admission	☐	☐	_____
Stomach ulcer	☐	☐	_____
Duodenal ulcer	☐	☐	_____
Stomach/duodenal ulcer operation	☐	☐	_____
Throat/neck surgery	☐	☐	_____

Have you ever had, or do you still have:
Tick one box only for each item.

	YES	NO
Cancer	☐	☐
Epilepsy	☐	☐
Migraine	☐	☐
Chronic bronchitis	☐	☐
Psoriasis	☐	☐
Osteoporosis	☐	☐
Fibromyalgia/fibrositis/ chronic pain syndrom	☐	☐
Psychological problems for which you have sought help	☐	☐
Thyroid disease	☐	☐
Liver disease	☐	☐
Thyroid disease	☐	☐
Liver disease	☐	☐
Recurrent urinary incontinence	☐	☐
Glaucoma	☐	☐
Cataract	☐	☐
Arthrosis (osteoarthritis)	☐	☐
Rheumatoid arthritis	☐	☐
Kidney stone	☐	☐
Appendectomy	☐	☐
Allergy and hypersensitivity		
Atopic eczema (e.g., childhood eczema)	☐	☐
Hand eczema	☐	☐
Hay fever	☐	☐
Food allergy	☐	☐
Other hypersensitivity (not allergy)	☐	☐

How many times have you had a cold, influenza (flue), diarrhea/vomiting, or similar in the last six months?

_____ times

Have you had any of these in the last two weeks?

YES ☐ NO ☐

ILLNESS IN THE FAMILY

Tick off relatives who have, or have ever had, any of the following conditions:
Tick "None" for conditions which none of your relatives have had.

	Mother	Father	Brother	Sister	Child	None
Stroke or brain haemorrhage	☐	☐	☐	☐	☐	☐
Myocardial infarction before age 60	☐	☐	☐	☐	☐	☐
Cancer	☐	☐	☐	☐	☐	☐
Hypertension	☐	☐	☐	☐	☐	☐
Asthma	☐	☐	☐	☐	☐	☐
Osteoporosis	☐	☐	☐	☐	☐	☐
Arthrosis (osteoarthritis)	☐	☐	☐	☐	☐	☐
Psychological problems	☐	☐	☐	☐	☐	☐
Dementia	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐	☐	☐
-age when they got diabetes	___	___	___	___	___	___

SYMPTOMS

	YES	NO
Do you cough daily for periods of the year?	☐	☐
If "Yes":		
Is your cough productive?	☐	☐
Have you had this kind of cough for as long as 3 months in each of the last two years?	☐	☐
Have you had periods of wheezing in your chest?	☐	☐
If "Yes", has this occurred: *Tick one box only for each item.*		
At night	☐	☐
In connection with respiratory infections	☐	☐
In connection with physical exertion	☐	☐
In connection with very cold weather	☐	☐
Have you noticed sudden changes in your pulse or heart rhythm in the last year?	☐	☐
Have you lost weight in the last year?	☐	☐

If "Yes":
How many kilograms? _____ kg

How often do you suffer from sleeplessness?

- Never, or just a few times a year ☐
- 1-2 times a month ☐
- Approximately once a week ☐
- More than once a week ☐

If you suffer from periods of sleeplessness, what times of the year does it affect you most?

- No particular time of year ☐
- Especially during the 'dark winter months' ☐
- Especially during the midnight sun period ☐
- Especially in spring and autumn ☐

Do you usually take a nap during the day? YES ☐ NO ☐

Do you feel that you normally get enough sleep? YES ☐ NO ☐

	No	A little	A lot
Do you suffer from:	☐	☐	☐
Dizziness	☐	☐	☐
Poor memory	☐	☐	☐
Lack of energy	☐	☐	☐
Constipation	☐	☐	☐

Does the thought of getting a serious illness ever worry you?

- Not at all ☐
- Only a little ☐
- Some ☐
- Very much ☐

BODILY FUNCTIONS

Can you manage the following everyday activities on your own without help from others?

	Yes	With some help	No
Walking indoors on one level	☐	☐	☐
Walking up/down stairs	☐	☐	☐
Walking outdoors	☐	☐	☐
Walking approx. 500 metres	☐	☐	☐
Going to the toilet	☐	☐	☐
Washing yourself	☐	☐	☐
Taking a bath/shower	☐	☐	☐
Dressing and undressing	☐	☐	☐
Getting in and out of bed	☐	☐	☐
Eating meals	☐	☐	☐
Cooking ☐	☐	☐	
Doing light housework (e.g., washing up)	☐	☐	☐
Doing heavier housework (e.g., cleaning floors)	☐	☐	☐
Going shopping	☐	☐	☐
Taking the bus	☐	☐	☐

	Yes	With difficulty	No
Can you hear normal speech (if necessary with a hearing aid)?	☐	☐	☐
Can you read (if necessary with glasses)?	☐	☐	☐

Are you dependent on any of the following aids?

	Yes	No
Walking stick	☐	☐
Crutches	☐	☐
Walking frame/Zimmer frame	☐	☐
Wheelchair	☐	☐
Hearing aid	☐	☐
Safety alarm device	☐	☐

USE OF HEALTH SERVICES

How many visits have you made during the past year due to your own health or illness:

Tick 0 if you have not had such contact

	Number of times the past year
To a general practitioner (GP)/ emergency GP	____
Psychologist or psychiatrist	____
Other medical specialist (not at a hospital)	____
Hospital out-patient clinic	____
Hospital admission	____
Physiotherapist	____
Chiropractor	____
Acupuncturist	____
Dentist	____
Chiropodist	____
Alternative medical practitioner (homoeopath, foot zone therapist, etc.)	____
Healer, Faith healer, clairvoyant	____

	Yes	No
Do you have domestic help?		
Private	☐	☐
Municipal	☐	☐
Do you receive services from the district nurse?	☐	☐

Are you pleased with the health care and home assistance services your municipality supplies?

	Yes	No	Don't know
Assigned family GP	☐	☐	☐
District nurse	☐	☐	☐
Home assistance	☐	☐	☐

Do you feel confident that you can receive the health care and home assistance you require if you need it?

- Confident ☐
- Not confident ☐
- Very unsure ☐
- Don't know ☐

MEDICATION AND DIETARY SUPPLEMENTS

Have you for any length of time in the past year used any of the following medicines every day or almost daily? Indicate how many months you used them for.

Write 0 for items you have not used.

Medication:

Painkillers	_____ mths
Sleeping pills	_____ mths
Tranquillizers	_____ mths
Antidepressants	_____ mths
Allergy drugs	_____ mths
Asthma drugs	_____ mths
Heart medicine (not blood pressure)	_____ mths
Insulin	_____ mths
Diabetes tablets	_____ mths
Thyroxin tablets (for metabolic disorder)	_____ mths
Cortisone tablets	_____ mths
Remedies for constipation	_____ mths

Dietary supplements:

Iron tablets	_____ mths
Vitamin D supplement	_____ mths
Other vitamin supplements	_____ mths
Calcium tablets or bonemeal	_____ mths
Cod liver oil or fish oil capsules	_____ mths

FAMILY AND FRIENDS

Do you have close relatives who can give you help and support when you need it? Yes ☐ No ☐

If "Yes", who can give you help?

- Spouse/partner ☐
- Children ☐
- Others ☐

How many good friends do you have whom you can talk confidentially with and who give you help when you need it?

_____good friends

Do not count people you live with, but do include other relatives!

Do you feel you have enough good friends? Yes ☐ No ☐

Do you feel that you belong to a community or group of people who can depend on each other and who feel committed to each other (e.g., a political party, religious group, relatives, neighbours, work place, or organisation)?

- Strong sense of belonging ☐
- Some sense of belonging ☐
- Not sure ☐
- Little or no sense of belonging ☐

How often do you normally take part in organised gatherings, e.g., sewing circles, sports clubs, political meetings, religious or other associations?

- Never, or just a few times a year ☐
- 1-2 times a month ☐
- Approximately once a week ☐
- More than once a week ☐

DIET

How many meals a day do you normally eat (dinner and smaller meals)? _____ Number

How many times a week do you eat a hot dinner? _____ Number

What kind of bread (bought or home-made) do you usually eat? *Tick one or two boxes!*

The bread I eat is most similar to

- White bread ☐
- Light textured brown bread ☐
- Ordinary brown bread ☐
- Coarse brown bread ☐
- Crisp bread ☐

What kind of fat is normally used in **cooking** (not on the bread) in your home?

- Creamery butter ☐
- Hard margarine ☐
- Soft margarine ☐
- Butter/margarine blend ☐
- Oils ☐

How much (in **number** of glasses, cups, potatoes or slices) do you usually eat or drink **daily** of the following foodstuffs? *Tick one box for each foodstuff.*

	0	Less than 1	1-2	3-4	5-6	6-
Milk of all types (glasses)	☐	☐	☐	☐	☐	☐
Orange juice (glasses)	☐	☐	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐	☐	☐
Slices of bread in total (incl. crispbread)	☐	☐	☐	☐	☐	☐
Slices of bread with fish (e.g., mackerel in tomato sauce)	☐	☐	☐	☐	☐	☐
- cheese (e.g., Norwegia)	☐	☐	☐	☐	☐	☐
- smoked cod caviar	☐	☐	☐	☐	☐	☐

How many **times per week** do you normally eat the following foodstuffs? *Tick a box for all foodstuffs listed.*

	Never	Less than 1	1	2-3	4-5	Roughly every day
Yoghurt	☐	☐	☐	☐	☐	☐
Boiled or fried egg	☐	☐	☐	☐	☐	☐
Breakfast cereal/ oat meal, etc.	☐	☐	☐	☐	☐	☐
For dinner						
- meat	☐	☐	☐	☐	☐	☐
- fat fish (e.g., salmon/ redfish)	☐	☐	☐	☐	☐	☐
- lean fish (e.g., cod)						
- vegetables (raw or cooked)	☐	☐	☐	☐	☐	☐
Carrots (raw or cooked)	☐	☐	☐	☐	☐	☐
Cauliflower/cabbage/broccoli	☐	☐	☐	☐	☐	☐
Apples/pears	☐	☐	☐	☐	☐	☐
Oranges, mandarines, etc.	☐	☐	☐	☐	☐	☐

WELL BEING

How content do you generally feel with growing old?

- Good ☐
- Quite good ☐
- Up and down ☐
- Bad ☐

What is your view of the future?

- Bright ☐
- Not too bad ☐
- Quite worried ☐
- Dark ☐

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

How old were you when you had your first menstruation? _____ years

How old were you when you stopped having menstruations? _____ years

PREGNANCY

How many children have you given birth to? _____children

If you have given birth, fill out for each child the year of birth and approximately how many months you breastfed the child. If you have given birth to more than 6 children, note their birthyear and number of months you breastfed at the space provided below for comments.

Child:	Year of birth:	Number of months breastfed:
1	_____	_____ months
2	_____	_____ months
3	_____	_____ months
4	_____	_____ months
5	_____	_____ months
6	_____	_____ months

During pregnancy, have you had high blood pressure and/or proteinuria? Yes ☐ No ☐

If "Yes", during which pregnancy?

	Pregnancy First	Later
High blood pressure	☐	☐
Proteinuria	☐	☐

OESTROGEN

Do you, or have you ever used oestrogen:

	Now	Used to	Never
Tablets or patches	☐	☐	☐
Cream or suppositories	☐	☐	☐

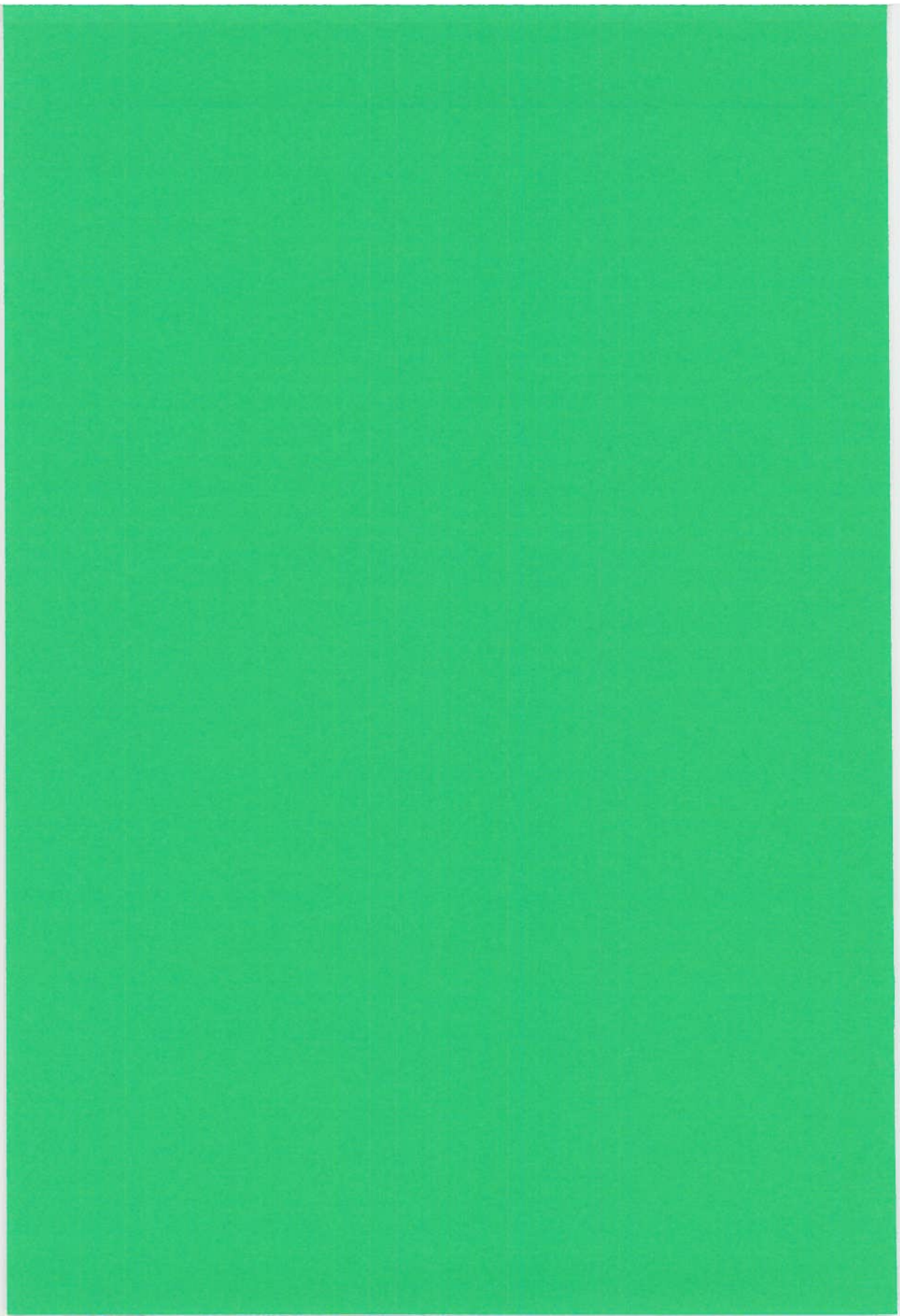
If you use oestrogen, what brand do you currently use?

_____

Your comments:

Thank you for helping us! Remember to post the form today! **Tromsø Health Survey**

Appendix D



Fracture registration *(protocol)*

Information from the radiographic descriptions was registered in a Microsoft Access file.

Description of the variables used in the fracture registration process (2002):

Akt. Rekv.nr.: The referral number in the archive of the department of radiology.

Navn: The name of the patient.

Usdag: The date of examination.

Side: The side of the examination, right (Dex) or left (Sin).

Brudd side: The side of the fracture, Dex or Sin.

If it wasn't match with the fracture site in the X-ray report, that will be mentioned in the comment bar.

Lokal: Code for the location of the fracture. See codes below.

-albue
-Ankel
-ansikt
-bekken
-cervicalcol.
-clavikula
-finger
-fotrot
-Håndledd
-håndrot
-hofte
-kne
-lårskaft
-legg
-lumbalcol.
-nese
-overarm
-ribben
-scapula
-skulder
-sternum
-tær
-thorocalcol.
-underarm

Utvkl : Code for the x-ray picture purpose. See codes description below.

Forbedring:
Forverring:
Gamle forandringer: Old changes.
Kontroll: Control picture.
Mistenkt:
Opr. Innlagt rtg. Tett mat.:
Postop. Forandringer:
Progresjon: Progression.
Regresjon: Regression.
Repoert:
Sekvele:

Brudd etter 94: If the fracture occurred after 1994 (ja/ yes) or before 1994 (nei/ no).

All fractures examined in 1994-95 with uncertain dates of fracture were reported as (Nei); not after 1994.

Sikkert Brudd:

Ja: the fracture was confirmed in the X-ray report.

Nei: No fracture in the X-ray report. The fracture was not certain, not confirmed in the X-ray report or been described as suspected, probable or possible fracture.

Brudd #: The number of fractures for the same person by the day of examination.

- Fractures of more than one bone at the same site or location (description of locations below) were counted as one fracture, for example Tib/Fib or Ulna/Rad.
- Refracture or a new fracture at the same site was counted as a new fracture when it occurred after the first one (not at the same day).
- If more than one fracture happened at the same time at different sites, for example in a car accident, the number of fractures at the time of examination was counted as the total number of fractures.

- If there was a fracture, which mentioned only in the X-ray report, it will be counted in the total number of fractures and its site will be stated in the comment bar.
- Vertebral compression fractures were counted as one fracture if they were at the same vertebral segment (ex. Lumber vertebrae). Each involved vertebra was mentioned in the comment bar.
- If a new vertebra within the same vertebral segment developed compression for the first time, it was counted as a new fracture in addition to the old compression counted before.
- Increase in the compression of one or more vertebrae wasn't counted as a new fracture.
- (21-03-02) start mentioning which bones were involved in finger, toe, hand root, foot root, carpal, tarsal and rib bones in the comment bar.

For finger and toe, we reported which digit and phalange were fractured

(ex. 1st, 3rd phal. = first digit, distal phalange).

For hand root, foot root, carpal, tarsal and rib, we reported the number of bones fractured.

Brudd lok. Describes the location of the fracture as one of the following sites:

Albu fx flere: Fracture of the elbow: involvement of more than two bones around the elbow.

Annet*: any other fracture not mentioned in the list below.

Ansikts fx : Fracture of the face: fracture of any bone of the face bones.

Bekken fx.: Fractures of the pelvis.

Cervicalcol : Fracture of the cervical vertebrae: wedge compression fracture of the vertebral body, fracture of the atlas, fracture of the dens of the axis and fracture of a spinous process.

Clavicula fx : Fracture of the clavicle.

Coccyx fx : Fracture of the coccyx.

Femur dist : Fracture of the distal part of the femur: supracondylar fracture or fracture of the femoral condyles.

Femur skaft : Fracture of the shaft of the femur.

Femur trock : Fracture of the femoral trochanteric region: any fracture that lies approximately between the greater and the lesser trochanter.

Femurcollum : Fracture of the neck of the femur.

Fibula dist.: Fracture of the distal part of the fibula, isolated fracture of the lateral malleolus.

Fibula prox.: Fracture of the proximal part of the fibula.

Fibula skaft : Fracture of the shaft of the fibula

Finger fx.: Fracture of the phalanges of the fingers.

Håndrots fx.: Fracture of the carpal bones.

Humerus dist : Fracture of the distal part of the humerus: fracture of the epicondyle, the condyle or supracondylar fracture.

Humerus prox.: Fracture of the proximal part of the humerus: fracture of the neck or fracture of the greater tuberosity.

Humerus skaft : Fracture of the shaft of the humerus.

Kne fx flere : Fracture about the knee involving more than one bone, the femoral condyles, the patella or the tibial condyles.

Lumbalcol.: Fracture of the lumbar vertebrae: wedge fracture compression of the vertebral body

Metacarp. fx.: Fracture of the metacarpal bones.

Metatars. fx.: Fracture of the metatarsal bones.

Radius dist.: Fracture of the distal part of the radius: fracture of the lower end of the radius (Colles's fracture).

Radius prox.: Fracture of the proximal part of the radius: the head of the radius.

Radius skaft : Fracture of the shaft of the radius.

Ribben : Fracture of the ribs

Sacrum fx.: Fracture of the sacrum.

Skulderblad fx.: Fracture of the scapula.

Sternum : Fracture of the sternum.

Tå fx.: Fracture of the phalanges of the toes.

Thoracalcol. : Fracture of the thoracic vertebrae: wedge fracture compression of the vertebral body.

Tib/Fib skaft : Fracture of the shafts of the tibia and fibula.

Tibia dist : Fracture of the distal part of the tibia, isolated fracture of the medial malleolus.

Tibia prox.: Fracture of the proximal part of the tibia, the condyles of the tibia.

Tibia skaft : Fracture of the shaft of the tibia.

Ulna dist.: Fracture of the distal part of the ulna.

Ulna prox : Fracture of the proximal part of the ulna: fracture of the olecranon process, the coronoid process and the upper most third of ulna.

Ulna skaft : Fracture of the shaft of the ulna.

Ulna/Radius skaft : Fracture of the shafts of the forearm bones: both ulna and radius.

* Patella fractures were reported as (Annet); others, and explained in the comment bar.

Energi: Description of the energy (the causative injury) when the fracture has occurred.

Usikker: No description for the energy in the medical report: fall.

Lav: law-energy fracture, the causative injury was slight: stumble, slip. At the level of the ground, the standing height, with no additional force.

Hoy: high-energy fracture, the causative injury was strong: traffic accident, fall from the stairs or any level above the ground level.

Patologi: the cause of fracture was a pathological disease in the bone, metastasis.

Sportsulykke: the fracture happened while practicing any kind of sport.

Snø/is: Involvement of snow or ice in the fracture mechanism.

Ukjent: there was no mention of the fracture mechanism or there was snow or ice in it.

Ja: snow or ice was mentioned in the medical report in the description of the fracture; slippery surface, slid on ice, skiing, skating, shuffling snow, etc.

Nei: the medical report described the mechanism of fracture inside the house (bedroom, kitchen, bathroom, etc), on the floor, on the street.

ISM SKRIFTSERIE - FØR UTGITT:

1. Bidrag til belysning av medisinske og sosiale forhold i Finnmark fylke, med særlig vekt på forholdene blant finskættede i Sør-Varanger kommune.
Av Anders Forsdahl, 1976. (nytt opplag 1990)

2. Sunnhetstilstanden, hygieniske og sosiale forhold i Sør-Varanger kommune 1869-1975 belyst ved medisinal-beretningene.
Av Anders Forsdahl, 1977.

3. Hjerte-karundersøkelsen i Finnmark - et eksempel på en populasjonsundersøkelse rettet mot cardiovasculære sykdommer. Beskrivelse og analyse av etterundersøkelsesgruppen.
Av Jan-Ivar Kvamme og Trond Haider, 1979.

4. D. The Tromsø Heart Study: Population studies of coronary risk factors with special emphasis on high density lipoprotein and the family occurrence of myocardial infarction.
Av Olav Helge Førde og Dag Steinar Thelle, 1979.

5. D. Reformer i distriktshelsetjenesten III: Hypertensjon i distriktshelsetjenesten.
Av Jan-Ivar Kvamme, 1980.

6. Til professor Knut Westlund på hans 60-års dag, 1983.

7.* Blodtrykksovervåkning og blodtrykksmåling.
Av Jan-Ivar Kvamme, Bernt Nesje og Anders Forsdahl, 1983.

8.* Merkesteiner i norsk medisin reist av allmennpraktikere - og enkelte utdrag av medisinalberetninger av kulturhistorisk verdi.
Av Anders Forsdahl, 1984.

9. "Balsfjordsystemet." EDB-basert journal, arkiv og statistikksystem for primærhelsetjenesten.
Av Toralf Hasvold, 1984.

10. D. Tvunget psykisk helsevern i Norge. Rettsikkerheten ved slikt helsevern med særlig vurdering av kontrollkommisjonsordningen.
Av Georg Høyer, 1986.

11. D. The use of self-administered questionnaires about food habits. Relationships with risk factors for coronary heart disease and associations between coffee drinking and mortality and cancer incidence.
Av Bjarne Koster Jacobsen, 1988.

12.* Helse og ulikhet. Vi trenger et handlingsprogram for Finnmark.
Av Anders Forsdahl, Atle Svendal, Aslak Syse og Dag Thelle, 1989.

13. D. Health education and self-care in dentistry - surveys and interventions.
Av Anne Johanne Søgaard, 1989.

14. Helsekontroller i praksis. Erfaringer fra prosjektet helsekontroller i Troms 1983-1985.
Av Harald Siem og Arild Johansen, 1989.

15. Til Anders Forsdahls 60-års dag, 1990.

16. D. Diagnosis of cancer in general practice. A study of delay problems and warning signals of cancer, with implications for public cancer information and for cancer diagnostic strategies in general practice.
Av Knut Holtedahl, 1991.

17. D. The Tromsø Survey. The family intervention study. Feasibility of using a family approach to intervention on coronary heart disease. The effect of lifestyle intervention of coronary risk factors.
Av Synnøve Fønnebø Knutsen, 1991.

18. Helhetsforståelse og kommunikasjon. Filosofi for klinikere.
Av Åge Wifstad, 1991.

19. D. Factors affecting self-evaluated general health status - and the use of professional health care services.
Av Knut Fylkesnes, 1991.

20. D. Serum gamma-glutamyltransferase: Population determinants and diagnostic characteristics in relation to intervention on risk drinkers.
Av Odd Nilssen, 1992.

21. D. The Healthy Faith. Pregnancy outcome, risk of disease, cancer morbidity and mortality in Norwegian Seventh-Day-Adventists.
Av Vinjar Fønnebø, 1992.

22. D. Aspects of breast and cervical cancer screening.
Av Inger Torhild Gram, 1992.

23. D. Population studies on dyspepsia and peptic ulcer disease: Occurrence, aetiology, and diagnosis. From The Tromsø Heart Study and The Sørreisa Gastrointestinal Disorder Studie.
Av Roar Johnsen, 1992.

24. D. Diagnosis of pneumonia in adults in general practice.
Av Hasse Melbye, 1992.

25. D. Relationship between hemodynamics and blood lipids in population surveys, and effects of n-3 fatty acids.
Av Kaare Bønaa, 1992.

26. D. Risk factors for, and 13-year mortality from cardiovascular disease by socioeconomic status. A study of 44690 men and 17540 women, ages 40-49. **Av Hanne Thürmer, 1993.**

27. Utdrag av medisinalberetninger fra Sulitjelma 1891-1990. **Av Anders Forsdahl, 1993.**

28. Helse, livsstil og levekår i Finnmark. Resultater fra Hjerte-karundersøkelsen i 1987-88. Finnmark III. **Av Knut Westlund og Anne Johanne Søgaard, 1993.**

29. D. Patterns and predictors of drug use. A pharmacoepidemiologic study, linking the analgesic drug prescriptions to a population health survey in Tromsø, Norway. **Av Anne Elise Eggen, 1994.**

30. D. ECG in health and disease. ECG findings in relation to CHD risk factors, constitutional variables and 16-year mortality in 2990 asymptomatic Oslo men aged 40-49 years in 1972. **Av Per G. Lund-Larsen, 1994.**

31. D. Arrhythmia, electrocardiographic signs, and physical activity in relation to coronary heart risk factors and disease. The Tromsø Study. **Av Maja-Lisa Løchen, 1995.**

32. D. The Military service: mental distress and changes in health behaviours among Norwegian army conscript. **Av Edvin Schei, 1995.**

33. D. The Harstad injury prevention study: Hospital-based injury recording and community-based intervention. **Av Børge Ytterstad, 1995.**

34.* D. Vilkår for begrepsdannelse og praksis i psykiatri. En filosofisk undersøkelse. **Av Åge Wifstad, 1996.** (utgitt Tano Aschehoug forlag 1997)

35. Dialog og refleksjon. Festskrift til professor Tom Andersen på hans 60-års dag, 1996.

36. D. Factors affecting doctors´ decision making. **Av Ivar Sønbø Kristiansen, 1996.**

37. D. The Sørreisa gastrointestinal disorder study. Dyspepsia, peptic ulcer and endoscopic findings in a population. **Av Bjørn Bernersen, 1996.**

38. D. Headache and neck or shoulder pain. An analysis of musculoskeletal problems in three comprehensive population studies in Northern Norway. **Av Toralf Hasvold, 1996.**

39. Senfølger av kjernefysiske prøvespreninger på øygruppen Novaya Semlya i perioden 1955 til 1962. Rapport etter programmet "Liv". Arkangelsk 1994.
Av A.V. Tkatchev, L.K. Dobrodeeva, A.I. Isaev, T.S. Podjakova, 1996.

40. Helse og livskvalitet på 78 grader nord. Rapport fra en befolkningsstudie på Svalbard høsten 1988. **Av Helge Schirmer, Georg Høyer, Odd Nilssen, Tormod Brenn og Siri Steine, 1997.**

41.* D. Physical activity and risk of cancer. A population based cohort study including prostate, testicular, colorectal, lung and breast cancer.
Av Inger Thune, 1997.

42. The Norwegian - Russian Health Study 1994/95. A cross-sectional study of pollution and health in the border area.
Av Tone Smith-Sivertsen, Valeri Tchachtchine, Eiliv Lund, Tor Norseth, Vladimir Bykov, 1997.

43. D. Use of alternative medicine by Norwegian cancer patients
Av Terje Risberg, 1998.

44 D. Incidence of and risk factors for myocardial infarction, stroke, and diabetes mellitus in a general population. The Finnmark Study 1974-1989.
Av Inger Njølstad, 1998.

45. D. General practitioner hospitals: Use and usefulness. A study from Finnmark County in North Norway.
Av Ivar Aaraas, 1998.

45B Sykestuer i Finnmark. En studie av bruk og nytteverdi.
Av Ivar Aaraas, 1998.

46. D. No går det på helsa laus. Helse, sykdom og risiko for sykdom i to nord-norske kystsamfunn.
Av Jorid Andersen, 1998.

47. D. The Tromsø Study: Risk factors for non-vertebral fractures in a middle-aged population.
Av Ragnar Martin Joakimsen, 1999.

48. D. The potential for reducing inappropriate hospital admissions: A study of health benefits and costs in a department of internal medicine.
Av Bjørn Odvar Eriksen, 1999.

49. D. Echocardiographic screening in a general population. Normal distribution of echocardiographic measurements and their relation to cardiovascular risk factors and disease. The Tromsø Study.
Av **Henrik Schirmer, 2000.**

50. D. Environmental and occupational exposure, life-style factors and pregnancy outcome in artic and subartic populations of Norway and Russia.
Av Jon Øyvind Odland, 2000.

50B Окружающая и профессиональная экспозиция, факторы стиля жизни и исход беременности у населения арктической и субарктической частей Норвегии и России
Юн Ойвин Удлан 2000

51. D. A population based study on coronary heart disease in families. The Finnmark Study 1974-1989.
Av Tormod Brenn, 2000.

52 D. Ultrasound assessed carotid atherosclerosis in a general population. The Tromsø Study.
Av Oddmund Joakimsen, 2000.

53. D. Risk factors for carotid intima-media thickness in a general population. The Tromsø Study 1979-1994.
Av Eva Stensland-Bugge, 2000.

54. D. The South Asian cataract management study.
Av Torkel Snellingen, 2000.

55. D. Air pollution and health in the Norwegian-Russian border area.
Av Tone Smith-Sivertsen, 2000.

56. D. Interpretation of forearm bone mineral density. The Tromsø Study.
Av Gro K. Rosvold Berntsen, 2000.

57. D. Individual fatty acids and cardiovascular risk factors.
Av Sameline Grimsgaard, 2001.

58. Finnmarkundersøkelsene
Av Anders Forsdahl, Fylkesnes K, Hermansen R, Lund E, Lupton B, Selmer R, Straume E, 2001.

59. D. Dietary data in the Norwegian women and cancer study. Validation and analyses of health related aspects.
Av Anette Hjartåker, 2001.

60. D. The stenotic carotid artery plaque. Prevalence, risk factors and relations to clinical disease. The Tromsø Study.
Av Ellisiv B. Mathiesen, 2001.

61. D. Studies in perinatal care from a sparsely populated area.
Av Jan Holt, 2001.

62. D. Fragile bones in patients with stroke? Bone mineral density in acute stroke patients and changes during one year of follow up.
Av Lone Jørgensen, 2001.

63. D. Psychiatric morbidity and mortality in northern Norway in the era of deinstitutionalisation. A psyhiatric case register study.
Av Vidje Hansen, 2001.

64. D. Ill health in two contrasting countries.
Av Tom Andersen, 1978/2002.

65. D. Longitudinal analyses of cardiovascular risk factors.
Av Tom Wilsgaard, 2002.

66. Helseundersøkelsen i Arkangelsk 2000.
Av Odd Nilssen, Alexei Kalinin, Tormod Brenn, Maria Averina et al.,2003.

67. D. Bio-psycho-social aspects of severe multiple trauma.
Av Audny G. W. Anke, 2003.

68. D. Persistent organic pollutants in human plasma from inhabitants of the artic.
Av Torkjel Manning Sandanger, 2003.

69. D. Aspects of women's health in relation to use of hormonal contraceptives and pattern of child bearing.
Av Merethe Kunmle, 2003.

70. Pasienterfaringer i primærlegetjenesten før og etter fastlegereformen.
Av Olaug Lian, 2003.

71. D. Vitamin D security in northern Norway in relation to marine food traditions.
Av Magritt Brustad, 2004.

72. D. Intervensjonsstudien i Finnmark. Evaluering av lokalsamfunns basert hjerte- og kar forebygging i kystkommunene Båtsfjord og Nordkapp.
Av Beate Lupton, 2004.

73. D. Environmental factors, metabolic profile, hormones and breast and endiometrial cancer risk.
Av Anne-Sofie Furberg, 2004.

74. D. Det skapende mellomrommet i møtet mellom pasient og lege.
Av Eli Berg, 2004.

75. Kreftregisteret i Arkhangelsk oblast i nordvest Russland. Med en sammenligning av kreftforekomst i Arkhangelsk oblast og Norge 1993 - 2001.
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