Arnulf Langhammer

Respiratory symptoms, lung function, and bone mineral density in a comprehensive population survey

The Nord-Trøndelag Health Study 1995-97

The Bronchial Obstruction in
Nord- Trøndelag Study

URN:NBN:no-3454

HUNT Research Centre, Verdal
Department of Public Health
and General Practice
Faculty of Medicine
Norwegian University of Science
and Technology, Trondheim

ISSN nr: 1503-3465
Thesis no. 232

Printed by Tapir Uttrykk

The picture at the front page illustrates a very old equipment for studies of the respiration, having been described in Jacobo Friderico Below's dissertation in November 1700. Studying breathing through a tube across a wall lead to the discovery that the flow of air into the lungs in inspiration, is a result of subatmospheric pressure in the airways, and not a result of some kind of vibration of the air, as previously believed.

URN:NBN:no-3454

Contents

Abstract

Background

The prevalence of respiratory symptoms and diseases, like asthma and chronic obstructive pulmonary disease (COPD), seem to have increased during the last decades. The reason for the increase in asthma related symptoms and allergy is uncertain. Some, but not all, of this increase might be ascribed to lowered threshold for use of the diagnosis by medical doctors, change in diagnostic criteria, and increased awareness of symptoms in the population. Studies have indicated that increased prevalence might be explained by a reduction during the last decades in exposure to environmental factors in infancy. These factors are supposed to stimulate the change from Th-2 to TH-1 helper cells (hygiene hypothesis), but even low level of allergen exposure seems to contribute to increase in risk for allergy. The increase in COPD in developed countries is closely related to the smoking pattern during the last two to four decades, and the increase, therefore, is mainly seen in women. Further, studies have indicated that women are more vulnerable for the deleterious effects of tobacco smoking than men are; if this is true the current smoking pattern with increasing female smoking, is worrying.

Spirometry is an important tool in diagnosing and follow-up of obstructive lung diseases, and the parameters are compared and expressed in percent of values matched for race, sex, age and height. The most commonly used reference values for expiratory parameters in Norway have been those published by the European Community for Coal and Steel (ECCS). Many studies have indicated that these underestimate the level of parameters as FEV_1 and FVC. Updated reference values for populations have been warranted in order to increase the validity of spirometry.

Inhaled corticosteroids are the cornerstone in the treatment of persistent asthma, and are even widely used in COPD. Because of well-documented negative side effects on bone by oral

corticosteroids, there is concern about such an effect even in use of the inhaled forms. Most studies have been performed in hospital settings, and real life studies in unselected populations have scarcely been performed.

Aims

- To estimate the prevalence of respiratory symptoms, obstructive lung diseases, and their risk factors in a general population with focus on sex differences in vulnerability to tobacco smoking.
- To develop prediction equations for expiratory flow volume spirometry
- To study the associations between use of inhaled corticosteroids and bone mineral density in a retrospective cohort study

Subjects

From August 1995 to June 1997 all residents aged 20 years and more (92,936), of the Nord-Trøndelag County, Norway, were invited to participate in the Nord-Trøndelag Health Study. Among 65.225 participants, a 5 % randomly selected sample and everyone answering positive to questions on asthma or asthma related symptoms, were invited to phase 1 of the BONT study.

Methods

The participants of the HUNT study answered comprehensive questionnaires on demographics, life style, risk factors, symptoms and diseases. Those selected to the BONT study additionally answered a more disease specific questionnaire, a structured interview with focus on asthma-related symptoms and use of medication, and performed flow volume spirometry and bone densitometry of the forearm.

Results and conclusions

The prevalence of respiratory symptoms in this county was higher than previously reported in Norway, but similar to results from more recent studies from Northern Europe. Tobacco smoking was strongly associated with higher prevalence of respiratory symptoms and lower lung function. Women had a larger relative reduction in lung function parameter as FEV_1 by smoking burden than men. However, this did not fully explain the higher increase in proportion of women reporting respiratory symptoms with increasing smoking burden compared to men. This might indicate that women are more vulnerable to the deleterious effects of tobacco smoking than men. The damage could be localised in the small airways, which is not reflected by spirometric parameters as FEV_1 and FVC. The lung damage adds to a long lists of smoking related health problems, and increased vulnerability in women combined with increasing prevalence of female smokers, warrant sex specific anti-smoking strategies.

Prediction equations for expiratory flow volume parameters were developed. The study confirms an underestimation of FEV_1 and FVC by the ECCS prediction equations, and the mean values are in crude agreement with reports from other recent studies. The use of appropriate reference values increases the sensitivity for discovering obstructive lung disease by spirometry. We, therefore, recommend selection of the most recent and population specific reference values for use in clinical practice; for this region, the present set should be the most relevant.

Users of inhaled corticosteroids had about 2 % lower BMD compared to never users. The lack of dose response relationship between ICS and BMD in this study might be due to a narrow dose range, or indicate that other characteristics of the patient group contribute to the difference. The doses of ICS used in this population were mainly moderate and are more in agreement with current treatment guidelines than guidelines published prior to the study.

Definitions and abbreviations

Definitions

Pack-years:	The number of years of daily smoking multiplied by the number of cigarettes smoked daily divided by twenty
Sensitivity:	The proportion of individuals testing positive if the disease is truly present
Specificity:	The proportion of individuals testing negative if the disease is truly absent
T-score:	The number of SD above or below the mean bone mineral density of healthy persons of same sex aged 25-45 years.
Team 1:	The team of technicians covering the 5 largest municipalities in Nord-Trøndelag; Stjørdal, Levanger, Verdal, Steinkjer and Namsos
Team 2:	The team of technicians covering the 19 smaller municipalities
Z-score:	The number of SD above or below the mean BMD of healthy persons at the same age and sex

Abbreviations

A:	Age
AHR:	Airway hyperresponsiveness
ATS:	American Thoracic Society
ATS-DLD:	American Thoracic Society + Division of Lung Diseases of the National Heart and Lung Institute
AUC:	Area under curve
BDP:	Beclomethasone dipropionate
BHR:	Bronchial hyperresponsiveness
BM:	Biochemical bone markers

BMC:	Bone mineral content
BMD:	Bone mineral density
BMI:	Body mass index
BMRC:	British Medical Research Council
BONT:	The Bronchial Obstruction in Nord-Trøndelag Study
BUD:	Budesonide
CS:	Corticosteroid
CSS:	Cross sectional study
DXA:	Dual-energy x-ray absorptiometry
ECCS:	The European Community for Coal and Steel
ECRHS:	European Community Respiratory Health Survey
ERS:	European Respiratory Society
FEF_{25-75}	Forced mid-expiratory flow
$FEV_{1:}$	Forced expiratory volume in one second
FP:	Fluticasone propionate
FVC:	Forced vital capacity
GINA:	Global Initiative for Asthma
GOLD:	Global Initiative for Chronic Obstructive Lung Disease
GPRD:	The general practice research database study
H:	Height
HUNT 1:	The Nord-Trøndelag Health Study 1984-86
HUNT 2:	The Nord-Trøndelag Health Study 1995-97
HUNT 3:	The Nord-Trøndelag Health Study planned 2006-07
ICS:	Inhaled corticosteroid
IUATLD:	International Union Against Tuberculosis and Lung Disease

LLN:	Lower limit of normal
LN:	Natural logarithm
LS:	Longitudinal study
MD:	Medical doctor
NTNU:	Norwegian University of Science and Technology
OCS:	Oral corticosteroid
PEF:	Peak expiratory flow
QCT:	Quantitative computed tomography
RCT:	Random clinical trial
SD:	Standard deviation
SRH:	Self-rated health
SXA:	Single x-ray absorptiometry
TCA:	Triamcinolone Acetate
TLC:	Total lung capacity
WHO:	World Health Organisation

Acknowledgements

The Nord-Trøndelag Health Study (HUNT) was a collaboration between The HUNT Research Centre, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), The National Institute of Public Health, The National Health Screening Service of Norway and Nord-Trøndelag County Council. The BONT Study was possible to perform thanks to this collaboration and the contribution by a large number of co-workers, to whom I hereby give my thanks without mentioning all by name. The technicians (the names are given below) at the BONT stations did a marvellous job characterised by enthusiasm and patience. Additionally, I thank all 65,225 participants in the county of Nord-Trøndelag for their immense contribution for research by answering hundreds of questions and accomplishing the measurements.

- The steering committee and consulting team deserves gratitude for their involvement in the BONT study.
- Professor Leif Bjermer has been my main and inspiring/spiritual advisor during planning, performance and writing process. I am grateful for his enthusiasm for both respiratory medicine and technical equipment, and support for my work.
- Professor Roar Johnsen has been the co-advisor and is the Head of the Department of Community Medicine and General Practice, NTNU. Blessed with an earthbound personality he has balanced the supporting team. I am thankful for his thorough participation especially in the writing process and his patience in sharing his great knowledge of statistics and ever-lasting optimism in transforming my mind in an analytical direction.
- Professor Jostein Holmen, has been the head of the HUNT Research Centre during the planning and performance of both HUNT 1 and HUNT 2. His including, patient,

encouraging, and optimistic attitude to the BONT study has been an inestimable contribution to this work.

- Associate Professor Turid Lingaas Holmen is to blame for capturing me into the respiratory field of medicine through the invitation to and collaboration in 1991 on developing guidelines for asthma treatment in childhood/adolescence. She has continued as a valuable respiratory inspirational co-worker, and has through empathic personality invited to sharing of frustrations of the academic world. She also deserves thanks for reading and commenting this thesis.
- Associate Professor Øystein Krüger had the main responsibility for data storing and quality control during and after the data collection period of the HUNT study. In addition, he willingly shared his knowledge of different software and solved technical problems at the Research Centre.
- Professor Amund Gulsvik at the University of Bergen, an authority in respiratory epidemiology in Norway during the last 3 decades, is thanked for willingness and important contribution of respiratory knowledge in the planning and writing process.
- HUNT Co-ordinator Grete Bratberg, Research technician Bitte Dillan, Office manager Aina Enes and Secretary Inger D. Holbø do all deserve my everlasting gratitude for willingness, contribution and constructive points of views during the performance of the BONT Study.
- Medical Adviser / Epidemiology Skill Leader Maria Gerhardsson de Verdier at AstraZeneca Reearch & Development in Lund, and Medical Adviser Ensio Norjavaara at AstraZeneca, Mølndal, and at the University of Göteborg, have been co-writers of paper 4. I am grateful for their thoroughness, positive attitude, and constructive responses.
- Post.doc fellow Gro Berntsen, at the University of Tromsø, was an important advisor in the planning of bone mineral densitometry and quality control of assessments in the

HUNT study. I am grateful for her willingness to share her immense knowledge in this field, and her work for promoting collaboration in this field of epidemiology.

- Dr.med. Anne Hildur Henriksen and dr.med. Malcolm Sue-Chu at the Lung Department, NTNU, are thanked for constructive collaboration and advise in the planning and performance of phase IV of the BONT study. Correspondingly, an important collaboration with the Osteoporosis study, represented by Professor Berit Schei, Senior Researcher Lisa Forsén and Associate Professor Siri Forsmo, has contributed to a common large database on bone mineral density.
- Last, but not least, AstraZeneca deserves gratitude for non-demanding funding of the BONT Study. I am grateful to Medical Director Henrik Lund and Head Clinical Department Jan Petter Akselsen at AstraZeneca, Norway, for their support and believe in the BONT study.

What are our main contributions in life?

Even if a thesis like this is a result of some heavy, but interesting work, it is highly perishable. I have, however, enjoyed the stimulating collaboration with co-workers at the HUNT Research Centre and at the same time the work in the clinic as general practitioner. Beyond comparison, however, my main contribution to the world, has to be shared with my excellent wife, Bjørg, being our children, Marit, Håvard and Astrid, of whom I am very proud.

Verdal, June 2003

Arnulf Langhammer

Steering Committee of the BONT Study 1995-2000

- The National Institute of Public Health

  Head of the department, initially Arild Bjørndal, later Professor Leif Bakketeig

- Astra Norway

  Medical Director Henrik Lund

- Institute of Community Medicine, NTNU

  Professor Lars Vatten, later Professor Roar Johnsen

- The Lung Department, NTNU

  Professor Leif Bjermer

- HUNT Research Centre (from 1997)

  Associate Professor Jostein Holmen

Consulting team

Professor Amund Gulsvik, Professor Leif Bjermer

Professor Lars Vatten, later replaced by Professor Roar Johnsen,

Senior Researcher Lars Larsson (at that time employed by Astra Sweden)

Technicians at Team I, Team II and at phase IV

Aune, Kirsti	Kaiser, Wenche	Risan, Annbjørg
Breivik, Anne	Kjølstad, Kristmar	Skaland, Turid
Fabritius, Merethe K.	Korsnes, Marit	Skrove, Kari Mette
Fjeldstad, Svein	Kroken, Grete	Trøan, Susann
Fostad, Ranveig	Lein, Hege	Vanebo, Tone
Haugen, Synnøve	Leirbekk, Inger	Vibstad, Maja
Holand, Anne Lise	Nervik, May Åse	Østby, Astrid

List of publications

1. Langhammer A, Johnsen R, Holmen J, Gulsvik A, Bjermer L. Cigarette smoking gives more respiratory symptoms among women than among men. The Nord-Trøndelag Health Study (HUNT). J Epidemiol Community Health 2000;54(12):917-22.

2. Langhammer A, Johnsen R, Gulsvik A, Holmen TL, Bjermer L. Forced spirometry reference values for Norwegian adults: the Bronchial Obstruction in Nord-Trøndelag Study. Eur Respir J 2001;18(5):770-779

3. Langhammer A, Johnsen R, Gulsvik A, Holmen TL, Bjermer L. Sex difference in lung vulnerability of tobacco smoking. Eur Respir J 2003;21(6):1017-1023.

4. Langhammer A, Norjavaara E, de Verdier MG, Johnsen R, Bjermer L. Use of inhaled corticosteroids and bone mineral density in a population based study. The Nord-Trøndelag Health Study (HUNT). Submitted May 2003.

URN:NBN:no-3454

1. Introduction

The Nord-Trøndelag Health Study (HUNT) is a comprehensive population based study having performed cross-sectional studies in the county twice, HUNT 1 in 1984-86 and HUNT 2 in 1995-97. In HUNT 1 lung related measures were questions on coughing and chest-x-ray of everyone.

Except for inclusion of some questions on coughing and asthma in the main questionnaire, no specific lung study was originally planned in HUNT 2. Having worked with asthma related projects in general practice from 1989, I found HUNT 2 a unique opportunity for further work in the field of respiratory medicine. A lot of topics might be addressed, but initially focus was on studies regarding; a) the increasing prevalence of respiratory symptoms and obstructive lung diseases in the western countries, b) the use of inappropriate estimates of normal lung function parameters because of widespread use of prediction equation from the European Community for Coal and Steal (ECCS) (1), and c) the concern about side effects of inhaled corticosteroids on bone.

My proposal to The HUNT organising committee in November 1994 of performing a lung study as part of the HUNT study was accepted, and a hectic planning phase began. The closing date for application for funding from the Norwegian Research Foundation had passed, and the only possibility for funding was enquiring pharmaceutical companies. Planning to ask all pharmaceutical companies with drugs in the field of respiratory medicine, I, to the second company on my telephone list, addressed the question of funding to Medical Director in Astra Norway, Henrik Lund. He was very positive to my request, and based on my preliminary protocol on The Bronchial Obstruction in Nord-Trøndelag Study (BONT) and three meetings, Astra Norway in Mai 1995 accepted funding of a total amount of Nkr 4.3 millions for the planning and data collection period of the study. The formal agreement was concluded between Astra Norway and the National Institute of Public Health, and I was

employed at the Community Medicine Research Centre in Verdal, which at that time was part of The National Institute of Public Health. For further planning and performance of a rather large lung study, I obviously needed teaching supervisors and co-workers being experts in the field of respiratory medicine. The preliminary protocol and information of the funding did not convince the first research group, that I got in touch with, that such a study was warranted in Norway. However, a meeting with an enthusiastic professor, Leif Bjermer at the Lung Department in Trondheim in February 1995, inspired for further work on the planning, and he willingly accepted being the main supervisor. A steering committee and a consulting team were established. Bo Lundbäck, the father of the Obstructive Lung Disease in Northern-Sweden Study (the OLIN-study), participated at the first meeting of the consulting team, but he, unfortunately, had not time for further involvement in the BONT study. His dissertation was, however, an important contribution in the planning phase of the BONT study (2). Professor Lars Vatten initially was co-supervisor, but because of his involvement in a huge number of studies in HUNT, Professor Roar Johnsen replaced him.

After a very hectic planning phase of the BONT Study, as well as of the total HUNT study, the data collection started in Levanger August 15th 1995. With the arrival of technical equipment few days before, and preliminary software solutions for the interview, the first month was marked by technical problems. Burglary and theft of both laptop and spirometer both the first and second week of the study did not diminish our problems, but extreme flexibility of Leif Bjermer and the contractor of the equipment contributed to only two days of loss of measurements. We changed from the use of laptops to stationary PCs, and supporting this choice was the burglary in the third week, when the only benefit for the thieves was the packing of the previous laptops. At team 1 covering the 5 largest municipalities, the BONT study was part of the screening station. Due to practical reasons, the BONT study had to

organise the measurements as follow-up study 6-12 weeks after the main screening in the 19 smaller municipalities. Initially more studies wanted to arrange follow-up study in these municipalities, but at last the BONT study, being indebted to an enthusiastic, and sometimes furious and crying, staff at the HUNT Research Centre, was the only study performing this. Bone mineral density measurements were, however, also measured for the selected samples for the Osteoporosis Study, which later on paid the economical extra costs for this. Having the responsibility for all transport and follow up of the equipment, education of and supervision of the staff, I was given the opportunity to spend a lot of ordinary working days, evenings, and weekends in 1995-97 on the roads or in offices in all municipalities of our county.
The data collection phase of HUNT 2 and BONT finished in November 1997, and thorough work regarding punching /optical reading of questionnaires began. For BONT quality assurance of measurements both of bone densitometry and spirometry had to be performed. For the BONT and Osteoporosis study Aina Enes and Bitte Dillan performed manual replacement of borders for site measurement on a total of 18,000 bone densitometry measurements. About 20,000 flow volume curves from 11,800 subjects were stored, and the processes of quality cheque have been time consuming and will continue, as more parameters of lung function will be included in analyses.

Through the BONT study the airway became one of the main topics in the HUNT 2 study. The study has contributed in adding to the comprehensive HUNT database information on lung related risk factors, respiratory symptoms and diseases, use of “asthma” medication, lung function, and bone mineral density. As the collected data in the BONT study are and will be an important basis for cross-sectional and prospective studies, the Method section also includes description of the phases not being further addressed in this dissertation.

2. Aims of the study

- To estimate the prevalence of respiratory symptoms, self-reported obstructive lung diseases, and their risk factors.

- To study the association between tobacco smoking and respiratory symptoms, obstructive lung diseases, self-reported health, and lung function by sex.

- To develop prediction equations for forced volume spirometry for Forced Expiratory Volume in 1 second (FEV_1), Forced Expiratory Volume (FVC), Peak Expiratory Flow (PEF), Forced mid-Expiratory Flow (FEF_{25-75}) and Area Under Curve (AUC).

- To compare these prediction equations with other commonly used equations.

- To study the association between use of inhaled corticosteroids and bone mineral density (BMD) of the forearm.

3. Background

This section is divided into three parts addressing each of the main subjects of this study.

3.1 Respiratory symptoms and obstructive lung diseases by tobacco smoking and gender

3.1.1 History

Table 1. Some important events in the history of obstructive lung diseases and treatment)

Year	History of obstructive lung disease and treatment (3;4)
-1550	➢ Asthma-like condition described in the Ebernes papyrus in Egypt. ➢ Treatment: Camel and crocodile droppings
-1000	➢ Neu Ching, the oldest medical textbook describes asthma in China. ➢ Treatment: the plant Ma Huang (active component ephedrine), herbal remedies, acupuncture, yoga and meditation.
-480 –370	➢ Hippocrates, teacher on Cos, thought that asthma was due to an imbalance of the bodily fluids. ➢ Treament: induce of vomiting, purging and bleeding
-81	➢ The first classification of asthma by the Greeks.
50-100	➢ Pedanus Discorides, Greek, the father of the science of pharmacy ➢ Treatment: inhaled fumigation – the start of inhaler therapy
129 – 200	➢ Galen, Greek physician, probably the most influential writer of all time on medical subjects. Large scale use of medications – polypharmacy ➢ Treatment: owl blood in wine
1135–1204	➢ Moses Maimonides, the most famous Jewish physician in Arabic Medicine. ➢ Treatment: Hot chicken soup, dry climate, avoidance of emotional turmoil and sexual activity
1559	➢ Sir Walter Raleigh brought tobacco to England
1600	➢ Treatments: tobacco smoking, stallions dung and tincture of fox's Lung

1621 – 1675	➢ Thomas Willis, Oxford physician ➢ Treatment: powdered shells and millipedes, antispasmodics and sedatives.
1803	➢ The use of fumigation of Datura ferox in treatment of asthma was imported to Great Britain from the Indians of Madras. Cigarettes with leaves of datura were used by asthmatics until 1992
1860	➢ Sir Henry Salter, a Victorian doctor ➢ Treatment: strong coffee (caffeine is related to theophylline) ➢ Theophylline isolated from cocoa, aminophylline produced in 1908.
1869	➢ Atropine was derived from the plant deadly nightshade
1900	➢ Adrenaline introduced – stimulates a, $ß_1$ and $ß_2$ receptors first administered by inhaler at Guys Hospital in 1929
1936	➢ Cortisone extracted from the adrenal gland, and first used in asthma treatment in 1950
1940	➢ Isoprenaline discovered - stimulates $ß_1$ and $ß_2$-receptors
1954	➢ Prednisolone developed
1967	➢ $ß_2$ receptors identified, led to development of salbutamol and terbutaline ➢ Disodium cromoglycate was derived from the seeds of an eastern Mediterranean plant Ammi Visnaga ➢ Importance in asthmatics of allergy to house dust mite was realised, and injections of mite allergen was started
1970s	➢ Development of beclomethasone, and later budesonide and fluticasone.
1982	➢ Bengt Samuelsson got Nobel Prize in Medicine for identification of leucotriens (previously called slow-reacting substance of anaphylaxis (SRS-A). Later the leucotrien receptor antagonists pranlukast, montelukast, and zafirlukast were developed.

3.1.2 Epidemiology of obstructive lung diseases

3.1.2.1 Asthma definition and prevalence

The Greek word is derived from the verbal root that means to blow, and signifies hard-drawn breath, panting or gasping from the toil. Despite a lot of research on asthma, there remains considerable discussion as to how much "asthma" of respiratory origin can be classified as being the same disease (5). On the other side, the symptoms may be misinterpreted; like the young man believing he was a good lover until his girlfriend told him that she had asthma.

Asthma has still no standard definition, and attempts to define asthma have generally resulted in descriptive statements (6). The latest from Global Initiatives for Asthma (GINA) defines asthma in the following way:

> *Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness (AHR) that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment* (7).

There have been debate whether there has been an increase in asthma prevalence in the industrialised world (8). In order to avoid concern about the reliability and validity of asthma diagnosis, epidemiological studies generally use self-reported wheeze in the past year as a marker of the disease. The prevalence of wheezy illness in children have increased over time, but the prevalence of diagnosed asthma has increased more rapidly, suggesting that the diagnosis has become more frequently used and that some of this increase may reflect only a different use of language (5). However, the consistency of the evidence from questionnaires,

the parallel increase in the prevalence of atopy and some evidence that there has been an increase in AHR makes it very likely that the increase in asthma prevalence is real. (5;6). There seem to be an agreement today that there is a trend reflecting a true increase in prevalence in children but a less striking increase in adults (7).

In countries with developed health services (including Norway and Sweden), asthma is reported by about 5 % of subjects aged 20-44 years (9), and in more than 10 % of children (10). The prevalence rates tend to be highest in economically developed countries with a temperate climate and low in rural subsistence and economically developing communities. Adoption of a more affluent lifestyle in the latter regions, however, leads to increasing prevalence (6). The highest prevalence of asthma is found in Australia, New Zealand and England.

3.1.2.2 Risk factors for asthma

Risk factors for asthma may be classified as host factors that predispose individuals to or protect them from developing asthma, and environmental factors that influence the susceptibility to the development of asthma in predisposed individuals, precipitate asthma exacerbations, and/or cause symptoms to persist (7).

- ***The host factors*** include the genetic predisposition to the development of asthma or atopy, airway hyperresponsiveness, gender, and race. Canadian epidemiological studies have indicated that asthma incidence in women, but not in men, is associated with smoking and household pets (11). Cyclical hormonal variations (12) and possible anti-oestrogen effect of tobacco smoking (13) might also contribute to higher prevalence of asthma in women compared to men. Further, in a time with increasing body mass index in the population, studies among women, interestingly, have reported body mass index and weight gain to be independent risk factor for onset of asthma (14).

- ***The main environmental factors*** are exposure to allergens and occupational sensitisers, viral and bacterial infections, diet, tobacco smoke, socio-economic status, and family size. There is some evidence that some risk factors (increased exposure to infection, acquisition of different intestinal commensal bacteria, and higher exposure to bacterial endotoxins) influence the balance between subgroups of CD4+ T-helper (Th) lymphocytes, inhibiting the change from mainly Th2 lymphocytes to Th1 lymphocytes during infancy (6;15). These cells secrete cytokines to support or suppress the allergic inflammatory response, respectively. This might partly explain the increasing prevalence of asthma and allergy, but studies have also indicated that even low levels of allergen exposure might contribute to this (16).

  The main factors responsible for causing exacerbations of asthma and /or the persistence of symptoms are exposure to allergens and respiratory infections.

3.1.2.3 COPD definition and prevalence

The Global Initiative for Chronic Obstructive Lung Diseases (GOLD) guidelines define chronic obstructive pulmonary disease (COPD) in the following way:

> *COPD is a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases* (17).

COPD consists of a variable mixture of three pathological lesions: emphysema in the alveolar region, mucous gland hyperplasia, predominantly in the large airways, and inflammation and fibrosis in small airways.

Previously the term emphysema and chronic bronchitis were included in the definition of COPD. Emphysema is a pathological term and describes only one of several structural abnormalities in COPD. Chronic bronchitis, is defined as self-reported cough and sputum production for at least three months in each of two consecutive years, and this remains a clinically and epidemiologically useful term (17). These symptoms may precede the development of airflow limitations, but some patients develop significant airflow limitation without chronic cough and sputum production. The prevalence of chronic bronchitis have been reported to be 3.7 % in Denmark (18), 4,8 % in Spain (19), and 4.5 % in Norway (20). Subjects underreport and physicians under-diagnose chronic bronchitis (21), and women seem to underreport phlegm more than men (12). Current smokers might regard coughing with and without phlegm as a natural consequence of smoking and not as a health problem, or simply find no reason for reporting symptoms caused by their life style.

COPD is a common, costly, and preventable disease with large implications for global health. It is the forth-leading cause of death in the United States, exceeded only by heart attacks, cancers, and stroke. Further, it has been estimated that by the year 2020, COPD will be fifth among conditions that will be the highest burden to society on a worldwide scale (22). In the USA there have been an increase in death rate for women from 20.1/100,000 in 1980 to 56.7/100,000 in 2000, with a more modest increase in men, from 73.0 to 82.6 per 100,000. For the first time, in 2000 more women than men died of COPD in USA (59,936 versus 59,118) (23). In Great Britain 10 % of men and 11 % of women aged 18-65 years had FEV_1 more than 2 SD below predicted, and in Spain 10.6 % of men and women had FEV_1/FVC less than 88 % and 89 %, respectively (19).

The prevalence data on COPD have been distorted by the use of different diagnostic terms and lung function criteria. The most common lung function criteria have been:

- The British Thoracic Society (BTS): $FEV_1/FVC < 0.70$ and FEV_1 % < 80 (24)
- American Thoracic Society (ATS): $FEV_1/FVC < 0.75$ (25)
- GOLD: $FEV_1/FVC < 0.70$ independent of symptoms (17).

The choice of criteria influences highly the reported prevalence. In Sweden the prevalence of COPD among subjects aged more than 45 was 8 % according to BTS criteria and 14 % according to GOLD criteria (26). Fig 1 illustrates the differences in prevalence of COPD using the different criteria in the total BONT sample.

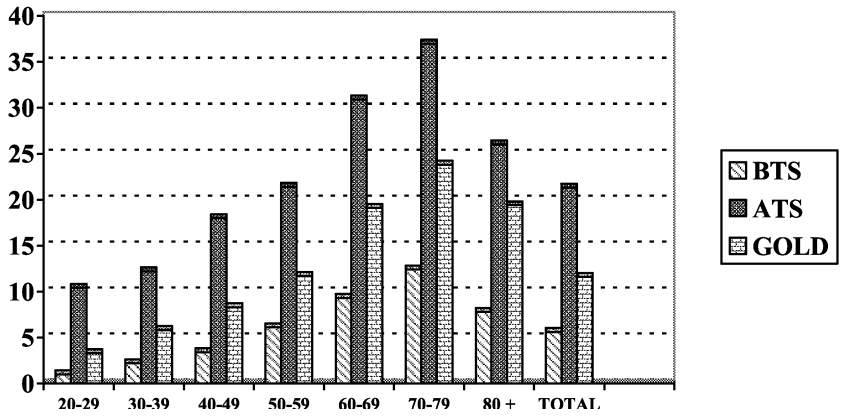


Fig 1 COPD prevalence by age applying the diagnostic criteria by BTS, ATS, and GOLD on the 5 % random sample of the BONT study.

3.1.2.4 Risk factors for COPD

COPD is a complex disease that is influenced by genetic factors, environmental influences and genotype-environmental interactions.

Host factors

- The genetics of alpha1-antitrypsin deficiency is well known, but the role of other genetic factors in COPD have only recently started to receive attention (27).

- Several studies have suggested that women may be at higher risk of developing COPD, but this has mainly been considered in relation to tobacco smoking. Compared to men, tobacco smoking in women has been reported in higher degree to restrain lung growth in adolescents (28), increase bronchial responsiveness (29;30), and increase rate of hospitalisation for COPD (31). Regarding decline in lung function, however, the results have been conflicting. Some studies have reported greater decline in lung function among men than women (32-37), other opposite results (12;31;37-40), whilst no difference by sex was found in a meta-analysis of eight large US population-based studies (41).

- The importance of factors as airway hyperresponsiveness (AHR) and asthma/atopy as predictors for COPD are unclear, but studies have supported the so-called "Dutch hypothesis" proposed by Dutch workers in the 1960s (42). According to this, asthma / AHR are risk factors of developing COPD, which is supported by Xu et al in a longitudinal study finding an association between AHR and chronic mucus hypersecretion, after adjusting for factors such as age, sex and smoking (43).

- Low birth weight, childhood respiratory illness and recurrent bronchopulmonary infections also have been associated with increased risk of COPD.

Environmental factors:

- Tobacco smoking causes respiratory symptoms like wheezing, breathlessness, and coughing (44-47), and is the most important aetiological factor for COPD (17). Most patients with COPD will have a smoking history of at least 20 pack-years (24). Smoking is believed to be the cause of 85-90% of COPD in men in the industrialised world, but only 15-20 % of smokers have been reported to develop the disease (48). The relatively low figures among smokers probably underestimates the prevalence, as COPD is both underdiagnosed and underappreciated (17), and Lundbäck et al in a recent study reported that about 50% of smokers developed COPD (26). Other confounding factors that complicate the relationship between number of cigarettes smoked and decline in lung function are the extent to which cigarette smoke is inhaled and the amount of tar. A reduction in cigarette tar content has been shown to have little effect on the decline in FEV_1 because of change in the pattern of the number of cigarettes smoked (49).

- Passive smoking as a risk factor for COPD and adult onset asthma has been demonstrated in a number of studies, but the magnitude of the associations have been small (50). Among non-smokers, adults exposed to passive smoking at home or work have a 40-60 % increased risk for self-reported asthma, and this exposure worsens respiratory symptoms and lung function among adult asthmatics.

- Other risk factors for COPD are increasing age, environmental pollution, occupational dust and chemicals, and socio-economic status (17). It is not clear, however, whether socio-economic status rather reflects indoor and outdoor air pollutants, crowding, poor nutrition etc. High levels of urban air pollution are harmful to individuals with heart or lung disease. However, the role of out-door air pollution in causing COPD is unclear, but

appear to be small when compared with that of tobacco smoking (17). In countries using biomass fuel for cooking and heating in poorly vented dwellings, the high level of particulate matter in indoor air is a risk factor for COPD (17).

3.1.3 Tobacco smoking

3.1.3.1 History

Christopher Columbus brought a few tobacco leaves and seeds with him back from South America to Europe in 1493, and the products were introduced to most Europeans in the mid-16th century. Even if the products initially were very expensive, the supposed medicinal and especially aphrodisiac effects made it very attractive.

At first, tobacco was produced mainly for pipe smoking, chewing, and snuff. Cigars did not become popular until the early 1800s, whilst cigarettes first became popular after the Civil War .The cigarette sales increased greatly after the invention of the first practical cigarette-making machine in the late 1880s.

During the 1920s the first medical reports linking smoking to lung cancer began to appear. Many newspaper editors refused to report these findings, as they did not want to offend tobacco companies who advertised heavily in the media. In 1930 German researchers reported a statistical correlation between cancer and smoking, and in 1944 the American Cancer Society began to warn about possible ill effects of smoking. In 1952 Reader's Digest published "Cancer by the Carton" an article about the dangers of smoking. The effect of the article was enormous; similar reports appeared in other periodicals and the following year, cigarette sales declined for the first time in over two decades. The tobacco industry responded by in 1954 forming the Tobacco Industry Research Council to counter the growing health concerns. This led to production of the filtered cigarettes and low-tar formulations that

promised a "healthier" smoke. The public responded, and soon sales increased again. In the early 1960s " the Surgeon General's Advisory Committee on Smoking and Health" was established. The committee released a report concluding that cigarette smoking was causally related to lung cancer in men, and though less extensive, pointed in the same direction for women.

Ever since, researchers, patient organisations, governments, and the WHO have increased their fight against the tobacco industry. The industry is, however, still profitable, and even if the prevalence of current smokers are decreasing in the U.S., Oceania, and Europe, the proportion of smokers is increasing in Africa and Asia. Today Brazil and Zimbabwe have become the leading countries in export of unmanufactured tobacco in the world, whilst China is the leading country in manufacturing of tobacco (51;52).

3.1.3.2 Smoking prevalence

Projections by WHO for the 1990s gave global estimates of the proportions of smokers as 47% among men and 12 % among women. The smoking pattern has, however, changed both in developed and developing countries, with especial increase in proportion of female smokers. The numbers of smoking women is expected to almost triple from 1990s to 2025, the increase is partly an effect of female emancipation and the use of tobacco smoking to gain weight control (53). The prevalence of smoking among women is > 20 % in Europe and US, and > 30 % in Brazil, Denmark, and Norway (54). Whilst Norwegian men in 1998 were ranked 62 in the world regarding smoking prevalence, Norwegian women were ranked 2 (54). The overall prevalence of daily smokers in age group 16-74 years in Norway were 32 % in women and 33 % in men in 1995, whilst the figures for 2001 were 29 % and 30 %

respectively (55;56). The prevalence of daily smokers in these age groups in 2001 in Nord-Trøndelag was 31 % in women and 27 % in men.

Table 2 Smoking pattern by sex in Nord-Trøndelag 1995-97

	Women	Men
Start age	19.8	18.4
Number of cigarettes	9.7	13.1
Pack-years	10.3	16.0
Current smokers (%)	30.6	29.7
Ex-smokers (%)	19.7	32.0
Never-smokers (%)	49.7	38.3

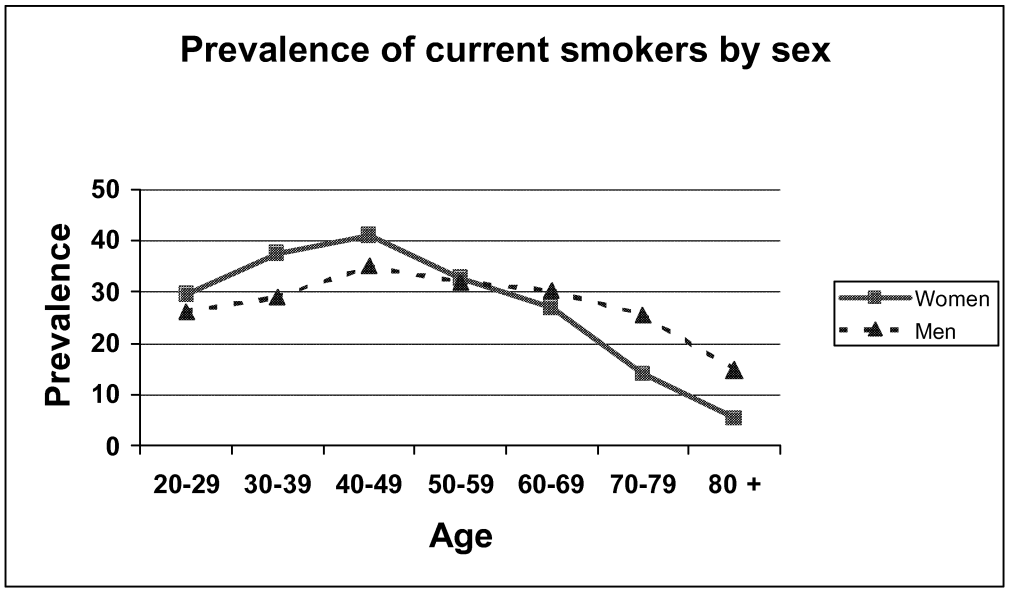


Fig 2. Prevalence of current smokers by sex and age in Nord-Trøndelag 1995-1997

3.1.3.3 Tobacco smoking and health

Tobacco use is the single most important preventable health risk in the developed world, and an important cause of premature death worldwide. Epidemiological research has revealed this causal relationship, and an important contribution to this has been the work of Sir Richard Doll. He was one of the co-workers of the first study showing the association between tobacco smoking and lung cancer in 1947. He also started the classical study of the smoking habits of British doctors in 1951, and follow up studies until 1991 on this cohort have shown that about half of all regular cigarette smokers will eventually be killed by their habit (57). In Norway the number of deaths due to tobacco smoking in 1998 was estimated to 7,700 subjects (20 % of all deaths). Smoking causes a wide range of diseases, including many types of cancer (located in the mouth, oesophagus, pharynx, larynx, lung, pancreas, and bladder), COPD, coronary heart disease, stroke, peripheral vascular disease, and peptic ulcer disease (58). Respiratory symptoms/diseases caused by tobacco smoking are dealt with in more detail in section 3.1.2. Compared to never-smoking women, smoking women are more likely to experience primary and secondary infertility, and regarding pregnancy outcomes abruptio placentae, preterm delivery, lower birth weight infant, and intrauterine or perinatal death of infant (53). Studies have in addition indicated that women who smoke have lower bone mineral density than non-smokers (59), and increased risk for hip fractures (60).

3.1.4 Questionnaires in respiratory epidemiology

3.1.4.1 Development of commonly used questionnaires

There have been a lot of epidemiological studies on obstructive lung diseases. However, the use of different questions has made the study of time trends and comparisons between regions difficult. Intending to avoid such limitations, several questionnaires for studying respiratory

diseases have been validated and internationally published (61). In 1960, the British Medical Research Council (BMRC) published a questionnaire on respiratory symptoms with items mainly selected for the identification of chronic bronchitis (62). There were only a few questions about wheezing and unspecified chest illnesses in this version. Questions on asthma-related symptoms later have been included, in addition to question on "ever having had asthma" and "doctor diagnosed asthma", both in newer versions of the BMRC questionnaire, the ATS and Division of Lung Diseases of the National Heart and Lung Institute questionnaire (ATS-DLD-78) (63), and in the International Union Against Tuberculosis and Lung Disease questionnaire (IUATLD) (64-66).

During the last decade, standardised methods to measure the prevalence of asthma and wheezing illnesses in children (International Study of Asthma and Allergies in Childhood – ISAAC) (10) and adults (European Community Respiratory Health Study (ECRHS) (67) have been developed. They will be important contributors for futures comparative studies on asthma prevalence. The ECRHS questionnaire was developed, where possible, from pre-existing questionnaires. The questions on cough and phlegm were taken form the BMRC-ECCS questionnaire and the questions on asthma and asthma-like symptoms from the IUATLD –1986 questionnaire. Many centres throughout Europe (including Bergen in Norway) are participating in the ECRHS. Questions from this study were included in the interview in the BONT study.

3.1.4.2 Cough related questions

Most commonly used questionnaires on chronic bronchitis and dyspnoea are modifications of the questionnaires developed by BMRC in 1960 (62) and by the ECCS in 1962. Compared to these question sets, more recently used sets have omitted the questions on seasons for cough. There are minor differences in the questions as some ask for cough and phlegm in the

morning (67) opposed to others asking for longstanding cough without specifying time of the day (2). In addition the questions on duration are not identical.

3.1.4.3 Questions on asthma and asthma-like symptoms

Comparisons of asthma incidence and prevalence between different regions and periods have been problematic due to lack of precise definitions of asthma and change in diagnostic criteria. A fundamental problem is that even when a single definition is accepted, the diagnosis of asthma involves an overall assessment of the patient's medical history, physical examination, and laboratory test results, and there are no universally accepted rules for combining the information from these various sources (68). For epidemiological purposes it is, therefore, most useful to define asthma in terms of the phenomena involved without making any etiologic implications. The prevalence data, therefore, have been based on questionnaires on symptoms (such as "wheeze ever or during the last 12 months", chest tightness, and cough), self reported asthma or doctor diagnosed asthma, lung function, and measurements of AHR. AHR and symptoms of asthma measure different abnormalities in the airways, but the presence of both defines "clinical important asthma" – that is, patients with high risk of persistent disease (7).

The questions on wheezing have high sensitivity, but low specificity as also other conditions than asthma give rise to this symptom (61). It has, however, reasonably sensibility and specificity for other prevalence measures like AHR (68), and have been used in most asthma symptom prevalence questionnaire, and usually with additional questions on the frequency of wheezing and the circumstances in which wheezing occur.

The IUATLD questionnaire has been tested against AHR (69), which at least is an objective measure of an important component of asthma. The studies confirmed the sensitivity of

wheeze and showed the usefulness of the question about being woken by shortness of breath. Another question that was independently predictive of bronchial reactivity was tightness in the chest when exposed to animals, dust or feathers (70). The validity of the different questions was highest for the question on wheeze, but the index was lower in Berlin and Paris, as these countries, like the Scandinavian countries, lack colloquial term for wheeze in their language.

Contrary to the questions on symptoms, the questions on asthma and physician diagnosed asthma have high specificity, but low sensitivity. The recognition of the disease depends on the quality of health services, the subjects' threshold for consulting doctors, and on doctors' readiness to attach the label "asthma" to asthma-like symptoms (61).

3.1.4.4 Self-rated health (SRH)

Questions on SRH like "How is your health at the moment?" have been found to be powerful predictors of future morbidity and mortality (71;72). Most studies have used five, seven, or nine categories, but we assessed global health by using four steps as this had been used previously in HUNT 1 as well as in other Norwegian population based studies (73). Four steps were originally chosen for HUNT 1 in order to force subjects to choose positive or negative categories.

3.2 Lung function – reference values

3.2.1 Spirometry

Spirometry is the most widely used test of lung function. It is used to evaluate and monitor diseases that affect heart and lung function, to monitor the effects of environmental, occupational, and drug exposures, to assess risks of surgery, and to assist in evaluations performed before employment or for insurance purposes (74). Assessments of a subject's lung function values should be primarily oriented toward previous findings of the subject (75). Inevitably, such measurements most often are lacking, and expression of the results as a percentage of reference mean values or of confidence limits established in qualitatively recommendable studies is necessary for the first investigations.

3.2.2 Spirometers

Spirometers measure by two different methods; either volume-displacement or flow-sensing measurement. Signals can be processed to calculate flow from volume and time, or volumes from flow and time.

3.2.3.1.Volume-displacement spirometers

The most commonly used are:

- Bellows (e.g. Vitalograph R or S Model)
- Bell or Water seal (e.g. Biomedin Baires)
- Rolling seal cylinder/piston (e.g. Ohio).

Because of their simplicity of action and fine tolerance, the volume measuring devices are considered being the gold standard (78).

3.2.3.2 Flow sensing spirometers

There are many available flow sensors using various principles:

- Pressure differential type spirometers measure a pressure drop across a fixed resistance so that the pressure change is directly proportional to the flow through the device.
    - Pneumotachograph
        - Fleisch-type (e.g. Vitalograph 2000 Series or Compact
        - Lilly-type (e.g. heated Jaeger or Spiroscreen, unheated Clement Clark VM1)

- Rotating vane type spirometers have a turbine fixture leading to a rotating vane, which receives the flow and rotates at a speed proportional to the flow delivered. (e.g. Turbine Cosmed Pony Graphic)

- Ultrasound spirometers measure the transit time of an ultrasound beam between the emitter and the sensor. They involve complex signal processing and allegedly do not require calibration.

3.2.3 Lung function measurements – history

Table 3. Some important events in the history of lung function measurements.

Year	**Spirometry and lung function tests** (76;77)
129-200	➢ Galen performed a volumetric experiment on human ventilation. A boy breathed in and out of a bladder. Galen found that the volume of the gas was unchanged after repeated expirations.
1681	➢ Borelli measured the inspiratory volume by sucking a liquid up a cylindrical tube.
1718	➢ Jurin J. blew air into a bladder and measured the volume of air in the bladder by the principles of Archimedes
1788	➢ Goodwyn E. sucked water into a pneumatic vessel which was weighted on scales, he corrected for temperature
1796	➢ Menzies R. plunged a man into water in a hogshead up to his chin and measured the raise and fall of the level in the cylinder round the chin (body plethysmography)
1845	➢ Vierordt published data on volumetric parameters, among which residual volume and vital capacity (VC) are still used.
1852	➢ Hutchinson, John published a paper about water spirometer, which is still used with little alterations only. He performed the first epidemiological study on lung function (VC) measuring > 2,000 men and 26 women. He found a linear relationship of VC to height, and that VC was independent of weight at any height.
1854	➢ Wintrich developed a modified and simpler spirometer than Hutchinson. He measured 4,000 persons, thereof about 500 pathological cases. He concluded that VC was determined by the three parameters height, weight and age.
1866	➢ Salter added the kymograph to the spirometer to record time as well as the volume.
1884	➢ Ellis concluded that VC is less in women than men, and postulated that there were gender differences in susceptibility to various treatments and poisons.
1902	➢ Brodie T.G: was the first using a dry bellow wedge spirometer, the precursor of the Fleisch spirometer, which is still used.

3.2.4 Lung function

3.2.4.1 Lung function and sex

Even though the lungs of girls and women are smaller than those of boys and men, they exhibit structural and functional advantages. These are measurable as higher flow rates in relation to lung size and they are evident prenatally and persist throughout the human lifespan (77). Women therefore have slightly higher FEV_1/FVC than men, but for a given height and age, men have a larger FEV_1, FVC, FEF_{25-75} and PEF.

3.2.4.2 Lung function and age

Lung function increases during childhood/adolescents, and decreases after the age of 30-40 years. VC continues to increase after growth in height ceases and may not be maximal until the age of 25 in boys, compared to 16-18 years in girls (79).

3.2.4.3 Lung function and height

All indices other than FEV_1/FVC increase with standing height. For subjects who cannot stand or who have a spinal deformity (eg, kyphoscoliosis), the arm span from finger tip to finger tip with arms stretched in opposite directions can be used as an estimate of height (79)

3.2.4.4 Ethnic origin

Caucasians have the largest FEV_1 and FVC and Polynesians are among the lowest. The values for the black race are 10-15% lower than for Caucasians of similar age, sex and height, probably because of smaller trunk/leg ratio (79). Chinese have been found to have an FVC about 20% lower and Indians about 10% lower than matched Caucasians. There is, however, little difference in PEF between ethnic groups.

3.2.5 Reference values for spirometry

For interpretation of ventilatory function tests in any individual, the results should be compared with reference values obtained in the defined population of normal subjects matched for sex, age, height and ethnic origin. Sex, size, and ageing account for approximately 30, 22, and 8%, respectively, of the variation in adults. Past and present health are other sources of inter-individual variation, and approximately 27 % of inter-individual variation remains unexplained (79).

Developing prediction equations fitting all ages have been difficult, and separate curves have been developed for children/adolescents and adults (80). Hankinson et al developed prediction equations for the age of 8 to the age of 80, but separate prediction equations had to be used under and over the age of 18 and 20 in girls and boys, respectively (81). There have been few prediction equation sets for the oldest part of the populations. This has partly been due to problems in recruiting never smoking men, problems with fulfilling the acceptability criteria, and low participation rate for this age group in studies. The upper age limits for different prediction equations have been; 60 years by Brändli et al (82), 70 years of age by ECCS (1), Gulsvik (83;84), Roca (85), 78 years of age by Gore et al (86), and 85 years of age by Enright et al (87).

No reference values had been developed for Northern-Europe in the 90-ties. In Scandinavia the most widely cited reference study has been that of Berglund et al published in 1963 (88). Reference values have otherwise been published in Finland by Viljanen in 1982 (89), Denmark by Groth et al in 1986 (90) and Oxhøj et al in 1988 (91), in Sweden by Fredriksson et al in 1981 (92) and Hedenstrôm et al in 1985 (93;94), and in Norway by Gulsvik in 1979 (83;84). In the Berglund study the subjects were not randomly selected from the general

population, and included smokers (88), other have not been based on a strict random population sample, have been age stratified (89-92) or have included smokers (83;84).

In Europe the most commonly used prediction equations have been those developed by Quanjar et al (ECCS) (1). These were summary equations compiled from a review of previously published equations in the years 1954 to 1980, including different populations and use of different spirometers and techniques. The summary equations were derived for the age range of 25-70 years, and for a height range of 1.55 – 1.95 m in men and 1.45 – 1.80 m in women. For subjects aged 18 –25 years, age was set to 25 to avoid overestimation of lung function in this age.

Several studies have indicated that the prediction equations from ECCS underestimate the lung function parameters FEV_1 and FVC (79;81;82;86;95). Comparing several lung-function reference values, Baur et al found that the ECCS reference values underestimated on average FEV_1 by 7%, FVC by 8%, and FEV_1/FVC by 3 % (75). This was also indicated by the European Community Respiratory Health Survey (ECRHS) reporting an underestimation of mean FEV_1 of 360 ml and FVC of 200 ml in subjects aged 20-44 years (96).

Several sets of normal values have been published over the last decades and “normality” for a given age and height may vary considerably across these data (74). Such variations may be explained by selection criteria of “normal “ population, measurement techniques and devices, biological variability across populations and statistical modelling (79). The skill and understanding of the technicians performing the tests probably are the most important factor affecting the test variability because of the complex, effort-depending interactions among the technicians, the instruments and the patient (74). In addition cohort effect (increasing mean

values within each age group over time) might influence the normal lung function parallel to what have been reported for other anthropometric measures as height. Glindmeyer et al reported 55 ml cohort increase per decade among 25 year old men of average height (173 cm) based on 18 cross sectional studies conducted over 130 years (97).

3.2.5.1 Regression models

Predicted mean values

Since 1846 it has been known that ventilatory function declines with age after about age 25 in men. Many studies have shown that in large cross-sectional samples the relation with age is close to linear, so that the annual "rate of decline" can be estimated by linear regression, giving an age coefficient of between 20 and 40 ml/year typically. The strong correlation between ventilatory function and body size, however, has been less easy to quantify. Many indices of body size have been considered, including body surface area, height, sitting height, weight, and chest circumference and chest expansion. Height has mostly been chosen as it is highly correlated with both FEV_1 and FVC and also is a very repeatable measurement.
For reasons of computational convenience, height often has been assumed linearly related to FEV_1 and FVC, so that age and height could be corrected for by using the multiple regression of lung function (LF) on age and height, expressed by a linear model:

$$LF = b_0 + b_1 * age + b_2 * height$$

A lot of studies have, however, confirmed that FEV_1 and FVC are proportionally rather than linearly related to height (Bolt et al (1973), Kroon et al (1964), Lowe et al (1968), Ashford et

al (1968), and Cole et al (1974), Rogan et al (1973) (98). The latter two found an age-height interaction, and an interaction model was written as:

$$LF = b_0 + b_2 * height + b_3 * age * height = b_0 + height * (b_2 + b_3 * age)$$

However, since FEV_1 and FVC are volumes, it should reasonably be proportional to a power of height closer to 3 than 1. By raising height to the power of k and setting the intercept b_0 to zero a proportional model is available:

$$LF = height^k (b_2 + b_3 * age)$$

In order to get simpler models, *k* has been set to 2, even if better figures might be 2.05 for FEV_1 and 2.25 for FVC. The proportional methods were found to be superior to linear models by Cole et al (98), and the equation could be simplified by dividing both sides by square height. Thereby it is shown that the indices $FEV_1/height^2$ and $FVC/height^2$ are independent of height and are linearly related to age in adults. This have been confirmed by Dockery et al (99) and Humerfelt et al (100), and this model was used in developing one of the two set of prediction equations in Norway published in 2001 by Gulsvik et al (101). One reason for selecting this in the latter study was, according to the authors, that a fixed height standardisation factor makes it possible to compare the regression coefficient of other predictors (age, smoking habits) in other surveys.

Another method of solving the non-linear regression problem of $LF = height^k f(age)$, is logarithmic transformation of the multiplicative model to a logarithmic additive model:

$$\boldsymbol{Ln}(LF) = k\,\boldsymbol{ln}\ height + \boldsymbol{ln}\ f(age)$$

The models could then be re-written in general form:

$$Mean\ lung\ function = \boldsymbol{exp}(b_0 + b_1 age + b_2 age^2 + b_3\,\boldsymbol{ln}(height).$$

This model have been used by Brändli et al (82) and was the one used in the BONT-study (see statistics) (95). Brändli et al computed also reference curves for the mean using Cole's proportional model ($LF = height^k\ (b_0 + b_1 age + b_2 age^2)$) (98). The result was almost identical to their model, showing that the particular choice of scale on which the lung function variables were considered only had a minor impact on the final results.

Lower limit of normal (LLN)

The lower limit of normal is a cut-off point defined for "normality". The results of spirometry should be considered as a supplement to the history of the patient. Clinical interpretation is usually straightforward when a pulmonary function result is well above or below LLN. A subject with FEV_1 just above LLN without any respiratory symptoms has a spirometry within normal limits, but similar result in a smoker with respiratory symptoms could be consistent with minor bronchial obstruction.

Three methods have been used for the evaluation of level of lung function or dysfunction (102):

1. Percent predicted with the normal range defined as values above 80% predicted is most commonly used in the clinic even if there is no statistical or physiological basis for its use.

This is only valid if the scatter of observed values around the mean is proportional to the level of lung function. Previous observations of adults have, however, shown a constant variance independent of lung function level (79;103;104). The use of a fixed value of percent predicted results in the following errors; shorter and older subjects will more readily be classified as "abnormal", whilst taller and younger adults will more likely be classified as normal (99). Percent predicted should, therefore, not be used to define LLN (79).

2. ATS has recommended the use of the 5th percentile as LLN (79). Thereby values within the upper 95% of healthy, never-smoking population with similar anthropometric characteristics are considered as normal. By definition, there will be a 5 % false-positive misclassification, a rate generally considered acceptable. The 5th percentile can be calculated directly from the data as done by Dockery et al (99), or empirically estimated as done by Knudson et al (104) and Paoletti et al (105). Brändli et al in the Swiss SAPALDIA Study computed fifth percentiles of residuals in consecutive age groups, and regressed these against the age means of respective groups and their squared values (82). They found that this approach provided more accurate estimates than when using a constant difference between then mean and the 5th percentiles. Compared to other studies their LLN had more stable alpha error (the probability of declaring a healthy person as being "below normal" was independent of age). Later, Brändli et al have re-estimated equations for the 5th percentiles using weighted L1 regression instead of the more commonly used least sum of square (minimising the sum of squared residuals) (106). This method appeared to provide plausible extrapolations beyond the age of 60 for all lung function parameters considered.

If the distribution of individual observations is close to Gaussian, the 5th percentile can be calculated by the predicted mean minus 1.645 times the standard error of the estimate (SEE). Ideally, the SD of the residuals should be constant across the full range of ages and heights (= homoscedasticity). This was found for height adjusted FVC and FEV_1 by Dockery et al (99), whilst Knudson et al reported Gaussian distribution in the middle range, but not the extremes (107). In the present study, the distribution was close to the Gaussian distribution, and the LLN was calculated on this basis (95). Lebowitz et al, however, found substantial agreement using the 5th percentile but not the mean minus 1.645 SEE in comparison of several prediction equations (108).

3. Percentile curves of lung function versus age also allow monitoring of the decline in lung function in adulthood. Height adjusted lung-function by division by squared height have been used to draw percentile curves (99), or the specific percentile could be calculated based on the prediction equation for the mean and the estimated standard deviation about the predicted mean (102). The use of percentile curves in the clinic would require height adjustment of the lung function and the plot of appropriate sets of percentile curves. Percentile curves are, however, an easily understood method for evaluating level of lung function of an individual patient, and their value is greatest with an accumulated record of repeated lung function tests over many years (102).

Table 4. Prediction equations for FVC and FEV_1 in men and women included for comparison

Men

	Equation FVC (L)	R^2	RSD
Brändli [1]	Exp (-10.321 + 2.1685lnH + 0.0655A – 0.001325 A^2)		
Brändli[2]	Exp (-9.540 + 2.1685lnH + 0.0030A – 0.000075 A^2)	0.40	0.62
Crapo[3]	0.0600H – 0.0214A - 4.650	0.53	0.64
Gore[4]	-0.0010736H^2 + 0.000004790H^3 – 0.0002764A^2 +12.675		
Hankinson[5]	0.00018642 H^2 + 0.00064A – 0.000269A^2 –0.1933	0.87	
ECCS[6]	0.0576H – 0.0260A - 4.345	0.85	0.61
Roca[7]	0.0678H – 0.0147A - 6.055	0.52	0.53
Enright[8]	0.0567H – 0.0206A – 4.37	0.27	

	Equation FEV_1 (L)	R^2	RSD
Brändli [1]	Exp (-9.280 + 1.9095lnH + 0.0795A – 0.001698 A^2)		
Brändli[2]	Exp (-8.240 + 1.9095lnH - 0.0037A – 0.000033 A^2)	0.38	0.50
Crapo[3]	0.0414H – 0.0244A – 2.190	0.64	0.49
Gore[4]	0.0000005846H^3 – 0.0001599AH + 2.081		
Hankinson[5]	0.00014098H^2 - 0.01303A – 0.000172A^2 + 0.5536	0.85	
ECCS[6]	0.0430H – 0.0290A – 2.490	0.86	0.51
Roca[7]	0.0514H – 0.0216A – 3.955	0.56	0.45
Enright[8]	0.0378H – 0.0271A – 1.73	0.27	

Women

	Equation FVC (L)	R^2	RSD
Brändli[2]	Exp (-9.457 + 2.0966lnH + 0.0091A – 0.000152 A^2)	0.38	0.50
Crapo[3]	0.0491H – 0.0216A - 3.590	0.74	0.39
Gore[4]	0.04680H – 0.0002525A^2 –3.598		
Hankinson[5]	0.00014815 H^2 + 0.01870A – 0.000382A^2 – 0.3560	0.73	
ECCS[6]	0.0443H – 0.0260A – 2.887	0.86	0.43
Roca[7]	0.0454H – 0.0211A - 2.825	0.56	0.40
Enright[8]	0.0365H – 0.0330A – 0.70	0.27	

	Equation FEV_1 (L)	R^2	RSD
Brändli[2]	Exp (-8.217 + 1.8475lnH + 0.0035A – 0.000130 A^2)	0.47	0.41
Crapo[3]	0.0342H – 0.0255A - 1.578	0.79	0.33
Gore[4]	0.00000001574 H^3 –0.0001574AH + 1.597		
Hankinson[5]	0.00011496H^2 - 0.00361A – 0.000194A^2 – 0.4333	0.73	
ECCS[6]	0.0395H – 0.0250A – 2.600	0.88	0.38
Roca[7]	0.0326H – 0.0253A – 1.286	0.67	0.32
Enright[8]	0.0281H – 0.00325A – 0.09	0.44	

[1]Age group 18-25years, [2]age group 26-60 years in men and 18-60 years in women (82), [3]age group 15-84 years (103), [4]age group 18-78 years (86), [5]age group 18-80 years in women and 20-80 years in men (81), [6]age group 18-70 years, for age group 18-25 years the age of 25 years is used (1), [7]age group 20-70 years (96), [8]age group 65-85 years (87).
A = age in years, H = height in cm. R^2 = explained variance, RSD = residual standard deviation.

3.3 Obstructive lung disease, inhaled corticosteroids and bone mineral density

3.3.1 Bone – normal loss

The skeleton is essential for terrestrial animal life, and human being have evolved bone light enough to allow rapid mobility and strong enough to avoid disabling fractures during the reproductive years (109). The peak bone mass in humans is usually attained between the ages of 25 and 30 years, with further age-associated bone loss of approximately 0.5-1% annually. In women the hormonal changes at the end of menopause cause a steep decrease in bone mass known as postmenopausal bone loss, 33% of lifetime bone loss in women may occur during this period (110).

At the distal forearm the bone mass remains relatively stable after achieved peak bone mass, but begin to decrease at the age of 40 years (111). Due to the large variations of the ratio of trabecular and cortical bone, age-related changes of bone mineral density (BMD) at the distal radius depend on the location of the scan line and can vary considerably. At the distal site the annual loss has been reported to be 1.5 %, whilst at the ultra-distal site corresponding loss is 0.4-0.7 % in some studies (111), whilst in the Tromsø study no or minor difference by site was found (112) (Table 5)

Table 5. Mean difference (g/cm^2) of BMD per year at distal and ultradistal site by age groups in men and women in the Tromsø study women aged 65+ (112)

	Women		Men	
Age	Distal BMD	Ultradistal BMD	Distal BMD	Ultradistal
25-50 yrs	- 0.1	- 0.1	- 0.1	- 0.1
51-65 yrs	- 1.3	- 1.5	- 0.6	- 0.6
> 65 yrs	- 0.7	- 0.8	- 0.6	- 0.6

3.3.2 Osteoporosis and fractures

Osteoporosis or low bone mineral density leading to fractures after minimal trauma, is a considerable problem both for the patients and the society. The World Health Organisation (WHO) has estimated that 30% of all women aged over 50 (postmenopausal) have osteoporosis according to a definition of BMD being more than 2.5 SD below the mean for young healthy adult women at any site. Several risk factors for fractures are correlated with BMD, i.e. age, sex, weight and race. Some risk factors for fractures are also independent of BMD; they improve the prediction of fracture even when BMD is known. Such factors are age, history of previous fracture, maternal history of hip fracture, conditions that increase the risk of falling, increased levels of markers of bone resorption, and very low levels of estradiol (113-115).

In Europe the Scandinavian countries currently have the highest prevalence of osteoporotic fractures, and the incidence is increasing more than would be expected from demographic changes in age and sex ratio (116). Hip fractures, which have become the international barometer of osteoporosis due to strong relation to low BMD, costly treatment, and high degree of disability, have higher age-adjusted incidence rates among Scandinavian women than in North America and Oceania (109).

3.3.3 Bone densitometry

Bone is composed of mineral, principally calcium hydroxyapatite, embedded in type I collagen and specialised proteins that make up the bone matrix. Calcium absorbs much more radiation than protein or soft tissue, and the amount of x-ray energy that is absorbed reflects the bone mineral content (BMC). BMD is BMC divided by the area of measured bone. As this

is assessed in 2 dimensions it is affected by the section size of the bone, so in a large and small bone with the same BMC, the larger will appear to have a higher BMD. Volumetric bone density, on the other hand, refers to bone mineral per defined volume of bone, and does not depend on size of the bone.

BMD may be measured with single-energy x-ray absorptiometry (SXA), dual-energy x-ray absorptiometry (DXA), quantitative computed tomography (QCT), and quantitative ultrasound. Except for QCT, the radiation doses for such measurements are low. The most common sites of measurement are the forearm, lumbar spine, hip, and calcaneus. Such measurements have become central to the diagnosis of osteoporosis and decisions about treatment to prevent fractures (114).

In the HUNT-study use of forearm measurements was mainly chosen out of practical reasons as:

- The bone densitometry was one of many stations at the screening. The total duration of assessment and necessary undressing had to be taken under consideration.
- The assessment is easy and readily standardised, and the equipment is far cheaper than DXA.

Fig 2 BMD measurement with Osteometer DTX100 (Aina Enes)

- The site is considered to be a good candidate for any screening based wholly or partly on BMD (117;118).
- Identical equipment had been used in the Tromsø Study 1994-95 (119) and planned used in follow up studies in Tromsø, Bergen and Oslo. This renders possible future national collaboration on follow up studies on BMD and fractures in large populations.
- Use of peripheral scanning sites reduces the radiation dose to the gonads limiting anxiety in a screening study also including women in fertile age.

3.3.3.1 Technique and site of measurement

For clinical practice, DXA at the hip is recommended if only one site is to be measured, because of its predictive value for hip fractures and it has been better standardised for diagnosis of osteoporosis. Spine and hip have similar value for predicting spine fractures, and spine BMD is more sensitive to the effects of corticosteroids than other sites. (114). The combined measurement of spine and hip are therefore most common in clinical practice today.

Measurements of spine/hip versus forearm

The limited amount of surrounding tissue of radius and ulna increases the accuracy and the precision of bone densitometry due to reduced polychromatic radiation (beam hardening) and negligible soft tissue correction (111). BMD measurements of the spine have an accuracy error of 8-10 % compared to 2 % in the forearm, whilst the precision error is about 1 % at both sites (119;120).

For a spine scanner the accuracy error is almost equal to the true biological variation of the spinal BMD in a healthy peri-menopausal population. Screening with this method for low

BMD therefore produces many false positive and negative results. The lower accuracy error for the forearm measurement combined with the same biological variation at this site gives the method a better profile. This may explain why spinal and forearm measurements appear to predict equally the true BMD of the spine in healthy peri-menopausal women in addition to fragility fractures (121;122). It is also possible that demineralisation may start at locations that are not so stressed by body weight (123).

Cortical versus trabecular bone

The metabolic response is much faster in trabecular bone, and therapeutic effects as well as postmenopausal bone loss, can be detected earlier in regions of trabecular bone compared to cortical bone.

The anatomy of the radius with thin cortex with mainly trabecular bone (70-80%) at the ultradistal site and pure cortical bone at the diaphyses (80%), enables the examination of both cortical and trabecular bone. However, appendicular trabecular bone contains more fatty marrow than does the axial skeleton with its large amount of haematopoietic marrow. The difference between bone types might, therefore, not be as large as in the axial skeleton (111). Cortical bone, on the other hand, contributes substantially to the strength of long bones, explaining why bone densitometry adds information for fracture risk assessment.

Fracture prediction by site

Cummings et al found that BMD in the forearm was as good as the lumbar spine for the prediction of hip fracture, although inferior to the use of the upper femur sites themselves (124). Black et al found that BMD at any site were strongly related to fracture risk, and that BMD of the femur spine, and appendicular sites had similar value with respect to predicting non-spine fractures (125). The correlation coefficient between BMD at the distal or ultradistal

forearm and the femoral neck or lumbar spine has been reported to be between 0.53 and 0.67 (126;127). T Jones et al found that forearm BMD identified 62% of subjects with osteoporosis (T-score – 2.5 at the spine, femoral neck, or both sites) with 89% specificity when they used an estimated cut-off value (0.34 g/cm2). This was estimated from receiver operating characteristics (ROC) curves that calculated the area under the curve (AUC) (128).
Hui et al in a 15 year follow-up study of > 500 women found that BMD of radius was predictive of time to fracture, both for all non-spine fractures and fractures at the hip. For each SD decline in BMD there was an increase in fracture risk of 120 % in the younger age groups and 50% in older retirement-home residents (129).

In a meta-analysis of 11 separate study populations with about 90.000 person years of observation time and over 2000 fractures, Marshall et al concluded that measurements of BMD can predict fracture risk, but cannot identify individuals who will have a fracture. BMD measurement at any site had similar predictive ability for a decrease of 1 SD in BMD except for measurements at hip and spine, which had better predictive ability for fractures in hip and spine, respectively (130). The predictive ability of decrease in BMD was roughly similar to (or, for hip or spine measurements, better than) that of a 1 SD increase in blood pressure for stroke and better than 1 SD increase in serum cholesterol concentration for cardiovascular disease.
With an increase in fracture risk of 1.5 for each 1 SD reduction in BMD, an individual with a measurement of –3 SD below the average value for age would have a 1.5^3 or greater than 3-fold higher risk than an individual with an average BMD.

Table 6 Relative risk for fracture per SD decrease in age specific BMD, by measurement site and fracture site (130).

	Fracture site			
Measurement site	Forearm	Hip	Spine	Any location
Distal radius	**1.7**	1.8	1.7	1.4
Hip	1.4	**2.6**	1.8	1.6
Spine	1.5	1.6	**2.3**	1.5
Calcaneus	1.6	2.0	2.4	1.5

Responsiveness

Longitudinal sensitivity for effect of different treatments does not depend solely on precision, but has to take into account the responsiveness as well. The responsiveness is dependent both on the form of treatment, the scanning technique and site of measurement. Ovarian hormone therapy (OHT) by oestrogen has been shown to be effective in the prevention of bone loss at the peripheral skeleton, and even more effective on the forearm and the spine compared with the femur. Forearm densitometry demonstrate the effect of bisphosphonate therapy, but the responsiveness is significantly lower than at the hip or spine (111). Further, the spine is affected earlier and more severely than the long bones during corticosteroid treatment (CS) (131-133). The effect of CS on forearm BMD has not been monitored by prospective studies, so far, but has been studied in a recent cross-sectional study in Sweden (134)

3.3.3.2 T and Z scores

Bone densitometry results are most often reported as T-scores and Z-scores. They represent the number of standard deviations (SD) above or below the mean BMD. The SD is a measure of the normal variability of a measurement. For T-score the SD is estimated from a normal population aged 25-45 years, whilst for Z-score the SD is estimated from subjects at the same age and sex. A T-score of 0 means that the subject has BMD exactly at the mean for young adults, whilst a Z-score of 0 means a BMD at the mean for subjects at the same age and sex. Because BMD declines with age, T-scores are consistently lower than Z-scores after the age of 40 years, and the difference increases with age.

3.3.3.3 Cut-off values for women and men

The WHO guidelines (135) defined osteoporosis in women as T-score $\leq$ 2.5. The use of such a criteria is heavily debated, and using a diagnostic labelling rather than focusing on low BMD as a risk factor, might contribute to unnecessary worry and medicalisation. The use of these diagnostic thresholds in measurements at the spine or hip identifies 15-20 % of postmenopausal women as having osteoporosis, whilst 30% fulfils this criteria in measurement at the hip, spine or wrist (136).

There are problems in the use of T-scores and in comparison between measurement sites;

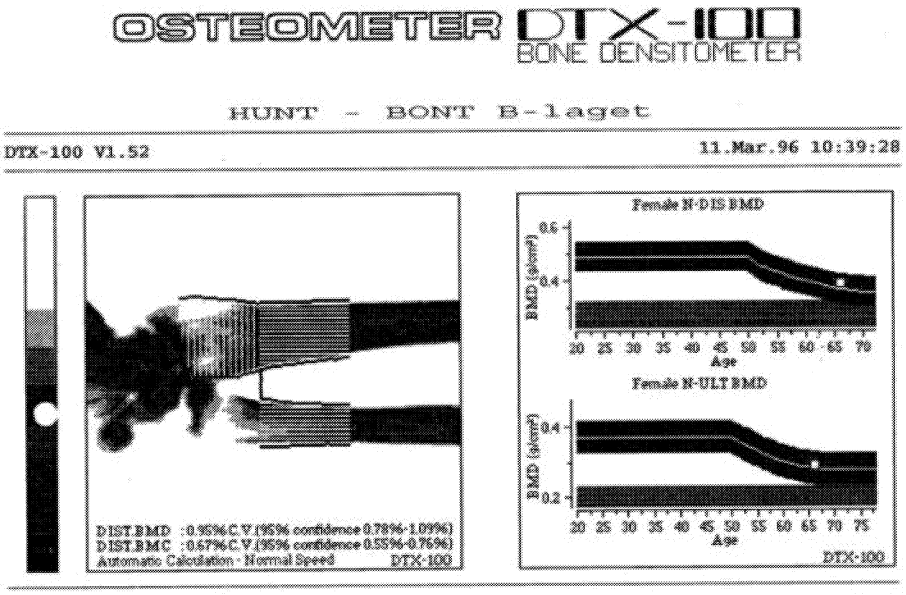
- The accuracy errors range from 2 % in measurement at the forearm to 5-10 % at the hip/ spine
- The variance of measurements in the population ranges from 10 to 20 % for absorptiometric techniques depending on the site used for measurement and any normalisation procedure applied.

- There are systematic inaccuracies, particularly at the spine since the vertebrae are irregular in shape and density, and the mineral content will depend upon the algorithm used for edge detection (136).
- Above the age of 65 there also is an increasing problem with degenerative arthritis of the spine as well as minerals in the aorta, resulting in artificially high BMD in the anterior-posterior directed measurements (137).
- In one study where the same population base was used, the prevalence of osteoporosis in women aged 50 years or more ranged from 10.9 % at the hip, 24.4 % at the spine, to 52.2 % at the distal radius, all measured by DTX (138).

Therefore, T-score should not be used interchangeably with different techniques and at different sites, and the – 2.5 threshold is only recommended to be applied to the hip (136).

There is so far no consensus on the definition of osteoporosis in men. Cut-off values have variously used values derived from the female or male populations. The use of the same absolute value of BMD as a cut-off in men as that used in women gives approximately the same absolute risk of vertebral and hip fractures (139), and is therefore recommended (136).

Fig. 3 Distal and ultradistal site with calculated Z and T-score



>>>>> BoneMass Calculation Results <<<<<

	Radius	Ulna	DISTAL	ULTRA	
BMC :	1.690	1.076	2.767	1.322	g
BMD :	0.400	0.365	0.386	0.292	g/cm²
Area :	4.22	2.95	7.17	4.53	cm²

Distal BMC percent of agematched	: 106 %	Z-score	: +0.3
Distal BMD percent of agematched	: 105 %	Z-score	: +0.3
Ultra BMD percent of agematched	: 103 %	Z-score	: +0.2
Distal BMC percent of reference age	: 83 %	T-score	: -1.2
Distal BMD percent of reference age	: 79 %	T-score	: -1.8
Ultra BMD percent of reference age	: 78 %	T-score	: -1.7

3.3.4 Corticosteroids and bone

3.3.4.1 Oral corticosteroids (OCS)

3.3.4.1.1 Oral corticosteroids (OCS) and bone

OCS in high doses causes reduced BMD and increased risk of fractures. (115;133;140;141). Untreated chronic inflammatory diseases are also associated with reduced BMD, but treatment with OCS is the most common reason for secondary osteoporosis (142). Studies

have indicated that the usual risk factors for osteoporosis like age, race, sex, menopausal state and parity, do not apply to the same extent to CS-induced bone loss (133;143). Van Staa et al in a recent review and study, however, concluded that the effects of cumulative CS dose on BMD were not influenced by age or sex, and they did neither find any difference in fracture risk with CS therapy by underlying diseases (144). In discussion of CS related bone loss, one must be aware of that the loss of the female sex hormone (oestrogen) still is the single most important factor associated with reduced BMD (145). Postmenopausal women receiving OCS are simply at a greater risk of fracture, because they have a lower bone mass when they initiate CS therapy (133).

The pathogenesis of CS-induced osteoporosis is multifactorial and still incompletely understood (115;131;133;146). OCS causes a reduction in bone formation because of inhibitory effect on osteoblasts (mainly through suppressive effect on osteoblastogenesis), and an increase in bone resorption through effect on osteoclast function, in addition to promotion of apoptosis of osteoblasts and osteocytes. Further CS induced myopathy reduces the bone stimulating effects of muscle activity. Conflicting results have been reported regarding negative effect of CS on sex-steroids, parathyroid hormone, and vitamin D levels, but a recent study and reviews have concluded that such effects are unlikely (147).

Bone loss is most rapid during the first six months of OCS treatment (on average 5%), after which there seems to be a slower but steady loss of bone (1-2% per year) (115;146;148).

3.3.4.1.2 OCS and fracture risk

Trabecular bone and the cortical rim of the vertebral body is affected earlier and more severely than cortical bone of the long bones (radius, humerus) during CS treatment (131-

133). Reid et al, in line with this, reported significant greater bone loss of the lumbar spine compared to distal radius (40% versus 20%) (149).

As a result of this, fractures are more common in the spine with high proportion of trabecular bone compared to appendicular skeleton as the radius with high proportion of cortical bone (150;151). Epidemiological data suggest that OCS treatment doubles the risk of fractures of the hip and distal radius and at least quadruples the risk of vertebral fractures (152), and 30-50% of patients taking OCS on a chronic basis will experience fractures (133). Adinoff et al reported an 11% prevalence of vertebral fractures in patients with asthma on OCS treatment for at least one year (131).

3.3.4.1.3 OCS dose and fracture risk

A dose threshold for fracture risk has been discussed. The increased risk of using doses > 7.5 mg of prednisolone or equivalents for prolonged periods has been well documented (133;148;153). Pearce et al suggested an increased risk of bone loss and fracture at prednisone doses as low as 6.0 mg/day for more than six months (154), Hollister et al found negative effect on bone at doses as low as 5 mg/day (155), whilst van Staa et al in the GPRD study, reported increased risk of fracture even in users of 2.5-7.5 mg prednisolone (140). In the latter study the fracture risk was stable at about 20 % higher for users of doses < 5 mg/day, increasing to about 60% higher compared to controls for those using 20 mg/daily (156). In addition to the correlation between daily dose and fracture, they found a weaker correlation between cumulative OCS dose and fractures.

Niewoehner et al in a review concluded that anyone receiving frequent or prolonged (> 3 months) OCS treatment was at increased risk for osteoporosis, but marked bone loss was seen in only 40% of patients (115). Recently, Dubois et al in a cross-sectional study found that

administration of multiple OCS courses for COPD was associated with more harmful effects against bone compared to continuous OCS treatment regimens (> 10 mg prednisolone/day) (157). An average OCS course consists of approximately 250 mg of prednisolone equivalent. The study indicated a cumulative dose threshold of 1000 mg of prednisolone, above which alarming bone loss could be expected. Higher bone loss during the first months of OCS treatment followed by a plateau (158) could support this as multiple courses of OCS could be associated with multiple episodes of rapid bone loss.

Studies have, however, indicated that CS induced osteoporosis is reversible (159). In a retrospective cohort study in the United Kingdom (GPRD) including 244,000 OCS users and controls (users of ICS only), the increased fracture risk declined toward baseline rapidly after cessation of OCS treatment (140). In line with this Lane et al previously have reported increased bone mass in the central skeleton of CS induced osteoporosis in postmenopausal women treated with parathyroid hormone (160), and this is also found after surgical treatment for Cushing ‘s syndrome (161).

3.3.4.1.4 OCS and bone mineral density

In a review of 66 studies, van Staa et al found consistently lower BMD in CS users than expected for a group of similar age and sex (144). The studies included had used single (SPA) or dual photon absorptiometry (DPA), QCT or DXA. BMD, in percent of expected, in CS users were at different sites: spine 89.4%, hip 88.8%, distal radius 88.3 %, and mid-shaft radius 92.2%. Limiting the analyses to studies having used DXA, however, BMD for the hip was 88.5 % and for distal radius 97.8% of expected, indicating highest influence by CS on the former site.

Daily dose/cumulative dose

In their meta-analysis van Staa et al found a strong correlation between cumulative CS dose and decreases in spine and hip BMD (144), but no statistically significant relationship between daily CS dose and decreases in BMD. Interpretation of these results was complicated because the daily doses used prior to the BMD measurement were frequently unknown and not taken into account. However, two randomised studies found an negative effect on spine BMD after short time use (20 and 12 weeks) of prednisolone 7.5 mg, (159;162), indicating a daily dose response effect too.

Results indicating a correlation between daily dose and fracture on one side, and cumulative dose and BMD on the other, might have been influenced by selection bias. Studies on CS and BMD are mainly conducted in specialist centres including patients using CS continuously over prolonged periods of time, whilst the GPRD study was based on patients from general practice with mainly intermittent use of CS and relatively few chronic users and patients with rheumatoid arthritis. However, if this difference was real, an explanation might be that CS decreases the rate of bone formation through promotion of apoptosis of osteoblasts. As only a small part of bone is being remodelled at one point in time, changes in BMD will occur slowly. CS effect on osteocyte apoptosis, however, could lead to a deterioration of bone quality and early increases in fracture risk. The combined effect on both osteoblasts and osteocytes could explain the relation between daily dose and fracture risk versus cumulative dose and low BMD (144). A parallel to this is seen in use of bisphosphonates, which have a protective effect against fracture despite relatively small increases in BMD, and they have been shown to prevent osteocyte and osteoblast apoptosis (163).

3.3.4.1.5 OCS and bone quality

It has been questioned if the OCS in addition to its effect on BMD, also causes an alteration in bone quality that means that fractures occur at a higher BMD than might be expected (164;165). Some studies have reported contrasting results (166), but van Staa et al from a meta-analysis strongly have suggested that fractures occurred at much higher rates than expected on the basis of BMD changes. This mean that BMD changes during CS therapy may only predict to a moderate extent the increases in fracture risk (144). In line with this, Clowes in a review reported substantially higher risk of fractures in CS-induced osteoporosis at a similar level of BMD compared to postmenopausal osteoporosis (167). Further, histomorphometric reports have indicated that bone loss due to OCS therapy occurs predominantly by trabecular thinning rather than by perforations or disconnections of trabecula as in idiopathic osteoporosis (144).

This means that OCS use is an independent risk factor for fracture over and above BMD. A higher threshold than set by the WHO for intervention with bone sparing treatment, therefore, have been recommended in these patients (T-score = –1.5 rather than –2.5) (168).

3.3.4.2 Inhaled corticosteroids

3.3.4.2.1 Use of inhaled corticosteroids

Knowledge on deleterious effect of OCS on bone has given concern about similar effect induced by inhaled corticosteroids (ICS) (169-171).

Inhaled corticosteroids (ICS) is the most effective anti-inflammatory treatment in chronic bronchial asthma (7) and during the last decades the trend has been to apply this treatment for milder disease and in younger age compared to previously. In addition, ICS is commonly used

in COPD even if the evidence for such use is poor (172) and guidelines (17;172;173) recommend such use only in:

- Symptomatic COPD patients with a documented spirometric response to ICS and
- Those with an FEV_1 < 50% predicted with repeated exacerbations requiring treatment with antibiotics or oral corticosteroids (CS).

The rationale for using ICS has been the deposition of medication in the lower airways with far less systemic bioavailability of the active drug compared to use of OCS. The systemic availability of drug deposited in the intrapulmonary airways probably is, however, as high as 80% (174). As no lower threshold for negative effect of OCS on bone has been found, more attention has been given on the possible systemic side effect of ICS.

There are many different types of ICS and devices available. In Norway there are beclomethasone dipropionate (BDP), budesonide (BUD) and fluticasone propionate (FP), which are inhaled either as aerosol (with or without inhalation chamber), or powder. There are extensive data from clinical trials regarding these three types with regard to bone metabolism, but limited data is so far available on flunisolide and triamcinolone acetonide, drugs that are not available in Norway for treatment of obstructive lung diseases. A possible difference in systemic effect of the different types of ICS depend on a complex interplay between factors comprising type of device, CS absorption from the gut and lung, hepatic first pass metabolism, active metabolites, receptor potency and affinity, tissue retention and plasma elimination (175).

3.3.4.2.2 Inhaled corticosteroids and bone

There have been a lot of studies on the relation between use of ICS and BMD/ bone markers, and the results have so far been conflicting. (Appendix) Some cross sectional studies have reported a negative association between ICS and BMD (176-185), whilst other have reported no such association (134;186-189). In a large cross sectional study among asthmatics in UK including 170,818 patients using ICS and 108,786 patients using only bronchodilator, Van Staa et al reported similar and increased risk for fractures in both groups (190). Further, conflicting results have been reported from longitudinal studies, some with negative association between ICS use and BMD (191-194), and others with no association (195-197). Regarding random clinical trials (RCT), the Lung Health Study reported higher percentage decrease in COPD patients using triamcinolone acetate compared to placebo (198), but no effect was found until year 3 in the study. Egan et al reported a significant decline in spine BMD measured by quantitative computed tomography (QCT) in the BDP group compared to FP group, but this was not found on dual energy x-ray absorptiometry (DXA), and because of high withdrawal rate, no firm conclusions were given (199). No negative association have been reported in other RCT (200-204). Pauwels et al in a random double blind cross over study with FP 500-1000 ug and BDP 1000-2000 ug, reported an increase in BMD in the FP group, but no difference in the BDP group (205). The subjects had used BDP or BUD 800-2000 ug prior to baseline, so whether ICS in these patients had reduced BMD cannot be said, but compared to baseline at least FP had a positive effect. Other studies have reported FP to be favourable regarding bone markers compared to BDP, but equal to BUD (195;199;200;206;207) comparing efficacy and side effects of different ICS.

3.3.4.2.3 Reviews on inhaled corticosteroids' effect on bone

A possible negative effect of ICS on bone metabolism has been a topic for many review papers:

- In 1998 Efthimiou and Barnes (208) in a review of 11 studies (1,240 patients) on biochemical bone markers and 14 studies (373 patients) on BMD (183;184;186;187;192;196;202;209-211) (references to abstracts and studies on children is not given here) over a wide dose range, found no indication of significant or clinically important effect on these measurements in adults or children with asthma in doses up to 1.000 ug/day and 400 ug/day of BDP, respectively
- In 1999 Goldstein (212) concluded that the long-term studies suggested that doses of ≤ 800-1200 ug/d BDP , ≤ 800-1000ug/d BUD, ≤ 750 ug FP, and ≤ 1000ug/d flunisolide may have limited or no effect on bone metabolism during chronic treatment (177;179;186;187;192;194;196;205;210;213).
- In 1999 Niewoehner et al concluded that the use of low doses ICS may be safe enough not to require special assessment of bone loss or preventing measures (179;186;188;196), but evidence was lacking on the risk of long-term use of higher doses (115).
- In 1999 Cave et al (214) concluded that even if changes in BMD occur at doses above 800 ug/day BDP or equivalent in both asthmatics and healthy adults, the clinical relevance of such changes was unknown because of the lack of long-term studies on BMD changes in patients receiving ICS with minimal or no life-time use of OCS. Additionally, in a literature search they did not find evidence for causal association between nasal CS and osteoporosis, but a theoretical risk remains at high doses.
- In 1999, Smith et al (131;165;179;183;186;209;211;215;216), concluded that criteria for causation were met to a moderate degree for OCS but poorly met for ICS, and that the roles of confounders had not been addressed (217).

- The latest Cochrane review on ICS and BMD (201;203;204;218-221) by Jones et al published in 2002, concluded that in patients with asthma or mild COPD, there is no evidence of an effect of ICS on BMD or vertebral fracture at conventional doses given for two or three years. Higher doses were associated with biochemical markers of increased bone turnover, but data on BMD and fractures at these doses were not available. Longer-term prospective studies of conventional and high doses of ICS were recommended (222).

3.3.4.2.4 Methodological problems of prior studies

Some of the smaller cross sectional studies have reported positive findings not confirmed by larger studies with use of higher ICS dose. This could partly be related to subject selection bias, post hoc sub-group analysis, and publication bias. Control data have varied between studies, and have included healthy subjects, asthmatic and/or COPD patients using no medication, only bronchodilator or low doses of ICS. In addition, subjects with previous use of OCS courses have variably been excluded in analyses of ICS effects.

A number of prospective studies have been published, mainly as abstracts, most of which have failed to find an effect of ICS on BMD. The possibility of type II errors (declaring that a difference does not exist when in fact it does) could not be ruled out. Short duration of ICS use, inclusion of OCS use, lack of information on confounders and few RCT studies have made the interpretation difficult. Wisniewski et al calculated that a prospective study comparing a dose of 1000 ug BDP or equivalent with placebo would require 2.500 patients in each limb for 95 % power to detect the difference of 0.1 SD in BMD found in their cross-sectional study (210). Regarding fractures, even larger studies with long duration is necessary in order to avoid type II errors, - because only a small number of subjects at risk actually

sustain a fracture during the observation time. For example, in any year, fractures occur in 1-2 per 100 women aged 65, 6-10 per 100 women aged 75, and only 1-2 per 2,000 of the 15 % of women < 60 years of age with osteoporosis (223). Pending on results from such studies, we have to rely on studies on surrogate markers for fracture risk as BMD and BM.

Results from RCT are regarded as having the highest evidence level. These, however, are conducted in idealised settings with motivated health professionals and patients, and most RCT studies have a rather short duration. Further, results are uncritically applied on other patient groups and treatment regiments are often not followed. This might influence both the effect and side effect of the treatment, necessitating real life studies to reveal both to what degree the promised effects are reached and if feared or new side effects have developed.

Among patients with obstructive lung diseases there is both an over- and under-use of medication (172). Some patients use unnecessary high doses of ICS because doctors have not instructed them to step down the doses to the lowest dose necessary to control the disease, and some use ICS without current guidelines recommending such treatment (i.e. most COPD patients). On the other side, under-use of ICS is common because of lack of compliance with medication regimen and inhalation technique in large patient groups, especially with prophylactic treatment like ICS. Cochrane et al in a review found that patients took the recommended doses of inhaled medication on 20-73% of days, and an frequency of efficient inhalation technique in 46-59% of patients (224).

3.3.5 Other factors influencing bone mineral density

3.3.5.1 Diet

Total energy intake, calcium and vitamin D seem to be the most important dietary factors for BMD and fracture risk (225). The Framingham Osteoporosis Study found that a good quality diet with high intakes of fruit, vegetables, and breakfast cereal might contribute to better accumulated BMD in old age, particularly in men. In women, alcohol seemed to be protective. Both men and women consuming nutrient-poor diets, particularly those with a high intake of candy, had significantly poorer BMD (225;226).

3.3.5.2 Physical activity

Physical activity both at leisure time and work is positively associated to bone mineral density (227), and is also found to protect against hip fractures (228). The stimulatory effect occurs when the skeleton is subjected to strains exceeding habitual skeletal loads, and the intensity of load is more important than the duration of the stimulus. Weight bearing activities, such as walking, have a greater effect than non-weight bearing activities, such as cycling and swimming. Physical activity during adolescents increases peak bone mass and during adulthood reduces the loss of bone mass. Further, reduction of loads as in bed resting or in space flights leads to bone loss (229;230). In a meta-analysis Berard et al found a significant effect of physical activity on bone mineral density at the L2-4 level of the lumbar column, but no effect could be seen, however, on forearm and femoral bone mass (231).

3.3.5.3 Tobacco smoking

Even if conflicting results regarding the effect of cigarette smoking have been reported, there seem to be a negative effect of this on BMD (145).

In a review of 29 cross-sectional studies (232) Law and Hackshaw found that:

- smoking had no material effect on BMD in premenopausal women,
- postmenopausal bone loss was greater in smokers, an additional 0.2% of bone mass each year
- current smokers had higher risk for hip fractures compared to non-smokers (17% at age 60, 41% at age 70, 71% at age 80, and 108% at age 90,
- the data in men was limited but suggested a similar proportionate effect in smokers,
- among all women, one hip fracture in eight was attributable to smoking.

Hermann et al (233) in a study on 2015 recently menopausal women found significant negative associations of cigarette smoking on bone mass in the lumbar spine, femoral neck, and total body. Quantitatively, the differences at theses sites between current smokers and never smokers were limited to 1.6, 2.9, and 1.9%, respectively. A statistical interaction was found between smoking and fat mass, indicating that women in the highest tertile of fat mass were unaffected by cigarette smoking. The average cumulated effect of pre-menopausal smoking on bone was small but biologically significant. Serum levels of 25-hydroxyvitamin D (25-OHD) and osteocalcin were lower in smokers, which might affect rate of bone loss.

Ward and Klesges analysed pooled data across 86 studies, enrolling 40,753 subjects (234). They found that smokers compared to non-smokers had significantly reduced bone mass at hip, lumbar spine, forearm, and heel. Deficit was especially pronounced at the hip with 1/3 SD, and on average 1/10 SD for all sites. Overall, effects were greatest in men and in the elderly, and were dose-dependent. Based on the data, the increase in lifetime risk of developing a vertebral fracture was estimated to be 13% in women and 32% in men. The risk was partially reversed by smoking cessation.

3.3.5.4 COPD patients

In addition to possible iatrogenic effects (due to CS, and even theophylline according to animal studies (235)), there are several lifestyle contributors to osteoporosis for patients with obstructive lung disease (236). Important contributors are poor nutrition and reduced dietary calcium intake (due to the belief that "milk makes mucus" (237)), decreased level of exposure to sunlight , low BMI, and reduced levels of physical activity due to both respiratory symptoms and muscle function alteration (238). In addition, in subjects with severe respiratory disease bone loss is accelerated because of inactivity during hospitalisations (239). Further, recent studies have indicated that the inflammatory process in the lungs induces a systemic hypercatabolic effect in COPD patients, which may partly be responsible for the observed association between COPD and osteoporosis (240).

3.3.5.5 Other HUNT results

Conflicting results have been reported regarding association between life style factors and BMD in other studies on the HUNT population (241;242), but interactions between confounders and inclusion of different age groups in the studies could explain this. In a study including women 19-35 years, age and weight were positively associated to BMD, whilst later age at menarche and lack of milk consumption were associated with lower BMD. No other life style factors were found to be significantly associated to BMD (242). In a study of women aged 50-59 years the strongest association with BMD was found for age, weight, time since menopause and a history of bilateral oophorectomy (241).

4 Material and Methods

4.1 The Nord-Trøndelag Health Study (The HUNT study)

4.1.1 Study area and population

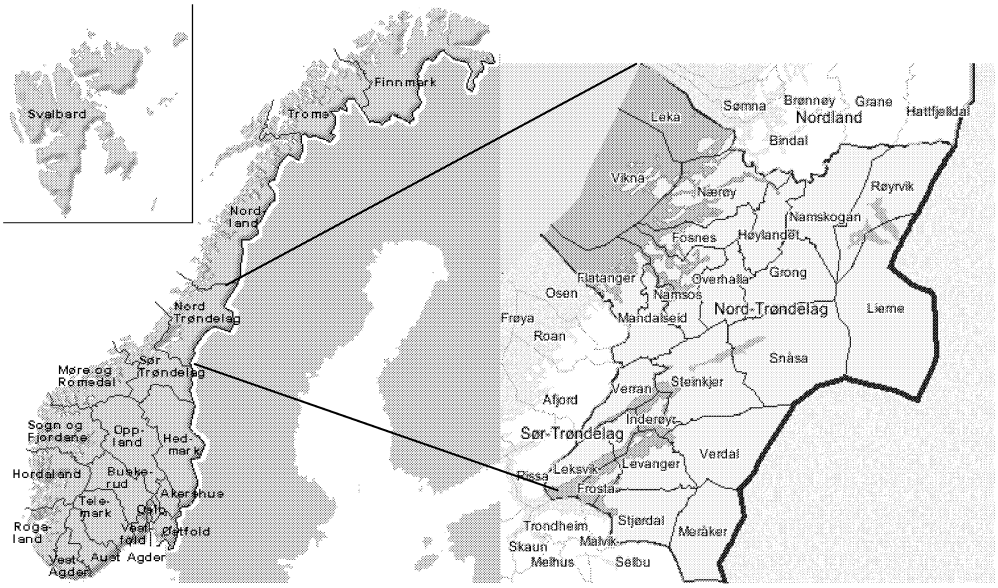
Nord-Trøndelag County (22,463 km^2) is one of 19 counties in Norway, and is situated in the middle part of country. The county is located at latitude of 64 degrees north, but the climate is milder than in other areas of the same latitude due to the Golf Stream. There is mostly mild coastal climate, but also typical inland areas with cold dry winters. The total population in 1995 was 127,000 residents, 97 % being of Caucasian origin. The area is generally rural with a scattered population, but with several densely populated areas and small cities, the largest of which has 21,000 residents. 15 % of men and 6 % of women worked as farmers. Except for previous mining industry in the two smallest municipalities, there is hardly any industrial pollution in the county.

Compared to other counties in Norway, Nord-Trøndelag has slightly lower levels of education, income and prevalence of current smokers in addition to the lack of large cities (56). Otherwise, Nord-Trøndelag is representative of Norway as a whole, for example regarding geography, economy, sources of income, age distribution, morbidity, mortality (55;243), and regarding respiratory diseases, the sale of anti-asthmatic drugs has been close to the Norwegian average (244).

4.1.1.2 HUNT 1 1984-86

Everyone aged 20 years or more by Dec. 31.st 1983 were invited to the study, and totally 74,994 persons (88.1%) participated (243). The main subjects were arterial hypertension, diabetes mellitus, quality of life, and x-ray screening of the chest.

Fig 4. Map of Norway and Nord-Trøndelag County with all municipalities



4.1.1.3 HUNT 2 1995-97

Everyone ≥ 20 years (having reached 20 years during the year of the screening in their municipality) were invited to the adult part of HUNT 2, whilst adolescents aged 13-19 years were invited to the Young-HUNT. Out of 92,936 invited adult persons, 65,225 (70.2 %) participated at the screening (Fig 5). In addition, 492 subjects answered questionnaire I without participating at the screening.

The subjects received together with the invitation a comprehensive Questionnaire 1, which was delivered at the screening station. All attendants received further Questionnaire 2 and samples received more disease specific Questionnaire 3 which should be returned by mail.

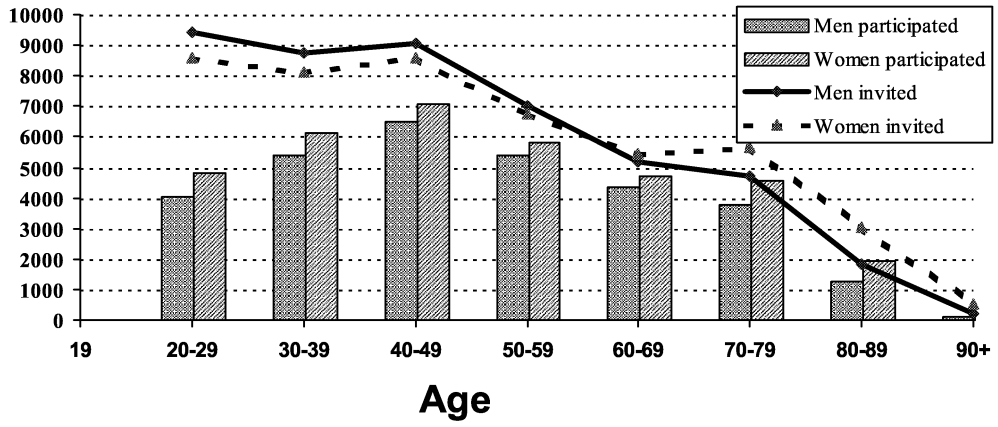


Fig 5. Invited and participants by age and sex.

Measurements at the screening station:

- Everyone: height, weight, waist and hip circumference, blood pressure, audiometry, vision test, blood samples analyzed for lipids, ferritin, thyroid hormones, glucose, etc. In addition full blood and serum are stored at minus 80 degree Celsius for future analyses.
- Samples: bone mineral density and lung function.

4.1.1.4 Questonnaires

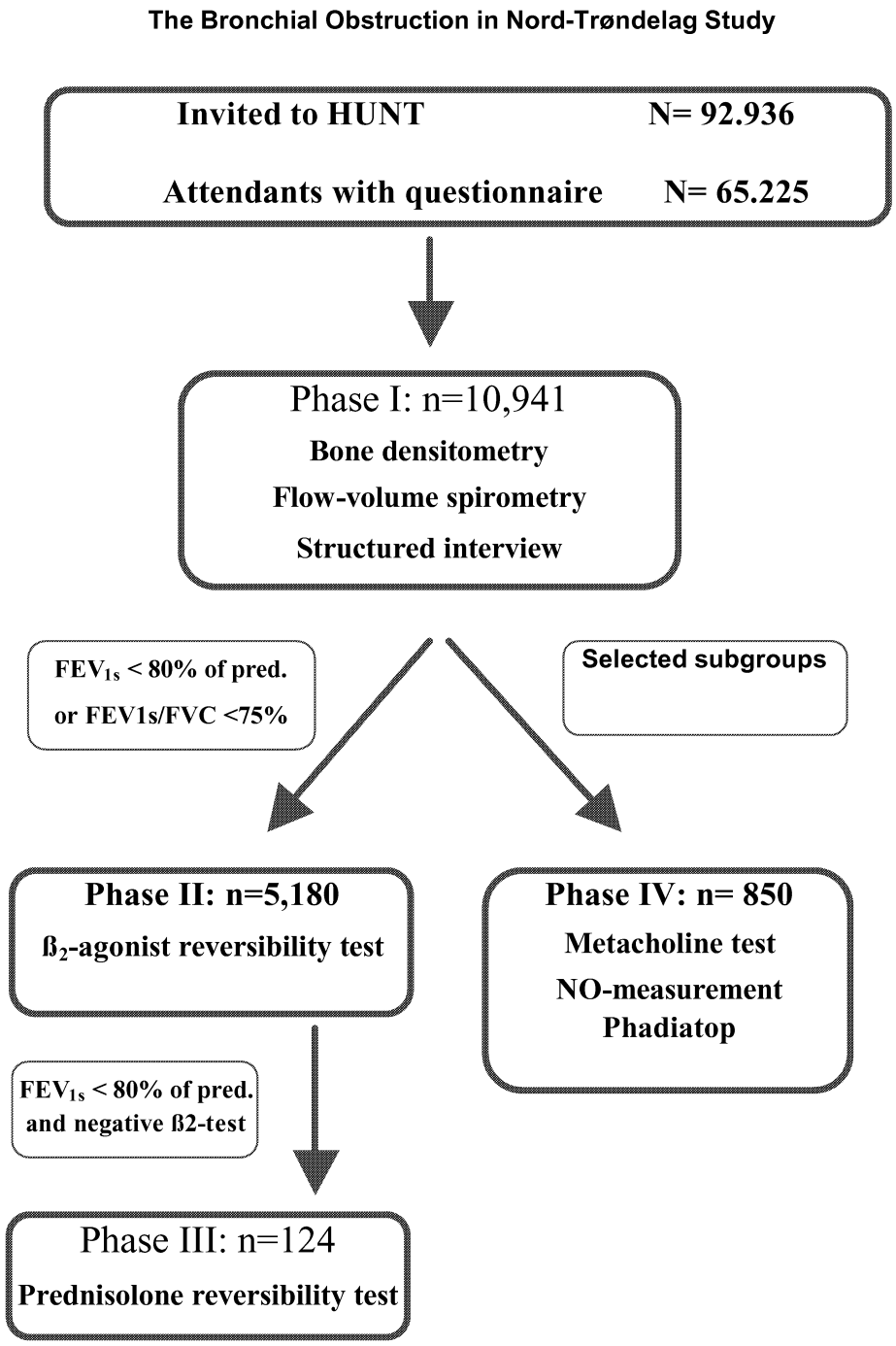
The questionnaires focused on demographic data, socioeconomic data, environment, life style and risk factors as physical activity, food habits, alcohol and smoking habits, fertile data in women, family diseases, previous diseases, current diseases as cardiovascular diseases, diabetes mellitus, hypo-hyperthyreosis, anxiety and depression, chronic pain, urine incontinence, hemochromatosis, and obstructive lung disease.

The selection of questions in Questionnaire 1 and 2 had to take into consideration different factors:

- Previous use of Cohort Norway (CONOR) questions. CONOR represents a planned cohort of 200,000 subjects included from different population based studies in Norway (Counties included are Finnmark, Troms, Nord-Trøndelag, Hordaland, Sogn and Fjordane, Oppland, Hedmark, and Oslo). The objectives of CONOR are studying of causal relationships for low prevalent diseases and the descriptive studies of diseases and risk factors in Norway. Identical questions have been used in these populations based studies in addition to storage of blood samples.
- Previous use of questions in HUNT 1
- Validated sets of questions
- Wishes by other sub-studies
- Available space on questionnaires

These selection criteria resulted in limited possibilities for the sub studies to decide which questions should be included. Except for the questions on tobacco smoking (245), and self-reported fractures (246), the questions have not been validated. Space on questionnaires and higher priority of the Conor and HUNT 1 questions did only permit validated sets of questions in a very limited extent in Questionnaire 1 and 2. Validated questions, therefore, were included in Questionnaire III and in the interview in phase 1.
The questions in the questionnaires and interview are given in the appendix.

Fig 6. The design of the BONT Study Phase I-IV



4.2 The BONT Study

This dissertation discusses only results from BONT phase I, but the methods of the entire BONT study is included, as this is an important basis for further studies.

4.2.1 BONT Phase I

4.2.1.1 Invited to participate

- 5 % random sample of the total population selected by the two last digits in the personal identification number. The digits were selected by random function on a HP 11C by The National Health Screening Service of Norway (SHUS). The selected digits were 03, 33, 37, 57, and 90. The invitations with Questionnaire 1 were marked SB (Spirometry/BONT) for those selected for the random sample

- Those having answered "Yes" to one of these questions:
  - Have you had any attack of wheezing or breathlessness during the last 12 months?
  - Do you have or have you had asthma?
  - Do you use or have you used asthma medication?

  At the screening station the nurse in charge of blood pressure measuring, selected subjects fulfilling the symptom/disease criteria of the BONT study.

4.2.1.2 Measurements

- Flow volume spirometry
- Bone densitometry of the forearm
- Interview

4.2.2 BONT phase 2

4.2.2.0 Aims

- To study bronchial reversibility in never-smokers without respiratory symptoms or diseases and estimate cut-off values for clinical practice
- To study the association between bronchial reversibility and respiratory symptoms
- To study bronchial reversibility in subjects with self-reported asthma and chronic bronchitis/emphysema

4.2.2.1 Invited to participate

- Team 1 (The 5 largest municipalities: Stjørdal, Levanger, Verdal, Steinkjer, Namsos):
  Subjects with FEV_1 < 80 % of predicted according to ECCS reference values (1) or $FEV_1/FVC < 0.75$
- Team 2 (The other 19 municipalities):
  All participants of BONT phase 1. The spirometry in phase I was used as the pre-bronchodilator measurement for BONT phase 2

4.2.2.2 Measurements

β_2-agonist reversibility test: FEV_1 before and 30 minutes after inhalation of 1 mg terbutaline

Team 1: BONT phase I was the last item at the screening station. Phase II was performed 6-8 weeks later, whilst phase III and phase IV were performed 1-2 and 3-4 months later, respectively.

Team 2: BONT phase I could not be performed at the same time as the main screening. Those selected for BONT therefore were invited for examinations/interview 4-8 weeks later, combining phase I and II.

4.2.3 BONT phase 3

4.2.3.0 Aims

- To study bronchial reversibility after a prednisolone course in subjects with bronchial obstruction without reversibility at baseline spirometry

4.2.3.1 Invited to participate

- Subjects living in parts covered by Team 1 and
- Participants of phase 2 having post bronchodilator FEV_1< 80 % predicted (1) and increase in FEV_1 less than 12 % of the initial level.
- Written consent given prior to prednisolone course

Exclusion criteria:

- Current use of warfarin, diuretics, digitoxin, dioxin, anti-psychotic or anti-depressive medication, oral corticosteroids, and immune suppressive therapy.
- Prior or current bleeding ulcer in ventricle or duodenum
- Current diabetes mellitus, pregnancy or infectious disease
- Age above 75 years
- Prior side effects of treatment with oral corticosteroids

4.2.3.2 Measurements

Three weeks after Phase II with daily use of Prednisolon 20 mg

- β_2-agonist reversibility test

4.2.4 BONT phase 4

4.2.4.0 Aims

- To study the levels of Nitric Oxide in exhaled air and airway responsiveness in subjects with respiratory symptoms
- To study the association between lung function, levels of Nitric Oxide, airway hyperresponsiveness and allergy against common inhalation allergens
- To estimate the prevalence of allergy against common inhalation allergens in a random sample and subjects reporting respiratory symptoms/diseases

4.2.4.1 Invited to participate

- 3 % random sample of subjects living in Levanger and Verdal. The digits were selected by SHUS in the same way as the 5 % random sample in phase 1, and the selected digits were 40, 81, and 87. Ideally, the measurements should have been performed on the 5 % random sample, but as this sample also participated in other sub-studies, we had to limit the burden on this group.
- 50% randomly chosen subjects among those having answered "Yes" on at least one sub-question among the three first main questions in Questionnaire 3 and
  - Having FEV_1 > 65 % of predicted (1) and
  - Not selected to the 5 % random sample and
  - No use of corticosteroids during the last 6 months and
  - Born after the year 1925

4.2.4.2 Measurements

- Nitric Oxide in exhaled air
- Methacholine provocation test
- Phadiatop screening test of inhalation allergy. In case of positive test, measurements of specific IgE were performed.

Table 7a: Participants in different phases of BONT by symptom and random sample in Team 1including the municipalities: Levanger, Verdal, Steinkjer, Stjørdal and Namsos

Phase and category	**Symptom sample**				**Random sample**			
	Women		Men		Women		Men	
	n	%	n	%	n	%	n	%
Phase 1								
Invited	3,276		2,942		1,128		965	
Participants	2,992	91.3	2,659	90.4	1,087	96.4	891	92.3
Phase 2								
Invited (% of participants phase 1)	1,042	34.8	1,248	46.9	213	19.6	254	28.5
Participants (% of invited phase 2)	686	65.8	884	70.8	131	61.5	166	65.4
Phase 3								
(Team 1 – Namsos (13.3%))								
Invited	126		158		12		19	
Participants (% of invited phase 3)	55	43.7	61	38.6	4	33.3	4	21.1
Phase 4								
Invited	434		355		242		248	
Participants (% of invited phase 4)	311	71.6	255	71.8	157	64.9	127	51.2

Reasons for not participating in phase 3 (more alternatives possible):

- 41% did not want to participate
- 59 % could not participate because of exclusion criteria
  - 18% because of current use of oral corticosteroids
  - 5 % because of infectious diseases
  - 36 % because of diseases/use of medication included in exclusion criteria

Table 7b: Participants in BONT phase I and II by symptom and random sample in Team 2 including the 19 smallest municipalities in Nord-Trøndelag

Category	Symptom sample				Random sample			
	Women		Men		Women		Men	
	n	%	n	%	n	%	n	%
Invitation phase 1 and 2	1,885		1,960		637		566	
Participants (% of invited)	1,262	66.9	1,238	63.2	423	66.4	390	68.9
Selection criteria for phase 2	442	27.3	583	47.1	75	17.7	115	29.5

Those selected for the BONT study were invited to combined phase 1 and 2
6-8 weeks after the main screening. Reversibility test was performed of everyone.

4.2.5 Bone densitometry -follow up study in 2001

The study was performed in collaboration between the BONT study and the Osteoporosis study. The latter study included samples of women aged 50 years or more.

4.2.5.0 Aims for the BONT study

- Study the change in BMD of the forearm in subjects with respiratory symptoms/diseases with or without use of ICS and in healthy subjects over a period of 4-5 years

4.2.5.1 Invited to participate in the BONT study:

- The 5 % random sample invited to BONT phase I
- Everyone reporting ever use of corticosteroids for asthma/chronic bronchitis/emphysema in BONT phase I.

Table 8 a. Age categories of women with acceptable bone densitometry by sample in the BONT study 1995-97 and the follow-up study in 2001.

Born year	HUNT 95-97				Follow up 2001		
	RS	ICS	Symptoms	**Total DTX**	RS	ICS	**Total DTX**
1897-1909	1	1	19	**21**		1	**1**
1910-1919	94	81	201	**355**	30	22	**52**
1920-1929	205	195	433	**788**	128	185	**313**
1930-1939	187	257	479	**883**	146	310	**456**
1940-1949	308	227	652	**1107**	241	361	**602**
1950-1959	330	197	675	**1112**	234	139	**373**
1960-1969	254	143	572	**918**	171	83	**254**
1970-1979	111	92	302	**486**	47	30	**77**
Total DTX	1490	1193	3333	**5670**	997	1131	**2128**

Table 8 b. Age categories of men with acceptable bone densitometry by sample in the BONT study 1995-97 and the follow-up study in 2001.

Born year	HUNT 95-97				Follow up 2001		
	RS	ICS	Symptoms	**Total DTX**	RS	ICS	Total DTX
1897-1909	3	3	12	**17**	1		1
1910-1919	74	94	175	**319**	15	33	48
1920-1929	181	254	471	**840**	111	120	231
1930-1939	184	187	481	**806**	130	117	247
1940-1949	286	152	662	**1024**	196	106	302
1950-1959	263	117	596	**962**	141	54	195
1960-1969	189	79	522	**753**	87	40	127
1970-1979	87	45	229	**368**	33	11	44
Total DTX	1267	931	3148	**5089**	714	481	1195

Overlapping categories, the figures in column total DTX, therefore, is less than the sum of each row. The symptom sample was not invited to the measurements in 2001.

4.2.5.2 Measurements

- Bone densitometry of the forearm
- Questionnaire and interview

4.2.6 Instruments in the BONT study

4.2.6.1 Questions (Appendix 1 and 2)

The use of validated question sets in Questionnaire 1 and 2 was limited because of higher priority of CONOR and HUNT 1 questions and lack of space in the questionnaires.
The cough related questions in Questionnaire 1 were CONOR questions. They were different from the cough questions used in HUNT 1 (*Do you normally: a) cough in the morning? b) Bring up phlegm from your chest in the morning*?), but similar to questions recommended for the epidemiological definition of chronic bronchitis (17;247), and were also used in The OLIN study (2).

Intending to include most subjects with asthma related symptoms or treatment for bronchial obstruction for further examinations in the BONT study, questions with high sensitivity were selected in Questionnaire I (66;69). Questionnaire 3 focused on symptoms of bronchial hyperresponsiveness (used in the OLIN study (2)), allergy (used in ECRHS (67), influence of respiratory symptoms on physical activity (67), and exposure for domestic animals at home in childhood (67). In addition questions on doctor-diagnosed asthma and chronic bronchitis/emphysema were included.

4.2.6.2 Interview (Appendix 2)

The questions of the interview focused on asthma related symptoms (67), use of asthma medication and use of any form of corticosteroid (injection, nasal, inhalation, oral, but not dermal). The latter questions were developed for the BONT study. In case of use of nasal or inhaled medications, pictures of the different devices were shown to the patients for identification. For the inhaled corticosteroids the different dose alternatives also were visualised in colour. The subjects were asked about their current use during the last week as this was thought to reflects the real use of medication better than the dose prescribed by their doctor.

The nurses/technicians were instructed to ask the questions exactly as the written form, and how the questions should be explained if the subjects did not understand the questions. The questionnaire of the interview was computerised, and the use of automatically jump functions related to the chosen answers, ensured that only relevant questions were asked and time saved. The interviews were performed during the bone mineral densitometry lasting about five minutes. This was sufficient for most subjects, but for elderly and those having used different medications and devices, the interview could last up to 15 minutes.

4.2.6.3 Spirometry

4.2.6.3.1 Equipment

Flow volume spirometry was recorded with three pneumotachographs (MasterScope Spirometer, version 4.15, Erich Jaeger GmbH, Wuerzburg, Germany). These are Lilly Type pneumotachographs. The advantages with these are that they are their being easy to use, light and easy to hold, reliable, reproducible, and easy to clean. The disadvantages are drifts with

temperature, need for regular calibrations if moved, affection by condensation, accuracy error calibration procedures (78). Regular checks for holes in the sensor, channel plugging and excess moisture was therefore performed.

Calibration was performed in the morning and in the afternoon. In addition the technicians measured their lung function every day working at the spirometry station.

4.2.6.3.2 Acceptability and reproducibility criteria for spirometry

We used criteria recommended by the ATS (248).

The acceptability criteria are;

1. Satisfactory start-of-test (Maximal effort curve and the back-extrapolated volume should be less than 5% of FVC or 0.15L)
2. Minimum FVC-exhalation time of 6 second
3. End of test criteria (during the two last seconds of expiration the volume change should not exceed 40 ml)

The reproducibility criterion is:

1. The largest and second FEV_1 should not vary by more than 0.2 L

Previously the criteria was a variation between the two best test within 5 % or 0.1 L (249). The change of criteria was performed because the within subject variability of FEV_1 and FVC had been shown to be independent of body size.

4.2.6.3.3. Technicians

The technicians were trained in the procedure prior to work at the stations, and repeatedly supervised by the project manager during the project period. Totally 20 different technicians were involved in spirometry. Fewer technicians had been wanted, but the high number was due to two teams working at the same time, rotation at the screening station to avoid worn-out among technicians, high number of municipalities, great geographical distances, and pregnancies.

In accordance with the 1994 American Thoracic Society (ATS) recommendations (248), the technicians were taught to instruct the subjects to perform three acceptable and reproducible manoeuvres, ensuring that the subjects produced the highest possible PEF and that the expiration continued for at least six second. If the subjects were unable to do this, up to five manoeuvres were performed. The flow volume curve with the highest sum of FEV_1 and FVC was retained. Even if this may have contributed to saving of curves with submaximal effort (250), we did not exclude such curves in accordance with the ATS. The computer provided the technicians with feedback as to whether the acceptability and reproducibility criteria were met. The error messages given were in accordance with the 1987 ATS recommendations (249), with a reproducibility criteria of < 100 ml or 5 % difference between FEV_1 and FVC in the two best tests, and a lower limit back extrapolated volume of 100 ml. In the 1994 ATS recommendations (248), these limits were 200 ml and 150 ml, respectively.

4.2.6.4 Bone densitometry

Forearm bone densitometry was performed with three sets of single x-ray absorptiometry (SXA) Osteometer DTX-100 (Osteometer MediTech, Inc., Hawthorne, California). The dominant arm was measured in case of previous fracture in the forearm of the non-dominant arm (2.5%), otherwise the non-dominant arm was measured (including 0.1% reporting previous fractures at both forearms).

The equipment used a single energy x-ray beam (29KeV), and the measurement lasted about 4.5 minutes. During the measurement the subject held a vertical pole in the densiometer's water basin throughout the scan in order to standardise the forearm position and limit the possibility of rotation and movements. In case of movement of the arm during measurement of the region of interest, a new measurement was performed. The subjects were interviewed on respiratory symptoms and use of medication for asthma or corticosteroids during the measurement, ensuring continuous observation during the procedure.

Starting from a point where the distance between radius and ulna was 8 mm, the distal site was defined as 24 mm in proximal direction of the ulna and radius, whilst the ultra-distal site was defined as the area of radius distal to this excluding the endplate. The 8 mm point identifies a transition zone between two different segments of radius, with the distal consisting mainly of cortical and the ultradistal of mainly trabecular bone.

The computer identified these sites automatically. However, mainly because of problems with automatically identification of the start of the endplate in subjects with low or high BMD, all measurements were recalculated after manual correction of site locations according to a procedure from the Tromsø study (251).

Calibrations of the equipment were performed by measurements of specific aluminium wedge phantoms twice daily according to recommendations from the manufacturer. Mean BMC phantom results were stable at the same level in all three densitometers (3.535 g, 3.709 g, and 3.624 g).

4.2.6.5 Instruments in phase IV

Phase IV was performed at the HUNT Research Centre in collaboration with the Young HUNT Study Phase II (252) under surveillance of a medical doctor.

4.2.6.5.1 Measurement of nitric oxide (NO)

Measurements of exhaled and nasal NO were performed in accordance with the ERS Task Force (253) with an LR 2000 nitric gas analyser (Loagan Research Ltd., Rochester, UK) and defined in parts per billion. The gas analyser was calibrated with a certified reference calibration gas mixture of a known concentration of NO in nitrogen ("SpectraSeal", BOC Speciality Gases, Guildford, UK) at a gas sample flow rate of 250 ml/minute. Ambient NO concentrations were assessed daily.

Exhaled NO (ENO) levels were measured with the subject in the seated position and a nose clip was applied immediately prior to oral inspiration to total lung capacity. With the help of a biofeedback monitor, the subject commenced controlled exhalations to residual volume against a target resistance of 4-5 cm H_2O and an expiratory flow rate of 250 ml/minute. For measuring nasal NO the subjects inspired to total lung capacity through the nose and was asked to perform a breath-hold for at least 15 s, during which gas was sampled from one nostril. All tests of NO were taken prior to the bronchial challenge test (254).

4.2.6.5.2 Screening for allergen sensitisation

Allergy screening was performed with serological testing. Total and specific serum immunoglobulin E (IgE) concentrations for dust mite, mould, mugworth, timothy grass and birch pollen, and dander from cat, dog, and horse were determined (Phadiatop CAP™ and RAST Pharmacia Diagnostics, Lund, Sweden). Specific IgE concentrations were recorded in a scale from 0-5, and a test result $\geq$ 2 was regarded as a positive RAST (254)

4.2.6.5.3 Bronchial provocation tests

Methacholine bronchoprovocation tests were carried out with a tidal volume triggered equipment, Automatic Provocation System (APS, Erich Jaeger Gmb, Höchberg, Germany) that delivered a cumulative dose of 2 mg methacholine in five increments. Airway hyperresponsiveness (AHR) was defined as a fall in FEV_1 $\geq$ 20 % (PD20 $\leq$ 2mg). If the pre-challenge FEV_1 was < 80% predicted, a reversibility test was performed, and an increase in FEV_1 of $\geq$ 15 % was regarded as positive (254).

5. Statistical methods

The statistical package of SPSS version 8.0 and 10.0 (SPSS Ltd., Chicago, Illionois, US) was used for analyses except stated otherwise. $P<0.05$ has been considered statistically significant, and 95 % confidence intervals have been given.

5.1 Tests used

Independent samples t-test were used for significance test of difference between men and women regarding continuous variables as age, height, weight, body mass index, smoking history (number of years smoked, number of cigarettes daily, pack-years

Chi square tests were used for significant test of difference for dichotomous variables as self-reported respiratory symptoms and diseases, ever use of asthma medication, and smoking categories between men and women, and responders and non-responders (Paper I-IV). For the latter comparison the prevalence among non-responders was age adjusted by direct method standardisation with the total study population as reference (Paper I) (255).

Analysis of variance (Univariate general linear models (GLM)) were used for comparisons between mean values for lung function (paper II, III) and BMD (paper IV) by factors as age groups, sex, pack-year groups, and ICS dose groups with covariates as age, height, weight, years since menopause. Analyses were performed both separate for each sex and smoke history category and in common models as interaction terms. Because of multiple comparisons, adjustments of confidence intervals with Bonferroni method were used.
GLM was also used in estimation of prevalence for respiratory symptoms and diseases adjusted for covariates as age, pack-years, and BMI (Paper I).

Binary logistic regression analyses were performed to estimate individual's risk (probability of symptom or disease) as a function of risk factors (odd ratio – OR). Analyses were performed for dependent variables as respiratory symptoms and disease (paper I + III), both for each categories of, and dichotomised, global self-reported health (SRH) (paper III), and self-reported fractures (paper IV). Interaction terms and polynominal terms of independent variables were tested in the models. The interaction sex*pack-year were included testing effect modification by sex on the association between pack-years and respiratory symptoms. Interaction terms in the models were also used as significance tests for trend, which also were tested by Mantel-Haenszel methods (Statistical package EpiInfo v. 6.0) (paper I, III, IV). Hosmer-Lemeshow goodness-of-fit tests were used in developing of the logistic regression models.

Linear regression models were used to estimate the contribution of independent covariates on continuous dependent variables as lung function (paper II, III) and bone mineral density (IV). Both independent continuous variables (age, square age, height, weight, BMI, number of pack-years, daily dose and cumulative dose of inhaled corticosteroids (ICS), hours of physical activity), dichotomous variables (sex, never-smoker/ever-smoker, use of hormone replacement therapy, family history of osteoporosis) and categorical variables (categories of pack-years, age-groups, ICS dose categories, level of education, and work physical load) were tested in the linear regression models.

5.2 Model building for prediction equations

Sex specific multiple linear regressions of lung function on height, age, weight, and body mass index (BMI) in various powers and interactions were performed. Statistical significance and fraction of explained variability were the main criteria for selecting independent variables and transformation of lung function variables. Independent variables were centered (i.e. observed values minus variable mean) in the regressions for selection of the best model in order to reduce collinearity among higher order and cross-product terms. The assumptions of linearity and homoscedasticity were controlled.

Scrutinising the plots, most lung function variables were non-linear with age and showed a plateau in younger adults with decline after the age of 35-40 years. Exploring the regression models, square age and ln(height) were found to contribute significantly to the explained variance of all lung function parameters except for FEV_1/FVC.

The prediction equations for the means were developed regressing the natural logarithms of lung function variables against ln(height), square age, and age as done in the SAPALDIA study (82;98). The use of ln (natural logarithms) and square age improved the explained variance one to two percent compared to linear models. Separate equations under and over the age of 25 years in men were tested (1;1;82), but polynomial regression equations provided a significantly better fit than linear regressions with breakpoints (81;256).

No significant interaction between age and height was found. Each of weight, $weight^2$ and BMI was a significant parameter for FEV_1 and FVC when included in the models, but was not included in the final prediction equations as this increased the adjusted explained variance less than 1%, and as these measures are less reliable than height (98).

The distributions of FEV_1, FVC, PEF and FEF_{25-75} were close to the Gaussian distribution, and the assumptions of homoscedasticity were met. One-sided lower 95 % prediction intervals therefore were used to determine the LLN of lung functions (1).

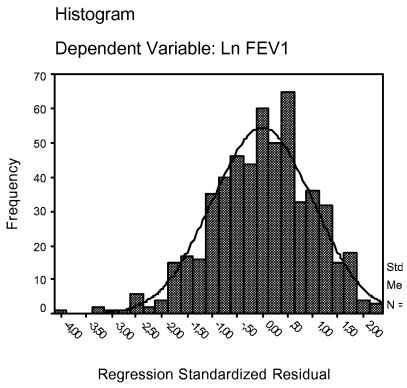
5.2.1 Regression analysis:

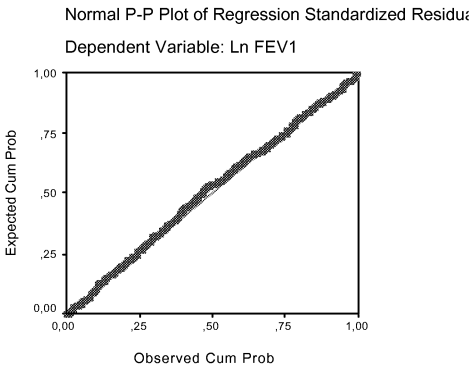
These assumptions should be met:

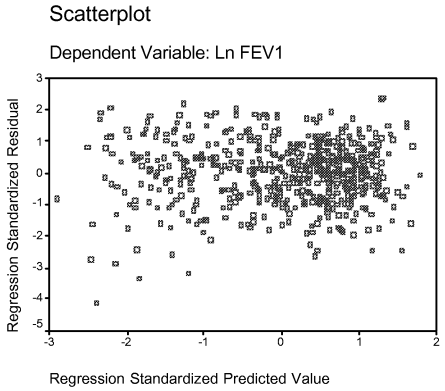
1. Normality – the dependent value should be normally distributed for each value of the independent variable. This will give normally distributed residuals with a mean of zero.
2. Homoscedasticity – constant standard deviation for all values of the independent variable. In a plot of standardised residuals against the standardised predicted values the points should be evenly scattered.
3. Linearity – there should be a linear relation between the independent and dependent variable. This is shown in a plot like that mentioned over.

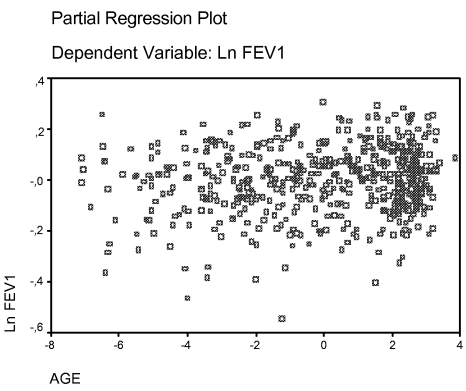
The assumption for linear regression analyses were met in the model for prediction equations, and the plots for the model in women for FEV_1 are shown in Fig 6 as an example of this.

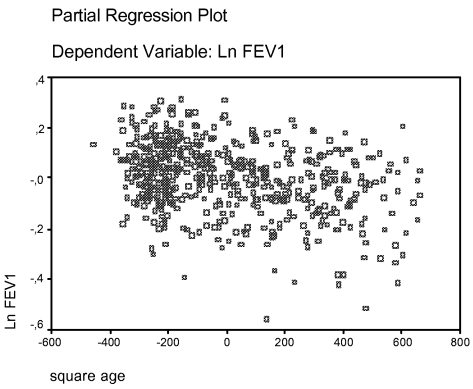
Fig.7. Plots from linear regression analyses in women

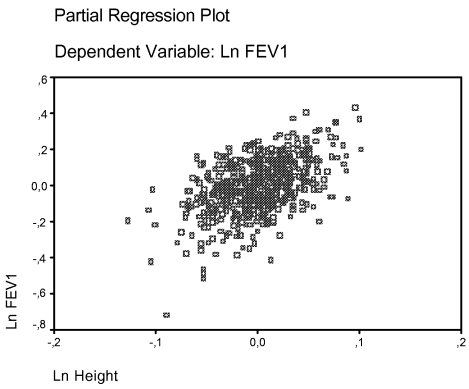












6 Main results

6.1 Review of paper 1

Cigarette smoking gives more respiratory symptoms among women than among men.

The Health Study of Nord-Trøndelag, Norway, (HUNT).

Langhammer Arnulf, Johnsen Roar, Holmen Jostein, Gulsvik A, Bjermer L.

J Epidemiol Community Health 2000; 54: 917-922

Study objective: Studies have indicated that women are more vulnerable to the effect of tobacco smoking compared to men. The aim of this study was to explore the prevalence of reported respiratory symptoms and diseases according to smoking burden, age and sex.

Methods: All inhabitants aged above 19 years living in the county of Nord-Trøndelag were invited to the adult part of the HUNT study in 1995-97. Among 92,936 invited subjects, 30,743 men (65.6%) and 34,974 women (73.9%) aged 20-97 years answered the main questionnaire including questions on respiratory illnesses, diseases and smoking habits.

Main results: In all, 12.7 % men and 12.1 % women reported attacks of wheezing or breathlessness during the last 12 months, 8.8 % men and 8.4 % women reported that they had or had had asthma, 7.5 % men and 8.2 % women had ever used asthma medication, and 4.0 % men and 3.0 % women reported chronic bronchitis. Thirty percent of men and 31 % of women were smokers, and average pack-years of smoking were 15.9 and 10.3, respectively. The prevalence of self-reported asthma and use of asthma medication was slightly higher than reported in previous Scandinavian studies (21;84;257;258), but in crude agreement with more recent studies (259;260).

Among previous and current smokers, significant more women reported attacks of wheezing or breathlessness, current asthma and persistent coughing compared to men with the same smoke burden (pack-years) and daily number of cigarettes.

An under-diagnosis of chronic bronchitis was confirmed in this study; the diagnosis was reported by 15 % of those reporting only daily cough in periods, 20% of those reporting cough with phlegm less than 3 months, and 33 % of those fulfilling the criteria of chronic bronchitis. In addition, among the 5 % random sample 4 % fulfilled the criteria of chronic bronchitis of whom 20 % had been given a diagnosis by a doctor. In contrast to other studies reporting a higher tendency for smoking men to be given the diagnosis of chronic bronchitis compared to smoking women (261), no such difference in diagnosing was found in the BONT study.

Conclusion: The prevalence of reported asthma and use of asthma medication was higher than reported in previous Scandinavian studies. Respiratory symptoms increased by smoking burden. Comparing the prevalence of symptoms and current asthma among women and men with the same smoke burden or daily cigarette consumption, women seemed to be more susceptible to the effect of tobacco smoking than men.

6.2 Review of paper 2

Forced spirometry - reference values for Norwegian adults. The Bronchial Obstruction in North Trøndelag (BONT) study.

Langhammer Arnulf, Johnsen Roar, Gulsvik A, Holmen Turid Lingaas, Bjermer L.

Eur Respir J 2001; 18: 770-779

Study objective: The objective of this study was to develop new prediction equations for flow volume spirometry parameters in asymptomatic, never smoking adults in Norway, and to assess any differences of these parameters applying the new and most commonly used equation sets.

Methods: Flow volume spirometry was measured according to the ATS criteria on 2.792 subjects aged 20 years or more, randomly selected among participants in the HUNT Study. Ever smokers and subjects with respiratory symptoms and/or diseases reported in questionnaires were excluded. A total of 546 women and 362 men met the inclusion criteria and were included in the analyses. Statistical significance and fraction of explained variability were the main criteria for selecting independent variables and transforming lung function variables.

Results: Most lung function variables were non-linear by age, after a plateau in younger adults, the variables declined by age. Proportional multiple regression models were superior to linear models, and the best solution included logarithmic transformation of the multiplicative models.

For FEV_1/FVC the best model in both sexes was:

$$Mean\ FEV_1/FVC = exp(b_0 - b_1 ln(height) - b_2 age)$$

For FEV_1, FVC, PEF, and FEF_{25-75} the best models were:

Men: $Mean\ lung\ function = exp(b_0 + b_1 ln(height) - b_2 age^2)$

Women: $Mean\ lung\ function = exp(b_0 + b_1 ln(height) - b_2 age^2 + b_3\ age)$

The reference values from the present study for forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were higher than those given by prediction equations from the ECCS, but in closer agreement with later studies from Europe, Australia and USA.

Conclusions: The prediction equations from the ECCS underestimate the mean lung function in this population and confirm the results from other studies in Europe, Oceania, and US. The results have clinical implications on the diagnosis and management of patients with obstructive lung disease. Accordingly, health care providers should be encouraged to reconsider their choice of prediction equations of spirometry.

6.3 Review of paper 3

Sex differences in lung vulnerability to tobacco smoking. The HUNT Study.

Langhammer Arnulf, Johnsen Roar, Gulsvik A, Holmen Turid Lingaas , Bjermer L.

Eur Respir J 2003; 21: 1017-1023.

Study objectives: Studies have indicated that women are more vulnerable to the deleterious effect of tobacco smoking than men. We aimed to investigate the associations between tobacco smoking and reported respiratory symptoms, self-rated health, and lung function by gender.

Methods: In 1995-97 65,225 subjects ≥ 20 years (71 % of invited) attended for screening within the HUNT Study. Among these, 10,941 subjects selected randomly or because of reporting asthma or asthma related symptoms, participated in the BONT study phase I consisting of spirometry, bone mineral densitometry, and personal interview.

Results: Tobacco smoking was associated with increased prevalence of respiratory symptoms, reduced lung function, and lower score on global self-rated health (SRH). Adjusted for smoking burden and lung function, women had a higher risk for reporting respiratory symptoms and lower SRH compared to men. Further, smoking burden was associated with a larger relative reduction in expiratory lung function in women than in men.

Conclusions: The study confirm previous findings of a dose-dependent increase in prevalence of respiratory symptoms and a corresponding negative effect on lung function by tobacco smoking. Even if smoking in women was associated with a larger reduction in percent predicted lung function compared to men, this does not fully explain higher symptom prevalence in women.

6.4 Review of paper 4

Use of inhaled corticosteroids and bone mineral density in a population based study. The Nord-Trøndelag Health Study (The HUNT Study)

Arnulf Langhammer, Ensio Norjavaara, Maria Gerhardsson de Verdier, Roar Johnsen, Leif Bjermer.

Study objectives: Inhaled corticosteroids (ICS) are used as first line treatment for chronic asthma and are also widely used in patients with COPD. Conflicting results have been reported of the long-term effect of treatment with ICS on bone. The objective of this study was to compare ICS users and non-users regarding bone mineral density (BMD) in a total population.

Methods: Totally, 65.225 adults participated in the HUNT Study 1995-97. Those reporting asthma, asthma-related symptoms, or use of asthma medication, were invited to bone densitometry of the forearm, flow volume spirometry and personal interview. Altogether 4,482 women and 4,142 men participated, of whom 2,113 reported ever use and 6,511 never use of ICS.

Results: Mean BMD adjusted for age, square age, sex, body mass index, height, physical activity, work load, pack-years, and in women number of years since menopause, was in never never-users of corticosteroids 0.493 g/cm^2 at the distal and 0.404 g/cm^2 at the ultradistal site. Subjects having only used ICS had 0.010 (95% CI 0.007 – 0.015) and 0.009 (0.005 – 0.014) g/cm^2 lower distal and ultradistal BMD, respectively. Similar result was found in those having had courses with prednisolone, whilst subjects having used prednisolone $\geq$ 6 months had 0.038 (0.021 – 0.055) and 0.021 (0.03 – 0.039) lower BMD at theses sites. However, there was no dose response association between ICS and BMD, and no difference in BMD by type of ICS was found.

Conclusions: ICS use was associated with lower BMD. The lack of dose response in this study both related to current dose or estimated cumulative dose, might be due to a narrow dose range or indicate that other characteristics of the patient group are contributing to the observed difference in ICS users compared to never-users.

7 General discussion

7.1 Methodological considerations

7.1.1 Choice of questions

In epidemiology, questionnaires are important sources and aim to obtain the responses that best describe the real situation of the subject (61). Essential qualities of such questionnaires are acceptability, reliability, and validity (sensitivity and specificity) (262). However, most often increasing sensitivity (finding the true positive) results in decreasing specificity (finding the true negative). The choice of questions in this regard, depends on the purpose of the study. For prevalence estimation of rare conditions, use of questions with high specificity is necessary to reduce misclassification. For a screening setting like Questionnaire 1 in HUNT, questions with high sensitivity for widely inclusion of subjects with asthma was intended. The combined use of the questions: a) ever having had asthma, b) ever having used asthma medication, and c) having had attacks of wheezing or breathlessness during the last 12 months, in the random sample had a sensitivity of 97.1 % and a specificity of 88.4% when reported doctor diagnosed asthma in Questionnaire 3 was used as the gold standard of asthma diagnosis. Testing on reliability and consistency, questions on ever having had asthma and ever having used asthma medication in questionnaire and the interview of BONT phase I were compared. This revealed an acceptable correlation coefficient (Pearson's r) of 0.886 and 0.836, respectively (p for both < 0.001).

7.1.2 Accuracy

Accuracy is defined as the degree to which a measurement or an estimate based on measurements represents the true value for the attribute that is being measured (263), and this

is an overall goal in epidemiological as well as other research. The accuracy error is the total error made in estimating the true value. It may be expressed as the standard deviation of the differences between measured and true values.

To achieve low accuracy error the study should be designed and conducted with the aim of reducing random (increasing precision) and systemic errors (increasing validity) (264).

7.1.3 Precision

Precision in measurement and estimation corresponds to the reduction of random error. Increasing the precision will narrow the confidence intervals. Random variation is that part of our experience that we cannot predict. Precision might be improved either by increasing the size of the study or increasing the efficiency with which information is obtained from a given number of study subjects (264).

In experimental studies the random error will decrease with increasing study size. In epidemiological studies, on the other hand, there is no guarantee that baseline risk will even out between the exposure groups as the study size increase, due to lack of randomisation (68). Even if a total population is included, as in the HUNT study, there are sampling errors, as the subjects are viewed as a sample of an even broader conceptual population.

The precision error of an instrument is the variability occurring with repeating measurements of the same object. This can be expressed as a percentage coefficient of variation: $CV\% = 100 * SD/Mean$

7.1.4 Validity

Validity is divided into internal validity (the degree to which the results of an observation are representative for the particular group of people being studied) and external validity (the degree to which the results of a study apply to people not in it – generalisability).

7.1.4.1 Internal validity

Systemic error (bias) occurs if there is a systematic difference between what the study is actually estimating and what it is intended to estimate. These refer to:

- biases arising from differences in baseline disease risk between the exposed and non-exposed sub-populations (confounding)
- biases resulting from the manner in which study participants are selected from the source population (selection bias)
- biases resulting from the misclassification of these study participants with respect to exposure or disease (information bias) (68).

7.1.4.1.1 Confounding factors

Confounding occurs when the exposed and non-exposed sub-populations of the source population are not comparable, because of inherent differences in background disease risk caused by exposure to other risk factors (68).

For variables to be considered as confounders, these criteria should be met:

- The factor is predictive of the disease in the absence of the exposure under study. It may either be a cause or marker for an actual cause of the disease. Age is a surrogate for other causal factors in respiratory diseases, and may be regarded as potential confounder.

- The factor is associated with the exposure under study in the source population. In case-control studies this implies that a confounder will tend to be associated with exposure among the controls. In line with other studies, measures of life style as tobacco smoking and level of physical activity are highly associated (paper IV).
- The variable should not be affected by the exposure under study (e.g., an intermediate in the pathway between exposure and disease). In paper III lung function measured as FEV_1 is not a confounder in the association between tobacco smoking and respiratory symptoms, as tobacco smoking causes decline in FEV_1.

In general, control of confounding requires careful use of a priori knowledge, together with assessment of the extent to which the effect estimate changes when the factor is controlled in the analyses. Tested confounders for paper I-IV were mainly selected on the basis of prior publications of relevant associations. If a priori known factor included in the analyses is found to influence the estimate in opposite direction of expected, the possibility of confounding by indication should be considered. Correspondingly, in paper IV we did not find any indications of a protective effect of intake of vitamin D, cod liver oil, or calcium probably because of confounding by indication (increased awareness among osteoporotic subjects).

Effect modification (statistical interaction or effect-measure modification) occurs when the measure of exposure effect depends on the level of another factor in the source population. It does not represent a bias, but a real effect. We reported higher risk of reporting respiratory symptoms in women compared to men with increasing smoke burden measured in pack-years or daily current smoking (paper I, III). The results were both confirmed in stratified analyses and inclusion of interaction terms in the multiple regression models.

7.1.4.1.2 Selection bias

Non-response will not seriously bias the survey findings if the reasons for non-response are unrelated to what we wish to measure. However, if subjects with particular symptoms are more likely to participate in the study than people without these symptoms, a low participation rate may seriously bias both the prevalence estimate and the comparison of prevalence between different groups or centres.

7.1.4.1.2.1 Participation at HUNT 2

Acceptability of questionnaires

In HUNT the participants together with the invitation received a comprehensive questionnaires covering many different topics. Acceptability of questionnaires among participants is important, and the HUNT administration was a bit anxious prior to the study about the attitude to some of questions and especially the most sensitive part being a set of questions on anxiety and depression (HAD). The response rate on different questions, however, were: somatic diseases 99 %, HAD, education and smoking history 93 %, somatic symptoms 88 –98 % (depending on order of questions in the questionnaire), and alcohol history 82 %. Further, a telephone survey of a random sample during the first month of HUNT 2 revealed that the topics of questions were not a reason for non-attendance (not published). This might indicate that lack of acceptability of the questionnaires is no important source for selection bias in the HUNT study.

Participation by age

The proportion of the population who participated in HUNT 2 was significant lower than in HUNT 1 (88.1 versus 70.2 %), a trend which has also been found in other population based

studies (246). Under the age of 60 the participation rate was lower in men than women, and in both sexes lowest in the youngest and oldest age groups.

The low prevalence in the youngest group might bias the estimated prevalence of diseases (like asthma) being most prevalent in these age groups. This do, however, to a little extent influence the estimated prevalence of respiratory symptoms and diseases related to tobacco smoking, as the prevalence of outcomes increase by age and burden of exposure.

Non-responder study

Some 685 subjects among non-responders were randomly selected for a non-responder study. If no contact per telephone was achieved after three trials on different days, a questionnaire with identical questions was sent. The questions focused on respiratory symptoms and diseases, diabetes mellitus, arterial hypertension, and smoking history. Totally 47.6 % answered the questions. The most important reason for non-attending in age-group 20-69 was lack of time/moved away (54%), while in those aged 70 years or more immobilising disease (21%) and follow up by medical doctor (28%) were important reasons (255).

We found lower prevalence of coughing in non-responders compared with responders, even though a significant higher prevalence of smoking was found in the non-responder group. The difference in smoking prevalence in responders and non-responders is in accordance with other studies focusing on smoking habits (265-267). In total, however, the non-responder study did not indicate serious selection bias.

7.1.4.1.2.2 Participation at BONT phase I

BONT was one of the largest and most complicated sub-studies in HUNT 2, with specific selection procedures, need for examination room, and having skill demanding and time

consuming procedures. In the largest municipalities BONT phase I was performed at the screening station. Participation was dependent on correct selection procedure at the station and the attendants wish to participate. Both the pre-set SB label for the 5 % random sample and the inclusion questions were in the upper part of Questionnaire 1 in order to facilitate the selection for BONT phase I by the nurse during blood pressure measurement. With response rates for the questions on attacks of wheezing/breathlessness of 98.4 %, on ever having had asthma of 99,7 %, and ever use of asthma medication of 99.3 %, and on at least one of these questions of 99.93, correct inclusion based on symptoms/disease should be possible.

Team 1

The BONT station was the last station at the screening. Problems with bottlenecks and limited flexibility at different stations often resulted in long waiting periods for the participants. Combined with time-consuming procedures at the BONT station, participants selected for many sub-studies had to spend up to 3 hours at the screening station. Taking this into account, a loss of less than 10% of the selected participants at the screening, is relatively acceptable.

Team 2

The BONT phase 1 could not be performed at the screening station in the 19 smaller municipalities, and the selected participants were given appointments in 6-8 weeks for combined phase 1 and 2. This explains a loss of about one third of the participants, which is similar to the loss of participants of Team 1 phase 2. As these examinations were carried out during short periods in the municipalities, the sending of reminders to selected subjects were not possible. Combined with the scattered population in this county, we have reason to be content on the participation rate. The participation rate is quite similar for those selected randomly and because of symptoms/disease at both teams, being an indication of minor bias

having been introduced because of selection. This is also confirmed by the lack of significance of the Team variable being introduced in multiple regression analyses.

7.1.4.1.3 Misclassification

Misclassification is the erroneous classification of an individual, a value or an attribute into a category other than that to which it should be assigned. The probability for misclassification may be the same in all study groups (non-differential) or may vary between groups (differential misclassification) (263). Non-differential misclassification of exposure tends to produce false negative findings and is of particular concern in studies that find a negligible association between exposure and disease.

7.1.4.1.3.1 Misclassification of exposure

Corticosteroids

The possibility of non-differential misclassification has been a major objection against not finding a dose response association between use of ICS and BMD reported in paper IV. Ideally, we should have had continuous data on ICS exposure for all users of ICS. There is so far no prescription registry in Norway, and even if such a registry had been available, there is the problem of low compliance in use of inhaled medication (224). In order to reduce possible misclassification of exposure we performed the analyses stratified by exposure time for ICS. Lack of dose-response even in those having used ICS only during the last 12 months indicate that the misclassification could not explain the results, assuming that the method of measurement was sensitive for ICS effect on bone and the power of the study was adequate. For further studies on ICS and BMD in this population, the reported use of ICS will be

validated against records at the out patient clinic of the local hospital (registration of these data was finished June 03).

In studies with positive findings, non-differential misclassification is of much less concern as the findings are likely to have been even more strongly positive if misclassification had not occurred. Misclassification is often a result of recall bias which is systematic error due to differences in accuracy or completeness of recall to memory of past events or experiences (263). Subjects developing diseases may remember details of exposure better than healthy subjects.

Tobacco smoking

In a study on respiratory symptoms and diseases the misclassification of exposure to tobacco smoking is an important possible bias.

Self-reported tobacco consumption has been shown to be lower than measured by sales data. The authors in a French study noted that the problem was greatest in heavy smokers, and that an underestimation by 30% among heavy (>20 cigarettes a day) smokers would explain almost entirely the distortion (268). Bernaards et al investigated the relative validity of retrospective calculated pack-years (py-retro) by comparing this with prospectively calculated packyears (py-pro) in a 23-year ongoing cohort study (269). They found that py-retro did not under or overestimate life-time tobacco smoking, but the individual differences between py-pro and py- retro became larger, the higher the number of pack-years (-0.039 and –1.17 (both confidence intervals included 0) when average pack-year was < 5.2 and > 5.2, respectively). They found that categorising py-retro into smoking groups resulted in a misclassification error that was smaller than the quantitative error in continuous py-retro, but information is then

lost. In a Danish study of smoking habits during pregnancy 0.5-3 years after delivery, information on smoking habits could be accurately obtained retrospectively independent of recall time and pregnancy outcome (270). In a collaborative study of 1,369 women in 10 countries, comparing questionnaire data and results from urine analyses, only 1.5% of the alleged non-smokers was reclassified as current light smokers (271).

In Questionnaire I in the HUNT study subjects were asked about passive smoking both in childhood and after the age of 20. Exposure to passive smoking after the age of 20 was significantly associated to increased risk of respiratory symptoms as wheezing or breathlessness, but no difference by gender was found. This might be an effect of differential misclassification of exposure. Women probably have been exposed to higher levels and longer duration of side stream gasses from cigarettes, as more men have been current smokers and men have had higher daily smoke consumption compared to women. Another problem is the lack of data on eventual different inhalation pattern during smoking in men and women.

Studies have indicated that error in self-report of tobacco smoking generally is biased on the side of social desirability with greater misclassification in groups that are more aggressively targeted. In the Lung Health Study the greatest discrepancies in smoking status was found for factors relating to stronger antismoking norms, older age, education level, difficulty with past cessation attempts and having a spouse who did not smoke (268). However, a Finnish community-based study validating self-reported smoking by serum cotinine measurement, reported a high validity of self-reported smoking, independent of area, age and socio-economic groups (272).

We studied the reported smoking status in HUNT 1 among 18,240 subjects reported to be never-smokers in HUNT 2. At HUNT 1 11 years previously, 3.3 % of these men and women

reported being ex-smokers and 1.2 % of women and 0.8 % men reported being current smokers (p=0.03). Mean estimated pack-years in these groups was 2.7 and 4.7 for ex-smokers and current smokers, respectively. We did not find increasing misclassification by age. The inclusion of these smokers as never-smokers in the analyses of HUNT 2 did not influence the results.

Physical activity

Different questions on physical activity have been used in different studies, and the questions used in HUNT 2 did also differ from those used in HUNT 1. The questions focused on intensity, frequency and duration of the activity at leisure time, and degree of weigh bearing at work. The questions are so far not validated, and data on type of activity is missing. For the bone densitometry, the non-dominant forearm was selected in order to avoid confounding by physical activity (231). Even though, in the present study there was a linear association between weekly duration of both light and heavy physical activity and BMD. If the difference between ever and never users of ICS should be explained by other characteristics of obstructive patients than the use of ICS, one possible explanation could be differential misclassification of the confounder physical activity. Healthy subjects probably define hard physical activity dissimilar to COPD patients. In follow up studies validated questionnaires on physical activities should be added, and bone densitometry of the forearm might be supplemented by densitometry of weight-bearing parts of the skeleton as for example the calcaneus.

7.1.4.1.3.2 Misclassification of outcome/disease

Recall bias

Possible recall bias or different thresholds for reporting symptoms or diseases might lead to misclassification. In a population-based study increasing prevalence of "ever having had asthma" with increasing age would be expected in never smokers. Lack of this (Paper I) as also reported by others (9;259), might be explained by increasing recall bias by age, low symptom perception, and under-diagnosis of asthma in elderly (273;274). The change of diagnostic criteria during the past decades could also mask increasing cumulative prevalence by age, but a cohort effect of higher asthma incidence in younger cohorts during the last decades might also contribute to a certain degree.

Spirometry

Acceptability and reproducibility

Spirometry is an effort-dependent manoeuvre depending on the skill and teaching ability of the technician and co-operativeness of the subject being measured. In order to increase internal validity of these measurements, modern equipment gives on-line feedback about acceptability and reproducibility of the spirometric performance. Independent on this, however, as reported in other studies, failure to meet the acceptability criteria (275-278) is common, and in line with other (276), about 7 % of the population in the present study did not meet the reproducibility criteria recommended by ATS. This might be a result of lack of co-operativeness, but is also an indicator on bronchial obstruction.

The acceptability criteria should be met, but there is a problem that for some subjects an unsatisfactory curve is their best possible performance. It is important not to be so strict regarding reproducibility criteria that that necessary information is lost (248). Eisen et al

(279) found than subjects who failed the ATS spirometry repeatability criteria lost lung function at a faster rate than those who met the criteria. Hankinson et al reported that both older and younger subjects had more difficulty satisfying the reproducibility criteria (280). Humerfelt et al found that failure to meet the reproducibility criteria was more prevalent in never smokers, single men and subjects with respiratory symptoms than in ever smokers, married and asymptomatic subjects, respectively (276). Exclusion of curves without fulfilled reproducibility criteria from interpretation would therefore introduce a bias into epidemiological studies. However, in development of reference values, these criteria should be fulfilled.

Strict fulfilment of the manoeuvre for start criteria as back-extrapolation of less than 5 % or less than 100 ml of FVC, should optimise FEV_1, and the end of plateau criteria and expiration time criteria should secure full expiration and thereby optimising FVC. This could account for some of the increase found in FEV_1 and FVC found in recent studies compared to older ones. Many subjects had problems with the end of plateau criterion based on the 1987 ATS recommendations (281). The curves were, therefore, visually controlled, and those with a plateau beginning at the volume/time curve were included in the analyses.

For PEF the difference between more recent studies (81;82;95) and ECCS (1) has been much smaller. There is so far no quality criteria defined for PEF by ATS or ERS and consequently not in the spirometer software and this might explain the lack of difference. Both time-to-PEF and use of an “effort ratio” like PEF/ FEF_{25-75} have been proposed, but studies on this are lacking. FEV_1 from a sub-maximal effort can be either smaller than those obtained when a maximal effort is performed because the subjects fail to reach a maximal TLC, or larger due to less dynamic compression of airways in subjects where airways are relatively more

collapsible (248). So far, there is uncertainty whether submaximal curves should be excluded or not in studies.

We found higher level of and less decline through age groups for FEV_1/FVC than reported in other studies (75;87;282;283). Selection bias of healthier elderly participating in the BONT-study, or a higher succession rate in other studies in getting optimal expiratory flow from the elderly, could partly explain this. However, less decline of FEV_1/FVC among elderly could also be a result of earlier airway closure because of loss of elastic recoil with ageing, in addition to muscle fatigue during forced expiration in old subjects (105;284).
Within the oldest group, "super-healthy" elderly survivors participating in the HUNT study, could lessen the slope of the regression curve for expiratory parameters, and spuriously increase the predicted values for the middle-aged (256). In the present study, however, the fitness of the prediction equations in the middle-aged was hardly affected by this.

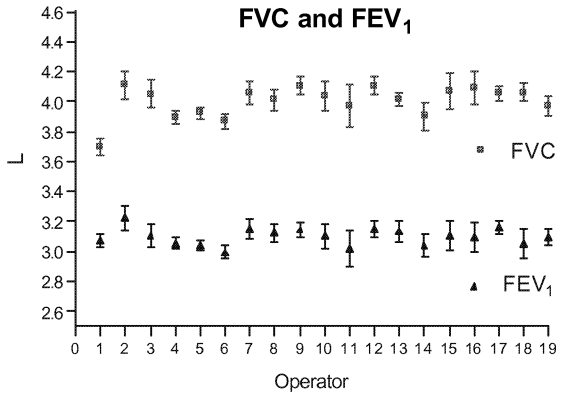
Technicians

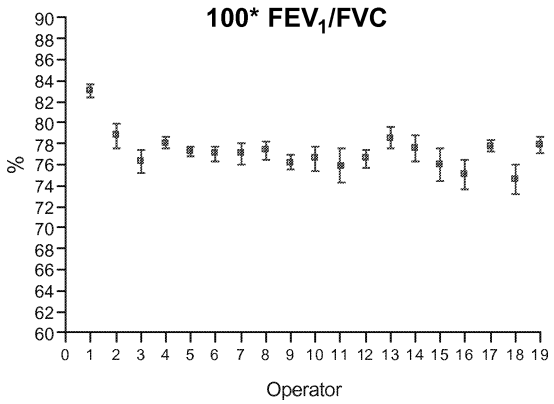
The study manager supervised the staff during the study period. Additionally, there should have been a continuously supervision of the spirometric curves like being performed by Hankinson et al (81). Studies of the curves have revealed that two technicians had significant lower FVC compared to the other technicians resulting in higher FEV_1/FVC. The reason for this is obviously too short expiratory time. Because of different reasons, these technicians had significantly less supervision than the other teams.
The instruction was to obtain an expiratory time of at least six seconds, and this was visualised at the screen by the change in colour from red to green on a bar. The equipment registered the end of expiration as the time when no further expiration was performed,

resulting in the feedback of too short expiration time even if this was far beyond six seconds. Comparing the registered mean forced expiratory time among technicians confirmed that these two technicians had about two second shorter time. As these technicians performed totally 7 % of all spirometries this resulted in the need for thorough control of many curves. The figures shows the differences in lung function parameters adjusted by age, sex and smoke burden when including all participants at BONT phase I, and among those included in the sample for developing prediction equations confirming that the bias is avoided in the latter group by excluding not acceptable curves.

As this bias will influence studies on FVC, FEV_1/FVC and FEF_{25-75}, further comparisons should be performed adjusting for technician. In Fig 10 and 11 the results from the two technicians with shorter expiration time is summarised in operator no 1. The latter figure shows that these problems should not influence the subjects being selected for development of prediction equation for spirometry.

Fig 9 Mean adjusted lung function with 95 % CI by operator. All participants included





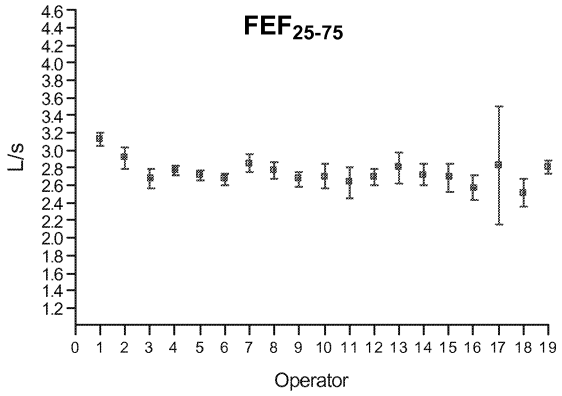
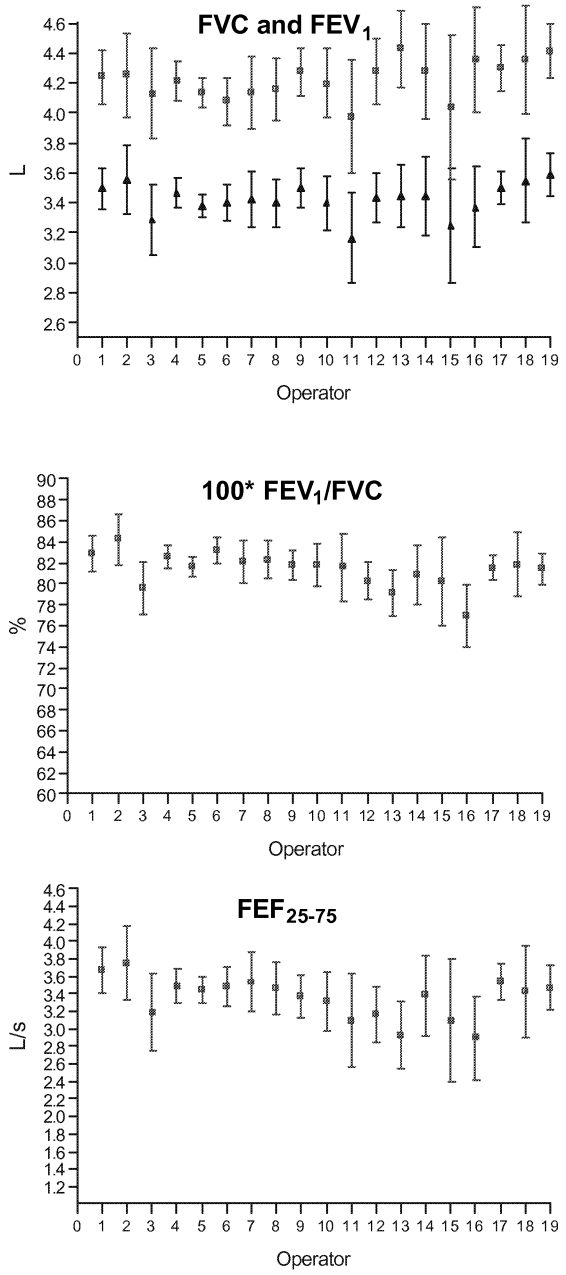


Fig 10 Mean adjusted lung function with 95 % CI operator. Only those selected for reference sample for developing prediction equations are included. Adjusted for age, sex, and packyear



Bone mineral density measurement

The sites of measurement for BMD are under debate, and the gold standard is without doubt measurements of the hip. CS induced reduction in BMD have been found to be largest in trabecular bone as the spine or hip. The present study, however, have confirmed previously known factors' association to BMD. Positive associations to BMD have been found for BMI, height, education, work load, and physical activity, and corresponding negative associations have been found for age over 50 years, time since menopause, and pack-years of cigarettes. Further, the largest negative association between CS and BMD was use of OCS for more than 6 months.

In addition, our results have confirmed the predictive value of BMD regarding fractures in line with other studies, even if this was a retrospective cohort study (data otherwise not shown) (Fig 12). These results indicate that measurements of the forearm are sensitive for general changes in bone mineral density.

Fig 11 a. Percentage of women reporting hip or wrist fractures with 95 % CI, and the population of women at risk (dotted lines) by distal bone mineral density.

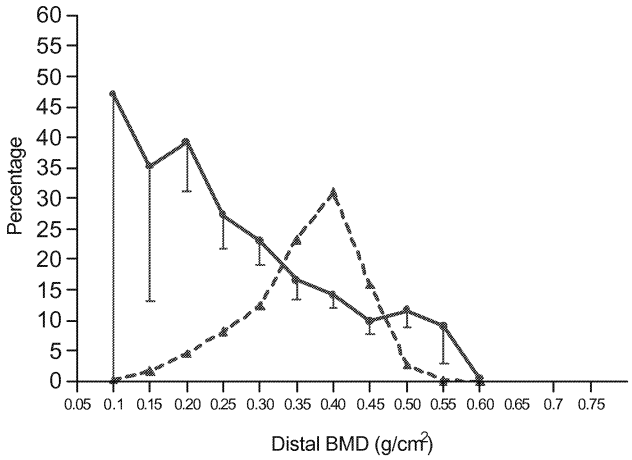
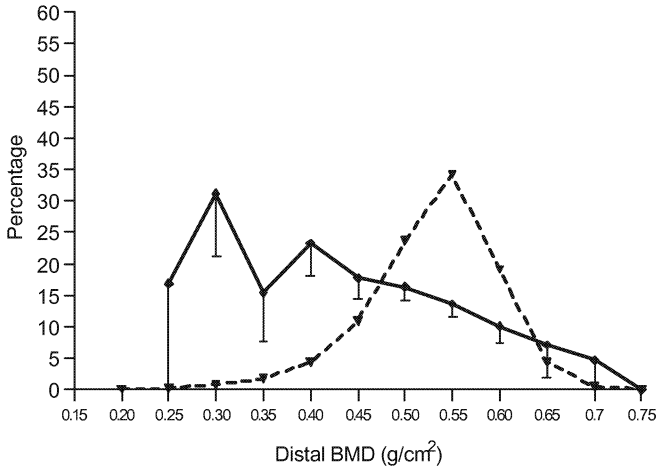


Fig 11 b. Percentage of men reporting hip or wrist fractures with 95 % CI, and the population of men at risk (dotted lines) by distal bone mineral density.



7.1.4.2 External validity – Generalisation

The county of Nord-Trøndelag is considered representative of Norway as a whole except for lack of large cities, low degree of pollution from industry and traffic, and lower prevalence of current smokers. This might influence the prevalence of respiratory symptoms and COPD, but not the external validity of associations between risk factors and symptoms/diseases. Regarding prediction equations for forced spirometry, the number of older men (age > 75 years) selected for the reference group was rather low because of low participation rate, low proportions of never smokers without any respiratory symptom, and at last low proportion coping with the acceptability criteria for spirometry. Comparing the prediction equations to

other recently published sets in age groups below 80 years (81-83;85;86;103), however, showed rather consistent results.

The reported lack of dose-response association between use of ICS and BMD in the present study might be debated. We found use of lower dose of ICS compared to other studies, but this might not be a result of real difference in dose, but rather discrepancy between prescribed medication and actually inhaled medication.

Otherwise, the results are in high degree consistent with findings in previous studies (29;31;222;259;260), and are judged to have international generalisability to people of same race and similar culture.

7.2 Information to the participants in HUNT

The participants of the HUNT study were informed about the results of all assessment being performed in relation to the screening and phase I examinations. A total of 18.265 participants in the HUNT study were included for bone densitometry. In such a screening setting, the leaders of the BONT and Osteoporosis study wanted to avoid anxiety and uncertainty regarding the diagnosis of Osteoporosis in a large proportion of the population, and we therefore chose to give the measurements as Z-scores. As the local hospital refers to T-score in their reports to patients, this has contributed to confusion among participants, a problem we would have avoided if no results had been given to participants as in the Tromsø study (285).

7.3 Financial conflicts of interest

Ideally, biomedical research should have been performed by academic institutions totally independent of funding from industry with financial interests in the research. Limited public resources have, however, contributed to increasing industry-academia relationships. Such relationships accelerate medical innovation and enhance patient access to medical advances, but have also resulted in heavily debate regarding the academia's role as independent truth-seeker (286-289).

Bekelman et al reviewed 37 studies on financial relationship between researchers and pharmaceutical companies (289). They pointed out that industry-sponsored research tended to yield pro-industry conclusions, less publication of negative conclusions, more use of inactive controls (i.e., placebo or no-therapy controls) increasing the likelihood of positive study results, publication delays and data withholding, and shift in research emphasis from basic research to clinical research as commercial considerations influenced choice of research topic.

An extensive collaboration on funding between public institutions, patient organisations and pharmaceutical companies, made the HUNT 2 study possible. The planning and examination phase of the BONT study phase I-IV and BONT follow up study in 2001, had not been possible without the funding from AstraZeneca Norway and AstraZeneca Sweden, respectively. However, acceptance of funding by pharmaceutical companies was preceded by a thorough fundamental discussion, and we have been quite aware of the possible treats to independent research related to this relationship. The following precautions have therefore been performed:

- The contract on funding of the BONT study 1995-97 was entered between the Medical Director of Astra Norway and the Director of the National Institute of Public Health.

- For the follow-up study in 2001 AstraZeneca, Sweden paid the costs of the examination phase to the Norwegian University of Science and Technology.
- The manager of the BONT study has been employed by the academic institutions mentioned above, without any personal obligations to the funding source
- The objections of the BONT study was defined prior to the request to AstraZeneca for funding, and no attempts from the company for interfering with the content of the study has been registered.
- AstraZeneca has not access to the data file for the BONT study. The co-writers of paper 4, which are employees at AstraZeneca, have, however, naturally, participated in the writing process in line with the other co-writers.
- The data file from the BONT study is part of the common HUNT data file and is available for researchers according to common directions developed by the HUNT administration.
- The funding of the BONT study has not been kept secret. This also is the case for the study manager's other relationship to other pharmaceutical companies including paid speaking engagements, participation in advisory boards, and as general practitioner participating in clinical multicentre studies for pharmaceutical companies. The study manager has no personal financial interest in pharmaceutical companies.
- The researchers and the funding source share the wish of focusing on important health problems. However, pharmaceutical companies are dependent on development of new medicines and profit of sales of medicines in order to satisfy shareholders. Independent researchers in studies like BONT, however, primarily should aim at finding low cost preventive strategies for respiratory diseases, and secondary to contribute to optimal examinations and treatment of patients.

- Undisguised attitude to conflicts of interest and continuous debate and focus on this in research institutions are important in order to avoid influence of funding resource on the results and consequences of biomedical research.

7.4 Importance of results and implications

7.4.1 Respiratory symptoms and obstructive lung disease by tobacco smoking and gender.

Tobacco smoking was associated with increased prevalence of respiratory symptoms, reduced lung function and lower SRH in both men and women. With increasing smoking burden, women compared to men, had a higher risk of reporting respiratory symptoms, lower SRH, and had a larger relative reduction in lung function. The difference in loss of lung function could, however, not fully explain the higher symptom prevalence and lower SRH in women. The reason for this might be that deleterious effects of tobacco smoking partly is in the small peripheral airways, which is not reflected by the currently used expiratory lung function measurements as FEV_1 and FVC (290). In search for other explanations, studies have indicated that women have lower threshold for reporting respiratory symptoms than men (45;291), whilst other have not found women to have lower complaining thresholds (292-294). Regardless of level of threshold, this does, however, not explain increasing sex difference with increasing smoking burden. It has also been proposed that respiratory symptoms are more sensitive markers of change in general health, but less specific markers regarding respiratory diseases in women compared to men (12). Anyway, studies have

reported that respiratory symptoms as shortness of breath seem to be equally predictive of mortality in both sexes (72;295).

There is enough knowledge on the deleterious effect of tobacco smoking on human health to support high priority in the health care and authorities for fighting against tobacco smoking both by preventing adolescents to start and encourage cessation in current smokers. High vulnerability in female airways adds to the list of special reasons for women to avoid smoking, a list already including tobacco smoking induced increased risk for tromboembolic diseases related to ovarian hormone therapy, pregnancy complications and increase morbidity and mortality of infants (53). Even though women feel more pressure from family and society to quit smoking, and are equally likely to quit smoking compared to men, they are less likely to remain abstinent. One important problem in motivating women to avoid smoking is their attitude to weight control as a benefit of smoking (296-298). Smoking cessation programs have so far had low succession rate, - development of more efficient programs is necessary, but different strategies are needed for men and women (299).

7.4.2 Spirometry and reference values

Spirometry is an important and necessary measurement in getting an objective measure of the lung function, and should also be natural part of the equipment both in hospitals and in general practice. However, computerised equipment can report more than 20 different spirometric variables, and knowing that high number of variables used in the test increases the number of false positive results, it is important to limit the number of variables to those with the least intra-individual variation. For clinical practice it is recommended to limit the variables in the basic interpretation to FEV_1, FVC, and FEV_1/FVC (74).

The most commonly used reference values from ECCS (1) underestimate the normal lung function. Use of updated reference values, which are well matched with the patient served by a particular office/laboratory, is important especially in screening of healthy subjects and in detecting early changes in lung function due to smoking or other environmental agents (79). The prediction equations developed from the BONT study represent an improvement compared to those from ECCS, and are recommended used in Norway. The equations are already included as an available option in the software of some of the spirometers commonly used in Norway.

7.4.3 Inhaled corticosteroids and bone mineral density

Osteopenia/osteoporosis is a major risk factor for low energy fractures in dorsal vertebras, costa, hips and wrists. The BMC increases during adolescents and young adulthood reaching peak bone mass, followed by a plateau, after which a decrease with age is seen in both sexes. In women there is an additional accelerating loss of bone mass during and after menopause. An ageing population in the developed countries, thereby, is associated with increasing prevalence of osteoporotic fractures. Use of OCS is the most important contributor to secondary osteoporosis, but there also is concern about possible negative effect on bone by use of ICS as the indications for such treatment have been widened during the last decade. In the present study we found a statistically significant lower level (2 %) of BMD in ICS users compared to never users. However, we did not find any dose response relationship between BMD and ICS, indicating that other characteristics of the patient group might explain the difference. Large real life studies on effect of ICS has not previously been performed in unselected populations, and we have no reason to believe that the present study should be seriously biased reducing the external validity.

Lack of dose response relationship, slightly lower BMD in ICS users compared to never users, and change in treatment guidelines for asthma in the direction of use of even lower doses ICS in combination therapy (300), might moderate the concern on ICS side effect at a population level. However, awareness on possible side effects on bone, as well as growth in childhood/adolescence, should be maintained because of differences in individual susceptibility to systemic side effect of CS treatment. In subjects with asthma, the dose of ICS should be stepped down to the lowest level keeping disease and symptom control (7). In COPD, however, the step down strategy is not recommended, as only high doses so far have documented effect on reduction of exacerbation rate (17). COPD patients are at increased risk for osteoporosis because of high age, smoking history, and low physical activity. Therefore, ICS treatment should be limited to those groups with proven effect on symptoms, quality of life and exacerbation rate, and patients at risk for osteoporosis should have their BMD measured.

8 Conclusions

8.1 Respiratory symptoms and diseases:

- The prevalence of reported asthma and use of asthma medication was higher than reported in previous Scandinavian studies
- Tobacco smoking is associated with increased prevalence of respiratory symptoms and obstructive lung disease, lower self-rated health and lower expiratory lung function parameters in both sexes.
- With increasing smoking burden there is an increasing difference by sex indicating that women are more vulnerable to tobacco smoking than men.
- Even if women have a larger relative reduction in lung function than men, this does not fully explain the sex difference in symptom prevalence and SRH

8.2 Reference values for forced volume spirometry

- The present developed prediction equations fit the population better than those developed from the ECCS, and are recommended for use in Norway.

8.3 Inhaled corticosteroids and bone mineral density

- Current users of ICS have 2 % lower BMD in the forearm than never-users.
- In the present study no dose-response relationship between daily dose, duration of use, or cumulative dose of ICS and BMD was found
- Narrow dose range of ICS in the present study or other patient characteristics might explain lower BMD in ICS users compared to never-users.
- More effectiveness studies of the widespread use of ICS for obstructive lung diseases are warranted

9 The BONT Study in the new millennium

The BONT study has collected data on risk factors, respiratory symptoms and diseases, which constitutes database for cross-sectional studies on prevalence and basic determinants of symptoms and diseases. This also renders possible longitudinal studies, both retrospective using variables on exposure from HUNT 1, and prospective through follow-up studies of selected groups or the total population. As part of the HUNT study, there is an unlimited possibility for studies on other factors' or diseases' influence on respiratory symptoms and diseases and vice versa. Collaboration with other epidemiological studies on osteoporosis is already established through Norwegian Epidemiological Osteoporosis Studies (NOREPOS).

High priority will be given to the following topics:

9.1 Reference values

The use of different reference values for different age groups gives problems with gaps in the transition zone of the sets. In Nord-Trøndelag the Young-HUNT study performed spirometry on adolescents aged 13-19 years during 1995-97. Young-HUNT and BONT should develop prediction equations covering age 13-80 years using available data. In addition, in HUNT 3 (2006-2007) further validation of the prediction equations for adults should be done, with special focus on the elderly group. Young-HUNT should consider inclusion of children under the age of 13 for spirometry.

9.2 Risk factors for obstructive lung disease

Tobacco smoking causes respiratory symptoms and obstructive lung disease and lung cancer. Different vulnerability by sex might be a result of differences in small airway disease. Research on strategies for smoking avoidance and cessation is warranted, but also studies on

finding sensitive tool for early recognition of subjects at risk of developing serious smoke related lung disease. The latter might be genetic susceptibility, symptoms or measurements of early lung damage.

9.3 Bronchial reversibility

Tests of bronchial variability are widely used in diagnosis and follow up of patients with obstructive lung disease. In BONT phase 2 almost 6,000 subjects performed reversibility tests and a sub-sample similar test after prednisolone test. Different cut-offs for positive reversibility tests are used, most common in Norway is 15 %, whilst ATS recommend 12 %. Studies on reversibility among healthy subjects (without respiratory symptoms), and those with symptoms with or without medical treatment will be performed.

9.4 Bone mineral density/fracture risk in subjects with asthma or COPD

We found 2 % lower BMD in ever users of ICS compared to never users. Whether this is a result of ICS or other factors and is of clinical significance, can only be answered by follow up studies with thorough data collection of exposure for ICS and confounders and use of fractures as dependent variable.

Follow up study with bone densitometry was performed in 2001 with new measurements of the 5 % random sample and those having using ICS at HUNT 2. So far, this data is not analysed. In addition a registry of fractures is established at both hospitals in the county, rendering studies with fracture as hard end point possible.

As corticosteroids seem to have greater impact on trabecular bone in the weigh-bearing part of the skeleton, measurement of weight-bearing skeleton as calcaneus is planned in HUNT 3. In addition repeated measurement at the forearm, and validation studies with DXA

measurements of the lumbar spine and hips of samples will be performed at the local hospital in Levanger.

9.5 Genetics

The BONT and HUNT studies include rather detailed information on phenotypes of obstructive lung diseases, and there will be further possibilities for improving this in HUNT 3. In addition blood samples for DNA extraction are available for all participants at HUNT 2 and will also be taken in HUNT 3, giving opportunities for analyses of phenotype and genotype associations. So far, genome screens with classical linkage and fine mapping approaches have suggested that many genes that have a moderate effect determine susceptibility to asthma. Identification of the precise loci involved has been difficult, and the identified genes probably are involved in disease initiation rather than in severity or progression (6). Epidemiological studies like HUNT and BONT might in the future contribute in the research to identify how genes that predispose individuals to asthma or COPD interact with environmental factors to cause disease and its progression.

10 References

(1) Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society [see comments]. Eur Respir J Suppl 1993; 16:5-40.

(2) Lundback B. Asthma, chronic bronchitis and respiratory symptoms: Prevalence and important determinants. The Obstructive Lung Disease in Northern Sweden Study I. University of Umeå, 1993.

(3) Lyans A, Petrucelli R. Medicine. An illustrated history. New York: 1978.

(4) Keeley D. Looking back, looking forward. National Asthma Campaign. 1997.
Ref Type: Electronic Citation

(5) Burney P. Asthma. In: Annesi-Maesano I, Gulsvik A, Viegi G, editors. Respiratory Epidemilogy in Europe. Sheffield: European Respiratory Society Journals Ltd, 2000: 48-66.

(6) Tattersfield AE, Knox AJ, Britton JR, Hall IP. Asthma. Lancet 2002; 360(9342):1313-1322.

(7) Global Initiatives for Asthma. Global Strategy for Asthma Management and Prevention NHLBI/WHO Workshop. 2002. National Heart, Lung, and Blood Institute, National Institute of Health, Bethesda, MD(US-DHHS/PHS/NIH Publication No.02-3659).
Ref Type: Report

(8) Magnus P, Jaakkola JJ. Secular trend in the occurrence of asthma among children and young adults: critical appraisal of repeated cross sectional surveys. BMJ 1997; 314(7097):1795-1799.

(9) Janson C, Chinn S, Jarvis D, Burney P. Physician-diagnosed asthma and drug utilization in the European Community Respiratory Health Survey. Eur Respir J 1997; 10(8):1795-1802.

(10) The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet 1998; 351(9111):1225-1232.

(11) Chen Y, Dales R, Tang M, Krewski D. Sex-related interactive effect of smoking and household pets on asthma incidence. Eur Respir J 2002; 20(5):1162-1166.

(12) Kauffmann F, Becklake MR. Maladies respiratoires obstructives. Un paradigme de la complexité des différences de santé entre femmes et hommes. In: Saurel-Cubizolles M-J, Blondel B, editors. La santé des femmes. Paris: Médecine-Sciences, Flammarion, 1996: 209-233.

(13) Key TJ, Pike MC, Baron JA, Moore JW, Wang DY, Thomas BS et al. Cigarette smoking and steroid hormones in women. J Steroid Biochem Mol Biol 1991; 39(4A):529-534.

(14) Camargo CAJ, Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult- onset asthma in women [see comments]. Arch Intern Med 1999; 159(21):2582-2588.

(15) Wahn U. What drives the allergic march? Allergy 2000; 55(7):591-599.

(16) Platts-Mills TA, Perzanowski M, Woodfolk JA, Lundback B. Relevance of early or current pet ownership to the prevalence of allergic disease. Clin Exp Allergy 2002; 32(3):335-338.

(17) Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. Respir Care 2001; 46(8):798-825.

(18) Lange P, Groth S, Nyboe J, Appleyard M, Mortensen J, Jensen G et al. Chronic obstructive lung disease in Copenhagen: cross-sectional epidemiological aspects. J Intern Med JID - 8904841 1989; 226(1):25-32.

(19) Sobradillo V, Miravitlles M, Jimenez CA, Gabriel R, Viejo JL, Masa JF et al. [Epidemiological study of chronic obstructive pulmonary disease in Spain (IBERPOC): prevalence of chronic respiratory symptoms and airflow limitation]. Arch Bronconeumol JID - 0354720 1999; 35(4):159-166.

(20) Bakke PS, Baste V, Hanoa R, Gulsvik A. Prevalence of obstructive lung disease in a general population: relation to occupational title and exposure to some airborne agents. Thorax 1991; 46(12):863-870.

(21) Lundback B, Stjernberg N, Nystrom L, Lundback K, Lindstrom M, Rosenhall L. An interview study to estimate prevalence of asthma and chronic bronchitis. The obstructive lung disease in northern Sweden study. Eur J Epidemiol 1993; 9(2):123-133.

(22) Hurd S. The impact of COPD on lung health worldwide: epidemiology and incidence. Chest 2000; 117(2 Suppl):1S-4S.

(23) Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance--United States, 1971-2000. Respir Care 2002; 47(10):1184-1199.

(24) British thoracic society, The COPD Guidelines Group of the Standards of Care Committee. Guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997; 52 Suppl 5:S1-28.

(25) American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 136(1):225-244.

(26) Lundback B, Lindberg A, Lindstrom M, Ronmark E, Jonsson AC, Jonsson E et al. Not 15 but 50% of smokers develop COPD?--Report from the Obstructive Lung Disease in Northern Sweden Studies. Respir Med 2003; 97(2):115-122.

(27) Sandford AJ, Silverman EK. Chronic obstructive pulmonary disease. 1: Susceptibility factors for COPD the genotype-environment interaction. Thorax 2002; 57(8):736-741.

(28) Gold DR, Wang X, Wypij D, Speizer FE, Ware JH, Dockery DW. Effects of cigarette smoking on lung function in adolescent boys and girls. N Engl J Med 1996; 335(13):931-937.

(29) Leynaert B, Bousquet J, Henry C, Liard R, Neukirch F. Is bronchial hyperresponsiveness more frequent in women than in men? A population-based study. Am J Respir Crit Care Med 1997; 156(5):1413-1420.

(30) Paoletti P, Carrozzi L, Viegi G, Modena P, Ballerin L, Di Pede F et al. Distribution of bronchial responsiveness in a general population: effect of sex, age, smoking, and level of pulmonary function. Am J Respir Crit Care Med JID - 9421642 1995; 151(6):1770-1777.

(31) Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. Eur Respir J 1997; 10(4):822-827.

(32) Camilli AE, Burrows B, Knudson RJ, Lyle SK, Lebowitz MD. Longitudinal changes in forced expiratory volume in one second in adults. Effects of smoking and smoking cessation. Am Rev Respir Dis JID - 0370523 1987; 135(4):794-799.

(33) Lange P, Groth S, Nyboe J, Mortensen J, Appleyard M, Jensen G et al. Decline of the lung function related to the type of tobacco smoked and inhalation. Thorax JID - 0417353 1990; 45(1):22-26.

(34) Tashkin DP, Clark VA, Coulson AH, Simmons M, Bourque LB, Reems C et al. The UCLA population studies of chronic obstructive respiratory disease. VIII. Effects of smoking cessation on lung function: a prospective study of a free-living population. Am Rev Respir Dis JID - 0370523 1984; 130(5):707-715.

(35) van Pelt W, Borsboom GJ, Rijcken B, Schouten JP, van Zomeren BC, Quanjer PH. Discrepancies between longitudinal and cross-sectional change in ventilatory function in 12 years of follow-up. Am J Respir Crit Care Med JID - 9421642 1994; 149(5):1218-1226.

(36) Viegi G, Paoletti P, Prediletto R, Carrozzi L, Fazzi P, Di Pede F et al. Prevalence of respiratory symptoms in an unpolluted area of northern Italy. Eur Respir J JID - 8803460 1988; 1(4):311-318.

(37) Xu X, Dockery DW, Ware JH, Speizer FE, Ferris BGJ. Effects of cigarette smoking on rate of loss of pulmonary function in adults: a longitudinal assessment. Am Rev Respir Dis 1992; 146(5 Pt 1):1345-1348.

(38) Burrows B, Knudson RJ, Cline MG, Lebowitz MD. Quantitative relationships between cigarette smoking and ventilatory function. Am Rev Respir Dis JID - 0370523 1977; 115(2):195-205.

(39) Chen Y, Horne SL, Dosman JA. Increased susceptibility to lung dysfunction in female smokers. Am Rev Respir Dis JID - 0370523 1991; 143(6):1224-1230.

(40) Lange P, Groth S, Nyboe GJ, Mortensen J, Appleyard M, Jensen G et al. Effects of smoking and changes in smoking habits on the decline of FEV1. Eur Respir J JID - 8803460 1989; 2(9):811-816.

(41) Vollmer WM, Enright PL, Pedula KL, Speizer F, Kuller LH, Kiley J et al. Race and gender differences in the effects of smoking on lung function. Chest 2000; 117(3):764-772.

(42) Orie N, Sluiter H, De Vreis K, Tammerling K, Wikop J. The host factor in bronchitis. 43-59. 1961. Assen, Netherlands, University of Groningen. Royal Van Gorcum. Bronchitis, an international symposium.
Ref Type: Report

(43) Xu X, Rijcken B, Schouten JP, Weiss ST. Airways responsiveness and development and remission of chronic respiratory symptoms in adults. Lancet 1997; 350(9089):1431-1434.

(44) Anthonisen NR. Epidemiology and the Lung Health Study. Eur Respir Rev 1997; 7(45):202-205.

(45) Brown CA, Crombie IK, Smith WC, Tunstall-Pedoe H. The impact of quitting smoking on symptoms of chronic bronchitis: results of the Scottish Heart Health Study. Thorax 1991; 46(2):112-116.

(46) Freund KM, Belanger AJ, D'Agostino RB, Kannel WB. The health risks of smoking. The Framingham Study: 34 years of follow- up. Ann Epidemiol 1993; 3(4):417-424.

(47) Ronmark E, Lundback B, Jonsson E, Jonsson AC, Lindstrom M, Sandstrom T. Incidence of asthma in adults--report from the Obstructive Lung Disease in Northern Sweden Study. Allergy 1997; 52(11):1071-1078.

(48) Sherrill DL, Lebowitz MD, Burrows B. Epidemiology of chronic obstructive pulmonary disease. Clin Chest Med 1990; 11(3):375-387.

(49) Tager IB, Segal MR, Speizer FE, Weiss ST. The natural history of forced expiratory volumes. Effect of cigarette smoking and respiratory symptoms. Am Rev Respir Dis 1988; 138(4):837-849.

(50) Coultas DB. Health effects of passive smoking. 8. Passive smoking and risk of adult asthma and COPD: an update. Thorax 1998; 53(5):381-387.

(51) Tobacco web. Smoking and tobacco related issues. The Cancer Council,New South Wales . 2003.
Ref Type: Electronic Citation

(52) Tobacco under attack. CNN Interactive . 2003.
Ref Type: Electronic Citation

(53) Ernster V, Kaufman N, Nichter M, Samet J, Yoon SY. Women and tobacco: moving from policy to action. Bull World Health Organ 2000; 78(7):891-901.

(54) WHO. Tobacco or health: A global status report. 1998. Geneva, W.H.O.
Ref Type: Report

(55) Løvbak P, Kristiansen J, Eidsaae P. Statistical Yearbook of Norway. Oslo/Kongsvinger: Statistics Norway, 1996.

(56) Lukerstuen Å. Statistical Yearbook of Norway. Oslo/Kongsvinger: Statistics Norway, 2002.

(57) Doll R. Risk from tobacco and potentials for health gain. Int J Tuberc Lung Dis 1999; 3(2):90-99.

(58) Fagerstrom K. The epidemiology of smoking: health consequences and benefits of cessation. Drugs 2002; 62 Suppl 2:1-9.

(59) Kiel DP, Zhang Y, Hannan MT, Anderson JJ, Baron JA, Felson DT. The effect of smoking at different life stages on bone mineral density in elderly men and women. Osteoporos Int 1996; 6(3):240-248.

(60) Forsen L, Bjorndal A, Bjartveit K, Edna TH, Holmen J, Jessen V et al. Interaction between current smoking, leanness, and physical inactivity in the prediction of hip fracture. J Bone Miner Res 1994; 9(11):1671-1678.

(61) Liard R, Neukirch F. Questionnaires: a major instrument for respiratory epidemiology. In: Annesi-Maesano I, Gulsvik A, Viegi G, editors. Respiratory Epidemiology in Europe. European Respiratory Society, 2000: 154-166.

(62) Medical Research Council's Committee on the Aetiology of Chronic Bronchitis. Standardized questionnaire on respiratory symtpoms. BMJ 1960; 2:1665.

(63) Ferris BG. Epidemiology Standardization Project (American Thoracic Society). Am Rev Respir Dis JID - 0370523 1978; 118(6 Pt 2):1-120.

(64) Abramson MJ, Hensley MJ, Saunders NA, Wlodarczyk JH. Evaluation of a new asthma questionnaire. J Asthma 1991; 28(2):129-139.

(65) Burney P, Chinn S. Developing a new questionnaire for measuring the prevalence and distribution of asthma. Chest 1987; 91(6 Suppl):79S-83S.

(66) Toren K, Brisman J, Jarvholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. Chest 1993; 104(2):600-608.

(67) Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. Eur Respir J 1994; 7(5):954-960.

(68) Pearce N, Beasley R, Burgess C, Crane J. Asthma Epidemiology, Principles and Methods. New York: Oxford University Press, 1998.

(69) Burney P, Laitinen LA, Perdrizet S, Huckauf H, Tattersfield AE, Chinn S et al. Validity and repeatability of the IUATLD(1984) bronchial symtpoms questionnaire: an international comparison. Eur Respir J 1989; 2:940-945.

(70) Burney PG, Chinn S, Britton JR, Tattersfield AE, Papacosta AO. What symptoms predict the bronchial response to histamine? Evaluation in a community survey of the bronchial symptoms questionnaire (1984) of the International Union Against Tuberculosis and Lung Disease. Int J Epidemiol JID - 7802871 1989; 18(1):165-173.

(71) Eriksson I, Unden AL, Elofsson S. Self-rated health. Comparisons between three different measures. Results from a population study. Int J Epidemiol JID - 7802871 2001; 30(2):326-333.

(72) Mossey JM, Shapiro E. Self-rated health: a predictor of mortality among the elderly. Am J Public Health 1982; 72(8):800-808.

(73) Wøien G, Øyen O, Graff-Iversen S. 22 years of cardiovascular surveys in Norwegian counties. Is the development in risk factors satisfactory? Nor J Epidemiol 1997; 7(2):255-266.

(74) Crapo RO. Pulmonary-function testing [see comments]. N Engl J Med 1994; 331(1):25-30.

(75) Baur X, Isringhausen-Bley S, Degens P. Comparison of lung-function reference values. Int Arch Occup Environ Health 1999; 72(2):69-83.

(76) A short history of spirometry and lung function tests. Meizin & MedTech - Verlag . 2003. Ref Type: Electronic Citation

(77) Becklake MR. Gender difference in airway behaviour (physiology) over the human lifespan. In: Buist S, Mapp CE, editors. Respiratory Diseases in Women. Sheffield: European Respiratory Society Journals Ltd, 2003: 8-25.

(78) Cooper B, Madsen F. Spirometry. European Respiratory Society - The buyer's guide 2000; 3:40-43.

(79) American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society [see comments]. Am Rev Respir Dis 1991; 144(5):1202-1218.

(80) Nysom K, Ulrik CS, Hesse B, Dirksen A. Published models and local data can bridge the gap between reference values of lung function for children and adults. Eur Respir J 1997; 10(7):1591-1598.

(81) Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999; 159(1):179-187.

(82) Brändli O, Schindler C, Kunzli N, Keller R, Perruchoud AP. Lung function in healthy never smoking adults: reference values and lower limits of normal of a Swiss population. Thorax 1996; 51(3):277-283.

(83) Gulsvik A. Obstructive lung disease in an urban population. Department of Lung Diseases, The National Hospital, University of Oslo, 1974.

(84) Gulsvik A. Prevalence and manifestations of obstructive lung disease in the city of Oslo. Scand J Respir Dis 1979; 60(5):286-296.

(85) Roca J, Sanchis J, Agusti-Vidal A, Segarra F, Navajas D, Rodriguez-Roisin R et al. Spirometric reference values from a Mediterranean population. Bull Eur Physiopathol Respir 1986; 22(3):217-224.

(86) Gore CJ, Crockett AJ, Pederson DG, Booth ML, Bauman A, Owen N. Spirometric standards for healthy adult lifetime nonsmokers in Australia. Eur Respir J 1995; 8(5):773-782.

(87) Enright PL, Kronmal RA, Higgins M, Schenker M, Haponik EF. Spirometry reference values for women and men 65 to 85 years of age. Cardiovascular health study. Am Rev Respir Dis 1993; 147(1):125-133.

(88) Berglund E, Birath G, Bjure, et al. Spirometric studies in normal subjects. I. Forced exspirograms in subjects between 7 and 70 years of age. Acta Med Scand 1963; 173:185-192.

(89) Viljanen AA, Halttunen PK, Kreus KE, Viljanen BC. Spirometric studies in non-smoking, healthy adults. Scand J Clin Lab Invest Suppl JID - 2984789R 1982; 159:5-20.

(90) Groth S, Dirksen A, Dirksen H, Rossing N. Pulmonary function in a sample of persons aged 30-70 years who had never smoked, resident in Copenhagen and who were representative for the population. The normal values for inter- and intraindividual variation. Ugeskr Laeger 1986; 148:3207-3213.

(91) Oxhoj H, Jeppesen GM, Larsen VH, Jorgensen B. Spirometry in healthy adult never-smokers. Clin Physiol 1988; 8(4):329-339.

(92) Fredriksson HV, Malmberg P, Hedenstrom H, Hillerdal G. Reference values for respiratory function tests in males. Prediction formulas with tobacco smoking parameters. Clin Physiol 1981; 1:349-364.

(93) Hedenström H, Malmberg P, Agarwal K. Reference values for lung function tests in females. Regression equations with smoking variables. Bull Eur Physiopathol Respir 1985; 21:551-557.

(94) Hedenström H, Malmberg P, Fridriksson HV. Reference values for lung function tests in men: Regression equations with smoking variables. Upsala J Med Sci 1986; 91:299-310.

(95) Langhammer A, Johnsen R, Gulsvik A, Holmen TL, Bjermer L. Forced spirometry reference values for Norwegian adults: the bronchial obstruction in Nord-Trondelag Study. Eur Respir J JID - 8803460 2001; 18(5):770-779.

(96) Roca J, Burgos F, Sunyer J, Saez M, Chinn S, Anto JM et al. References values for forced spirometry. Group of the European Community Respiratory Health Survey. Eur Respir J 1998; 11(6):1354-1362.

(97) Glindmeyer HW, Diem JE, Jones RN, Weill H. Noncomparability of longitudinally and cross-sectionally determined annual change in spirometry. Am Rev Respir Dis 1982; 125(5):544-548.

(98) Cole TJ. Linear and Proportional Regression Models in the Prediction of Ventilatory Function. J Royal Stat Soc 1975; 138:297-338.

(99) Dockery DW, Ware JH, Ferris BGJ, Glicksberg DS, Fay ME, Spiro A et al. Distribution of forced expiratory volume in one second and forced vital capacity in healthy, white, adult never-smokers in six U.S. cities. Am Rev Respir Dis 1985; 131(4):511-520.

(100) Humerfelt S, Eide GE, Kvale G, Gulsvik A. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) variability in asymptomatic never-smoking men. Clin Physiol 1998; 18(4):387-396.

(101) Gulsvik A, Tosteson T, Bakke P, Humerfelt S, Weiss ST, Speizer FE. Expiratory and inspiratory forced vital capacity and one-second forced volume in asymptomatic never-smokers in Norway. Clin Physiol JID - 8309768 2001; 21(6):648-660.

(102) Dockery DW. Percentile curves for evaluation of repeated measures of lung function. Occup Med JID - 8605629 1993; 8(2):323-338.

(103) Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. Am Rev Respir Dis 1981; 123(6):659-664.

(104) Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am Rev Respir Dis 1983; 127(6):725-734.

(105) Paoletti P, Pistelli G, Fazzi P, Viegi G, Di Pede F, Giuliano G et al. Reference values for vital capacity and flow-volume curves from a general population study. Bull Eur Physiopathol Respir 1986; 22(5):451-459.

(106) Brändli O, Schindler C, Leuenberger PH, Baur X, Degens P, Kunzli N et al. Re-estimated equations for 5th percentiles of lung function variables. Thorax 2000; 55(2):173-174.

(107) Knudson RJ, Slatin RC, Lebowitz MD, Burrows B. The maximal expiratory flow-volume curve. Normal standards, variability, and effects of age. Am Rev Respir Dis 1976; 113(5):587-600.

(108) Lebowitz MD, Holberg CJ. Comparisons of spirometric reference values and the proportions of abnormal subjects among male smokers and those symptomatic in a community population. Am Rev Respir Dis 1990; 141(6):1491-1496.

(109) Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet 2002; 359(9319):1761-1767.

(110) Recker RR, Davies KM, Hinders SM, Heaney RP, Stegman MR, Kimmel DB. Bone gain in young adult women. JAMA 1992; 268(17):2403-2408.

(111) Augat P, Fuerst T, Genant HK. Quantitative bone mineral assessment at the forearm: a review. Osteoporos Int 1998; 8(4):299-310.

(112) Berntsen GK, Fonnebo V, Tollan A, Sogaard AJ, Magnus JH. Forearm bone mineral density by age in 7,620 men and women: the Tromso study, a population-based study. Am J Epidemiol 2001; 153(5):465-473.

(113) Van Staa TP, Leufkens HG, Cooper C. Does a fracture at one site predict later fractures at other sites? A British cohort study. Osteoporos Int 2002; 13(8):624-629.

(114) Cummings SR, Bates D, Black DM. Clinical use of bone densitometry: scientific review. JAMA 2002; 288(15):1889-1897.

(115) Niewoehner CB, Niewoehner DE. Steroid-induced osteoporosis. Are your asthmatic patients at risk? Postgrad Med 1999; 105(3):79-91.

(116) Cooper C, Campion G, Melton LJ, III. Hip fractures in the elderly: a world-wide projection. Osteoporos Int 1992; 2(6):285-289.

(117) Johnston CCJ, Slemenda CW. Identification of patients with low bone mass by single photon absorptiometry and single-energy X-ray absorptiometry. Am J Med 1995; 98(2A):37S-40S.

(118) Kleerekoper M, Nelson DA. Peripheral bone densitometry: an old friend revisited. Trans Am Clin Climatol Assoc 1998; 109:62-70.

(119) Rosvold Berntsen GK, Fonnebo V, Tollan A, Sogaard AJ, Joakimsen RM, Magnus JH. The Tromso study: determinants of precision in bone densitometry. J Clin Epidemiol 2000; 53(11):1104-1112.

(120) Hassager C, Jensen S, Gotfredsen A, Christiansen C. The impact of measurement errors on the diagnostic value of bone mass measurements: theoretical considerations. Osteoporosis Int 1991; 1:250-256.

(121) Gardsell P, Johnell O, Nilsson BE, Gullberg B. Predicting various fragility fractures in women by forearm bone densitometry: a follow-up study. Calcif Tissue Int 1993; 52(5):348-353.

(122) Wasnich R. Bone mass measurement: prediction of risk. Am J Med 1993; 95(5A):6S-10S.

(123) Heilmann P, Wuster C, Prolingheuer C, Gotz M, Ziegler R. Measurement of forearm bone mineral density: comparison of precision of five different instruments. Calcif Tissue Int 1998; 62(5):383-387.

(124) Cummings S, Black D, Nevitt M, Browner W, Cauley J, Ensrud K et al. Bone density at various sites for prediction of hip fractures. The Lancet 1993; 341:72-75.

(125) Black DM, Cummings SR, Genant HK, Nevitt MC, Palermo L, Browner W. Axial and appendicular bone density predict fractures in older women. J Bone Miner Res 1992; 7(6):633-638.

(126) Nieves JW, Cosman F, Mars C, Lindsay R. Comparative assessment of bone mineral density of the forearm using single photon and dual X-ray absorptiometry. Calcif Tissue Int 1992; 51(5):352-355.

(127) Ravn P, Overgaard K, Huang C, Ross PD, Green D, McClung M. Comparison of bone densitometry of the phalanges, distal forearm and axial skeleton in early postmenopausal women participating in the EPIC Study. Osteoporos Int 1996; 6(4):308-313.

(128) Jones T, Davie MW. Bone mineral density at distal forearm can identify patients with osteoporosis at spine or femoral neck. Br J Rheumatol 1998; 37(5):539-543.

(129) Hui S, Slemenda C, Johnston C. Baseline measurement of bone mass predicts fracture in white women. Ann Intern Med 1989; 111:355-361.

(130) Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures [see comments]. BMJ 1996; 312(7041):1254-1259.

(131) Adinoff AD, Hollister JR. Steroid-induced fractures and bone loss in patients with asthma. N Engl J Med 1983; 309(5):265-268.

(132) Seeman E, Wahner HW, Offord KP, Kumar R, Johnson WJ, Riggs BL. Differential effects of endocrine dysfunction on the axial and the appendicular skeleton. J Clin Invest 1982; 69(6):1302-1309.

(133) Lane NE, Lukert B. The science and therapy of glucocorticoid-induced bone loss. Endocrinol Metab Clin North Am 1998; 27(2):465-483.

(134) Elmstahl S, Ekstrom H, Galvard H, Johnell O, Gerhardsson d, V, Norjavaara E. Is there an association between inhaled corticosteroids and bone density in postmenopausal women? J Allergy Clin Immunol 2003; 111(1):91-96.

(135) WHO Study Group. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser 1994; 843:1-129.

(136) Kanis JA, Gluer CC. An update on the diagnosis and assessment of osteoporosis with densitometry. Committee of Scientific Advisors, International Osteoporosis Foundation. Osteoporos Int 2000; 11(3):192-202.

(137) Steiger P, Cummings SR, Black DM, Spencer NE, Genant HK. Age-related decrements in bone mineral density in women over 65. J Bone Miner Res 1992; 7(6):625-632.

(138) Orimo H, Sugioka Y, Fukunaga M, Muto Y, Hotokebuchi T, Gorai I et al. The Committee of the Japanese Society for Bone and Mineral Research for Development of Diagnostic criteria of Osteoporosis: Diagnostic criteria of primary osteoporosis. J Bone Miner Metab 1998; 16:139-150.

(139) De Laet CE, van Hout BA, Burger H, Hofman A, Pols HA. Bone density and risk of hip fracture in men and women: cross sectional analysis. BMJ 1997; 315(7102):221-225.

(140) Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures [see comments]. J Bone Miner Res 2000; 15(6):993-1000.

(141) Villareal MS, Klaustermeyer WB, Hahn TJ, Gordon EH. Osteoporosis in steroid-dependent asthma. Ann Allergy Asthma Immunol 1996; 76(4):369-372.

(142) Gennari C, Martini G, Nuti R. Secondary osteoporosis. Aging (Milano) 1998; 10(3):214-224.

(143) Ruegsegger P, Medici TC, Anliker M. Corticosteroid-induced bone loss. A longitudinal study of alternate day therapy in patients with bronchial asthma using quantitative computed tomography. Eur J Clin Pharmacol 1983; 25(5):615-620.

(144) Van Staa TP, Leufkens HG, Cooper C. The Epidemiology of Corticosteroid-Induced Osteoporosis: a Meta-analysis. Osteoporos Int 2002; 13(10):777-787.

(145) The Swedish Council on Technology Assessment in Health Care. Bone density measurement--a systematic review. A report from SBU, the Swedish Council on Technology Assessment in Health Care. J Intern Med Suppl 1997; 739:1-60.

(146) Adachi JD, Ioannidis G. Calcium and vitamin D therapy in corticosteroid-induced bone loss: what is the evidence? Calcif Tissue Int 1999; 65(4):332-336.

(147) Manolagas SC, Weinstein RS. New developments in the pathogenesis and treatment of steroid-induced osteoporosis[Editorial]. J Bone Miner Res 1999; 14(7):1061-1066.

(148) Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management [see comments]. Ann Intern Med 1990; 112(5):352-364.

(149) Reid IR, Heap SW. Determinants of vertebral mineral density in patients receiving long-term glucocorticoid therapy. Arch Intern Med 1990; 150(12):2545-2548.

(150) Dykman TR, Haralson KM, Gluck OS, Murphy WA, Teitelbaum SL, Hahn TJ et al. Effect of oral 1,25-dihydroxyvitamin D and calcium on glucocorticoid-induced osteopenia in patients with rheumatic diseases. Arthritis Rheum 1984; 27(12):1336-1343.

(151) Hahn TJ, Halstead LR, Teitelbaum SL, Hahn BH. Altered mineral metabolism in glucocorticoid-induced osteopenia. Effect of 25-hydroxyvitamin D administration. J Clin Invest 1979; 64(2):655-665.

(152) Lips P. Prevention of corticosteroid induced osteoporosis [editorial] [see comments]. BMJ 1999; 318(7195):1366-1367.

(153) American College of Rheumatology. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. American College of Rheumatology Task Force on Osteoporosis Guidelines [see comments]. Arthritis Rheum 1996; 39(11):1791-1801.

(154) Pearce G, Ryan PF, Delmas PD, Tabensky DA, Seeman E. The deleterious effects of low-dose corticosteroids on bone density in patients with polymyalgia rheumatica. Br J Rheumatol 1998; 37(3):292-299.

(155) Hollister JR. The untoward effects of steroid treatment on the musculoskeletal system and what to do about them. J Asthma 1992; 29(6):363-368.

(156) Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology (Oxford) 2000; 39(12):1383-1389.

(157) Dubois EF, Roder E, Dekhuijzen PN, Zwinderman AE, Schweitzer DH. Dual energy X-ray absorptiometry outcomes in male COPD patients after treatment with different glucocorticoid regimens. Chest 2002; 121(5):1456-1463.

(158) Sambrook PN, Kelly PJ, Keogh AM, Macdonald P, Spratt P, Freund J et al. Bone loss after heart transplantation: a prospective study. J Heart Lung Transplant 1994; 13(1 Pt 1):116-120.

(159) Laan RF, van Riel PL, van de Putte LB, van Erning LJ, van't Hof MA, Lemmens JA. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. Ann Intern Med 1993; 119(10):963-968.

(160) Lane NE, Sanchez S, Modin GW, Genant HK, Pierini E, Arnaud CD. Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. Results of a randomized controlled clinical trial. J Clin Invest 1998; 102(8):1627-1633.

(161) Luisetto G, Zangari M, Camozzi V, Boscaro M, Sonino N, Fallo F. Recovery of bone mineral density after surgical cure, but not by ketoconazole treatment, in Cushing's syndrome. Osteoporos Int 2001; 12(11):956-960.

(162) McKenzie R, Reynolds JC, O'Fallon A, Dale J, Deloria M, Blackwelder W et al. Decreased bone mineral density during low dose glucocorticoid administration in a randomized, placebo controlled trial. J Rheumatol 2000; 27(9):2222-2226.

(163) Plotkin LI, Weinstein RS, Parfitt AM, Roberson PK, Manolagas SC, Bellido T. Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin. J Clin Invest 1999; 104(10):1363-1374.

(164) Peel NF, Moore DJ, Barrington NA, Bax DE, Eastell R. Risk of vertebral fracture and relationship to bone mineral density in steroid treated rheumatoid arthritis. Ann Rheum Dis 1995; 54(10):801-806.

(165) Luengo M, Picado C, del Rio L, Guanabens N, Montserrat JM, Setoain J. Vertebral fractures in steroid dependent asthma and involutional osteoporosis: a comparative study. Thorax 1991; 46(11):803-806.

(166) Selby PL, Halsey JP, Adams KR, Klimiuk P, Knight SM, Pal B et al. Corticosteroids do not alter the threshold for vertebral fracture. J Bone Miner Res 2000; 15(5):952-956.

(167) Clowes JA, Peel N, Eastell R. Glucocorticoid-induced osteoporosis. Curr Opin Rheumatol 2001; 13(4):326-332.

(168) Blake GM, Fogelman I. Bone densitometry, steroids and osteoporosis. Curr Opin Nephrol Hypertens 2002; 11(6):641-647.

(169) Hanania NA, Chapman KR, Kesten S. Adverse effects of inhaled corticosteroids. Am J Med 1995; 98:196-208.

(170) Lipworth BJ, Jackson CM. Safety of inhaled and intranasal corticosteroids: lessons for the new millennium. Drug Saf 2000; 23(1):11-33.

(171) Wong CA, Subakumar G, Casey PM. Effects of asthma and asthma therapies on bone mineral density. Curr Opin Pulm Med 2002; 8(1):39-44.

(172) Roche N, Lepage T, Bourcereau J, Terrioux P. Guidelines versus clinical practice in the treatment of chronic obstructive pulmonary disease. Eur Respir J 2001; 18(6):903-908.

(173) Pauwels R. Inhaled glucocorticosteroids and chronic obstructive pulmonary disease: how full is the glass? Am J Respir Crit Care Med 2002; 165(12):1579-1580.

(174) Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. Am J Respir Crit Care Med 1998; 157(3 Pt 2):S1-53.

(175) Lipworth BJ. Airway and systemic effects of inhaled corticosteroids in asthma: dose response relationship. Pulm Pharmacol 1996; 9(1):19-27.

(176) Bonala SB, Reddy BM, Silverman BA, Bassett CW, Rao YA, Amara S et al. Bone mineral density in women with asthma on long-term inhaled corticosteroid therapy. Ann Allergy Asthma Immunol 2000; 85(6 Pt 1):495-500.

(177) Ebeling PR, Erbas B, Hopper JL, Wark JD, Rubinfeld AR. Bone mineral density and bone turnover in asthmatics treated with long-term inhaled or oral glucocorticoids. J Bone Miner Res 1998; 13(8):1283-1289.

(178) Fujita K, Kasayama S, Hashimoto J, Nagasaka Y, Nakano N, Morimoto Y et al. Inhaled corticosteroids reduce bone mineral density in early postmenopausal but not premenopausal asthmatic women. J Bone Miner Res 2001; 16(4):782-787.

(179) Ip M, Lam K, Yam L, Kung A, Ng M. Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids [see comments]. Chest 1994; 105(6):1722-1727.

(180) Laatikainen AK, Kroger HP, Tukiainen HO, Honkanen RJ, Saarikoski SV. Bone mineral density in perimenopausal women with asthma: a population-based cross-sectional study. Am J Respir Crit Care Med 1999; 159(4 Pt 1):1179-1185.

(181) Lau EM, Li M, Woo J, Lai C. Bone mineral density and body composition in patients with airflow obstruction--the role of inhaled steroid therapy, disease and lifestyle [see comments]. Clin Exp Allergy 1998; 28(9):1066-1071.

(182) Marystone JF, Barrett-Connor EL, Morton DJ. Inhaled and oral corticosteroids: their effects on bone mineral density in older adults. Am J Public Health 1995; 85(12):1693-1695.

(183) Packe GE, Douglas JG, McDonald AF, Robins SP, Reid DM. Bone density in asthmatic patients taking high dose inhaled beclomethasone dipropionate and intermittent systemic corticosteroids. Thorax 1992; 47(6):414-417.

(184) Toogood JH, Baskerville JC, Markov AE, Hodsman AB, Fraher LJ, Jennings B et al. Bone mineral density and the risk of fracture in patients receiving long-term inhaled steroid therapy for asthma. J Allergy Clin Immunol 1995; 96(2):157-166.

(185) Wong CA, Walsh LJ, Smith CJ, Wisniewski AF, Lewis SA, Hubbard R et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma [see comments]. Lancet 2000; 355(9213):1399-1403.

(186) Boulet LP, Giguere MC, Milot J, Brown J. Effects of long-term use of high-dose inhaled steroids on bone density and calcium metabolism. J Allergy Clin Immunol 1994; 94(5):796-803.

(187) Luengo M, del Rio L, Pons F, Picado C. Bone mineral density in asthmatic patients treated with inhaled corticosteroids: a case-control study. Eur Respir J 1997; 10(9):2110-2113.

(188) McEvoy CE, Ensrud KE, Bender E, Genant HK, Yu W, Griffith JM et al. Association between corticosteroid use and vertebral fractures in older men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998; 157(3 Pt 1):704-709.

(189) Tug T, Kamanli A, Tug E. Effects of long-term inhaled steroid use on bone mineral density in asthma patients. J Investig Allergol Clin Immunol 2001; 11(4):300-302.

(190) Van Staa TP, Leufkens HG, Cooper C. Use of inhaled corticosteroids and risk of fractures. J Bone Miner Res JID - 8610640 2001; 16(3):581-588.

(191) Boulet LP, Milot J, Gagnon L, Poubelle PE, Brown J. Long-term influence of inhaled corticosteroids on bone metabolism and density. Are biological markers predictors of bone loss? Am J Respir Crit Care Med 1999; 159(3):838-844.

(192) Hanania NA, Chapman KR, Sturtridge WC, Szalai JP, Kesten S. Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. J Allergy Clin Immunol 1995; 96(5 Pt 1):571-579.

(193) Israel E, Banerjee TR, Fitzmaurice GM, Kotlov TV, LaHive K, Leboff MS. Effects of inhaled glucocorticoids on bone density in premenopausal women. N Engl J Med 2001; 345(13):941-947.

(194) Packe GE, Robb O, Robins SP, Reid DM, Douglas JG. Bone density in asthmatic patients taking inhaled corticosteroids: comparison of budesonide and beclomethasone dipropionate. J R Coll Physicians Lond 1996; 30(2):128-132.

(195) Harmanci E, Ak I, Ozdemir N, Vardareli E, Elbek O, Ucgun I. The comparison of the effects of fluticasone propionate and budesonide on clinical indices and on bone mineral density in the asthmatic patients: a one year treatment study [see comments]. Allergol Immunopathol (Madr) 1999; 27(6):298-303.

(196) Herrala J, Puolijoki H, Impivaara O, Liippo K, Tala E, Nieminen MM. Bone mineral density in asthmatic women on high-dose inhaled beclomethasone dipropionate. Bone 1994; 15(6):621-623.

(197) Matsumoto H, Ishihara K, Hasegawa T, Umeda B, Niimi A, Hino M. Effects of inhaled corticosteroid and short courses of oral corticosteroids on bone mineral density in asthmatic patients : a 4-year longitudinal study. Chest 2001; 120(5):1468-1473.

(198) Wise RA, Connett J, Weinmann GG, Scanlon P, Skeans M. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 2000; 343(26):1902-1909.

(199) Egan JJ, Maden C, Kalra S, Adams JE, Eastell R, Woodcock AA. A randomized, double-blind study comparing the effects of beclomethasone and fluticasone on bone density over two years. Eur Respir J 1999; 13(6):1267-1275.

(200) Hughes JA, Conry BG, Male SM, Eastell R. One year prospective open study of the effect of high dose inhaled steroids, fluticasone propionate, and budesonide on bone markers and bone mineral density. Thorax 1999; 54(3):223-229.

(201) Li JT, Ford LB, Chervinsky P, Weisberg SC, Kellerman DJ, Faulkner KG et al. Fluticasone propionate powder and lack of clinically significant effects on hypothalamic-pituitary-adrenal axis and bone mineral density over 2 years in adults with mild asthma. J Allergy Clin Immunol 1999; 103(6):1062-1068.

(202) Medici TC, Grebski E, Hacki M, Ruegsegger P, Maden C, Efthimiou J. Effect of one year treatment with inhaled fluticasone propionate or beclomethasone dipropionate on bone density and bone metabolism: a randomised parallel group study in adult asthmatic subjects. Thorax 2000; 55(5):375-382.

(203) Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med 1999; 340(25):1948-1953.

(204) Tattersfield AE, Town GI, Johnell O, Picado C, Aubier M, Braillon P et al. Bone mineral density in subjects with mild asthma randomised to treatment with inhaled corticosteroids or non-corticosteroid treatment for two years. Thorax 2001; 56(4):272-278.

(205) Pauwels RA, Yernault JC, Demedts MG, Geusens P. Safety and efficacy of fluticasone and beclomethasone in moderate to severe asthma. Belgian Multicenter Study Group. Am J Respir Crit Care Med 1998; 157(3 Pt 1):827-832.

(206) Harmanci E, Colak O, Metintas M, Alatas O, Yurdasiper A. Fluticasone propionate and budesonide do not influence bone metabolism in the long term treatment of asthma. Allergol Immunopathol (Madr) 2001; 29(1):22-27.

(207) Bootsma GP, Dekhuijzen PN, Festen J, Mulder PG, Swinkels LM, van Herwaarden CL. Fluticasone propionate does not influence bone metabolism in contrast to beclomethasone dipropionate. Am J Respir Crit Care Med 1996; 153(3):924-930.

(208) Efthimiou J, Barnes PJ. Effect of inhaled corticosteroids on bones and growth [see comments]. Eur Respir J 1998; 11(5):1167-1177.

(209) Medici TC, Ruegsegger P. Does alternate-day cloprednol therapy prevent bone loss? A longitudinal double-blind, controlled clinical study. Clin Pharmacol Ther 1990; 48(4):455-466.

(210) Wisniewski AF, Lewis SA, Green DJ, Maslanka W, Burrell H, Tattersfield AE. Cross sectional investigation of the effects of inhaled corticosteroids on bone density and bone metabolism in patients with asthma. Thorax 1997; 52(10):853-860.

(211) Wolff AH, Adelsberg B, Aloia J, Zitt M. Effect of inhaled corticosteroid on bone density in asthmatic patients: a pilot study. Ann Allergy 1991; 67(2 Pt 1):117-121.

(212) Goldstein MF, Fallon JJ, Jr., Harning R. Chronic glucocorticoid therapy-induced osteoporosis in patients with obstructive lung disease. Chest 1999; 116(6):1733-1749.

(213) Gagnon L, Boulet LP, Brown J, Desrosiers T. Influence of inhaled corticosteroids and dietary intake on bone density and metabolism in patients with moderate to severe asthma. J Am Diet Assoc 1997; 97(12):1401-1406.

(214) Cave A, Arlett P, Lee E. Inhaled and nasal corticosteroids: factors affecting the risks of systemic adverse effects. Pharmacol Ther 1999; 83(3):153-179.

(215) Reid DM, Nicoll JJ, Smith MA, Higgins B, Tothill P, Nuki G. Corticosteroids and bone mass in asthma: comparisons with rheumatoid arthritis and polymyalgia rheumatica. Br Med J (Clin Res Ed) 1986; 293(6560):1463-1466.

(216) Reid IR, Evans MC, Wattie DJ, Ames R, Cundy TF. Bone mineral density of the proximal femur and lumbar spine in glucocorticoid-treated asthmatic patients. Osteoporos Int 1992; 2(2):103-105.

(217) Smith BJ, Phillips PJ, Heller RF. Asthma and chronic obstructive airway diseases are associated with osteoporosis and fractures: a literature review. Respirology 1999; 4(2):101-109.

(218) Toogood JH, Jennings B, Hodsman AB, Baskerville J, Fraher LJ. Effects of dose and dosing schedule of inhaled budesonide on bone turnover. J Allergy Clin Immunol 1991; 88(4):572-580.

(219) Leech JA, Hodder RV, Ooi DS, Gay J. Effects of short-term inhaled budesonide and beclomethasone dipropionate on serum osteocalcin in premenopausal women. Am Rev Respir Dis 1993; 148(1):113-115.

(220) Kerstjens HA, Postma DS, van Doormaal JJ, van Zanten AK, Brand PL, Dekhuijzen PN et al. Effects of short-term and long-term treatment with inhaled corticosteroids on bone metabolism in patients with airways obstruction. Dutch CNSLD Study Group. Thorax 1994; 49(7):652-656.

(221) Hodsman AB, Toogood JH, Jennings B, Fraher LJ, Baskerville JC. Differential effects of inhaled budesonide and oral prednisolone on serum osteocalcin. J Clin Endocrinol Metab 1991; 72(3):530-540.

(222) Jones A, Fay JK, Burr M, Stone M, Hood K, Roberts G. Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease (Cochrane Review). Cochrane Database Syst Rev JID - 100909747 2002;(1):CD003537.

(223) Seeman E. Osteoporosis: trials and tribulations. Am J Med 1997; 103(2A):74S-87S.

(224) Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben-Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. Chest 2000; 117(2):542-550.

(225) Cummings R, Nevitt M. Calcium for prevention of osteoporotic fractures in postmenopausal women. J Bone Miner Res 1997; 12:1321-1329.

(226) Tucker KL, Chen H, Hannan MT, Cupples LA, Wilson PW, Felson D et al. Bone mineral density and dietary patterns in older adults: the Framingham Osteoporosis Study. Am J Clin Nutr 2002; 76(1):245-252.

(227) Layne JE, Nelson ME. The effects of progressive resistance training on bone density: a review. Med Sci Sports Exerc 1999; 31(1):25-30.

(228) Joakimsen RM, Magnus JH, Fonnebo V. Physical activity and predisposition for hip fractures: a review. Osteoporos Int 1997; 7(6):503-513.

(229) Branca F. Physical activity, diet and skeletal health. Public Health Nutr 1999; 2(3A):391-396.

(230) Kemper HC, Bakker I, Twisk JW, Van Mechelen W. Validation of a physical activity questionnaire to measure the effect of mechanical strain on bone mass. Bone 2002; 30(5):799-804.

(231) Berard A, Bravo G, Gauthier P. Meta-analysis of the effectiveness of physical activity for the prevention of bone loss in postmenopausal women. Osteoporos Int 1997; 7(4):331-337.

(232) Law MR, Hackshaw AK. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. BMJ 1997; 315(7112):841-846.

(233) Hermann AP, Brot C, Gram J, Kolthoff N, Mosekilde L. Premenopausal smoking and bone density in 2015 perimenopausal women. J Bone Miner Res 2000; 15(4):780-787.

(234) Ward KD, Klesges RC. A meta-analysis of the effects of cigarette smoking on bone mineral density. Calcif Tissue Int 2001; 68(5):259-270.

(235) Fortenbery EJ, McDermott MT, Duncan WE. Effect of theophylline on calcium metabolism and circulating vitamin D metabolites. J Bone Miner Res 1990; 5(4):321-324.

(236) Biskobing DM. COPD and osteoporosis. Chest 2002; 121(2):609-620.

(237) Arney WK, Pinnock CB. The milk mucus belief: sensations associated with the belief and characteristics of believers. Appetite 1993; 20(1):53-60.

(238) Serres I, Gautier V, Varray A, Prefaut C. Impaired skeletal muscle endurance related to physical inactivity and altered lung function in COPD patients. Chest 1998; 113(4):900-905.

(239) Minaire P. Immobilization osteoporosis: a review. Clin Rheumatol 1989; 8 Suppl 2:95-103.

(240) Sin DD, Man JP, Man SF. The risk of osteoporosis in Caucasian men and women with obstructive airways disease. Am J Med 2003; 114(1):10-14.

(241) Forsmo S, Schei B, Langhammer A, Forsen L. How do reproductive and lifestyle factors influence bone density in distal and ultradistal radius of early postmenopausal women? The Nord-Trondelag Health Survey, Norway. Osteoporos Int 2001; 12(3):222-229.

(242) Hawker GA, Forsmo S, Cadarette SM, Schei B, Jaglal SB, Forsen L et al. Correlates of forearm bone mineral density in young Norwegian women: the Nord-Trondelag Health Study. Am J Epidemiol 2002; 156(5):418-427.

(243) Holmen J, Midthjell K, Bjartveit K, et al. The Nord-Trøndelag health survey 1984-86. Purpose, background and methods. Participation, non-participation and frequency distributions. National Institute of Public Health, Centre of Community Medicine Research 4, 176-182. 1990. Ref Type: Report

(244) Øydvin K. Drug Consumption in Norway 1993-1997. Øydvin K, editor. 190-191. 1999. Oslo, Norwegian Medisinal Depot. Ref Type: Report

(245) Fønnebø Knutsen S. The Tromsø survey: The family intervention study (Thesis). University of Tromsø, 1990.

(246) Joakimsen RM. Risk factors for non-vertebral fractures in a middle-aged population (Thesis). Institute of Community Medicine, University of Tromsø, 1999.

(247) Medical Research Council. Definition and classification of chronic bronchitis for clinical and epidemiological purposes: a report to the Medical Research Council by their Committee on the Aetiology of Chronic Bronchitis. Lancet 1965; 1:775-780.

(248) American Thoracic Society. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med 1995; 152(3):1107-1136.

(249) American Thoracic Society. Standardization of spirometry: a summary of recommendations from the American Thoracic Society. The 1987 update. Ann Intern Med 1988; 108(2):217-220.

(250) Krowka MJ, Enright PL, Rodarte JR, Hyatt RE. Effect of effort on measurement of forced expiratory volume in one second. Am Rev Respir Dis 1987; 136(4):829-833.

(251) Berntsen GK, Tollan A, Magnus JH, Sogaard AJ, Ringberg T, Fonnebo V. The Tromso Study: artifacts in forearm bone densitometry--prevalence and effect. Osteoporos Int 1999; 10(5):425-432.

(252) Henriksen AH. Symptoms of allergy and asthma versus markers of lower airway inflammation among adolescents. Department of Lung Medicine, Norwegian University of Science and Technology, Trondheim, 2002.

(253) Kharitonov S, Alving K, Barnes PJ. Exhaled and nasal nitric oxide measurements: recommendations. The European Respiratory Society Task Force. Eur Respir J 1997; 10(7):1683-1693.

(254) Henriksen AH, Holmen TL, Bjermer L. Sensitization and exposure to pet allergens in asthmatics versus non-asthmatics with allergic rhinitis. Respir Med 2001; 95(2):122-129.

(255) Langhammer A, Johnsen R, Holmen J, Gulsvik A, Bjermer L. Cigarette smoking gives more respiratory symptoms among women than among men. J Epidemiol Community Health 2000; 54(12):917-922.

(256) Glindmeyer HW, Lefante JJ, McColloster C, Jones RN, Weill H. Blue-collar normative spirometric values for Caucasian and African-American men and women aged 18 to 65. Am J Respir Crit Care Med 1995; 151(2 Pt 1):412-422.

(257) Keiding L. Asthma, allergy, and other types of hypersensitivity in Denmark - and the development 1987-1994. (in Danish, summary in English). DIKE, editor. ISBN 87-89662-98-9. 1997. Copenhagen, Denmark, DIKE. Ref Type: Report

(258) Bakke P, Gulsvik A. [Allergic diseases in Norway. Operative definition, occurrence and risk factors]. Nord Med 1992; 107(4):108-9, 111.

(259) Montnémery P, Ädelroth E, Heuman K, Johannisson A, Johansson S-Å, Linholm L-H et al. Prevalence of obstructive lung diseases and respiratory symptoms in southern Sweden. Respir Med 1998; 92:1337-1345.

(260) Pallasaho P, Lundback B, Laspa SL, Jonsson E, Kotaniemi J, Sovijarvi AR et al. Increasing prevalence of asthma but not of chronic bronchitis in Finland? Report from the FinEsS-Helsinki Study. Respir Med 1999; 93(11):798-809.

(261) Dodge R, Cline MG, Burrows B. Comparisons of asthma, emphysema, and chronic bronchitis diagnoses in a general population sample. Am Rev Respir Dis 1986; 133(6):981-986.

(262) Samet JM. A historical and epidemiologic perspective on respiratory symptoms questionnaires. Am J Epidemiol 1978; 108(6):435-446.

(263) A dictionary of epidemiology. 4 ed. New York: Oxford University Press, 20031.

(264) Rothman KJ, Greenland S. Modern epidemiology. Philadelphia: Lippincott-Raven Publishers, 1998.

(265) Bakke P, Gulsvik A, Lilleng P, Overa O, Hanoa R, Eide GE. Postal survey on airborne occupational exposure and respiratory disorders in Norway: causes and consequences of non-response. J Epidemiol Community Health 1990; 44(4):316-320.

(266) Chinn S, Burney PG. On measuring repeatability of data from self-administered questionnaires. Int J Epidemiol 1987; 16(1):121-127.

(267) Holmen J, Midthjell K, Forsen L, Skjerve K, Gorseth M, Oseland A. [A health survey in Nord-Trondelag 1984-86. Participation and comparison of attendants and non-attendants]. Tidsskr Nor Laegeforen 1990; 110(15):1973-1977.

(268) Slama K. Active smoking. In: Annesi-Maesano I, Gulsvik A, Viegi G, editors. Respiratory Epidemiology in Europe. Sheffield: European Respiratory Society Journals Ltd, 20030: 305-321.

(269) Bernaards CM, Twisk JW, Snel J, Van Mechelen W, Kemper HC. Is calculating pack-years retrospectively a valid method to estimate life-time tobacco smoking? A comparison between prospectively calculated pack-years and retrospectively calculated pack-years. Addiction JID - 9304118 2001; 96(11):1653-1661.

(270) Kesmodel U, Olsen SF. Smoking habits among pregnant Danish women: reliability of information recorded after delivery. J Epidemiol Community Health 1999; 53(4):239-242.

(271) Riboli E, Haley NJ, Tredaniel J, Saracci R, Preston-Martin S, Trichopoulos D. Misclassification of smoking status among women in relation to exposure to environmental tobacco smoke. Eur Respir J 1995; 8(2):285-290.

(272) Vartiainen E, Seppala T, Lillsunde P, Puska P. Validation of self reported smoking by serum cotinine measurement in a community-based study. J Epidemiol Community Health 2002; 56(3):167-170.

(273) Parameswaran K, Hildreth AJ, Chadha D, Keaney NP, Taylor IK, Bansal SK. Asthma in the elderly: underperceived, underdiagnosed and undertreated; a community survey. Respir Med 1998; 92(3):573-577.

(274) Weiner P, Magadle R, Waizman J, Weiner M, Rabner M, Zamir D. Characteristics of asthma in the elderly. Eur Respir J 1998; 12(3):564-568.

(275) Enright PL, Johnson LR, Connett JE, Voelker H, Buist AS. Spirometry in the Lung Health Study. 1. Methods and quality control. Am Rev Respir Dis 1991; 143(6):1215-1223.

(276) Humerfelt S, Eide GE, Kvale G, Gulsvik A. Predictors of spirometric test failure: a comparison of the 1983 and 1993 acceptability criteria from the European Community for Coal and Steel. Occup Environ Med 1995; 52(8):547-553.

(277) Ng'Ang'a LW, Ernst P, Jaakkola MS, Gerardi G, Hanley JH, Becklake MR. Spirometric lung function. Distribution and determinants of test failure in a young adult population. Am Rev Respir Dis 1992; 145(1):48-52.

(278) Swanney MP, Jensen RL, Crichton DA, Beckert LE, Cardno LA, Crapo RO. FEV(6) is an acceptable surrogate for FVC in the spirometric diagnosis of airway obstruction and restriction. Am J Respir Crit Care Med 2000; 162(3 Pt 1):917-919.

(279) Eisen EA, Robins JM, Greaves IA, Wegman DH. Selection effects of repeatability criteria applied to lung spirometry. Am J Epidemiol JID - 7910653 1984; 120(5):734-742.

(280) Hankinson JL, Bang KM. Acceptability and reproducibility criteria of the American Thoracic Society as observed in a sample of the general population. Am Rev Respir Dis 1991; 143(3):516-521.

(281) Stoller JK, Basheda S, Laskowski D, Goormastic M, McCarthy K. Trial of standard versus modified expiration to achieve end-of-test spirometry criteria. Am Rev Respir Dis 1993; 148(2):275-280.

(282) Milne JS, Williamson J. Respiratory function tests in older people. Clinical Science 1972; 42:371-381.

(283) Schmidt CD, Dickman ML, Gardner RM, Brough FK. Spirometric standards for healthy elderly men and women. 532 subjects, ages 55 through 94 years. Am Rev Respir Dis 1973; 108(4):933-939.

(284) Brandstetter RD, Kazemi H. Aging and the respiratory system. Med Clin North Am 1983; 67(2):419-431.

(285) Berntsen GK. Interpretation of forearm bone mineral density. Institute of Community Medicine, University of Tromsø, Norway, 2000.

(286) Johns MM, Barnes M, Florencio PS. Restoring balance to industry-academia relationships in an era of institutional financial conflicts of interest: promoting research while maintaining trust. JAMA 2003; 289(6):741-746.

(287) Blumenthal D, Causino N, Campbell E, Louis KS. Relationships between academic institutions and industry in the life sciences--an industry survey. N Engl J Med 1996; 334(6):368-373.

(288) Blumenthal D, Campbell EG, Causino N, Louis KS. Participation of life-science faculty in research relationships with industry. N Engl J Med 1996; 335(23):1734-1739.

(289) Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA 2003; 289(4):454-465.

(290) Wagner EM, Liu MC, Weinmann GG, Permutt S, Bleecker ER. Peripheral lung resistance in normal and asthmatic subjects. Am Rev Respir Dis JID - 0370523 1990; 141(3):584-588.

(291) Gulsvik A. Prevalence of respiratory symptoms in the city of Oslo. Scand J Respir Dis 1979; 60(5):275-285.

(292) Emslie C, Hunt K, Macintyre S. Gender differences in minor morbidity among full time employees of a British university. J Epidemiol Community Health JID - 7909766 1999; 53(8):465-475.

(293) Gijsbers vWC, Huisman H, Kolk AM. Gender differences in physical symptoms and illness behavior. A health diary study. Soc Sci Med JID - 8303205 1999; 49(8):1061-1074.

(294) Macintyre S, Ford G, Hunt K. Do women 'over-report' morbidity? Men's and women's responses to structured prompting on a standard question on long standing illness. Soc Sci Med JID - 8303205 1999; 48(1):89-98.

(295) Carpenter L, Beral V, Strachan D, Ebi-Kryston KL, Inskip H. Respiratory symptoms as predictors of 27 year mortality in a representative sample of British adults. BMJ 1989; 299(6695):357-361.

(296) Moffatt RJ, Owens SG. Cessation from cigarette smoking: changes in body weight, body composition, resting metabolism, and energy consumption. Metabolism 1991; 40(5):465-470.

(297) Waldron I. Patterns and causes of gender differences in smoking. Soc Sci Med 1991; 32(9):989-1005.

(298) Williamson DF, Madans J, Anda RF, Kleinman JC, Giovino GA, Byers T. Smoking cessation and severity of weight gain in a national cohort [see comments]. N Engl J Med 1991; 324(11):739-745.

(299) Amos A. Women and smoking. Br Med Bull 1996; 52(1):74-89.

(300) Dahl R, Bjermer L. Nordic consensus report on asthma management. Nordic Asthma Consensus Group. Respir Med 2000; 94(4):299-327.

Paper I

Reprinted from JOURNAL OF EPIDEMIOLOGY & COMMUNITY HEALTH, December 2000, Vol 54, No 12, p 917-922

Cigarette smoking gives more respiratory symptoms among women than among men
The Nord-Trøndelag Health Study (HUNT)

Arnulf Langhammer, Roar Johnsen, Jostein Holmen, A Gulsvik, L Bjermer

Abstract

***Study objective*—Studies have indicated that women are more vulnerable to the effect of tobacco smoking compared with men. The aim of this study was to explore the prevalence of reported respiratory symptoms and diseases according to smoking burden, age and sex.**

***Design*—Questionnaire in a cross sectional population based study.**

***Setting*—The BONT (Bronchial obstruction in Nord-Trøndelag) study is part of a comprehensive health survey of all inhabitants aged above 19 years in the county of Nord-Trøndelag, Norway, which was carried out from 1995 to 1997.**

***Participants*—A total of 65 717 subjects, 71.3% of the total population aged 20–100, answered the main questionnaire.**

***Main results*—In all, 12.7% men and 12.1% women reported episodes of wheezing or breathlessness during the past 12 months, 8.8% men and 8.4% women reported that they had or had had asthma, 7.5% men and 8.2% women had ever used asthma medication, and 4.0% men and 3.0% women reported chronic bronchitis. Thirty per cent of men and 31% of women were smokers, and average pack years of smoking were 15.9 and 10.3, respectively. Among previous and current smokers, significant more women reported episodes of wheezing or breathlessness, current asthma and persistent coughing compared with men with the same smoke burden (pack years) and daily number of cigarettes.**

***Conclusion*—The prevalence of reported asthma and use of asthma medication was higher than reported in previous Scandinavian studies. Respiratory symptoms increased by smoking burden. Comparing the prevalence of symptoms and current asthma among women and men with the same smoke burden or daily cigarette consumption, women seemed to be more susceptible to the effect of tobacco smoking than men.**

(*J Epidemiol Community Health* 2000;54:917–922)

National Institute of Public Health, Community Medicine Research Unit, Neptunveien 1, N-7650 Verdal, Norway
A Langhammer
J Holmen

The Norwegian University of Technology and Science, Trondheim, Norway
R Johnsen
J Holmen
L Bjermer

University of Bergen, Norway
A Gulsvik

Correspondence to:
Dr Langhammer
(verdalfh@online.no)

Accepted for publication
20 June 2000

Respiratory symptoms vary by sex, smoking habits and age. There is increasing evidence of higher susceptibility in women to tobacco smoking compared with men.[1] Studies indicate that women have increased smoking related bronchial responsiveness, lower level and faster decline of FEV1, and higher prevalence of asthma compared with smoking men.[2–6] Studies from Copenhagen showed greater impact of smoking on lung function and higher risk of being admitted to hospital for chronic obstructive pulmonary disease (COPD) in women than in men.[7 8]

The aim of this study was to estimate the prevalence of respiratory symptoms and diseases in a large adult population covering the age range from 20 to 100 years old by sex, age, current cigarette smoking habits and lifelong cigarette smoking burden.

Methods

From August 1995 to June 1997 all residents aged 20 years and more (92 000), of the Nord-Trøndelag County, Norway, were invited to participate in a health study (HUNT). The invitation included a comprehensive Questionnaire I with focus on health, diseases, symptoms and risk factors. At the screening further questionnaires with more disease specific questions were added.

STUDY AREA

Nord-Trøndelag County (22 463 km^2) is situated in the middle part of Norway. The county has mostly mild coastal climate, but also typical inland areas with cold dry winters. The total population in 1995 was 127 000 residents, 97% being of white origin. The area is generally rural with a scattered population, but with several densely populated areas and small cities, the largest of which has 21 000 residents. Fifteen per cent of men and 6% of women worked as farmers. Except for previous mining industry in the two smallest municipalities, there is hardly any industrial pollution in the county.

QUESTIONNAIRES

The questions related to respiratory illnesses, diseases and smoking habits are listed in the appendix. Subjects, who reported "ever asthma" (having had asthma at one time or another) and episodes of wheezing or breathlessness during the past 12 months, were defined as having current asthma. Chronic bronchitis was defined as coughing with phlegm in periods of at least three months during each of the past two years.[9]

The smoking status was classified as never smokers (never smoked daily), ex-smokers (ceased smoking one or more years earlier) and current smokers.

Pack years was calculated as number of years of smoking × number of cigarettes a day/20.

Table 1 Mean age, body mass index, and number of pack years in ever smokers with standard deviation (SD), and smoking habits by sex and age groups. Nord-Trøndelag, Norway 1997

	Age 20–44 years		Age 45–69 years		Age 70+ years		All	
	Men	Women	Men	Women	Men	Women	Men	Women
Number	12 602	14 442	13 119	14 074	5022	6458	30 743	34 974
Age	33.4 (7.0)	33.1 (7.1)	55.6 (7.3)	55.8 (7.3)	76.5 (5.7)	77.3 (5.5)	50.0 (17.0)	50.4 (17.8)
Body mass index (kg/m^2)	25.9 (3.5)	25.0 (4.3)	27.0 (3.4)	26.9 (4.6)	26.5 (3.5)	27.6 (4.6)	26.5 (3.5)	26.3 (4.6)
Number of pack years in ever smokers	9.3 (7.7)	7.2 (5.9)	19.0 (14.4)	13.2 (9.9)	21.9 (17.0)	12.8 (10.9)	16.0 (13.9)	10.3 (4.6)
Smoking habits*								
Never smoker	6 444	6 404	3 700	5 810	1058	3908	11 202	16 122
Ex-smoker	2 016	2 449	4 872	3 139	2468	804	9 356	6 392
Current smoker	3 539	4 977	4 079	4 338	1057	619	8 675	9 934

*1510 men and 2526 women had missing data on smoking habits.

NON-RESPONDER STUDY

In a non-responder study, 2.5% of the non-responders (685 persons) were randomly selected for a telephone interview with the same questions as in the survey. If no telephone contact was established after three attempts made for each subject on various occasions, a questionnaire was mailed to the subjects.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences version 8.0 (SPSS Inc, Chicago, Illinois) was used for all analyses. Differences between continuous variables were analysed by Student's t test and dichotomous variables by the χ^2 test. The Mantel-Haenszel method was used to analyse significance of trends. Body mass index (BMI, kg/m^2) has been reported to be an independent risk factor for onset of asthma in adult women,[6 10] and was therefore included in the analyses. Analyses of covariance were used to calculate prevalence adjusted for covariates as age, pack years and BMI. Sex specific risk of reporting respiratory diseases and symptoms by smoke exposure were calculated by multiple logistic regression with age, BMI, pack years or number of daily cigarettes in current smokers in the model. When education and different work categories were included in the model, education did not contribute significantly to the explained variance, but some work categories did. They did not, however, in the saturated model change the β estimates significantly for BMI or pack years, and were therefore not included in the final model (table 3). Interaction of sex and pack years was used to test sex dependent susceptibility to smoke burden. The direct method of standardisation[11] was used in age adjustment of prevalence in the non-responder group.

ETHICS

The study was approved by the Regional Committee for Ethics in Medical Research and the Norwegian Data Inspectorate.

Results

ATTENDANCE

A total of 73.9% women and 65.6% men completed the main questionnaire (total 71.3%) (table 1). The response rates were 48.9% (20–29 years), 69.7% (30–39 years), 80.6% (40–69 years), 76.6% (70–79 years) and 51% (80+ years).

Table 2 Prevalence (%) of self reported asthma, use of asthma medication, coughing and smoking status in responders (n=65 717) and in non-responders (n=326). Nord-Trøndelag, Norway 1997

Self reported symptoms and smoking habits	Responders (%)	Non-responders (%)	p Value
Ever asthma	8.6	9.1	0.79
Asthma medication	8.0	9.5	0.52
Coughing	14.9	10.8	0.04
Coughing with phlegm	8.3	6.2	0.08
Chronic bronchitis	3.5	3.0	0.74
Never smoker	44.3	39.7	0.10
Ex-smoker	25.5	24.8	0.78
Current smoker	30.2	35.5	0.04

Prevalence in non-responders age adjusted by direct method standardisation (total study population as reference).

NON-RESPONDER STUDY

Of 685 subjects randomly selected to the non-responder study, 326 subjects (47.6%) responded either to a telephone interview or the questionnaire. The most important reason for non-attending in age group 20–69 was lack of time/moved away (54%), while in those aged 70 years or more immobilising disease (21%) and follow up by medical doctor (28%) were important reasons.

The only significant difference in reported symptoms and diseases was lower prevalence of coughing in non-responders compared with responders, even though a significant higher prevalence of smoking was found in the non-responder group (table 2).

SMOKING HABITS

A total of 29.7% of men and 30.6% of women reported current smoking, while 32% of men and 19.7% of women were ex-smokers (table 1). In age group 20–59 years smoking was more prevalent in women than in men (35.8% versus 31.0%, p<0.001), in contrast with subjects aged 60 or more (18.4% versus 26.5% in women and men respectively, p<0.001). On average men started to smoke at younger age than women (18.4 versus 19.8 years, p<0.001), and had higher average daily cigarette consumption (13.1 versus 9.7 cigarettes, p<0.001). In "ever smokers" the average number of pack years were 16.0 and 10.3 for men and women respectively (p<0.001).

SYMPTOMS AND RESPIRATORY DISEASE

Episodes of wheezing or breathlessness

In all, 12.7% of men and 12.1% of women reported episodes of wheezing or breathlessness during the past 12 months. Smokers reported these symptoms twice as prevalent as never smokers, and the prevalence increased by

Table 3 Prevalence (%) of self reported respiratory symptoms, asthma, chronic bronchitis and use of asthma medication in 34 974 women and 30 743 men by age groups and smoking habits, with 95% confidence intervals. Nord-Trøndelag, Norway 1997

	Age 20–44 years				Age 45–69 years				Age 70+ years			
	Men		Women		Men		Women		Men		Women	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Wheezing/breathless												
Never smoker	7.9	7.2, 8.6	7.7	7.0, 8.4	7.6	6.7, 8.5	9.2	8.4, 10.0	11.4	9.5, 13.3	12.4	11.4, 13.4
Ex-smoker	9.9	8.6, 11.2	9.8	8.6, 11.0	12.5	11.6, 13.4	12.2	11.0, 13.4	18.9	17.3, 20.5	18.0	15.3, 20.7
Smoker	15.4	14.2, 16.6	15.9	14.9, 16.9	18.6	17.4, 19.8	17.7	16.6, 18.8	24.0	21.4, 26.6	20.7	17.5, 23.9
Total	10.3	9.8, 10.8	10.9	10.4, 11.4	13.0	12.4, 13.6	12.7	12.1, 13.3	18.2	17.1, 19.3	13.9	13.0, 14.8
Ever asthma												
Never smoker	8.1	7.4, 8.8	7.7	7.0, 8.4	7.3	6.5, 8.1	6.8	6.2, 7.4	6.8	5.3, 8.3	7.6	6.8, 8.4
Ex-smoker	9.8	8.5, 11.1	9.7	8.5, 10.9	9.3	8.5, 10.1	8.8	7.8, 9.8	12.2	10.9, 13.5	11.9	9.7, 14.1
Smoker	8.3	7.4, 9.2	9.0	8.2, 9.8	8.4	7.5, 9.3	9.8	8.9, 10.7	11.2	9.3, 13.1	10.6	8.2, 13.0
Total	8.5	8.0, 9.0	8.5	8.0, 9.0	8.4	7.9, 8.9	8.3	7.8, 8.8	10.7	9.8, 11.6	8.5	7.8, 9.2
Asthma medication												
Never smoker	7.3	6.7, 7.9	7.9	7.2, 8.6	5.6	4.9, 6.3	6.7	6.1, 7.3	5.9	4.5, 7.3	6.6	5.8, 7.4
Ex-smoker	9.0	7.7, 10.3	9.3	8.1, 10.5	8.2	7.4, 9.0	9.0	8.0, 10.0	11.9	10.6, 13.2	12.4	10.1, 14.7
Smoker	6.5	5.7, 7.3	9.5	8.7, 10.3	6.8	6.0, 7.6	9.3	8.4, 10.2	11.2	9.3, 13.1	9.4	7.1, 11.7
Total	7.3	6.8, 7.8	8.7	8.2, 9.2	7.1	6.7, 7.5	8.1	7.6, 8.6	10.3	9.4, 11.2	7.6	6.9, 8.3
Daily coughing in periods												
Never smoker	9.8	9.1, 10.5	9.7	9.0, 10.4	10.8	9.8, 11.8	11.8	11.0, 12.6	11.5	9.6, 13.4	11.7	10.7, 12.7
Ex-smoker	11.2	9.8, 12.6	9.8	8.6, 11.0	10.6	9.7, 11.5	11.7	10.6, 12.8	16.2	14.7, 17.7	14.7	12.2, 17.2
Smoker	24.3	22.9, 25.7	23.2	22.0, 24.4	29.4	28.0, 30.8	23.4	22.1, 24.7	29.7	26.9, 32.5	21.6	18.4, 24.8
Total	14.2	13.6, 14.8	14.4	13.8, 15.0	16.5	15.9, 17.1	15.3	14.7, 15.9	17.9	16.8, 19.0	13.0	12.2, 13.8
Coughing with phlegm												
Never smoker	4.9	4.4, 5.5	4.5	4.0, 5.0	5.3	4.6, 6.0	5.6	5.0, 6.2	7.2	5.6, 8.8	5.9	5.2, 6.7
Ex-smoker	6.4	5.4, 7.5	4.5	3.7, 5.4	6.4	5.7, 7.1	5.9	5.1, 6.8	10.4	9.2, 11.6	9.5	7.5, 11.5
Smoker	13.8	12.7, 15.0	13.1	12.2, 14.1	17.2	16.0, 18.4	13.0	12.0, 14.0	22.1	19.6, 24.7	14.3	11.5, 17.0
Total	7.7	7.3, 8.2	7.6	7.1, 8.0	9.4	8.9, 9.9	8.0	7.5, 8.4	12.1	11.2, 13.0	7.2	6.6, 7.9
Chronic bronchitis												
Never smoker	1.4	1.1, 1.7	1.2	0.9, 1.5	2.3	1.8, 2.8	2.7	2.3, 3.1	2.6	1.6, 3.5	3.0	2.4, 3.5
Ex-smoker	1.5	1.0, 2.0	1.4	1.0, 1.9	3.5	3.0, 4.0	2.8	2.2, 3.4	5.7	4.8, 6.7	5.0	3.5, 6.5
Smoker	4.7	4.0, 5.4	3.8	3.3, 4.4	8.4	7.6, 9.3	5.5	4.8, 6.2	12.7	10.7, 14.7	7.3	5.3, 9.4
Total	2.4	2.1, 2.6	2.2	1.9, 2.4	4.7	4.3, 5.0	3.7	3.3, 4.0	6.5	5.8, 7.2	3.6	3.1, 4.1

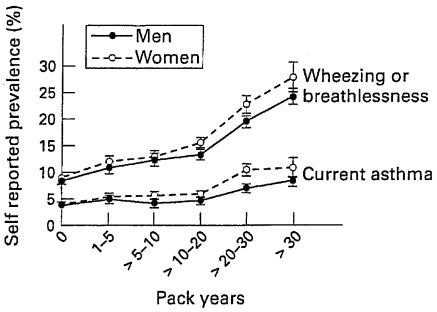


Figure 1 Age adjusted prevalence (%) of self reported episodes of wheezing or breathlessness in the past 12 months and current asthma by number of pack years in men and women (95% confidence intervals). Nord-Trøndelag, Norway 1997.

smoking burden (p for trend<0.001) (table 3, fig 1). Among never smokers more women than men (9.2% versus 8.6% when adjusted by age and BMI, p < 0.001), reported wheezing or breathlessness and the difference between sexes increased by increasing smoke burden (pack years) (table 4, fig 1).

Ever asthma and current asthma

Some 8.8% of men and 8.4% of women reported "ever asthma" (table 3), and 4.8% of men and 5.1% of women was categorised as having current asthma. The lowest cumulative prevalence of asthma was reported in the group aged 40–49 (7.9%) as compared with the groups aged 20–29 (9.3%, p<0.001) and 70–79 (9.6%, p<0.001). In those reporting ever asthma, 97.5% of women and 96.9% of men reported that they had been given the diagnosis by a medical doctor.

"Ever smoking" women reported current asthma more frequently than "ever smoking" men (6.4% versus 5.7%, p=0.005). A similar pattern was also found among current smokers (fig 1). The prevalence of current asthma increased with increasing number of cigarettes per day in women, amounting to 10.4% in those smoking more than 20 cigarettes per day. In men, however, no such increase with increasing cigarette consumption was found. With increasing smoke burden and current smoker's daily cigarette consumption, more

Table 4 Multiple logistic regression of episodes of wheezing or breathlessness, current asthma, persistent coughing and chronic bronchitis in men (n=26 914) and women (n=30 809) by pack year adjusted by age and body mass index. Nord-Trøndelag, Norway 1997

	Wheezing or breathlessness		Current asthma		Persistent coughing		Chronic bronchitis	
Independent variables	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Men								
Age (y)	1.005	1.002, 1.007	1.008	1.004, 1.012	0.996	0.994, 0.998	1.022	1.017, 1.026
Body mass index (kg/m²)	1.053	1.042, 1.064	1.050	1.034, 1.066	1.002	0.992, 1.011	0.982	0.964, 1.001
Number of pack years	1.025	1.023, 1.028	1.015	1.011, 1.018	1.032	1.030, 1.035	1.015	1.011, 1.020
Women								
Age (y)	1.001	0.999, 1.003	0.998	0.995, 1.001	0.997	0.995, 0.999	1.010	1,006, 1.014
Body mass index (kg/m²)	1.063	1.054, 1.070	1.062	1.051, 1.073	1.021	1.014, 1.028	1.025	1.011, 1.040
Number of pack years	1.038	1.035, 1.042	1.030	1.025, 1.035	1.048	1.044, 1.051	1.030	1.023, 1.036

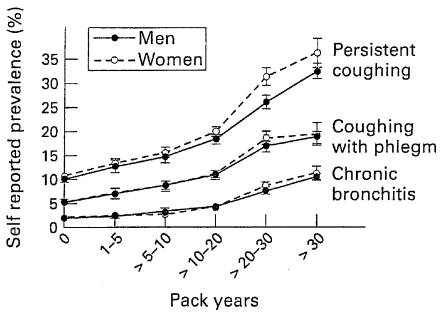


Figure 2 Age adjusted prevalence of persistent coughing, coughing with phlegm and chronic bronchitis by number of pack years in men and women (95% confidence intervals). Nord-Trøndelag, Norway 1997.

women than men reported current asthma (table 4, fig 1).

Coughing, phlegm and chronic bronchitis

Persistent coughing was reported more than twice among smokers compared with never smokers throughout all age groups except in the oldest group of women. Men reported higher crude prevalence than women did in all cough related questions. With increasing smoking burden and daily cigarette consumption the prevalence of coughing increased, and even for this symptom we found higher susceptibility in women compared with men (table 4, fig 2).

SMOKING CESSATION IN RELATION TO SYMPTOMS AND SEX

Among women who reported coughing, there was an increase of 40% that had quit smoking compared with those without symptoms (table 5). Among men, no such relation was seen. Among reporters of asthma related complaints, twice as many women and 1.7 as many men had quit smoking compared with those without respiratory symptoms. However, more "ever smoking" men than women had quit smoking, regardless of whether they reported respiratory symptoms at the screening or not. In subjects with current asthma 23.3% women and 39% men were ex-smokers and 38.5% women and 32.8% men were current smokers.

Discussion

In this population based cross sectional study we found higher prevalence of self reported asthma and use of asthma medication than previous studies in eastern Norway, including the city of Oslo 1972,[12] Northern Sweden 1986,[13] Southern Sweden 1992[14] and Denmark 1997.[15] The reporting of "ever asthma", ever having used asthma medication and current asthma had the lowest prevalence in the middle aged group (40–49 years). There was a strong association between tobacco smoking and respiratory symptoms, and smokers reported symptoms more than twice as frequent compared with never smokers. With increasing smoking burden, more women reported symptoms such as episodes of wheezing or breathlessness, persistent coughing, in addition to current asthma than men did. In a cross sectional study, however, causation cannot be directly inferred.

Table 5 Sex specific and age adjusted prevalence of self reported smoking cessation in ever smoking women (16 326) and men (18 031) according to symptoms, chronic bronchitis, asthma and use of asthma medication. (95% confidence intervals). Nord-Trøndelag, Norway 1997

	Women		Men	
Symptom/disease	*%*	*95% CI*	*%*	*95% CI*
No symptom	19.3	18.8, 19.8	32.0	31.4, 32.5
Coughing in periods	27.3	25.8, 28.9	31.0	29.4, 32.5
Coughing with phlegm	25.8	23.7, 28.0	31.3	29.3, 33.4
Chronic bronchitis	29.6	26.1, 33.4	32.9	30.0, 36.0
Wheezing or breathlessness	35.2	33.2, 37.2	43.2	41.4, 45.0
Ever asthma	42.7	40.3, 45.2	54.5	52.1, 56.8
Current asthma	41.1	38.1, 44.1	52.4	49.3, 55.5
Use of asthma medication	43.1	40.6, 45.6	56.3	53.8, 58.8

KEY POINTS

- Higher prevalence of reported asthma and use of asthma medication than reported in previous Scandinavian studies.
- The prevalence of respiratory symptoms increased by smoking burden (number of pack years).
- More women than men were current smokers.
- Women seemed to be more susceptible to the effect of tobacco smoking than men.

The questions of asthma, asthma medication and coughing used in this study were similar to those used by others.[16 17] Unlike others, we combined the question of wheezing and breathlessness in one question, limiting the comparison of these symptoms with other studies.

PARTICIPANTS AND QUESTIONS

The participation rate was about 10% lower in all age groups compared with a similar health survey in 1984–86,[18] with lowest rates in younger age groups, especially among men. Some people are sceptical of such studies and actively choose not to participate. This could explain that only about 50% answered the non-responder study. Other reasons for non-attendants in this survey were time consuming examinations and absence from work. A high prevalence of smokers in non-responders or late responders compared with early responders is in accordance with other studies where smoking habits have been examined.[18–20] Equal distributions of respiratory symptoms do not preclude non-responder bias,[21] but we have no reason to believe that our study overestimates the prevalence of respiratory symptoms and diseases.

RESPIRATORY SYMPTOMS AND DISEASES BY SEX

The study confirms a clear relation between tobacco smoking and respiratory symptoms like wheezing, breathlessness and coughing.[22–25]

More women reported respiratory symptoms compared with men in never smokers and smokers with comparable smoke burden or number of cigarettes. Generally, women seem to have lower threshold for reporting such symptoms compared with men.[24 26] It has however, been proposed that respiratory symptoms

are more sensitive markers of change in general health, but less specific markers regarding respiratory diseases in women compared with men.[1] This is confirmed by studies showing that respiratory symptom as shortness of breath is equally predictive of mortality in both sexes.[27 28] Although, this does not explain the increasing sex difference with increasing smoke burden.

Regarding coughing with phlegm, no sex difference by increasing smoke burden was reported. This symptom is probably underestimated in women as they are less likely to report phlegm than men.[1]

Higher prevalence of respiratory symptoms and current asthma in women compared with men with the same smoke burden or daily cigarette consumption indicate that women are more susceptible to tobacco smoking than men. Cyclical hormonal variations[1] and possible anti-oestrogenic effect of smoking[29] have been discussed as reasons. Given the same degree of inhalation per cigarette, female airways probably are exposed to higher relative concentration of gases and particles compared with men. In Copenhagen comparable sex difference in smoking effect was found both on lung function and risk of hospitalisation for patients with COPD.[8] Higher prevalence of coughing as well as wheezing and breathlessness attributable to tobacco smoking in women than men could indicate future increase of COPD, especially among women.

DISEASE AND SYMPTOM PREVALENCE

There is a wide geographical variation in prevalence of asthma and use of asthma medication.[30] The prevalence of self reported asthma and use of asthma medication was higher than found in earlier Scandinavian studies[12 13 15 31] and in crude agreement with more recent studies.[14 32] This could reflect an increasing incidence of asthma, but also increased focus on asthma and asthma treatment in Norway. A high prevalence of asthma in the group aged 20–29, consistent with other studies,[14] could support the hypothesis of increasing asthma incidence in younger age cohorts, but this is under debate.[33]

Lack of increase in prevalence of "ever asthma" or current asthma with age in never smokers, are in agreement with the ECHRS study[30] and a study from Southern Sweden.[14] In a chronic disease like asthma, one could expect increase in cumulative prevalence. The absence of this age effect could partly be explained by increasing recall bias with age, low symptom perception, and under-diagnosis of asthma in elderly.[34 35] A change of diagnostic criteria during the past decades could also mask an increasing prevalence with age.

SMOKING AND SMOKING CESSATION

According to the WHO the overall smoking prevalence in Norway is 35.5% in women and 36.4% in men, and only Danish women have higher proportion of smoking than Norwegian women have. Norwegian men are ranked 62 in the world.[36] We found that men reported smoking cessation more frequently than women did, regardless of reporting respiratory symptoms at the screening or not.

Even though women feel more pressure from family and society to quit smoking, and are equally likely to quit smoking compared with men, they are less likely to remain abstinent than men are. One important problem in motivating women to cease smoking is that they more probably view weight control as a benefit of smoking.[37–39]

A higher prevalence of asthma among ex-smokers compared with smokers have been found in several studies.[40 41] We confirmed this among men, but not among women. There was a similar sex difference in reported use of asthma medication. These findings might support the view that mostly men without asthma-like symptoms go on smoking (the healthy smoker effect).[42] A previous study has indicated a higher tendency for smoking men to be given the diagnosis of chronic obstructive lung disease compared with women.[43] This study could not identify differences in use of diagnosis as chronic bronchitis and asthma between the sexes.

In conclusion, the respiratory symptoms were clearly associated with tobacco smoking. At the same smoking burden, more women reported respiratory symptoms and current asthma than men did. Even if symptoms seemed to motivate more women than men to cease smoking, more men had quit smoking regardless of whether they had or did not have respiratory symptoms. High prevalence of smoking in young women combined with a possible increased susceptibility to tobacco smoking compared with men, might contribute to future increase in serious smoke related diseases in Norwegian women. To prevent this scenario it is necessary to develop programmes that encourage non-smoking in adolescents and effectively aid adults in ceasing to smoke. Different strategies seem to be necessary for men and women.[44]

The Nord-Trøndelag Health Study 1995–97 (The HUNT study) was performed in collaboration between The National Institute of Public Health, Oslo, The National Health Screening Service, Oslo, The Norwegian University of Technology and Science, Trondheim and Nord-Trøndelag County Council.

Funding: The Bronchial Obstruction in Nord-Trøndelag (The BONT study) was funded by Astra Norway.
Conflicts of interest: none.

Appendix

Questions regarding respiratory symptoms and diseases: (in parentheses the questions as given in tables and text).

QUESTIONNAIRE I

1 Do you cough daily during periods of the year? (persistent coughing)
  If Yes:
  Do you usually bring up pleghm when coughing? (coughing with phlegm)
  Have you had cough with phlegm for periods of at least three months during each of the past two years? (chronic bronchitis)
2 Have you had any attack of wheezing or breathlessness during the past 12 months? (wheezing or breathlessness past 12 months)

3 Do you have or have you had asthma? (ever asthma)
4 Do you use or have you used asthma medication? (ever use of asthma medications)
5 Do you smoke?
Cigarettes daily?
Cigars/cigarillos daily?
Pipe daily?
Never smoked daily
6 If you have smoked earlier; how many years is it since you stopped?
7 If you smoke daily now or have smoked earlier:
How many cigarettes do you smoke or did you smoke usually per day?
How old were you when you started smoking?
How many years altogether have you smoked?

QUESTIONNAIRE II

1 Have you been diagnosed as having asthma by your doctor?
2 Have you been diagnosed as having chronic bronchitis or emphysema by your doctor?

1 Kauffmann F, Becklake MR, Saurel-Cubizolles M-J, *et al. La santé des femmes.* Paris: Médecine-Sciences, Flammarion, 1996:209–33.
2 Xu X, Dockery DW, Ware JH, *et al.* Effects of cigarette smoking on rate of loss of pulmonary function in adults: a longitudinal assessment. *Am Rev Respir Dis* 1992;**146**: 1345–8.
3 Xu X, Weiss ST, Rijcken B, *et al.* Smoking, changes in smoking habits, and rate of decline in FEV1: new insight into gender differences. *Eur Respir J* 1994;7:1056–61.
4 Xu X, Li B, Wang L. Gender difference in smoking effects on adult pulmonary function. *Eur Respir J* 1994;7:477–83.
5 Gold DR, Wang X, Wypij D, *et al.* Effects of cigarette smoking on lung function in adolescent boys and girls. *N Engl J Med* 1996;**335**:931–7.
6 Chen Y, Dales R, Krewski D, *et al.* Increased effects of smoking and obesity on asthma among female Canadians: the National Population Health Survey, 1994–1995. *Am J Epidemiol* 1999;**150**:255–62.
7 Prescott E, Osler M, Andersen PK, *et al.* Mortality in women and men in relation to smoking. *Int J Epidemiol* 1998;**27**:27–32.
8 Prescott E, Bjerg AM, Andersen PK, *et al.* Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. *Eur Respir J* 1997;**10**:822–7.
9 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;**152**:S77–121.
10 Camargo CAJ, Weiss ST, Zhang S, *et al.* Prospective study of body mass index, weight change, and risk of adult- onset asthma in women. *Arch Intern Med* 1999;**159**:2582–8.
11 Armitage P, Berry G. *Statistical methods in medical research.* Oxford: Blackwell Scientific Publications, 1987:399–405.
12 Gulsvik A. Prevalence and manifestations of obstructive lung disease in the city of Oslo. *Scand J Respir Dis* 1979;**60**: 286–96.
13 Lundback B, Stjernberg N, Nystrom L, *et al.* An interview study to estimate prevalence of asthma and chronic bronchitis. The obstructive lung disease in northern Sweden study. *Eur J Epidemiol* 1993;**9**:123–33.
14 Montnémery P, Adelroth E, Heuman K, *et al.* Prevalence of obstructive lung diseases and respiratory symptoms in southern Sweden. *Respir Med* 1998;**92**:1337–45.
15 Keiding L, ed. *Asthma, allergy, and other types of hypersensitivity in Denmark - and the development 1987–1994.* (in Danish, summary in English). Copenhagen: DIKE, 1997. ISBN 87-89662-98-9.
16 Burney PG, Luczynska C, Chinn S, *et al.* The European Community Respiratory Health Survey. *Eur Respir J* 1994; 7:954–60.
17 Lundback B, Nystrom L, Rosenhall L, *et al.* Obstructive lung disease in northern Sweden: respiratory symptoms assessed in a postal survey. *Eur Respir J* 1991;**4**:257–66.
18 Holmen J, Midthjell K, Forsen L, *et al.* [A health survey in Nord-Trondelag 1984–86. Participation and comparison of attendants and non-attendants]. *Tidsskr Nor Laegeforen* 1990;**110**:1973–7.
19 Chinn S, Burney PG. On measuring repeatability of data from self-administered questionnaires. *Int J Epidemiol* 1987;**16**:121–7.
20 Bakke P, Gulsvik A, Lilleng P, *et al.* Postal survey on airborne occupational exposure and respiratory disorders in Norway: causes and consequences of non-response. *J Epidemiol Community Health* 1990;**44**:316–20.
21 Vestbo J, Rasmussen FV. Baseline characteristics are not sufficient indicators of non-response bias follow up studies. *J Epidemiol Community Health* 1992;**46**:617–19.
22 Anthonisen NR. Epidemiology and the Lung Health Study. *Eur Respir Rev* 1997;7:202–5.
23 Ronmark E, Lundback B, Jonsson E, *et al.* Incidence of asthma in adults–report from the Obstructive Lung Disease in Northern Sweden Study. *Allergy* 1997;**52**:1071–8.
24 Brown CA, Crombie IK, Smith WC, *et al.* The impact of quitting smoking on symptoms of chronic bronchitis: results of the Scottish Heart Health Study. *J Epidemiol Community Health* 1991;**46**:112–16.
25 Freund KM, Belanger AJ, D'Agostino RB, *et al.* The health risks of smoking. The Framingham Study: 34 years of follow-up. *Ann Epidemiol* 1993;**3**:417–24.
26 Gulsvik A. Prevalence of respiratory symptoms in the city of Oslo. *Scand J Respir Dis* 1979;**60**:275–85.
27 Mossey JM, Shapiro E. Self-rated health: a predictor of mortality among the elderly. *Am J Public Health* 1982;**72**: 800–8.
28 Carpenter L, Beral V, Strachan D, *et al.* Respiratory symptoms as predictors of 27 year mortality in a representative sample of British adults. *BMJ* 1989;**299**:357–61.
29 Key TJ, Pike MC, Baron JA, *et al.* Cigarette smoking and steroid hormones in women. *J Steroid Biochem Mol Biol* 1991;**39**:529–34.
30 Janson C, Chinn S, Jarvis D, *et al.* Physician-diagnosed asthma and drug utilization in the European Community Respiratory Health Survey. *Eur Respir J* 1997;**10**:1795–802.
31 Bakke P, Gulsvik A. [Allergic diseases in Norway. Operative definition, occurrence and risk factors]. *Nord Med* 1992; **107**:108–9, 111.
32 Pallasaho P, Lundback B, Laspa SL, *et al.* Increasing prevalence of asthma but not of chronic bronchitis in Finland? Report from the FinEsS-Helsinki Study. *Respir Med* 1999; **93**:798–809.
33 Magnus P, Jaakkola JJ. Secular trend in the occurrence of asthma among children and young adults: critical appraisal of repeated cross sectional surveys. *BMJ* 1997;**314**:1795–9.
34 Weiner P, Magadle R, Waizman J, *et al.* Characteristics of asthma in the elderly. *Eur Respir J* 1998;**12**:564–8.
35 Parameswaran K, Hildreth AJ, Chadha D, *et al.* Asthma in the elderly: underperceived, underdiagnosed and undertreated; a community survey. *Respir Med* 1998;**92**: 573–7.
36 WHO. *Tobacco or health: a global status report.* Geneva: WHO, 1998.
37 Waldron I. Patterns and causes of gender differences in smoking. *Soc Sci Med* 1991;**32**:989–1005.
38 Moffatt RJ, Owens SG. Cessation from cigarette smoking: changes in body weight, body composition, resting metabolism, and energy consumption. *Metabolism* 1991;**40**: 465–70.
39 Williamson DF, Madans J, Anda RF, *et al.* Smoking cessation and severity of weight gain in a national cohort. *N Engl J Med* 1991;**324**:739–45.
40 Flodin U, Jonsson P, Ziegler J, *et al.* An epidemiologic study of bronchial asthma and smoking. *Epidemiology* 1995;**6**: 503–5.
41 Vesterinen E, Kaprio J, Koskenvuo M. Prospective study of asthma in relation to smoking habits among 14,729 adults. *Thorax* 1988;**43**:534–9.
42 Becklake MR, Lalloo U. The "healthy smoker": a phenomenon of health selection? *Respiration* 1990;**57**:137–44.
43 Dodge R, Cline MG, Burrows B. Comparisons of asthma, emphysema, and chronic bronchitis diagnoses in a general population sample. *Am Rev Respir Dis* 1986;**133**:981–6.
44 Amos A. Women and smoking. *Br Med Bull* 1996;**52**:74–89.

Paper II

Eur Respir J 2001; 18: 770–779
Printed in UK – all rights reserved

European Respiratory Journal
ISSN 0903-1936

Forced spirometry reference values for Norwegian adults: the Bronchial Obstruction in Nord-Trøndelag study

A. Langhammer*, R. Johnsen#, A. Gulsvik¶, T.L. Holmen*, L. Bjermer+

Forced spirometry reference values for Norwegian adults: the Bronchial Obstruction in Nord-Trøndelag study. A. Langhammer, R. Johnsen, A. Gulsvik, T.L. Holmen, L. Bjermer. ©ERS Journals Ltd 2001.

ABSTRACT: The purpose of this study was to develop new prediction equations for flow/volume spirometry parameters in asymptomatic, never-smoking adults in Norway, and to assess any differences of these parameters when applying the new and most commonly used equation sets.

Flow/volume spirometry was measured according to the American Thoracic Society criteria in 2,792 subjects aged ⩾20 yrs, randomly selected from participants in the Nord-Trøndelag Health Study. Ever-smokers and subjects with respiratory symptoms and/or diseases reported in this questionnaire were excluded. A total of 546 females and 362 males met the inclusion criteria and were included in the analyses.

Most lung function variables were nonlinear by age and had to be transformed. After a plateau in younger adults, the variables declined by age. The reference values for forced expiratory volume in one second and forced vital capacity from the present study, were higher than those given by prediction equations from the European Community for Coal and Steel, but in closer agreement with later studies from Europe, Australia and the USA.

Healthcare providers should be encouraged to reconsider their choice of prediction equations of spirometry in order to improve management of obstructive lung diseases. *Eur Respir J 2001; 18: 770–779.*

*The Nord-Trøndelag Health Study (HUNT) Research Centre, The Norwegian University of Science and Technology (NTNU), Verdal, #Institute of Community Medicine and General Practice, NTNU, Trondheim, ¶Dept of Thoracic Medicine, University of Bergen, Bergen, +Dept of Pulmonary Medicine, NTNU, Trondheim, Norway.

Correspondence: A. Langhammer, The Nord-Trøndelag Health Study Research Centre, The Norwegian University of Science and Technology, Neptunveien 1, N-7650 Verdal, Norway.
Fax: 47 74075181

Keywords: Adults
forced expiratory volume in one second
forced spirometry
forced vital capacity
reference values

Received: January 30 2001
Accepted after revision July 3 2001

The Bronchial Obstruction in Nord-Trøndelag study was funded by Astra-Zeneca Norway and The Norwegian Research Council.

Studies on spirometric reference values have demonstrated substantial differences in both predicted forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) [1]. Even though prediction equations for FEV1 and FVC have previously been developed in Scandinavia [2–6], the prediction equations from the European Community for Coal and Steel (ECCS) [7] are more commonly used in Norway. Several studies have indicated that these equations significantly underestimate predicted FEV1 and FVC [8–11], which was confirmed by the European Community Respiratory Health Survey (ECRHS) [1]. As general health status, lung function and measurement devices are subject to cohort effect, regular review of reference equations has been recommended [8]. Previous Scandinavian prediction equations were linear [2, 6] and, therefore, did not reflect accelerating decline by age. They included smokers [2], or a limited number of never-smokers [4, 5], and presented limited data from the elderly [11–14]. Literature on flow/volume area under curve (AUC) from population studies has not previously been found, and is therefore included in this study.

The aim of this study was to establish new Norwegian reference prediction equations for lung parameters, such as FVC, FEV1, peak expiratory flow (PEF), forced mid-expiratory flow, ($FEF_{25\%-75\%}$) and AUC, in subjects aged 20–80 yrs. In addition, the authors have assessed differences in lung function parameters using the new prediction equations, those from the ECCS [7] and other equations from Caucasians in different parts of the world [9, 10, 15–18].

Method

Subjects

During 1995–1997, all residents of the Nord-Trøndelag County aged ⩾20 yrs (n=92,434), were invited to participate in the adult part of The Nord-Trøndelag Health Study (HUNT) [19]. The county is situated in a central area of Norway, and 97% of the residents are of Caucasian origin. Apart from not having a large city, the geographical and

demographical structure of the Nord-Trøndelag County is fairly representative of Norway as a whole [20]. The education and income level and the prevalence of current smokers are slightly lower than the average for Norway [21], but the sale of antiasthmatic drugs is close to the Norwegian average [22]. From 65,225 subjects (71% of those invited) who attended the primary screening, a randomly selected sample of 5% (n=3,297) was invited to phase one of the Bronchial Obstruction in Nord-Trøndelag (BONT) study. This consisted of flow/volume spirometry and an interview with a nurse. In total, 2,792 subjects participated.

Spirometric measurements and quality control

Staff, consisting of 19 nurses and technicians organized into two teams, performed the flow/volume spirometry and the interview. Team I covered the five most densely inhabited municipalities (58,805 inhabitants) and team II covered the 18 smaller municipalities (33,629 inhabitants).

Flow/volume spirometry was recorded with three pneumotachographs (MasterScope spirometer, version 4.15, Erich Jaeger GmbH, Wuerzburg, Germany). The instruments were calibrated twice daily with a 1 L syringe. The staff also performed a daily biological control by assessing their own lung function. The participants were seated and wore a noseclip, and extension or flexion of the neck was avoided. Height and weight were measured barefoot and in light clothing with standardized equipment. Barometer pressure, temperature and relative humidity were registered every morning, and the integrated volumes were automatically converted from ambient temperature and pressure to body temperature and pressure, saturated conditions.

The staff initially went through formal training and were then continuously monitored during the entire study by the head of the project. In accordance with the 1994 American Thoracic Society (ATS) recommendations [23], they were taught to instruct the subjects to perform three acceptable and reproducible manoeuvres, ensuring that the subjects produced the highest possible peak flows and that the expiration continued for ≥ 6 s. If the subjects were unable to do this, up to five manoeuvres were performed. The flow/volume curve with the highest sum of FEV_1 and FVC was retained. The computer provided the technicians with feedback as to whether the acceptability and reproducibility criteria were met. The error messages given were in accordance with the 1987 ATS recommendations, with a reproducibility criteria of <100 mL or 5% difference between FEV_1 and FVC in the two best tests, and a lower limit back extrapolated volume of 100 mL [24]. In the 1994 ATS recommendations, these limits were 200 mL and 150 mL, respectively [23].

Reference sample

The reference sample was selected from the 5% randomized sample (n=2,792), based on questionnaire results. The selection criteria followed ATS recommendations [8]: 1) life-time never-smokers; 2) no respiratory disease (self-reported or medical doctor diagnosed asthma, emphysema or chronic bronchitis); and 3) no reported respiratory symptoms (wheezing or breathlessness during the last 12 months, persistent coughing or complaints of breathlessness for any reason).

Prediction equations and statistics

Sex-specific multiple linear regressions of lung function on height, age, weight, and body mass index (BMI) in various powers and interactions were performed. Statistical significance and fraction of explained variability were the main criteria for selecting independent variables and transforming lung function variables. Independent variables were centred (*i.e.* observed values minus variable mean) in the regressions for selection of the best model in order to reduce collinearity among higher order and cross-product terms. The assumptions of linearity and homoscedasticity were controlled.

The selection of prediction equations for comparison was based on common use [7, 15, 18], use of nonlinear equations [9, 10, 17] and inclusion of the elderly [12]. The differences between predicted values based on the prediction equations from the present study and others are given as Bland Altman plots, whilst the differences between observed values and values predicted by the prediction equations are given as mean difference in per cent of mean observed values and mean squared difference.

Comparisons of lung function between the groups were performed by analysis of variance, adjusting for covariates. A p-value of <0.05 was considered statistically significant.

Results

Participants

After the exclusion of previous and current smokers, and those reporting respiratory symptoms or disease [8], a total of 546 females and 362 males aged 20–80 yrs were included in the reference sample (tables 1 and 2). Subjects with adiposity or a low score for global health questions were not excluded, as this did not significantly influence the parameters (data not shown).

Quality control

The staff. The nurses/technicians assessed their lung function on the days that they worked at the spirometry stations. A total of 975 such flow/volume assessments were recorded by 19 nurses/technicians. When three nurses with known asthma were excluded, the intra-individual coefficient of variation (=100×SD divided by the mean) of FEV_1 during the 2-yr survey period varied from 2.6–5.5%, with 4.0% as the mean.

Table 1. – The reference sample selected according to American Thoracic Society criteria, included 1,282 males (M) and 1,510 females (F), and represented the 5% random sample of the total population

Criteria	Prevalence %		Number excluded		Number remaining	
	M	F	M	F	M	F
Unacceptable spirometry	2.7	2.6	34	52	1248	1458
Exsmokers	29.3	18.9	374	287	874	1171
Current smokers	29.5	30.0	375	449	499	722
MD diagnosis of asthma	5.1	5.4	22	40	477	682
MD diagnosis of chronic bronchitis	3.9	2.3	5	8	472	674
Self-reported ever-asthma	8.5	8.5	17	14	455	660
Wheezing or breathlessness during last 12 months	13.3	12.3	29	35	426	625
Persistent cough	17.0	15.2	52	52	374	573
Difficulty in breathing of any cause	7.8	7.5	10	18	365	555
Age >80 yrs	2.0	2.4	3	9	362	546

MD: Doctor of Medicine.

The study population. When using the 1987 ATS recommendations, 12.7% of females and 7.7% of males failed to meet the FEV1 reproducibility criteria. In contrast, 6.8% of females and 7.1% of males failed to meet the criteria when the 1994 ATS recommendations were applied.

With the inclusion of the whole study sample (n= 2,792), the comparison between the two test teams of the mean FEV1 and FVC showed only minor differences, 1.4% and 0.8% for FEV1 and FVC, respectively (adjusted for age, sex, height, and pack-yrs).

Prediction equations

Scrutinizing the plots, most lung function variables were nonlinear with age and showed a plateau in younger adults with a decline after the age of 35–40 yrs. Exploring the regression models, square age and ln(height) were found to contribute significantly to the explained variance of all lung function parameters, except FEV1/FVC.

The prediction equations for the means were developed by regressing the natural logarithms of lung function variables against ln(height), square age, and age, as performed in the Swiss Study on Air Pollution and Lung Diseases in Adults [10, 25]. The use of natural logarithms and square age improved the explained variance by 1–2%, compared to linear models (table 3). Separate equations were tested in males under and over the age of 25 yrs [7, 10], but polynomial regression equations provided a significantly better fit than linear regressions with breakpoints [17, 26].

No significant interaction between age and height was found. Weight, weight^2 and BMI were significant parameters for FEV1 and FVC when included in the models, but they were not included in the final prediction equations as this increased the adjusted explained variance by <1%, and these measures are less reliable than height [25].

The distributions of FEV1, FVC, PEF and $FEF_{25\%-75\%}$ were similar to the Gaussian distribution, and the assumptions of homoscedasticity were met. Therefore, one-sided lower 95% prediction intervals were used to determine the lower limit of normal lung functions [7, 26] (table 3).

From the age of 35–39 yrs, FEV1, FVC, AUC and $FEF_{25\%-75\%}$ declined with age (figs. 1 and 2). For both FEV1 and FVC, regression coefficients for age decreased with increasing age, whereas, with regard to the regression coefficients for height, no significant change was found with age except for higher coefficients in the youngest female group ($p<0.05$) (table 4). FEV1/FVC decreased with the age of the cohort in both sexes (0.12–0.14%·yr^{-1}, p-value for trend <0.05) (fig. 2).

Table 2. – Sex and age distribution in the 20–80 yrs age group of the reference sample and the total population

Age yrs	Reference sample		Total population#	
	M	F	M %	F %
20–29	73 (20.1)	76 (13.9)	21.5	23.2
30–39	91 (25.1)	86 (15.7)	18.7	19.5
40–49	72 (19.8)	91 (16.6)	19.6	20.4
50–59	66 (18.2)	117 (21.4)	14.6	14.8
60–69	33 (9.1)	77 (14.1)	12.5	11.6
70–80	27 (7.4)	99 (18.1)	12.8	10.3
Total	362 (100)	546 (100)	100	100

Data are presented as n (%) unless otherwise stated. M: males; F: females. #: per cent of 43,789 females and 44,811 males.

Comparison with other prediction equations. When the prediction equations from the present study (table 4) were compared with other prediction equations [7, 9, 10, 12, 15, 17, 18], the authors found that the closest agreement for FEV1, FVC, PEF and $FEF_{25\%-75\%}$ in females was with HANKINSON *et al.* [17]. In males, similar agreements were found for FVC and PEF, but for FEV1, the closest agreement was with the prediction equation of ROCA *et al.* [18] (table 5).

The difference by mean predicted value between the present study and the ECCS was fairly constant for FEV1 in both sexes (fig. 3) and FVC in females (fig. 4). For FVC in males, the relation increased proportionally when the present prediction values

Table 3. – Prediction equations from the Bronchial Obstruction in Nord-Trøndelag (BONT) study for particular parameters with explained variance (adjusted R^2) and residual standard deviation (RSD) based on 362 males and 546 females

Parameter	Males			Females		
	Equation	R^2	RSD	Equation	R^2	RSD
FVC	Exp (-12.396+2.733 ln(H)-0.0000592 A^2)	0.63	0.12	Exp (-9.851+2.189 ln(H)-0.000143A^2+0.006439A	0.68	0.13
FEV_1	Exp (-10.556+2.342 ln(H)-0.0000685 A^2)	0.60	0.12	Exp (-9.091+2.004 ln(H)-0.000163 A^2+0.007237A	0.72	0.13
FEV_1/FVC	Exp (6.433-0.385 ln(H)-0.000923A)	0.05	0.07	Exp (5.403-0.185 ln(H)-0.00115A)	0.06	0.07
PEF $L \cdot s^{-1}$	Exp (-6.632+1.731 ln(H)-0.000436A^2)	0.16	0.23	Exp (-7.726+1.808 ln(H)-0.000286A^2+0.022A)	0.34	0.25
$FEF_{25\%-75\%}$ $L \cdot s^{-1}$	Exp (-3.764+1.037 ln(H)-0.000102A^2)	0.26	0.27	Exp (-6.442+1.474 ln(H)-0.000243A^2+0.01199A)	0.41	0.30
Log AUC $L \times L \cdot s^{-1}$	Exp (-156.16+37.12 ln(H)-0.184H-0.00012A^2)	0.51	0.27	Exp (-16.597+3.698 ln(H)-0.00041A^2+0.02408A)	0.65	0.29

A: age in yrs; H: height in cm; Exp (x): e^x; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow; $FEF_{25\%-75\%}$: forced mid-expiratory flow; AUC: area under curve. The predicted value for FEV_1 in a 20-yr-old male with height 180 cm is computed as: $FEV_1 = e^{(-10.556+2.342 \times \ln(180)-0.0000685 \times 400)} = e^{1.5785} = 4.848$. The lower limit of normal (LLN) is computed as: $LLN\ FEV_1 = e^{(predicted-1.645 \times RSD)} = e^{1.3811} = 3.979$.

were compared with those from ECCS [7], HANKINSON *et al.* [17] and BRÄNDLI *et al.* [10] (fig. 4). Unlike the regression coefficient for age, the coefficient for height in the present study was significantly higher than that reported in other studies that used linear regression models without polynominal terms (~0.080 *versus* 0.056–0.057) [7, 12, 15, 18] (table 4). This is, however, in agreement with previous studies from Norway and Sweden [2, 5] (figs. 3 and 4).

The Bland Altman plots confirm the underestimation of both FEV_1 and FVC by prediction equations from the ECCS *versus* the present study (figs. 3 and 4). However, closer agreement is confirmed between the present study and other studies included in the comparisons (table 5 and figs. 3 and 4).

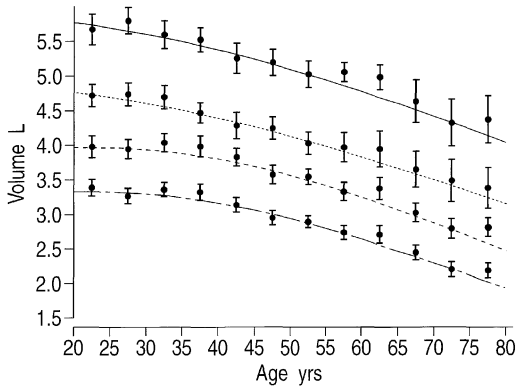


Fig. 1. – Mean observed forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) in 5-yr intervals with 95% confidence intervals (●) and FEV_1 and FVC predicted by the Bronchial Obstruction in Nord-Trøndelag (BONT) study in males and females. BONT predicted is indicated by the following lines: ——: FVC males; -------: FEV_1 males; – – – –: FVC females; —·—·—: FEV_1 females.

Discussion

Based on a random sample that only included asymptomatic never-smokers, the authors have estimated prediction equations for lung function variables. The present study confirms that the ECCS prediction equations, which are the most commonly used in Norway, significantly underestimate FEV_1 and FVC. According to the Global Initiative for Chronic Obstructive Lung Disease, the British Thoracic Society, and the European Respiratory Society guidelines, FEV_1 level in per cent of predicted gives the severity of airflow limitation. The choice of reference values may, therefore, be of clinical importance.

As a cross-sectional population study, the data from the present study are subject to cohort bias due to a variety of host and environmental factors [8]. Compared to longitudinal studies, cross-sectional studies are cheaper and more practical for developing prediction equations, but need to be repeated regularly in different regions. No reference values are available from northern Europe in the 1990s. The strengths of this study are the random selection of the reference group from a total adult population, surveillance of the technicians and equipment by the same person, and direct feedback to the technicians about the acceptability and reproducibility of the flow/volume curves.

Participation

Of the 5% random sample, 85% participated in the BONT study. A nonresponder study did not reveal differences in respiratory symptoms or diseases between the responder and the nonresponder groups [19]. There were no indications of selection bias caused by the number of nonresponders, except in the elderly, where the healthiest and most mobile subjects might have been over-represented.

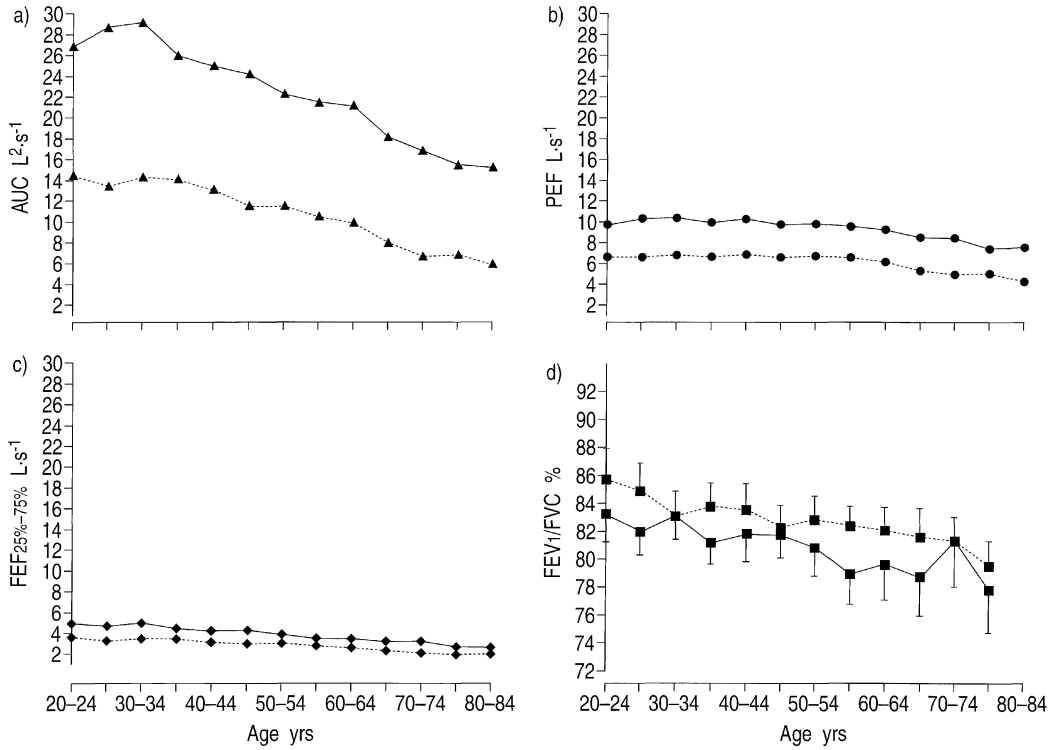


Fig. 2.–Mean observed a) area under curve (AUC), b) peak expiratory flow (PEF), c) forced mid-expiratory flow ($FEF_{25\%-75\%}$), and d) forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) % in 5-yr intervals in males (——) and females (----) by age. 95% confidence intervals are shown in d).

Technical factors

Failure to meet the acceptability criteria for spirometry has been reported in many studies [27–30]. Using the 1987 ATS recommendation for FEV_1 and FVC [7], the authors observed similar percentages of test failure as HUMERFELT *et al.* [29]. Many had problems with the end of plateau criterion based on the 1987 ATS recommendations [31]. The curves were, therefore, visually controlled, and those with a plateau beginning at the volume/time curve were included in the present analyses. Lack of end of plateau could cause an underestimation of FVC and overestimation of FEV_1/FVC [23]. Subjects >80 yrs of age were excluded because of a low participation rate, few asymptomatic never-smokers, and problems with the reproducibility and acceptability criteria.

Automatically retaining the curve with the largest sum of FEV_1 or FVC might have retained some curves with submaximal effort. KROWKA *et al.* [32] found that FEV_1 was inversely dependent on effort, but in accordance with the ATS, the present authors did not exclude curves with submaximal effort [23]. Saving such curves and the lack of quality control

Table 4.–Regression coefficients for age and height in females and males in age-stratified multiple linear regression analysis with forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) as dependent variables

Variable	Age 20–39 yrs		Age 40–59 yrs		Age 60–80 yrs	
	FVC	FEV_1	FVC	FEV_1	FVC	FEV_1
Females						
Age	-0.0025 (0.007)	-0.002 (0.006)	-0.034* (0.005)	-0.027* (0.004)	-0.042* (0.007)	-0.040* (0.005)
Height	0.053* (0.007)	0.042* (0.006)	0.043* (0.005)	0.033* (0.004)	0.041* (0.006)	0.028* (0.004)
Males						
Age	-0.015* (0.009)	-0.019* (0.008)	-0.020* (0.010)	-0.023* (0.008)	-0.039* (0.012)	-0.032* (0.010)
Height	0.079* (0.008)	0.051* (0.007)	0.074* (0.008)	0.053* (0.007)	0.093* (0.013)	0.067* (0.011)

Data are presented as regression coefficient (standard error). *: $p<0.05$.

Table 5. – The per cent mean differences and mean square of differences between observed values in this study and predicted values according to different prediction equations

Variable	Age yrs	Females				Males			
		n	Mean difference %	Mean squared difference	Rank	n	Mean difference %	Mean squared difference	Rank
FVC									
Present	20–80	546	0.9	0.198	1	362	0.4	0.369	1
BRÄNDLI [10]	20–60	346	-0.9	0.212	3	275	-1.0	0.418	5
CRAPO [15]	15–84	546	4.2	0.232	6	362	2.6	0.419	6
GORE [9]	18–78	524	4.5	0.224	5	340	1.4	0.377	3
HANKINSON [17]	20–80	546	0.7	0.207	2	362	0.9	0.374	2
QUANJER [7]	18–70	458	12.9	0.441	7	338	9.1	0.629	7
ROCA [18]	20–70	458	0.0	0.215	4	338	-1.9	0.409	4
ENRIGHT [12]	65–85	144	-0.8	0.191	#	42	4.2	0.335	#
FEV_1									
Present	20–80	546	0.6	0.129	1	362	0.4	0.198	1
BRÄNDLI [10]	20–60	346	2.4	0.140	3	275	2.5	0.314	6
CRAPO [15]	15–84	546	4.8	0.153	5	362	3.4	0.304	4
GORE [9]	18–78	524	4.1	0.150	4	340	2.8	0.292	3
HANKINSON [17]	20–80	546	2.9	0.136	2	362	3.8	0.305	5
QUANJER [7]	18–70	458	9.2	0.221	7	338	8.5	0.426	7
ROCA [18]	20–70	458	3.6	0.155	6	338	0.3	0.288	2
ENRIGHT [12]	65–85	144	5.3	0.116	#	42	13.2	0.361	#
FEV_1/FVC									
Present	20–80	546	0.0	32.592	1	362	0.0	28.893	1
BRÄNDLI [10]	20–60	346	3.2	41.887	6	275	3.4	40.713	5
CRAPO [15]	15–84	546	1.4	40.168	4	362	0.9	31.007	2
GORE [9]	18–78	524	1.3	38.255	3	340	0.8	32.286	3
HANKINSON [17]	20–80	546	2.3	41.665	5	362	2.8	40.913	6
QUANJER [7]	18–70	458	2.7	38.231	2	338	2.0	35.341	4
ROCA [18]	20–70	458	7.2	72.593	7	338	4.5	46.722	7
ENRIGHT [12]	65–85	144	6.4	64.187	#	42	8.1	68.598	#
PEF									
Present	20–80	546	0.0	1.940	1	362	0.2	3.984	1
BRÄNDLI [10]	20–60	346	6.8	2.198	5	275	4.7	4.291	4
GORE [9]	18–78	524	-5.5	2.,223	6	340	-7.6	4.584	6
HANKINSON [17]	20–80	546	-4.1	2.021	2	362	-0.9	4.022	2
QUANJER [7]	18–70	458	-1.0	2.092	3	338	5.8	4.429	5
ROCA [18]	20–70	458	3.4	2.164	4	338	-3.7	4.230	3
$FEF_{25\%–75\%}$									
Present	20–80	546	0.0	0.602	1	362	0.3	1.228	1
BRÄNDLI [10]	20–60	346	5.8	0.785	7	275	9.8	1.486	7
CRAPO [15]	15–84	546	0.1	0.667	4	362	2.4	1.239	2
GORE [9]	18–78	524	1.4	0.660	3	340	3.9	1.332	4
HANKINSON [17]	20–80	546	5.8	0.649	2	362	9.3	1.464	6
QUANJER [7]	18–70	458	-10.8	0.757	5	338	-1.6	1.301	3
ROCA [18]	20–70	458	9.0	0.782	6	338	5.4	1.383	5

Ranks of the mean square are shown and comparisons are restricted to age groups from which the different equations are estimated. FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow; $FEF_{25\%–75\%}$: forced mid-expiratory flow. #: not included in the ranking because of inclusion of 65–80 yrs age group only.

criteria for PEF in the software might have caused underestimation of PEF. Only minor differences between the present study and the ECCS of this parameter compared to FEV_1 and FVC could indicate such underestimation. A possible criterion for effort based on the PEF/$FEF_{50\%}$ ratio could solve this problem in future studies.

Lung function by age

The associations between FEV_1, FVC and age found in this population are similar to results from previous cross-sectional studies [7, 14, 33–36]. The authors found that FEV_1/FVC uniformly reduced with age, but the levels were higher and declined less through age groups than reported in other studies [13, 33, 34]. Within the oldest group, "super-healthy" elderly survivors could lessen the slope of the regression curve, and spuriously increase the predicted values for the middle-aged [26]. In the present study, the fitness of the prediction equations in the middle-aged was hardly affected by this.

Comparison with other prediction equations

The estimates from the prediction equations for FEV_1 and FVC were in closer agreement with the results from other studies [9–11, 15, 17, 18] than those

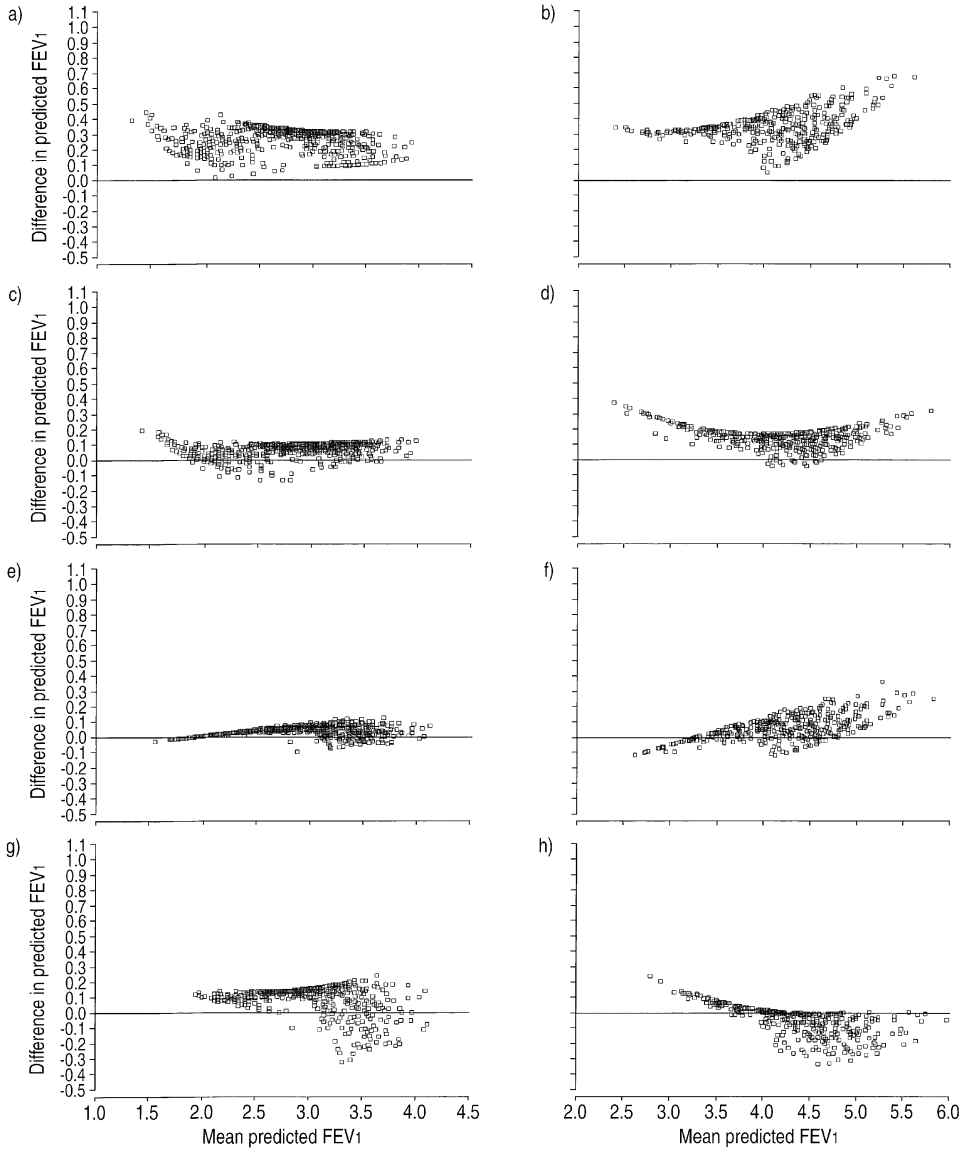


Fig. 3.–Bland Altman plots showing the difference between forced expiratory volume in one second (FEV1) against mean FEV1 predicted by a) and b) Bronchial Obstruction in Nord-Trøndelag (BONT) *versus* European Community for Coal and Steel [7], c) and d) BONT *versus* HANKINSON *et al.* [17] e) and f) BONT *versus* BRÄNDLI *et al.* [10], and g) and h) BONT *versus* GULSVIK [2] in females (a, c, e, g) and males (b, d, f, h).

from the ECCS [7]. Even if asymptomatic smokers were included in the previous set of equations from Norway [3], the present study is in greater agreement with this study than that of the ECCS.

ROCA *et al.* [1] estimated prediction deviations (observed values minus values estimated by ECCS equations) for FEV1 and FVC from the ECRHS. Using the same inclusion criteria, the prediction deviations of FEV1 were nearly identical in the ECRHS and the present study, whilst an ~10% higher deviation of FVC in both sexes was found in the present study compared to ECRHS (data not shown).

The ECCS prediction equations were summary equations compiled from a review of previously published equations, including different populations and using different spirometers and techniques. Comparisons with other studies do not indicate that

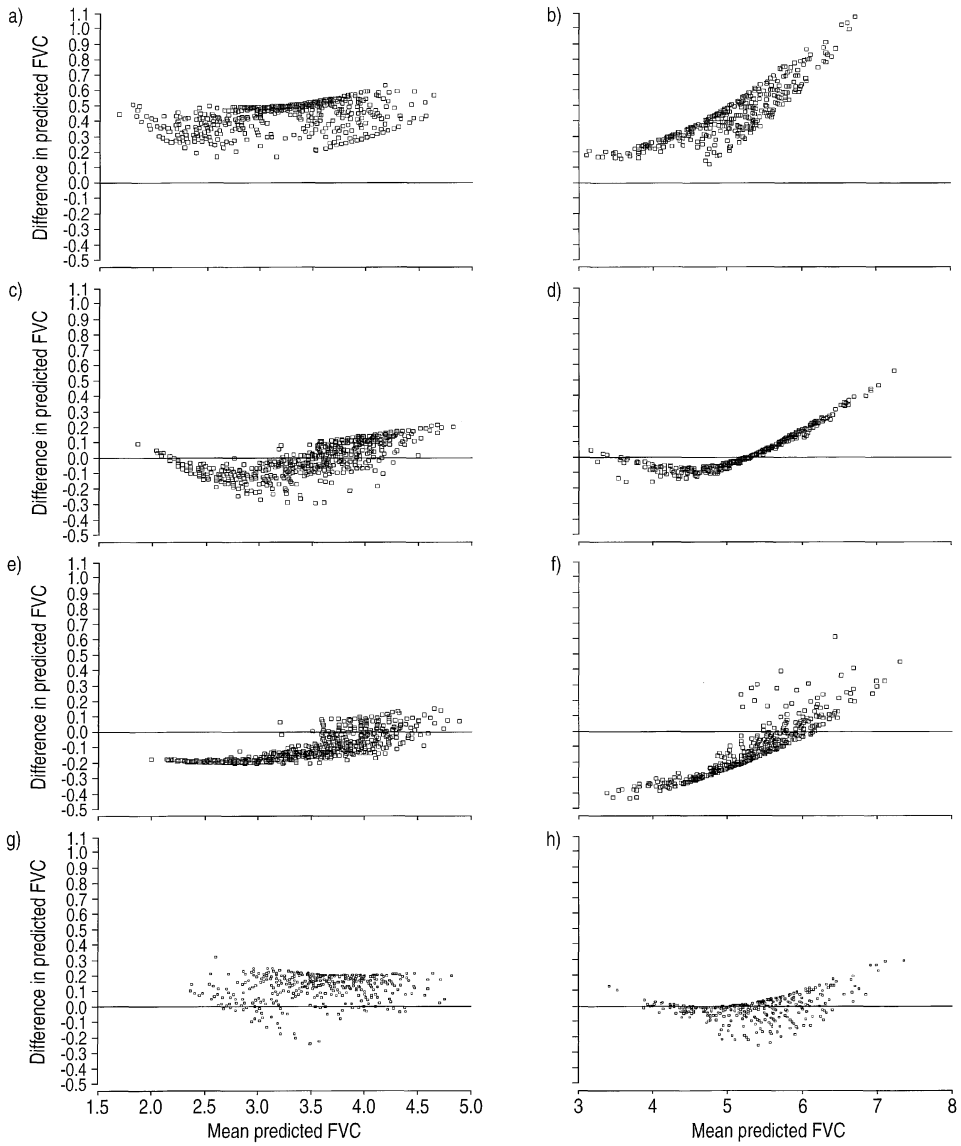


Fig. 4.–Bland Altman plots showing the difference between forced vital capacity (FVC) against mean FVC predicted by a) and b) Bronchial Obstruction in Nord-Trøndelag (BONT) *versus* European Community for Coal and Steel [7], c) and d) BONT *versus* HANKINSON *et al.* [17] e) and f), BONT *versus* BRÄNDLI *et al.* [10], and g) and h) BONT *versus* GULSVIK [3] in females (a, c, e, g) and males (b, d, f, h).

the type of spirometer [9, 15, 17, 36] explains the difference compared to the prediction equations from the ECCS. The differences between the prediction equations from the ECCS and later studies may be the result of a significant increase in lung function parameters, as is seen in other anthropometric measures, such as height [37, 38], change of technique and different exclusion criteria for the reference sample, or use of qualitative controls, such as immediate feedback on acceptability and reproducibility of spirometric measurement [10]. Increased awareness and better reporting of respiratory symptoms in the population could also result in the selection of healthier subjects in more recent reference samples. If the authors included subjects that had respiratory symptoms but had not been diagnosed as having a

respiratory disease, this had little effect on the predicted values (data not shown). This, therefore, does not explain the differences compared to ECCS.

Higher levels of FEV1/FVC were found than has been predicted by other studies. The prediction equations of ROCA *et al.* [18] and ENRIGHT *et al.* [16] showed a different pattern with a higher decrease by age than the present study. Including light exsmokers in the present analyses, as seen in the study of ENRIGHT *et al.* [16], resulted in a 0.4% reduction of FEV1/FVC, which does not explain the differences found. The differences could have been caused by a bias toward healthier subjects in the elderly group compared to other studies, or by a higher succession rate in getting optimal expiration from the elderly in the study of ENRIGHT *et al.* [16]. Comparably low explained variance of regression models for this parameter have also been reported in other studies and are also dependent upon the number of subjects included [6, 10, 12].

Conclusion

The authors have developed prediction equations for lung function parameters from a random sample of never-smokers without reported symptoms or diseases. The present study confirms the results from recent studies from Europe, the USA and Australia, all of which indicate a higher level of predicted lung function parameters than those predicted by the equations from the European Community for Coal and Steel. The results have substantial clinical implications on the diagnosis and management of patients with symptoms of obstructive lung disease. Healthcare providers should be encouraged to reconsider their choice of prediction equations of spirometry; the authors recommend the use of the Norwegian prediction equations.

Acknowledgements. The Nord-Trøndelag Health Study (HUNT) is a collaboration between the HUNT Research Centre, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Verdal, The National Institute of Public Health, The National Health Screening Service of Norway, and Nord-Trøndelag County Council.

References

1. Roca J, Burgos F, Sunyer J, *et al.* References values for forced spirometry. Group of the European Community Respiratory Health Survey. *Eur Respir J* 1998; 11: 1354–1362.
2. Gulsvik A. Prevalence and manifestations of obstructive lung disease in the city of Oslo. *Scand J Respir Dis* 1979; 60: 286–296.
3. Gulsvik A. Obstructive lung disease in an urban population. Department of Lung Diseases, The National Hospital, University of Oslo, Thesis, 1974.
4. Hedenström H, Malmberg P, Agarwal K. Reference values for lung function tests in females. Regression equations with smoking variables. *Bull Eur Physiopathol Respir* 1985; 21: 551–557.
5. Hedenström H, Malmberg P, Fridriksson HV. Reference values for lung function tests in men: Regression equations with smoking variables. *Upsala J Med Sci* 1986; 91: 299–310.
6. Oxhoj H, Jeppesen GM, Larsen VH, Jorgensen B. Spirometry in healthy adult never-smokers. *Clin Physiol* 1988; 8: 329–339.
7. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993; 6: Suppl. 16, 5s–40s.
8. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. *Am Rev Respir Dis* 1991; 144: 1202–1218.
9. Gore CJ, Crockett AJ, Pederson DG, Booth ML, Bauman A, Owen N. Spirometric standards for healthy adult lifetime nonsmokers in Australia. *Eur Respir J* 1995; 8: 773–782.
10. Brändli O, Schindler C, Kunzli N, Keller R, Perruchoud AP. Lung function in healthy never smoking adults: reference values and lower limits of normal of a Swiss population. *Thorax* 1996; 51: 277–283.
11. Baur X, Isringhausen-Bley S, Degens P. Comparison of lung-function reference values. *Int Arch Occup Environ Health* 1999; 72: 69–83.
12. Enright PL, Kronmal RA, Higgins M, Schenker M, Haponik EF. Spirometry reference values for women and men 65 to 85 years of age. Cardiovascular health study. *Am Rev Respir Dis* 1993; 147: 125–133.
13. McDonnell WF, Enright PL, Abbey DE, *et al.* Spirometric reference equations for older adults. *Respir Med* 1998; 92: 914–921.
14. Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. *Eur Respir J* 1999; 13: 197–205.
15. Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981; 123: 659–664.
16. Enright PL, Adams AB, Boyle PJ, Sherrill DL. Spirometry and maximal respiratory pressure references from healthy Minnesota 65- to 85-year-old women and men. *Chest* 1995; 108: 663–669 (published erratum appears in *Chest* 1995; 108: 1776).
17. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; 159: 179–187.
18. Roca J, Sanchis J, Agusti-Vidal A, *et al.* Spirometric reference values from a Mediterranean population. *Bull Eur Physiopathol Respir* 1986; 22: 217–224.
19. Langhammer A, Johnsen R, Holmen J, Gulsvik A, Bjermer L. Cigarette smoking gives more respiratory symptoms among women than among men. *J Epidemiol Community Health* 2000; 54: 917–922.
20. Holmen J, Midthjell K, Bjartveit K, *et al.* The Nord-Trøndelag Health Survey 1984–86. Purpose, background and methods. Participation, non-participation and frequency distributions. Oslo, National Institute of Public Health 1990, report no. 4; p. 176.

21. Lukerstuen Å . Statistical Yearbook of Norway. Oslo/ Kongvinger, Statistics Norway, 2000.
22. Øydvin K, ed. Drug Consumption in Norway 1993–1997. Oslo, Norwegian Medicinal Depot, 1999; p. 190.
23. American Thoracic Society. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995; 152: 1107–1136.
24. American Thoracic Society. Standardization of spirometry: a summary of recommendations from the American Thoracic Society. The 1987 update. *Ann Intern Med* 1988; 108: 217–220.
25. Cole TJ. Linear and proportional tregression models in the prediction of ventilatory function. *J Royal Stat Soc* 1975; 138: 297–338.
26. Glindmeyer HW, Lefante JJ, McColloster C, Jones RN, Weill H. Blue-collar normative spirometric values for Caucasian and African-American men and women aged 18 to 65. *Am J Respir Crit Care Med* 1995; 151: 412–422.
27. Enright PL, Johnson LR, Connett JE, Voelker H, Buist AS. Spirometry in the lung health study. 1. Methods and quality control. *Am Rev Respir Dis* 1991; 143: 1215–1223.
28. Ng'Ang'a LW, Ernst P, Jaakkola MS, Gerardi G, Hanley JH, Becklake MR. Spirometric lung function. Distribution and determinants of test failure in a young adult population. *Am Rev Respir Dis* 1992; 145: 48–52.
29. Humerfelt S, Eide GE, Kvale G, Gulsvik A. Predictors of spirometric test failure: a comparison of the 1983 and 1993 acceptability criteria from the European Community for Coal and Steel. *Occup Environ Med* 1995; 52: 547–553.
30. Swanney MP, Jensen RL, Crichton DA, Beckert LE, Cardno LA, Crapo RO. FEV(6) is an acceptable surrogate for FVC in the spirometric diagnosis of airway obstruction and restriction. *Am J Respir Crit Care Med* 2000; 162: 917–919.
31. Stoller JK, Basheda S, Laskowski D, Goormastic M, McCarthy K. Trial of standard *versus* modified expiration to achieve end-of-test spirometry criteria. *Am Rev Respir Dis* 1993; 148: 275–280.
32. Krowka MJ, Enright PL, Rodarte JR, Hyatt RE. Effect of effort on measurement of forced expiratory volume in one second. *Am Rev Respir Dis* 1987; 136: 829–833.
33. Milne JS, Williamson J. Respiratory function tests in older people. *Clin Sci* 1972; 42: 371–381.
34. Schmidt CD, Dickman ML, Gardner RM, Brough FK. Spirometric standards for healthy elderly men and women. 532 subjects, ages 55 through 94 years. *Am Rev Respir Dis* 1973; 108: 933–939.
35. Hankinson JL, Bang KM. Acceptability and reproducibility criteria of the American Thoracic Society as observed in a sample of the general population. *Am Rev Respir Dis* 1991; 143: 516–521.
36. Knudson RJ, Slatin RC, Lebowitz MD, Burrows B. The maximal expiratory flow-volume curve. Normal standards, variability, and effects of age. *Am Rev Respir Dis* 1976; 113: 587–600.
37. Glindmeyer HW, Diem JE, Jones RN, Weill H. Noncomparability of longitudinally and cross-sectionally determined annual change in spirometry. *Am Rev Respir Dis* 1982; 125: 544–566.
38. Xu X, Laird N, Dockery DW, Schouten JP, Rijcken B, Weiss ST. Age, period, and cohort effects on pulmonary function in a 24-year longitudinal study. *Am J Epidemiol* 1995; 141: 554–566.

Corrected table 3

Table 3 Predictions equations from the BONT study for FEV1, FVC, FEV1/FVC, PEF, FEF25-75 and log AUC with explained variance (adjusted R^2) and residual standard deviation (RSD) based on 362 men and 546 women.

	Men			Women		
Parameter	Equation	R^2	RSD	Equation	R^2	RSD
FVC	Exp (-12,396 + 2,733 ln(H) – 0,0000592 A^2)	0,63	0,12	Exp (-9,851 + 2,189 ln(H) – 0,000143A^2 + 0,006439A	0,68	0,13
FEV1	Exp (-10,556 + 2,342 ln(H) – 0,0000685 A^2)	0,60	0,12	Exp (-9,091 + 2,004 ln(H) – 0,000163 A^2 + 0,007237A	0,72	0,13
FEV1/FVC	Exp (6,433 - 0,385 ln(H) – 0,000923A)	0,05	0,07	Exp (5,403 – 0,185ln(H) – 0,00115A)	0,06	0,07
PEF (l/s)	Exp (-6,632 + 1,731 ln(H) – 0,0000436A^2)	0,16	0,23	Exp (-7,726 + 1,808 ln(H) – 0,000286A^2+ 0,022A)	0,34	0,25
FEF25-75 (l/s)	Exp (-3,764 + 1,037 ln(H) – 0,000102A^2)	0,26	0,27	Exp (-6,442 + 1,474 ln(H)– 0,000243A^2+ 0,01199A)	0,41	0,30
Log AUC (l*l/s)	Exp (-156,16+ 37,12ln(H) - 0,184H– 0,00012A^2)	0,51	0,27	Exp (-16,597+ 3,698 ln(H) – 0,00041A^2+ 0,02408A)	0,65	0,29

A= age (years); H = height (cm); exp (x) = e^x.

The predicted value for FEV1 in a 20 years old man with height 180 cm is computed as: FEV1= $e^{(-10.556 + 2.342*\ln(180) - 0.0000685*400)} = e^{1.5785} = 4.848$

The lower limit of normal (LLN) is computed as: LLN FEV1 = $e^{(predicted-1.645*RSD)} = e^{1.3811} = 3.979$

Paper III

Eur Respir J 2003; 21: 1017–1023
DOI: 10.1183/09031936.03.00053202

European Respiratory Journal
ISSN 0903-1936

Sex differences in lung vulnerability to tobacco smoking

A. Langhammer*,#, R. Johnsen#, A. Gulsvik¶, T.L. Holmen*,#, L. Bjermer+

Sex differences in lung vulnerability to tobacco smoking. A. Langhammer, R. Johnsen, A. Gulsvik, T.L. Holmen, L. Bjermer. ©ERS Journals Ltd 2003.

ABSTRACT: Studies have indicated that females are more vulnerable to the deleterious effect of tobacco smoking than males. The current study aimed to investigate the associations between tobacco smoking and reported respiratory symptoms, self-rated health, and lung function by sex.

In 1995–1997 65,225 subjects aged ⩾20 yrs (71% of invited) attended for screening within the Nord-Trøndelag Health Study. Among these, 10,941 subjects selected randomly or because they reported having asthma or asthma-related symptoms, participated in the Bronchial Obstruction in Nord-Trøndelag study consisting of spirometry and a personal interview.

Tobacco smoking was associated with increased prevalence of respiratory symptoms, reduced lung function, and lower score on global self-rated health (SRH). Adjusted for smoking burden and lung function, females had a higher risk for reporting respiratory symptoms and lower SRH compared with males. Further, smoking burden was associated with a larger relative reduction in expiratory lung function in females than in males.

Females reported more symptoms and lower self-rated health compared with males with similar smoking burden. Even if smoking in females was associated with a larger reduction in per cent predicted lung function compared with males, this does not fully explain the higher symptom prevalence in females.

Eur Respir J 2003; 21: 1017–1023.

*Nord-Trøndelag Health Study Research Centre, Norwegian University of Science and Technology (NTNU), Verdal, #Dept of Community Medicine and General Practice, NTNU, Trondheim, ¶Dept of Thoracic Medicine, University of Bergen, Bergen, Norway. +Dept of Respiratory Medicine and Allergology, University Hospital, Lund, Sweden.

Correspondence: A. Langhammer, Nord-Trøndelag Health Study Research Centre, Norwegian University of Science and Technology, Neptunveien 1, N-7650 Verdal, Norway.
Fax: 47 74075181
E-mail: arnulf.langhammer@medisin.ntnu.no

Keywords: Lung function, respiratory symptoms, self-rated health, sex, tobacco smoking

Received: June 20 2002
Accepted after revision: January 29 2003

This study was supported by the Norwegian Research Council and AstraZeneca.

Some studies have reported higher vulnerability to the deleterious effects of tobacco smoking in females compared with males. These results include negative effect on lung growth [1], lower lung function in adulthood [2], increased bronchial responsiveness [3], higher rate of hospitalisation for chronic obstructive pulmonary disease [4], and higher risk of respiratory symptoms [5]. There are, however, conflicting reports on sex differences for the negative effect on lung function of tobacco smoking [2, 6]. Even if there are sex-related differences in perception, reporting and interpretation of respiratory symptoms and diseases [7], a symptom like shortness of breath is found to be associated with quality of life and to predict mortality equally well in both sexes [8]. It has therefore been proposed that respiratory symptoms are more related to general health in females and are more specific for respiratory and cardiac diseases in males.

The objective of this study was to analyse the effect of tobacco smoking on lung function, and to study the association between respiratory symptoms, lung function and global self-rated health (SRH) in males and females.

Materials and methods

In 1995–1997 all inhabitants of the Nord-Trøndelag County, Norway, aged ⩾20 yrs were invited to the adult part of the Nord-Trøndelag Health Study (HUNT). The invitation included a comprehensive questionnaire on health, diseases, symptoms and risk factors. At the screening station, a further questionnaire with more disease-specific questions was asked. Among the participants in the HUNT study, two groups were invited to the Bronchial Obstruction in Nord-Trøndelag (BONT) study, phase I including: 1) a 5% random sample of the total population; and 2) a symptom group with positive answers to questions either on ever-asthma, ever-use of asthma medication or attacks of wheezing or breathlessness during the last 12 months. A third questionnaire focusing on respiratory symptoms was also given to those invited to the BONT study and those reporting persistent cough in questionnaire I (fig. 1). The questions concerning respiratory illnesses, diseases and smoking habits have been published previously [5]. The question on SRH; "How is your health at the moment?" could be answered as "poor", "not well", "well" and "very well" [9].

The BONT study phase I consisted of flow/volume spirometry and a structured, personal interview on respiratory symptoms, diagnosis and treatment. Flow/volume spirometry was recorded with three pneumotachographs (MasterScope spirometer, version 4.15; Erich Jaeger GmbH, Wuerzburg, Germany) by trained staff in accordance with recommendations by the American Thoracic Society [10]. The predicted forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were calculated using prediction equations estimated for this population [11].

The study was approved by the Regional Committee for Ethics in Medical Research and the Norwegian Data Inspectorate.

Analysis

Descriptive data are presented as mean±SD as well as mean and 95% confidence interval (CI). Analyses of variance were

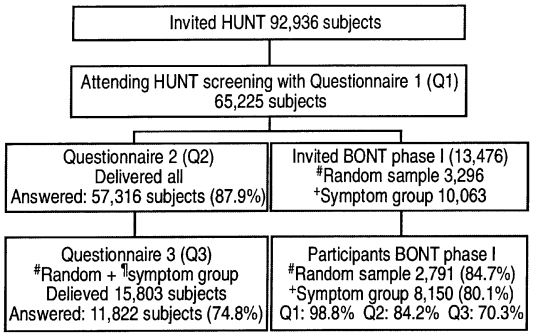


Fig. 1.–Participants and responders of questionnaires in the Nord-Trøndelag Health Study (HUNT) and the Bronchial Obstruction in the Nord Trøndelag (BONT) study 1995–1997. #: 5% random sample of the total population; ¶: subjects reporting ever having had asthma or asthma-related symptoms during the last 12 months, or long-standing cough; +: subjects reporting ever having had asthma or asthma-related symptoms during the last 12 months.

used for continuous data. Linear regression analysis was used to evaluate the impact of independent variables on lung function, and logistic regression to evaluate the impact of independent variables on the risk of symptom reporting and global SRH. Interactions between the independent variables were tested and the results are reported where statistically significant. SRH was used as a dependent variable both in separate models for each level of SRH and as one dichotomised variable (negative=poor or not well, positive= well or very well) in the logistic regression models. Sex differences were tested including interactions in the regression models. In the analysis of the association between tobacco smoking and lung function, only never- and current smokers were included. For linear regression models, the assumptions of linearity and homogeneity were tested, and goodness of fits for logistic regression models were tested with Hosmer Lemeshow tests. All p-values were two-tailed, and a $p<0.05$ was considered significant.

Estimation of the prevalence of symptoms in the population was restricted to the 5% random sample. In the further analyses the group reporting respiratory symptoms was also included.

Subjects, who reported both "ever-asthma" (having had asthma at one time or another) and attacks of wheezing or breathlessness during the last 12 months, were defined as having current asthma. Chronic bronchitis was defined as reported cough with phlegm in periods of at least 3 months during the last 2 yrs.

The smoking status was classified as never-smokers (never smoked daily), exsmokers (ceased smoking ≥ 1 yrs earlier) and current daily smokers. The latter two groups were classified as ever-smokers. Number of pack-yrs was calculated as: years of smoking multiplied by number of cigarettes a day divided by 20. Those reporting only current pipe smoking (0.9% males and 0.1% females) or cigar/cigarillos smoking (0.2% males and 0.1% females) were categorised as current daily smokers, but number of pack-yrs could not be estimated.

Results

Participants and smoking history

In total, 65,225 subjects (71%) attended the HUNT study and 10,941 subjects participated in BONT phase I (fig. 1). The 5% random sample did not differ from the total screening population regarding demographical characteristics, respiratory symptoms and smoking habits except for a slightly higher prevalence of reported daily coughing (17.6 *versus* 15.8%), chronic bronchitis (5.1 *versus* 4.0%) and never-smokers (41.1 *versus* 38.3%) in males, in the random sample (all $p<0.05$).

Amongst all participants at the screening, there was a minor difference in prevalence of current smokers among females and males (30.6 *versus* 29.6%, $p=0.01$), and in the random and symptom group, a corresponding but nonsignificant difference was found (table 1). Amongst all participants, ever-smoking males reported a higher daily cigarette consumption (13.1 *versus* 9.7 cigarettes) and had started to smoke at a younger age (18.4 *versus* 19.8 yrs) compared with females ($p<0.001$). The current smoking females were significantly younger than males (45.7 *versus* 50.2 yrs), in contrast to never-smokers (52.7 *versus* 44.4 yrs) (both $p<0.01$). Further, 64% of all participants reported exposure to passive smoking in childhood and 60% reported this in adulthood. Amongst never-smokers, 48% of females and 35% of males reported exposure to passive smoking in adulthood ($p<0.01$).

Respiratory symptoms, diagnosis and tobacco smoking

Adjusted for age and body mass index (BMI), females had a significantly higher risk per 10 pack-yrs of reporting attacks of wheezing or breathlessness (odds ratio (OR) 1.38 *versus* 1.25), current asthma (1.30 *versus* 1.15), and persistent cough (1.48 *versus* 1.32) (all $p<0.01$) compared with males, when all participants in the main screening were included in the analyses [5]. A similar relationship was found among participants at BONT phase I, and statistically significant differences were found even when an intermediate variable, such as lung function (FEV_1 % predicted) and the interaction term sex * FEV_1 % pred were included in the model (data not shown). Analyses of the interview data revealed that females, adjusted for age and BMI, had significantly greater risk than males of reporting wheezing (OR 1.38 (95% CI 1.35–1.45) *versus* 1.25 (1.20–1.30)) and breathlessness (1.18 (1.11–1.24) *versus* 1.08 (1.04–1.12)) per 10 pack-yrs. Inclusion of the group (random sample or symptom group) as an independent variable did not alter these results.

Exposure to tobacco smoking in childhood was significantly associated with the risk of reporting attacks of wheezing or breathlessness in females (1.20 (1.10–1.30)) but not in males, when age, pack-yrs, BMI, and smoking category (never, ex- or current smoker) were included as independent variables. Exposure to passive smoking after the age of 20 yrs, included in a similar model, was also associated with increased risk of these symptoms, but in this case, no difference with sex was found (1.23 (1.16–1.31)).

In the random sample, 8.7% of both females and males reported doctor-diagnosed asthma. Further, doctor-diagnosed chronic bronchitis/emphysema was reported by 2.3% females and 4.0% males ($p<0.01$), but the difference became statistically insignificant when adjusted for BMI, FEV_1 % pred and pack-yrs. Smoking burden was not associated with being given the diagnosis of asthma by a doctor, but the OR for the diagnosis of chronic bronchitis/emphysema was 2.3 per pack-yr in both sexes.

Lung function and exposure to tobacco smoking

Tobacco smoking was associated with lower lung function in all age groups, the greatest decline being found in current smokers (fig. 2a and b). Correspondingly, passive smoking after the age of 20 yrs, adjusted for age and pack-yrs, was

Table 1. – Demographical data, lung function, smoke history, reported respiratory symptoms and global self-rated health (SRH), among participants in the Bronchial Obstruction in Nord-Trøndelag (BONT) study phase I random sample (5% random sample of the total population) and symptom group (those reporting ever having had asthma, ever use of asthma medications or attacks of wheezing or breathlessness during the last 12 months)

Characteristics	5% Random sample		Symptom group#	
	Females	Males	Females	Males
Number¶	1510 (85.5)	1281 (83.7)	4254 (82.2)	3896 (79.4)
Age yrs	49.6±16.5	50.1±16.1	50.1±17.1	51.5±17.0
Weight kg	70.8±12.5	83.7±12.4	72.7±14.2	84.4±13.7
Height cm	163.9±6.4	177.4±7.1	163.7±6.4	176.6±6.7
Body mass index $kg \cdot m^{-2}$	26.3±4.4	26.5±3.4	27.2±5.2	27.0±3.9
Lung function				
FEV1 L+	2.80 (96.4)	3.82 (94.3)	2.56 (88.6)	3.40 (84.8)
FVC L+	3.44 (97.5)	4.85 (97.3)	3.25 (92.6)	4.52 (92.2)
Smoking habit				
Never-smoker	50.7	41.1**	43.1	29.7**
Exsmoker	18.9	29.3**	19.5	33.9**
Current smoker	30.0	29.6	37.3	36.2
Pack-yrs in ever smokers§	11.5±8.8	15.5±14.8**	12.9±9.9	17.9±15.6**
Respiratory symptoms/diseases				
Attacks of wheezing or breathlessness during the last 12 months	13.7	13.9	73.0	73.3
Ever having had asthma	8.6	8.4	54.5	53.4
Ever having used asthma medication	8.1	7.9	53.3	46.6**
Current asthma	5.6	4.6	33.8	30.9**
Daily coughing in periods	15.3	17.6**	47.8	44.4**
Cough with phlegm	8.4	10.2	27.9	28.7
Chronic bronchitis	3.2	5.1*	12.6	14.4*
Global SRH				
Poor	1.5	1.6	3.3	4.2*
Not so good	27.4	23.1*	44.8	39.9**
Good	56.4	59.1	44.8	49.1**
Very good	14.7	16.1	7.1	6.8

Data are presented as mean±SD or mean (%) unless otherwise stated. #: excluded those who reported symptoms in the 5% random sample; ¶: (per cent of those invited to BONT phase I among participants at the main screening); +: % predicted; §: adjusted by age. In each sample the difference by sex was tested by the Chi-squared test for proportions and variance analyses for mean number of pack-yrs. FEV1: forced expiratory flow in one second; FVC: forced vital capacity; SRH: self related health. *: $p<0.05$; **: $p<0.01$.

associated with 1.5% lower FEV1 % in both sexes ($p<0.05$), compared with nonexposed. When the analyses were restricted to never-smokers, a minor and nonsignificant ($p=0.07$) lower FEV1 % pred was found in females exposed to passive smoking compared with those without such exposure (fig. 2b).

Decreased FVC, FEV1, FEV1/FVC (fig. 3), and forced expiratory flow at 25–75% of forced vital capacity (FEF25–75) (data not shown) were associated with tobacco smoking in ever smokers according to both pack-yrs and current daily cigarette consumption ($p<0.01$ for trend). No sex difference in absolute values was found for any of the lung function parameters and this was independent of age. Age and height adjusted FEV1, FVC and FEF25–75 were associated with a reduction of 12, 10, and 27 $mL \cdot s^{-1}$ per pack-yr, respectively. However, this means that females have a larger reduction in these lung function parameters in % pred terms than males. One pack-yr was associated with 0.52 and 0.32% lower FEV1 % pred in females and males ($p<0.001$), respectively, and the corresponding figures for FVC% reduction were 0.28 and 0.16% ($p<0.001$).

Respiratory symptoms, diagnosis, and self-rated health by lung function and sex

Females reported a higher prevalence of wheezing or breathlessness and coughing, independent of FEV1 % pred, compared with males for both the total BONT sample (fig. 4) and when the analyses were restricted to only the 5% random sample. Further, females aged >60 yrs had significantly higher FEV1 % pred compared with males, regardless of reporting respiratory symptoms or doctor-diagnosed respiratory disease ($p<0.01$) (fig. 5).

In the total BONT sample, SRH was reported to be "poor" in 2% and "very well" in 16% of cases, independent of sex. Independent of lung function, the category "well" was reported by fewer females than males (23.2 *versus* 27.8%), with reciprocal results in the category "not very well" (both $p<0.01$). A similar pattern was found for SRH, dichotomised in those reporting "positive" and "negative" score by FEV1 % pred adjusted for age and pack-yrs (fig. 6).

A decreased score in SRH was associated with specific respiratory symptoms, including attacks of wheezing, breathlessness, or cough, without any difference with sex. These results were not significantly influenced by pack-yrs, level of education and BMI as covariates in the model.

Discussion

A higher proportion of females reported respiratory symptoms compared with males, adjusted for smoking burden and lung function. Further, reporting of respiratory symptoms was associated with poorer SRH in both sexes, but females reported poorer SRH compared with males independent of

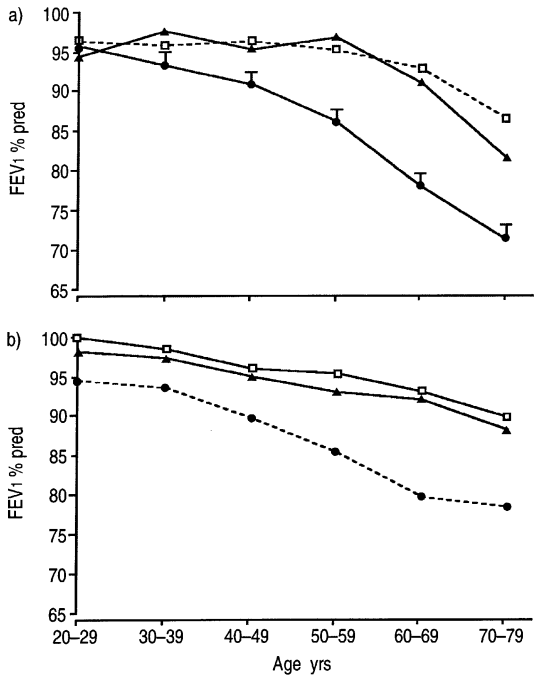


Fig. 2.–Forced expiratory volume in one second (FEV1) in % predicted by age, among never-smokers exposed (▲) and not exposed (□) to passive smoke, and among ever-smokers (●) in a) males and b) females.

lung function. The results from this study confirm previous findings of a dose-dependent increase in prevalence of respiratory symptoms and a corresponding negative effect on lung function with tobacco smoking [12]. However, females had a larger reduction in lung function in terms of % pred than males.

BONT was part of a comprehensive cross-sectional study

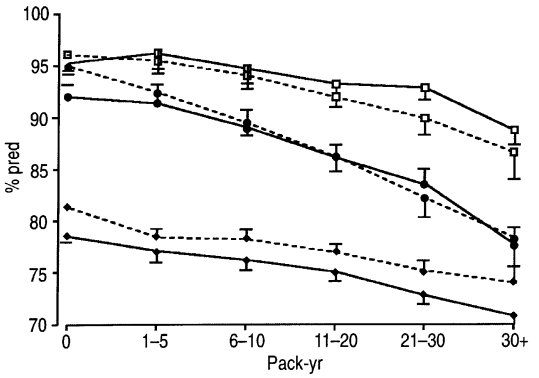


Fig. 3.–Age-adjusted forced expiratory volume in one second (FEV1) (□), forced vital capacity (FVC) (●) as % predicted and FEV1/FVC (◆) by pack-yrs in males (–) and females (------) in the total Bronchial Obstruction in the Nord Trøndelag study group (random sample 2,791 subjects and symptom group 8,150 subjects).

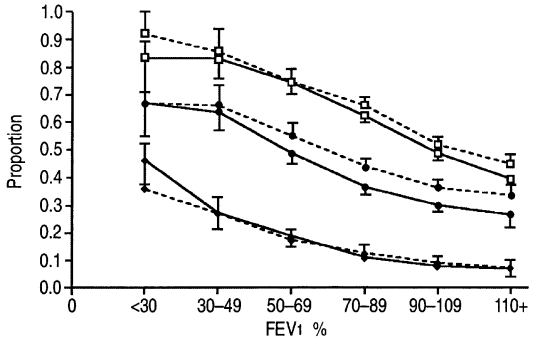


Fig. 4.–Proportion of subjects in the Bronchial Obstruction in the Nord Trøndelag study sample reporting respiratory symptoms by forced expiratory volume in one second (FEV1) % predicted in males (–) and females (------), adjusted by age and pack-yrs. □: wheeze or breathlessness; ●: daily cough in periods; ◆: chronic bronchitis.

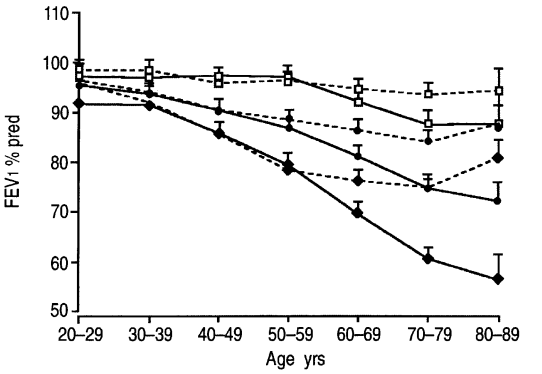


Fig. 5.–Forced expiratory volume in one second (FEV1) % predicted in males (–) and females (------), reporting no respiratory symptoms and respiratory symptoms with and without diagnosis of respiratory disease, by age. □: no respiratory symptoms; ●: respiratory symptoms; ◆: respiratory symptoms and doctor diagnosed asthma or chronic bronchitis/emphysema.

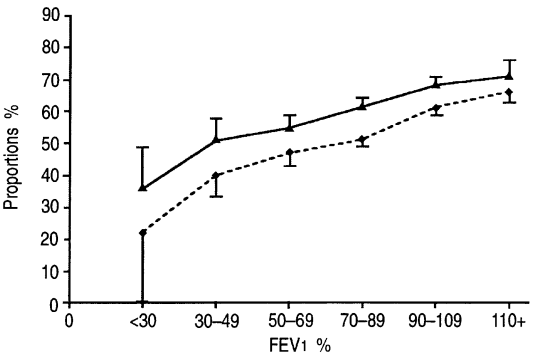


Fig. 6.–Age and pack-yrs adjusted proportions (%) reporting "very well" or "well" to questioning on self-rated global health by forced expiratory volume in one second (FEV1) and sex, with 95% confidence intervals in the total Bronchial Obstruction in the Nord Trøndelag study sample. ▲: males; ◆: females.

of a complete adult population, including a 5% representative random sample of the total population and a symptom group, both with high attendance rate [5]. A study of non-responders at the main screening did not reveal any specific selection biases [5]. The level of industrial and traffic pollution is very low in Nord-Trøndelag County, Norway, the population is homogenous, and the combination of questionnaires and interviews secured high-quality data for the explored risk factors. Nevertheless, the authors fully realise the limitations of the cross-sectional design, and therefore report presence of associations and not causal relationships.

Tobacco smoking and lung function

Tobacco smoking has a noxious effect on the airways. In this study, a strong, dose-dependent association between tobacco smoking and reduced FEV1, FVC and FEV1/FVC was found in both sexes. This is in agreement with the results from a meta-analysis of eight large US population-based studies [6] and a longitudinal study from Netherlands [13]. But, other cross-sectional studies, such as the Beijing respiratory health study [2], a Canadian study [14], the French Cooperative study [8], the Tucson Airways study [15] and both a cross-sectional and longitudinal study from Copenhagen [4, 16] have reported a greater decline in lung function among females than males, associated with tobacco smoking. On the other hand, opposite results have been found in both cross-sectional and longitudinal studies, such as the Six Cities study [17], the Tucson Airways Study [18], the cross-sectional part of the Netherlands study [13], the Copenhagen study (after redefining exclusion criteria, but not adjusting for quantity smoked) [19], an Italian study [20] and the UCLA study from Los Angeles [21]. Comparisons between cross-sectional and longitudinal studies are distorted, as those with better lung function are more likely to continue in longitudinal studies [13].

The healthy-smoker effect (*i.e.* without respiratory symptoms) and different smoking prevalence could partly explain the divergent results found in previous studies, when never-smokers are used as reference groups. XU *et al.* [22] showed that in the studies reporting greater smoking effects on lung function in females than in males, there was a relatively low prevalence of male never-smokers (11–25%), whilst the opposite results were found in studies with higher prevalence of male never-smokers (27–43%). Given that "unhealthy" subjects (*i.e.* with respiratory symptoms) are a constant proportion of the population, and because such subjects with respiratory and cardiovascular diseases have a lower tendency to start or continue smoking compared with healthy subjects, the proportion of these in a never-smoking reference group would be higher in populations with a low prevalence of never-smokers. Any smoke-related difference between smokers and never-smokers would then be diluted. The present study, with a prevalence of never-smokers of 38.3% in males and 49.7% in females, is probably not prone to such prevalence effects.

Different sex effects of tobacco smoking could also be influenced by the fact that female never-smokers were older than female smokers, in contrast to that was found in males, but adjustments for age should take account of this.

Tobacco smoking and respiratory symptoms

The authors have previously reported that adjusted for age and smoking burden, more females than males reported respiratory symptoms, such as wheezing, breathlessness and cough without phlegm [5]. In the present study, similar sex associations independent of lung function were found, and significant higher FEV1 % pred in females compared with males aged >60 yrs in asymptomatic and symptomatic subjects, independent of doctor-diagnosed lung disease or not. Even if tobacco smoking in females was associated with greater percentage reduction in FEV1, FVC, and FEF25–75 compared with males, this does not fully explain the discrepancy in symptom reporting related to smoking burden between sexes. There are many different contributory factors to this. First, females might be more aware of illness and diseases than males. Assuming that FEV1 and FVC reflected all deleterious effects of tobacco smoking in the airways, the present results of a higher prevalence of symptom reporting in females compared with males at similar levels of lung function, would have supported such an explanation. However, conflicting results on this issue have been reported. MACINTYRE *et al.* [23] did not find any sex differences in the reporting of conditions, including trivial and mental conditions. Further, GIJSBERS *et al.* [24] found that even if females, when compared with males, reported more physical symptoms, they reported similar illness behaviour. In addition, different work exposure rather than different vulnerability has been found to explain sex differences in health [25].

Secondly, there could be a selection bias among current smokers if symptomatic males succeeded in smoking cessation more often than symptomatic females. In the present population, males reported smoking cessation more frequently than females, regardless of reporting respiratory symptoms [5]. However, even if analyses revealed a lower OR for respiratory symptoms by number of pack-yrs when the analyses were restricted to never-smokers/exsmokers compared with never-smokers/current smokers, similar difference with sex in reporting symptom by pack-yr was found (data not shown).

Thirdly, respiratory symptoms might be more strongly associated with global health and less specific for lung diseases in females compared with males [8]. The authors' assessed global health by using a SRH measure with four steps, as this had been used previously in Norwegian population-based studies [9]. Generally, the differences between SRH measures are marginal, females' rate poorer or similar to males, and in both sexes SRH measurements are found to be powerful predictors of future morbidity and mortality [26]. In the present study, the association between respiratory symptoms and SRH was independent of sex, indicating a similar influence of respiratory symptoms on quality of life in males and females, independent of objective measurements, such as flow volume spirometry. Higher risk for reporting SRH "not very well" by pack-yr among females than among males is consistent with sex difference in association between pack-yrs and respiratory symptoms.

Fourthly, sex differences in symptoms could be due to differences in airway diameter. As the resistance to flow in a tube is inversely proportional to the fourth power of its radius, a similar reduction in radius in a small and large tube would influence the flow most in the former. In the present study, when including FEV1 % pred and thus taking different airway calibre into account, the sex difference in respiratory symptoms was still present, as also found by LEYNAERT *et al.* [3].

Fifthly, symptoms could be a more sensitive parameter of vulnerability in the peripheral airways, compared with FEV1 and FVC, reflecting changes mainly in the larger airways. There are differences in airway calibre and lung size between males and females of the same size, and this might influence the deposition of tobacco-smoke products [27]. Females with smaller airway diameter would thus theoretically be more vulnerable to noxious gases deposited in the peripheral airways. Experimental studies by WAGNER *et al.* [28] on

patients with mild asthma, showed a considerable increase in peripheral resistance, despite having a normal lung function measured as FEV1 and FVC. WAGNER *et al.* [28] also showed a strong correlation between increase in peripheral resistance and degree of bronchial hyperresponsiveness to methacholine. Interestingly, studies have shown a higher smoke-related bronchial hyperresponsiveness in females compared with males [3] and lower cough threshold in females than males when they were exposed to cough stimuli (capsaicin) [29]. Further measurements of bronchial hyperresponsiveness in population-based studies might clarify this. So far, these have been mainly direct provocation tests (methacholine and histamine), but results regarding sensitivity and specificity of studies of simpler, indirect tests (mannitol) are promising for inclusion of such tests in large-scale studies [30].

Sixthly, there could be sex differences in validity of self-reported smoking behaviour and of inhalation pattern and exposure for passive smoking. Both estimation of pack-yrs and smoking behaviour have been reported to be fairly accurate in most studies [31, 32]. The authors do not have data on whether there are different inhalation patterns between sexes. Due to a higher prevalence of smokers and smoking burden in males compared with females, both smoking and nonsmoking females have probably been exposed to more passive smoking than males, and this would dilute any deleterious effect of tobacco smoking in females compared with males. However, including passive smoking in the analyses did not influence the results in the present study.

To conclude, smoking burden was associated with similar absolute reduction in expiratory lung function measures in males and females, meaning that females had larger relative reductions in lung function. However, adjusted for age and pack-yrs, more females than males reported respiratory symptoms and the category "not very well" on self-rated health, adjusted for lung function. The associations between respiratory symptoms and self-rated health were independent of sex. This might support the hypotheses that females have greater perceived vulnerability for the deleterious effect of tobacco smoking than males. Whether this increased perception of symptoms are reflecting unmeasured pathological changes in the peripheral airways in addition to changes reflected by lung function measurements such as forced expiratory volume in one second or forced vital capacity, cannot be answered in this study. Use of more sophisticated lung function measurements and/or prospective follow-up of those with and without reported symptoms are possible ways of establishing whether symptom perception is a more sensitive tool indicating early deteriorating changes in the lower airways.

Acknowledgements. The Nord-Trøndelag Health Study (the HUNT study) is a collaboration between the HUNT Research Centre, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Verdal, the National Institute of Public Health, the National Health Screening Service of Norway, and Nord-Trøndelag County Council. The authors would like to thank D. Price for language and content review.

References

1. Gold DR, Wang X, Wypij D, Speizer FE, Ware JH, Dockery DW. Effects of cigarette smoking on lung function in adolescent boys and girls. *N Engl J Med* 1996; 335: 931–937.
2. Xu X, Li B, Wang L. Gender difference in smoking effects on adult pulmonary function. *Eur Respir J* 1994; 7: 477–483.
3. Leynaert B, Bousquet J, Henry C, Liard R, Neukirch F. Is bronchial hyperresponsiveness more frequent in women than in men? A population-based study. *Am J Respir Crit Care Med* 1997; 156: 1413–1420.
4. Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. *Eur Respir J* 1997; 10: 822–827.
5. Langhammer A, Johnsen R, Holmen J, Gulsvik A, Bjermer L. Cigarette smoking gives more respiratory symptoms among women than among men. *J Epidemiol Community Health* 2000; 54: 917–922.
6. Vollmer WM, Enright PL, Pedula KL, *et al.* Race and gender differences in the effects of smoking on lung function. *Chest* 2000; 117: 764–772.
7. Kauffmann F, Becklake MR. Sex and Gender. *Eur Respir Mon* 2000; 5: 288–304.
8. Kauffmann F, Becklake MR. Maladies respiratoires obstructives. Un paradigme de la complexité des différences de santé entre femmes et hommes. *In*: Saurel-Cubizolles MJ, Blondel B, eds. La santé des femmes. Paris, Médecine-Sciences, 1996; pp. 209–233.
9. Wøien G, Øyen O, Graff-Iversen S. 22 years of cardiovascular surveys in Norwegian counties. Is the development in risk factors satisfactory? *Nor J Epidemiol* 1997; 7: 255–266.
10. American Thoracic Society. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995; 152: 1107–1136.
11. Langhammer A, Johnsen R, Gulsvik A, Holmen TL, Bjermer L. Forced spirometry reference values for Norwegian adults: the bronchial obstruction in Nord-Trondelag Study. *Eur Respir J* 2001; 18: 770–779.
12. American Thoracic Society. Cigarette smoking and health. *Am J Respir Crit Care Med* 1996; 153: 861–865.
13. van Pelt W, Borsboom GJ, Rijcken B, Schouten JP, van Zomeren BC, Quanjer PH. Discrepancies between longitudinal and cross-sectional change in ventilatory function in 12 years of follow-up. *Am J Respir Crit Care Med* 1994; 149: 1218–1226.
14. Chen Y, Horne SL, Dosman JA. Increased susceptibility to lung dysfunction in female smokers. *Am Rev Respir Dis* 1991; 143: 1224–1230.
15. Burrows B, Knudson RJ, Cline MG, Lebowitz MD. Quantitative relationships between cigarette smoking and ventilatory function. *Am Rev Respir Dis* 1977; 115: 195–205.
16. Lange P, Groth S, Nyboe GJ, *et al.* Effects of smoking and changes in smoking habits on the decline of FEV1. *Eur Respir J* 1989; 2: 811–816.
17. Xu X, Dockery DW, Ware JH, Speizer FE, Ferris BGJ. Effects of cigarette smoking on rate of loss of pulmonary function in adults: a longitudinal assessment. *Am Rev Respir Dis* 1992; 146: 1345–1348.
18. Camilli AE, Burrows B, Knudson RJ, Lyle SK, Lebowitz MD. Longitudinal changes in forced expiratory volume in one second in adults. Effects of smoking and smoking cessation. *Am Rev Respir Dis* 1987; 135: 794–799.
19. Lange P, Groth S, Nyboe J, *et al.* Decline of the lung function related to the type of tobacco smoked and inhalation. *Thorax* 1990; 45: 22–26.
20. Viegi G, Paoletti P, Prediletto R, *et al.* Prevalence of respiratory symptoms in an unpolluted area of northern Italy. *Eur Respir J* 1988; 1: 311–318.
21. Tashkin DP, Clark VA, Coulson AH, *et al.* The University College of Los Angeles (UCLA) population studies of chronic obstructive respiratory disease. VIII. Effects of smoking cessation on lung function: a prospective study of a free-living population. *Am Rev Respir Dis* 1984; 130: 707–715.
22. Xu X, Weiss ST, Rijcken B, Schouten JP. Smoking, changes in smoking habits, and rate of decline in FEV1: new insight into gender differences. *Eur Respir J* 1994; 7: 1056–1061.

23. Macintyre S, Ford G, Hunt K. Do women 'over-report' morbidity? Men's and women's responses to structured prompting on a standard question on long standing illness. *Soc Sci Med* 1999; 48: 89–98.
24. Gijsbers VWC, Huisman H, Kolk AM. Gender differences in physical symptoms and illness behavior. A health diary study. *Soc Sci Med* 1999; 49: 1061–1074.
25. Emslie C, Hunt K, Macintyre S. Gender differences in minor morbidity among full time employees of a British university. *J Epidemiol Community Health* 1999; 53: 465–475.
26. Eriksson I, Unden AL, Elofsson S. Self-rated health. Comparisons between three different measures. Results from a population study. *Int J Epidemiol* 2001; 30: 326–333.
27. Mead J. Dysanapsis in normal lungs assessed by the relationship between maximal flow, static recoil, and vital capacity. *Am Rev Respir Dis* 1980; 121: 339–342.
28. Wagner EM, Liu MC, Weinmann GG, Permutt S, Bleecker ER. Peripheral lung resistance in normal and asthmatic subjects. *Am Rev Respir Dis* 1990; 141: 584–588.
29. Fujimura M, Kasahara K, Kamio Y, Naruse M, Hashimoto T, Matsuda T. Female gender as a determinant of cough threshold to inhaled capsaicin. *Eur Respir J* 1996; 9: 1624–1626.
30. Leuppi JD, Brannan JD, Anderson SD. Bronchial provocation tests: The rationale for using inhaled mannitol as a test for airway hyperresponsiveness. *Swiss Med Wkly* 2002; 132: 151–158.
31. Patrick DL, Cheadle A, Thompson DC, Diehr P, Koepsell T, Kinne S. The validity of self-reported smoking: a review and meta-analysis. *Am J Public Health* 1994; 84: 1086–1093.
32. Bernaards CM, Twisk JW, Snel J, Van Mechelen W, Kemper HC. Is calculating pack-years retrospectively a valid method to estimate life-time tobacco smoking? A comparison between prospectively calculated pack-years and retrospectively calculated pack-years. *Addiction* 2001; 96: 1653–1661.

Paper IV

Use of inhaled corticosteroids and bone mineral density in a population based study.

The Nord-Trøndelag Health Study (The HUNT Study)

Arnulf Langhammer[1], Ensio Norjavaara[2,3], Maria Gerhardsson de Verdier[3], Roar Johnsen [4], Leif Bjermer[5]

[1] HUNT Research Centre, Norwegian University of Science and Technology (NTNU), Verdal, Norway, [2] The Göteborg Paediatric Growth Research Centre, University of Göteborg, Göteborg, Sweden, [3]AstraZeneca R&D, Lund, Sweden, [4] Department of Community Medicine and General Practice, NTNU, Trondheim, Norway, [5]Department of Respiratory Medicine and Allergology, University Hospital, Lund, Sweden.

Funding sources: AstraZeneca, Norwegian Research Council, Norwegian Osteoporosis Foundation

Running title: Inhaled corticosteroids and bone mineral density

Contact person: Dr. A. Langhammer, Hunt Research Centre, Norwegian University of Science and Technology (NTNU), Neptunveien 1, N-7650 Verdal, Norway

Phone: +47 74 07 51 87 Fax: +47 74 07 51 81

Email: arnulf.langhammer@medisin.ntnu.no

Text: Number of words: 3,552 (abstract and references not included)

Abstract: Number of words: 250

Number of figures: 2 Number of tables: 4

25.06.03

Abstract

Conflicting results have been reported of the long-term effect of treatment with ICS on bone. The objective of this study was to compare ICS users and non-users regarding bone mineral density (BMD) in a large population.

A total of 65.225 adults participated in a cross-sectional study in the Nord-Trøndelag Health Study 1995-97. Those reporting asthma or asthma-related symptoms were invited to have bone densitometry of the forearm, flow volume spirometry and a personal interview. Altogether 4,482 women and 4,142 men participated, of whom 2,113 reported ever use and 6,511 never use of ICS.

Never-users of corticosteroids had a mean BMD, adjusted for confounders (age, square age, sex, body mass index, height, physical activity, work load, pack-years, family history of osteoporosis, and in women number of years since menopause and use of hormone replacement therapy), of 0.493 g/cm^2 at the distal site. Subjects having only used ICS or combined with courses of prednisolone, had 0.010 g/cm^2 (95% CI 0.007 – 0.013) lower BMD whilst users of prednisolone $\geq$ 6 months had 0.038 g/cm^2 (0.021 – 0.055) lower level. No dose response association between ICS and BMD, or difference in BMD by type of ICS was found. The association between CS use and BMD was independent of the measuring site.

ICS use was associated with lower BMD. The lack of dose response in this study might be due to a narrow dose range or indicate that other characteristics of the patient group are contributing to the observed difference in ICS users compared to never-users.

25.06.03

Key words:
Asthma, bone mineral density, corticosteroids, chronic obstructive pulmonary disease, cross-sectional study, forearm, inhaled corticosteroids, and single x-ray absorptiometry.

Take-home messages

- Bone mineral density (BMD) of the forearm was compared between 2,113 users and 6,511 never-users of inhaled corticosteroid (ICS)
- Compared to never-users, users of ICS had 2 % and users of prednisolone $\geq$ 6 months had 8 % lower BMD both at the distal and ultradistal site.
- No dose response association was found between daily dose, duration of use or cumulative dose of ICS and BMD

25.06.03

URN:NBN:no-3454

Introduction

Airway inflammation is believed to play a prominent role in asthma, and the efficacy of inhaled corticosteroids (ICS) in its treatment was established during the 1980s and 1990s. Today, ICS are recommended as first line therapy for mild persistent and more severe forms of asthma (1), and are often used in patients with chronic obstructive pulmonary disease (COPD) despite poor evidence (2-4). However, as oral corticosteroids (OCS) decrease bone mineral density (BMD) and increase the risk of fractures (5-7), there is concern regarding similar long-term effects with inhaled corticosteroid (ICS) usage in patients with chronic asthma and chronic obstructive pulmonary disease (COPD) (6). Studies with ICSs have not shown an increased risk for fractures, but results of studies on their effect on BMD are conflicting (8-10). Of course, BMD measurement cannot identify subjects with future fractures, but independent of measuring site, one SD reduction in BMD is associated with an increase in overall fracture risk of about 1.5 (11).

Most studies on ICS and BMD have included small groups of patients, and studies of "real life" effects of ICS use on BMD is lacking. The objective of this large population based study was to evaluate the association between self reported use of ICS and OCS on BMD of the forearm among persons reporting having had asthma or asthma related symptoms without exclusion of COPD patients.

Materials and Methods

Participants

In 1995-97 all residents aged at least 20 years (92,936) of Nord-Trøndelag County, Norway, were invited to participate in the Nord-Trøndelag Health Study (The HUNT Study) (12), which included questions on respiratory disease. Those who reported previous or current asthma, use of asthma medication, or asthma-related symptoms during the last 12 months were invited to participate in the Bronchial Obstruction in Nord-Trøndelag Study (BONT) phase I.

Measurements

The BONT study phase I included bone densitometry, flow volume spirometry according to ATS recommendations (MasterScope spirometer, version 4.1,Erich Jaeger GmbH, Wuerzburg, Germany), and a personal interview. The non-dominant forearm was assessed with Single Energy X-ray Absorptiometry (SXA) (Osteometer DTX 100, Osteometer AS, Copenhagen). In case of previous fracture in the non-dominant wrist, the dominant forearm was assessed. Starting from a point where the distance between radius and ulna was 8 mm, the distal site was defined as 24 mm in a proximal direction of the ulna and radius, whilst the ultra-distal site was defined as the area of radius distal to this excluding the endplate.
All sites for measurement were manually controlled and corrected (13).

Questionnaires and interview

Questionnaires covered smoking history, respiratory symptoms/diseases, use of asthma medication, family history of osteoporosis, fractures of the hips or forearm (Table 1), intake of vitamins, physical activity, chronic diseases, education, and occupation. Women also

answered questions about menstrual history and use of hormonal replacement therapy. At the time of the study bisphosphonates were not registered for use in Norway, and these are therefore not asked for. The questions on life style/risk factors are being used in many Norwegian population-based studies, but validation studies have only been performed on the questions on physical activity in leisure time, tobacco smoking and self-reported fractures (14).

The interview focused on asthma related symptoms, with questions identical to those used in the European Community Respiratory Health Survey (15), current treatment and all previous treatment with corticosteroids for any reason except for dermatological diseases. The subjects identified previous and current inhalation devices on coloured pictures.

Statistical analysis

Analyses

The Statistical Package for the Social Sciences version 10.0 (SPSS Inc, Chicago, Illinois) was used. Sex stratified associations, adjusted by squared age, between potential risk factors and distal and ultra distal BMD were explored in linear regression analyses (Table 2). Further, these risk factors, and data on thyroid disease or use of thyroxin, were tested by multiple linear regression models with BMD as dependent variable. Commonly used independent variables were tested (16), and variables contributing significantly to the explained variance as age, squared age, height, pack-years, physical activity, work physical load, family history of osteoporosis, and in women years since menopause and use of hormone replacement therapy, were included as covariates in variance analyses and the full multiple regression model. Further, analyses were performed both including and excluding forced expiratory volume in one second in percent of predicted (FEV1 %) in the model. In addition among

users of corticosteroids (CS), independent variables as ever use of CS, daily dose, duration and log cumulative dose of ICS, and dose and duration of oral CS were tested in these models. Dose and duration were included as continuous variables.

Variable definitions:

T-scores of distal and ultradistal BMD were calculated as (observed – mean value) / SD, where mean and standard deviation (SD) were estimated for age group 20-49 years.

The cumulative dose of inhaled corticosteroids in milligrams was calculated as (the daily dose last week) x (duration of use of ICS in years) x 365.

According to CS use, the subjects were put into one of 7 mutually exclusive categories and entered as a 7 level factor. The categories were; a) never use of CS, b) use of only CS injections or nasal CS, c) previous use of ICS with or without OCS, d) current use of ICS and never use of OCS, e) current use of ICS and OCS courses during the last 2 years, f) current use of ICS and use of OCS $\geq$ 6 months, and g) use of OCS for non-respiratory diseases.

Smoking burden was defined as the number of pack-years calculated as (numbers of years of smoking) x (cigarettes a day)/20. For the 10 % of subjects having missing data on smoking, number of pack-years were set to zero.

Physical activity was calculated as the sum of reported hours weekly with light and heavy physical activity, each of these having a positive linear association to BMD.

Subjects reporting never use of OCS but having missing answers on questions regarding the use of nasal CS and injections (the first half of the study population), were included in analyses as never users of ICS. This did not influence the results.

The 324 persons with measurement of the dominant arm because of previous fracture in the non-dominant arm were included in the analyses, as this did not influence the estimates.

25.06.03

Ethics

The study was approved by the Regional Committee for Ethics in Medical Research and the Norwegian Data Inspectorate.

Results

Description of the groups

In all 70.2 % of those invited to the HUNT study attended the screening. Among those invited to the BONT-study for respiratory symptoms/disease 81 % accepted further participation (Fig 1). The prevalence of smokers and smoking burden was higher in this symptom group compared to all participants at screening (37.5 % versus 30.3 % and 15.3 packyears versus 13.0 packyears, $p < 0.001$). Among subjects $\geq$ 45 years 9.4 % of women and 4.4 % of men reported a family history of osteoporosis, and 22 % of women reported use of hormone replacement therapy. Other characteristics of the symptom group are given in table (table 1). Further, they reported a 25-50% higher prevalence of other diseases such as arthrosis, spondyloarthropathies, fibromyalgia and rheumatoid arthritis (data not shown). Including these diseases as covariates in the analyses did not change the BMD in subjects using different categories of CS.

BMD at distal and ultradistal site

The correlation coefficient (Pearson's r) between distal and ultradistal BMD was 0.91 in women and 0.88 in men ($p<0.01$). The associations between confounders or use of CS and BMD were independent of site of measurement (table 2), and further results are therefore given for distal BMD only.

There was a non-linear relationship between BMD and age, and the relationship was best expressed as age plus square age. For the other potential risk factors there were linear relationships with BMD. In those reporting respiratory symptoms during the last 12 months a positive association was found between T-score of BMD and FEV_1 % (regression coefficient 0.007, CI95% 0.005-0.009, $p< 0.01$) adjusted for age, square age, packyears, use of OCS, and use of ICS during the last 6 months. This finding was independent of whether they had received a diagnosis of asthma and chronic bronchitis/emphysema or not. No such association was found among subjects without respiratory symptoms.

Use of corticosteroids

Among the 8,624 subjects included in the analyses 43.4 % reported ever using any CS, 24.5 % ever using ICS, and 17.6 % having used ICS during the last 6 months (Fig 1). Corresponding figures for the total population at the screening were 5.7 %, 3.2 % and 2.3 %, respectively. Among current users of ICS at the time of the screening 78% used budesonide (BUD) (mean daily dose 670 µg), 15% beclomethasone dipropionate (BDP) (mean daily dose 605 µg) and 6% fluticasone propionate (FP) (mean daily dose 793 µg). In total 663 subjects reported daily doses during the last week $\geq$ 800 µg and 717 subjects reported having used ICS $\geq$ 5 years (table 3). Further, the median estimated cumulative dose was 876 mg. Some 88% of women and 81% of men used dry powder inhalers.

In total 652 subjects reported ever using OCS for asthma only, 494 for other diseases only, in addition to 54 subjects for both asthma and other diseases. Nobody reported use of other OCS than prednisolone. Among OCS use for other diseases 17 % reported a diagnosis of rheumatoid arthritis. Among 124 subjects reporting use of OCS for asthma during the last week, the mean and median daily doses were 10.5 mg and 5 mg, respectively. No information

on dose or current use of OCS was available for subjects reporting ever use of OCS for other diseases.

An increasing dose of ICS was associated with increasing age, decreasing FEV_1 and increased use of OCS (Table 4). Those who had used OCS courses reported a higher age-adjusted prevalence of respiratory symptoms, diagnosis of lung diseases, and more use of β_2-agonists than those reporting only use of ICS did.

Corticosteroids and BMD

Compared to non-users the mean distal BMD adjusted for covariates (including sex) was 0.010 (2%) and 0.038 g/cm^2 (8 %) lower in those reporting current use of ICS only and combined with OCS for more than 6 months ($p<0.01$), respectively (Table 4). In the full regression model with distal BMD as dependent variable and the confounders listed in table 4 as independent variables, the adjusted explained variance increased from 64.0 % with less than 0.1% when use of ICS and 0.2% when use of OCS > 6 months was included. If ever smokers were excluded, lower BMD was found among men having used OCS for more than 6 months, in contrast to women where lower BMD also was found in current users of only ICS. Inclusion of FEV_1 % as covariate reduced the negative associations, but these were still statistically significant (regression coefficients –0.126 and –0.447, respectively).
Among those who reported current use of ICS no dose response association was seen between BMD and categories of increasing dose, duration of use, or cumulative dose of ICS (Fig 2). Neither stratification according to FEV1/FVC less or higher than 0.70 nor exclusion of smokers did change this pattern. Correspondingly, dose and duration were not significant explanatory variables when they were tested in the models as continuous variables ($p>0.5$). If

duration of ICS use was stratified into < 1 year, 1-5 year, and > 5 years, a significant negative association between BMD and ICS (in mg), was found in women having used ICS for 1-5 years (regression coefficient – 0.021, 95%CI –0.038, -0.005). This association, however, disappeared when FEV1 % was included as covariate in the model.

No significant difference was found in adjusted mean BMD between different types of ICS. Exclusion of subjects using BDP and FP in the analyses did not influence the results.

Among subjects using OCS for asthma/asthma related symptoms, there was a decreasing BMD by increasing duration of use (p=0.015). No association, however, between BMD and OCS dose used during the last week was found.

Discussion

ICS are recommended as first line therapy for mild persistent and more severe forms of asthma, and are often used in patients with COPD. The widespread and increasing use of ICS make it imperative to examine their long-term side effects, including effects on the bone metabolism, which may have great implications both for society and the individual. The advantage of large retrospective cohort studies, like the BONT study, is the opportunity to study "real life" effects of medication used in a heterogeneous sample. This increases the generalisability of the study. On the other hand, the design implies lower precision of outcome measures and risk factors, and description of associations rather than assessment of causation.

In this study we found lower BMD in those reporting ever use of ICS. We were, however, unable to establish any association between current dose, type of ICS medication, duration of

treatment, or estimated cumulative dose, and BMD. Before making final conclusions it is thus important to consider possible methodological problems that may influence these results.

The measurements

We measured the BMD with SXA of the non-dominant forearm, whilst most other studies on the effect of CS on BMD have been performed with DXA of the spine and hip. However, most of these studies have included < 100 ICS users from selected populations (8;9;17-27). Among the larger studies, Wong et al included 196 asthma patients mainly from hospital settings (16), Lau et al included 106 asthma and COPD patients from a specialist centre (28), and in placebo controlled random clinical trials Tattersfield et al included 238 patients with mild asthma from four countries (29), and the EUROSCOP and the Lung Health Study included both more than thousand COPD patients (30) (31).

Studies have indicated that during CS treatment trabecular bone is affected earlier, more severely, and with increased risk of fractures compared to cortical bone (5). The ultradistal site of the forearm consist of up to 80 % trabecular bone, compared to mainly cortical bone at the distal site (32). Despite this, however, the associations between confounders or use of CS and BMD were independent of site of measurement in the present study. This might be explained by higher content of fatty marrow in trabecular bone at this site compared with the axial skeleton with its large amount of haematopoietic marrow (32). Other factors might be less mechanical load compared to axial skeleton, moderate levels of ICS in this population, or simply an equal long-term effect of CS.

BMD measurements at appendicular sites seem to be as effective as measurements of the central skeleton in identifying patients with low bone mass (32). Lack of expected superiority in this regard for the spine, might be explained by an accuracy error (total error in estimation of the true value) of 8-10 % at this site, compared to 2 % at appendicular sites measured by either SXA or DXA. Further, forearm BMD is a good predictor of future fractures at any site in women (11). Hui et al in a 15 years follow up study found that for each SD decline in BMD at baseline there was an increase in fracture risk of 120 % in younger age groups and 50% in older retirement-home residents (33). Melton et al even reported stronger association to male fragility fractures than BMD at other sites (34). Interestingly, in the present study similar association was indicated for persons aged over 40. Further, we found an increased risk of historical fractures in the wrist or hip by one standard deviation reduction in BMD at the same level as in other prospective and retrospective studies (data not shown) (35).

Contrary to other methods, SXA of the forearm may be assessed in large-scale population-based studies, and should be less influenced by weight and physical activity. The latter might diminish the bias of inactivity among patients with chronic respiratory disease in estimating the effect of use of corticosteroids on BMD.

The present study supports the thinking that SXA of the forearm is sensitive to the effect of different covariates on bone. Regarding CS use, the largest negative association was found between use of OCS and BMD. Physical activity, physical workload, and intake of calcium were positively associated to BMD, whilst smoking burden had the opposite effect in accordance with previous reports (36;37). As reported by others (38), we did not find any indications of a protective effect of intake of vitamin D, cod liver oil, or calcium (data not

shown) probably because of confounding by indication (increased awareness among osteoporotic subjects).

Reported use of corticosteroids

In 1995-1997, BUD was the ICS predominantly used in Nord-Trøndelag County, and the prevalence of subjects on ICS treatment, was similar to previous reports from Norway (15). There was a shift from BDP to BUD in the 1980-s and FP was introduced in the middle of 1990-s. As many patients have used 2-3 different types of ICS, and there still is no consensus as to the relative systemic effects of these, we did not convert reported current dose of ICS to a standard dose of BDP.

All participants were asked about the doses they were currently using instead of the prescribed doses. Naturally, this does not reflect the previous doses exactly, but in lack of registry of medicine prescriptions in Norway, this was the best estimation of exposure available. If there had been a systematic reduction in dose over time prior to the study, this might have biased the findings against finding a dose dependent association between ICS and BMD. The lack of dose relationship between daily dose of ICS and BMD independent of duration of ICS use, indicate that no serious misclassification by exposure is introduced in the analyses. Further, the study was performed prior to changes in guidelines recommending lower doses of ICS combined with other medication. On the other hand, the use of prescribed dose of ICS might also introduce bias in the analyses, because of overestimation of the level of used ICS dose. Low compliance with medical regiments in this patient group is well known (39). Our choice of measure of ICS dose might thereby explain a lower median dose of ICS compared to others (18). Only 17% reported use of daily doses higher than 800 µg, compared to 33% in a population based study in UK (40).

The subjects were asked for all use of CS (except for dermal application). Based on this, we had the opportunity to study oral CS naive ICS users in our study, in contrast to many prior studies having been biased by the use of oral corticosteroids in analyses of ICS use.
The literature on ICS and BMD is inconclusive. We did not find any dose response association between ICS and BMD. Some studies have shown decreasing BMD with increasing dose or cumulative doses of ICSs (16;17;20;24), but most randomised controlled clinical trials have detected no or minor negative effects (9;23;26;29) . Wong et al (16) found a negative association between BMD and cumulative dose and duration of use of ICS, whilst Israel et al reported a dose response between daily dose of ICS and decline in BMD at the trochanter (24).

Negative associations between ICS and BMD have been reported in some studies including use of triamcinolone acetonide, BDP and/or BUD, but not in other studies including BUD and FP (6;8;16;23;26;30;41;42). Combined use of different types of ICS and use of moderate doses in this population might explain why we did not identify any difference between ICSs regarding effect on BMD.

Lack of dose response between ICS and BMD in the present study could be due to a narrow range of doses in this population, as only 10 % of ICS users reported daily doses $\geq$ 900 µg subjects. On the other hand, lower BMD in ICS users might also be associated with other characteristics of this patient group. A large retrospective cohort study in UK on use of ICS and risk of fractures found increased, but similar, risk of fractures in the hip and spine in both users of ICS and bronchodilators compared to the control group. (43). Conflicting results in studies on ICS's and BMD could partly be explained by differences in or insufficient

adjustment for confounders as physical activity and tobacco smoking. No association in the present study between ICS use and BMD in male never smokers support this.

A statistically significant lower level of BMD was found in ICS users compared to never users. We have not found reason to believe that misclassification of ICS exposure explains the lack of dose response relationship in the present study with use of moderate doses, and questions if this really is an effect of CS. However, further prospective studies on unselected populations are warranted in order to study the relation between ICS, BMD, and fracture risk. Whether 2 % lower BMD (equals to 0.16 SD) has clinical significance can only be answered by studies including fractures as outcome.

Acknowledgement

The Nord-Trøndelag Health Study (The HUNT study) is collaboration between The HUNT Research Centre, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Verdal, The National Institute of Public Health, The National Health Screening Service of Norway, and Nord-Trøndelag County Council.
We thank Jonas Ranstam (Erdeven Medical Statistics Kb; Lund, Sweden) for statistical advices, and professor David Price, University of Aberdeen, for language and content review.

25.06.03

Reference List

(1) Global Initiatives for Asthma. Global Strategy for Asthma Management and Prevention NHLBI/WHO Workshop. 2002. National Heart, Lung, and Blood Institute, National Institute of Health, Bethesda, MD(US-DHHS/PHS/NIH Publication No.02-3659).
Ref Type: Report

(2) American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995; 152(5 Pt 2):S77-121.

(3) British thoracic society, The COPD Guidelines Group of the Standards of Care Committee. Guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997; 52 Suppl 5:S1-28.

(4) Roche N, Lepage T, Bourcereau J, Terrioux P. Guidelines versus clinical practice in the treatment of chronic obstructive pulmonary disease. Eur Respir J 2001; 18(6):903-908.

(5) Lane NE, Lukert B. The science and therapy of glucocorticoid-induced bone loss. Endocrinol Metab Clin North Am 1998; 27(2):465-483.

(6) Niewoehner CB, Niewoehner DE. Steroid-induced osteoporosis. Are your asthmatic patients at risk? Postgrad Med 1999; 105(3):79-91.

(7) Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures [see comments]. J Bone Miner Res 2000; 15(6):993-1000.

(8) Efthimiou J, Barnes PJ. Effect of inhaled corticosteroids on bones and growth [see comments]. Eur Respir J 1998; 11(5):1167-1177.

(9) Egan JJ, Maden C, Kalra S, Adams JE, Eastell R, Woodcock AA. A randomized, double-blind study comparing the effects of beclomethasone and fluticasone on bone density over two years. Eur Respir J 1999; 13(6):1267-1275.

(10) Wong CA, Subakumar G, Casey PM. Effects of asthma and asthma therapies on bone mineral density. Curr Opin Pulm Med 2002; 8(1):39-44.

(11) Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures [see comments]. BMJ 1996; 312(7041):1254-1259.

(12) Langhammer A, Johnsen R, Holmen J, Gulsvik A, Bjermer L. Cigarette smoking gives more respiratory symptoms among women than among men. J Epidemiol Community Health 2000; 54(12):917-922.

(13) Berntsen GK, Tollan A, Magnus JH, Sogaard AJ, Ringberg T, Fonnebo V. The Tromso Study: artifacts in forearm bone densitometry--prevalence and effect. Osteoporos Int 1999; 10(5):425-432.

25.06.03

(14) Joakimsen RM. Risk factors for non-vertebral fractures in a middle-aged population (Thesis). Institute of Community Medicine, University of Tromsø, 1999.

(15) Janson C, Chinn S, Jarvis D, Burney P. Individual use of antiasthmatic drugs in the European Community Respiratory Health Survey. Eur Respir J 1998; 12(3):557-563.

(16) Wong CA, Walsh LJ, Smith CJ, Wisniewski AF, Lewis SA, Hubbard R et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma [see comments]. Lancet 2000; 355(9213):1399-1403.

(17) Baron YM, Brincat M, Galea R. Increased reduction in bone density and skin thickness in postmenopausal women on long-term corticosteroid therapy. A suggested role for estrogen add back therapy. Adv Exp Med Biol 1999; 455:429-436.

(18) Bonala SB, Reddy BM, Silverman BA, Bassett CW, Rao YA, Amara S et al. Bone mineral density in women with asthma on long-term inhaled corticosteroid therapy. Ann Allergy Asthma Immunol 2000; 85(6 Pt 1):495-500.

(19) Boulet LP, Milot J, Gagnon L, Poubelle PE, Brown J. Long-term influence of inhaled corticosteroids on bone metabolism and density. Are biological markers predictors of bone loss? Am J Respir Crit Care Med 1999; 159(3):838-844.

(20) Ebeling PR, Erbas B, Hopper JL, Wark JD, Rubinfeld AR. Bone mineral density and bone turnover in asthmatics treated with long-term inhaled or oral glucocorticoids. J Bone Miner Res 1998; 13(8):1283-1289.

(21) Fujita K, Kasayama S, Hashimoto J, Nagasaka Y, Nakano N, Morimoto Y et al. Inhaled corticosteroids reduce bone mineral density in early postmenopausal but not premenopausal asthmatic women. J Bone Miner Res 2001; 16(4):782-787.

(22) Harmanci E, Ak I, Ozdemir N, Vardareli E, Elbek O, Ucgun I. The comparison of the effects of fluticasone propionate and budesonide on clinical indices and on bone mineral density in the asthmatic patients: a one year treatment study [see comments]. Allergol Immunopathol (Madr) 1999; 27(6):298-303.

(23) Hughes JA, Conry BG, Male SM, Eastell R. One year prospective open study of the effect of high dose inhaled steroids, fluticasone propionate, and budesonide on bone markers and bone mineral density [see comments]. Thorax 1999; 54(3):223-229.

(24) Israel E, Banerjee TR, Fitzmaurice GM, Kotlov TV, LaHive K, Leboff MS. Effects of inhaled glucocorticoids on bone density in premenopausal women. N Engl J Med 2001; 345(13):941-947.

(25) Li JT, Ford LB, Chervinsky P, Weisberg SC, Kellerman DJ, Faulkner KG et al. Fluticasone propionate powder and lack of clinically significant effects on hypothalamic-pituitary-adrenal axis and bone mineral density over 2 years in adults with mild asthma. J Allergy Clin Immunol 1999; 103(6):1062-1068.

(26) Medici TC, Grebski E, Hacki M, Ruegsegger P, Maden C, Efthimiou J. Effect of one year treatment with inhaled fluticasone propionate or beclomethasone dipropionate on bone density and bone metabolism: a randomised parallel group study in adult asthmatic subjects. Thorax 2000; 55(5):375-382.

25.06.03

(27) Tug T, Kamanli A, Tug E. Effects of long-term inhaled steroid use on bone mineral density in asthma patients. J Investig Allergol Clin Immunol 2001; 11(4):300-302.

(28) Lau EM, Li M, Woo J, Lai C. Bone mineral density and body composition in patients with airflow obstruction--the role of inhaled steroid therapy, disease and lifestyle [see comments]. Clin Exp Allergy 1998; 28(9):1066-1071.

(29) Tattersfield AE, Town GI, Johnell O, Picado C, Aubier M, Braillon P et al. Bone mineral density in subjects with mild asthma randomised to treatment with inhaled corticosteroids or non-corticosteroid treatment for two years. Thorax 2001; 56(4):272-278.

(30) Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med 1999; 340(25):1948-1953.

(31) Wise RA, Connett J, Weinmann GG, Scanlon P, Skeans M. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 2000; 343(26):1902-1909.

(32) Augat P, Fuerst T, Genant HK. Quantitative bone mineral assessment at the forearm: a review. Osteoporos Int 1998; 8(4):299-310.

(33) Hui S, Slemenda C, Johnston C. Baseline measurement of bone mass predicts fracture in white women. Ann Intern Med 1989; 111:355-361.

(34) Melton LJ, Atkinson EJ, O'Connor MK, O'Fallon WM, Riggs BL. Bone density and fracture risk in men. J Bone Miner Res 1998; 13(12):1915-1923.

(35) Wasnich R. Bone mass measurement: prediction of risk. Am J Med 1993; 95(5A):6S-10S.

(36) Heinonen A, Kannus P, Sievanen H, Oja P, Pasanen M, Rinne M et al. Randomised controlled trial of effect of high-impact exercise on selected risk factors for osteoporotic fractures. Lancet 1996; 348(9038):1343-1347.

(37) Ortego-Centeno N, Munoz-Torres M, Jodar E, Hernandez-Quero J, Jurado-Duce A, de la Higuera T. Effect of tobacco consumption on bone mineral density in healthy young males. Calcif Tissue Int 1997; 60(6):496-500.

(38) Cummings R, Nevitt M. Calcium for prevention of osteoporotic fractures in postmenopausal women. J Bone Miner Res 1997; 12:1321-1329.

(39) Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben-Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. Chest 2000; 117(2):542-550.

(40) Walsh LJ, Wong CA, Cooper S, Guhan AR, Pringle M, Tattersfield AE. Morbidity from asthma in relation to regular treatment: a community based study. Thorax 1999; 54(4):296-300.

25.06.03

(41) Elmstahl S, Ekstrom H, Galvard H, Johnell O, Gerhardsson d, V, Norjavaara E. Is there an association between inhaled corticosteroids and bone density in postmenopausal women? J Allergy Clin Immunol 2003; 111(1):91-96.

(42) Marystone JF, Barrett-Connor EL, Morton DJ. Inhaled and oral corticosteroids: their effects on bone mineral density in older adults. Am J Public Health 1995; 85(12):1693-1695.

(43) Van Staa TP, Leufkens HG, Cooper C. Use of inhaled corticosteroids and risk of fractures. J Bone Miner Res JID - 8610640 2001; 16(3):581-588.

25.06.03

Table 1. Characteristics of 4,482 women and 4,142 men included according to respiratory symptoms in the BONT study phase I. Nord-Trøndelag, Norway, 1997.

Characteristics	Women	Men
Demographics		
Median (IQR)[1] age (years)	49.9 (36-64)	51.4 (38-66)
Median (IQR) height (cm)	163.7 (159-168)	176.6 (172-181)
Median (IQR) weight (kg)	72.7 (63-81)	84.2 (75.4-92)
Median (IQR) BMI (kg/m2)	27.2 (23.4-30.1)	27.0 (24.3-29.1)
Smoking status		
Never smokers, n (%)	1,895 (42.3)	1,236 (29.8)
Ex-smokers, n (%)	870 (19.4)	1,382 (33.4)
Current smokers, n (%)	1,714 (38.2)	1,521 (36.7)
Mean pack years in ever smokers (SD)	12.0 (9.9)	18.9 (15.7)
Respiratory symptoms/diseases		
Attacks of wheeze or breathlessness during the last 12 months, n (%)	3,223 (72.6)	2,941 (71.7)
Ever asthma, n (%)	2,417 (53.9)	2,152 (52.0)
Medical diagnosis of asthma, n (%) [2]	1,624 (51.5)	1,428 (47.5)
Persistent daily coughing, n (%)	2,220 (47.7)	1,909 (46.1)
- with sputum, n (%)	1,288 (28.7)	1,217 (29.4)
- chronic bronchitis, n (%)[3]	569 (12.7)	613 (14.8)
MD diagnosis of chronic bronchitis/emphysema, n (%) [2]	515 (16.3)	577 (19.2)
Mean FEV1 in % of predicted (SD)	88.3 (19.0)	84.5 (20.6)
Fracture/family history		
Fracture in forearm or hip, n (%)	652 (14.5)	598 (14.4)
MD diagnosis of osteoporosis, n (%)	226 (5.0)	17 (0.4)
Family history of osteoporosis, n (%)	374 (8.3)	158 (3.8)

Bone densiometry		
Distal BMD[4] mean T-score (SD)		
Age 50-69 years	-1.26 (1.56)	-0.61 (1.33)
Age 70 + years	- 3.26 (1.61)	- 1.80 (1.73)
Ultradistal BMD[4] mean T-score (SD)		
Age 50-69 years	- 1.19 (1.34)	- 0.62 (1.18)
Age 70 + years	- 2.66 (1.27)	- 1.43 (1.41)

[1]Inter quartile range. [2]These questions were part of a questionnaire responded by only 3,151 women and 3,004 men. [3]Persistent coughing with phlegm for at least 3 months during the two last years. [4]Bone mineral density

Table 2 Associations (beta-coefficients x 10^{-3}) between potential risk factors and distal and ultradistal BMD adjusted by age + square age stratified by sex, in subjects reporting respiratory symptoms participating in the BONT study phase I in linear regression analyses Nord-Trøndelag, Norway, 1997.

	Distal BMD				Ultradistal BMD			
	Women		Men		Women		Men	
	β-coeff.	95 % CI	β-coeff.	95 % CI	β-coeff.	95 % CI	β-coeff.	95 % CI
Demographics								
Weight (per kg)	0.78**	0.67- 0.89	0.87**	0.74- 1.00	0.85**	0.74- 0.97	0.95**	080- 1.10
Height (per cm)	0.54**	0.26- 0.81	0.60**	0.31- 0.89	0.76**	0.47- 1.04	0.81**	0.48- 1.13
Body mass index (per kg/m2)	2.06**	1.75- 2.38	2.85**	2.39- 3.31	2.17**	1.85- 2.49	2.97**	2.45- 3.48
Education (per category 1-5)[1]	2.25**	0.76- 3.75	- 1.35	-2.99- 0.28	3.43**	1.89- 4.97	-0.36	-2.19- 1.48
Smoking								
Smoker (never=0, ever=1)	- 7.31**	-10.68- -3.94	- 5.28*	-9.38- -1.17	- 7.96**	-11.40- -4.52	- 7.07**	-11.66- -2.49
Pack years in all (numbers)	- 0.34**	-0.51- -0.16	- 0.28**	-0.40- -0.15	- 0.38**	-0.57- -0.20	- 0.33**	-0.47- -0.19
Physical activity/workload								
Physical activity (hours)	1.71**	0.87- 2.55	1.70**	0.82- 2.60	2.31**	1.46- 3.17	2.11**	1.13- 3.08
Physical workload (per category 1-4)[2]	3.15**	1.80- 4.49	3.94**	2.73- 5.15	3.31**	1.93- 4.68	4.04**	2.67- 5.39
Lung function/disease								
FEV_1 (% predicted)	0.39**	0.30- 0.47	0.47**	0.37- 0.56	0.38**	0.30- 0.47	0.44**	0.33- 0.55
MD[3] diagnosis asthma (no=0, yes=1)	- 5.47**	-8.83- -2.10	- 2.55	-6.33- 1.23	- 5.34**	-8.76- -1.93	- 2.29	-6.51- 1.94

Asthma duration (years)	- 0.23**	-0.35- -0.11	- 0.01	-0.03- 0.01	- 0.16*	-0.28- -0.04	- 0.05	-0.02- 0.01
MD chronic bronchitis/emphysema (no=0, yes=1)	- 10.83**	-16.32- -6.42	- 5.41*	-10.70- -0.18	- 9.85**	-15.05- -4.65	- 4.27	-10.16- 1.64
Family history of osteoporosis								
(no=0, yes=1)	- 7.24*	-13.09- -1.39	- 13.63**	-23.00- -4.25	- 7.1*	-13.06- -1.14	- 16.54**	-27.00- -6.08
Hormonal factors								
Hormonal replacement therapy (never=0, ever=1)	5.65*	0.88- 10.41			5.95*	1.10- 10.81		
Time since menopause (years)	- 0.46**	-0.70- -0.21			- 0.56**	-0.81- -0.31		

**: p<0.01, *:p < 0.05,

[1]Category 1 = primary school 7 years, category 2 = first stage, up to 10 years ground school, category 3 = second stage, category 4 = high school or university < 4 years, category 5 = high school or university ≥ 4 years.

[2]Category 1 = mainly sedentary work, category 2 = mainly standing or walking work, category 3 = mainly walking and lifting labour, category 4 = heavy manual labour.

[3]Medical doctor.

Table 3 Use of inhaled corticosteroids (ICS) combined with or without oral corticosteroids (OCS) by sex in subjects reporting respiratory symptoms or ever use of asthma medication. Nord-Trøndelag, Norway, 1997.

Use of inhaled corticosteroids		Women (n=4,482)		Men (n=4,142)	
		ICS + OCS	Only ICS	ICS + OCS	Only ICS
Ever		1,185	722	928	626
Total duration	< 1 yrs	358	263	230	175
	1 - 4 yrs	443	268	351	250
	5 – 10 yrs	260	138	217	130
	> 10 yrs	117	40	123	60
During last 6 months		808	469	708	484
Daily dose last week	0 µg	62	46	50	39
	50 – 200 µg	108	74	84	66
	250-400 µg	259	164	197	143
	500-800 µg	267	148	252	182
	900 – 1,500 µg	51	18	51	21
	≥ 1,600 µg	61	19	74	33

Missing data on duration of use in 7 women and 7 men. Users of only nasal ICS or injections of CS for allergy/tendinitis are not categorised as users of OCS.

Table 4 Mean age, FEV_1 in percent of predicted, current dose of inhaled corticosteroid (ICS) and adjusted[1] mean difference of distal BMD (g/cm^2) between different categories of corticosteroid (CS) users and never users as reference in women and men reporting respiratory symptoms or ever use of asthma medication. Mean BMD in never corticosteroid users was 0.437 and 0.554 in women and men respectively. Nord-Trøndelag, Norway, 1997.

	Number		Age (SD)	FEV_1 %	Current dose ICS	Adjusted mean difference in distal bone density[2] (g/cm^2) x 10^{-3}			
						Women		Men	
Use of corticosteroid	Women	Men		pred (SD)	(SD)	Diff.	95 % CI	Diff.	95 % CI
Never	2,373	2,479	48.6 (17.2)	88.9 (18.0)	0	0		0	
CS – only nasal or injections[2]	606	515	50.3 (15.2)	91.5 (16.5)	0	- 1,9	-6.8 , 2.9	3.2	- 2.3, 8.7
Previous[3] use of ICS with or without OCS	378	222	47.5 (16.6)	89.0 (18.8)		-5,1	-11.0, 0.7	-3.9	-11.7, 3.8
Current use of ICS (daily dose last week > 0 ug)									
ICS only	420	443	57.1 (16.5)	76.6 (23.2)	600 (364)	- 11.5**	-17.1 , -6.0	- 12.4**	- 18.2, -6.5
ICS and prednisolone courses during the last 2 yrs	305	183	58.9 (14.3)	71.1 (23.3)	777 (528)	- 9.8*	-16.2 , -3.3	- 8.3	-16.9, 0.4
ICS and use of prednisolone ≥ 6 months	14	29	66.6 (15.0)	57.3 (25.0)	806 (397)	-28.5*	-56.9, -0.7	-47.4**	-68.3 , -26.4
OCS for non-respiratory diseases	295	199	54.2 (16.2)	85.8 (19.1)		-6.9*	-13.4, -0.5	-5.0	-13.3, 3.2

[1]Adjusted for age, square age, height, BMI, number of pack-years cigarettes, physical activity, work physical load, family history of osteoporosis, and in women years since menopause and use of hormone replacement therapy. [2]These questions were only included in the interview for the last half of the study population (2.797 women and 2.338 men). [3]No use during the last 6 months, * $p< 0.05$ ** $p< 0.01$. Results are not given for subjects having used ICS during the 6 last months, but not at the screening (62 women, 50 men), and subjects with missing answer on OCS use (5 women and 3 men).

Fig 1. Participants of the HUNT Study with use of corticosteroids for respiratory diseases

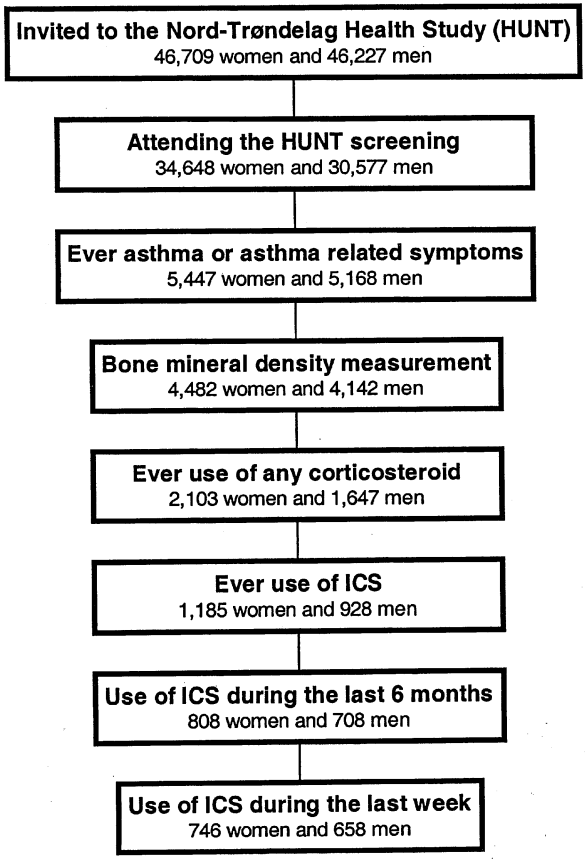
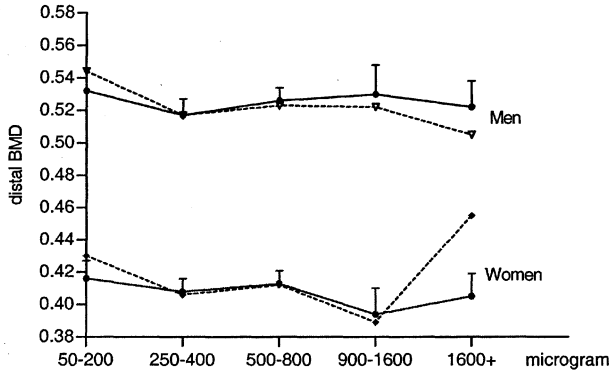
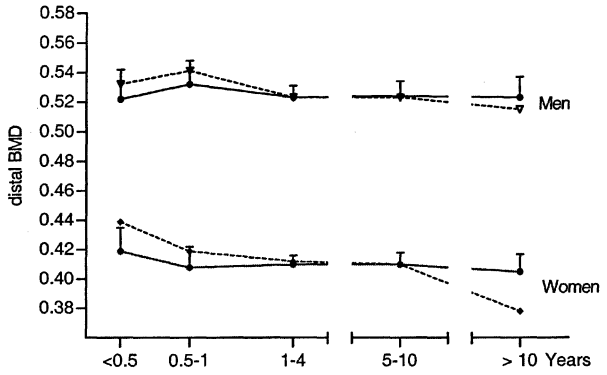


Fig 2a Unadjusted (dotted lines) and adjusted distal BMD with 95% CI by dose of ICS in 741 women and 658 men reporting such use during the last week.



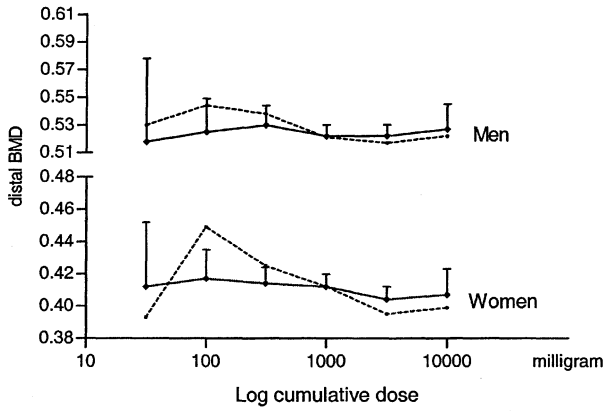
Adjusted by age, square age, height, body mass index, physical activity, work physical load, pack-years, use of oral corticosteroids, family history of osteoporosis, and in women years since menopause and use of hormone replacement therapy.

Fig 2b Unadjusted (dotted lines) and adjusted distal BMD with 95% CI by duration of use of ICS in 741 women and 658 men reporting such use during the last week.



Adjusted by age, square age, height, body mass index, physical activity, work
physical load, pack-years, use of oral corticosteroids, family history of osteoporosis,
and in women years since menopause and use of hormone replacement therapy.

Fig 2c Unadjusted (dotted lines) and adjusted distal BMD with 95% CI by cumulative dose of ICS in 741 women and 658 men reporting such use during the last week.



Adjusted by age, square age, height, body mass index, physical activity, work
physical load, pack-years, use of oral corticosteroids, family history of osteoporosis,
and in women years since menopause and use of hormone replacement therapy.

Appendices

1. **Invitation to HUNT with Questionnaire I**

2. **Questionnaire II**
   Women 20-69 years
   Men 20 – 69 years
   Women 70 years and older
   Men 70 years and older

   Questionnaire III – Lung
   Version I used 15th Aug 1995 – 27th Jan 1997
   Version II used 28th Jan 1997 – Nov 1997

   Questions at the interview

3. **English version of key questions at questionnaires and interview**

4. **Invitation to sub-studies at the screening station and phase II**

   Written informed consent for sub-studies and BONT phase III

5. **Information to participants of lung function measurement results:**
   Spirometry phase I
   Bone densitometry phase I
   Phase II - Reversibility test
   Phase III - Reversibility test after prednisolone course

6. **Information letter to medical doctors**

7. **Non-responder study**

8. **Follow-up study 2001 – invitation and questionnaires**

9. **Studies on inhaled corticosteroids and BMD/fracture risk**

URN:NBN:no-3454

Appendix 1

Invitation to HUNT with Questionnaire I

URN:NBN:no-3454

HELSEUNDERSØKELSEN
I NORD-TRØNDELAG

«JA, nå er det min tur!»

Personlig innbydelse

URN:NBN:no-3454

Spørreskjemaet er en viktig del av Helseundersøkelsen. Her finner du spørsmål om tidligere sykdom og om andre forhold som har betydning for helsa. Vennligst fyll ut skjemaet på forhånd og ta det med til Helseundersøkelsen. Dersom enkelte spørsmål er uklare, lar du dem bare stå ubesvarte til du møter fram, og drøfter dem med personalet som gjennomfører undersøkelsen. Alle svar vil bli behandlet strengt fortrolig.

Flere steder i skjemaet ber vi deg oppgi din alder da eventuell sykdom inntrådte. Hvis du ikke husker nøyaktig hvor gammel du var, skriver du et tall som er nærmest det du antar er korrekt.

Når resultatene fra undersøkelsen foreligger, vil det være enkelte som trenger ny undersøkelse hos egen lege. Dette vil du få beskjed om i det brevet som vi sender deg om dine resultater. Samtidig sender vi melding om resultatene dine til legen din. Det er derfor om å gjøre at du i rubrikken helt til slutt i skjemaet oppgir navnet på den allmennpraktiserende lege, kommunelege eller det helsesenter som du ønsker skal ta hånd om eventuell etterundersøkelse, og som vi skal sende resultatene til.

Med vennlig hilsen

Helsetjenesten i Nord-Trøndelag • Statens helseundersøkelser • Statens Institutt for Folkehelse

DET HANDLER OM HELSA DI

Hvordan er helsa di nå?
Bare ett kryss

Dårlig	12	☐ 1
Ikke helt god		☐ 2
God		☐ 3
Svært god		☐ 4

LUFTVEGSPLAGER

		JA	NEI
Hoster du daglig i perioder av året?			
Hvis JA:			
Er hosten vanligvis ledsaget av oppspytt?	14		
Har du hatt hoste med oppspytt i minst 3 mnd. sammenhengende i hvert av de to siste åra?			
Har du hatt noe anfall med pipende eller tung pust de siste 12 måneder?	16		

		JA	NEI	Alder første gang
Har du eller har du hatt astma?	17			år

		JA	NEI
Har du brukt eller bruker du astmamedisiner?	20		

HJERTE-KARSYKDOMMER, DIABETES

Har du, eller har du hatt:		JA	NEI	Alder første gang
Hjerteinfarkt	21			år
Angina pectoris (hjertekrampe)	24			år
Hjerneslag/hjerneblødning	27			år
Diabetes (sukkersyke)	30			år

Hva ble resultatet siste gang du målte blodtrykket ditt?
Bare ett kryss

Begynne med/fortsette med blodtrykksmedisin	33	☐ 1
Komme til kontroll, men ikke ta blodtrykksmedisin		☐ 2
Ingen kontroll og ingen medisin nødvendig		☐ 3
Har aldri fått målt blodtrykket		☐ 4

Bruker du medisin mot høyt blodtrykk?
Bare ett kryss

Nå	34	☐ 1
Før, men ikke nå		☐ 2
Aldri brukt		☐ 3

	JA	NEI	VET IKKE
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)?			

STOFFSKIFTE

Har du noen gang fått påvist:		JA	NEI	Alder første gang
for høyt stoffskifte	36			år
for lavt stoffskifte	39			år
struma	42			år
annen sykdom i skjoldbruskkjertelen				år
Bruker du eller har du brukt noen av disse medisinene:				
Thyroxin	48			år
Neo-Mercazole	51			år
Er du operert i skjoldbruskkjertelen				år
Har du fått radiojodbehandling	57			år

MUSKEL/SKJELETT-PLAGER

		JA	NEI
Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende?	60		

Hvis NEI, gå videre til neste side øverst.
Hvis JA, svar på følgende:

Hvor har du hatt disse plagene?

		JA	NEI
Nakke	61		
Skuldre (aksler)			
Albuer			
Håndledd, hender			
Bryst/mage	65		
Øvre del av ryggen			
Korsryggen			
Hofter			
Knær			
Ankler, føtter	70		

Hvis du har hatt plager i flere områder i minst 3 mnd. det siste året, setter du ring rundt det ja-krysset hvor plagene har vart lengst

Hvor lenge har plagene vart sammenhengende?
Svar for det området hvor plagene har vart lengst

Hvis under 1 år, oppgi antall mnd.	71	Antall mnd.
Hvis 1 år eller mer, oppgi antall år.	73	Antall år

Har plagene redusert din arbeidsevne det siste året?
Gjelder også hjemmearbeidende. Bare ett kryss

Nei/ubetydelig	I noen grad	I betydelig grad	Vet ikke
☐	☐	☐	☐

		JA	NEI	IKKE I ARBEID
Har du vært sykmeldt pga. disse plagene det siste året?	76			

	JA	NEI
Har plagene ført til redusert aktivitet i fritida?		

URN:NBN:no-3454

Har lege noen gang sagt at du har/har hatt noen av disse sykdommene:

	JA	NEI
Beinskjørhet (osteoporose) ... 78		
Fibromyalgi (fibrositt/kronisk smertesyndrom)		
Leddgikt (reumatoid artritt) ...		
Slitasjegikt (artrose) ...		
Bechterews sykdom ... 82		
Andre langvarige skjelett- eller muskelsykdommer		

Har du noen gang hatt:

	JA	NEI	Alder *siste* gang
Lårhalsbrudd ... 84			år
Brudd i håndledd/underarm ... 87			år
Nakkesleng (whiplash) ... 90			år
Skade som førte til sykehusinnleggelse			år

ANDRE PLAGER

I hvilken grad har du hatt disse plagene i de siste 12 månedene?

	Ikke plaget	Litt plaget	Mye plaget
Kvalme ... 96	☐	☐	☐
Brystbrann/sure oppstøt ...	☐	☐	☐
Diaré ...	☐	☐	☐
Treg mage ...	☐	☐	☐
Hjertebank ...	☐	☐	☐
Åndenød ... 101	☐	☐	☐

ANDRE SYKDOMMER

Har du eller har du noen gang hatt:

	JA	NEI	Alder første gang
Epilepsi ... 102			år
Psykiske plager hvor du har søkt hjelp			år
Kreftsykdom ... 108			år
Annen langvarig sykdom ... 111			

DAGLIGE FUNKSJONER

Har du noen langvarig sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv? ... 112

JA	NEI

Langvarig: minst ett år

Hvis JA:

Hvor mye vil du si at dine funksjoner er nedsatt?

	Litt nedsatt	Middels nedsatt	Mye nedsatt
Er bevegelseshemmet ... 113	☐	☐	☐
Har nedsatt syn ...	☐	☐	☐
Har nedsatt hørsel ...	☐	☐	☐
Hemmet pga. kroppslig sykdom.	☐	☐	☐
Hemmet pga. psykiske plager... 117	☐	☐	☐

MENN fortsetter øverst neste spalte

BESVARES BARE AV KVINNER

Hvor mange barn har du født? ... 118
Sett 0 hvis du ikke har født barn
Antall barn

Hvis du har født barn, besvar:

Hvor gammel var du da du fødte ditt første barn? ... 120
Alder ... år

Hvor gammel var du da du fødte ditt siste barn? ... 122
... år
Besvares ikke hvis du har født bare ett barn

Hvor gammel var du da du fikk menstruasjon? ... 124
... år
Sett 0 hvis du ikke noen gang har hatt menstruasjon

Fortsett neste spalte øverst

RØYKING

Røykte noen av de voksne hjemme da du vokste opp? ... 126

JA	NEI

Bor du, eller har du bodd, sammen med noen dagligrøykere etter at du fylte 20 år? ... 127

JA	NEI

Hvor lenge er du vanligvis daglig til stede i røykfylt rom? ... 128
Sett 0 hvis du ikke oppholder deg i røykfylt rom
Antall timer

Røyker du selv?

	JA	NEI
Sigaretter daglig? ... 130		
Sigarer/sigarillos daglig? ...		
Pipe daglig? ... 132		

Aldri røykt daglig ... *(Sett kryss)* ☐

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? ... 134
Antall år

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? ... 136
Antall sigaretter

Hvor gammel var du da du begynte å røyke daglig? ... 140
Alder ... år

Hvor mange år tilsammen har du røykt daglig? ... 142
Antall år

KAFFE/TE/ALKOHOL

Hvor mange kopper kaffe/te drikker du daglig?
Sett 0 hvis du ikke drikker kaffe/te daglig

	Antall kopper
Kokekaffe ... 144	
Annen kaffe ... 146	
Te ... 148	

Alkohol:
Er du total avholdsmann/-kvinne? ... 150

JA	NEI

Hvor mange ganger i måneden drikker du vanligvis alkohol? ... 151
Antall ganger
Regn ikke med lettøl. Sett 0 hvis mindre enn 1 gang i mnd.

Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av to uker?

Regn ikke med lettøl.
Sett 0 hvis du ikke drikker alkohol 153

Øl	Vin	Brennevin
glass	glass	glass

FYSISK AKTIVITET

I FRITIDA

Hvordan har din fysiske aktivitet i fritida vært det siste året? *Tenk deg et ukentlig gjennomsnitt for året.*

Arbeidsveg regnes som fritid

	Timer pr. uke: Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)* ... 159	☐	☐	☐	☐
Hard fysisk aktivitet *(svett/andpusten)* ... 160	☐ 1	☐ 2	☐ 3	☐ 4

UNDER ARBEID
Hvis du er i lønnet eller ulønnet arbeid:

Hvorledes vil du beskrive arbeidet ditt?
Bare ett kryss

For det meste stillesittende arbeid *(f.eks. skrivebordsarbeid, montering)* ... 161 ☐ 1

Arbeid som krever at du går mye *(f.eks. ekspeditørarb., lett industriarb., undervisning)* ... ☐ 2

Arbeid hvor du går og løfter mye *(f.eks. postbud, pleier, bygningsarbeid)* ... ☐ 3

Tungt kroppsarbeid *(f.eks. skogsarbeid, tungt jordbruksarb.,tungt bygningsarb.)* ☐ 4

URN:NBN:no-3454

HVORLEDES FØLER DU DEG?

Har du de siste to ukene følt deg:

	Nei	Litt	En god del	Svært mye
Trygg og rolig? 162	☐	☐	☐	☐
Glad og optimistisk?	☐	☐	☐	☐
Har du følt deg:				
Nervøs og urolig?	☐	☐	☐	☐
Plaget av angst? 165	☐	☐	☐	☐
Irritabel?	☐	☐	☐	☐
Nedfor/deprimert?	☐	☐	☐	☐
Ensom? 168	☐ 1	☐ 2	☐ 3	☐ 4

Her kommer noen flere spørsmål om hvorledes du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser ***den siste uka.*** *Ikke tenk for lenge på svaret - de spontane svarene er best*

Jeg gleder meg fortsatt over ting slik jeg pleide før 169
Avgjort like mye ..... ☐ 1 Bare lite grann ..... ☐ 3
Ikke fullt så mye ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg har en urofølelse som om noe forferdelig vil skje 170
Ja, og noe svært ille .... ☐ 1 Litt, bekymrer meg lite . ☐ 3
Ja, ikke så veldig ille ... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg kan le og se det morsomme i situasjoner 171
Like mye nå som før .... ☐ 1 Avgjort ikke som før .... ☐ 3
Ikke like mye nå som før ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg har hodet fullt av bekymringer 172
Veldig ofte ..... ☐ 1 Av og til ..... ☐ 3
Ganske ofte ..... ☐ 2 En gang i blant ..... ☐ 4

Jeg er i godt humør 173
Aldri ..... ☐ 1 Ganske ofte ..... ☐ 3
Noen ganger ..... ☐ 2 For det meste ..... ☐ 4

Jeg kan sitte i fred og ro og kjenne meg avslappet 174
Ja, helt klart ..... ☐ 1 Ikke så ofte ..... ☐ 3
Vanligvis ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg føler meg som om alt går langsommere 175
Nesten hele tiden ..... ☐ 1 Fra tid til annen ..... ☐ 3
Svært ofte ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg føler meg urolig som om jeg har sommerfugler i magen 176
Ikke i det hele tatt ..... ☐ 1 Ganske ofte ..... ☐ 3
Fra tid til annen ..... ☐ 2 Svært ofte ..... ☐ 4

Jeg bryr meg ikke lenger om hvordan jeg ser ut 177
Ja, har sluttet å bry meg ☐ 1 Kan hende ikke nok .... ☐ 3
Ikke som jeg burde ..... ☐ 2 Bryr meg som før ..... ☐ 4

Jeg er rastløs som om jeg stadig må være aktiv 178
Uten tvil svært mye ..... ☐ 1 Ikke så veldig mye ..... ☐ 3
Ganske mye..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg ser med glede frem til hendelser og ting 179
Like mye som før ..... ☐ 1 Avgjort mindre enn før . ☐ 3
Heller mindre enn før ... ☐ 2 Nesten ikke i det hele tatt ☐ 4

Jeg kan plutselig få en følelse av panikk 180
Uten tvil svært ofte ..... ☐ 1 Ikke så veldig ofte ..... ☐ 3
Ganske ofte ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg kan glede meg over gode bøker, radio og TV 181
Ofte ..... ☐ 1 Ikke så ofte ..... ☐ 3
Fra tid til annen ..... ☐ 2 Svært sjelden ..... ☐ 4

UTDANNING

Hvilken utdanning er den høyeste du har fullført?

Grunnskole 7-10 år, framhaldsskole, folkehøgskole ..... 182 ☐ 1
Realskole, middelskole, yrkesskole, 1-2 årig videregående skole ..... ☐ 2
Artium, øk.gymnas, allmennfaglig retning i videregående skole ..... ☐ 3
Høgskole/universitet, mindre enn 4 år ..... ☐ 4
Høgskole/universitet, 4 år eller mer ..... ☐ 5

ARBEID

Hva slags arbeidssituasjon har du nå?
Ett eller flere kryss

Lønnet arbeid ..... 183 ☐
Selvstendig næringsdrivende..... ☐
Heltids husarbeid ..... ☐
Utdanning, militærtjeneste ..... ☐
Arbeidsledig, permittert..... ☐
Pensjonist/trygdet..... 188 ☐

Hvor mange timer lønnet arbeid har du i uka? ..... 189 Antall timer

Har du skiftarbeid, nattarbeid eller går vakt? JA ☐ NEI ☐

ALT I ALT

Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen eller er du stort sett misfornøyd?
Bare ett kryss

Svært fornøyd ..... 192 ☐ 1
Meget fornøyd ..... ☐ 2
Ganske fornøyd..... ☐ 3
Både/og..... ☐ 4
Nokså misfornøyd ..... ☐ 5
Meget misfornøyd..... ☐ 6
Svært misfornøyd..... ☐ 7

DIN LEGE

Hvis denne helseundersøkelsen viser at du bør undersøkes nærmere, hvilken allmennpraktiserende lege/kommunelege ønsker du skal foreta undersøkelsen?
Skriv navnet på legen her: 193 *Ikke skriv her*

Takk for utfyllingen!

Nok en gang:

Velkommen til undersøkelsen!

IE 332 5201 - 50.000 - 09.96

Appendix 2

Questionnaire II

- Women 20-69 years
- Men 20 – 69 years
- Women 70 years and older
- Men 70 years and older

Questionnaire III – Lung

- Version I used 15th Aug 1995 – 27th Jan 1997
- Version II used 28th Jan 1997 – Nov 1997

Questions at the interview

URN:NBN:no-3454

hunt
Helseundersøkelsen i Nord-Trøndelag

SKJEMA FOR KVINNER 20–69 ÅR

Takk for frammøtet til undersøkelsen!
Vi vil også be deg fylle ut dette spørreskjemaet. Opplysningene vil bli brukt i større forskningsarbeider om forebyggende helsearbeid. Noen av spørsmålene likner på spørsmål du har svart på i det skjemaet du fylte ut heime og leverte ved frammøte til helseundersøkelsen. Det er likevel viktig at du svarer på alle spørsmålene også i dette skjemaet. Det utfylte skjemaet returneres i vedlagte svarkonvolutt. Porto er betalt.
Alle opplysningene er underlagt streng taushetsplikt.

Vennlig hilsen
Helsetjenesten i Nord-Trøndelag
Statens Institutt for Folkehelse Statens helseundersøkelser

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss her og returner skjemaet. Da slipper du purring.
Jeg ønsker ikke å besvare skjemaet ○

UTFYLLING

Dato for utfylling av skjema: / 19 [19]

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?
Hvis du ikke bodde i Norge, oppgi ***land*** *i stedet for kommune.*

[24]

ARBEID

Nåværende eller tidligere arbeid:
Hva slags inntektsgivende arbeid har du og event. din ektefelle/samboer? *Hvis du/dere ikke har inntektsgivende arbeid nå: Oppgi det siste yrket.*

	Deg selv	Ektefelle/ samboer
Spesialarbeider eller ufaglært arbeider [25]	☐	☐ [36]
Fagarbeider, handverker, formann	☐	☐
Underordnet funksjonær (f.eks. butikk, kontor, off. tjenester)	☐	☐
Fagfunksjonær (f.eks. sykepleier, tekniker, lærer)	☐	☐
Overordnet stilling i off. eller privat virksomhet	☐	☐
Sjåfør [30]	☐	☐ [41]
Gårdbruker eller skogeier	☐	☐
Fisker	☐	☐
Selvstendig i akademisk erverv (f.eks. tannlege, advokat)	☐	☐
Annen selvstendig næringsvirksomhet	☐	☐
Har ikke vært i inntektsgivende arbeid [35]	☐	☐ [46]

Hvis du NÅ ikke har inntektsgivende arbeid eller du ikke har heltids husarbeid: Gå til BOLIG.

Har du i løpet av de siste 12 månedene hatt sykefravær:

	Ja	Nei
med egenmelding [47]	☐	☐
med sykmelding fra lege [48]	☐	☐

Hvis «Ja»: **Hvor lenge *tilsammen*?** *Bare ett kryss*
2 uker eller mindre [49] ☐ 1
2-8 uker ☐ 2
Mer enn 8 uker ☐ 3

Har du i løpet av de siste 12 månedene vurdert å skifte yrke eller arbeidsplass? [50] Ja ☐ Nei ☐

Er arbeidet ditt så fysisk anstrengende at du ofte er sliten i kroppen etter en arbeidsdag? *Bare ett kryss* [51]
Ja, nesten alltid ☐ 1 Ganske sjelden ☐ 3
Ganske ofte ☐ 2 Aldri, eller nesten aldri ☐ 4

Krever arbeidet ditt så mye konsentrasjon og oppmerksomhet at du ofte føler deg utslitt etter en arbeidsdag? [52]
Ja, nesten alltid ☐ 1 Ganske sjelden ☐ 3
Ganske ofte ☐ 2 Aldri, eller nesten aldri ☐ 4

Hvordan trives du alt i alt med arbeidet ditt? [53]
Veldig godt ☐ 1 Ikke særlig godt ☐ 3
Godt ☐ 2 Dårlig ☐ 4

BOLIG

Hvem bor du sammen med?
Ett kryss for hver linje og angi antall

	Ja	Nei	Antall
Ektefelle/samboer [54]	☐	☐	
Andre personer over 18 år [55]	☐	☐	
Personer under 18 år [56]	☐	☐	

Hvor mange av barna har plass i barnehage? [61] Antall

Hvilken type bolig bor du i? *Bare ett kryss*
Enebolig/villa [63] ☐ 1
Gårdsbruk ☐ 2
Blokk/terrasseleilighet ☐ 3
Rekkehus/2-4 mannsbolig ☐ 4
Annen bolig ☐ 5

Hvor stor er din boenhet? [64] kvm

	Ja	Nei
Er det heldekkende tepper i stua? [67]	☐	☐
Er det heldekkende tepper på ditt soverom?	☐	☐
Er det katt i boligen? [69]	☐	☐
Er det hund i boligen?	☐	☐
Er det andre pelskledde dyr eller fugler i boligen?	☐	☐

ØKONOMI

Mottar du noen av følgende *offentlige* ytelser?

	Ja	Nei
Sykepenger/sykelønn/rehabiliteringspenger [72]	☐	☐
Ytelser under yrkesrettet attføring	☐	☐
Uførepensjon [74]	☐	☐
Alderspensjon	☐	☐
Sosialstøtte	☐	☐
Arbeidsløshetstrygd	☐	☐
Overgangsstønad	☐	☐
Etterlattepensjon [79]	☐	☐
Andre ytelser	☐	☐

Har det i løpet av det siste året hendt at husholdningen har hatt vansker med å klare de løpende utgifter til mat, transport, bolig og liknende? *Bare ett kryss* [81]
Ja, ofte ☐ 1 Ja, en sjelden gang ☐ 3
Ja, av og til ☐ 2 Nei, aldri ☐ 4

VENNER

Hvor mange gode venner har du?
Regn med de du kan snakke fortrolig med og som kan gi deg god hjelp når du trenger det [82] Antall
Tell ikke med de du bor sammen med, men regn med andre slektninger

Føler du at du har mange nok gode venner? [84] Ja ☐ Nei ☐

Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. syklubb, idrettslag, politiske lag, religiøse eller andre foreninger? [85]
Aldri, eller noen få ganger i året ☐ 1 Omtrent en gang i uka ☐ 1
1-2 ganger i måneden ☐ 2 Mer enn en gang i uka ☐ 2

URN:NBN:no-3454

DER DU BOR

Svar ut fra nærmiljøet, dvs. nabolaget/grenda:
Ett kryss for hvert spørsmål

Jeg føler et sterkt fellesskap med de som bor her 86
Helt enig ☐ 1 Delvis enig ☐ 2 Usikker ☐ 3 Delvis uenig ☐ 4 Helt uenig ☐ 5

Selv om noen tar initiativ, er det ingen som blir med på det som settes i gang her 87
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Hvis jeg flytter herfra, vil jeg lengte tilbake 88
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Man kan ikke stole på hverandre her 89
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Når noe skal gjøres her, er det lett å få folk med 90
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er vanskelig å få kontakt med folk her 91
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er godt samhold her 92
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Ingen orker å ta initiativ til noe lenger her 93
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk trives godt her 94
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk her kan ha store problemer uten at naboen vet noe 95
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er alltid noen som tar initiativ til å løse nødvendige oppgaver her 96
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk snakker lite med hverandre her 97
Helt enig ☐ 1 Delvis enig ☐ 2 Usikker ☐ 3 Delvis uenig ☐ 4 Helt uenig ☐ 5

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene. Kryss av for "ingen" hvis ingen av slektningene har hatt denne sykdommen: *Evt. flere kryss på hver linje*

		Mor	*Far*	*Bror*	*Søster*	*Barn*	*Ingen*
Hjerneslag eller hjerneblødning	98	☐	☐	☐	☐	☐	☐
Hjerteinfarkt før 60 års alder	104	☐	☐	☐	☐	☐	☐
Astma	110	☐	☐	☐	☐	☐	☐
Allergi	116	☐	☐	☐	☐	☐	☐
Kreftsykdom	122	☐	☐	☐	☐	☐	☐
Høyt blodtrykk	128	☐	☐	☐	☐	☐	☐
Psykiske plager	134	☐	☐	☐	☐	☐	☐
Osteoporose (benskjørhet)	140	☐	☐	☐	☐	☐	☐
Diabetes (sukkersyke)	146	☐	☐	☐	☐	☐	☐
Alder da de fikk diabetes	152	☐ år	☐ år	☐ år	☐ år	☐ år	

Har du *selv* høysnue eller neseallergi? 162 *Ja* ☐ *Nei* ☐

BRUK AV HELSETJENESTER

Har du i løpet av de siste 12 månedene vært hos:
Ett kryss på hver linje

		Ja	*Nei*
allmennpraktiserende lege (kommunelege, privatpraktiserende lege, turnuskandidat)	183	☐	☐
bedriftslege		☐	☐
lege ved sykehus (uten at du var innlagt)		☐	☐
annen lege		☐	☐
fysioterapeut		☐	☐
kiropraktor		☐	☐
homøopat	189	☐	☐
annen behandler (naturmedisiner, fotsoneterapeut, håndspålegger, "healer", "synsk", e.l.)		☐	☐

		Ja	*Nei*
Har du vært innlagt i sykehus de siste 5 åra?	171	☐	☐

ALKOHOL

Hvis du er totalavholdskvinne: Gå til KOSTHOLD.

Ett kryss for hver spørsmål

		Ja	*Nei*
Har du noen gang følt at du burde redusere alkoholforbruket ditt?	172	☐	☐
Har andre noen gang kritisert alkoholbruken din?	173	☐	☐
Har du noen gang følt ubehag eller skyldfølelse pga. alkoholbruken din?	174	☐	☐
Har det å ta en drink noen gang vært det første du har gjort om morgenen for å roe nervene, kurere bakrus eller som en oppkvikker?	175	☐	☐

KOSTHOLD

Hvor mange måltider spiser du vanligvis daglig (middag og brødmåltid)? 176 — Antall: ____

Hvor mange dager i uka spiser du varm middag? — Antall: ____

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis? *Inntil to kryss*

Brødtypen ligner mest på		*Loff*	*Fint brød*	*Knekke-brød*	*Grov-brød*	*Knekke-brød*
	178	☐	☐	☐	☐	☐

Hva slags *fett* blir vanligvis brukt i din husholdning?
Ett kryss for matlaging og ett kryss for brød

	Til matlaging	*På brød*
Bruker *ikke* smør eller margarin	183 ☐ 1	184 ☐ 1
Meierismør	☐ 2	☐ 2
Hard margarin	☐ 3	☐ 3
Bløt (soft) margarin	☐ 4	☐ 4
Smør/margarin blanding	☐ 5	☐ 5
Lettmargarin	☐ 6	☐ 6
Oljer	☐ 7	

MEDISINBRUK

Har du i deler av de siste 12 måneder brukt noen medisiner daglig eller nesten daglig? 185 *Ja* ☐ *Nei* ☐

Hvis «Ja»:
Angi hvor mange måneder du brukte følgende medisiner: *Sett 0 hvis du ikke har brukt medisinene*

		Antall mndr.			Antall mndr.
smertestillende	186		hjertemedisin (ikke blodtrykksmedisin)		
sovemedisin	188		annen medisin		
beroligende medisin			*Kosttilskudd:*		
medisin mot depresjon					
allergimedisin	194		jerntabletter	202	
astmamedisin	196		vitamintilskudd		
			tran/fiskeoljer	206	

Hvor ofte har du brukt avslappende/beroligende medisin eller sovemedisin den siste måneden? 208
Daglig ☐ 1 Sjeldnere enn hver uke ☐ 3
Hver uke, men ikke hver dag ☐ 2 Aldri ☐ 4

HODEPINE

Har du vært plaget av hodepine i løpet av de siste 12 måneder? 209
Ja, anfallsvis (migrene)..... ☐ 1
Ja, annen slags hodepine.... ☐ 2
Nei ..... ☐ 3

Antall anfall siste 12 mndr. 210 ☐☐☐

Hvis «Nei»: Gå til MUSKEL-/SKJELETTPLAGER

Omtrent hvor mange dager i pr. måned har du hodepine?
Mindre enn 7 dager ☐ 1 7 til 14 dager ☐ 2 Mer enn 14 d. ☐ 3

Hvor lenge varer hodepinen vanligvis hver gang? 213
Mindre enn 4 timer ☐ 1 4 timer–3 døgn ☐ 2 Mer enn 3 døgn ☐ 3

Hvor ofte er hodepinen preget av eller ledsaget av:

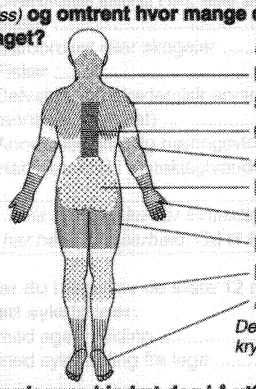
Ett kryss på hver linje	*Sjelden eller aldri*	*Av og til*	*Ofte*
bankende/dunkende smerte 214	☐	☐	☐
pressende smerte	☐	☐	☐
halvsidighet, alltid samme side	☐	☐	☐
halvsidighet, vekselvis h. og v. side	☐	☐	☐
smerter i «hele hodet»	☐	☐	☐
kvalme 219	☐	☐	☐
lys- og/eller lydskyhet	☐	☐	☐
forverring ved fysisk aktivitet.....	☐	☐	☐
synsforstyrrelser *før* hodepine 222	☐	☐	☐

Hvor mange tabletter/stikkpiller har du eventuelt brukt av disse medisinene *alt i alt i løpet av den siste måneden*?
Skriv 0 hvis du ikke har brukt medisinen.
Cafergot 223 ☐☐ Anervan 225 ☐☐ Imigran 227 ☐☐

MUSKEL-/SKJELETTPLAGER

Har du hatt plager (smerter, verk, ubehag) i muskler og/eller ledd i *den siste måneden*? 229 *Ja* ☐ *Nei* ☐

Hvis «Ja»: **Hvor har du hatt disse plagene** *(ett eller flere kryss)* **og omtrent hvor mange dager tilsammen var du plaget?**



Plager (Sett kryss)	Antall dager
Nakke 230	☐☐
Skuldre/aksler 233	☐☐
Øvre del av ryggen	☐☐
Albuer 239	☐☐
Korsryggen 242	☐☐
Handledd/hender 245	☐☐
Hofter 248	☐☐
Knær 251	☐☐
Ankler/føtter 254	☐☐

*Dersom flere kryss: Sett **ring** rundt krysset **der plagen var verst***

Har plagene hindret deg i å utføre daglige aktiviteter den siste måneden?

	Ja	*Nei*
I arbeidet 257	☐	☐
I fritida 258	☐	☐

SMERTER I BEINA

	Ja	*Nei*
Har du sår på tå, fot eller ankel som ikke vil gro? 259	☐	☐
Har du smerter i det ene eller i begge beina når du går? 260	☐	☐
Har du oppsøkt lege p.g.a. smerter i beina? 261	☐	☐

Hvis «NEI» på disse spørsmålene: Gå til MENSTRUASJON

	Ja	*Nei*
Kan du gå lenger enn 50 meter? 262	☐	☐
Forsvinner smerten når du står stille en stund? 263	☐	☐
Må du sette deg for at smerten skal gå over? 264	☐	☐

Hvor gjør det mest vondt? *Ett kryss* 265
Fot ☐ Legg ☐ Lår ☐ Hofte ☐

	Ja	*Nei*
Har du smerter i beina når du er i ro? 266	☐	☐
Er smertene verst når du ligger i senga? 267	☐	☐
Blir søvnen forstyrret av smertene? 268	☐	☐
Får du mindre vondt når beinet ligger høyt? 269	☐	☐
Får du mindre vondt når beinet ligger lavt, f.eks. om beinet henger utfor sengekanten? 270	☐	☐
Bedres smertene når du står opp og går litt? 271	☐	☐

MENSTRUASJON

	Ja	*Nei*
Har du menstruasjon fremdeles? 272	☐	☐

Hvis «Nei»: **Hvor gammel var du da den sluttet?** 273 ☐☐ år

	Ja	*Nei*	*Vet ikke*
Er du gravid nå? 275	☐	☐	☐

	Ja	*Nei*
Har du innsatt spiral nå? 276	☐	☐

Når hadde du siste menstruasjon? ..... 277 *Dag Måned År* ☐☐ ☐☐ ☐☐☐☐
Husker du ikke dag, bare angi måned og år, husker du bare år, angi år.

Menstruasjonen din de siste 12 måneder:

	Ja	*Nei*	*Usikker*
Har du det siste året hatt regelmessige menstruasjoner? *At menstruasjonen har vært omtrent like lenge hver gang med omtrent like lange mellomrom* 283	☐	☐	☐

Hvor mange dager hadde du blødning siste gang du hadde menstruasjon? ..... 284 *Antall dager* ☐☐

Hvor mange dager var du uten blødning mellom nest siste og siste menstruasjon? ... 286 *Antall dager* ☐☐

	Ja	*Nei*
Har menstruasjonen din det siste året uteblitt i mer enn 3 måneder uten at du var gravid? 289	☐	☐

Hvis «Ja»: **Hvor mange måneder i trekk har du vært uten menstruasjonsblødninger?** ..... 290 *Antall mndr.* ☐☐

	Ja	*Nei*
Hvis «Ja»: **Oppsøkte du lege?** 292	☐	☐

Menstruasjonen tidligere (dvs. før de siste 12 månedene):

	Ja	*Nei*
Har menstruasjonen din tidligere uteblitt uten at du var gravid? 293	☐	☐

Hvis «Ja»: **Hvor lenge og hvor ofte var den borte sammenhengende?** *Sett kryss eventuelt flere steder*

	1 gang	*2 ganger*	*Oftere*
3–6 måneder..... 294	☐	☐	☐
6–12 måneder.....	☐	☐	☐
Over ett år..... 296	☐	☐	☐

OPERASJONER I UNDERLIVET

Har du noen gang blitt operert i underlivet? 297 — Ja ☐ Nei ☐ Vet ikke ☐

Hvis «Ja»: **Kryss av for hver operasjon:**

	Ja	Nei	Vet ikke
Fjernet deler av eller bare én eggstokk 298	☐	☐	☐
Fjernet begge eggstokkene (totalt) 299	☐	☐	☐

Hvis du har fjernet begge eggstokkene, hvor gammel var du da? 300 ____ år

	Ja	Nei	Vet ikke
Operert for endometriose 302	☐	☐	☐
Sterilisert	☐	☐	☐
Utskraping fra livmor (sykehus)	☐	☐	☐
Fjernet hele livmoren 305	☐	☐	☐

Hvis du har fjernet hele livmoren, hvor gammel var du da? 306 ____ år

P-PILLER

Har du noen gang brukt p-piller, minipiller inkludert? 308 — Ja ☐ Nei ☐

Hvis «Ja»: **Hvor gammel var du første gang du brukte p-piller?** 309 ____ år

Hvor lenge har du brukt p-piller i alt? 311 ____ år ____ mndr.

Hvis under ett år, antall måneder 313

Bruker du p-piller nå? — Ja ☐ Nei ☐

Hvilket merke bruker du? 316 ____

HORMONBEHANDLING

Utenom p-piller

Har du noen gang brukt medisiner som inneholder østrogen? Vanlige navn på slike medisiner er: Cyclabil, Estraderm, Kilogest, Ovesterin, Progynova, Trisekvens.

	Nå	Før	Aldri
Tabletter eller plaster 318	☐	☐	☐
Krem eller stikkpiller 319	☐	☐	☐

Hvis «Ja»: **Hvor gammel var du første gang du fikk østrogenmedisin, og omtrent hvor mange år brukte du slik medisin?**

	Din alder	Antall år
Tabletter eller plaster 320		
Krem eller stikkpiller 324		

Hvis du bruker østrogenmedisin nå, hvilket merke bruker du? 328 ____

PROBLEMER MED Å BLI GRAVID

Har du noen gang prøvd i mer enn ett år å bli gravid? 329 — Ja ☐ Nei ☐

Hvis «Ja»: **Hvor gammel var du første gang du hadde problemer med å bli gravid?** 330 ____ år

Har du noen gang oppsøkt lege fordi du hadde problemer med å bli gravid? 332 — Ja ☐ Nei ☐

GRAVIDITETER, FØDSLER OG AMMING

Hvor mange ganger har du vært gravid totalt?
*Regn med **alle** svangerskap, spontane eller selvbestemte aborter, så vel som fødsler (også dødfødsler)* 333 ____ ganger

Hvor mange barn har du født? 335 ____ barn

Fyll ut for hvert barn (de første 7) opplysninger om fødselsår og omtrent antall måneder du ammet hvert barn og antall måneder menstruasjonen din var borte etter fødselen (fylles ut også for dødfødte eller for barn som er døde senere i livet).

Barn	Fødselsår	Antall måneder med amming	Antall blødningsfrie måneder
1 338	19		
2 342	19		
3 346	19		
4 354	19		
5 360	19		
6 366	19		
7 372	19		

URINLEKKASJE

Har du ufrivillig urinlekkasje? 378 — Ja ☐ Nei ☐

Hvis «Nei»: Gå til KALK I KOSTEN ...

Hvor ofte har du urinlekkasje? 379
- sjeldnere enn en gang pr. måned ☐
- en eller flere ganger pr. måned ☐
- en eller flere ganger pr. uke ☐
- hver dag og/eller natt ☐

Hvor mye urin lekker du vanligvis hver gang? 380
dråper eller lite ☐ små skvetter ☐ større mengder ☐

Har du lekkasje av urin i forbindelse med hosting, nysing, latter, tunge løft 381 — Ja ☐ Nei ☐

Har du lekkasje av urin i forbindelse med plutselig og sterk vannlatingstrang? 382 — Ja ☐ Nei ☐

Hvor lenge har du hatt urinlekkasje? 383
0-5 år ☐ 5-10 år ☐ Over 10 år ☐

Har du søkt lege på grunn av urinlekkasje? 384 — Ja ☐ Nei ☐

Hvordan opplever du lekkasjeplagene dine? 386 *Ett kryss*
- ikke noe problem ☐
- en liten plage ☐
- en del plaget ☐
- mye plaget ☐
- svært stort problem ☐

KALK I KOSTEN OG KOSTTILSKUDD

Hvor mange glass melk (alle sorter, også drikkeyoghurt) drikker du vanligvis daglig? *Bare ett kryss* 386
- Ingen ☐ 1
- Mindre enn ett ☐ 2
- 1–2 glass ☐ 3
- 3 eller mer ☐ 4

Hvor mange brødskiver med kvitost spiser du vanligvis daglig? *Bare ett kryss*
- Ingen ☐ 1
- Mindre enn en ☐ 2
- 1–2 skiver ☐ 3
- 3 eller mer ☐ 4

Bruker du vanligvis noen av disse kosttilskuddene?

	Ja	Nei
vitamin D-tilskudd 388	☐	☐
kalktabletter eller benmel	☐	☐

HUMØR OG TRIVSEL

Ett kryss på hver linje

Angi hvordan du har følt deg den siste måneden:

	Aldri	*Noen ganger*	*Ganske ofte*	*For det meste*
i godt humør 390	☐	☐	☐	☐
i dårlig humør 391	☐	☐	☐	☐

	Svært treg	*Ganske treg*	*Ganske rask*	*Svært rask*
Er du rask til å oppfatte et humoristisk poeng? 392	☐	☐	☐	☐

Er du enig i at det er noe ansvarsløst over folk som stadig prøver å være morsomme? 393

Nei, slett ikke ☐1 Ganske enig ☐3
I noen grad ☐2 Ja, absolutt ☐4

Er du en munter person? 394

Nei, slett ikke ☐1 Ganske munter ☐3
I noen grad ☐2 Ja, absolutt ☐4

SINNE

Sett kryss på det svaret som best beskriver deg i forhold til de to påstandene nedenfor:

Jeg gir uttrykk for mitt sinne, og andre mennesker vet at jeg er sint 395

Nesten aldri ☐1 Ganske ofte ☐3
Noen ganger ☐2 Nesten alltid ☐4

Jeg koker av sinne, men jeg viser det ikke til andre 396

Nesten aldri ☐1 Ganske ofte ☐3
Noen ganger ☐2 Nesten alltid ☐4

HVILE OG AVSLAPPING

Hvor mange timer tilbringer du *vanligvis* i *liggende* stilling i løpet av et døgn?
(nattesøvn, middagshvil) ....397 Antall timer

Hvor mange timer tilbringer du *vanligvis* i *sittende* stilling i løpet av et døgn?
(arbeid, måltider, TV, bil etc.) ....399 Antall timer

Hvor ofte er du plaget av søvnløshet? 401

Aldri, eller noen få ganger i året ☐1
1–2 ganger i måneden ☐2
Omtrent 1 gang i uka ☐3
Mer enn en gang i uka ☐4

	Ja	*Nei*
Har du siste år vært plaget av søvnløshet slik at det har gått ut over arbeidsevnen? 402	☐	☐

Har du i løpet av siste måned hatt innsovningsproblemer? *Bare ett kryss* 403

Nesten hver natt ☐1 Av og til ☐3
Ofte ☐2 Aldri ☐4

Har du i løpet av siste måned våknet for tidlig og ikke fått sove igjen? *Bare ett kryss* 404

Nesten hver natt ☐1 Av og til ☐3
Ofte ☐2 Aldri ☐4

Har du i løpet av siste måned vært plaget av nervøsitet (irritabel, urolig, anspent eller rastløs)? 405

Nesten hele tida ☐1
Ofte ☐2
Av og til ☐3
Aldri ☐4

HVORDAN DU HAR HATT DET

Har det noen gang i løpet av ditt liv vært *sammenhengende perioder på 2 uker eller mer* da du:	*Ja*	*Nei*
følte deg deprimert, trist og nedfor 406	☐	☐
hadde problemer med matlysten eller spiste alt for lite	☐	☐
var plaget av kraftløshet eller mangel på overskudd	☐	☐
virkelig bebreidet deg selv og følte deg verdiløs ...	☐	☐
hadde problemer med å konsentrere deg eller vanskelig for å ta beslutninger	☐	☐
hadde minst tre av de problemene som er nevnt ovenfor samtidig 411	☐	☐

HVORDAN DU SER PÅ DEG SELV

Folk ser på seg selv på ulike måter. Kryss av for hvert utsagn hvor enig eller uenig du er. *Ett kryss på hver linje*

	Svært enig	*Enig*	*Uenig*	*Svært uenig*
Jeg har en positiv holdning til meg selv 412	☐	☐	☐	☐
Jeg føler meg virkelig ubrukelig til tider 413	☐	☐	☐	☐
Jeg føler at jeg ikke har mye å være stolt av 414	☐	☐	☐	☐
Jeg føler at jeg er en verdifull person, i allefall på lik linje med andre 415	☐	☐	☐	☐

	Ja	*Nei*
Synes du at du har funnet et virkelig betydningsfullt innhold i livet ditt? 416	☐	☐
Føler du at du lever fullt ut? 417	☐	☐

HVORDAN DU FØLER DEG NÅ

*Sett kryss i den ruta utenfor det svaret som best beskriver dine følelser **den siste uka.** Bare ett kryss*

Er du vanligvis glad eller nedstemt? 418

Svært nedstemt ☐1
Nedstemt ☐2
Nokså nedstemt ☐3
Både – og ☐4
Nokså glad ☐5
Glad ☐6
Svært glad ☐7

Har du i det store og hele en rolig og god følelse inne i deg? 419

Nesten hele tida ☐1
Ofte ☐2
Av og til ☐3
Aldri ☐4

Føler du deg stort sett sterk og opplagt, eller trøtt og sliten? 420

Meget sterk og opplagt ☐1
Sterk og opplagt ☐2
Ganske sterk og opplagt ☐3
Både – og ☐4
Ganske trøtt og sliten ☐5
Trøtt og sliten ☐6
Svært trøtt og sliten ☐7

Legg det utfylte spørreskjemaet i den vedlagte svarkonvolutten og postlegg den så snart som mulig!
Porto er betalt.
Hjertelig takk for hjelpa!

Steinkjer Trykkeri AS – 74 16 80 00

hunt
Helseundersøkelsen i Nord-Trøndelag

SKJEMA FOR MENN 20–69 ÅR

Takk for frammøtet til undersøkelsen!
Vi vil også be deg fylle ut dette spørreskjemaet. Opplysningene vil bli brukt i større forskningsarbeider om forebyggende helsearbeid. Noen av spørsmålene likner på spørsmål du har svart på i det skjemaet du fylte ut heime og leverte ved frammøte til helseundersøkelsen. Det er likevel viktig at du svarer på alle spørsmålene også i dette skjemaet. Det utfylte skjemaet returneres i vedlagte svarkonvolutt. Porto er betalt.
Alle opplysningene er underlagt streng taushetsplikt.

Vennlig hilsen
Helsetjenesten i Nord-Trøndelag
Statens Institutt for Folkehelse Statens helseundersøkelser

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss her og returner skjemaet. Da slipper du purring.
Jeg ønsker ikke å besvare skjemaet ○

UTFYLLING

Dato for utfylling av skjema: / 19 [19]

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?
Hvis du ikke bodde i Norge, oppgi ***land*** *i stedet for kommune.*

[24]

ARBEID

Nåværende eller tidligere arbeid:
Hva slags inntektsgivende arbeid har du og event. din ektefelle/samboer? *Hvis du/dere ikke har inntektsgivende arbeid nå: Oppgi det siste yrket.*

		Deg selv	Ektefelle/ samboer	
Spesialarbeider eller ufaglært arbeider	25	☐	☐	36
Fagarbeider, handverker, formann		☐	☐	
Underordnet funksjonær (f.eks. butikk, kontor, off. tjenester)		☐	☐	
Fagfunksjonær (f.eks. sykepleier, tekniker, lærer)		☐	☐	
Overordnet stilling i off. eller privat virksomhet		☐	☐	
Sjåfør	30	☐	☐	41
Gårdbruker eller skogeier		☐	☐	
Fisker		☐	☐	
Selvstendig i akademisk erverv (f.eks. tannlege, advokat)		☐	☐	
Annen selvstendig næringsvirksomhet		☐	☐	
Har ikke vært i inntektsgivende arbeid	35	☐	☐	46

Hvis du NÅ ikke har inntektsgivende arbeid eller du ikke har heltids husarbeid: Gå til BOLIG.

Har du i løpet av de siste 12 månedene hatt sykefravær:

		Ja	Nei
med egenmelding	47	☐	☐
med sykmelding fra lege	48	☐	☐

Hvis «Ja»: Hvor lenge *tilsammen*? *Bare ett kryss*

2 uker eller mindre	49	☐	1
2-8 uker		☐	2
Mer enn 8 uker		☐	3

		Ja	Nei
Har du i løpet av de siste 12 månedene vurdert å skifte yrke eller arbeidsplass?	50	☐	☐

Er arbeidet ditt så fysisk anstrengende at du ofte er sliten i kroppen etter en arbeidsdag? *Bare ett kryss* 51

Ja, nesten alltid	☐	1	Ganske sjelden	☐	3
Ganske ofte	☐	2	Aldri, eller nesten aldri	☐	4

Krever arbeidet ditt så mye konsentrasjon og oppmerksomhet at du ofte føler deg utslitt etter en arbeidsdag? 52

Ja, nesten alltid	☐	1	Ganske sjelden	☐	3
Ganske ofte	☐	2	Aldri, eller nesten aldri	☐	4

Hvordan trives du alt i alt med arbeidet ditt? 53

Veldig godt	☐	1	Ikke særlig godt	☐	3
Godt	☐	2	Dårlig	☐	4

BOLIG

Hvem bor du sammen med?
Ett kryss for hver linje og angi antall

		Ja	Nei	Antall
Ektefelle/samboer	54	☐	☐	
Andre personer over 18 år	55	☐	☐	
Personer under 18 år	58	☐	☐	

Hvor mange av barna har plass i barnehage? [61] Antall

Hvilken type bolig bor du i? *Bare ett kryss*

Enebolig/villa	63	☐	1
Gårdsbruk		☐	2
Blokk/terrasseleilighet		☐	3
Rekkehus/2-4 mannsbolig		☐	4
Annen bolig		☐	5

Hvor stor er din boenhet? [64] kvm

		Ja	Nei
Er det heldekkende tepper i stua?	67	☐	☐
Er det heldekkende tepper på ditt soverom?		☐	☐
Er det katt i boligen?	69	☐	☐
Er det hund i boligen?		☐	☐
Er det andre pelskledde dyr eller fugler i boligen?		☐	☐

ØKONOMI

Mottar du noen av følgende *offentlige* ytelser?

		Ja	Nei
Sykepenger/sykelønn/rehabiliteringspenger	72	☐	☐
Ytelser under yrkesrettet attføring		☐	☐
Uførepensjon	74	☐	☐
Alderspensjon		☐	☐
Sosialstøtte		☐	☐
Arbeidsløshetstrygd		☐	☐
Overgangsstønad		☐	☐
Etterlattepensjon	79	☐	☐
Andre ytelser		☐	☐

Har det i løpet av det siste året hendt at husholdningen har hatt vansker med å klare de løpende utgifter til mat, transport, bolig og liknende? *Bare ett kryss* 81

Ja, ofte	☐	1	Ja, en sjelden gang	☐	3
Ja, av og til	☐	2	Nei, aldri	☐	4

VENNER

Hvor mange gode venner har du?
Regn med de du kan snakke fortrolig med og som kan gi deg god hjelp når du trenger det [82] Antall
Tell ikke med de du bor sammen med, men regn med andre slektninger

		Ja	Nei
Føler du at du har mange nok gode venner?	84	☐	☐

Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. syklubb, idrettslag, politiske lag, religiøse eller andre foreninger? 85

Aldri, eller noen få ganger i året	☐	1	Omtrent en gang i uka	☐	1
1-2 ganger i måneden	☐	2	Mer enn en gang i uka	☐	2

URN:NBN:no-3454

DER DU BOR

Svar ut fra nærmiljøet, dvs. nabolaget/grenda.
Ett kryss for hvert spørsmål

Jeg føler et sterkt fellesskap med de som bor her 86
Helt enig ☐ 1 Delvis enig ☐ 2 Usikker ☐ 3 Delvis uenig ☐ 4 Helt uenig ☐ 5

Selv om noen tar initiativ, er det ingen som blir med på det som settes i gang her 87
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Hvis jeg flytter herfra, vil jeg lengte tilbake 88
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Man kan ikke stole på hverandre her 89
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Når noe skal gjøres her, er det lett å få folk med 90
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er vanskelig å få kontakt med folk her 91
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er godt samhold her 92
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Ingen orker å ta initiativ til noe lenger her 93
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk trives godt her 94
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk her kan ha store problemer uten at naboen vet noe 95
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er alltid noen som tar initiativ til å løse nødvendige oppgaver her 96
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk snakker lite med hverandre her 97
Helt enig ☐ 1 Delvis enig ☐ 2 Usikker ☐ 3 Delvis uenig ☐ 4 Helt uenig ☐ 5

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene. Kryss av for «ingen» hvis ingen av slektningene har hatt denne sykdommen. *Evt. flere kryss på hver linje*

		Mor	*Far*	*Bror*	*Søster*	*Barn*	*Ingen*
Hjerneslag eller hjerneblødning	98	☐	☐	☐	☐	☐	☐
Hjerteinfarkt før 60 års alder	104	☐	☐	☐	☐	☐	☐
Astma	110	☐	☐	☐	☐	☐	☐
Allergi	116	☐	☐	☐	☐	☐	☐
Kreftsykdom	122	☐	☐	☐	☐	☐	☐
Høyt blodtrykk	128	☐	☐	☐	☐	☐	☐
Psykiske plager	134	☐	☐	☐	☐	☐	☐
Osteoporose (benskjørhet)	140	☐	☐	☐	☐	☐	☐
Diabetes (sukkersyke)	146	☐	☐	☐	☐	☐	☐
Alder da de fikk diabetes	152	år	år	år	år	år	

Har du *selv* høysnue eller neseallergi? 162 *Ja* ☐ *Nei* ☐

BRUK AV HELSETJENESTER

Har du i løpet av de siste 12 månedene vært hos :
Ett kryss på hver linje

		Ja	*Nei*
allmennpraktiserende lege (kommunelege, privatpraktiserende lege, turnuskandidat)	163	☐	☐
bedriftslege		☐	☐
lege ved sykehus (uten at du var innlagt)		☐	☐
annen lege		☐	☐
fysioterapeut		☐	☐
kiropraktor		☐	☐
homøopat	169	☐	☐
annen behandler (naturmedisiner, fotsoneterapeut, håndspålegger, "healer", "synsk", e.l.)		☐	☐

Har du vært innlagt i sykehus de siste 5 åra? 171 *Ja* ☐ *Nei* ☐

ALKOHOL

Hvis du er totalavholdsmann: Gå til KOSTHOLD.

Ett kryss for hver spørsmål

		Ja	*Nei*
Har du noen gang følt at du burde redusere alkoholforbruket ditt?	172	☐	☐
Har andre noen gang kritisert alkoholbruken din?	173	☐	☐
Har du noen gang følt ubehag eller skyldfølelse pga. alkoholbruken din?	174	☐	☐
Har det å ta en drink noen gang vært det første du har gjort om morgenen for å roe nervene, kurere bakrus eller som en oppkvikker?	175	☐	☐

KOSTHOLD

Hvor mange måltider spiser du vanligvis daglig (middag og brødmåltid)? 176 Antall: ____

Hvor mange dager i uka spiser du varm middag? Antall: ____

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis? *Inntil to kryss.*

Brødtypen ligner mest på		*Loff*	*Fint brød*	*Knepp-brød*	*Grov-brød*	*Knekke-brød*
	178	☐	☐	☐	☐	☐

Hva slags *fett* blir vanligvis brukt i din husholdning?
Ett kryss for matlaging og ett kryss for brød

	Til matlaging	*På brød*
Bruker *ikke* smør eller margarin	183 ☐ 1	184 ☐ 1
Meierismør	☐ 2	☐ 2
Hard margarin	☐ 3	☐ 3
Bløt (soft) margarin	☐ 4	☐ 4
Smør/margarin blanding	☐ 5	☐ 5
Lettmargarin	☐ 6	☐ 6
Oljer	☐ 7	

MEDISINBRUK

Har du i deler av de siste 12 måneder brukt noen medisiner daglig eller nesten daglig? 185 *Ja* ☐ *Nei* ☐

Hvis «Ja»:
Angi hvor mange måneder du brukte følgende medisiner: *Sett 0 hvis du ikke har brukt medisinene*

		Antall mndr.		Antall mndr.
smertestillende	186		hjertemedisin (ikke blodtrykksmedisin)	
sovemedisin	188		annen medisin	
beroligende medisin			*Kosttilskudd:*	
medisin mot depresjon				
allergimedisin	194		jerntabletter	202
astmamedisin	196		vitamintilskudd	
			tran/fiskeoljer	206

Hvor ofte har du brukt avslappende/beroligende medisin eller sovemedisin den siste måneden? 208
Daglig ☐ 1 Sjeldnere enn hver uke ☐ 3
Hver uke, men ikke hver dag ☐ 2 Aldri ☐ 4

HODEPINE

Har du vært plaget av hodepine i løpet av de siste 12 måneder? 209
Ja, anfallsvis (migrene) ☐ 1
Ja, annen slags hodepine ☐ 2
Nei ☐ 3

Antall anfall siste 12 mndr. 210

Hvis «Nei»: Gå til MUSKEL-/SKJELETTPLAGER

Omtrent hvor mange dager i pr. måned har du hodepine?
Mindre enn 7 dager ☐ 1 7 til 14 dager ☐ 2 Mer enn 14 d. ☐ 3

Hvor lenge varer hodepinen vanligvis hver gang? 213
Mindre enn 4 timer ☐ 1 4 timer–3 døgn ☐ 2 Mer enn 3 døgn ☐ 3

Hvor ofte er hodepinen preget av eller ledsaget av:

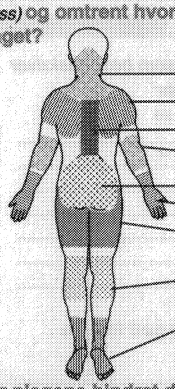
Ett kryss på hver linje	*Sjelden eller aldri*	*Av og til*	*Ofte*
bankende/dunkende smerte 214	☐	☐	☐
pressende smerte	☐	☐	☐
halvsidighet, alltid samme side	☐	☐	☐
halvsidighet, vekselvis h. og v. side	☐	☐	☐
smerter i «hele hodet»	☐	☐	☐
kvalme 219	☐	☐	☐
lys- og/eller lydskyhet	☐	☐	☐
forverring ved fysisk aktivitet	☐	☐	☐
synsforstyrrelser *før* hodepine 222	☐	☐	☐

Hvor mange tabletter/stikkpiller har du eventuelt brukt av disse medisinene *alt i alt i løpet av den siste måneden*?
Skriv 0 hvis du ikke har brukt medisinen.
Cafergot 223 ☐ Anervan 225 ☐ Imigran 227 ☐

MUSKEL-/SKJELETTPLAGER

Har du hatt plager (smerter, verk, ubehag) i muskler og/eller ledd i *den siste måneden*? 229 Ja ☐ Nei ☐

Hvis «Ja»: **Hvor har du hatt disse plagene** *(ett eller flere kryss)* **og omtrent hvor mange dager tilsammen var du plaget?**



Plager (Sett kryss)	Antall dager
Nakke 230	
Skuldre/aksler 233	
Øvre del av ryggen	
Albuer 239	
Korsryggen 242	
Handledd/hender 245	
Hofter 248	
Knær 251	
Ankler/føtter 254	

*Dersom flere kryss: Sett **ring** rundt krysset **der plagen var verst***

Har plagene hindret deg i å utføre daglige aktiviteter den siste måneden?

	Ja	Nei
I arbeidet 257	☐	☐
I fritida 258	☐	☐

SMERTER I BEINA

	Ja	Nei
Har du sår på tå, fot eller ankel som ikke vil gro? 259	☐	☐
Har du smerter i det ene eller i begge beina når du går? 260	☐	☐
Har du oppsøkt lege p.g.a. smerter i beina? 261	☐	☐

Hvis «NEI» på disse spørsmålene: Gå til URINVEGS...

	Ja	Nei
Kan du gå lenger enn 50 meter? 262	☐	☐
Forsvinner smerten når du står stille en stund? 263	☐	☐
Må du sette deg for at smerten skal gå over? 264	☐	☐

Hvor gjør det mest vondt? *Ett kryss* 265
Fot ☐ Legg ☐ Lår ☐ Hofte ☐

	Ja	Nei
Har du smerter i beina når du er i ro? 266	☐	☐
Er smertene verst når du ligger i senga? 267	☐	☐
Blir søvnen forstyrret av smertene? 268	☐	☐
Får du mindre vondt når beinet ligger høyt? 269	☐	☐
Får du mindre vondt når beinet ligger lavt, f.eks. om beinet henger utfor sengekanten? 270	☐	☐
Bedres smertene når du står opp og går litt? 271	☐	☐

URINVEGS- OG PROSTATAPLAGER

Ett kryss på hver linje

Har du noen gang blitt fortalt av lege at du har:	Ja	Nei
forstørret prostata 272	☐	☐
prostatakreft 273	☐	☐

Har du gjennomgått noe av følgende:	Ja	Nei
sterilisering 274	☐	☐
tatt vevsprøve (biopsi) av prostata 275	☐	☐
kirurgisk fjerning av prostata (helt eller delvis) 276	☐	☐

De neste spørsmålene gjelder siste måned
Bare ett kryss for hvert hver spørsmål

Hvor ofte har du hatt følelsen av at blæren ikke er blitt fullstendig tømt etter avsluttet vannlating? 277
Aldri ☐ 1 Omtrent annenhver gang ☐ 4
Omtrent 1 av 5 ganger ☐ 2 Omtrent 2 av 3 ganger ☐ 5
Omtrent 1 av 3 ganger ☐ 3 Nesten alltid ☐ 6

Hvor ofte har du måttet late vannet på nytt mindre enn 2 timer etter forrige vannlating? 278
Aldri ☐ 1 Omtrent annenhver gang ☐ 4
Omtrent 1 av 5 ganger ☐ 2 Omtrent 2 av 3 ganger ☐ 5
Omtrent 1 av 3 ganger ☐ 3 Nesten alltid ☐ 6

Hvor ofte har du måttet stoppe og starte flere ganger under vannlatingingen? 279
Aldri ☐ 1 Omtrent annenhver gang ☐ 4
Omtrent 1 av 5 ganger ☐ 2 Omtrent 2 av 3 ganger ☐ 5
Omtrent 1 av 3 ganger ☐ 3 Nesten alltid ☐ 6

Hvor ofte syns du det har vært vanskelig å holde igjen når du har følt trang til å late vannet? 280
Aldri ☐ 1 Omtrent annenhver gang ☐ 4
Omtrent 1 av 5 ganger ☐ 2 Omtrent 2 av 3 ganger ☐ 5
Omtrent 1 av 3 ganger ☐ 3 Nesten alltid ☐ 6

Hvor ofte har du hatt svak urinstråle? 281
Aldri ☐ 1 Omtrent annenhver gang ☐ 4
Omtrent 1 av 5 ganger ☐ 2 Omtrent 2 av 3 ganger ☐ 5
Omtrent 1 av 3 ganger ☐ 3 Nesten alltid ☐ 6

Hvor ofte har du måttet trykke eller presse for å begynne vannlatingen? 282
Aldri ☐ 1 Omtrent annenhver gang ☐ 4
Omtrent 1 av 5 ganger ☐ 2 Omtrent 2 av 3 ganger ☐ 5
Omtrent 1 av 3 ganger ☐ 3 Nesten alltid ☐ 6

Hvor mange ganger har du vanligvis måttet stå opp i løpet av natta for å late vannet? 283
Ingen ☐ 1 2 ganger ☐ 3 4 ganger ☐ 5
1 gang ☐ 2 3 ganger ☐ 4 5 ganger eller mer ☐ 6

Hvis du resten av livet måtte leve med de vannlatingeproblemene du har nå, hvordan ville du føle det? 284
Være meget godt fornøyd ☐ 1 Være for det meste utilfreds ☐ 5
Være fornøyd ☐ 2 Være misfornøyd ☐ 6
Være for det meste tilfreds ☐ 3 Ha det forferdelig ☐ 7
Ha blandete følelser ☐ 4

HUMØR OG TRIVSEL

Ett kryss på hver linje

Angi hvordan du har følt deg den siste måneden:	*Aldri*	*Noen ganger*	*Ganske ofte*	*For det meste*
i godt humør 285	☐	☐	☐	☐
i dårlig humør 286	☐	☐	☐	☐

Er du rask til å oppfatte et humoristisk poeng? 287	*Svært treg*	*Ganske treg*	*Ganske rask*	*Svært rask*
	☐	☐	☐	☐

Er du enig i at det er noe ansvarsløst over folk som stadig prøver å være morsomme? 288

Nei, slett ikke ..... ☐1 Ganske enig ..... ☐3
I noen grad ..... ☐2 Ja, absolutt ..... ☐4

Er du en munter person? 289

Nei, slett ikke ..... ☐1 Ganske munter ..... ☐3
I noen grad ..... ☐2 Ja, absolutt ..... ☐4

SINNE

Sett kryss på det svaret som best beskriver deg i forhold til de to påstandene nedenfor:

Jeg gir uttrykk for mitt sinne, og andre mennesker vet at jeg er sint. 290

Nesten aldri ..... ☐1 Ganske ofte ..... ☐3
Noen ganger ..... ☐2 Nesten alltid ..... ☐4

Jeg koker av sinne, men jeg viser det ikke til andre. 291

Nesten aldri ..... ☐1 Ganske ofte ..... ☐3
Noen ganger ..... ☐2 Nesten alltid ..... ☐4

HVILE OG AVSLAPPING

Hvor mange timer tilbringer du *vanligvis* i *liggende* stilling i løpet av et døgn? (nattesøvn, middagshvil) ..... 292 — Antall timer: ____

Hvor mange timer tilbringer du *vanligvis* i *sittende* stilling i løpet av et døgn? (arbeid, måltider, TV, bil etc.) ..... 294 — Antall timer: ____

Hvor ofte er du plaget av søvnløshet? 296

Aldri, eller noen få ganger i året ..... ☐1
1–2 ganger i måneden ..... ☐2
Omtrent 1 gang i uka ..... ☐3
Mer enn en gang i uka ..... ☐4

Har du siste år vært plaget av søvnløshet slik at det har gått ut over arbeidsevnen? 297	*Ja*	*Nei*
	☐	☐

Har du i løpet av siste måned hatt innsovningsproblemer? ***Bare ett kryss*** 298

Nesten hver natt ..... ☐1 Av og til ..... ☐3
Ofte ..... ☐2 Aldri ..... ☐4

Har du i løpet av siste måned våknet for tidlig og ikke fått sove igjen? ***Bare ett kryss*** 299

Nesten hver natt ..... ☐1 Av og til ..... ☐3
Ofte ..... ☐2 Aldri ..... ☐4

Har du i løpet av siste måned vært plaget av nervøsitet (irritabel, urolig, anspent eller rastløs)? 300

Nesten hele tida ..... ☐1
Ofte ..... ☐2
Av og til ..... ☐3
Aldri ..... ☐4

HVORDAN DU HAR HATT DET

Har det noen gang i løpet av ditt liv vært *sammenhengende perioder på 2 uker eller mer* da du:	*Ja*	*Nei*
følte deg deprimert, trist og nedfor 301	☐	☐
hadde problemer med matlysten eller spiste alt for lite	☐	☐
var plaget av kraftløshet eller mangel på overskudd	☐	☐
virkelig bebreidet deg selv og følte deg verdiløs ...	☐	☐
hadde problemer med å konsentrere deg eller vanskelig for å ta beslutninger	☐	☐
hadde minst tre av de problemene som er nevnt ovenfor samtidig 306	☐	☐

HVORDAN DU SER PÅ DEG SELV

Folk ser på seg selv på ulike måter. Kryss av for hvert utsagn hvor enig eller uenig du er. *Ett kryss på hver linje*

	Svært enig	*Enig*	*Uenig*	*Svært uenig*
Jeg har en positiv holdning til meg selv 307	☐	☐	☐	☐
Jeg føler meg virkelig ubrukelig til tider 308	☐	☐	☐	☐
Jeg føler at jeg ikke har mye å være stolt av 309	☐	☐	☐	☐
Jeg føler at jeg er en verdifull person, i allefall på lik linje med andre 310	☐	☐	☐	☐

	Ja	*Nei*
Synes du at du har funnet et virkelig betydningsfullt innhold i livet ditt? 311	☐	☐
Føler du at du lever fullt ut? 312	☐	☐

HVORDAN DU FØLER DEG NÅ

Sett kryss i den ruta utenfor det svaret som best beskriver dine følelser ***den siste uka.*** *Bare ett kryss*

Er du vanligvis glad eller nedstemt? 313

Svært nedstemt ..... ☐1
Nedstemt ..... ☐2
Nokså nedstemt ..... ☐3
Både – og ..... ☐4
Nokså glad ..... ☐5
Glad ..... ☐6
Svært glad ..... ☐7

Har du i det store og hele en rolig og god følelse inne i deg? 314

Nesten hele tida ..... ☐1
Ofte ..... ☐2
Av og til ..... ☐3
Aldri ..... ☐4

Føler du deg stort sett sterk og opplagt, eller trøtt og sliten? 315

Meget sterk og opplagt ..... ☐1
Sterk og opplagt ..... ☐2
Ganske sterk og opplagt ..... ☐3
Både – og ..... ☐4
Ganske trøtt og sliten ..... ☐5
Trøtt og sliten ..... ☐6
Svært trøtt og sliten ..... ☐7

Legg det utfylte spørreskjemaet i den vedlagte svarkonvolutten og postlegg den så snart som mulig!
Porto er betalt.
Hjertelig takk for hjelpa!

Steinkjer Trykkeri AS – 74 16 30 00

hunt
Helseundersøkelsen i Nord-Trøndelag

SKJEMA FOR KVINNER 70 ÅR OG ELDRE

Takk for frammøtet til undersøkelsen!
Vi vil også be deg fylle ut dette spørreskjemaet. Opplysningene vil bli brukt i større forskningsarbeider om forebyggende helsearbeid. Noen av spørsmålene likner på spørsmål du har svart på i det skjemaet du fylte ut heime og leverte ved frammøte til helseundersøkelsen. Det er likevel viktig at du svarer på alle spørsmålene også i dette skjemaet. Det utfylte skjemaet returneres i vedlagte svarkonvolutt. Porto er betalt.
Alle opplysningene er underlagt streng taushetsplikt.

Vennlig hilsen
Helsetjenesten i Nord-Trøndelag
Statens Institutt for Folkehelse Statens helseundersøkelser

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss her og returner skjemaet. Da slipper du purring.
Jeg ønsker ikke å besvare skjemaet ○

UTFYLLING

Dato for utfylling av skjema: / 19 19

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?
*Hvis du ikke bodde i Norge, oppgi **land** i stedet for kommune*

24

BOLIG

Hvilken type bolig bor du i? *Bare ett kryss*

- Enebolig/villa 25 ☐ 1
- Gårdsbruk ☐ 2
- Blokk/terrasseleilighet ☐ 3
- Rekkehus/2-4 mannsbolig ☐ 4
- Trygdebolig/aldersbolig/servicebolig ☐ 5
- Sykeheim/aldersheim ☐ 6
- Annen bolig ☐ 7

Hvor stor er din boenhet? 26 kvm

	Ja	Nei
Er det heldekkende tepper i stua? 29	☐	☐
Er det heldekkende tepper på ditt soverom?	☐	☐
Er det katt i boligen? 31	☐	☐
Er det hund i boligen?	☐	☐
Er det andre pelskledde dyr eller fugler i boligen?	☐	☐

Hvem bor du sammen med? *Ett eller flere kryss*

- Ektefelle/samboer 34 ☐
- Barn/svigerbarn ☐
- Bor alene 36 ☐
- Søster/bror 37 ☐
- Annen familie/slekt ☐
- Andre 39 ☐

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene. Kryss av for "ingen" hvis ingen av slektningene har hatt denne sykdommen. *Evt. flere kryss på hver linje*

	Mor	Far	Bror	Søster	Barn	Ingen
Hjerneslag eller hjerneblødning 40	☐	☐	☐	☐	☐	☐
Hjerteinfarkt før 60 års alder 46	☐	☐	☐	☐	☐	☐
Astma 52	☐	☐	☐	☐	☐	☐
Allergi 58	☐	☐	☐	☐	☐	☐
Kreftsykdom 64	☐	☐	☐	☐	☐	☐
Høyt blodtrykk 70	☐	☐	☐	☐	☐	☐
Psykiske plager 76	☐	☐	☐	☐	☐	☐
Osteoporose (benskjørhet) 82	☐	☐	☐	☐	☐	☐
Diabetes (sukkersyke) 88	☐	☐	☐	☐	☐	☐
Alder da de fikk diabetes 94	år	år	år	år	år	

	Ja	Nei
Har du *selv* høysnue eller neseallergi? 104	☐	☐

SIVILSTAND

Hva er din sivilstand? 105

- Gift ☐ 1
- Skilt/separert ☐ 2
- Enke ☐ 3
- Har aldri vært gift ☐ 4

BRUK AV HELSETJENESTER

Har du i løpet av de siste 12 månedene vært hos:

Ett kryss på hver linje	Ja	Nei
allmennpraktiserende lege (kommunelege, privatpraktiserende lege, turnuskandidat) 106	☐	☐
lege ved sykehus (uten at du var innlagt)	☐	☐
annen lege	☐	☐
fysioterapeut	☐	☐
kiropraktor	☐	☐
homøopat 111	☐	☐
annen behandler (naturmedisiner, fotsoneterapeut, håndspålegger, "healer", "synsk", e.l.)	☐	☐

SYKEHUS

	Ja	Nei
Har du vært innlagt i sykehus de siste 5 åra? 113	☐	☐

Hvis «Ja»: Svar ut fra siste gang du var innlagt

Synes du at du ble utskrevet for tidlig, i passe tid eller for seint? 114

- For tidlig ☐
- I passe tid ☐
- For seint ☐

Hvor ble du utskrevet til? 115

- Heim ☐
- Kuropphold ☐
- Sykeheim ☐

	Ja	Nei
Fikk du tilstrekkelig hjelp og oppfølging etter utskrivingen? 116	☐	☐

HEIMEHJELP

	Ja	Nei
Har du heimehjelp?		
Privat 117	☐	☐
Kommunal 118	☐	☐

Dersom du har KOMMUNAL heimehjelp: **Har du nok kommunal heimehjelp, eller trenger du mer?** 119

- Ja, jeg har nok ☐
- Nei, jeg trenger mer ☐

I tilfelle du IKKE har kommunal heimehjelp:	Ja	Nei
Trenger du kommunal heimehjelp? 120	☐	☐

URN:NBN:no-3454

HEIMESYKEPLEIE

	Ja	Nei
Har du heimesykepleie? 121	☐	☐

Hvis «Ja»:

Har du nok heimesykepleie, eller trenger du mer?

- Ja, jeg har nok ☐
- Nei, jeg trenger mer ☐

SYKEHEIM

Har du vært innlagt på sykeheim i løpet av de siste 12 månedene? 123

- Nei ☐
- Ja, jeg har vært der en periode ☐
- Ja, jeg bor der fast ☐

Hvis «Nei», kan du hoppe over de neste to spørsmålene

Hvis «Ja»:

Hvor var du FØR du ble innlagt på sykeheimen siste gang? 124

- Bodde i egen heim ☐
- Var innlagt i sykehus ☐
- Var annet sted ☐

Hvis du har vært på sykeheimen EN PERIODE i løpet av de siste 12 mndr.:

Bodde du på sykeheimen passe lenge? 125

- Det var for kort tid ☐
- Passe tid ☐
- Det var for lang tid ☐

KOMMUNAL HJELP ALT I ALT

Hvordan er du alt i alt fornøyd med hjelpa du får fra kommunen? 126

- Meget fornøyd ..... ☐ 1
- Nokså fornøyd ..... ☐ 2
- Nokså misfornøyd .. ☐ 3
- Meget misfornøyd .. ☐ 4
- Jeg får ingen hjelp, men burde ha hatt det ..... ☐ 5
- Jeg får ingen hjelp, og trenger det ikke ..... ☐ 6

KOSTHOLD

Hvor mange måltider spiser du vanlig daglig (middag og brødmåltid)? 127 — Antall: ☐

Hvor mange dager i uka spiser du varm middag? ☐

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis? *Inntil to kryss*

Brødtypen ligner mest på 129	*Loff*	*Fint brød*	*Kneipp-brød*	*Grov-brød*	*Knekke-brød*
	☐	☐	☐	☐	☐

Hva slags *fett* blir vanligvis brukt i din husholdning?

Ett kryss for matlaging og ett kryss for brød

	Til matlaging 134	*På brød* 135
Bruker *ikke* smør eller margarin	☐ 1	☐ 1
Meierismør	☐ 2	☐ 2
Hard margarin	☐ 3	☐ 3
Bløt (soft) margarin	☐ 4	☐ 4
Smør/margarin blanding	☐ 5	☐ 5
Lettmargarin	☐ 6	☐ 6
Oljer	☐ 7	

Hvor mange glass melk (alle sorter, også drikkeyoghurt) drikker du vanligvis daglig? *Bare ett kryss* 136

- Ingen ☐ 1
- Mindre enn ett ☐ 2
- 1–2 glass ☐ 3
- 3 eller mer ☐ 4

Hvor mange brødskiver med kvitost spiser du vanligvis daglig? *Bare ett kryss* 137

- Ingen ☐ 1
- Mindre enn en ☐ 2
- 1–2 skiver ☐ 3
- 3 eller mer ☐ 4

HVILE OG AVSLAPPING

Hvor mange timer tilbringer du *vanligvis* i *liggende* stilling i løpet av et døgn?
(nattesøvn, middagshvil) 138 — Antall timer: ☐

Hvor mange timer tilbringer du *vanligvis* i *sittende* stilling i løpet av et døgn?
(arbeid, måltider, TV, bil etc.) 140 — Antall timer: ☐

Har du i løpet av siste måned hatt innsovningsproblemer? *Bare ett kryss* 142

- Nesten hver natt ☐ 1
- Ofte ☐ 2
- Av og til ☐ 3
- Aldri ☐ 4

Har du i løpet av siste måned våknet for tidlig og ikke fått sove igjen? *Bare ett kryss* 143

- Nesten hver natt ☐ 1
- Ofte ☐ 2
- Av og til ☐ 3
- Aldri ☐ 4

MEDISINBRUK

	Ja	*Nei*
Har du i deler av de siste 12 måneder brukt noen medisiner daglig eller nesten daglig? 144	☐	☐

Hvis "Ja":

Angi hvor mange måneder du brukte følgende medisiner: *Sett 0 hvis du ikke har brukt medisinene*

	Antall mndr.		Antall mndr.
smertestillende 145		hjertemedisin (ikke blodtrykksmedisin)	
sovemedisin 147		annen medisin	
beroligende medisin		*Kosttilskudd:*	
medisin mot depresjon		jerntabletter 161	
allergimedisin 153		vitamin D-tilskudd	
astmamedisin 155		andre vitamintilskudd	
		tran/fiskeoljer 167	

Hvor ofte har du brukt avslappende/beroligende medisin eller sovemedisin den siste måneden? 169

- Daglig ☐ 1
- Hver uke, men ikke hver dag ☐ 2
- Sjeldnere enn hver uke ☐ 3
- Aldri ☐ 4

VENNER

Hvor mange gode venner har du?
Regn med de du kan snakke fortrolig med og som kan gi deg god hjelp når du trenger det 170 — Antall: ☐
Tell ikke med de du bor sammen med, men regn med andre slektninger

	Ja	*Nei*
Føler du at du har mange nok gode venner? 172	☐	☐

Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. syklubb, eldresenter, pensjonistforening, politiske lag, religiøse eller andre foreninger? *Bare ett kryss* 173

Aldri, eller noen
få ganger i året ..... ☐1 Omtrent en gang i uka ... ☐3
1–2 ganger i måneden ... ☐2 Mer enn en gang i uka ... ☐4

HUMØR OG TRIVSEL

Ett kryss på hver linje

Angi hvordan du har følt deg den siste måneden:	*Aldri*	*Noen ganger*	*Ganske ofte*	*For det meste*
i godt humør 174	☐	☐	☐	☐
i dårlig humør 175	☐	☐	☐	☐

Er du rask til å oppfatte et humoristisk poeng? 176	*Svært treg*	*Ganske treg*	*Ganske rask*	*Svært rask*
	☐	☐	☐	☐

Er du enig i at det er noe ansvarsløst over folk som stadig prøver å være morsomme? 177

Nei, slett ikke ..... ☐1 Ganske enig ..... ☐3
I noen grad ..... ☐2 Ja, absolutt ..... ☐4

Er du en munter person? 178

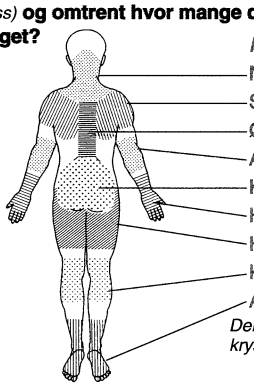
Nei, slett ikke ..... ☐1 Ganske munter ..... ☐3
I noen grad ..... ☐2 Ja, absolutt ..... ☐4

MUSKEL-/SKJELETTPLAGER

Har du hatt plager (smerter, verk, ubehag) i muskler og/eller ledd i *den siste måneden*? ..... 179 *Ja* ☐ *Nei* ☐

Hvis «Nei»: Gå til HODEPINE

Hvis «Ja»: Hvor har du hatt disse plagene *(ett eller flere kryss)* **og omtrent hvor mange dager tilsammen var du plaget?**



Plager (Sett kryss)	Antall dager
Nakke 180	
Skuldre/aksler.....183	
Øvre del av ryggen	
Albuer 189	
Korsryggen 192	
Handledd/hender	
Hofter.....198	
Knær.....201	
Ankler/føtter 204	

*Dersom flere kryss: Sett **ring** rundt krysset **der plagen var verst***

Har plagene hindret deg i å utføre daglige aktiviteter den siste måneden? ..... 207 *Ja* ☐ *Nei* ☐

HODEPINE

Har du vært plaget av hodepine i løpet av de siste 12 måneder? 208

Ja, anfallsvis (migrene)..... 1 ☐
Ja, annen slags hodepine.. 2 ☐
Nei ..... 3 ☐

Antall anfall siste 12 mndr. 209 ☐☐

Hvis «Nei»: Gå til URINLEKKASJE

Omtrent hvor mange dager pr. måned har du hodepine?

Mindre enn 7 dager ☐1 7 til 14 dager ☐2 Mer enn 14 d. ☐3

Hvor lenge varer hodepinen vanligvis hver gang? 212

Mindre enn 4 timer ☐1 4 timer–3 døgn ☐2 Mer enn 3 døgn ☐3

Hvor ofte er hodepinen preget av eller ledsaget av:

Ett kryss på hver linje	*Sjelden eller aldri*	*Av og til*	*Ofte*
bankende/dunkende smerte 213	☐	☐	☐
pressende smerte	☐	☐	☐
halvsidighet, alltid samme side	☐	☐	☐
halvsidighet, vekselvis h. og v. side	☐	☐	☐
smerter i «hele hodet»	☐	☐	☐
kvalme 218	☐	☐	☐
lys- og/eller lydskyhet	☐	☐	☐
forverring ved fysisk aktivitet.....	☐	☐	☐
synsforstyrrelser *før* hodepine 221	☐	☐	☐

Hvor mange tabletter/stikkpiller har du eventuelt brukt av disse medisinene *alt i alt i løpet av den siste måneden*?

Skriv 0 hvis du ikke har brukt medisinen.

Cafergot 222 ☐☐ Anervan 224 ☐☐ Imigran 226 ☐☐

URINLEKKASJE

Har du ufrivillig urinlekkasje? .....228 *Ja* ☐ *Nei* ☐

Hvis «Nei»: Gå til MENSTRUASJON OG OVERGANG...

Hvor ofte har du urinlekkasje? 229

sjeldnere enn en gang pr. måned ..... ☐
en eller flere ganger pr. måned ..... ☐
en eller flere ganger pr. uke ..... ☐
hver dag og/eller natt ..... ☐

Hvor mye urin lekker du vanligvis hver gang? 230

dråper eller lite ☐ små skvetter ☐ større mengder ☐

Har du lekkasje av urin i forbindelse med *Ja* *Nei*

hosting, nysing, latter, tunge løft .....231 ☐ ☐

Har du lekkasje av urin i forbindelse med plutselig og sterk vannlatingstrang? 232 *Ja* ☐ *Nei* ☐

Hvor lenge har du hatt urinlekkasje? 233

0-5 år ☐ 5-10 år ☐ Over 10 år ☐

Har du søkt lege på grunn av urinlekkasje? 234 *Ja* ☐ *Nei* ☐

Hvordan opplever du lekkasjeplagene dine? 235 *Ett kryss*

ikke noe problem ☐ mye plaget ☐
en liten plage ☐ svært stort problem ☐
en del plaget ☐

MENSTRUASJON OG OVERGANGSALDER

Hvor gammel var du da menstruasjonen sluttet? ☐☐ år

HORMONBEHANDLING

Utenom p-piller

Har du noen gang brukt medisiner som inneholder østrogen? Vanlige navn på slike medisiner er: Cyclabil, Estraderm, Kilogest, Ovesterin, Progynova, Trisekvens.

	Nå	*Før*	*Aldri*
Tabletter eller plaster 238	☐	☐	☐
Krem eller stikkpiller 239	☐	☐	☐

Hvis «Ja»: Hvor gammel var du første gang du fikk østrogenmedisin, og omtrent hvor mange år brukte du slik medisin?

	Din alder	*Antall år*
Tabletter eller plaster 240	☐☐	☐☐
Krem eller stikkpiller 244	☐☐	☐☐

Hvis du bruker østrogenmedisin nå, hvilket merke bruker du? 248

OPERASJONER I UNDERLIVET

	Ja	Nei	Vet ikke
Har du fått fjernet begge eggstokkene (totalt)? 249	☐	☐	☐

Hvis du har fjernet begge eggstokkene, hvor gammel var du da? 250 ____ år

	Ja	Nei	Vet ikke
Har du fått fjernet hele livmoren? 252	☐	☐	☐

Hvis du har fjernet hele livmoren, hvor gammel var du da? 253 ____ år

GRAVIDITETER, FØDSLER OG AMMING

Hvor mange ganger har du vært gravid totalt?
*Regn med **alle** svangerskap, spontane eller selv-bestemte aborter, så vel som fødsler (også dødfødsler).* 255 ____ ganger

Hvor mange barn har du født? 257 ____ barn

Fyll ut for hvert barn (de første 6) opplysninger om fødselsår og omtrent antall måneder du ammet hvert barn og antall måneder menstruasjonen din var borte etter fødselen (fylles ut også for dødfødte eller for barn som er døde senere i livet).

Barn	Fødselsår	Antall måneder med amming	Antall blødningsfrie måneder
1	258 19		
2	264 19		
3	270 19		
4	276 19		
5	282 19		
6	288 19		

HVORDAN DU SER PÅ DEG SELV

Folk ser på seg selv på ulike måter. Kryss av for hvert utsagn hvor enig eller uenig du er. *Ett kryss på hver linje*

	Svært enig	Enig	Uenig	Svært uenig
Jeg har en positiv holdning til meg selv 294	☐	☐	☐	☐
Jeg føler meg virkelig ubrukelig til tider 295	☐	☐	☐	☐
Jeg føler at jeg ikke har mye å være stolt av 296	☐	☐	☐	☐
Jeg føler at jeg er en verdifull person, i allefall på lik linje med andre 297	☐	☐	☐	☐

	Ja	Nei
Synes du at du har funnet et virkelig betydningsfullt innhold i livet ditt? 298	☐	☐
Føler du at du lever fullt ut? 299	☐	☐

HVORDAN DU FØLER DEG NÅ

*Sett kryss i den ruta utenfor det svaret som best beskriver dine følelser **den siste uka.** Bare ett kryss*

Føler du deg stort sett sterk og opplagt, eller trøtt og sliten? 300

- ☐ 1 Meget sterk og opplagt
- ☐ 2 Sterk og opplagt
- ☐ 3 Ganske sterk og opplagt
- ☐ 4 Både – og
- ☐ 5 Ganske trøtt og sliten
- ☐ 6 Trøtt og sliten
- ☐ 7 Svært trøtt og sliten

Har du i det store og hele en rolig og god følelse inne i deg? 301

- ☐ 1 Nesten hele tida
- ☐ 2 Ofte
- ☐ 3 Av og til
- ☐ 4 Aldri

Er du vanligvis glad eller nedstemt? 302

- ☐ 1 Svært nedstemt
- ☐ 2 Nedstemt
- ☐ 3 Nokså nedstemt
- ☐ 4 Både – og
- ☐ 5 Nokså glad
- ☐ 6 Glad
- ☐ 7 Svært glad

LEGEMLIGE FUNKSJONER

Klarer du selv, uten hjelp av andre, i det daglige å:
Ett kryss på hver linje

	Ja	Med noe hjelp	Nei
Gå innendørs i samme etasje 303	☐	☐	☐
Gå på toalettet	☐	☐	☐
Vaske deg på kroppen 305	☐	☐	☐
Bade eller dusje	☐	☐	☐
Kle på og av deg 307	☐	☐	☐
Legge deg og stå opp	☐	☐	☐
Spise selv 309	☐	☐	☐

Hvis du har hatt hjelp til noe av dette, omtrent hvor lenge har du hatt hjelp? *Bare ett kryss* 310

- ☐ 1 Under 3 måneder
- ☐ 2 3 – 6 måneder
- ☐ 3 1/2 – 1 år
- ☐ 4 1 – 5 år
- ☐ 5 Mer enn 5 år

Hvis du trenger hjelp til ett eller flere av disse gjøremålene, hvem er det som for det meste hjelper deg?
Bare ett kryss

- ☐ 1 Ektefelle/samboer
- ☐ 2 Barn/svigerbarn
- ☐ 3 Søster/bror
- ☐ 4 Annen familie/slekt
- ☐ 5 Andre

DAGLIGE OPPGAVER

Klarer du selv disse gjøremålene i det daglige uten hjelp fra andre? *Ett kryss på hver linje*

	Ja	Med noe hjelp	Nei
Lage varm mat 312	☐	☐	☐
Gjøre lett husarbeid (f.eks. oppvask)	☐	☐	☐
Gjøre tyngre husarbeid (f.eks. gulvvask) 314	☐	☐	☐
Vaske klær	☐	☐	☐
Betale regninger 316	☐	☐	☐
Ta medisinene	☐	☐	☐
Komme deg ut 318	☐	☐	☐
Gjøre innkjøp	☐	☐	☐
Ta bussen 320	☐	☐	☐

Hvis du trenger hjelp til ett eller flere av disse gjøremålene, omtrent hvor lenge har du hatt hjelp?
Bare ett kryss 321

- ☐ 1 Under 3 måneder
- ☐ 2 3 – 6 måneder
- ☐ 3 1/2 – 1 år
- ☐ 4 1 – 5 år
- ☐ 5 Mer enn 5 år

Hvis du trenger hjelp til ett eller flere av disse gjøremålene, hvem er det som for det meste hjelper deg?
Bare ett kryss 322

- ☐ 1 Ektefelle/samboer
- ☐ 2 Barn/svigerbarn
- ☐ 3 Søster/bror
- ☐ 4 Annen familie/slekt
- ☐ 5 Andre

Legg det utfylte spørreskjemaet i den vedlagte svarkonvolutten og postlegg den så snart som mulig!
Porto er betalt.
Hjertelig takk for hjelpa!

Steinkjer Trykkeri AS – 74 16 30 00

hunt
Helseundersøkelsen i Nord-Trøndelag

SKJEMA FOR MENN 70 ÅR OG ELDRE

Takk for frammøtet til undersøkelsen!
Vi vil også be deg fylle ut dette spørreskjemaet. Opplysningene vil bli brukt i større forskningsarbeider om forebyggende helsearbeid. Noen av spørsmålene likner på spørsmål du har svart på i det skjemaet du fylte ut heime og leverte ved frammøte til helseundersøkelsen. Det er likevel viktig at du svarer på alle spørsmålene også i dette skjemaet. Det utfylte skjemaet returneres i vedlagte svarkonvolutt. Porto er betalt.
Alle opplysningene er underlagt streng taushetsplikt.

Vennlig hilsen
Helsetjenesten i Nord-Trøndelag
Statens Institutt for Folkehelse Statens helseundersøkelser

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss her og returner skjemaet. Da slipper du purring.
Jeg ønsker ikke å besvare skjemaet ○

UTFYLLING

Dato for utfylling av skjema: / 19 [19]

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?
Hvis du ikke bodde i Norge, oppgi ***land*** *i stedet for kommune*

[24]

BOLIG

Hvilken type bolig bor du i? *Bare ett kryss*

Enebolig/villa	25	☐ 1
Gårdsbruk		☐ 2
Blokk/terrasseleilighet		☐ 3
Rekkehus/2-4 mannsbolig		☐ 4
Trygdebolig/aldersbolig/servicebolig		☐ 5
Sykeheim/aldersheim		☐ 6
Annen bolig		☐ 7

Hvor stor er din boenhet? [26] kvm

	Ja	Nei
Er det heldekkende tepper i stua? [29]	☐	☐
Er det heldekkende tepper på ditt soverom?	☐	☐
Er det katt i boligen? [31]	☐	☐
Er det hund i boligen?	☐	☐
Er det andre pelskledde dyr eller fugler i boligen?	☐	☐

Hvem bor du sammen med? *Ett eller flere kryss*

Ektefelle/samboer	34 ☐	Søster/bror	37 ☐
Barn/svigerbarn	☐	Annen familie/slekt	☐
Bor alene	36 ☐	Andre	39 ☐

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene. Kryss av for "ingen" hvis ingen av slektningene har hatt denne sykdommen. *Evt. flere kryss på hver linje*

	Mor	Far	Bror	Søster	Barn	Ingen
Hjerneslag eller hjerneblødning [40]	☐	☐	☐	☐	☐	☐
Hjerteinfarkt før 60 års alder [46]	☐	☐	☐	☐	☐	☐
Astma [52]	☐	☐	☐	☐	☐	☐
Allergi [58]	☐	☐	☐	☐	☐	☐
Kreftsykdom [64]	☐	☐	☐	☐	☐	☐
Høyt blodtrykk [70]	☐	☐	☐	☐	☐	☐
Psykiske plager [76]	☐	☐	☐	☐	☐	☐
Osteoporose (benskjørhet) [82]	☐	☐	☐	☐	☐	☐
Diabetes (sukkersyke) [88]	☐	☐	☐	☐	☐	☐
Alder da de fikk diabetes [94]	år	år	år	år	år	

	Ja	Nei
Har du *selv* høysnue eller neseallergi? [104]	☐	☐

SIVILSTAND

Hva er din sivilstand? [105]

Gift	☐ 1	Enkemann	☐ 3
Skilt/separert	☐ 2	Har aldri vært gift	☐ 4

BRUK AV HELSETJENESTER

Har du i løpet av de siste 12 månedene vært hos:

Ett kryss på hver linje		Ja	Nei
allmennpraktiserende lege (kommunelege, privatpraktiserende lege, turnuskandidat)	106	☐	☐
lege ved sykehus (uten at du var innlagt)		☐	☐
annen lege		☐	☐
fysioterapeut		☐	☐
kiropraktor		☐	☐
homøopat	111	☐	☐
annen behandler (naturmedisiner, fotsoneterapeut, håndspålegger, "healer", "synsk", e.l.)		☐	☐

SYKEHUS

		Ja	Nei
Har du vært innlagt i sykehus de siste 5 åra?	113	☐	☐

Hvis «Ja»: Svar ut fra siste gang du var innlagt

Synes du at du ble utskrevet for tidlig, i passe tid eller for seint? [114]

For tidlig	☐
I passe tid	☐
For seint	☐

Hvor ble du utskrevet til? [115]

Heim	☐
Kuropphold	☐
Sykeheim	☐

		Ja	Nei
Fikk du tilstrekkelig hjelp og oppfølging etter utskrivingen?	116	☐	☐

HEIMEHJELP

		Ja	Nei
Har du heimehjelp?			
Privat	117	☐	☐
Kommunal	118	☐	☐

Dersom du har KOMMUNAL heimehjelp: Har du nok kommunal heimehjelp, eller trenger du mer? [119]

Ja, jeg har nok	☐
Nei, jeg trenger mer	☐

I tilfelle du IKKE har kommunal heimehjelp:		Ja	Nei
Trenger du kommunal heimehjelp?	120	☐	☐

URN:NBN:no-3454

HEIMESYKEPLEIE

Ja Nei

Har du heimesykepleie? ..... 121 ☐ ☐

Hvis «Ja»:

Har du nok heimesykepleie, eller trenger du mer?

Ja, jeg har nok ..... ☐

Nei, jeg trenger mer ..... ☐

SYKEHEIM

Har du vært innlagt på sykeheim i løpet av de siste 12 månedene? 123

Nei ..... ☐

Ja, jeg har vært der en periode ..... ☐

Ja, jeg bor der fast ..... ☐

Hvis «Nei», kan du hoppe over de neste to spørsmålene

Hvis «Ja»:

Hvor var du FØR du ble innlagt på sykeheimen siste gang? 124

Bodde i egen heim ..... ☐

Var innlagt i sykehus ..... ☐

Var annet sted ..... ☐

Hvis du har vært på sykeheimen EN PERIODE i løpet av de siste 12 mndr.:

Bodde du på sykeheimen passe lenge? 125

Det var for kort tid ..... ☐

Passe tid ..... ☐

Det var for lang tid ..... ☐

KOMMUNAL HJELP ALT I ALT

Hvordan er du alt i alt fornøyd med hjelpa du får fra kommunen? 126

Meget fornøyd ..... ☐ 1

Nokså fornøyd ..... ☐ 2

Nokså misfornøyd .. ☐ 3

Meget misfornøyd .. ☐ 4

Jeg får ingen hjelp, men burde ha hatt det ..... ☐ 5

Jeg får ingen hjelp, og trenger det ikke ..... ☐ 6

KOSTHOLD

Hvor mange måltider spiser du vanligvis daglig (middag og brødmåltid)? ..... 127 (Antall)

Hvor mange dager i uka spiser du varm middag?

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis? *Inntil to kryss*

Brødtypen ligner mest på 129	*Loff* ☐	*Fint brød* ☐	*Kneipp-brød* ☐	*Grov-brød* ☐	*Knekke-brød* ☐

Hva slags *fett* blir vanligvis brukt i din husholding?

Ett kryss for matlaging og ett kryss for brød	*Til matlaging*		*På brød*	
Bruker *ikke* smør eller margarin	134 ☐	1	135 ☐	1
Meierismør	☐	2	☐	2
Hard margarin	☐	3	☐	3
Bløt (soft) margarin	☐	4	☐	4
Smør/margarin blanding	☐	5	☐	5
Lettmargarin	☐	6	☐	6
Oljer	☐	7		

Hvor mange glass melk (alle sorter, også drikkeyoghurt) drikker du vanligvis daglig? *Bare ett kryss* 136

Ingen ..... ☐ 1 — 1–2 glass ..... ☐ 3

Mindre enn ett ..... ☐ 2 — 3 eller mer ..... ☐ 4

Hvor mange brødskiver med kvitost spiser du vanligvis daglig? *Bare ett kryss* 137

Ingen ..... ☐ 1 — 1–2 skiver ..... ☐ 3

Mindre enn en ..... ☐ 2 — 3 eller mer ..... ☐ 4

HVILE OG AVSLAPPING

Hvor mange timer tilbringer du *vanligvis* i *liggende* stilling i løpet av et døgn? (nattesøvn, middagshvil) ..... 138 (Antall timer)

Hvor mange timer tilbringer du *vanligvis* i *sittende* stilling i løpet av et døgn? (arbeid, måltider, TV, bil etc.) ..... 140 (Antall timer)

Har du i løpet av siste måned hatt innsovningsproblemer? *Bare ett kryss* 142

Nesten hver natt ..... ☐ 1 — Av og til ..... ☐ 3

Ofte ..... ☐ 2 — Aldri ..... ☐ 4

Har du i løpet av siste måned våknet for tidlig og ikke fått sove igjen? *Bare ett kryss* 143

Nesten hver natt ..... ☐ 1 — Av og til ..... ☐ 3

Ofte ..... ☐ 2 — Aldri ..... ☐ 4

MEDISINBRUK

Har du i deler av de siste 12 måneder brukt noen medisiner daglig eller nesten daglig? ..... 144 Ja ☐ Nei ☐

Hvis "Ja":

Angi hvor mange måneder du brukte følgende medisiner: *Sett 0 hvis du ikke har brukt medisinene*

	Antall mndr.		Antall mndr.
smertestillende 145		hjertemedisin (ikke blodtrykksmedisin)	
sovemedisin 147		annen medisin	
beroligende medisin		*Kosttilskudd:*	
medisin mot depresjon		jerntabletter 161	
allergimedisin 153		vitamin D-tilskudd	
astmamedisin 155		andre vitamintilskudd	
		tran/fiskeoljer 167	

Hvor ofte har du brukt avslappende/beroligende medisin eller sovemedisin den siste måneden? 169

Daglig ..... ☐ 1 — Sjeldnere enn hver uke ☐ 3

Hver uke, men ikke hver dag ☐ 2 — Aldri ..... ☐ 4

VENNER

Hvor mange gode venner har du? Regn med de du kan snakke fortrolig med og som kan gi deg god hjelp når du trenger det ..... 170 (Antall)

Tell ikke med de du bor sammen med, men regn med andre slektninger

Føler du at du har mange nok gode venner? ..... 172 Ja ☐ Nei ☐

Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. syklubb, eldresenter, pensjonistforening, politiske lag, religiøse eller andre foreninger? *Bare ett kryss* 173

Aldri, eller noen få ganger i året ☐1 Omtrent en gang i uka ☐3
1–2 ganger i måneden ☐2 Mer enn en gang i uka ☐4

HUMØR OG TRIVSEL

Ett kryss på hver linje

Angi hvordan du har følt deg den siste måneden:	*Aldri*	*Noen ganger*	*Ganske ofte*	*For det meste*
i godt humør 174	☐	☐	☐	☐
i dårlig humør 175	☐	☐	☐	☐

	Svært treg	*Ganske treg*	*Ganske rask*	*Svært rask*
Er du rask til å oppfatte et humoristisk poeng? 176	☐	☐	☐	☐

Er du enig i at det er noe ansvarsløst over folk som stadig prøver å være morsomme? 177

Nei, slett ikke ☐1 Ganske enig ☐3
I noen grad ☐2 Ja, absolutt ☐4

Er du en munter person? 178

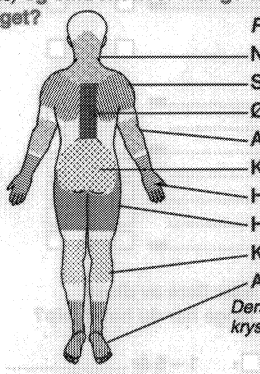
Nei, slett ikke ☐1 Ganske munter ☐3
I noen grad ☐2 Ja, absolutt ☐4

MUSKEL-/SKJELETTPLAGER

Har du hatt plager (smerter, verk, ubehag) i muskler og/eller ledd i *den siste måneden*? 179 — *Ja* ☐ *Nei* ☐

Hvis «Nei»: Gå til HODEPINE

Hvis «Ja»: Hvor har du hatt disse plagene *(ett eller flere kryss)* og omtrent hvor mange dager tilsammen var du plaget?



Plager (Sett kryss)		Antall dager
Nakke 180	☐	
Skuldre/aksler 183	☐	
Øvre del av ryggen	☐	
Albuer 189	☐	
Korsryggen 192	☐	
Handledd/hender	☐	
Hofter 198	☐	
Knær 201	☐	
Ankler/føtter 204	☐	

Dersom flere kryss: Sett ***ring*** *rundt krysset* ***der plagen var verst***

Har plagene hindret deg i å utføre daglige aktiviteter den siste måneden? 207 — *Ja* ☐ *Nei* ☐

HODEPINE

Har du vært plaget av hodepine i løpet av de siste 12 måneder? 208

Ja, anfallsvis (migrene) 1 ☐
Ja, annen slags hodepine 2 ☐
Nei 3 ☐

Antall anfall siste 12 mndr. 209 ☐☐☐

Hvis «Nei»: Gå til URINLEKKASJE

Omtrent hvor mange dager pr. måned har du hodepine?
Mindre enn 7 dager ☐1 7 til 14 dager ☐2 Mer enn 14 d. ☐3

Hvor lenge varer hodepinen vanligvis hver gang? 212
Mindre enn 4 timer ☐1 4 timer–3 døgn ☐2 Mer enn 3 døgn ☐3

Hvor ofte er hodepinen preget av eller ledsaget av:

Ett kryss på hver linje	*Sjelden eller aldri*	*Av og til*	*Ofte*
bankende/dunkende smerte 213	☐	☐	☐
pressende smerte	☐	☐	☐
halvsidighet, alltid samme side	☐	☐	☐
halvsidighet, vekselvis h. og v. side	☐	☐	☐
smerter i «hele hodet»	☐	☐	☐
kvalme 218	☐	☐	☐
lys- og/eller lydskyhet	☐	☐	☐
forverring ved fysisk aktivitet	☐	☐	☐
synsforstyrrelser *før* hodepine 221	☐	☐	☐

Hvor mange tabletter/stikkpiller har du eventuelt brukt av disse medisinene *alt i alt i løpet av den siste måneden*?

Skriv 0 hvis du ikke har brukt medisinen.

Cafergot 222 ☐☐ Anervan 224 ☐☐ Imigran 226 ☐☐

URINVEGS- OG PROSTATAPLAGER

Ett kryss på hver linje

Har du noen gang blitt fortalt av lege at du har:	*Ja*	*Nei*
forstørret prostata 228	☐	☐
prostatakreft 229	☐	☐

Har du gjennomgått noe av følgende:	*Ja*	*Nei*
sterilisering 230	☐	☐
tatt vevsprøve (biopsi) av prostata 231	☐	☐
kirurgisk fjerning av prostata (helt eller delvis) 232	☐	☐

De neste spørsmålene gjelder siste måned
Bare ett kryss for hvert hver spørsmål

Hvor ofte har du hatt følelsen av at blæren ikke er blitt fullstendig tømt etter avsluttet vannlating? 233

Aldri ☐1 Omtrent annenhver gang ☐4
Omtrent 1 av 5 ganger ☐2 Omtrent 2 av 3 ganger ☐5
Omtrent 1 av 3 ganger ☐3 Nesten alltid ☐6

Hvor ofte har du måttet late vannet på nytt mindre enn 2 timer etter forrige vannlating? 234

Aldri ☐1 Omtrent annenhver gang ☐4
Omtrent 1 av 5 ganger ☐2 Omtrent 2 av 3 ganger ☐5
Omtrent 1 av 3 ganger ☐3 Nesten alltid ☐6

Hvor ofte har du måttet stoppe og starte flere ganger under vannlatingingen? 235

Aldri ☐1 Omtrent annenhver gang ☐4
Omtrent 1 av 5 ganger ☐2 Omtrent 2 av 3 ganger ☐5
Omtrent 1 av 3 ganger ☐3 Nesten alltid ☐6

Hvor ofte syns du det har vært vanskelig å holde igjen når du har følt trang til å late vannet? 236

Aldri ☐1 Omtrent annenhver gang ☐4
Omtrent 1 av 5 ganger ☐2 Omtrent 2 av 3 ganger ☐5
Omtrent 1 av 3 ganger ☐3 Nesten alltid ☐6

Hvor ofte har du hatt svak urinstråle? 237

Aldri ☐1 Omtrent annenhver gang ☐4
Omtrent 1 av 5 ganger ☐2 Omtrent 2 av 3 ganger ☐5
Omtrent 1 av 3 ganger ☐3 Nesten alltid ☐6

Hvor ofte har du måttet trykke eller presse for å begynne vannlatingen? 238

Aldri ☐1 Omtrent annenhver gang ☐4
Omtrent 1 av 5 ganger ☐2 Omtrent 2 av 3 ganger ☐5
Omtrent 1 av 3 ganger ☐3 Nesten alltid ☐6

Hvor mange ganger har du vanligvis måttet stå opp i løpet av natta for å late vannet? 239

Ingen ☐1 2 ganger ☐3 4 ganger ☐5
1 gang ☐2 3 ganger ☐4 5 ganger eller mer ☐6

Hvis du resten av livet måtte leve med de vannlatingsproblemene du har nå, hvordan ville du føle det? 240

Være meget godt fornøyd ☐1 Være for det meste utilfreds ☐5
Være fornøyd ☐2 Være misfornøyd ☐6
Være for det meste tilfreds ☐3 Ha det forferdelig ☐7
Ha blandete følelser ☐4

HVORDAN DU SER PÅ DEG SELV

Folk ser på seg selv på ulike måter. Kryss av for hvert utsagn hvor enig eller uenig du er. ***Ett kryss på hver linje***

	Svært enig	*Enig*	*Uenig*	*Svært uenig*
Jeg har en positiv holdning til meg selv 241	☐	☐	☐	☐
Jeg føler meg virkelig ubrukelig til tider 242	☐	☐	☐	☐
Jeg føler at jeg ikke har mye å være stolt av 243	☐	☐	☐	☐
Jeg føler at jeg er en verdifull person, i allefall på lik linje med andre 244	☐	☐	☐	☐

	Ja	*Nei*
Synes du at du har funnet et virkelig betydningsfullt innhold i livet ditt? 245	☐	☐
Føler du at du lever fullt ut? 246	☐	☐

HVORDAN DU FØLER DEG NÅ

Sett kryss i den ruta utenfor det svaret som best beskriver dine følelser ***den siste uka.*** ***Bare ett kryss***

Føler du deg stort sett sterk og opplagt, eller trøtt og sliten? 247

Meget sterk og opplagt ☐1 Ganske trøtt og sliten ☐5
Sterk og opplagt ☐2 Trøtt og sliten ☐6
Ganske sterk og opplagt ☐3 Svært trøtt og sliten ☐7
Både – og ☐4

Har du i det store og hele en rolig og god følelse inne i deg? 248

Nesten hele tida ☐1 Av og til ☐3
Ofte ☐2 Aldri ☐4

Er du vanligvis glad eller nedstemt? 249

Svært nedstemt ☐1 Nokså glad ☐5
Nedstemt ☐2 Glad ☐6
Nokså nedstemt ☐3 Svært glad ☐7
Både – og ☐4

LEGEMLIGE FUNKSJONER

Klarer du selv, uten hjelp av andre, i det daglige å:
Ett kryss på hver linje

	Ja	*Med noe hjelp*	*Nei*
Gå innendørs i samme etasje 250	☐	☐	☐
Gå på toalettet	☐	☐	☐
Vaske deg på kroppen 252	☐	☐	☐
Bade eller dusje	☐	☐	☐
Kle på og av deg 254	☐	☐	☐
Legge deg og stå opp	☐	☐	☐
Spise selv 256	☐	☐	☐

Hvis du har hatt hjelp til noe av dette, omtrent hvor lenge har du hatt hjelp? ***Bare ett kryss*** 257

Under 3 måneder ☐1 1 – 5 år ☐4
3 – 6 måneder ☐2 Mer enn 5 år ☐5
1/2 – 1 år ☐3

Hvis du trenger hjelp til ett eller flere av disse gjøremålene, hvem er det som for det meste hjelper deg? ***Bare ett kryss***

Ektefelle/samboer ☐1 Annen familie/slekt ☐4
Barn/svigerbarn ☐2 Andre ☐5
Søster/bror ☐3

DAGLIGE OPPGAVER

Klarer du selv disse gjøremålene i det daglige uten hjelp fra andre? ***Ett kryss på hver linje***

	Ja	*Med noe hjelp*	*Nei*
Lage varm mat 259	☐	☐	☐
Gjøre lett husarbeid (f.eks. oppvask)	☐	☐	☐
Gjøre tyngre husarbeid (f.eks. gulvvask) 261	☐	☐	☐
Vaske klær	☐	☐	☐
Betale regninger 263	☐	☐	☐
Ta medisinene	☐	☐	☐
Komme deg ut 265	☐	☐	☐
Gjøre innkjøp	☐	☐	☐
Ta bussen 267	☐	☐	☐

Hvis du trenger hjelp til ett eller flere av disse gjøremålene, omtrent hvor lenge har du hatt hjelp? ***Bare ett kryss*** 268

Under 3 måneder ☐1 1 – 5 år ☐4
3 – 6 måneder ☐2 Mer enn 5 år ☐5
1/2 – 1 år ☐3

Hvis du trenger hjelp til ett eller flere av disse gjøremålene, hvem er det som for det meste hjelper deg? ***Bare ett kryss*** 269

Ektefelle/samboer ☐1 Annen familie/slekt ☐4
Barn/svigerbarn ☐2 Andre ☐5
Søster/bror ☐3

Legg det utfylte spørreskjemaet i den vedlagte svarkonvolutten og postlegg den så snart som mulig!
Porto er betalt.
Hjertelig takk for hjelpa!

Steinkjer Trykkeri AS – 74 16 30 00

hunt-lunge

Helseundersøkelsen i Nord-Trøndelag

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss her og returner skjemaet. Da slipper du purring.
Jeg ønsker ikke å besvare skjemaet ○

Ved at du fyller ut dette skjemaet hjelper du oss i arbeidet med å forbedre behandlingen av lungesykdommer ! Les forøvrig brosjyren «hunt - spesial» som du fikk ved Helseundersøkelsen.

Lykke til !

Blir du vanligvis tungpust, får piping i brystet eller uttalt hoste i disse situasjoner:

	Ja	Nei
* Ved fysisk aktivitet utendørs i kaldt vær?	☐	☐ 01
* I støvete eller røykfylte omgivelser?	☐	☐ 02
* Ved mye bileksos eller andre former for luftforurensning?	☐	☐ 03
* Ved sterke lukter, parfymer, krydder, såper, trykksverte osv?	☐	☐ 04

Når du er i nærheten av dyr, fjær eller i en støvfylt del av huset, har du da noen gang opplevd at du:

	Ja	Nei
* Starter å hoste?	☐	☐ 05
* Får piping i brystet?	☐	☐ 06
* Føler deg tett i brystet?	☐	☐ 07
* Føler deg tungpust?	☐	☐ 08
* Får tett eller rennende nese eller begynner å nyse?	☐	☐ 09
* Får kløe eller renning fra øyne?	☐	☐ 10

Når du er i nærheten av trær, gress, blomster eller når det er mye pollen, har du da noen gang opplevd at du:

	Ja	Nei
* Starter å hoste?	☐	☐ 11
* Får piping i brystet?	☐	☐ 12
* Føler deg tett i brystet?	☐	☐ 13
* Føler deg tungpust?	☐	☐ 14
* Får tett eller rennende nese eller begynner å nyse?	☐	☐ 15
* Får kløe eller renning fra øyne?	☐	☐ 16

	Ja	Nei
Får du tung pust eller pipelyder i brystet under arbeid?	☐	☐ 17
Har du noen gang skiftet eller sluttet i arbeid fordi du ble plaget med pusten?	☐	☐ 18

Hvis «Ja» på forrige spørsmål, hvilket yrke var det?

..... 19
(Skriv hvilket yrke her)

	Ja	Nei
Blir du mer tungpust (andpusten) enn jevnaldrende når du går i motbakker?	☐	☐ 20
Blir du tungpust når du går opp 2 etasjer i vanlig fart?	☐	☐ 21
Blir du tungpust når du går med vanlig fart på flat mark?	☐	☐ 22
Er du tungpust når du sitter i ro?	☐	☐ 23

I hvor stor grad vil du si at pusteplager hemmer dine daglige aktiviteter? (sett ett kryss)

Ikke i det hele tatt	Litt	I stor grad	I svært stor grad	
☐	☐	☐	☐	24

Da du var barn, hadde dere noen av følgende kjæledyr:

	Ja	Nei
* Katter ?	☐	☐ 25
* Hunder ?	☐	☐ 26
* Hester ?	☐	☐ 27
* Fugler ?	☐	☐ 28
* Andre pelskledde dyr?	☐	☐ 29

	Ja	Nei
Har du fått diagnosen astma av lege?	☐	☐ 30
Har du fått diagnosen kronisk bronkitt eller emfysem av lege?	☐	☐ 31
Har du vært til undersøkelse hos allmennpraktiserende lege pga pusteplager?	☐	☐ 32
Hvis «Ja», er det tatt pusteprøve av deg der?	☐	☐ 33
Har du vært til undersøkelse hos barnelege, lungelege eller annen sykehuslege pga pusteplager?	☐	☐ 34
Hvis «Ja», har du vært til undersøkelse hos slik lege siste 12 mnd?	☐	☐ 35

Vennligst legg skjemaet i samme konvolutt som det andre skjemaet du fikk ved Helseundersøkelsen og postlegg den snarest. Porto er betalt.

Hjertelig takk for hjelpen!

hunt-lunge

Helseundersøkelsen i Nord-Trøndelag

Personnr: ☐☐☐☐☐☐☐☐☐☐☐

Utfylt dato ☐☐☐☐☐☐

Blir du vanligvis tungpust, får piping i brystet eller uttalt hoste i disse situasjoner:

	Ja	Nei
* Ved fysisk aktivitet utendørs i kaldt vær?	☐	☐ 01
* I støvete eller røykfylte omgivelser?	☐	☐ 02
* Ved mye bileksos eller andre former for luftforurensning?	☐	☐ 03
* Ved sterke lukter, parfymer, krydder, såper, trykksverte osv?	☐	☐ 04

Når du er i nærheten av dyr, fjær eller i en støvfylt del av huset, har du da noen gang opplevd at du:

	Ja	Nei
* Starter å hoste?	☐	☐ 05
* Får piping i brystet?	☐	☐ 06
* Føler deg tett i brystet?	☐	☐ 07
* Føler deg tungpust?	☐	☐ 08
* Får tett eller rennende nese eller begynner å nyse?	☐	☐ 09
* Får kløe eller renning fra øyne?	☐	☐ 10

Når du er i nærheten av trær, gress, blomster eller når det er mye pollen, har du da noen gang opplevd at du:

	Ja	Nei
* Starter å hoste?	☐	☐ 11
* Får piping i brystet?	☐	☐ 12
* Føler deg tett i brystet?	☐	☐ 13
* Føler deg tungpust?	☐	☐ 14
* Får tett eller rennende nese eller begynner å nyse?	☐	☐ 15
* Får kløe eller renning fra øyne?	☐	☐ 16

	Ja	Nei
Får du tung pust eller pipelyder i brystet under arbeid?	☐	☐ 17
Har du noen gang skiftet eller sluttet i arbeid fordi du ble plaget med pusten?	☐	☐ 18

Hvis «Ja» på forrige spørsmål, hvilket yrke var det?

..... 19

(Skriv hvilket yrke her)

	Ja	Nei
Blir du mer tungpust (andpusten) enn jevnaldrende når du går i motbakker?	☐	☐ 20
Blir du tungpust når du går opp 2 etasjer i vanlig fart?	☐	☐ 21
Blir du tungpust når du går med vanlig fart på flat mark?	☐	☐ 22
Er du tungpust når du sitter i ro?	☐	☐ 23

I hvor stor grad vil du si at pusteplager hemmer dine daglige aktiviteter? (sett ett kryss)

Ikke i det hele tatt	Litt	I stor grad	I svært stor grad	
☐	☐	☐	☐	24

Da du var barn, hadde dere noen av følgende kjæledyr:	Ja	Nei
* Katter ?	☐	☐ 25
* Hunder ?	☐	☐ 26
* Hester ?	☐	☐ 27
* Fugler ?	☐	☐ 28
* Andre pelskledde dyr?	☐	☐ 29

	Ja	Nei
Har du fått diagnosen astma av lege?	☐	☐ 30
Har du fått diagnosen kronisk bronkitt eller emfysem av lege?	☐	☐ 31
Har du vært til undersøkelse hos allmennpraktiserende lege pga pusteplager?	☐	☐ 32
Hvis «Ja», er det tatt pusteprøve av deg der?	☐	☐ 33
Har du vært til undersøkelse hos barnelege, lungelege eller annen sykehuslege pga pusteplager?	☐	☐ 34
Hvis «Ja», har du vært til undersøkelse hos slik lege siste 12 mnd?	☐	☐ 35
Har du i løpet av de siste 12 måneder brukt medisiner for å lette pusten ?	☐	☐ 36

Hvis «Ja», hvor ofte er medisiner som berotec, bricanyl, ventolin eller salbuvent brukt siste måned?

aldri	sjeldnere enn en gang i uken	flere ganger i uken, men ikke hver dag	daglig	
☐	☐	☐	☐	37

Vennligst fortsett på neste side.

URN:NBN:no-3454

Har du brukt medisiner som pustes inn av type Becotide, Flutide eller Pulmicort regelmessig noen gang? *Ja* ☐ *Nei* ☐ 39

Hvis «Ja»

Har du brukt slike medisiner regelmessig siste halvår? *Ja* ☐ *Nei* ☐ 40

Bruker du slike medisiner nå? *Ja* ☐ *Nei* ☐ 41

Har du brukt medisiner som Becotide, Flutide, Lokilan eller Rhinocort i nesen regelmessig noen gang? *Ja* ☐ *Nei* ☐ 42

Hvis «Ja»

Har du brukt slike medisiner regelmessig siste halvår? *Ja* ☐ *Nei* ☐ 43

Bruker du slike medisiner nå? *Ja* ☐ *Nei* ☐ 44

Har du siste 2 måneder fått kortisonsprøyte for allergi, senebetennelse eller leddbetennelse? *Ja* ☐ *Nei* ☐ 45

Har du siste 2 måneder brukt Prednisolon eller Prednison tabletter? *Ja* ☐ *Nei* ☐ 46

Har du noen gang problemer med pusten? *Ja* ☐ *Nei* ☐ 47

Hvis nei, gå til spørsmål 51
hvis ja, fortsett med neste spørsmål.

Hvis du har problemer med pusten, har du det:

sett kryss i en rute

A. Svært sjelden ☐ 48

B. Gjentatte ganger, men blir oftest helt bra ☐

C. Hele tiden og er aldri helt bra ☐

Hvis du tenker på hvordan du har hatt det siste 6 måndeder; hvor ofte har du hatt episoder med tung og/eller pipende pust OM DAGEN?

sett kryss i en rute

aldri ☐ 49

sjeldnere enn 1 gang pr måned ☐

1-2ganger per måned ☐

3-4ganger per måned ☐

oftere enn 4ganger per måned ☐

oftere enn 3 ganger per uke ☐

Hvis du tenker på hvordan du har hatt det siste 6 måndeder; hvor ofte har du hatt episoder med tung og/eller pipende pust OM NATTEN?

sett kryss i en rute

aldri ☐ 50

sjeldnere enn 1 gang pr måned ☐

1-2ganger per måned ☐

3-4ganger per måned ☐

oftere enn 4ganger per måned ☐

oftere enn 3 ganger per uke ☐

Spørsmål 51:

Har du vansker med førligheten av annen grunn enn lungesykdom?

Nei ☐ 51

Ja, p.g.a hjertesykdom ☐

Ja, p.g.a. annen sykdom ☐

Har noen av spørsmålene på dette skjemaet vært vanskelig å forstå? *Ja* ☐ *Nei* ☐ 52

Hvis ja; angi nummer på vanskelige spørsmål:

☐☐ ☐☐ ☐☐ ☐☐ ☐☐

Takk for hjelpen!

Appendix 3

English version of key questions at questionnaires and interview

URN:NBN:no-3454

English version of key questions and alternative answers used in the study

Questionnaire I

Do you cough daily during periods of the year? Yes No

If Yes:

Do you usually bring up pleghm when coughing? Yes No

Have you had cough with phlegm for periods of at least three months during each of the last two years? Yes No

Have you had any attack of wheezing or breathlessness during the last 12 months? Yes No

Do you have or have you had asthma? Yes No

Do you use or have you used asthma medication? Yes No

Did any of the adults smoke in your home when you were a child? Yes No

Do you live or have lived together with daily smokers after the age of 20 years? Yes No

How many hours do you usually spend in rooms with tobacco smoke? .....hours

Do you smoke?

Cigarettes daily? Yes No

Cigars/cigarillos daily? Yes No

Pipe daily? Yes No

Never smoked daily ☐

If you have smoked earlier; how many years is it since you stopped? .....Years

If You smoke daily now or have smoked earlier:

How many cigarettes do you smoke or did you smoke usually per day? .....

How old were you when you started smoking? .....Years

How many Years altogether have you smoked? .....Years

Interview

1. Have you had wheezing in your chest at any time in the last 12 months? Yes No
   - 1.1 Have you been at all breathless when the wheezing noise was present? Yes No
   - 1.2 Have you had this wheezing when you did not have a cold? Yes No

2 . Have you any time during the last 12 months had breathlessness during the day when you were not doing anything strenuous? Yes No

3 Have you any time during the last 12 months had attacks of breathlessness after strenuous activity? Yes No

4 Have you any time during the last 12 months been woken at night because of breathlessness? Yes No

5 Have you ever had asthma? Yes No
   - 5.1 How old were you first time you had symptoms of asthma? ☐☐ Years
   - 5.2 How old were you last time you had symptoms of asthma? ☐☐Years
   - 5.3 Have you had symptoms of asthma (breathlessness, wheezing) last 12 months? Yes No

6 Have you during the last 12 months used medicine to relieve breathlessness? (asthma medicine)? Yes No
   if No:
   - 6.1 Have you used such medicine earlier? Yes No

	Daily	2-6 times/week	≤1/week
7 If you use asthma medicine now:			
7.1 How often have you last month used Bricanyl, Ventoline, or Salbuvent?	☐	☐	☐
7.2 How often have you last month used Serevent	☐	☐	☐
7.3 How often have you last month used Atrovent?	☐	☐	☐
7.4 How often have you last month used tablets as Nuelin Depot or TheoDur?	☐	☐	☐
7.5 How often have you last month used Lomudal?	☐	☐	☐

8. Have you ever used medicines as Becotide, Flutide, Pulmicort or viarox regularly? Yes No

9. Have you used such medicines regularly last 6 months? Yes No

9.1 If Yes; which type have you used?
- Becotide/Viarox ☐
- Flutide ☐
- Flunitec ☐
- Pulmicort ☐
- Don't know ☐

9.2 Which daily dose of medicines have you used last week?
(microgram x inhalations) (don't know = 999) ☐☐☐☐ ug

9.3 How is this medicine inhaled the last year? (Becotide, Flutide, Pulmicort)?
Powder☐ Aerosol☐ Aerosol with inhaler ☐

9.4 For how long time have you altogether used medicines as Becotide, Flutide, Pulmicort and Viarox?
< 6 months ☐ 6-12 months ☐ 1-4 Years ☐ 5-10 Years ☐ > 10 Years ☐

10. Have you ever used cortisone tablets (Prednisone, Prednisolone, Celestone) because of breathlessness/asthma? Yes No

11. Have you used cortisone tablets regularly because of breathlessness/asthma last month? Yes No
11.1 If Yes, which type?
Prednisone ☐ Prednisolone ☐ Celestone ☐ others ☐
11.2 What is the daily dose last week? ☐☐ mg
11.3 For how long time have you altogether used Cortisone tablets (Prednisone, Prednisolone, Celestone) because of asthma?
< 6 months ☐ 6-12 months ☐ 1-4 Years ☐ 5-10 years ☐ >10 Years ☐

12 If you haven't used cortisone tablets regularly;
haveyou used it during periods of exacerbations of the disease? Yes No
If Yes:
12.1. How many courses last 12 months? ☐☐
12.2. How many courses last 24 months? ☐☐

13. Have you used Cortisone tablets (Prednisone / Prednisolone or Celestone) because of other disease than asthma? Yes No
13.1 If Yes, for how long time have you altogether used Cortisone tablets for other disease than asthma?
< 6 months ☐ 6-12 months ☐ 1-4 Years ☐ 5-10 years ☐ >10 Years ☐

14. Sitting height ..... cm

In addition from January 1997

15. Have you ever used nasal aerosol or powder as Becotide, Flutide, Lokilan or Rhinocort regularly? Yes No

16. For how long time have you altogether used such medicine in the nose?
< 6 months ☐ 6-12 months ☐ 1-4 Years ☐ 5-10 years ☐ >10 Years ☐

17. Have you ever got any injection with cortisone because of allergy, tendinitis or arthritis? Yes ☐ No ☐

18. How many injections have you got during the last 2 years? ☐☐☐

19. Do you at any time have breathing trouble? Yes ☐ No ☐

19.1. Which of the following statements do best describe your breathing?

A. I rarely have trouble with my breathing ☐

B. I get repeated trouble with my breathing, but it usually gets completely better ☐

C. I have trouble with my breathing all the time and is never quite right ☐

20. How often have you during the last 6 months had attacks of breathlessness and/or wheezing during the day?

never ☐ <1 time/month ☐ 1-2 times/month ☐
3-4 times/month ☐ >4 times/month ☐ >3 times/week ☐

21. How often have you during the last 6 months had attacks of breathlessness and/or wheezing during the night?

never ☐ <1 time/month ☐ 1-2 times/month ☐
3-4 times/month ☐ >4 times/month ☐ >3 times/week ☐

22. Are your activity level reduced because of any other reason than pulmonary disease?

No ☐ Yes; because of cardial disease ☐ Yes; because of other disease ☐

hunt-lung Identific: ☐☐☐☐☐☐☐☐☐☐☐

The Health Survey in Nord-Trøndelag Date ☐☐☐☐☐☐

Do You usually have breathlessness, wheeze or severe cough:

	Yes	No
* at exercise in cold weather	☐	☐ 1
* in dusty or smoky environment.....	☐	☐02
* by car exhaust or other air pollution	☐	☐ 03
* by strong smelling scents (perfumes, spices, printing ink etc.)	☐	☐04

When You are in a dusty part of the house or near animals, or feathers, have you ever:

	Yes	No	
* Started to cough?.....	☐	☐	5
* Got wheezing in the chest.....	☐	☐	6
* Got a feeling of tightness in the chest.....	☐	☐	7
* Had breathlessness.....	☐	☐	8
* Got nasal stenosis or secretion, or started sneezing.....	☐	☐	9
* Got itching in the eyes.....	☐	☐	10

When You are near threes, grass, flowers or at periods with high level of pollen, have you ever:

	Yes	No
* Started to cough?.....	☐	☐11
* Got wheezing in the chest.....	☐	☐12
* Got a feeling of tightness in the chest.....	☐	☐13
* Had breathlessness.....	☐	☐14
* Got nasal stenosis or secretion, or started sneezing.....	☐	☐15
* Got itching in the eyes.....	☐	☐16

Do You have breathlessness or wheezing during work? Yes ☐ No ☐17

Have You ever had to quit a job because of trouble with your breathing? Yes ☐ No ☐ 18

If «Yes» which job did you quit?

..... 19

Do You get more breathlessness than other persons at your age when walking uphill? ☐ ☐20

Do You get breathlessness when ascending the stairs for two levels at usual speed..... ☐ ☐ 21

Do You get breathlessness when walking at usual speed ..... ☐ ☐22

Do You have breathlessness at rest? ☐ ☐ 23

To what extent do Your breathing trouble limit yours daily activities?

Not at all	Little	Much	Very much	
☐	☐	☐	☐	24

When You were a child, did You have any of these animals?

	Yes	No
* Cats?.....	☐	☐25
* Dogs?.....	☐	☐26
* Horses?.....	☐	☐27
* Birds?.....	☐	☐28
* Other?	☐	☐29

	Yes	No
Have You been diagnosed as having asthma by Your doctor?	☐	☐30
Have You been diagnosed as having chronic bronchitis or emphysema by your doctor?	☐	☐31
Have You been to a general practitioner because of breathing trouble?....	☐	☐32
If «Yes», was any lung function measurement performed?.....	☐	☐33
Have You been to a paediatrician, pulmonologist or other doctor at hospital because of breathing trouble?	☐	☐34
If «Yes», have You been there last 12 months?.....	☐	☐35

Appendix 4

Invitation to sub-studies at the screening station and phase II
Written informed consent for sub-studies and BONT phase III

URN:NBN:no-3454

hunt - spesial

Helseundersøkelsen i Nord-Trøndelag

I denne brosjyren kan du lese om de spesialundersøkelsene som inngår i ***hunt***. Du bør lese den første siden og videre om de undersøkelsene som er aktuelle for deg. De er merket av med kryss.

Du har fått en orientering om Helseundersøkelsen i Nord-Trøndelag ***(hunt)*** i brosjyren som var vedlagt invitasjonsbrevet til undersøkelsen. Brosjyren gir en oversikt over de basisundersøkelsene som inngår. I tillegg omfatter ***hunt*** også en del spesialundersøkelser ***(hunt-spesial).*** Alle får tilbud om disse to spesialundersøkelsene:

* *Hørsel*
* *Jernmetning i blodet*

I tillegg får mange tilbud om andre spesialundersøkelser, enten fordi de har bestemte sykdommer eller plager, eller fordi de er valgt ut til å få en ekstra helsesjekk. Dette gjelder undersøkelser for:

* *Lungesykdommer*
* *Beinskjørhet (osteoporose)*
* *Eggehvite (albumin) i urin*
* *Diabetes (sukkersyke)*
* *Høgt blodtrykk*
* *Syn*
* *Stoffskifte*
* *Magesårbakterien*

Resultatene fra undersøkelsene kan være viktige for deg, og vi håper du vil være med!

Men ikke bare for din egen skyld!

Undersøkelsene er også viktige for å gi bedre kunnskap om ulike sykdommer, slik at disse kan forebygges eller behandles bedre. Navn og personnummer fjernes før forskerne får tilgang på data. Det vil ikke bli offentliggjort data eller statistikk der enkeltpersoner kan gjenkjennes. Helseundersøkelsen er godkjent av Datatilsynet og Regional komite for medisinsk forskningsetikk. Andre forskere enn de som står bak de ulike delene av ***hunt,*** vil bare få tilgang til data etter begrunnet søknad til og godkjenning fra disse.

Resultatene fra ***hunt*** vil få stor betydning for medisinsk forskning i mange år framover, og Datatilsynet har derfor ikke satt noen spesiell tidsbegrensning for hvor lenge opplysningene kan lagres. Data vil altså ikke bli slettet uten at den enkelte selv ber om det.

Samtykkeerklæringen som vi har bedt deg fylle ut, omhandler både basisundersøkelsene og spesialundersøkelsene ***(hunt-spesial).*** Du kan fritt nå eller seinere takke nei til å være med på hele eller deler av undersøkelsen.

Ønsker du nærmere opplysninger om hunt kan du ringe Folkehelsa i Verdal, tlf. 74 07 03 01, eller kontakte den aktuelle prosjektlederen

☐ Hørsel

**** Hvem får dette tilbudet ?***
Alle som blir undersøkt fra januar 1996, dersom kommunen har sagt ja til denne undersøkelsen.
**** Hva går undersøkelsen ut på ?***
- Spørreskjema som fylles ut på venterommet før selve undersøkelsen.
- Hørselsundersøkelse som gjennomføres i et lydisolert rom og med hodetelefoner. Du markerer at du hører en lyd ved å trykke på en knapp. Undersøkelsen tar 10-15 minutter.

**** Hva får du vite ?***
Hvis du får registrert et hørselstap over ei viss grense, vil du seinere få et brev med beskjed om hva slags hørselstap du har. Hvis hørselen din er kraftig nedsatt, og opplysninger i spørreskjemaet tyder på at du trenger en grundigere undersøkelse, blir du anbefalt å be om time hos lege. Om nødvendig vil legen henvise deg videre til hørselspesialist ved Namdal eller Innherred sykehus.

Prosjektleder: Professor Kristian Tambs, Folkehelsa, Oslo

☐ Jernmetning

**** Hvem får dette tilbudet ?***
Alle som deltar i Helseundersøkelsen.
**** Hvorfor er dette viktig ?***
Hovedformålet er å finne fram til de som har unormalt *høy* jernmetning. Jernmetning har sammenheng med jerninnhold i blodet.
For *høy* jernmetning - *hemokromatose* - er en arvelig tilstand som etter mange år uten behandling kan føre til alvorlig sykdom. Vi vet ikke hvor vanlig dette er. Dersom diagnosen stilles i rett tid, er behandlingen enkel og effektiv.
Ved denne undersøkelsen vil vi også finne ut om du har for *lav* jernmetning, selv om dette ikke har noe med *hemokromatose* å gjøre.
**** Hva går undersøkelsen ut på ?***
Målingene gjøres i den blodprøven som blir tatt av deg, og som blir sendt til Innherred sykehus.
**** Hva får du vite ?***
Dersom prøven tyder på at jernmetningen er for *høy* eller for *lav*, får du brev om det fra Innherred sykehus. Dersom prøven tyder på at jernmetningen er for *høy*, vil du også få beskjed om å ta ny prøve.
Om *denne* blodprøven også viser for høy verdi, vil du få tilbud om legeundersøkelse ved Innherred eller Namdal sykehus.
Hvis jernmetningen er for *lav*, kan du få ulike råd avhengig av alder og kjønn. Dersom du oppfordres om å kontakte lege er det viktig at du gjør dette.

Prosjektleder: Overlege Kristian Hveem, Innherred sykehus

☐ Lungesykdommer

**** Hvem får dette tilbudet ?***
Du får tilbud om disse undersøkelsene dersom du har brukt astmamedisiner, har astma, eller har astmalignende symptomer. Om du er trukket ut, kan du få dette tilbudet selv om du ikke har spesielle plager.
**** Hva går undersøkelsen ut på ?***
- *Spørreskjema* om lungesykdommer.
- *Undersøkelse 1*: Pusteprøve for å måle lunge-kapasiteten, spørsmål om medisinbruk, måling av beinmasse. Undersøkelsen varer 10-15 min. I de fem største kommunene blir disse undersøkelsene gjennomført samtidig med basisundersøkelsen. I de andre kommunene blir de gjennomført noen måneder seinere.
- *Undersøkelse 2:* Dersom du har nedsatt pustekapasitet eller det er tvil om dette, får du tilbud om ny pusteprøve.
-*Undersøkelse 3*: I Levanger, Verdal og Steinkjer vil noen med og noen uten symptomer på overfølsomme luftveier få invitasjon til utvidet pusteprøve og allergitest.

**** Hva får du vite?***
Etter undersøkelsen får du vite om resultatet av pusteprøven er normalt eller for lavt. Om du ønsker det, vil resultatene bli sendt til legen din. Hvis du ikke får spesiell beskjed, er det *ikke* nødvendig at du kontakter egen lege om resultatet, men du kan drøfte det med legen din ved anledning.

Prosjektleder: Allmennpraktiserende lege/stipendiat Arnulf Langhammer, Steinkjer/Folkehelsa,Verdal.

☐ Beinskjørhet (osteoporose)

**** Hvem får dette tilbudet ?***
Beinskjørhet er vanligst hos kvinner og øker med alderen. I ***hunt*** tilbyr vi derfor beinmassemåling til kvinner over 65 år og omtrent halvparten av kvinner i alderen 32-41 år og 50-59 år. Et utvalg kvinner og menn i ulike andre aldersgrupper vil også bli tilbudt undersøkelse.
I første omgang er det de som bor i kommunene Levanger, Steinkjer, Verdal, Stjørdal og Namsos som får tilbud om beinmassemåling.
Beinmassemåling gjøres også i andre kommuner på de gruppene som er nevnt under lungesykdommer.
**** Hva går undersøkelsen ut på ?***
Du sitter med underarma i et vannbad i ca. fem minutter. Ved hjelp av meget svake røntgenstråler måles beinmassen i underarma. Undersøkelsen er smertefri og uten risiko. Strålemengden er ikke større enn den strålingen alle får i løpet av to dager der de bor. Gravide kan derfor trygt undersøkes.
**** Hva får du vite?***
Etter undersøkelsen får du beskjed om resultatet av beinmassemålingen. Du får vite om resultatet er innenfor normalområdet eller lavere.
Ved lave verdier vil du bli anbefalt å ta kontakt med lege, og vi sender da også resultatene til legen din om du ønsker det.

Prosjektleder: Forskningsleder Berit Schei, Institutt for samfunnsmedisinske fag, NTNU, Trondheim

☐ Måling av eggehvite (albumin) i urin

**** Hvorfor er dette viktig ?***
Undersøkelsen kan påvise *små* mengder eggehvite (albumin) i urinen og er mye mer følsom enn vanlig urinundersøkelse. Økt kunnskap om dette kan ha betydning i arbeidet med å forebygge hjerte- og karsykdommer og nyreskader. I mange tilfeller vil små mengder eggehvite ikke ha noen spesiell betydning, men dette må avklares gjennom en ny prøve. I andre tilfeller kan dette tyde på en begynnende skade av nyrene. Ved å oppdage dette tidlig kan det gis behandling, slik at forverring unngås eller forsinkes.
****Hvem får dette tilbudet?*** Du får tilbud om denne undersøkelsen dersom du har svart at du har diabetes (sukkersyke), eller om du bruker medisin mot høgt blodtrykk eller dersom du er trukket ut til å delta i denne undersøkelsen.
**** Hva går undersøkelsen ut på ?***
Du får med en konvolutt med tre prøveglass og tre plastbegre. Vi ber deg sende inn urinprøver fra tre dager (morgenurin) i disse glassene. Det er vedlagt egen veiledning for hvordan prøvene skal tas. Porto er betalt.
**** Hva får du vite ?***
Hvis du har *diabetes* eller bruker *blodtrykksmedisin*, vil legen din få beskjed om resultatet dersom du ønsker det. Du kan drøfte resultatet med legen neste gang du møter til kontroll. Det er ikke nødvendig å bestille ny ekstra time, dersom du allerede har avtale om regelmessig legekontroll. Dersom du *ikke* har diabetes og *ikke* bruker blodtrykksmedisin og prøveresultatet *ikke* er normalt, vil du bli kontaktet spesielt om videre oppfølging.

Prosjektledere: Overlege Hans Hallan, Innherred sykehus og kommunelege I Kurt Kvenild, Nærøy

☐ Diabetes (sukkersyke)

**** Hvem får dette tilbudet ?***
Du som har svart at du har eller har hatt diabetes.
**** Hva går undersøkelsen ut på ?***
- Du blir bedt om å fylle ut et spørreskjema om diabetes, og du får tilbud om en spesiell urinundersøkelse (se foran).
- Litt seinere vil du få tilbud om en *fastende* blodprøve som sier noe om hvilken type diabetes du har.
- Du kan også bli valgt ut til å få tilbud om en ekstra undersøkelse av nervefunksjonen og evt. også blodsirkulasjonen i beina.
- Du tilbys også å delta i en langsiktig oppfølging. Det kan da bli aktuelt å kontakte deg eller legen din seinere med tilbud om nye undersøkelser.

**** Hva får du vite ?***
Du får resultatet av spesialundersøkelsene, enten direkte eller gjennom legen din. Dersom du ikke får beskjed om noe annet, kan du vente med å drøfte dette med legen din til neste kontroll, og du trenger da ikke å bestille ekstra time for dette.

Prosjektleder: Bedriftslege/forsker Kristian Midthjell, Folkehelsa, Verdal

☐ Høgt blodtrykk

Dersom du bruker blodtrykksmedisin nå eller *har brukt slik medisin tidligere*, håper vi du kan fylle ut et ekstra spørreskjema. For at behandlingen skal bli bedre, er vi avhengige av å få del i dine erfaringer som blodtrykkspasient.

Det er viktig at du fyller ut spørsmålene selv *om du **ikke** bruker blodtrykksmedisin **nå**.* Vi vet at noen kan slutte med blodtrykksmedisiner etter å ha brukt medisiner ei tid. Men vi vet for lite om hvor mange dette er og hvordan de har det. Det er derfor viktig at du svarer på de aktuelle spørsmålene selv om du har sluttet med medisin.

Prosjektleder:Kommunelege/forsker Jostein Holmen, Folkehelsa, Verdal.

☐ Stoffskifte

**** Hvem får dette tilbudet ?***
Alle kvinner 40 år og eldre, halvparten av menn 50 år og eldre, og et utvalg av andre aldersgrupper av begge kjønn.
****Hva går undersøkelsen ut på ?***
Målingene gjøres i den blodprøven som tas, og utføres ved Hormonlaboratoriet ved Aker sykehus.
**** Hva får du vite ?***
I svarbrevet alle får fra Statens helseundersøkelser står det om stoffskifteprøven (TSH) er *normal,* for *høy* eller for *lav.* Dersom den er for høy eller for lav, får du råd om å ta ny blodprøve hos legen din. Dersom prøven viser grenseverdi, kan det være tilstrekkelig med ny prøve om 1-2 år. Dersom også den andre prøven viser for høy eller for lav verdi får du råd om å bestille time hos din egen lege.

Prosjektleder: Overlege Trine Bjøro, Hormonlaboratoriet, Aker sykehus

☐ Magesårbakterien

**** Hvorfor er dette viktig ?***
For få år siden ble det oppdaget at en spesiell bakterie (helicobacter pylori) er en viktig årsak til magesår. Dette har endret helt på behandlingen av magesårsykdommen. Vi antar at ca 25% av befolkningen har denne bakterien , men av disse er det svært få som utvikler magesår. Gjennom denne undersøkelsen får vi vite mer om hvor vanlig denne bakterien er, og om evt. sammenheng med annen sykdom.
**** Hvem får dette tilbudet ?***
Et utvalg av de som blir undersøkt fra høsten 1996.
**** Hva går undersøkelsen ut på ?***
I blodprøven, som sendes til Innherred sykehus, blir det målt antistoffer mot bakterien.
**** Hva får du vite ?***
Skulle undersøkelsen vise *klare* sammenhenger mellom generelle mageplager og denne spesielle bakterien, kan du bli kontaktet. Ellers vet vi i dag ikke nok om dette til å gi hver enkelt praktiske eller helsemessige råd. De som utvikler magesår har også andre tilleggsfaktorer.

Prosjektleder: Overlege Kristian Hveem, Innherred sykehus

☐ Syn

**** Hvem får dette tilbudet ?***
Et utvalg av kvinner og menn som møter fra høsten 1996 og som er 20-25 år eller 40-45 år.
**** Hva går undersøkelsen ut på ?***
Du sitter ved et apparat og fester blikket på et bilde inne i apparatet. Det blir sendt en svak lysstråle mot øyet, og den måler brytningen. Dette gir et mål for om du har en brytningsfeil i øyet. Undersøkelsen tar ca 5 minutter, er ufarlig og medfører ikke ubehag.
**** Hva får du vite ?***
Brytningsfeil i øyet kan bety at du er langsynt eller nærsynt og at du evt. trenger briller.
Dersom det måles større brytningsfeil og du ikke bruker briller fra før, får du evt. anbefaling om å kontakte optiker eller lege/øyelege for ny synsundersøkelse.

Prosjektleder: Førsteamanuensis/overlege Anna Midelfart, NTNU, Trondheim

hunt-lunge
Helseundersøkelsen i Nord-Trøndelag

Tilbud om etterundersøkelser

Vi inviterer deg herved til undersøkelser som omfatter måling av ***lungefunksjonen*** gjennom pusteprøver, og til måling av ***beinmasse/beintetthet*** i underarmen. Lungeundersøkelsen er en oppfølging av Helseundersøkelsen i Nord-Trøndelag som du tidligere har deltatt i.

Undersøkelsene er nærmere beskrevet i brosjyren ***hunt-spesial*** som du fikk utlevert ved tidligere oppmøte på bussen.

Målet for denne undersøkelsen er å se på forekomst av lungesykdommer som astma og kronisk bronkitt. I tillegg undersøker vi om sykdom og /eller behandling innvirker på utvikling av beinskjørhet. For at vi skal kunne gi svar på dette, er det nødvendig at vi undersøker både de som har og noen av de som ikke har sykdom.

Du er blant de 5% av innbyggerne som får tilbud om undersøkelser *uavhengig* av hva du har svart på spørsmål om lungesymptomer i spørreskjemaet.

Undersøkelsen varer fra 30 - 60 minutter. Undersøkelsene er ikke ubehagelige og innebærer ingen risiko. Du får vite resultatet straks og dersom verdiene kan tyde på sykdom, kan din lege få tilsendt svarene om du ønsker dette. Les mer om undersøkelsen på baksiden av arket.

Sted for undersøkelsen:

Vi har satt av tid for deg til undersøkelse : _____dag _____-9 kl. _____

(Se baksiden av brevet vedrørende åpningstid og aktuelle telefonnr.).

Ta med innkallingsbrevet til undersøkelsen.
Helseundersøkelsen i Nord-Trøndelag er en av de største undersøkelser av denne type som er gjennomført i verden og din medvirkning er viktig.

Velkommen til undersøkelse!

Med vennlig hilsen

Arnulf Langhammer
prosjektleder lungeprosjektet

Samfunnsmedisinsk forskningsinstitutt, Folkehelsa Verdal, Tlf. 74 07 71 44
Neptunveien 1, 7650 verdal

hunt-lunge
Helseundersøkelsen i Nord-Trøndelag

Tilbud om etterundersøkelser

Vi inviterer deg herved til undersøkelser som omfatter måling av av ***lungefunksjonen*** gjennom pusteprøver, og til måling av ***beinmasse/beintetthet*** i underarmen. Lungeundersøkelsen er en oppfølging av Helseundersøkelsen i Nord-Trøndelag som du tidligere har deltatt i. Du har blitt valgt ut til slik undersøkelse ut fra dine svar på spørsmål om lungesymptomer.

Undersøkelsene er nærmere beskrevet i brosjyren ***hunt-spesial*** som du fikk utlevert ved tidligere oppmøte på bussen.

Målet for denne undersøkelsen er å se på forekomst av lungesykdommer som astma og kronisk bronkitt. I tillegg undersøker vi om sykdom og /eller behandling innvirker på utvikling av beinskjørhet.

Undersøkelsen varer fra 30 - 60 minutter. Undersøkelsene er ikke ubehagelige og innebærer ingen risiko. Du får vite resultatet straks og dersom verdiene tyder på sykdom, kan prøvesvarene oversendes din lege om du ønsker dette. Les mer om undersøkelsen på baksiden av arket.

Sted for undersøkelsen:

Vi har satt av tid for deg til undersøkelse : _____dag _____-9 kl. _____

(Se baksiden av brevet vedrørende åpningstid og aktuelle telefonnr.)

Ta med innkallingsbrevet til undersøkelsen.

Helseundersøkelsen i Nord-Trøndelag er en av de største undersøkelser av denne type som er gjennomført i verden og din medvirkning er viktig.

Velkommen til undersøkelse!
Med vennlig hilsen

Arnulf Langhammer
prosjektleder lungeprosjektet

Samfunnsmedisinsk forskningsinstitutt, Folkehelsa Verdal, Tlf. 74 07 71 44
Neptunveien 1, 7650 Verdal

Nærmere om undersøkelsen:

Før du møter (dersom du bruker medisiner): Hvis du kan klare deg uten, er det best for undersøkelsen dersom du ikke tar følgende medisiner undersøkelsesdagen: Atrovent, Bertotec, Bricanyl, Salbuvent, Serevent, Ventoline, eller tabletter som Theo-dur eller Nuelin-Depot. Dersom du har time sent på dagen og du vet at du blir svært tungpust uten medisin, kan du ringe og avtale nytt tidspunkt for undersøkelse. Becotide eller Pulmicort kan du ta som vanlig.

Når du møter fram: Det blir en pusteprøve før og 30 minutter etter at du har fått pustet inn en medisin (Bricanyl). Dette er en medisin som vanligvis brukes ved astma, den har ingen skadelige bivirkninger og kan også brukes av gravide.
Benmassemålingen foretas av en underarm. Du merker ikke noe ubehag i forbindelse med dette og det innebærer ingen risiko. Målingen kan derfor trygt også gjennomføres på gravide.

Etter undersøkelsen får du informasjon om hvordan lungefunksjonen er, eventuelt hva slags diagnose som er mest sannsynlig, og eventuelt hva slags medisiner du kan ha nytte av.

Vi gjør oppmerksom på at vi dessverre ikke kan betale reisen.

hunt - lunge
HELSEUNDERSØKELSEN I NORD-TRØNDELAG

TABLETTKUR MED PREDNISOLON

Dersom resultatet ved dagens undersøkelse viste at din FEV1 var under 80% og at du ikke hadde bedring av FEV1 på 12% etter inntak av medisiner, er det ønskelig med en tilleggsundersøkelse for å se om lungefunksjonen din kan bedres med en annen type medisiner.

Dette inngår i denne undersøkelsen:

* Du skal ta én tablett Prednisolon 20 mg hver dag i 3 uker
* Du kommer til en ny pusteprøve dagen etter siste tablett

Du kan ikke delta i denne undersøkelsen dersom du:

* bruker:
  * Marevan tabletter («blodfortynnende medisin»)
  * Vanndrivende medisiner eller Digitoxin/Digitrin pga hjertesvikt
  * Daglige medisiner for psykisk sykdom
  * Prednisolon tabletter nå

* tidligere har hatt blødende magesår
* har sukkersyke
* har infeksjon med feber nå
* er gravid eller ammer
* er over 75 år
* tidligere har hatt bivirkninger ved bruk av prednisolon/prednison tabletter

Dette er en undersøkelse som er helt vanlig å utføre både på sykehus og hos allmennpraktiserende leger. Undersøkelen er ikke farlig eller ubehagelig. Disse tablettene vil ved langvarig bruk i høye doser kunne ha skadelig effekt blant annet på skjelettet. Den dosen som brukes i denne kortvarige kuren medfører ikke slik risiko.

Hvis du ønsker denne tilleggsundersøkelsen, vil prosjektleder snakke med deg slik at du kan få svar på eventuelle tilleggsspørsmål. Dette kan eventuelt skje pr telefon, du vil da få tilsendt tablettene i løpet av få dager.

Med vennlig hilsen

Arnulf Langhammer
Prosjektleder/spes. i allmennmedisin

Jeg ønsker delta i denne undersøkelsen:

_____ sted _____ dato _____ underskrift

Jeg kan nås på telefon: _____ privat _____ jobb

Samfunnsmedisinsk Forskningssenter, Folkehelsa
Neptunveien 1, 7650 Verdal. Tlf 74077144, Fax 74077095

hunt - lunge
HELSEUNDERSØKELSEN I NORD-TRØNDELAG

.....

_____

_____

_____

INVITASJON TIL UTVIDET LUNGEUNDERSØKELSE

Helseundersøkelsen i Nord-Trøndelag har i løpet av 1995 og 1996 gjennomført undersøkelser i Levanger, Verdal og Steinkjer. Mange har møtt til basisundersøkelsen og til forskjellige tilleggsundersøkelser.
Lungeprosjektet planlegger nå en tilleggsundersøkelse for å undersøke hvor vanlig det er med allergi og annen overfølsomhet i luftveiene. Vi ønsker å undersøke nærmere de som ved helseundersøkelsen anga symptomer som kan ligne på astma, men som hadde normale funn ved pusteprøver. I tillegg inviteres mange som er tilfeldig utvalgt på grunnlag av personnummer. Dette er nødvendig for at vi skal kunne se om det er forskjell mellom de som har symptomer og de som ikke har dette. Totalt skal 750 voksne og 750 ungdommer undersøkes.

Hva går undersøkelsen ut på?
1. Allergitest i form av en blodprøve

2. Undersøkelse av om du har overfølsomme luftveier. Vi måler lungefunksjonen din flere ganger mens du puster inn et medikament som virker lett irriterende i luftveiene. Vi skal da se om luftveiene dine reagerer på lavere dose enn normalt på denne irritasjonen. Umiddelbart etter testen får du så puste inn astmamedisin som straks opphever effekten dersom du har blitt litt tungpust. Denne undersøkelsen er brukt ved flere slike undersøkelser tidligere, og brukes rutinemessig ved lungeavdelinger.

3. Måling av en gass (nitrogenmonoksyd) som du puster ut. Dersom det er betennelse i luftveiene slik man har ved astma, vil personen ha høyere nivå av denne gassen i luften som pustes ut. Målingen foregår ved at du puster rolig ut gjennom et lite munnstykke. Dette innebærer ingen form for ubehag. Dette er en helt ny undersøkelsesmetode i Norge, og vi skal her bruke det utstyret som Regionsykehuset i Trondheim nylig har anskaffet.

Undersøkelsen er godkjent av Datatilsynet og Regional Etisk Komite for Helseregion

Samfunnsmedisinsk Forskningssenter, Folkehelsa
Neptunvn. 1, 7650 Verdal, Tlf 74077144, Fax 74077095

Hva får du vite?

Du får svar på de to siste undersøkelsene umiddelbart etter testen. Dersom man påviser allergi ved blodprøven, vil du senere få tilsendt brev med resultatet.

Undersøkelsene foregår ved UV-senteret, Neptunvn. 1, i Verdal, tar totalt 40 minutter og er gratis. Vi har dessverre ikke anledning til å dekke skyssutgifter.

Veibeskrivelse: Ta av E6 og kjør mot Aker Verdal. UV-senteret er siste kontorbygg på høyre side før Aker Verdal, rett over veien for Partek Nordspenn.

Du inviteres herved til å møte til undersøkelse:

.....dag, .../..... 1997 kl .....

Dersom du bruker medisiner som Bricanyl, Ventolin eller Atrovent, er det fint om du ikke tar dette om morgenen undersøkelsesdagen. Dersom du bruker Serevent bør du heller ikke ta dette kvelden før undersøkelsen.

Vennligst svar på spørsmålene under og send dette i vedlagte konvolutt. Ta med selve invitasjonsbrevet når du møter til undersøkelsen

klipp.....
klipp

hunt - lunge
HELSEUNDERSØKELSEN I NORD-TRØNDELAG

Ja, jeg ønsker å delta i undersøkelsen og møter til angitt tidspunkt. ☐

Ja, jeg ønsker å delta i undersøkelen, men tidspunktet passer ikke. ☐

Jeg kan nås på dette telefonnummer for å avtale nytt tidspunkt:

....
jobb privat

Nei, jeg ønsker ikke å delta i denne undersøkelsen. ☐

....
Sted dato Underskrift

Samfunnsmedisinsk Forskningssenter, Folkehelsa
Neptunvn. 1, 7650 Verdal, Tlf 74077144, Fax 74077095

hunt - lunge
HELSEUNDERSØKELSEN I NORD-TRØNDELAG

.....

_____

_____

_____

PÅMINNELSE OM UNDERSØKELSE

For en tid siden fikk du invitasjon til undersøkelse av overfølsomhet i lunger og allergitest. På svarbrevet krysset du av at du ønsket møte. Da du ikke møtte forstår vi at du ble forhindret, men vi ber om at du ringer hit for å avtale nytt tidspunkt dersom du fortsatt ønsker delta.

Som nevnt i forrige brev inviterer vi de som ved helseundersøkelsen anga symptomer som kan ligne på astma, men som hadde normale funn ved pusteprøver. I tillegg inviteres mange som er tilfeldig utvalgt på grunnlag av personnummer. Dette er nødvendig for at vi skal kunne se om det er forskjell mellom de som har symptomer og de som ikke har dette. Totalt skal 750 voksne og 750 ungdommer undersøkes.

Helseundersøkelsen kan bidra med viktig kunnskap om disse utbredte plager, men skal vi nå dette mål, er vi er helt avhengig av at de som blir invitert ønsker møte opp.

Hva får du vite?
Du får umiddelbart svar på om dine luftveier er overfølsomme. Dersom man påviser allergi ved blodprøven, vil du senere få tilsendt brev med resultatet.

Undersøkelsene foregår ved UV-senteret, Neptunvn. 1, i Verdal, tar totalt 40-50 minutter og er gratis. Vi har dessverre ikke anledning til å dekke skyssutgifter.

Veibeskrivelse: Ta av E6 og kjør mot Aker Verdal. UV-senteret er siste kontorbygg på høyre side før Aker Verdal, rett over veien for Partek Nordspenn.

Dersom du bruker medisiner som Bricanyl, Ventolin eller Atrovent, er det fint om du ikke tar dette om morgenen undersøkelsesdagen. Dersom du bruker Serevent bør du heller ikke ta dette kvelden før undersøkelsen.

Vennligst ring nummer 74 07 71 44 og avtal tidspunkt med Inger.

Med vennlig hilsen

Arnulf Langhammer
prosjektleder

Samfunnsmedisinsk Forskningssenter, Folkehelsa
Neptunvn. 1, 7650 Verdal, Tlf 74077144, Fax 74077095

REGISTRERINGSSKJEMA VED UTVIDET LUNGEUNDERSØKELSE

Dato: ☐☐.☐☐.☐☐

Etternavn:..... Fornavn.....

Personnummer ☐☐☐☐☐☐☐☐☐☐☐

SPØRSMÅL

1. Røyker du? Ja ☐ Nei ☐
1.2. Har du røykt siste 30 minutter? Ja ☐ Nei ☐
1.3. Hvis du røyker daglig, hvor mange sigaretter røyker du vanligvis per dag?
0-5 ☐ 6-15 ☐ 16 eller mer ☐

2. Er du forkjølt nå? Ja ☐ Nei ☐
2.1 Hvis du ikke er forkjølt nå, hvor lenge er det siden du var det?
mindre enn 6 uker ☐ mer enn 6 uker ☐

3. **Besvares kun av jenter/kvinner i alder med menstruasjon**
3.1 Bruker du P-piller? Ja ☐ Nei ☐
3.2 Hvor mange dager er det siden 1.dag i siste menstruasjon? ☐☐
3.3 Hvor mange dager har du mellom 1.dag i 2 menstruasjoner?
mindre enn 20 ☐ 20-23 ☐ 24-27 ☐
28-31 ☐ 32 eller mer ☐

NO - måling **Registreringsnummer** ☐☐☐☐☐☐☐☐

NO - Tidal: 1: ☐☐☐☐,☐ 2: ☐☐☐☐,☐ 3: ☐☐☐☐,☐
NO – Nasal 1: ☐☐☐☐,☐ 2: ☐☐☐☐,☐ 3: ☐☐☐☐,☐

Merknad:.....
Gjennomført undersøkelse:
NO-måling: ☐ Metacholintest: ☐ Blodprøve: ☐ Spørsmål: ☐

Appendix 5

Information to participants of lung function measurement results:

- Spirometry phase I
- Bone densitometry phase I
- Phase II - Reversibility test
- Phase III - Reversibility test after prednisolone course

URN:NBN:no-3454

RESULTAT AV PUSTEPRØVE

Ved pusteprøven kan vi se om du har sykdommer som begrenser pustefunksjonen din, spesielt gjelder dette astma og emfysem. Resultatet av din måling sammenlignes med jevnaldrende personer av samme kjønn. Normalområdet for den verdien som kalles FEV1 er mellom 80-120 % og for FEV1/FVC mer enn 75%. Pustefunksjonen varierer fra dag til dag hos de som har astma. En normal enkeltmåling på en bra dag utelukker derfor ikke astma hos en som ellers har symptomer på astma.
Dersom dine verdier er lavere enn det som er angitt over, kan dette tyde på lungesykdom. Dersom du har kjent lungesykdom og går til regelmessig kontroll hos lege for dette, er det ikke nødvendig å bestille ekstra time hos lege. De som har lave måleresultat på disse prøvene , vil få invitasjon til videre undersøkelse av lungefunksjonen ved dette prosjektet.

Resultatet av din måling er:

FEV1 = _____ FEV1/FVC = _____

Din lege får resultatet av målingen hvis dine verdier er lave dersom du har samtykket i dette.

TAKK FOR AT DU HAR DELTATT I DENNE UNDERSØKELSEN!

RESULTAT AV BEINMASSEMÅLINGEN

Vi har fortsatt mangelfull kunnskap om betydningen av forskjellige verdier ved måling av beinmasse. Målet for denne undersøkelsen er blant annet å øke denne kunnskapen.

Beinmassemålinger blir vanligvis foretatt i underarmen, ryggen, hoften eller hælen. Uavhengig av målestedet, viser lave verdier at personen totalt sett har økt risiko for brudd. Mange kan imidlertid ha stor forskjell i beinmasse i forskjellige deler av skjelettet, slik at det f.eks kan være normal eller høy beinmasse i underarm, mens det er lav beinmasse i rygg eller hofte. For å kunne si noe om bruddrisikoen i en spesiell del av skjelettet, vil derfor beinmassemåling av dette området gi det beste grunnlaget. Målingen ved ***hunt*** foretas i en underarm.

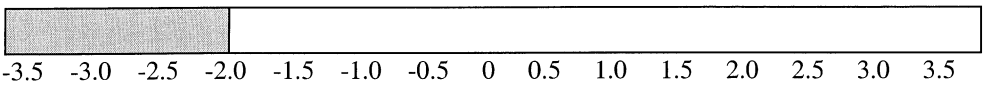
«Normalverdiene» som dine resultat sammenlignes med er fra Danmark, ettersom det foreløpig ikke finnes normalverdier ut fra norske undersøkelser.
Verdien din blir sammenlignet med gjennomsnittet for personer på din alder.
Hos de yngste voksne ser det ut til at det danske materialet ikke er helt sammenlignbart, og noen vil derfor muligens få angitt for lave verdier.
95 % av befolkningen har verdi fra - 2 til + 2, og dette defineres foreløpig som « normalområdet». Dersom dine verdier er under -2, kan dette bety at du har økt risiko for brudd, men det er viktig å være klar over at også andre forhold i stor grad påvirker risikoen for bruddskader.

Gunstige tiltak for å unngå reduksjon av beinmasse og bruddskader er:

* *røykestopp*
* *daglig mosjon*
* *kosthold med tilstrekkelig kalk og D-vitamininntak*

I tillegg ser det ut til at det å være svært tynn også øker risikoen for brudd.
Bruddrisiko kan reduseres ved en sunn livsstil. Les mer om dette i brosjyren du får med deg fra Osteoporoseforeningen.

Resultatet av din måling er:



Dersom denne verdien er mindre enn -2, dvs i det grå området, vil vi anbefale at du kontakter din lege og ber om totalvurdering og råd.
Din lege får resultatet av målingen hvis svaret er mindre enn -2 , dersom du har samtykket i dette.

hunt - lunge
HELSEUNDERSØKELSEN I NORD-TRØNDELAG

TIL DE SOM HAR DELTATT I UTVIDET LUNGEUNDERSØKELSE

Takk for at du møter til lungeundersøkelsen.
Hensikten med denne undersøkelsen er blant annet å finne ut om du har astma eller det som kalles kronisk obstruktiv lungesykdom (KOLS). Til KOLS hører sykdommer som kronisk bronkitt med emfysem, men noen med astma får også KOLS etter mange år. Det er ikke alltid like lett å skille klart mellom astma og KOLS, og noen har begge deler.
Ved astma er luftrørene trange når du har plager, men kan være helt åpne og normale i perioder uten plager. Plagene (tung og/eller pipende pust, hoste) og resultatet av pusteprøvene kan varierere fra dag til dag. I tillegg vil pusteplagene avta når du får medisiner som utvider luftrørene hvis disse på forhånd var trange.
Ved KOLS er luftrørene mer eller mindre trange nesten bestandig. Det er derfor mindre forandringer i pusteprøvene fra dag til dag, men ved forverrelser vil disse kunne bli dårligere.
Det er viktig å undersøke om du har astma eller KOLS fordi det kan ha betydning for hvilke medisiner du bør bruke.

Ved undersøkelsen i dag er to forhold undersøkt:

1. Har du nedsatt lungefunksjon?
   Vi tar utgangspunkt i hvor mye du puster ut i løpet av 1 sekund, dette kalles FEV1. Normal verdi av dette er 80% eller mer.
2. Bedres lungefunksjonen din minst 12 % når du får medisiner som utvider luftrørene?

Resultat:
FEV1 etter medisin: _____Bedring av FEV1 _____

Normale verdier viser at dine luftrør idag er normale. Dette utelukker imidlertid ikke astma.
Dersom FEV1 etter medisin er over 80% og øker med mer enn 12% tyder dette på astma.
Dersom FEV1 etter medisin er under 80% og ikke øker med mer enn 12% kan det være KOLS. Noen får tilbud om ny test etter tablettkur for nærmere avklaring av dette.

Dersom du ønsker det, blir resultatet av undersøkelsen sendt din faste lege. Det er viktig at du kun foretar endringer i din medisinbruk etter avtale med din faste lege.

Med vennlig hilsen

Arnulf Langhammer
prosjektleder

Samfunnsmedisinsk Forskningssenter, Folkehelsa
Neptunveien 1, 7650 Verdal. Tlf 74077144, Fax 74077095

hunt - lunge
HELSEUNDERSØKELSEN I NORD-TRØNDELAG

RESULTAT AV UNDERSØKELSE ETTER PREDNISOLONKUR

Denne undersøkelsen ble gjennomført for å se om du har astma eller kronisk obstruktiv lungesykdom (KOLS) og om du blir bedre av å bruke prednisolontabletter.

Dersom du ble bedre, kan det være gunstig for deg at du bruker slike medisiner i en form som pustes inn (spray eller pulver). Dette foretrekkes framfor tabletter da det ved bruk over lang tid har langt mindre bivirkninger.

Dersom du ikke har fått bedring av dine pusteprøver etter denne tablettkuren, tyder det på at du vil ha liten nytte av å begynne med slike medisiner som daglig behandling av din lungesykdom. Det vil imidlertid allikevel kunne være aktuelt med slik behandling ved forverrelser av din tungpusthet. Dersom du allerede bruker slike medisiner (Becotide, Flutide eller Pulmicort) er det viktig at du ikke endrer bruk av disse uten å snakke med din faste lege først. Selv om du ikke skulle ha effekt av slike medisiner, har de fleste effekt av medisiner som letter pusten (Atrovent, Bricanyl, Salbuvent, Ventoline, TheoDur, Nuelin Depot og andre).

Medisiner har en viktig plass i behandlingen av disse lungesykdommene. Det er imidlertid svært viktig at du ikke røyker eller utsettes for andres tobakksrøyk, da dette har klart uheldig effekt.

Resultat:
FEV1 etter prednisolonkur: _____

Endring av FEV1 etter prednisolonkur: _____

Dersom FEV1 er mindre enn 80% og økning av FEV1 er mindre enn 12% har du ikke hatt sikker effekt av tablettkuren. Dette kan tyde på KOLS.
Dersom FEV1 er over 80% eller FEV1 har økt mer enn 12% har du hatt effekt, og dette kan tyde på astma.
Dersom FEV1 er under 80% og FEV1 har økt med mer enn 12 % tyder det på at du har astma og KOLS.

Med vennlig hilsen

Arnulf Langhammer
Prosjektleder

Samfunnsmedisinsk Forskningssenter, Folkehelsa
Neptunveien 1, 7650 Verdal. Tlf 74077144, Fax 74077095

hunt - lunge
HELSEUNDERSØKELSEN I NORD-TRØNDELAG

Verdal,

.....

_____
_____

_____

SVAR PÅ ALLERGIPRØVE

Takk for at du møtte til lungeundersøkelsen på Folkehelsa i Verdal. Det ble tatt blodprøve for undersøkelse av eventuell allergi, og dere som hadde positive tester får herved resultatet.

Allergitesten var positiv for:

	Husstøv-midd (D1)	Katt (E1)	Hest (E3)	Hund (E5)	Timotei G6 (gress)	Bjørk T3	Burot W6	Mugg-sopp M2
SVAR								

Forklaring:

0 = negativ test, dvs ingen påvist allergi
1 = kan bety lett allergi, men testen er ikke sikker positiv. Dersom du ikke har merket reaksjon overfor denne kilden, oppfattes resultatet som negativt.
2-5 = Positiv allergitest, 5 viser sterkest reaksjon

Dersom du har allergi, bør du unngå å utsette deg for dette allergenet. Dette er spesielt viktig i hjemmet hvor du oppholder deg det meste av tiden. Har du allergi mot husdyr bør du ikke ha dette i huset. Ved allergi mot husstøvmidd bør du spesielt være nøye med renhold av soverom og sengetøy. Mengden husstøvmidd bør i så fall reduseres, og det oppnås bl.a. ved å lufte sengetøy på dager med kuldegrader, vaske sengetøy i varmere vann enn 55°C og grundig støvsuging av madrass.
Dersom du er i tvil om betydningen av disse resultat, anbefales det at du drøfter dette med din lege.

Med vennlig hilsen

Arnulf Langhammer
prosjektleder

Samfunnsmedisinsk Forskningssenter, Folkehelsa
Neptunvn 1, 7650 Verdal, Telefon 74077144

Appendix 6

Information letter to medical doctors

URN:NBN:no-3454

hunt

Helseundersøkelsen i Nord-Trøndelag

Orientering om benmassemålinger

Ved Helseundersøkelsen i Nord-Trøndelag blir det målt benmasse/bentetthet som en del av Osteoporoseprosjektet og Lungeprosjektet. (Osteoporoseprosjektet gjennomføres ikke i alle kommuner). Det gjennomføres måling av radius og ulna ved røntgen absorptiometri-teknikk. Det måles to områder, det ultradistale som omfatter distale del av radius og det distale som er et 24 mm langt område lenger proksimalt.

Resultatutskrift

På vedlagte utskrift fra Osteometer er pasientens BMC (bone mineral content) og BMD (bone mineral density) angitt i prosent av verdi forventet for personer med samme alder og kjønn (agematched), og i prosent av verdi forventet for unge voksne (referenceage). I tillegg er det angitt Z-score og T-score, dette viser antall standardavvik forskjell i forhold til referanseverdi for jevnaldrende (Z) og unge voksne (T). Svarene angis i forhold til et dansk referansemateriale da det foreløpig ikke eksisterer norsk referansemateriale. Det må derfor tas forbehold om at dette materialet er representativt for Norge. Det ser foreløpig ut til at spesielt unge voksne får lave Z og T verdier, og man bør derfor være svært forsiktig med å tolke resultatet hos disse.
I HUNT vil personene få vite sitt resultat som Z-verdi. De som har Z < -2 får råd om å kontakte lege for en totalvurdering. Alle som deltar får imidlertid muntlige og skriftlige råd om generelle forebyggende tiltak.

Hva betyr lav benmasse?

Det er fortsatt mye usikkerhet om betydningen av benmassemålinger. Benmassemålinger blir vanligvis foretatt i underarm, lumbalcolumna, hofte eller hæl. Uavhengig av målested, viser lav verdi at personen har økt total risiko for brudd. Mange kan imidlertid ha stor forskjell i benmasse i forskjellige deler av skjelettet, slik at det f.eks kan være normal eller høy benmasse i underarm, mens det er lav benmasse i lumbalcolumna. Det kan også være stor forskjell i benmasse mellom to nabovirvler, slik at den ene er osteoporotisk og dermed utsatt for kompresjonsfraktur, mens den andre er normal. For å kunne uttale seg om bruddrisiko i en konkret del av skjelettet, vil derfor benmassemåling av dette området gi best grunnlag.
Ved vurdering av bruddrisiko for den enkelte person er det derfor viktig at resultatet av benmassemåling sammenholdes med andre risikofaktorer. Slike risikofaktorer er høyde (bruddrisiko øker 40% for hver økning i høyde på 6 cm), tobakksrøyk, lite aktivitet, tidligere brudd, medikamenter og ernæringsstatus.

Samfunnsmedisinsk Forskningssenter, Folkehelsa.
Neptunvn. 1, 7650 Verdal. Tlf 74077144, Fax 74077095

Hva kan legen gjøre?

* Vurdere om det er bakenforliggende sykdommer
* Revurdere dose og indikasjon for medikamenter med uheldig effekt på benmasse
* Ved symptomgivende osteoporose (f.eks. påviste kompresjonsfrakturer på rtg) vurderes medikamentell behandling. Dette kan være hormonterapi postmenopausalt, bisfosfonater eller Miacalcic.

Det foreligger dessverre ingen konsensus i Norge om konkrete forebyggende tiltak ved påvist asymptomatisk lav bentetthet uten kjent årsak. Følgende tiltak/råd kan imidlertid ha betydning:

* sikre et adekvat kosthold med tilstrekkelig kalk (1500mg/døgn for eldre og 1200 mg/døgn for ungdom) og D-vitaminer . I Sverige anbefales tilskudd av D-vitaminer til alle over 70 år.
* unngå overdreven slanking
* være i fysisk aktivitet, men ekstrem fysisk aktivitet er ikke gunstig
* røykeslutt
* unngå alkoholmisbruk
* fallforebyggende tiltak hos eldre

Skal målingene gjentas?

I de tilfeller der det kan være særlig viktig å følge utviklingen av bentap, kan det enten være aktuelt å ta regelmessige målinger med 3 måneders intervaller eller å gjenta målingen etter 2 år.

Verdal, 20.12.96

Berit Schei

Forskningsleder
Prosjektleder Osteoporoseprosjektet

Arnulf Langhammer

Spes. allmennmedisin
Prosjektleder Lungeprosjektet (BONT)

Samfunnsmedisinsk Forskningssenter, Folkehelsa.
Neptunvn. 1, 7650 Verdal. Tlf 74077144, Fax 74077095

hunt - lunge
HELSEUNDERSØKELSEN I NORD-TRØNDELAG

RESULTAT FRA LUNGEUNDERSØKELSEN (BONT)

BONT (= bronkial obstruksjon i Nord-Trøndelag) er et delprosjekt ved Helseundersøkelsen i Nord-Trøndelag. De som ved helseundersøkelsen anga symptomer på lungesykdom eller bruk av astmamedisiner, ble invitert til en etterundersøkelse. Denne omfattet spirometri med reversibilitetstest (spirometri før og 30 minutter etter inhalasjon av 0.75 mg Bricanyl på turbuhaler) og bentetthetsmåling av underarm. Det vises til egen brev som omhandler bentetthetsmålingen.

Svarbrevet viser:

Pred.	- forventet verdi ut fra høyde, alder, kjønn og rase
Pre	- resultat ved spirometri før bricanyl
%Obs/p	- resultat i prosent av forventet verdi
Post	- resultat ved spirometri etter bricanyl
%Obs/p	- resultat etter bricanyl i prosent av forventet
D%2/1	- prosent endring mellom de to målinger

Tolkning av resultatet:
FEV1 $\leq$ 80% tyder på bronkial obstruksjon. Negativ reversibilitetstest og FEV1 < 80% etter bricanyl tyder på KOLS. Positiv reversibilitetstest tyder på astma.
Positiv reversibilitetstest: $\geq$ 12% økning av FEV1 etter Bricanyl.
En del personer har hatt problemer med å gjennomføre spirometri, negativ reversibilitet skyldes som regel dette. Det understrekes at funnene må sammenholdes med symptomer før eventuell diagnose settes.

Informasjon til de undersøkte:
Personene har fått svarbrev med resultatet av FEV1 og prosent endring ved reversibilitetstest. Dersom FEV1 etter reversibilitetstest er mindre enn 80% eller det er en økning ved reversibilitetstest på 12% , er de anbefalt å ta kontakt med lege dersom de ikke på forhånd hadde kjent obstruktiv lungesykdom.

Hvilke resultat oversendes fast lege?
For de pasientene som ønsket dette, oversendes resultatene for de som hadde FEV1 $\leq$ 80% eller økning ved reversibilitetstest $\geq$ 12%. Vi vil anbefale at nærmere diagnostisk avklaring blir gjennomført dersom man ikke på forhånd har kjennskap om lungesykdom hos de aktuelle pasienter.

Med vennlig hilsen

Arnulf Langhammer
Prosjektleder BONT

Samfunnsmedisinsk Forskningssenter, Folkehelsa
Neptunvn. 1, 7650 Verdal
Telefon: 74077144 Telefax: 74077095

hunt - lunge
Helseundersøkelsen i Nord-Trøndelag

Til legene i Levanger, Verdal, Steinkjer og Stjørdal

RESULTAT FRA LUNGEUNDERSØKELSEN BONT (= Bronkial Obstruksjon i NT)

Aktuelle undersøkelser og utvalg:

Fase 1: Spirometri, intervju og benmassemåling.
Utvalg: De som svarte positivt på spørsmål i spørreskjema om astma eller astmasymptomer.

Fase 2: Spirometri med reversibilitetstest med Bricanyl turbuhaler 0.75 mg.
Utvalg: FEV1 ≤ 80% av forventet eller FEV1/FVC ≤ 75% av forventet i fase 1.

Fase 3: Reversibilitetstest med Prednisolon 20 mg x 1 i 3 uker.
Utvalg: symptomer på lungesykdom og FEV1 < 80% av forventet og reversibilitet < 12% etter beta2agonist i fase 2.
Eksklusjonskriterier: diabetes mellitus, tidligere ulcussykdom, infeksjonssykdom, bruk av psykofarmaka eller Marevan, alder > 75 år, graviditet og amming.

Svarbrev:

Svarbrev sendes den faste legen når personen har ønsket dette. Etter fase 3 sendes svarbrev for alle, mens etter fase 2 sendes svar ved FEV1<80% av forventet etter Bricanyl, eller ved økning av FEV1≥12%. Personene har selv fått svarbrev med resultatene.
I svarbrevet er angitt FVC, FEV1, FEF50 og Substans(medikament). Det angis predicted (forventet) verdi i tillegg til resultat ved observasjon 1 (= før beta2agonist), observasjon 2 (= etter beta2agonist), observasjon 3 (før beta2agonist etter prednisolonkur) og observasjon 4 (etter beta2agonist etter prednisolonkur). I tillegg angis differansen i prosent mellom de forskjellige observasjoner (D%obs 2/1)

Tolkning av resultatet:

FEV1 ≤ 80% av forventet tyder på bronkial obstruksjon. Positiv reversibilitetstest og FEV1> 80% av forventet før eller etter prednisolonkur tyder på astma. Positiv reversibilitetstest defineres her som økning av FEV1>12%.
Negativ reversibilitetstest og FEV1< 80% etter Bricanyl og prednisolonkur tyder på KOLS (kronisk obstruktiv lungesykdom). Positiv reversibilitetstest og FEV1< 80% tyder på kombinasjon av astma og KOLS. En del personer har hatt problemer med å gjennomføre spirometri, og reduksjon av FEV1 etter Bricanyl skyldes som regel dette

Forslag til journalføring: Reversibilitetstest:

Etter Bricanyl FEV1 __ FEV1% av forventet: __ Økning i % 2/1: __ (pos/neg)

Etter Prednisolon: FEV1 __ FEV1 % av forventet: __ Økning i %: 4/1 __ (pos/neg)

Videre utredning:

Det anbefales nærmere diagnostisk avklaring ved tegn til obstruksjon, dersom man fra før ikke har kjennskap til lungesykdom hos pasienten. Ved spirometri fanger vi opp kun de som var obstruktive den aktuelle dag, normal spirometri ved helseundersøkelsen utelukker derfor ikke at pasienten har astma. Det understrekes at funnene må sammenholdes med symptomer før eventuell diagnose settes.

Med vennlig hilsen

Arnulf Langhammer
Prosjektleder BONT

Samfunnsmedisinsk Forskningssenter, Folkehelsa.
Neptunvn.1, 7650 Verdal. Tlf 74077144, Fax 74077095

hunt - lunge
HELSEUNDERSØKELSEN I NORD-TRØNDELAG

Verdal, 16.05.97

RESULTAT AV UTVIDET LUNGEUNDERSØKELSE

Helseundersøkelsen i Nort-Trøndelag avsluttet screeningundersøkelsen i Levanger og Verdal høsten 95/ vinteren 96. Lungeprosjektet (BONT) har gjennomført en del tilleggsundersøkelser og det er tidligere utsendt svar på de som har patologiske verdier ved spirometri og reversibilitetstest.
Herved utsendes svar på utvidet lungeundersøkelse som gjennomføres høsten 96/vinteren 97.

Hvem er innkalt til denne undersøkelsen?

* Et tilfeldig utvalg på 3% av befolkningen
* Et utvalg av de som har angitt symptomer på bronkial hyperreaktivitet i spørreskjema ved screeningundersøkelsen, men som hadde normale lungefunksjonsmålinger.

Hva måles?

* Nitrogenmonoksyd i ekspirasjonsluft. Det er en viss basisproduksjon av NO i cellene. Det er vist at denne produksjonen er økt ved inflammasjon, og det forskes mye på om man kan bruke dette som et mål på den inflammasjon som foreligger i luftveiene hos pasienter med symptomer på astma. Det er anskaffet utstyr for slike målinger ved 3 regionsykehus, og vi låner RIT's utstyr ved dette prosjekt. Det er ikke foretatt slike målinger før i Norge.

* Bronkial hyperreaktivitet med metacholine provokasjonstest. Personen inhalerer metacholin i repeterte doser og spirometri måles etter hver dose. Dersom personen får et fall i FEV1 på 20% i forhold til startnivå, er testen postitiv. Testen gjennomføres ikke hvis personen er obstruktiv ved første måling.

* Phadiatop - screeningtest på inhalasjonsallergi. Det påvises da IgE mot et standardpanel av inhalasjonsallergener. Dette omfatter bjørk, timotei, burot, hund, katt, hest, husstøvmidd, muggsopp og oliven.

Melding sendes til primærlegen:

* Ved positiv metacholintest
* Ved positiv NO-test (NO-konsentrasjon i ekspirert luft > 20ppb)
* Testpersonen får vite resultatet av metacholintest og NO-test umiddelbart. Ved positiv allergitest informeres testpersonen skriftlig om resultatet.

Hvilke behandlingsmessige konsekvenser har dette?

Dette er supplerende undersøkelser som kan være til hjelp dersom en er i tvil om pasienten har astma. Dersom pasienten har symptomer i form av tung, pipende pust eller vedvarende hoste, kan positive resultat på disse undersøkelser støtte astmadiagnose. Dersom pasienten ikke har noen plager, men allikevel positive resultat, kan de ha økt risiko for senere utvikling av obstruktiv lungesykdom.

Med vennlig hilsen

Arnulf Langhammer (prosjektleder BONT)

Samfunnsmedisinsk Forskningssenter, Folkehelsa.
Neptunvn. 1, 7650 Verdal. Tlf 74077144, Fax 74077095

hunt - lunge
HELSEUNDERSØKELSEN I NORD-TRØNDELAG

Verdal,

.....

Dr. .....

RESULTAT AV UTVIDET LUNGEUNDERSØKELSE

Navn: ..... Født: .....

NO - måling:

I ekspirasjonsluft ble det målt: ..... ppb (verdi over 20 ppb tyder på inflammasjon)

Metacholintest:

FEV_1 før test:	..... l/s	..... % av forventet
FEV_1 etter test:	..... l/s	..... % reduksjon
FEV_1 etter ev. Bricanyl	..... l/s	..... % av utgangsverdi

PD_{20}: ..... µg (total dose metacholin som gir 20% fall i FEV_1)

Konklusjon:
Pasienten har: liten ☐ moderat ☐ stor grad ☐ av bronkial hyperreaktivitet.

Pasienter med positiv metacholintest som har symptomer i form av tung, pipende pust eller vedvarende hoste, blir anbefalt å ta kontakt med egen lege. Disse kan ha astma og bør vurderes med tanke på medikamentell behandling og oppfølging. Foreløpig er man tilbakeholdende med å gi konkrete råd ut fra NO-måling, da dette er usikkert.

Med vennlig hilsen

Arnulf Langhammer
prosjektleder

Samfunnsmedisinsk Forskningssenter, Folkehelsa.
Neptunvn. 1, 7650 Verdal. Tlf 74077144, Fax 74077095

Appendix 7

Non-responder study

URN:NBN:no-3454

15.03.98

HELSEUNDERSØKELSEN I NORD-TRØNDELAG

SPØRREUNDERSØKELSE BLANT DE SOM IKKE MØTTE.

I 1995-1997 ble det gjennomført en stor helseundersøkelse i Nord-Trøndelag hvor alle som var 20 år og eldre ble invitert. Vi er godt fornøyd med at ca 70% ønsket/hadde anledning til å møte opp.

Et av formålene for denne undersøkelsen var å finne hvor mange som har forskjellige plager/sykdommer. For å kunne få mest mulig pålitelige data om dette, er det nødvendig å undersøke om det er forskjell i slik forekomst blant de som ikke møtte i forhold til de som møtte.

For å få svar på dette er det gjennomført telefonintervju blant et tilfeldig utvalg av de som ikke møtte. Vi har ikke klart å nå deg per telefon, og tillater oss derfor å sende dette spørreskjema. Du vil gi et viktig bidrag til flere forskningsprosjekter om du kan besvare disse spørsmålene. Undersøkelsen er anonym, og du skal ikke skrive navn på skjemaet.

Takk for hjelpen!

Med vennlig hilsen

Kristian Midthjell
Prosjektleder
Diabetesprosjektet

Øystein Krüger
Daglig leder

Arnulf Langhammer
Prosjektleder
Lungeprosjektet

Spørreskjema

Dato for utfylling: ...../..... 1998

Alder: ☐☐ år Kjønn: Mann ☐ Kvinne ☐

Først noen spørsmål om pustebesvær:

	JA	NEI
1. Hoster du daglig i perioder av året?	☐	☐
Hvis ja:		
1.1.Er hosten vanligvis ledsaget av oppspytt?	☐	☐
1.2 Har du hatt hoste med oppspytt i minst 3 mnd sammenhengende i hvert av de siste 2 år?	☐	☐
2. Har du noen gang i løpet av de siste 12 månedene hatt pipelyder i brystet?	☐	☐
Hvis ja:		
2.1 Har du vært tungpust i forbindelse med at du hadde pipelyder i brystet?	☐	☐
2.2. Har du hatt slike pipelyder når du ikke har vært forkjølt?	☐	☐
3. Har du noen gang i løpet av de siste 12 månedene hatt tung pust om dagen når du har vært i ro?	☐	☐
4. Har du noen gang i løpet av de siste 12 månedene hatt anfall med tung pust etter en anstrengelse?	☐	☐
5. Har du noen gang i løpet av de siste 12 månedene våknet med tung pust?	☐	☐
6. Har du eller har du hatt astma?	☐	☐
Hvis ja:		
6.1 Hvor gammel var du da du første gang merket symptomer på astma?	☐	☐
7. Vil du si at du har problemer med pusten ? (sett ett kryss)	☐	☐
Hvis ja:		
Hvilken beskrivelse passer best for dine pusteplager?		
Jeg har problemer med pusten: (sett ett kryss)		
A. Svært sjelden ☐		
B. Gjentatte ganger, men blir oftest helt bra ☐		
C. Hele tiden og er aldri helt bra ☐		
8. Har du i løpet av de siste 12 måneder brukt legemidler for å lette pusten (astma-medisiner)?	☐	☐
Hvis ja:		
8.1 Har du siste måned brukt Bricanyl, Ventolin, Salbuvent eller Berotec?	☐	☐
Hvis ja på spørsmål 8.1:		
8.2 Hvor ofte har du brukt denne medisinen i gjennomsnitt siste måned? (sett ett kryss)		
Vet ikke ☐		
En gang i uken eller sjeldnere ☐		
Ikke hver dag, men flere ganger i uken ☐		
Hver dag ☐		

Hvis nei på spørsmål 8:

8.3 Har du tidligere brukt legemidler for å lette pusten? JA ☐ NEI ☐

9. Har du brukt astmamedisiner som Becotide, Flutide eller Pulmicort noen gang? ☐ ☐

Hvis ja:

9.1. Har du brukt slik medisin regelmessig siste 6 måneder? ☐ ☐

Eventuell kommentar: .....

Så noen spørsmål om diabetes (sukkersyke) og høyt blodtrykk:

10. Har du eller har du hatt diabetes (sukkersyke)? ☐ ☐

Hvis nei; gå til spørsmål 11

Hvis ja:

10.1. Hvor gammel var du da du fikk dette? ☐☐ år

10.2. Bruker du insulin (sprøyter, penn) mot din diabetes nå? ☐ ☐

10.3. Bruker du tabletter mot din diabetes nå? ☐ ☐

10.4. Måler du noen gang hjemme hvor mye sukker (glukose) du har i blodet (blodsukker) ? (svar ja også om noen hjelper deg eller gjør det for deg) ☐ ☐

10.5. Går du til regelmessig kontroll hos lege for din diabetes? ☐ ☐

Kommentarer: _____

_____

11. Bruker du medisin mot høyt blodtrykk?

Nå ☐ Før, men ikke nå ☐ Aldri brukt ☐

12. Så er det noen spørsmål om røyking:

12.1. Røyker du selv daglig? JA ☐ Røyker ikke nå, men har røykt tidligere ☐ NEI ☐

12.2 Hvis du har røykt tidligere, hvor lenge er det siden du sluttet? ☐☐ år

12.3. Hvor mange sigaretter røyker du eller røykte du vanligvis daglig? ☐☐

13. Dersom du ønsker det, ville det være av stor verdi for oss om du kan si noe om grunnen til at du ikke møtte til Helseundersøkelsen:

_____

_____

Hjertelig takk for hjelpen!

Appendix 8

Follow-up study 2001 – invitation and questionnaires

URN:NBN:no-3454

hunt

Helseundersøkelsen i Nord-Trøndelag

Forespørsel om deltagelse i en vitenskapelig undersøkelse om benskjørhet

Alle voksne personer bosatt i Nord-Trøndelag ble i 1995-97 invitert til helseundersøkelsen ***hunt***. Dette er en av verdens største undersøkelser i sitt slag med rundt 65.000 deltakere. Omtrent 18.000 personer fikk målt benmasse og 11.000 av disse deltok også i lunge-prosjektet. Benmasse ble målt for å studere forekomst av og årsaker til benskjørhet. Denne type forskning er svært viktig ettersom lav benmasse gir høyere risiko for brudd. Vi vet i dag for lite om hvorfor forekomsten av brudd i Norge er helt på verdenstoppen, og hvordan vi skal snu denne utviklingen. For å øke kunnskapen om dette ønsker vi se på endring av benmasse hos personer med og uten kjente risikofaktorer for benskjørhet.

Tre grupper forespørres:

1. Tilfeldig utvalg på 5% av menn og kvinner med alder 20-100 år
2. Utvalg av kvinner over 50 år, også kvinner som ikke ble målt i 1995-97.
3. Alle som oppga at de hadde brukt kortisonbehandling for astma/kronisk bronkitt/emfysem/KOLS ved ***hunt*** 95-97.

For at vi skal få sikre resultater, er vi avhengige av at det er god deltagelse i alle grupper. Vi håper derfor at du blir med.

Deltagelse i undersøkelsen er selvsagt frivillig og gratis.

Du har fått time for måling: / / 2001 kl. _____ _____
Adresse

Dersom tidspunktet over ikke passer, eller du lurer på noe, vennligst ring **tlf. 9201 9638**.

Selve undersøkelsen tar ca. 10 minutter, er ikke ubehagelig og innebærer ingen helserisiko. Maksimal ventetid vil være 15 minutter. Vennligst fyll ut det vedlagte spørreskjemaet og ta det med til undersøkelsen. Der vil du også få hjelp om noe er vanskelig.

Helseundersøkelsen er godkjent av Datatilsynet og tilrådd av Regional komite for medisinsk forskningsetikk i Helseregion Midt-Norge. Svarene skal utelukkende brukes til forskning og behandles strengt fortrolig. Opplysningene kan senere etter vedtatte regler for personvern bli sammenholdt med andre helse- og sykdomsregistre som tidligere helseundersøkelser, bruddregistre ved sykehusene, familieregisteret og kreftregisteret.

Dine svar og ditt fremmøte er et viktig bidrag i forskningen om benskjørhet.

Med vennlig hilsen

Siri Forsmo
Forsker dr.med. NTNU, Trondheim

Arnulf Langhammer
Stipendiat Hunt Forskningssenter, NTNU, Verdal
Spes.allmennmedisin

SAMTYKKEERKLÆRING (tas med til undersøkelsen)

Jeg samtykker i at mine resultater blir brukt til medisinsk forskning, og at disse kan sammenholdes med opplysninger fra andre helseregistre som nevnt over. Framgangsmåten i slike tilfeller vil bli avklart i samråd med Datatilsynet og Regional komité for medisinsk forskningsetikk i helseregion IV.

_____ _____ _____
Sted Dato Underskrift

URN:NBN:no-3454

hunt

Helseundersøkelsen i Nord-Trøndelag

Etikett

Spørreskjema

Benmasse 2001

Vennligst svar på alle spørsmål. Sett kryss og tall nøyaktig i de angitte rutene. Dersom noe er uklart, kan du spørre når du møter til undersøkelsen. Bruk blokkbokstaver om du skal skrive.

1. Helsen din

Hvordan er helsen din nå?

(ett kryss)

- Svært god ☐
- God ☐
- Ikke helt god ☐
- Dårlig ☐

2. Måling av bentetthet (benskjørhet)

Har du tidligere målt bentettheten? *(inntil to kryss)*	Ved HUNT	Annet sted	Vet ikke	Ikke målt
	☐	☐	☐	☐

Husker du resultatet av din siste måling?

(ett kryss)

- Normal ☐
- Litt lav ☐
- Benskjørhet ☐
- Husker ikke ☐

3. Benskjørhet (osteoporose)

	Ja	Nei	Vet ikke
Har lege sagt at du har benskjørhet?	☐	☐	☐
Har noen i nær familie benskjørhet? *(Mor, far, søsken)*	☐	☐	☐

4. Brudd

Har du noen gang hatt brudd (knokler)?	Ja	Nei
	☐	☐

Hvis ja: *(ett eller flere kryss)* — Ca. alder ved siste brudd:

Håndledd/underarm	☐	_____ år gammel
Overarm	☐	_____ år gammel
Lårhals (hofte)	☐	_____ år gammel
Ankel/legg	☐	_____ år gammel
Ryggvirvel	☐	_____ år gammel
Ribben	☐	_____ år gammel
Andre brudd	☐	_____ år gammel

5. Fall

	Ja	Nei
Føler du at du har god balanse?	☐	☐

Har du falt/ramlet siste året? *(Kryss for innendørs og/eller utendørs)*	Inne	Ute	Nei
	☐	☐	☐

Hvis du falt utendørs, hvor skjedde det? *(Sett kryss for alt som passer)*	Underlag: Snø/is	Bart
På vei/gate/i hagen/åker	☐	☐
I terrenget (skog, fjell, ulendt)	☐	☐

6.Fysisk aktivitet

Hvordan har din fysiske aktivitet i fritiden vært det siste året? *(Tenk deg et ukentlig gjennomsnitt for året)*

Arbeidsvei regnes som fritid	**Timer pr. uke** Ingen	Under 1	1-2	3 og mer
• Lett aktivitet *(ikke svett/andpusten)*	☐	☐	☐	☐
• Hard fysisk aktivitet *(svett/andpusten)*	☐	☐	☐	☐

Hva slags fysisk aktivitet bedriver du?

(ett eller flere kryss)

- Ingen ☐
- Går (også ski) ☐
- Sykler ☐
- Jogger/løper (også langrenn) ☐
- Svømmer ☐
- Gymnastikk/aerobics/turn ☐
- Styrketrening *(øvelser, løfte vekter)* ☐
- Lagspill *(håndball, volleyball o.a.)* ☐

Noter hvis ikke noe passer for deg

- Annet _____

Aktivitet i arbeid: *(lønnet eller ulønnet, inkl. hjemmearbeid)*

- For det meste stillesittende *(f.eks. skrivebordsarbeid)* ☐
- Arbeid som krever at du går mye *(f.eks undervisning)* ☐
- Arbeid hvor du går og løfter mye *(f.eks.postbud, pleier)* ☐
- Tungt kroppsarbeid *(f.eks. tungt jordbruk, rengjøring)* ☐

Hvor mange timer i uken har du av denne typen arbeid? _____ Timer pr.uke

Som barn, hvordan kom du deg på skolen? *(transportmåte)*

Ett eller flere kryss for den vanligste fremkomstmåten

	Alder 7-10 år	13-16 år
Skoleskyss/bil/båt	☐	☐
Gikk (også ski/spark)	☐	☐
Sykkel	☐	☐

Avstand hjem-skole i kilometer?	km	km

7. Slanking

Har du noen gang forsøkt å slanke deg?	Ja	Nei
	☐	☐

Hvis ja:	Før 20 år	Etter 20 år
• **Hvor mange ganger har du forsøkt å slanke deg?**		
• **Hvor mye har du på det meste gått ned i vekt?**	kg	kg

Ca. hvor mye veide du da du var 20 år? _____ kg

8. Kosttilskudd

Har du det siste året periodevis brukt noen av de følgende midler daglig eller nesten daglig?	Ja	Nei
Kalktabletter eller benmel	☐	☐
Vitamin D-tilskudd	☐	☐
Andre vitamintilskudd	☐	☐
Tran eller tran-/fiskeoljekapsler	☐	☐
Jerntabletter	☐	☐

URN:NBN:no-3454

9. Symptomer fra luftveiene

	Ja	Nei
Hoster du daglig i perioder av året	☐	☐
Hvis ja: Er hosten vanligvis ledsaget av oppspytt?	☐	☐
Har du hatt hoste med oppspytt i minst 3 mnd. sammenhengende i hvert av de to siste årene	☐	☐
Har du hatt noe anfall med pipende eller tung pust de siste 12 månedene?	☐	☐
Har du eller har du hatt astma?	☐	☐
Hvis ja: Har du fått diagnosen astma av lege?	☐	☐
Har du hatt symptomer siste 12 mnd?	☐	☐

Hvor gammel var du 1.gang du merket symptomer på astma (tungpust, piping)? _____ år gml.

	Ja	Nei
Har du fått diagnosen kronisk bronkitt eller emfysem av lege?	☐	☐

Hvis ja: Hvor gammel var du da du fikk slik diagnose? _____ år gml.

Hemmer pusteplager dine daglige aktiviteter?

(ett kryss)
- Ikke i det hele tatt..... ☐
- Litt..... ☐
- I stor grad..... ☐
- I svært stor grad..... ☐

10. Medisiner for astma/luftveiene

	Ja	Nei	Vet ikke
A. Har du brukt eller bruker du astmamedisiner? *(medisiner mot pustevansker)*	☐	☐	☐

Hvis nei, gå til spørsmål 11

	Ja	Nei	Vet ikke
B. Har du noen gang brukt forebyggende behandling? *(Becotide, Flutide, Pulmicort, Seretide)*	☐	☐	☐

Hvis ja: **Hvis nei, gå til spørsmål 10 C**

	Ja	Nei
• Har du brukt slike medisiner regelmessig siste halvår?	☐	☐

Ett eller flere kryss for medisiner du har brukt siste halvår mot astma og luftveisplager
- Becotide..... ☐
- Flutide..... ☐
- Pulmicort..... ☐
- Seretide..... ☐
- Vet ikke..... ☐

- Omtrent i hvor mange år har du til sammen brukt slike medisiner? _____ år
- Hvor mye slik medisin har du brukt daglig siste uke?

Styrke i mikrogram _____ Antall doser/dag _____

	Ja	Nei	Vet ikke
C. Har du noen gang brukt kortison tabletter pga. pustevansker? *Prednisolon, prednison, celestone*	☐	☐	☐

Hvis ja: **Hvis nei, gå til spørsmål 11**

	Ja	Nei
• Har du brukt dette som 1-4 ukers kurer ved forverrelse av sykdommen?	☐	☐

Hvor mange slike kurer har du hatt siste to år? _____

	Ja	Nei
• Har du brukt kortisontabl. regelmessig mer enn en måned pga. astma/pustevansker?	☐	☐

Hvor lenge har du totalt brukt slike tabletter? _____ år

11. Kortison for annet enn lungesykdommer

	Ja	Nei	Vet ikke
Har du brukt kortison tabletter *Prednisolon, prednison, celestone* **for annen sykdom?** *Eks: leddgikt, polymyalgi, nyresykdom, tarmsykdom m.fl..*	☐	☐	☐

Hvis ja: Hvor mange år har du til sammen brukt slik medisin? _____ år

	Ja	Nei	Vet ikke
Har du noen gang brukt Becotide nasal, Lokilan, Rhinocort, Flutide, Nasonex, Nasocort i nesen pga. nesetetthet/allergi?	☐	☐	☐

Hvis ja: Hvor mange år har du til sammen brukt slik medisin? _____ år

	Ja	Nei	Vet ikke
Har du noen gang fått kortisonsprøyte for allergi, sene- eller leddbetennelser?	☐	☐	☐

Hvis ja: Hvor mange sprøyter siste 24 måneder _____

12. Røyking

	Nå	Tidligere	Aldri
Røyker du eller har du røykt daglig?	☐	☐	☐

Hvis du røyker eller har røykt daglig:

- Hvor gammel var du da du begynte? _____ år gml.
- Hvor mange sigaretter e.l. røyker/røykte du vanligvis daglig? _____ sig.
- Hvor mange år tilsammen har du røykt daglig? _____ år

Hvis du tidligere har røykt, hvor gammel var du da du sluttet for godt? _____ år

13. Alkoholbruk

	Ja	Nei
Er du totalavholdende?	☐	☐

Hvis nei: Hvor mange ganger drikker du alkohol *(ikke lettøl)* i løpet av *en måned*? _____ ganger

Hvor mange *glass* har du drukket de siste to uker av:

Øl: _____ Vin: _____ Brennevin: _____

Spørsmål for kvinner:
14. Menstruasjon og overgangsalder

	Ja	Nei
Har du fortsatt menstruasjon?	☐	☐

Hvis nei: Hvor gammel var du da menstruasjonen sluttet? _____ år gammel

	Ja	Nei
• Hadde/har du plager i forbindelse med overgangsalderen *(hetetokter m.m.)*	☐	☐
Hormonbehandling (ikke prevensjon, p-piller): Har du brukt østrogen (tabletter/plaster)?	☐	☐

Hvis ja, kryss for det merket du bruker/brukte sist

Ett kryss
- Trisekvens..... ☐
- Cyclabil..... ☐
- Kliogest..... ☐
- Livial..... ☐
- Evista..... ☐
- Activelle..... ☐
- Ovesterin..... ☐

Noter hvis ikke noe passer for deg
- Andre _____

- Hvor gammel var du da du begynte med østrogen? _____ år gammel
- Hvor lenge til sammen har du brukt østrogen?

Hvis mindre enn ett år _____ måneder

Hvis mer enn ett år _____ år

Takk for at du har svart på disse spørsmålene!

Vennligst ta med dette spørreskjemaet når du møter til undersøkelsen. I tillegg ville det være fint om du tar med resept(ene) på *faste* medisiner du bruker.

	Ja	Nei
For tekniker: Samtykke	☐	☐

Intervjuskjema

Etikett

Tekst i kursiv er informasjon til intervjuer

Innledning:
Kan jeg stille deg noen korte spørsmål om matvanene dine?

Kosthold

A. De følgende spørsmålene gjelder hva du spiser eller drikker pr. dag:
(Antall glass, kopper, brødskiver, en knekkebrødskive regnes som en brødskive)

		Pr. dag:					
	Sett kryss	Aldri/ sjelden	Mindre enn 1	1-2	3-4	5-6	Mer enn 6
Melk	1. Hvor mange glass melk drikker du pr. dag?.....	☐	☐	☐	☐	☐	☐
Kaffe	2. Hvor mange kopper kaffe drikker du pr. dag?....	☐	☐	☐	☐	☐	☐
Te	3. Hvor mange kopper te drikker du pr. dag?.....	☐	☐	☐	☐	☐	☐
Juice	4. Hvor mange glass appelsinjuice pr. dag?.....	☐	☐	☐	☐	☐	☐
Brød	5. Hvor mange brødskiver spiser du i alt pr. dag?..	☐	☐	☐	☐	☐	☐
Brød med ost	6. Hvor mange brødskiver spiser du med gulost?...	☐	☐	☐	☐	☐	☐
	7. Hvor mange brødskiver spiser du med brunost?.	☐	☐	☐	☐	☐	☐
	8. Hvor mange brødskiver spiser du med annen ost	☐	☐	☐	☐	☐	☐
Fisk	9. Hvor mange br.skiver spiser du med fiskepålegg	☐	☐	☐	☐	☐	☐

B. Nå kommer noen spørsmål om hva du spiser og drikker i uken:

		I uken:					
	Sett kryss	Aldri	Mindre enn 1	1-2	3-4	5-6	Daglig
Yoghurt	10. Hvor ofte spiser du yoghurt? (i uken).....	☐	☐	☐	☐	☐	☐
	Middag						
Fisk	11. Hvor ofte spiser du middag med fet fisk (laks, uer, kveite, sild m.fl.)	☐	☐	☐	☐	☐	☐
	12. Hvor ofte spiser du middag med mager fisk (torsk, sei m.fl.).....	☐	☐	☐	☐	☐	☐
Kjøtt	13. Hvor ofte spiser du middag med rent kjøtt?	☐	☐	☐	☐	☐	☐
Grønt	14. Hvor ofte spiser du middag med grønnsaker?	☐	☐	☐	☐	☐	☐
Gulrøtter	15. Hvor ofte spiser du rå eller kokte gulrøtter?	☐	☐	☐	☐	☐	☐
Brokkoli	16. Hvor ofte spiser du rå eller kokt brokkoli og/eller blomkål?	☐	☐	☐	☐	☐	☐
Frukt	17. Hvor ofte spiser du frukt?	☐	☐	☐	☐	☐	☐
Brus	18. Hvor ofte drikker du sukkerholdige leskedrikker	☐	☐	☐	☐	☐	☐
Light brus	19. Hvor ofte drikker du sukkerfrie "Light" leskedrikker?	☐	☐	☐	☐	☐	☐

20. Hva slags type brød *(kjøpt/hjemmebakt)* **spiser du vanligvis?**

1-2 kryss	Loff	Fint brød	Kneipbrød	Grovbrød	Knekkebrød
	☐	☐	☐	☐	☐

21. Hvis du drikker melk, hvilken type er det vanligvis? *Søt og sur*

Ett kryss	Helmelk	Lettmelk	Ekstra lett	Skummet
	☐	☐	☐	☐

Spørsmålene 22-23 gjelder barne-/oppvekstår, dvs .til og med puberteten/tenårene. Be dem tenke på fra de begynte på skolen og fremover.

22. Husker du omtrent hvor mye melk du drakk daglig som barn?

Drakk ikke/sjelden melk	1-2 glass	3-4 glass	5-6 glass	Mer enn 6
☐	☐	☐	☐	☐

23. Under oppveksten, tok du tran/trankapsler daglig?

Ett kryss	Hele året	Høst/ vinter	Ikke regekmessig	Aldri
	☐	☐	☐	☐

Det var alt, tusen takk!

Appendix 9

Studies on inhaled corticosteroids and BMD/fracture risk

URN:NBN:no-3454

Appendix 9. Observational studies with controls (cross-sectional (CSS) and longitudinal studies (LS)) and random clinical trials (RCT) on the effect of bone mineral density or fracture by inhaled corticosteroids.

Author Year -type	Groups and number by sex	Mean Age/ range	ICS Type Dose in ug	Mean duration	Disease	Outcome BMD/ F / M	Results
Bonala 2000 – CSS	A: 56 W		Long-term ICS		Asthma	BMD: LS-H	Prevalence of low BMD increased with increasing ICS dose: 5% in the low dose group; 50% in the high dose group. Significant linear trend of decline by dose in mean BMD for the hip and LS. (1)
Boulet 1994 - CSS	A: 23 M + 14 W B: 21 M + 16 W	46.8 45.4	BDP/BUD > 800 BDP/BUD 0-500 OCS not excluded	34.2 months 15.7 months	Asthma	BMD:LS-H M	BMD: No difference M: S-Osteocalcin lower in group A, other markers no difference. (2)
Boulet 1999 - LS	A: 22 M + 6 W B: 15 M + 8 W	49.9 47.4	BDP/BUD > 800 BDP/BUD 0-500	3 year follow up (2)	Asthma	BMD: LS-H M	Correlation between daily ICS dose and bone loss high dose group, but minimal changes over a period of 3 years. No difference between high dose versus low doses of ICS for more than 5 years. Bone markers or initial BMD did not predict bone loss. (3)

Ebeling 1998 -CSS	A: 9 M + 17 W B: 10 M + 17 W	43.9 42.6	BDP/BUD >1500 + OCS > 1 month	3 years	Asthma	BMD: LS-H M	LS and proximal femur BMD lower in high-dose ICS and OCS, potentially equivalent to a doubling of the risk of fracture. Dose response relationship between mean daily dose and BMD. (4)
Egan 1999 – RCT	A: 7 M + 10 W B: 9 M + 7 W C1: 8 M + 8 W C2: 5 M + 3 W C3: 4 M + 3 W (A and B double blind, C open controls)	36 33 30 42 32	FP 1000 BDP 2000 ICS low dose Oral CS No CS	All 2 years	Asthma Asthma Asthma Asthma Healthy	BMD: QCT: LS DXA:LS-H- SPA:Forearm M	QCT significant decline in spine BMD in the BDP group compared to FP group Otherwise no effect was found on BMD, and no difference between doses of ICS. Users of OCS had significant lower BMD both at baseline and during follow up compared to the other groups. No firm conclusions due to high withdrawal rate (2 in FP and 7 in BDP group). (5)
Elmståhl 2003 - CSS	A: 106 W B: 49 W C: 674 W	58.1 59.0 57.6	ICS +Oral CS/injections No CS		Asthma/COPD Asthma/COPD Controls	SXA:Forearm	No difference in BMD between group A and C, nor dose response relationship between ICS therapy and BMD. (6)
Fujita 2001 – CSS	A: 36 W B: 45 W	Pre and post menop	BDP 542 Controls		Asthma Healthy	BMD: LS- H M	In pre-menopausal women there was no difference between the groups, but in early postmenopausal women BMD and S-Osteocalcin were significantly lower in group A than B. (7)

Hanania 1995 - LS	A: 6 M + 12 W B: 6 M + 12 W	36.6 33.4	BDP/BUD 800-2000 Bronchodilator	24 months 24 months	Asthma	BMD: LS-H M	Femoral neck BMD reduced (Z-0.78) in group A, no difference in Ward's triangle or LS. Lower S-Osteocalcin adrenal function in group A. (8)
Harmanci 1999 - LS	A: 1 M + 9 W B: 2 M + 11 W	41.2 39.5	BUD 800 FP 400	1 year	Asthma	BMD: LS - H	Similar anti-asthma control without any adverse effect on BMD in mild to moderate asthmatics. The treatment groups were not randomises. (9)
Herrala 1994 -LS	A: 19 W B: 19 W	52.6 52.6	BDP 1000 No ICS	1 year	Asthma Healthy	BMD: LS- H	No difference between groups in BMD after 1 year compared to baseline. (10)
Hughes 1999 – RCT	A: 17 M + 13 W B: 19 M + 10 W	50 56	FP 1000 BUD 1600	1 years	Asthma Asthma	BMD LS-H M	BMD of spine and osteocalcin increased slightly in both groups. No change in other markers. 17 withdrawals, 10 in group A and 7 in group B.(11)
Ip 1994 - CSS	A: 12 M + 18 W B: 12 M + 18W	32.5 32.5	BDP or BUD 1100 No ICS	40 months	Asthma Healthy	BMD LS- H	Lower BMD in women with ICS independent of use of prednisolone courses. No difference in men. (12)
Israel 2001 – LS	A: 39 W B: 42 W C: 28 W	33 37 34	TCA : 400-800 TCA: > 800 No ICS	3 years	Asthma Asthma Asthma	BMD: LS –H M	Direct relation between higher dose of ICS and small yearly decrease in BMD of the total hip and the trochanter independent of use of OCS or not. Estimated doubling of fracture risk after 20 year with 1200 ug TCA. None of the measured markers predicted or was correlated with bone loss. (13)

Lau 1998 - CSS	A: 33 M + 73 W B: 24 M + 14 W C: 66 M + 146 W	54.2 72.2 59.1	ICS 500 – 4000 No ICS No ICS – age matched	42 weeks	Asthma/COPD Asthma/COPD Healthy	BMD: LS-H	Men: Group A: lower BMD at spine, but not at hip Women: No significant difference. (14)
Li 1999 – RCT	A: 32 B: 32	29.5	FP 1000 Placebo	2 years	Asthma Asthma	BMD: LS M	No difference between groups of BMD or bone markers. (15)
Luengo 1997 - CSS	A: 15 M +33 W B: 15 M + 33 W	56 55	BDP/BUD 300-100 Controls	10.6 years	Asthma Healthy	BMD: LS	No differences between users of ICS (with or without courses with oral CS) and never-users. (16)
Laatikainen 1999 – CS	A: 119 W B: 3103 W	47-56	No ICS Only ICS ICS + OCS Control		Asthma Asthma Asthma Non-asthmatics	BMD: LS-H	Asthmatics without hormone replacement therapy had lower mean spinal and femoral BMD value than non-asthmatics. ICS users had similar BMD as non-users, but the duration of use correlated negatively with spinal BMD and was also associated with spinal BMD in multiple regression analysis. (17;18)
Marystone 1995 - CSS	A: 34 B: 44 C: 1,595	(56 – 91)	ICS: 220 ug OCS: 9 mg No CS	3.8 years	Asthma/COPD Asthma/COPD Controls	BMD: LS-H- R	Women: use of OCS significantly associated with lower BMD compared to never CS users. ICS users intermediate group A and C. Men no difference. (19)
Matsumoto 2001 – LS	A: 15 M + 20 W	60.6	BDP Low dose 615 High dose 1268	Treatment: 4.2 years Observation	Asthma	BMD: LS	BMD in LS unchanged during the study, but the Z-score increased significantly. No BMD difference between low and high dose, but significant lower Z-

				:4.2 years			score when > 2.5 short courses OCS/year compared to ≤ 2.5 courses. (20)
McEvoy 1998 – CSS	A: 70 M B: 125 M C: 117 M		ICS OCS No CS	3.5 years 163 weeks	COPD COPD COPD	F	Compared to group C, the OR for vertebral fracture in group B was 1.8. In group B the fractures were more likely to be multiple and more severe. The OR for group A compared to C was 1.35 (ns). (21)
Medici 2000 – RCT	A: 22 B: 21 C: 13 D: 13	39 years	FP 400 BDP 800 FP 750 BDP 1500	1 year	Asthma	BMD : QCT: radius/ tibia DXA:LS M	No significant effect on bone density or bone metabolism during 1 years treatment. (subjects using more than 3 courses CS excluded). (22)
Packe 1992 - CSS	A: 11 M + 9 W B: 13 M + 7 W C: 6 M + 11 W	37.7 38.9 36.3	BDP 1000-2000 + PC BDP 1000-2000 No ICS	1-7 years 1-7 years	Asthma Asthma Asthma	BMD LS	BMD reduced in group A and B (- 0.84 SD). (23)
Packe 1996 -LS	A: 7 M + 13 W B: 11 M + 9 W C: 6 M + 11 W	36.8 37.7 36.3	BUD 800 + PC BDP 1000 + PC No ICS	1-10 years 1-10 years	Asthma Asthma Asthma	BMD LS M	BMD reduced in group A and B, but normal indices of bone turnover. (24)
Pauwels Euroscope	A: 464 M + 179 W B: 473 M +	52.4 52.5	BUD 800 Placebo	3 years	COPD COPD	BMD: LS +H of 102 group A and 92	No significant change over time and no significant effect of treatment on BMD, except for a small but significant difference at the femoral trochanter in

1999 – RCT	170 W					group B Th and LS radiographs	favour of BUD (decline BMD 0.38% in group B and 0.04 in group A). During the study new fractures were unusual and similarly distributed (p=0.5). (25)
Pauwels 1998 –RCT Double blind Cross-over	A: M 92 + W 75 B: M 104 + W 69	46.6 46.2	FP -- BDP BDP – FP FP dose: 500-1000 BDP dose: 1000-2000	6 months crossover	Asthma Asthma	BMD: LS +H At baseline and 6 months, Gr.A: n=85 Gr.B: n=88 M	At baseline subjects used BDP/BUD 800-2000 ug and had not used OCS within the last month, asthmatics had significantly lower BMD compared to healthy control subjects. After 6 months of FP, BMD increased 1 % in LS and 2.9 % in femoral Ward's triangle, no difference was found in BDP group. No change in bone markers was found. (26)
Tattersfield 2001 – RCT	A: 31 M + 56 W B: 18 M + 56 W C: 29 M + 49 W	37 36 36	BUD 400 BDP 500 No ICS	2 years	Asthma Asthma Asthma	BMD: LS +H + total body. M	64 % completed the study. Group A and B had better asthma control than group C. Change in BMD did not differ between the three groups over 2 years, nor correlate with changes in bone markers metabolism. (27)
Toogood 1995 - CSS	A: 26 M + 43 W	59.9	ICS: 1300 OCS: 3.0 mg	10.1 year 10.7 year	Asthma	BMD: LS	High daily dose of ICS and duration of prednisolone use associated with lower BMD. Larger cumulative doses ICS associated with higher BMD and fewer patients at risk of fracture. Oestrogen therapy may

							offset bone-depleting effect in postmen. women. (28)
Tug 2001 – CSS	A: 3 M + 15 W B: 2 M + 12 W		ICS No ICS		Asthma Healthy	BMD LS-H	No detectable difference between the groups. (18)
Van Staa 2000 -CSS	A: 244,235 B: 244,235	57.1 56.9	OS mean 6.8 prescriptions		asthma /COPD in 40%	F	Dose dependent fracture risk; Hip fractures: doses < 2.5 mg OR 0.99 relative to controls, 2.5-7.5 mg OR 1.77, >7.5 mg OR 2.27. Vertebral fractures OR1.55, 2.59 and 5.18 respectively. Totally : Hip F OR 1.61, Forearm F OR 1.09, Vertebral F: OR 2.60 F risk rapid decline on cessation of OS. (29)
Van Staa 2001 – CSS	A: 170,818 B: 108,786 C: 170,818	45.1 49.3 45.2	BDP/BUD/FP Bronchodilator (BD) No ICS or BD		Asthma/COPD Asthma/COPD Controls	F	Excluded those with concomitant OS use. In both group A and B increased OR for fractures compared to controls: non-vertebral F OR 1.15, hip F OR 1.22, vertebral F OR 1.51. Increased risk independent of ICS use. (30)
Villareal 1996 – CSS	A: 16 M	64	OCS : > 5 mg	8 years	Asthma	BMD: LS –H	Prolonged OCS therapy causes significant osteoporosis. Abnormal BMD was more commonly in the LS (38%) than the hip (19%). Cumulative doses of prednisolone > 5.6 g was associated with

							decreased BMD. (31)
Wise 2000 – RCT The Lung Health Study	A: 358M+ 201W B: 346M + 211W	56.2 56.4	TCA 1200 Placebo	40 months	COPD COPD	BMD: LS -H of 412 subj. but 328 subj. after 3 years	The TCA group had higher percentage decrease than the placebo group from baseline to 36 months of BMD both at LS (0.35%) and femoral neck (2.0%). Effect on bone was not found until year 3. (32)
Wisniewski 1997 - CSS	A: 19 M + 28 W B: 19 M + 15 W	32.3/ 32.0 30.3/ 25.6	BDP/BUD 500 No ICS	9 / 6.3 years	Asthma Asthma	BMD: LS-H- R F: vertebral M	ICS use was not related to BMD at the wrist or hip in women or at any skeletal site in men. In women lower BMD in the spine and lower level of osteocalcin compared no never-users. (33)
Wong 2000 -CSS	A: 77 M + 119W	35/31	BDP, BUD, FP Med cum dose 876 mg	Median duration 6 years	Asthma	BMD LS-H	Negative dose response association between duration and cumulative dose of ICS and BMD. No association between mean daily dose and BMD. (34)

Abbreviations: CSS = cross sectional study, LS = Longitudinal study, RCT = random clinical trial, M = Men, W = Women, CS = corticosteroids, ICS = inhaled CS, OCS = oral CS, BDP = Bechlomethasone Dipropionate, BUD = Budesonide, FP = Fluticasone Propionate, TCA = Triamcinolone acetate, BMD = Bone mineral density, F = Fracture, M = marker of bone metabolism, Th = thoracic columna, LS = lumbal spine, H = hip, R = radius, QCT = Quantitative computer tomography,

Reference List

(1) Bonala SB, Reddy BM, Silverman BA, Bassett CW, Rao YA, Amara S et al. Bone mineral density in women with asthma on long-term inhaled corticosteroid therapy. Ann Allergy Asthma Immunol 2000; 85(6 Pt 1):495-500.

(2) Boulet LP, Giguere MC, Milot J, Brown J. Effects of long-term use of high-dose inhaled steroids on bone density and calcium metabolism. J Allergy Clin Immunol 1994; 94(5):796-803.

(3) Boulet LP, Milot J, Gagnon L, Poubelle PE, Brown J. Long-term influence of inhaled corticosteroids on bone metabolism and density. Are biological markers predictors of bone loss? Am J Respir Crit Care Med 1999; 159(3):838-844.

(4) Ebeling PR, Erbas B, Hopper JL, Wark JD, Rubinfeld AR. Bone mineral density and bone turnover in asthmatics treated with long-term inhaled or oral glucocorticoids. J Bone Miner Res 1998; 13(8):1283-1289.

(5) Egan JJ, Maden C, Kalra S, Adams JE, Eastell R, Woodcock AA. A randomized, double-blind study comparing the effects of beclomethasone and fluticasone on bone density over two years. Eur Respir J 1999; 13(6):1267-1275.

(6) Elmstahl S, Ekstrom H, Galvard H, Johnell O, Gerhardsson d, V, Norjavaara E. Is there an association between inhaled corticosteroids and bone density in postmenopausal women? J Allergy Clin Immunol 2003; 111(1):91-96.

(7) Fujita K, Kasayama S, Hashimoto J, Nagasaka Y, Nakano N, Morimoto Y et al. Inhaled corticosteroids reduce bone mineral density in early postmenopausal but not premenopausal asthmatic women. J Bone Miner Res 2001; 16(4):782-787.

(8) Hanania NA, Chapman KR, Sturtridge WC, Szalai JP, Kesten S. Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. J Allergy Clin Immunol 1995; 96(5 Pt 1):571-579.

(9) Harmanci E, Ak I, Ozdemir N, Vardareli E, Elbek O, Ucgun I. The comparison of the effects of fluticasone propionate and budesonide on clinical indices and on bone mineral density in the asthmatic patients: a one year treatment study [see comments]. Allergol Immunopathol (Madr) 1999; 27(6):298-303.

(10) Herrala J, Puolijoki H, Impivaara O, Liippo K, Tala E, Nieminen MM. Bone mineral density in asthmatic women on high-dose inhaled beclomethasone dipropionate. Bone 1994; 15(6):621-623.

(11) Hughes JA, Conry BG, Male SM, Eastell R. One year prospective open study of the effect of high dose inhaled steroids, fluticasone propionate, and budesonide on bone markers and bone mineral density. Thorax 1999; 54(3):223-229.

(12) Ip M, Lam K, Yam L, Kung A, Ng M. Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids [see comments]. Chest 1994; 105(6):1722-1727.

(13) Israel E, Banerjee TR, Fitzmaurice GM, Kotlov TV, LaHive K, Leboff MS. Effects of inhaled glucocorticoids on bone density in premenopausal women. N Engl J Med 2001; 345(13):941-947.

(14) Lau EM, Li M, Woo J, Lai C. Bone mineral density and body composition in patients with airflow obstruction--the role of inhaled steroid therapy, disease and lifestyle [see comments]. Clin Exp Allergy 1998; 28(9):1066-1071.

(15) Li JT, Ford LB, Chervinsky P, Weisberg SC, Kellerman DJ, Faulkner KG et al. Fluticasone propionate powder and lack of clinically significant effects on hypothalamic-pituitary-adrenal axis and bone mineral density over 2 years in adults with mild asthma. J Allergy Clin Immunol 1999; 103(6):1062-1068.

(16) Luengo M, del Rio L, Pons F, Picado C. Bone mineral density in asthmatic patients treated with inhaled corticosteroids: a case-control study. Eur Respir J 1997; 10(9):2110-2113.

(17) Laatikainen AK, Kroger HP, Tukiainen HO, Honkanen RJ, Saarikoski SV. Bone mineral density in perimenopausal women with asthma: a population-based cross-sectional study. Am J Respir Crit Care Med 1999; 159(4 Pt 1):1179-1185.

(18) Tug T, Kamanli A, Tug E. Effects of long-term inhaled steroid use on bone mineral density in asthma patients. J Investig Allergol Clin Immunol 2001; 11(4):300-302.

(19) Marystone JF, Barrett-Connor EL, Morton DJ. Inhaled and oral corticosteroids: their effects on bone mineral density in older adults. Am J Public Health 1995; 85(12):1693-1695.

(20) Matsumoto H, Ishihara K, Hasegawa T, Umeda B, Niimi A, Hino M. Effects of inhaled corticosteroid and short courses of oral corticosteroids on bone mineral density in asthmatic patients : a 4-year longitudinal study. Chest 2001; 120(5):1468-1473.

(21) McEvoy CE, Ensrud KE, Bender E, Genant HK, Yu W, Griffith JM et al. Association between corticosteroid use and vertebral fractures in older men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998; 157(3 Pt 1):704-709.

(22) Medici TC, Grebski E, Hacki M, Ruegsegger P, Maden C, Efthimiou J. Effect of one year treatment with inhaled fluticasone propionate or beclomethasone dipropionate on bone density and bone metabolism: a randomised parallel group study in adult asthmatic subjects. Thorax 2000; 55(5):375-382.

(23) Packe GE, Douglas JG, McDonald AF, Robins SP, Reid DM. Bone density in asthmatic patients taking high dose inhaled beclomethasone dipropionate and intermittent systemic corticosteroids. Thorax 1992; 47(6):414-417.

(24) Packe GE, Robb O, Robins SP, Reid DM, Douglas JG. Bone density in asthmatic patients taking inhaled corticosteroids: comparison of budesonide and beclomethasone dipropionate. J R Coll Physicians Lond 1996; 30(2):128-132.

(25) Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB et al. Long-term treatment with inhaled budesonide in rsons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med 1999; 340(25):1948-1953.

(26) Pauwels RA, Yernault JC, Demedts MG, Geusens P. Safety and efficacy of fluticasone and beclomethasone in moderate to severe asthma. Belgian Multicenter Study Group. Am J Respir Crit Care Med 1998; 157(3 Pt 1):827-832.

(27) Tattersfield AE, Town GI, Johnell O, Picado C, Aubier M, Braillon P et al. Bone mineral density in subjects with mild asthma randomised to treatment with inhaled corticosteroids or non-corticosteroid treatment for two years. Thorax 2001; 56(4):272-278.

(28) Toogood JH, Baskerville JC, Markov AE, Hodsman AB, Fraher LJ, Jennings B et al. Bone mineral density and the risk of fracture in patients receiving long-term inhaled steroid therapy for asthma. J Allergy Clin Immunol 1995; 96(2):157-166.

(29) Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures [see comments]. J Bone Miner Res 2000; 15(6):993-1000.

(30) Van Staa TP, Leufkens HG, Cooper C. Use of inhaled corticosteroids and risk of fractures. J Bone Miner Res JID - 8610640 2001; 16(3):581-588.

(31) Villareal MS, Klaustermeyer WB, Hahn TJ, Gordon EH. Osteoporosis in steroid-dependent asthma. Ann Allergy Asthma Immunol 1996; 76(4):369-372.

(32) Wise RA, Connett J, Weinmann GG, Scanlon P, Skeans M. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 2000; 343(26):1902-1909.

(33) Wisniewski AF, Lewis SA, Green DJ, Maslanka W, Burrell H, Tattersfield AE. Cross sectional investigation of the effects of inhaled corticosteroids on bone density and bone metabolism in patients with asthma. Thorax 1997; 52(10):853-860.

(34) Wong CA, Walsh LJ, Smith CJ, Wisniewski AF, Lewis SA, Hubbard R et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma [see comments]. Lancet 2000; 355(9213):1399-1403.

URN:NBN:no-3454

Dissertations at the Faculty of Medicine, NTNU

1977
1. Knut Joachim Berg: EFFECT OF ACETYLSALICYLIC ACID ON RENAL FUNCTION
2. Karl Erik Viken and Arne Ødegaard: STUDIES ON HUMAN MONOCYTES CULTURED *IN VITRO*

1978
3. Karel Bjørn Cyvin: CONGENITAL DISLOCATION OF THE HIP JOINT.
4. Alf O. Brubakk: METHODS FOR STUDYING FLOW DYNAMICS IN THE LEFT VENTRICLE AND THE AORTA IN MAN.

1979
5. Geirmund Unsgaard: CYTOSTATIC AND IMMUNOREGULATORY ABILITIES OF HUMAN BLOOD MONOCYTES CULTURED IN VITRO

1980
6. Størker Jørstad: URAEMIC TOXINS
7. Arne Olav Jenssen: SOME RHEOLOGICAL, CHEMICAL AND STRUCTURAL PROPERTIES OF MUCOID SPUTUM FROM PATIENTS WITH CHRONIC OBSTRUCTIVE BRONCHITIS

1981
8. Jens Hammerstrøm: CYTOSTATIC AND CYTOLYTIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS *IN VITRO*

1983
9. Tore Syversen: EFFECTS OF METHYLMERCURY ON RAT BRAIN PROTEIN.
10. Torbjørn Iversen: SQUAMOUS CELL CARCINOMA OF THE VULVA.

1984
11. Tor-Erik Widerøe: ASPECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.
12. Anton Hole: ALTERATIONS OF MONOCYTE AND LYMPHOCYTE FUNCTIONS IN REALTION TO SURGERY UNDER EPIDURAL OR GENERAL ANAESTHESIA.
13. Terje Terjesen: FRACTURE HEALING AN STRESS-PROTECTION AFTER METAL PLATE FIXATION AND EXTERNAL FIXATION.
14. Carsten Saunte: CLUSTER HEADACHE SYNDROME.
15. Inggard Lereim: TRAFFIC ACCIDENTS AND THEIR CONSEQUENCES.
16. Bjørn Magne Eggen: STUDIES IN CYTOTOXICITY IN HUMAN ADHERENT MONONUCLEAR BLOOD CELLS.
17. Trond Haug: FACTORS REGULATING BEHAVIORAL EFFECTS OG DRUGS.

1985
18. Sven Erik Gisvold: RESUSCITATION AFTER COMPLETE GLOBAL BRAIN ISCHEMIA.
19. Terje Espevik: THE CYTOSKELETON OF HUMAN MONOCYTES.
20. Lars Bevanger: STUDIES OF THE Ibc (c) PROTEIN ANTIGENS OF GROUP B STREPTOCOCCI.
21. Ole-Jan Iversen: RETROVIRUS-LIKE PARTICLES IN THE PATHOGENESIS OF PSORIASIS.
22. Lasse Eriksen: EVALUATION AND TREATMENT OF ALCOHOL DEPENDENT BEHAVIOUR.
23. Per I. Lundmo: ANDROGEN METABOLISM IN THE PROSTATE.

1986
24. Dagfinn Berntzen: ANALYSIS AND MANAGEMENT OF EXPERIMENTAL AND CLINICAL PAIN.
25. Odd Arnold Kildahl-Andersen: PRODUCTION AND CHARACTERIZATION OF MONOCYTE-DERIVED CYTOTOXIN AND ITS ROLE IN MONOCYTE-MEDIATED CYTOTOXICITY.
26. Ola Dale: VOLATILE ANAESTHETICS.

1987
27. Per Martin Kleveland: STUDIES ON GASTRIN.
28. Audun N. Øksendal: THE CALCIUM PARADOX AND THE HEART.
29. Vilhjalmur R. Finsen: HIP FRACTURES

1988
30. Rigmor Austgulen: TUMOR NECROSIS FACTOR: A MONOCYTE-DERIVED REGULATOR OF CELLULAR GROWTH.
31. Tom-Harald Edna: HEAD INJURIES ADMITTED TO HOSPITAL.
32. Joseph D. Borsi: NEW ASPECTS OF THE CLINICAL PHARMACOKINETICS OF METHOTREXATE.

URN:NBN:no-3454

33. Olav F. M. Sellevold: GLUCOCORTICOIDS IN MYOCARDIAL PROTECTION.
34. Terje Skjærpe: NONINVASIVE QUANTITATION OF GLOBAL PARAMETERS ON LEFT VENTRICULAR FUNCTION: THE SYSTOLIC PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT.
35. Eyvind Rødahl: STUDIES OF IMMUNE COMPLEXES AND RETROVIRUS-LIKE ANTIGENS IN PATIENTS WITH ANKYLOSING SPONDYLITIS.
36. Ketil Thorstensen: STUDIES ON THE MECHANISMS OF CELLULAR UPTAKE OF IRON FROM TRANSFERRIN.
37. Anna Midelfart: STUDIES OF THE MECHANISMS OF ION AND FLUID TRANSPORT IN THE BOVINE CORNEA.
38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

1989

43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

1990

52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

1991

65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.

68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

1993

82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

1994

92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.

109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANSER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

1997

124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

1998

132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.

139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

1999

141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

2000

158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING
159. CLINICAL AND EXPERIMENTAL STUDIES
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.

URN:NBN:no-3454

168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

2001

178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM

198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

2002

201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

2003

216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL

URN:NBN:no-3454

224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION, AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97

URN:NBN:no-3454