Longitudinal changes in forearm bone mineral density in women and men from 25 to 84 years

The Tromsø Study

by
Nina Emaus

Tromsø 2006

Institute of Community Medicine
University of Tromsø, Norway
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Nina Ernaus,

Tromsø, October 2005.
1. List of papers

This thesis is based on the following papers:


2.0. Introduction

2.1. TROST - Tromsø Osteoporosis Study

Osteoporotic fractures constitute a major health problem with substantial morbidity and costs (1, 2). Although the frequency of fractures appears to be increasing in many countries (3), the incidence of fractures varies (4, 5), and together with Northern America, the Scandinavian countries have the highest incidence of hip and forearm fractures in the world (5-11). As a response to the growing awareness of the fragility fracture epidemic, TROST (Tromsø Osteoporosis Study) was established in 1993 as an included part of the Tromsø Study. The main goals of TROST were to identify risk factors for fragility fractures by as cheap and simple methods as possible, and to find ways to implement such knowledge into fracture prevention programmes. TROST works in close collaboration with NOREPOS (Norwegian Epidemiological Osteoporosis Study) which comprise four large population-based multipurpose studies in the cities of Oslo (the Oslo Health Study, HUBRO, 2000-2001), Bergen (the Hordaland Health Study, HUSK, 1998 – 99), Tromsø (The Tromsø Study/Tromsø Osteoporosis Study, TROST, 1994-95 – 2001) and Nord-Trøndelag (the Nord-Trøndelag Health Study, HUNT, 1995-1997) (12).

2.2. Bone fragility

The causation of fracture is complex, but bone fragility is an important contributor to fracture risk (1, 13, 14). Bone fragility, or the opposite: bone strength, is connected to several composites of bone tissue as well as to the turnover rate.
2.2.1. Bone as a tissue

Bone is a dynamic, specialized connective tissue that together with cartilage, makes the skeletal system which in principle has three main functions; mechanical (as support and site of muscle attachment for locomotion), protective (for vital organs and bone marrow) and metabolic (as a reserve of irons, especially calcium and phosphate, for the maintenance of serum homeostasis) (15). There are two main types of bone, cortical (compact) and trabecular (cancellous) bone. They are made of the same cells and the same matrix, but there are structural differences (15) and they can be seen as separate functional entities that do not change with age in the same way (16).

Cortical bone is dense or compact bone. It comprises 85% of the total bone in the body and is most abundant in the long shafts of the appendicular skeleton. As 80-90% of the volume of cortical bone is calcified, the cortical bone fulfills mainly a mechanical and protective function (15). The volume of cortical bone is regulated with bone formation on the periosteal surface, endosteal resorption and resorption within the Haversian canals. With age, these processes might lead to increased porosity of cortical bone. However, periosteal bone formation continues to increase the diameter of cortical bone throughout life, representing a possible compensation for the loss of strength induced by the age related bone mass reduction (17-19). Cortical bone loss is thought to begin after the age of 40, with an acceleration of loss that occurs for 5-15 years after menopause in women. Loss of cortical bone is the major predisposing factor for fractures that occur at the hip and around the wrist (16).
Trabecular bone comprises approximately 15% of the skeleton, and only 15–25% of its volume is calcified, the remainder being occupied by bone marrow, blood vessels and connective tissue (16). In the lumbar spine, the most common site of fracture associated with osteoporosis, trabecular bone comprises more than 65% of the total bone. The inter-trochanteric area of femur comprises 50% trabecular bone, the neck of femur 25%. Decline in trabecular bone mass is thought to begin earlier than the decline of cortical bone mass, but there are studies suggesting that decline in trabecular bone begins later, and that its decline is not as prominent as the accelerated loss of cortical bone after menopause (16). The loss of trabecular bone that occurs with aging is not simply due to thinning of the bone plates, but is rather caused by complete perforation and fragmentation of trabeculae (16). The resulting change in architecture leads to a loss of strength not always proportionate of the amount of bone lost (20).

2.2.2. Bone remodelling

The responsiveness of bone to mechanical forces and metabolic regulatory signals are operative throughout life. Bone tissue therefore undergo remodelling, a continual process of resorption and renewal (21). Remodelling is a process both involved in bone development and growth, and in the turnover mechanism by which old bone is replaced by new bone. In the normal adult skeleton, after the period of development and growth, bone is formed mostly where bone resorption has previously occurred, in focal and discrete packets throughout the skeleton (16). The sequence of events at the remodelling unit is the activation-resorption-formation (ARF) sequence that was first described by H. Frost (22). The ARF sequence is regulated through regulatory signals among the cell populations (21),
and the complete remodelling cycle at each microscopic site takes about 3-6 months with the same principles in both cortical and trabecular bone (15).

The remodelling that occurs in each basic multicellular unit (BMU), (or bone structural unit), is geographically and chronologically separated from other units. The sequence is always the same, and five different phases can be distinguished over time (16):

1. osteoclastic resorption
2. reversal
3. preosteoblastic migration and differentiation into osteoblasts
4. ostoblastic matrix (osteoid) formation
5. mineralization

In physiological as well as most pathological circumstances, there is a coupling between bone formation and previous bone resorption. Packets of bone that are removed during resorption are replaced during formation. The balance in coupling between bone formation and previous bone resorption maintain the material and structural properties of bone, whereas an imbalance of construction and reconstruction during aging lead to bone fragility and loss of strength (16).

2.2.3. Material and structural properties of bone

Bone is formed by collagen fibres (type 1) and non-collagenous proteins. Spindle- or plate-shaped crystals of hydroxyapatite (3Ca\(_3\)PO\(_4\)2(OH)2) are found on the collagen fibres, within them and in the ground substance, which is primarily composed of glycoproteins and proteoglycans. The collagen fibres alternates from
layer to layer in adult bone with an orientation giving bones their typical lamellar structure and allowing the highest density of collagen per unit volume of tissue (15). Both the material and structural properties of bone meet the contradictory needs of strength for load bearing, lightness for speed, stiffness for movement against gravity and static loading, as well as flexibility for energy absorption (17). The stiffness of the rope-like triple helical fibres of type 1 collagen with mineral crystals, provide resistance to bending, but excessive stiffness would produce glass-like brittleness (18). The collagen weave confers flexibility that allows storage of energy in reversible (elastic) deformation during impact loading or muscle contraction. When the elastic limit is exceeded, bone can store more energy by plastic (irreversible) deformation, but at the price of micro-damage. If the imparted energy exceeds the elastic and plastic limits of deformation, fractures arise (17).

Strength and lightness are also achieved by the geometrical structure of bones. Long bones are weight bearing and should not bend too much, stiffness favoured over flexibility. The long bones are tubular structures that contain a marrow cavity, so that the cortical mass is placed distant from the central long axis. A unit area of bone placed distant from the long axis confers greater bending strength than the same unit area near the long axis because bending strength is a function of the square of the distance from this long axis (18). Size is therefore an important determinant of bone strength and small changes in size, particularly in external diameter, have a major effect on mechanical properties of bones (23). Thus for load bearing and movement, bones must be stiff, but not too stiff as they become brittle (lose “toughness” or the ability to resist micro-damage). Bones
must also be flexible, able to absorb energy in deformation, but not too flexible. As greater bone tissue mineral content or tissue mineral density, confers greater bone stiffness and toleration of greater peak stress, the most important material property of bone is its degree of mineralization (18). For full understanding of the structural and biomechanical components responsible for bone fragility, we would however need more knowledge about the specific material and structural properties such as tissue mineral content, micro-damage burden, porosity, cortical and trabecular architecture, and their interaction (18). The figure below (Fig 1) displays the key components of bone strength, including the interrelationship between bone remodelling, or bone turnover, and bone strength.

![Diagram showing bone strength components](image)

**Figure 1.** Visualisation of the key components of bone strength, and the interrelationship between bone turnover and bone strength.
2.2.4. Aging and fragility

During advancing age bone remodelling (the focal replacement of old or damaged bone with new bone) becomes impaired. For reasons that are still unclear, less bone is formed by each BMU, which leads to less bone. The amount of trabecular bone lost during aging in women and men is believed to be similar, or only slightly less in men than in women, but bone loss results mainly in thinning of trabeculae in men and in loss of connectivity in women (24). In women, the menopause-related estrogen deficiency increases bone remodelling and makes BMU balance more negative, as oestrogen deficiency increases the life span of osteoclasts and reduces the life span of osteoblasts (25). As the increased remodelling results in an increase in the amount of bone replaced ("turned over"), older, more mineralised bone is replaced by younger less mineralised bone. This less mature bone has reduced stiffness. The same loads are imposed on a structure with diminished cross sectional area. The stress (load per unit area) increase, predisposing to micro-damage and ultimately fracture (18).

During aging, periosteal apposition continues as it did during growth, but more slowly. In both sexes, it is likely that bone balance becomes progressively less positive at a time when bone mass is neither increasing nor beginning to decline. At some time in young adulthood, and well before menopause in women, bone balance probably starts to become negative because of a reduction in the amount of bone formed in the BMU, not because of an increase in the resorption in each BMU. This negative bone balance within each BMU is the structural basis of irreversible bone loss (19).
between load and bone strength is better maintained in men than in women (18).

Structural failure occurs less in men than in women because the relationship stress on bone decreases more in men and strength of the bone decreases less. Adding more bone to the outer perimeter of the bone in men during a lifetime that load, resulting in an increase in the cross-sectional area of the bone, changing relationship between the imposed load and the bone's ability to tolerate structural failure emerges during aging in men and women because of the and hence – the larger bone in men is subjected to correspondingly larger loads. The vertebral body is greater in young men than in women because men are taller in women, bones have higher relative absorptive loads. The absorptive load imposed on

The larger section achieved during growth produces stronger bones in men than
In the two-dimensional grey-scale scan image that is generated on basis of the
computer uses the x-ray absorption to calculate the amount of bone mineral present
so that issue during the scan. With an highest detected area, this
needs to be improved in a water bath which behaves like a standardized layer of
the detection that X-ray can only be performed at apparent sites or the height
of the radiation is absorbed by the tissue that is between the x-ray source and
detector. This sends a single energy beam through the limb and detects how much
in the present study we have used the X-ray densitometry. The single x-ray
enhanced image resolution and improved precision (28, 29).

DEXA DXA, represents several improvements with standard scan times,
in the 1980's single and dual energy x-ray absorptionmetry (DXA) or
needed frequent replacement, the development of x-ray based densitometers in
resolution scan took a long time to complete (20 min) and the radiation
DPA) used 1000's of days source of radiation. These had relatively low spatial
bone densities, the single and dual photon absorptionmetry devices (SPA,
which then been disposed of is through a new analytical method. The first
radiography examination and the DXA results reflect the amount of radiation
strongly expressed by bone mineral density. Bone destruction is a
1960-20 (27) set the stage for the first non-invasive measurements of bone
strongly (22). The destruction technique development that started in the
are still not clear (18). Despite its helpful in capturing the components of bone
into damage burden and processes of differences between axes of between mass
inherent number, thickness and connective tissue mineral content.

2.3 THE BMD MEASUREMENT
absorption pattern. Each pixel represents the estimated bone mass at that particular anatomical point (30), or bone mineral content per projected area in g/cm$^2$ (29).

2.5. TROST and BMD measurements

The peripheral location and the relatively small amount of surrounding soft tissue made the distal forearm an obvious early choice for the assessment of a subject's bone mineral density. The limited amount of surrounding tissue increased the accuracy and the precision of bone mass measurements, the peripheral scanning site reduced the radiation dose and made the equipment requirements simpler and less expensive (29). In addition, the anatomy of the radius with a thin cortex with mainly trabecular bone at the ulnradial end and pure cortical bone along the radial shaft enabled the examination of both trabecular and cortical bone (29). When it was decided for TROST to have bone density measured in the Tromsø Study 1994-95, the SXA of the forearm was an easy choice. At that time, the DEXA scanning still took 30 minutes, which was too time-consuming for such a large study.

Despite the development and availability of densitometric techniques, BMD and its changes throughout life in both sexes was hardly studied when TROST planned for the Tromsø IV study in 1994. Most of the existing studies were cross-sectional (31-42), the majority of them based on healthy volunteer populations. Some longitudinal studies existed, describing BMD changes in younger (43-51) and older (52-60) women, but studies from general populations were rare (61-67), and to our knowledge only one of them included men (63). Normal BMD changes
in both sexes from the younger to the older age groups were therefore not thoroughly described and the pattern of bone loss not well understood (68). As both peak bone mass and subsequent rate of loss both contribute to low bone mass later in life (69), knowledge about normal bone loss rates would be an important part of understanding the mechanisms behind bone fragility and fracture risk later in life. With its connection to the population based Tromsø Study, TROST had a unique possibility to study BMD changes in both sexes, from the younger part of the population to the elderly, both cross-sectionally (Tromsø IV) (70) and longitudinally (Tromsø IV and V), in a Scandinavian high-risk population.

2.4. BMD measurements in longitudinal studies

According to Henney, few fields of clinical medicine possess tools as precise as bone densitometry (71). However, scanning instabilities and technical malfunctions might influence the quantitative results of bone mineral measurements (29) and bone densitometry can provide misleading information if it is not applied appropriately (26). Rigorous quality control is mandatory in the application of quantitative densitometry, and in longitudinal studies it is important to secure that the documented changes are real and not only due to densitometer drift or fluctuations (72-74) or due to variation between densitometers (72). Quality control of densitometer performance as well as cross-calibration between different machines (75) and different methods can be performed in vivo or in vitro with special-purpose scan phantoms (76). Planning for Tromsø IV and V in 1994, there were studies focusing on the problems of long-term precision within the field of bone mass measurements (62, 72, 77-80), as well as on the problems of comparability of BMD measurements between densitometers, even of the same
make and model (81-83). With this awareness, it was important for TROST to
develop and evaluate quality control routines for observation of densitometer
performance during its studies, as well as comparability of the participating
densitometers’ measurement level. Our main concern has been how well
densitometer phantoms would reflect differences between densitometers and in
densitometer performance.

3.0. Aim of thesis

On the given background, the aim of the theses is two-fold:

1. To study BMD changes and its variation in women and men between 25 –
   85 years in a population based longitudinal study. (Paper II and III)
2. To study how precision of BMD measurements can be assessed and
   secured in longitudinal studies. (Paper I and IV)

4.0. Materials and method

4.1. Main study population, TROST (paper I – III)

Through the Tromsø Study, TROST had in Tromsø IV, 1994 95, 10213 subjects
invited for bone densitometry measurement and 7948 (78%) persons attended the
examination (30, 70). In Tromsø V, 7386 persons still living in Tromsø were
invited for a re-examination, and 5771 (78%) attended. This number corresponds
to 57% of the originally invited cohort (Figure 2 and table 1). Table 1 displays the
attendance rates within three age-groups. All age groups are included in paper I,
age groups 25-44 in paper II, and age groups 45-84 in paper III.
Figure 3. Flow chart presenting numbers of persons invited and attended in the longitudinal study Tromsø IV and Tromsø V, 1994-95 and 2001.

Table 1. Attendance rates according to three respective age groups in 1994 for both sexes in the longitudinal study, Tromsø IV and Tromsø V, 1994-95 and 2001.

<table>
<thead>
<tr>
<th>Age</th>
<th>Invited Tromsø IV</th>
<th>Attended Tromsø IV</th>
<th>Response</th>
<th>Invited Tromsø V</th>
<th>Attended Tromsø V</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-44</td>
<td>617</td>
<td>396</td>
<td>64,2</td>
<td>391</td>
<td>258</td>
<td>66,0</td>
</tr>
<tr>
<td>45-64</td>
<td>3358</td>
<td>2738</td>
<td>81,5</td>
<td>2661</td>
<td>2226</td>
<td>83,7</td>
</tr>
<tr>
<td>65-84</td>
<td>1820</td>
<td>1418</td>
<td>77,9</td>
<td>1284</td>
<td>943</td>
<td>73,4</td>
</tr>
<tr>
<td>All</td>
<td>5795</td>
<td>4558</td>
<td>78,7</td>
<td>4341</td>
<td>3427</td>
<td>78,9</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-44</td>
<td>427</td>
<td>241</td>
<td>56,4</td>
<td>240</td>
<td>147</td>
<td>61,3</td>
</tr>
<tr>
<td>45-64</td>
<td>2494</td>
<td>1974</td>
<td>79,1</td>
<td>1841</td>
<td>1504</td>
<td>81,7</td>
</tr>
<tr>
<td>65-84</td>
<td>1497</td>
<td>1171</td>
<td>78,2</td>
<td>964</td>
<td>693</td>
<td>71,9</td>
</tr>
<tr>
<td>All</td>
<td>4418</td>
<td>3390</td>
<td>76,7</td>
<td>3045</td>
<td>2344</td>
<td>77,0</td>
</tr>
</tbody>
</table>
4.2. The course of the longitudinal study (paper I – III)

The course of the longitudinal study is displayed in figure 4. In Tromsø IV, 1994 – 95, we started out with the two densitometers, nicknamed “Adam” and “Eva”. Before starting the second survey in 2001, both densitometers were transported and used in other studies in NOREPOS (12, 84). Starting the second survey, “Eva” had to undergo a major repair and was principally replaced by “Henry”. Three and four months into the second survey, the x-ray tube had to be replaced on both densitometers, which therefore were nicknamed “Adam-01/1 and 2” and “Henry – 01/1 and 2” respectively.

Because of the densitometers breakdown, when the Tromsø Study ended phase I in December 2001, TROST had only measured BMD on 4681 persons, which corresponded to 63% of those invited to the survey. As TROST still could use the same localities, we arranged an “extra-invitation” to those who had attended the Tromsø V survey, phase I, without having the BMD measured. Of the 1527 persons invited, 1090 met (71%), and had their BMD measured in March 2002. With this “extra-invitation”, the total number of persons with repeated BMD measurements reached 5771.

Through both studies, quality control was performed on a daily basis with the aluminium forearm phantom (AFP) provided by the manufacturer. In 1999, the European forearm phantom (EFP) (QRM-Germany) was purchased. This is a semi-anthropomorphic phantom, comprising three hydroxyapatite bone imitations with different densities within the human range, 0.662 g/cm² at the highest density level, 0.415 g/cm² at the mid-density level and 0.314 g/cm² at the
lowest density level. From 1999, and through the second survey, regular measurements with the EFP, was also included into the study protocol. After finishing the survey in March 2002, we had three sources at disposal for retrospective analysis of densitometer performance in our study, and the analysis and comparison of these three sources serve as a background to paper 1.

1. Repeated human measurements at the distal and ultradistal forearm sites in altogether eight densitometer combinations.

2. Repeated measurements of the equipment specific aluminium forearm phantom provided by the manufacturer.

3. Repeated measurements of the European forearm phantom which was purchased in 1999.

**Figure 4.** The course of the longitudinal study displayed, Tromsø IV and Tromsø IV, 1994-95 and 2001. Human BMD, n=valid measurements at the distal forearm site.
4.3. Quality control and exclusion of invalid scans (paper I – III)

In both studies, all scans were reviewed and reanalysed from the protocol developed during Tromsø IV (85). Analyses of the scans lead to exclusions of 81 and 113 scans at the distal and ultradistal sites respectively in women, and 53 and 42 scans at the distal and ultradistal sites respectively in men. Reasons for exclusions were, in both studies, mainly excessive movement artefacts at the distal site and region of interest out of scan at the ultradistal site. Table 2 displays the numbers of measured, excluded and valid scans.

Table 2. Valid repeated measurements TROST, Tromsø IV 1994-95 and Tromsø V 2001.

<table>
<thead>
<tr>
<th></th>
<th>Repeated measurements Tromsø IV-V</th>
<th>Excluded measurements Tromsø IV</th>
<th>Excluded measurements Tromsø V</th>
<th>Valid repeated measurements Tromsø IV-V</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal site</td>
<td>3427</td>
<td>51</td>
<td>32*</td>
<td>3346</td>
</tr>
<tr>
<td>Ultradistal</td>
<td>3427</td>
<td>81</td>
<td>37**</td>
<td>3313</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal site</td>
<td>2344</td>
<td>32</td>
<td>21</td>
<td>2291</td>
</tr>
<tr>
<td>Ultradistal</td>
<td>2344</td>
<td>22</td>
<td>20</td>
<td>2302</td>
</tr>
</tbody>
</table>

* 2 persons had their scans excluded in both studies at the distal site
** 4 persons had their scans excluded in both studies at the ultradistal site

4.4. Study population, NOREPOS Study (paper IV)

In this study we wanted a selected study population with a wide range of characteristics that possibly could influence BMD measurements. The inclusion criteria are thoroughly described in paper IV. For clarification, volunteers for the study were recruited among employees at the University of Tromsø (UiTØ) and they were asked information about age, height and weight as surrogates for bone mass, bone size and BMI. From this information, persons were selected to the
study through the following system, containing at least three persons in each group:

Table 3. Chosen characteristics of study participants for the initial recruitment phase, NOREPOS Study.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 - 44</td>
<td>&lt;162</td>
<td>57 - 67</td>
</tr>
<tr>
<td>45 - 64</td>
<td>163 - 171</td>
<td>67 - 79</td>
</tr>
<tr>
<td>65 - 70</td>
<td>&gt;171</td>
<td>80 - 92</td>
</tr>
</tbody>
</table>

20 participants fitting into any of these groups, underwent a preliminary DEXA examination and were included into the study from following criteria: variation in BMD levels (g/cm²), bone size (cm²) measured by DEXA (total hip) and variation in BMI (kg/m²). The chosen range of variation was provided through data from Tromsø V. From these measures we had a total of 9 categories where participants were included until there were a minimum of 3 participants fitting into each category (Table 1, paper IV). Finally a total of 17 participants were included into the study.

4.5. BMD measurements, NOREPOS Study (paper IV)

Bone densitometry was performed as in the main study on the distal forearm, on the five similar SXA-devices formerly used in NOREPOS sub-studies (84), two of these used in the main study. Each of the 17 participants had three measurements done on each densitometer with full repositioning between each measurement, from the same protocol as used in the main study as well as in the former studies in NOREPOS (12). All scans were reviewed and reanalysed according to the same quality control protocol as in the main study (86).
4.6. Data management and statistics.

Data management and statistical analysis are thoroughly described in the respective papers.

5.0. Summary of papers and main results

5.1. The choice of densitometer phantoms in longitudinal studies (paper I)

BMD changes differed significantly on the eight densitometer combinations in the longitudinal study, also when adjusting for sex and age, indicating a difference in densitometer measurement level. The main purpose of this study was to investigate to what degree two different densitometer phantoms reflected densitometer performance which was observed in the human BMD change data. The indicated differences were predicted by the anthropomorphic forearm phantom, EFP, and not by the aluminium forearm phantom, AFP. The EFP measurements indicated that one of the densitometers ("Adam-94" and "Adam-01/1") measured at a higher level (0.005 g/cm²) before x-ray tube replacement compared to the other densitometers. The EFP data also indicated that measurement level within each time of function of the densitometers (CV%) was stable. Based on these results from this, we adjusted the data measured on "Adam-94" and "Adam-01/1" and concluded that daily assessment of densitometer performance in longitudinal studies should be performed by anthropomorphic and not aluminium phantoms.

5.2. BMD changes in women and men 25 - 44 years (paper II)

The main purpose of this study was to describe and compare BMD changes in women and men aged 25 - 44 years. At the distal site, a small annual gain of
approximately 0.1 percent turned to a small loss from age 34 and 36 in men and women respectively. In both sexes the change was significantly predicted by age. At the ultradistal site, BMD change was only predicted by age in women, bone loss starting from age 38. A high degree of tracking of BMD measurements were observed in both sexes at both sites. Depending on total BMD change, participants were grouped into “losers”, “non-losers” and “gainers”, and more than 6 percent lost more than the smallest detectable change, >-3.46 and >-5.14 percent, at the distal and ultradistal sites respectively. In both sexes the bone mineral content (BMC) (g) decreased whereas area (cm²) increased significantly in “losers” compared to “gainers”, representing a possible physiological compensation preserving bone strength. No cohort effects were observed when measures from similar age groups from 1994 and 2001 were compared. We conclude that BMD changes in the age group 25-44 are significantly explained by age, but not by sex.

5.3. BMD changes in women and men 45 – 84 years (paper III)

The main purpose of this study was to describe BMD changes in women and men aged 45 – 84 years. The mean annual bone loss was −0.5 and −0.4 percent in men, −0.9 and −0.8 percent in women not using hormone replacement therapy (HRT), at the distal and ultradistal sites respectively. Age was a negative predictor of BMD change at both sites in men. Women not using HRT had the highest bone loss rates at the ultradistal site 1 – 5 years after menopause. The correlation between the two measurements were high; r=0.93 and r=0.90 in women, and r=0.96 and r=0.93 in men, distal and ultradistal sites respectively. More than 70 percent kept their quartile positions. The degree of tracking of BMD measurements was therefore high. The observed bone loss rates in this study
population were not higher compared to other cohorts. We conclude that BMD changes in men are significantly explained by age at the distal and ulnadistal forearm sites, whereas women not using HRT experience the highest loss rates 1-5 years after menopause.

5.4. Can in vitro replace in vivo densitometry cross-calibration? (paper IV)

Based on the results from paper I, and on studies reporting conflicting results concerning agreement between in vitro and in vivo measurements, we wanted to study the agreement between AFP, EFP and in vivo densitometry at the distal forearm site in a cross-calibration study. Representing the gold standard for calibration, the human measurements revealed that one of the five densitometers reported a higher BMD level than the other four densitometers. The EFP followed the direction of difference observed in the human measurements better than the AFP, but tended to overestimate the difference between the densitometers. We conclude that densitometers of same make and model might differ significantly in performance. In vivo measurements remain the most valid tool for detection of densitometer differences although differences in densitometer performance are better captured by calcium-hydroxyapatite then aluminium phantoms. In longitudinal studies, regular use of phantoms of calcium-hydroxyapatite is still recommended for daily quality assessment and for comparison of different densitometer's measurement level.
6.0. Discussion

6.1. Internal validity

The internal validity refers to whether results from a study are valid or true for the study population (87). Selection bias, information bias and confounding may threaten the internal validity of a study (87). Bias may be defined as any systematic error in an epidemiologic study that results in an incorrect estimate of the association between exposure and outcome (88). Confounding might be defined as confusion, or mixing, of effects. This definition implies that the effect of the exposure is mixed together with the effect of another variable so that the association between exposure and outcome may be distorted by a third variable, which is related to both the exposure and the outcome (89). Age and sex are very likely to be confounding variables. As those are the most central variables studied in relation to BMD changes in this theses, we have, to avoid confounding, done the analysis both age and sex stratified. We are, therefore, mostly concerned about the possible effect from selection and information bias in our studies on BMD changes (paper II and III), where the aim is to gain knowledge of BMD changes and its variation in both sexes in a normal population.

6.1.1. Selection bias

Selection bias is a systematic error in a study that stems from the procedures used to select subjects and from factors that influence study participation (89). The Tromsø Study is a population based study famous for the high attendance rates in its surveys, and as displayed in table 1, the attendance rates in both Tromsø IV and V were well above 75% in both sexes. The attendance rates do however vary between the different age groups, being highest in the older age groups, and
lowest in the youngest age groups, which comprise the study population of paper II. Data for the first study, Tromsø IV, were compared for non-responders, partial responders and full responders (30, 70), the analysis gave no indication for any differences between these groups (30). After Tromsø V, we could use baseline characteristics from Tromsø IV to compare participants lost for follow-up with those who attended both studies. The results from the analysis are displayed and thoroughly discussed in paper II and III. Here we summarize our main findings.

In the youngest age groups, women and men 25-44 years, participants lost for follow-up were younger than those who participated in both studies. We have presented the data in 5-years age groups, which gives us small numbers in the youngest age groups. It was therefore a great concern to discover possible selection favours. With information gained from questionnaires in Tromsø IV we analysed whether the two groups differed with regard to central lifestyle variables which might influence bone loss rates (90-105). The only observed difference between the two groups was connected to smoking status in both sexes. The percentage of present smokers was equal among participating women compared to participants lost for follow up (p=0.03), but participating women had smoked one year longer than those lost for follow up. Total amount of cigarettes smoked were however not significantly different when the two groups were compared. The percentage of present smokers tended to be higher among the male participants lost for follow-up (p=0.06), but smoking years and total amount of cigarettes smoked were not significantly different in the compared groups. Smoking might influence bone health in a negative direction, with a cumulative effect by age (106), but smoking years did not predict BMD changes in women (p= 0.163 and
p=0.222 at the distal and ultradistal site respectively) and smoking status did not predict BMD changes in men (p=0.218 and p=0.051 at the distal and ultradistal site respectively) in this material. We therefore assume that the results presented in paper II are not seriously influenced by selection bias.

For the older age groups, 45 – 84 years, women lost for follow up were shorter, had a greater BMI, were more often smokers, had a higher percentage perceiving their own health as bad, and had a lower baseline BMD at both the distal and ultradistal site. Men lost for follow up were shorter, weighing less, were more often smokers and more often perceived their own health as bad compared to those who participated in both studies. Baseline BMD at both the distal and ultradistal site was also lower in participants lost for follow-up. As thoroughly discussed in paper III, the differences between the two groups indicate that participants lost for follow-up in general seem to be less healthy or having less healthy life-style than those who participated in both studies. 556 persons with a mean age of 65.8 years, were either dead or had moved out town between the two surveys. When these persons were excluded from the analyses, age, height, weight, BMI and smoking years (women) were no longer significantly different between the two groups, but baseline BMD remained significantly different at both sites. Bone health is a powerful predictor of general health status (107), and despite high attendance rates, we must conclude that there is a possible "healthy" selection bias in the material. Our bone loss rates might therefore be slightly underestimated. As we have discussed in paper III, this tendency towards "healthy" selection bias is also observed in other longitudinal studies within the field of osteoporosis research (108, 109).
As part of the Tromsø study, the Family Intervention Study (FIS) was an open randomised trial aimed at improvement of the cardiovascular risk profile in male subjects who either had a high total cholesterol or a low HDL to total cholesterol ratio (110). In Tromsø IV, 328 male participants, being members of FIS, had their BMD measured. In the presentation of our cross sectional data, these men were excluded from the analysis as they were not viewed as representative of the general population with respect to BMD level (70). In Tromsø V, 251 of the FIS cohort members had the BMD measurements repeated. Since their bone loss rates did not differ significantly in comparison to the other men in the respective age groups, we have not excluded the FIS-cohort members from the BMD change analysis. Table 4 displays the bone loss rates in the respective age groups.

Table 4. Comparison of BMD changes (mg/cm²) in male participants categorized as “FIS- members” and “non-FIS members”.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>FIS-members, BMD change (mg/cm²)</th>
<th>Non-FIS members, BMD change (mg/cm²)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mg/cm²</td>
<td>95% CI</td>
</tr>
<tr>
<td>40-44</td>
<td>15</td>
<td>-1.41</td>
<td>(-2.31, -0.51)</td>
</tr>
<tr>
<td>45-50</td>
<td>113</td>
<td>-1.41</td>
<td>(-1.80, -1.02)</td>
</tr>
<tr>
<td>50-54</td>
<td>122</td>
<td>-1.60</td>
<td>(-1.98, -1.22)</td>
</tr>
<tr>
<td>55-59</td>
<td>1</td>
<td>-2.40</td>
<td></td>
</tr>
</tbody>
</table>

6.1.2. Information bias

Systematic error in a study can arise because the information collected about or from the study subjects is erroneous (39). The SXA measurement of the distal forearm is thought to be one of the most precise densitometric methods (111-114), and the low coefficient of variation (CV%) on our densitometers during their time of function confirmed that assertion (paper I). From the post hoc analysis (paper I) we found that the AFP and the EFP predicted densitometer performances
differently and since the EFP measurements reflected the differences seen in the human material, we decided to use the EFP measurements in the final evaluation of densitometer performance, which lead to an adjustment of minus 0.005 g/cm² of the measurement levels of "Adam – 94" and "Adam-01/1" (paper I). In the NOREPOS study (paper IV), we had the opportunity to evaluate densitometer performance through human measurements from a wide range of BMD levels. As the human measurements represent the gold standard, the performance of EFP and AFP is compared directly with the human measurements. From the results we concluded that EFP followed the human measurements, however tending to overestimate the real densitometer differences. These findings indicated that the correction based on the EFP probably represent an "over-adjustment". Table 5 displays the BMD change estimates in mg/cm² at the distal forearm sites, unadjusted data and data adjusted on basis of the EFP measurements (paper I). In addition, we display the BMD change estimates which are adjusted on basis of the human measurements: minus 0.003 g/cm² of the measurement levels of "Adam – 94" and "Adam-01/1".
Table 5. BMD change estimates in mg/cm² at the distal forearm sites, data adjusted based on EFP (paper I), data adjusted based on human measurements and unadjusted data, Tromsø IV 1994-94 and Tromsø V 2001.

<table>
<thead>
<tr>
<th>Women</th>
<th>N</th>
<th>Adjusted -0.005 mg/cm² (95%CI)</th>
<th>Adjusted -0.003 mg/cm² (95%CI)</th>
<th>Unadjusted mg/cm² (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-29</td>
<td>36</td>
<td>0.44 (-0.2, 1.09)</td>
<td>0.32 (-0.3, 0.94)</td>
<td>0.14 (-0.47, 0.74)</td>
</tr>
<tr>
<td>30-34</td>
<td>75</td>
<td>0.38 (-0.05, 0.82)</td>
<td>0.29 (-0.14, 0.72)</td>
<td>0.16 (-0.28, 0.59)</td>
</tr>
<tr>
<td>35-39</td>
<td>72</td>
<td>-0.18 (-0.61, 0.26)</td>
<td>-0.25 (-0.68, 0.18)</td>
<td>-0.35 (-0.79, 0.08)</td>
</tr>
<tr>
<td>40-44</td>
<td>70</td>
<td>-0.31 (-0.81, 0.19)</td>
<td>-0.40 (-0.89, 0.09)</td>
<td>-0.54 (-1.01, -0.06)</td>
</tr>
<tr>
<td>45-49</td>
<td>82</td>
<td>-2.11 (-2.72, -1.50)</td>
<td>-2.18 (-2.78, -1.58)</td>
<td>-2.27 (-2.87, -1.68)</td>
</tr>
<tr>
<td>50-54</td>
<td>862</td>
<td>-3.35 (-3.62, -3.07)</td>
<td>-3.41 (-3.68, -3.14)</td>
<td>-3.51 (-3.78, -3.24)</td>
</tr>
<tr>
<td>55-59</td>
<td>686</td>
<td>-3.14 (-3.44, -2.85)</td>
<td>-3.21 (-3.50, -2.94)</td>
<td>-3.32 (-3.61, -3.02)</td>
</tr>
<tr>
<td>60-64</td>
<td>548</td>
<td>-2.89 (-3.20, -2.59)</td>
<td>-2.94 (-3.25, -2.64)</td>
<td>-3.02 (-3.33, -2.77)</td>
</tr>
<tr>
<td>65-69</td>
<td>545</td>
<td>-3.18 (-3.50, -2.85)</td>
<td>-3.25 (-3.57, -2.93)</td>
<td>-3.37 (-3.69, -3.05)</td>
</tr>
<tr>
<td>70-74</td>
<td>355</td>
<td>-2.94 (-3.38, -2.51)</td>
<td>-3.00 (-3.42, -2.57)</td>
<td>-3.07 (-3.50, -2.6)</td>
</tr>
<tr>
<td>75+</td>
<td>15</td>
<td>-5.49 (-8.13, -2.85)</td>
<td>-5.67 (-8.34, -3.00)</td>
<td>-5.94 (-8.65, -3.22)</td>
</tr>
<tr>
<td>Total</td>
<td>3346</td>
<td>-2.88 (-3.01, -2.75)</td>
<td>-2.95 (-3.08, -2.82)</td>
<td>-3.05 (-3.18, -2.92)</td>
</tr>
</tbody>
</table>

| Men | | | | |
| Age groups | N  | Adjusted -0.005 mg/cm² (95%CI) | Adjusted -0.003 mg/cm² (95%CI) | Unadjusted mg/cm² (95%CI) |
| 25-29 | 24 | 0.91 (-0.05, 1.87) | 0.88 (-0.09, 1.84) | 0.83 (-0.16, 1.82) |
| 30-34 | 29 | 0.17 (-0.47, 0.80) | 0.10 (-0.56, 0.75) | -0.01 (-0.71, 0.68) |
| 35-39 | 43 | -0.78 (-1.38, -0.18) | -0.91 (-1.58, -0.30) | -1.11 (-1.74, -0.48) |
| 40-44 | 45 | -0.96 (-1.40, -0.51) | -1.05 (-1.51, -0.59) | -1.19 (-1.69, -0.69) |
| 45-49 | 166 | -1.49 (-1.84, -1.14) | -1.55 (-1.90, -1.19) | -1.63 (-1.99, -1.26) |
| 50-54 | 184 | -1.54 (-1.83, -1.25) | -1.61 (-1.91, -1.32) | -1.72 (-2.02, -1.42) |
| 55-59 | 602 | -1.92 (-2.12, -1.73) | -1.97 (-2.16, -1.78) | -2.04 (-2.22, -1.84) |
| 60-64 | 524 | -2.70 (-2.96, -2.43) | -2.75 (-3.02, -2.49) | -2.83 (-3.10, -2.57) |
| 65-69 | 393 | -3.24 (-3.59, -2.89) | -3.30 (-3.62, -2.95) | -3.39 (-3.74, -3.04) |
| 70-74 | 271 | -3.77 (-4.21, -3.34) | -3.85 (-4.28, -3.41) | -3.96 (-4.40, -3.52) |
| 75+ | 10 | -3.29 (-5.84, -0.74) | -3.32 (-5.79, -0.85) | -3.37 (-5.72, -1.02) |
| Total | 2291 | -2.39 (-2.52, -2.27) | -2.45 (-2.58, -2.33) | -2.54 (-2.67, -2.42) |

As reflected in Table 5, the unadjusted BMD change estimates report slightly higher (but not significantly different) bone loss rates (from age group 35-39 and 30 – 34 in women and men respectively), than the adjusted data. The adjusted BMD change estimates are therefore more conservative that the unadjusted. The most conservative BMD change estimates are those based on EFP (paper I, II and III), where the measurements from “Adam-94” and Adam-01/1” where reduced by -0.005 g/cm². These estimates probably represent an underestimation of the
real bone loss rates. Adjustments of “Adam-94” and Adam-01/1” with -0.003 g/cm³, based on the human material reduced differences observed between densitometer combinations in paper I (from \( p > 0.001 \) to \( p = 0.865 \), ANOVA), and most probably represent the “true” BMD changes. With this information bias, our published BMD change estimates are probably slightly underestimated. But, the differences in change estimates are neither statistically nor clinically significant (the mean difference in annual BMD change being less than 0.07 mg/cm³, or 0.01 percent points in both sexes), and do not have any significant influence on the reported results.

In paper II and III we have classified women according to menstrual status and use of hormone replacement therapy based on answers to questionnaires. There might be some recall bias influencing the answers which might represent a misclassification with some influence on the reported BMD changes in women, although we believe that the effect is minor.

6.1.3. Summary internal validity
This longitudinal population-based study has an overall high response rate, indicating that the results are generalisable to the majority of the subjects in the source population. The non-response in the younger population (ages 25-44) is probably not related to changes in BMD, but non-response among the older subjects may be due to health related issues which might influence bone loss rates. With the densitometer adjustments we have made in this study, our reported bone loss rates in both sexes, might therefore be slightly underestimated, but with effects we believe are neither statistically nor clinically significant.
6.2. External validity

External validity refers to whether results that are found to be valid for the source population also are generalisable to other populations, the question of generalisability relying heavily on the source population being representative of other populations.

The Tromsø population does not differ substantially from the Norwegian population at large with respect to age and sex distribution (30). The city is situated at 69 degrees north, approximately 400 km north of the Artic Circle. The daylight exposure varies, and the high latitude strongly affects the amount and intensity of UV-exposure available (115). The inhabitants of Tromsø each year experience a "vitamin D winter" of approximately three months, with UV-radiation below the stated threshold need for vitamin D production in the skin (115). The essential role Vitamin D plays in maintaining a healthy mineralized skeleton has long been acknowledged (116, 117). Sunlight causes the photoproduction of vitamin D3 in the skin. Once formed, vitamin D3 is metabolized sequentially in the liver and kidney to 1,25-dihydroxyvitamin D. The major biological function of 1,25-dihydroxyvitamin D is to keep the serum calcium and phosphorus concentrations within the normal range to maintain essential cellular functions and to promote mineralization of the skeleton and exposure to sunlight provides most humans with their vitamin D requirement (116).

With its location, it could be expected the population of Tromsø having higher bone loss rates, and the results from this longitudinal study therefore not being
representative of other populations. There are difficulties in comparing BMD change rates between population, because of the use of different densitometer techniques and different sorting between age groups; but as discussed in paper III, the loss rates in the age groups 45-84 observed in Tromsø are not higher compared to other cohorts (62-64, 67, 109, 118, 119). Our findings of a small bone loss starting in both sexes in mid-thirties in the age groups 25-44 are slightly in contrast to some studies reporting no loss in the comparable age groups (120, 121), but in agreement with other researches (17). We therefore believe that the BMD change rates from the distal and ulradistal forearm site in women and men between 25-84 observed in this study are generalisable to other populations. It would however be interesting to do a direct comparison of BMD-loss rates with other studies internationally.

6.3. Significance of results

Through this study we have learnt that quality assessment of densitometer measurement levels preferably should be through in vivo cross-calibration. For long-term stability anthropomorphic phantoms of hydroxy-apatite represent more valid tools than aluminium phantoms.

At the distal forearm sites, bone density continue to increase before it turns to a small decline from the mid thirties in both sexes. In men the rates of bone loss increase with increasing age, whereas in women, the rate of loss is highest 1-5 years after menopause. Despite a high degree of tracking of BMD measurements, there are interindividual variations of bone loss rates within each age group, and in both sexes.
6.3.1. BMD changes and types of bone

With the forearm sites, we had the possibility of studying age-related BMD changes in cortical (distal site) as well as trabecular (ultradistal site) bone (Figure 5). In contrast to what is generally believed (16), cortical bone loss started in both sexes in the mid-thirties. In men, BMD loss became significant in the age group 35-39, thereafter it increased linearly with age so that the highest bone loss rates were observed in the oldest age groups. In women, cortical BMD loss became significant in the age group 45-49, doubled in the age group 50-54, whereafter followed a “stable” period with high bone loss rates until old age.

As indicated in the literature (16), the observed changes display a slightly different pattern in trabecular bone. In men, trabecular BMD loss started later than cortical bone loss (became significant from the age group 45-49), thereafter it increased linearly by age with the same pattern as observed at the cortical site, but with significantly smaller loss rates in all age groups. In women, the significant increase in trabecular bone in the age group 25-29 turned dramatically to a significant decrease in from age group 45 – 50. The highest bone loss rates were measured in the age group 50-54 (and 1-5 years after menopause), thereafter the loss rates actually slowed down. In summary, trabecular bone loss starts at the same time as cortical loss in women, it follows the same change pattern, but it is more pronounced, strongly influenced by the menopause-related estrogen deficiency (16-18, 20).
6.3.2. BMD changes and bone strength

The results from this longitudinal study confirm findings from other longitudinal studies that BMD continue to decline in both sexes throughout life (66, 108, 109). Comprising age groups from 25 years to old age, the results also demonstrate how women lose bone at a higher rate than men from the age of 45. Women also lose bone from lower baseline density, mean BMD level 0.482 and 0.377 g/cm² at the distal and ultradistal sites respectively in women, 0.588 and 0.507 g/cm² in men, in the age group 30-34. With the larger skeleton achieved during growth in men, the results from this study displays why bone strength is better maintained.
throughout life in men compared to women, and why structural failure occurs less in men than in women (18).

6.3.3. Area changes
As geometrical structure contribute significantly to bone strength, we have analysed our data on area changes in both sexes from 25-84 years, the results as annual area changes in mm² are displayed in table 6. In men, the area changes are not significantly different from 0 in the age groups 15-44 years. After 45, there is actually a significant area loss in men, with more or less the same picture observed in women too. The changes are in both sexes not significantly explained by age (p=0.73 in women, p=0.49 in men). Our findings of area loss, is in contrast to what is generally believed, that periosteal apposition increases area by age (17) and also confirmed in a longitudinal study of Ahlborg following 108 postmenopausal women over a period of 15 years, concluding that by six years after menopause, BMD had decreased significantly, whereas the periosteal diameter had increased significantly at the distal radius (122). Our findings are however in concordance with Heaney (23) who followed 191 caucasian women, aged 35 - 45 years, more than 20 years. They found that the cortical area of both the metacarpals and radial shaft declined by age with a magnitude similar to our findings, whereas both femur shaft diameter and cortical area increased modestly and significantly with age. According to Heaney, these observed changes at the upper extremity are small enough to be without much structural significance. The greater expansion at femur of 5% over the span of the study, is however considered as increasing the structural stiffness of femoral shaft, more than change in mass would predict (23). In conclusion, at the distal forearm site of the
non-dominant hand, we did not observe geometrical changes which possibly
could compensate loss of bone strength induced by loss of BMD.

Table 6. Annual area changes (mm²) in women and men 25.84 in the longitudinal study, Tromsø IV and Tromsø V, 1994-95 – 2001, with 95 percent confidence intervals (95% CI)

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Women Mean change</th>
<th>95% CI</th>
<th>Men Mean change</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-29</td>
<td>-0.036</td>
<td>(-0.101, 0.028)</td>
<td>-0.052</td>
<td>(-0.144, 0.04)</td>
</tr>
<tr>
<td>30-34</td>
<td>-0.038</td>
<td>(-0.08, 0.005)</td>
<td>-0.024</td>
<td>(-0.094, 0.046)</td>
</tr>
<tr>
<td>35-39</td>
<td>-0.053</td>
<td>(-0.101, -0.006)</td>
<td>-0.042</td>
<td>(-0.111, 0.027)</td>
</tr>
<tr>
<td>40-44</td>
<td>-0.053</td>
<td>(-0.091, -0.015)</td>
<td>-0.047</td>
<td>(-0.110, 0.016)</td>
</tr>
<tr>
<td>45-49</td>
<td>0.018</td>
<td>(-0.038, 0.073)</td>
<td>-0.047</td>
<td>(-0.081, -0.014)</td>
</tr>
<tr>
<td>50-54</td>
<td>-0.031</td>
<td>(-0.049, -0.012)</td>
<td>-0.049</td>
<td>(-0.079, -0.019)</td>
</tr>
<tr>
<td>55-59</td>
<td>-0.030</td>
<td>(-0.05, -0.01)</td>
<td>-0.050</td>
<td>(-0.069, -0.031)</td>
</tr>
<tr>
<td>60-64</td>
<td>-0.045</td>
<td>(-0.067, -0.023)</td>
<td>-0.052</td>
<td>(-0.073, -0.030)</td>
</tr>
<tr>
<td>65-69</td>
<td>-0.053</td>
<td>(-0.077, -0.029)</td>
<td>-0.054</td>
<td>(-0.08, -0.029)</td>
</tr>
<tr>
<td>70-74</td>
<td>-0.068</td>
<td>(-0.101, -0.035)</td>
<td>-0.061</td>
<td>(-0.088, -0.035)</td>
</tr>
<tr>
<td>75+</td>
<td>-0.019</td>
<td>(-0.206, 0.168)</td>
<td>-0.110</td>
<td>(-0.278, 0.057)</td>
</tr>
<tr>
<td>Total</td>
<td>-0.040</td>
<td>(-0.05, -0.031)</td>
<td>-0.052</td>
<td>(-0.062, -0.042)</td>
</tr>
</tbody>
</table>

6.3.4. BMD measures and fracture risk

The limitation of BMD in assessing bone strength and fracture risk, is recently
emphasized by Kanis (123) stating that BMD forms only one component of bone
strength and one component of fracture risk. The ability of bone mineral density
to predict fracture is comparable to the use of blood pressure to predict stroke, and
better than serum cholesterol to predict myocardial infarction (124-126).

Accuracy is improved by site-specific measurements, so that for forearm
fractures, the risk should ideally be measured at the forearm, and for hip fracture,
at the hip (123, 125). Measurements at any sites, predict any osteoporotic fracture
equally well, with a gradient of risk approximately 1.5 per standard deviation
decrease in bone mineral density (125). It should also be recognised that, just
because BMD is normal, there is no guarantee that fracture will not occur (123)
and most fractures indeed occur in persons without osteoporosis (127).
Conversely, if BMD is in the osteoporotic range, fractures are more likely, but
might not necessarily occur. The low sensitivity is one of the reasons why
widespread population base screening is not widely recommended (127). Kanis
(123) suggests the following use of BMD measurements in the assessment of
fracture risk:

Assessment of fracture probability based solely on clinical risk factors. This is
supposed to identify three groups of individuals:

1. Individuals at very high risk of fracture, a BMD test would not alter their
classification. These patients can be offered treatment irrespective of
BMD. In practice, BMD might be measured so that response to treatment
can be monitored (Although there is a poor correlation between increases
in BMD seen with anti-resorptive treatment and the degree to which these
drugs reduce the risk of fractures (128)).

2. Individuals at very low probability of osteoporotic fractures, a BMD test
would not alter their classification.

3. An intermediate group are those in whom fracture probability is close to
an intervention threshold where the probability is high that a BMD test
might re-categorise individuals at high to low risk, or vice versa.

One of the main findings of our longitudinal study is that the degree of tracking of
BMD measurements is high (paper II and III). There is thus a high correlation
between baseline and follow-up BMD measure even after more than six years, and
most persons keep their quartile position according to the population distribution
of BMD levels. One BMD measure therefore expresses a person's BMD level well. Repeated BMD measurements should rarely be regarded necessary. Based on these considerations, we are very supportive of the restrictive use of BMD measures, as suggested by Kanis (123).

7.0. Concluding remarks and further perspectives

Despite its limitations both in explaining bone strength and in prediction of future fracture, the diagnosis of osteoporosis still depends on the measurements of bone mineral density. TROST has, through the Tromsø study, Tromsø IV and V, gained repeated BMD forearm measurements from a population based sample comprising both sexes. We have therefore been able to describe changes in BMD and its variation from young adulthood into old age. We have also been able to evaluate densitometer performance and we have made a contribution into the research on quality assessment in studies using bone densitometry.

Further research based on these data from TROST, are warranted. In Tromsø V, TROST had BMD measured at the total hip in 4938 persons. In the forthcoming Tromsø VI repeated measurements are planned for. This will provide opportunity to describe BMD changes at the hip, where the most serious osteoporotic fractures occur. In addition to BMD change data, fractures in the respective population are registered from 2001 to July 2005. We have the opportunity to assess the association between fracture risk and rate of bone loss, independent of BMD level. The rate of lifetime bone loss has not yet been estimated based on "hard data". On the longitudinal TROST data the lifetime bone loss and it variation can be studied. Furthermore, with information on lifestyle variables from Tromsø IV
and V, we also have the opportunity to assess the association between different lifestyles, and changes in life style and the life time bone loss. Firm knowledge of possible associations can help to develop well documented bone loss and thereby fracture preventive strategies.
References


ERRATA


AUTHORSHIP PAPER IV

The first author had main responsibility for the statistical analysis, the second author for data collection and text writing.
Paper 1
Bone mineral density measures in longitudinal studies: The choice of phantom is crucial for quality assessment. The Tromsø study, a population-based study

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V. Fannebo

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Abstract Determination of change in bone mineral density (BMD) requires high-precision densitometry techniques. The purpose of the study is to investigate to what degree different densitometer phantoms reflect observed changes in human BMD and to investigate to what degree fluctuations in densitometers' measurement level influence bone loss estimates. Densitometer influence was assessed using the aluminum forearm phantom (AFP) provided by the manufacturer, the European forearm phantom (EFP) of semi-anthropomorphic calcium-hydroxyapatite, and repeated population measurements on different densitometer combinations. The mean follow-up time was 6.4 years (SD 0.6). Measured population bone loss varied from 4.6%/year to 3.2%/year, depending on densitometer combinations. These variations could not be explained by differences in sex, age, height, weight and baseline BMD. They were predicted by EFP measurements, but not AFP measurements. The EFP measurements indicate that X-ray tube replacement changed the densitometers' measurement level in one of three instances, whereas “wear and tear” did not. We used the EFP data for adjustment of the densitometers’ measurement levels. After adjustment, the overall crude bone loss was reduced from 4.14% to 3.92%. Mean annual loss was reduced from 0.64% or 0.61%. We conclude that densitometer performance might influence the accuracy of bone loss estimates. Changes in performance are not detected by aluminum phantoms. Quality control of BMD measurements in longitudinal studies should be performed with anthropomorphic calcium-hydroxyapatite phantoms in order to detect possible differences between the participating densitometers’ measurement levels.

Keywords Bone mineral density · Quality assessment · Population-based · Tromso study

Introduction

Peak bone mass and postmenopausal and age-related bone loss determine the likelihood of developing clinical osteoporosis [1]. To accurately delineate differences and determinants of bone loss, a large sample must be followed over time [2]. Determination of bone mass change requires densitometry techniques with high precision [3-6]. The ultimate goal is to verify that observed change in measured bone density is real and not due to densitometer drift or fluctuation [7, 8].

Peripheral bone mineral density (BMD) measurement is associated with fracture risk at peripheral and central sites [9-12], and single X-ray absorptiometry (SXA) is a relevant tool for monitoring BMD changes due to high precision, ease of use, low radiation doses and moderate cost [13-18]. Baseline and follow-up examinations should be acquired on the same make and model [19]. Clinically relevant differences may occur even among devices from the same manufacturer [20], or after maintenance or upgrade [7, 21]. Quality control and calibration are performed using phantoms, which more or less resemble normal anatomy [20]. Phantoms of calcium hydroxyapatite in tissue-equivalent plastic most closely mimic human bone and soft tissue [7].

By the use of an anthropomorphic spine phantom, Orwell et al. found a minor, but significant, drift in several DXA densitometers used in a longitudinal study [22]. They concluded that densitometer performance was most frequently affected by discrete “step” alterations that often could be explained in light of events described in the research protocol [22]. In our 6-year longitudinal study, using two SXA devices, breakdowns have oc-
curred that required both X-ray tube and total densitometer replacement. This could influence the densitometers’ measurement level and estimated individual changes in BMD. We have investigated how two different types of phantoms, the aluminum forearm phantom (AFP) provided by the manufacturer and the semi-anthropomorphic European forearm phantom (EFP), predict densitometer performance.

The purpose of the present study is therefore:

- To investigate to what degree two different densitometer phantoms reflect observed changes in human BMD
- To investigate to what degree fluctuations in densitometer measurement level influence estimates of bone loss

Materials and methods

Human measurements

The Tromsø Osteoporosis Study (TROST) is part of the Tromsø study, a longitudinal population-based multipurpose study focusing on lifestyle-related diseases. The first Tromsø study (Tromsø I) took place in 1974 and the fifth survey in 2001 (Tromsø V). In 1994 (Tromsø IV) 10,213 persons were invited for an extended examination including a bone mineral density measurement on 7,938 subjects (4,552 women and 3,386 men) from 25–84 years (attendance rate 78%) [23]. In 2001, 7,386 of these still living in Tromsø were invited for a reexamination. Of the invited, 5,771 subjects (3,427 women and 2,344 men), 78% attended (57% of the originally invited population in 1994).

Bone densitometry was performed on the distal forearm (radius and ulna from the 8-mm point and 24 mm proximally) using two SXA devices (DTX-100; Osteometer Meditech, Hawthorne, CA, USA). Participants were allocated to the two densitometers dependant on accessibility. The same protocol was used in both studies. Only measurements from the distal site are presented in this study, as the ultradistal measurements followed the same pattern. All scans were reviewed and reanalyzed according to a rigorous quality-control protocol [24]. This led 136 distal scans to be excluded from the baseline and three distal scans from the follow-up study. Reasons for exclusion of invalid scans were mainly serious movement artifacts [24]. After exclusion of invalid scans 5,637 people (3,346 women and 2,291 men) remained with valid repeated measurements at the distal forearm site. Mean follow-up time was 6.4 years (SD 0.6). Informed consent was obtained prior to both examinations. The regional committee of research ethics recommended, and the Norwegian Data Inspectorate approved the study.

The timeline of the study is shown in Table 1. In Tromsø IV two densitometers, nicknamed “Adam-94” and “Eva-94”, were used (Table 1). The densitometers were used in other studies before the start of Tromsø V. When Tromsø V was about to start in March 2001, Eva-94 had a breakdown and was replaced by a new DTX-100 device from the supplier, “Henry-01/2”. Three months into the Tromsø V survey, in June 2001, the X-ray tube had to be replaced, and it was renamed “Henry-01/2”. In September 2001, 6 months into the Tromsø V survey, the Adam-94 X-ray tube also had to be replaced. Consequently, when used in the 2001 survey, Adam-94 was named “Adam-01/1” and “Adam-01/2” (Table 1). Because of these events, the densitometers participating in both studies are classified as six separate units, with two units from Tromsø IV and four units from Tromsø V.

Starting Tromsø IV, Eva-94 and Adam-94 were cross-calibrated in vivo to the same measurement level with support from the manufacturer, and the devices had an equal measurement level as evaluated by the AFP at the time. During Tromsø IV, we also performed an in vitro precision study [16]. This study indicated a systematic difference between the two densitometers’ measurement levels, and this data led to adjustment of the

| Table 1 General view of the course of the longitudinal study from 1994 to 2002. TROST (Tromsø Osteoporosis Study, AFP aluminium forearm phantom, BMD bone mineral density) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Human          | Human           | Human           | Human           |
| Densitometers  | BMD             | AFP             | EFP             | BMD             | AFP             | EFP             |
| Adam-94        | n = 2,660       | n = 405         | n = 44          | n = 1,454       | n = 92          | n = 66          |
| Eva-94         | n = 2,968       | n = 417         | n = 73          | n = 1,279       | n = 92          | n = 87          |
| Adam-01/1      | n = 1,583       | n = 0           | n = 27          | n = 2,021       | n = 62          | n = 140         |
| Adam-01/2      | n = 1,454       | n = 92          | n = 66          | n = 1,279       | n = 92          | n = 87          |
| Henry-01/1     | n = 1,279       | n = 92          | n = 87          | n = 2,021       | n = 62          | n = 140         |
| Henry-01/2     | n = 1,454       | n = 92          | n = 66          | n = 1,279       | n = 92          | n = 87          |

^1 Tromsø IV 1994–1995  
^2European forearm phantom (AFP) became available  
^3Tromsø V 2001–2002  
^4Age and sex distribution is not significantly different on the different machines  
^5Before X-ray tube replacement  
^6After X-ray tube replacement
our reported baseline cross-sectional data [23], since Adam-94 measured at a higher level than Eva-94.

Aluminium forearm phantom (AFP)

In Tromso IV, measurements were performed on both densitometers once or twice daily with the aluminium forearm phantom provided by the manufacturer (Table 1). In Tromso V, measurements were performed once daily with the same aluminium forearm phantom. Stability was regarded as adequate if phantom measurements were within ±1.5% limits of the calibration value on both densitometers. No correction of stability was required during the time of function of any of the six units. The measurements from Henry-01/1 and Henry-01/2 were from the last 3 months of the study only, unfortunately, due to loss of backup data.

European forearm phantom (EFP) (QRM-Germany)

In 1999 the recently developed European forearm phantom (EFP) (QRM-Germany) was purchased [23–27], a semi-anthropomorphic phantom, comprising three hydroxyapatite bone imitations with different densities within the human range, 0.662 g/cm² at the highest density level, 0.415 g/cm² at the mid-density level and 0.314 g/cm² at the lowest density level. Several EFP measurements were performed on the two machines before they were used in other studies (Table 1). Throughout Tromso V, we continued the EFP measurements regularly. All EFP scans were analyzed by the same two people according to protocol using the special calculation options on the densitometer’s software.

Statistical analysis

Bone loss was estimated by calculating the BMD differences between Tromso V and Tromso IV. This estimate was divided by each participant’s follow-up time to calculate bone loss rates. Bone loss rates in different densitometer combinations were compared by one-way analysis of variance (ANOVA) with post hoc pairwise comparisons, applying the Bonferroni correction. Chi-square testing and one-way ANOVA were used to compare the sex and age distribution, height, weight, body mass index (BMI), baseline BMD and the mean phantom measurement level between densitometers. Intra-variation within each densitometer was expressed as coefficient of variance. In addition, internal variation was studied by dividing the EFP measurements of each of the six densitometers arbitrarily into subgroups corresponding to periods of 2–3 months, comparing these by one-way ANOVA. In the final presentation of BMD change in humans (Table 2), the Adam-94 and Adam-01/1 measurements are adjusted on the basis of the mean difference between these two densitometers and the other four measured by EFP. A p value less than 0.05 is regarded as statistically significant. All statistical analyses were performed using SPSS software, version 11.

Results

Human measurements

Bone loss in humans according to eight possible densitometer combinations are displayed in Table 2. Individuals measured on the different densitometer combinations do not differ significantly with regard to sex (p = 0.469), age (p = 0.276), height (p = 0.069), weight (p = 0.009) and baseline BMD (p = 0.867), but do with regard to BMI (p = 0.039). Overall mean crude bone loss is 0.0185 g/cm² or 4.14%. Mean annual loss, which “adjusts” for difference in mean time between studies, is 0.003 g/cm² or 0.64%. Bone loss is equal to or higher than the mean in all combinations comprising Adam-94, and smaller than the mean in all combinations comprising Eva-94 (Table 2). Mean bone loss is significantly different when comparing densitometer combinations (p < 0.001), also when adjusting for BMI.

Table 2 Bone loss estimates in the longitudinal study, not adjusted and adjusted data. *(TROST Tromsø Osteoporosis Study), 1994–95 and 2001*

<table>
<thead>
<tr>
<th>Densitometer combinations</th>
<th>n</th>
<th>Not adjusted data, mean loss</th>
<th>Adjusted data, mean loss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>g/cm²</td>
<td>SD</td>
</tr>
<tr>
<td>Adam-94/Adam-01/1</td>
<td>683</td>
<td>-0.0117 (0.02)</td>
<td>-4.17 (5.4)</td>
</tr>
<tr>
<td>Adam-94/Adam-01/2</td>
<td>771</td>
<td>-0.0213 (0.02)</td>
<td>-4.48 (5.3)</td>
</tr>
<tr>
<td>Adam-94/Henry-01/1</td>
<td>283</td>
<td>-0.0150 (0.02)</td>
<td>-4.20 (5.2)</td>
</tr>
<tr>
<td>Adam-94/Henry-01/2</td>
<td>930</td>
<td>-0.0208 (0.02)</td>
<td>-4.38 (6.2)</td>
</tr>
<tr>
<td>EVA-94/Adam-01/1</td>
<td>769</td>
<td>-0.0145 (0.02)</td>
<td>-4.25 (5.3)</td>
</tr>
<tr>
<td>EVA-94/Adam-01/2</td>
<td>898</td>
<td>-0.0178 (0.02)</td>
<td>-4.00 (5.2)</td>
</tr>
<tr>
<td>EVA-94/Henry-01/1</td>
<td>300</td>
<td>-0.0177 (0.02)</td>
<td>-4.06 (5.4)</td>
</tr>
<tr>
<td>EVA-94/Henry-01/2</td>
<td>1391</td>
<td>-0.0177 (0.02)</td>
<td>-4.04 (5.8)</td>
</tr>
<tr>
<td>Total mean</td>
<td>5657</td>
<td>-0.0185 (0.02)</td>
<td>-4.14 (5.6)</td>
</tr>
</tbody>
</table>
Aluminium forearm phantom (AFP)

AFP measurements (Table 3 and Fig. 1) indicate that the mean bone density level varies between the different densitometers, with a range from 0.392 g/cm² in Eva-94 to 0.396 g/cm² in Henry-01/2 (p < 0.001), the only densitometers that are not significantly different are Adam-01/1 and Adam-01/2. Therefore, according to AFP, X-ray tube replacement does not change the densitometers' measurement levels, while long-term drift does (Adam-94 compared with Adam-01/1). The CV% is below 0.4% on the densitometers used in Tromso IV, and below 0.3% on the ones used in Tromso V. From the AFP measurements, we would expect the estimates of bone loss in humans to be smallest in combinations comprising Henry-01/2. We would also expect the combinations Eva-94/Adam-01/1 and Eva-94/Adam-01/2 to be equal (Table 2). This pattern is not seen in the human material (Table 2 and Fig. 2). Differences in bone loss observed in humans are thus not reflected in the AFP measurements.

European forearm phantom (EFP) (QRM-Germany)

The EFP measurements (Table 4 and Fig. 1) indicate that the mean bone density level varies on the different densitometers. At the highest density level, the range of variation between the densitometers is 0.011 g/cm², at the mid-density level 0.007 g/cm², and at the lowest density level 0.006 g/cm². The CV% varies from 0.2% to 1.5% (mean 0.9%) depending on density level. At all density levels, Adam-94 and Adam-01/1 measure significantly higher than the other densitometers. Henry-01/2 measures the lowest values, but only statistically significantly different from Adam-94 and Adam-01/1. The mean difference between Adam-94 and Adam-01/1 and the other densitometers is 0.005 g/cm².

There are thus differences between the densitometers' measurement levels. Adam-94 measures higher than Eva-94. From this, we would expect the highest bone loss estimates in the human material to be seen in Adam-94 combined either with Adam-01/2, Henry-01/1 or Henry-01/2 and the smallest estimate to be seen in the combination Eva-94 and Adam-01/1. This is actually the pattern seen in the human material (Table 2 and Fig. 2). From this we conclude that the EFP measurements reflect the differences in bone loss observed in the human material.

For further study of internal variation, the EFP measurements are also used to compare different time periods within each densitometer. There are no significant differences in level of measurement when the three periods of Adam-01/1 are compared or when the three periods of Adam-01/2 are compared with each other. Adam-94 is also not significantly different in level of measurement compared with any of the time periods of Adam-01/1. There are no significant differences in level of measurement between the five time periods of Henry-01/2, except at the low BMD level between two of the time periods. Eva-94 and Henry-01/1 are also not significantly different in level of measurement from any of the time periods of Henry-01/2, except at the low BMD level between two of the time periods. From these EFP measurements, we conclude that each densitometer is stable and does not vary according to measurement level during its specific time of function. This is illustrated in Fig. 3 with EFP measurements from the high density level.

Human measurements after adjustments

Since EFP measurements predicted the differences observed in the human material, we adjusted the measurement level of Adam-94 and Adam-01/1 by the mean 0.005 g/cm² difference (Table 2). Mean bone loss throughout the study period is reduced from −0.0135 g/cm² to −0.0174 g/cm² or from −4.14% to −5.92%. Mean annual loss is reduced from −0.00285 g/cm² to −0.00269 g/cm², or from −0.64% to −0.61%. The variation between the densitometer combinations is still

Table 3 Aluminium forearm phantom measurements from the different densitometers in the longitudinal study. FROST (Tromso Osteoporosis Study), 1994-95 and 2001

<table>
<thead>
<tr>
<th>Densitometers</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adam-94</td>
<td>405</td>
<td>0.392</td>
<td>0.003</td>
<td>0.76</td>
</tr>
<tr>
<td>Eva-94</td>
<td>417</td>
<td>0.392</td>
<td>0.003</td>
<td>0.77</td>
</tr>
<tr>
<td>Adam-01/1</td>
<td>92</td>
<td>0.394</td>
<td>0.006</td>
<td>1.5</td>
</tr>
<tr>
<td>Adam-01/2</td>
<td>92</td>
<td>0.394</td>
<td>0.001</td>
<td>0.22</td>
</tr>
<tr>
<td>Henry-01/2</td>
<td>62</td>
<td>0.396</td>
<td>0.001</td>
<td>0.22</td>
</tr>
<tr>
<td>Pairwise differences 1</td>
<td>Eva-94</td>
<td>Adam-01/1</td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>Adam-94</td>
<td>p value</td>
<td>p value</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Eva-94</td>
<td>0.001</td>
<td>0.001</td>
<td>1.000</td>
<td>0.001</td>
</tr>
<tr>
<td>Adam-01/1</td>
<td>0.001</td>
<td>0.001</td>
<td>1.000</td>
<td>0.001</td>
</tr>
<tr>
<td>Adam-01/2</td>
<td>0.001</td>
<td>0.001</td>
<td>1.000</td>
<td>0.001</td>
</tr>
</tbody>
</table>

1The densitometers compared, p value
One of the strengths of this study is that phantom measurements can be compared with measured BMD change in a large population sample. The participants were allocated to the densitometers dependant on machine availability, not through randomizing procedures. However, as the participants’ age, sex, height, weight and baseline BMD distribution were not significantly different when the different densitometer combinations were compared, we assumed that estimates of bone loss should be approximately the same in the different densitometer combinations.

One of the limitations of the study is that we do not have aluminum phantom measurements on Henry-01/11. However, since these measurements were stable (CV 0.25%) throughout the last part of the study (Henry-01/2), we think that this would not change our estimates. Another limitation is that the EFP became available only in 1999, 4 years after the completion of Tromso IV. The densitometers from Tromso IV had hardly been used in the period between 1995 and 1999. After 1999, the densitometers were used in other studies; several measurements were performed, and the densitometers were transported. Because of this, the time span between 1989 and 2001 was the most vulnerable period for the densitometers. The difference seen between Adam-94 and Eva-94 in 1999 also corresponds to the differences seen in the in vitro precision study that was performed during Tromso IV [16]. Adam-94 and Adam-01/1 are also comparable—whereas Adam-01/2 is not—indicating that it is not wear and tear, but the change of X-ray tube that introduces the change in performance. We
therefore think that the measurements from 1999 are representative of the measurement level in Tromsø IV, but we might have missed some long-term densitometer drift.

After 6 years' use, central elements of both the original densitometers had to be replaced. We do not believe our densitometers to be of lesser quality than other densitometry devices, regardless of model or manufacturer. What we have observed in our study might apply to any other device used in longitudinal studies, and as such, be of relevance for devices of any make and model.

We have assumed that the phantoms themselves do not change over time. This might be a possible information bias. Phantoms are, however, regarded to be stable at any point in time [28].

When comparing the various densitometer combinations, we found that differences in bone loss estimates were predicted by the EFF measurements, making them the appropriate reference for adjustment of the BMD levels in the population. In this study we used the mean difference for all the three BMD-levels of the EFF as basis for adjustments. Another option would be to do the adjustments according to BMD level by regression estimates, as we have reported earlier on our cross-sectional data [18, 23]. However, the BMD differences seen between the machines in the Tromsø IV human study were not dependant on BMD level. Furthermore, we found that the use of linear regression estimates introduced a greater variation in adjusted values of the population material than the mean difference.

After adjustment, the mean total bone loss was reduced from 4.15% to 3.93% in 6 years. As the 1-year bone loss rate can be estimated to be approximately 1% after menopause in women [4, 5], our initial apparently small overestimation could be argued to be of little clinical relevance, and by epidemiological standards the error of our BMD change measurements is small. However, the adjustment can affect results, especially in subgroups where we would not expect bone loss, such as young women and men. The uncorrected densitometer differences could report a false bone loss in these groups. An overestimation of bone loss might also introduce bias when defining the age of peak bone mass and the commencement of bone loss. When measurement of BMD is used to monitor treatment progress, the accuracy of the measured bone change is also of ultimate importance.

This study highlights the importance of careful assessment of densitometer performance during longitudinal studies. Changes in densitometer performance might influence the accuracy of bone loss estimates. Important differences between densitometers and changes in densitometer performance might not be detected by aluminum phantoms. Further studies are needed to evaluate how different phantoms mimic human bone density. Based on the experiences from this study, we propose the following recommendations for quality control of BMD measurements in longitudinal studies:

- Different devices of the same manufacturer (even the same model) give different results. Therefore, even when follow-up of patients in longitudinal studies is performed on the same device, its long term stability should be documented.
- Different phantoms give different results. The estimates of densitometer BMD level differed significantly between AFP and EFF, both in direction and magnitude.
- In vivo and in vitro results are different. Semi-anthropomorphic phantoms reflect in vivo results in a better way than aluminum phantoms. Therefore, during study periods, daily measurements should be
performed with an anthropomorphic phantom of calcium hydroxyapatite in tissue-equivalent plastic.

- Repeated phantom measurements should be used to evaluate possible differences between the participating densitometers' measurement levels. Events that may interfere with densitometer function (transportation, X-ray tube replacement or any maintenance) should be carefully monitored.

References


Paper II
Longitudinal Changes in Forearm Bone Mineral Density in Women and Men Aged 25–44 Years

The Tromsø Study: A Population-based Study

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The aim of this study was to describe and compare bone mineral density (BMD) development in Norwegian women and men aged 25–44 years in a population-based, longitudinal study. BMD was measured twice at distal and ultradistal forearm sites by single x-ray absorptiometry in 258 women and 147 men (mean follow-up time, 6.4 (standard deviation, 0.6) years). At the distal site, a small annual gain of approximately 0.1% became a small loss beginning at age 34 years in men and age 38 years in women. At the ultradistal site, BMD change was predicted by age in women only, and bone loss started at age 38 years. A high degree of tracking of BMD measurements was observed for both sexes and both sites, r > 0.93. Depending on total BMD change, participants were grouped into "losers," "nonlosers," and "gainers," and more than 6% lost more than the smallest detectable amount of BMD: ≥3.45% at the distal site and ≥8.14% at the ultradistal site. In both sexes, bone mineral content (grams) decreased, whereas area (centimeters squared) increased significantly in "losers" compared with "gainers." This finding might represent physiologic compensation preserving bone strength. No cohort effects were observed when 1994 and 2001 measures from similar age groups were compared.

Bone density; bone development; densitometry; follow-up studies; forearm; longitudinal studies; men; women

Abbreviations: BMD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density.

Osteoporotic fractures are a major health problem, with substantial morbidity and costs (1, 2). The cause of fracture is complex, but bone fragility is an important contributor to fracture risk (3). Bone mineral density (BMD) is a good surrogate measure of bone strength, predicting 60–70 percent of its variation (4). A strong relation between BMD level and the probability of fracture has been documented (5). Although fracture risk is best predicted by BMD measurements from the same anatomic site, no site is superior with respect to predicting all types of fragility fracture (5). Single x-ray absorptiometry of the distal forearm is thought to be one of the most precise densitometric methods (6–9), and peripheral BMD measurements can be used to assess fracture risk at both peripheral and central sites (5, 10, 11).

BMD in the elderly is a function of the amount of bone gained during growth and the amount of bone lost during aging (12, 13). As such, both peak BMD and subsequent bone loss as a result of decreasing bone mass and development of microarchitectural abnormalities and microdamage, are important determinants of the risk of osteoporotic fracture later in life (14–17). Although a period of stability after completion of growth is generally assumed, bone loss probably begins when growth ceases (18) and might therefore start during the early adult years in both women and men. The ages at which peak bone values are reached, menopauseal bone loss occurs in women, and bone loss occurs in young men have not yet been determined with certainty (19–22). The associations among change in BMD (in grams per centimeter squared), area (in centimeters squared), and

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bone mineral content (BMC) (in grams) in young women and men are not clear either (23).

Longitudinal studies on BMD changes during the third to fifth decades of life in women (24-37) exist, but only those of Sowers et al. (27, 29), Guthrie et al. (30), Chaupurat et al. (31), Melton et al. (32), and Bainbridge et al. (36) are population based. Some longitudinal studies on BMD changes in young men have been published (28, 34-40); only the study of Khoia et al. (39) is population based. Longitudinal studies including both sexes are scarce and are based on healthy volunteers (28, 34). Because studies based on selected populations may be subject to selection bias (41), their accuracy might be questionable (20). Development of bone mass in the age group 25-44 years therefore has not been investigated sufficiently. In this age group, tracking and cohort effects have, to our knowledge, not been studied. The aim of the present study was to describe, compare, and explore aspects of BMD development in men and women aged 25-44 years in a population-based longitudinal study through the following research questions:

- How does BMD develop in a general population between ages 25 and 44 years?
- Is BMD development similar in the two sexes?
- How well does initial BMD predict BMD at follow-up after 6 years?
- Can any cohort effects be seen before middle age?

MATERIALS AND METHODS

Study design and subjects

The Tromsø Osteoporosis Study (TROST) is part of the Tromsø study, a longitudinal, population-based, multipurpose study focusing on lifestyle-related diseases (42). The Tromsø study was initiated in 1974, with surveys repeated in 1979-1980, 1986-1987, 1994-1995, and 2001. In 1994 (Tromsø IV), the Tromsø Osteoporosis Study measured bone density in 637 subjects (396 women and 241 men) aged 25-44 years. These numbers corresponded to 64 percent of the women and 56 percent of the men invited to participate (43). In 2001 (Tromsø V), 631 of the subjects still living in Tromsø were invited for a reexamination. Bone densitometry was performed on 403 subjects (258 women and 147 men)—65 percent of the invited women and 60 percent of the invited men. The follow-up examination included 42 percent of the women and 34 percent of the men originally invited in 1994. After we excluded invalid scans, 235 repeated measurements at both sites in women and 141 and 142 repeated measurements at the distal and ultradistal sites, respectively, in men remained. Mean age at baseline was 36 (standard deviation, 5.3) years for participating women and 36.5 (standard deviation, 5.8) years for participating men. Mean follow-up time was 6.4 (standard deviation, 0.6) years.

Informed consent was obtained prior to both examinations. The regional Committee of Research Ethics and the Norwegian Data Inspectorate approved the study.

Measurements

Bone densitometry was performed at both surveys at the distal and ultradistal forearm sites with two single x-ray absorptiometry devices (DXA-100; Osteometer Meditech Inc., Hawthorne, California). The distal site includes both the radius and ulna from the 8-mm point (the point at which the ulna and radius are separated by 8 mm) and 24 mm proximally. The ultradistal site includes only the radius and stretches from the 8-mm point up to the radial endplate. The nondominant arm was measured except when it was considered ineligible because of wounds, plaster casts, and so on.

Starting at the second survey, one of the two densitometers underwent a major repair. Later, the x-ray tube had to be replaced in both densitometers. Quality control routines, in which the European Forearm Phantom (QRM GmbH, Meinhofendorf, Germany) was used, revealed that one of the machines measured at a higher BMD level before the x-ray tube was replaced, the mean difference being 0.005 g/cm². The European Forearm Phantom data were used to adjust the differences in densitometer measurement level. The internal variation in each machine studied by using the coefficient of variation (coefficient of variation percent = standard deviation/mean × 100) and by comparing the European Forearm Phantom measurement level during different time periods was satisfactory, with a mean coefficient of variation of 0.9 percent (44).

The same protocol was used in both studies. Quality control with respect to precision and correction of artifacts in Tromsø IV has been reported previously (9, 45). Four trained technicians, one of whom also conducted the Tromsø IV analysis, reanalyzed the scans from Tromsø V. To test for reliability, we obtained three intra-tests (each technician compared with himself or herself) and three inter-tests (each technician compared with the other technicians). Each pair of technicians reviewed a minimum of 27 and a maximum of 127 similar scans. We missed one intra- and inter-test possibility for one technician reviewing 19 of the scans included in this study. At the distal site, there were no significant differences with respect to BMD between the technicians in either intra- or inter-testing. At the ultradistal site, however, there were significant differences in BMD between the technicians in two of the three intra- and two of the three inter-tests. From these tests, we could determine that the measurements of one technician, who reviewed 245 scans, were approximately 0.001 g/cm² lower than those of the others. This difference would entail an effect of less than 1 percent on the annual bone loss estimates (in grams per centimeter squared) and reduce the percentage change estimates by 0.02 percentage points. We compared annual change estimates (in grams per centimeter squared), and they were not technician influenced, r > 0.29, at any sites (analysis of variance). We therefore decided not to correct the data.

Other measurements

Height and weight were measured, using a Jenix DS-102 stadiometer (Dong Sahn Jenix Co., Ltd., Seoul, Korea), to the nearest centimeter and half kilogram, respectively; study participants wore light clothing without shoes. Conditions
that unduly influenced the measurements were recorded. Body mass index was calculated as weight in kilograms divided by the square of height in meters.

**Questionnaires**

The Tromsø IV participants filled in two self-administered questionnaires on different lifestyle variables, one before entering the study and one during the study. We used data on self-perceived health, level of physical activity, smoking status, and calcium intake to assess possible selection bias in the material. Women’s menstral status at baseline was also derived from answers on the questionnaires or from measured follicle-stimulating hormone levels in 152 of the participants. Women who were not using hormone replacement therapy, who were not pregnant, whose time since last menstruation was less than 180 days, or whose follicle-stimulating hormone level was less than 23 were classified as premenopausal (n = 234). Women who were not using hormone replacement therapy, who were not pregnant, and whose time since last menstruation was less than 180-365 days were classified as perimenopausal (n = 1). Women not using hormone replacement therapy and whose time since last menstruation was more than 365 days were classified as postmenopausal (n = 5). Finally, women using hormone replacement therapy were classified as hormone replacement therapy users (n = 5). When information about menstruation or follicle-stimulating hormone levels was lacking, menopausal status was defined as missing (n = 3). Results of analyses conducted with and without data on nonpremenopausal women were similar, which is why we chose to present the analysis for the entire population only.

**Statistical analysis**

BMD measurements from intra- and inter-testing were compared by using a one-sample paired t test. To investigate
TABLE 2. Baseline characteristics of the participants in the Tromsø IV (1994–1996) and Tromsø V (2001) longitudinal studies, Norway, according to 5-year age groups

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Age group (years)</th>
<th>Trend</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean</td>
<td>SD*</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>37</td>
<td>167</td>
<td>6.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>96</td>
<td>95</td>
<td>10.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>86</td>
<td>33</td>
<td>3.2</td>
</tr>
<tr>
<td>Calcium intake (mg)</td>
<td>33</td>
<td>756</td>
<td>251</td>
</tr>
<tr>
<td>Premenopausal (%)</td>
<td>33</td>
<td>86</td>
<td>67</td>
</tr>
<tr>
<td>Parimenopausal (%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal (%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>HRT* user (%)</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Menopause status missing (%)</td>
<td>3</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Distal BMD* (g/cm²)</td>
<td>36</td>
<td>0.462</td>
<td>0.04</td>
</tr>
<tr>
<td>Ultrasound BMD (g/cm²)</td>
<td>36</td>
<td>0.365</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>25</td>
<td>179</td>
<td>7.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>25</td>
<td>75</td>
<td>11.1</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25</td>
<td>25</td>
<td>2.7</td>
</tr>
<tr>
<td>Calcium intake (mg)</td>
<td>24</td>
<td>810</td>
<td>310</td>
</tr>
<tr>
<td>Distal BMD (g/cm²)</td>
<td>24</td>
<td>0.582</td>
<td>0.04</td>
</tr>
<tr>
<td>Ultrasound BMD (g/cm²)</td>
<td>24</td>
<td>0.479</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* SD, standard deviation; HRT, hormone replacement therapy; BMD, bone mineral density.

To estimate peak bone mass, we plotted annual change against baseline age by using scatter plots with a regression line. The point at which the line of regression crossed zero on the y-axis was interpreted as "end-of-gain and start-of-loss age." The amount of total BMD change was used to categorize the groups into “losers,” “nonlosers,” and “gainers.” The minimal difference, which represents true biologic change with 95 percent certainty (95 percent detection limit), can theoretically be calculated by using the following formula: Delta = 1.96 × √2 × coefficient of variation percent (47). For an intermediate term between two measurements, median coefficients of variation estimated on our data were 1.25 at the distal site and 1.86 percent at the ultrastral site (9). Participants gaining or losing more than ±3.46 percent were categorized as true “gainers/losers” at the distal site. At the ultrastral site, the equivalent detection limit was ±3.14 percent. Area and BMC development in the different loss groups was compared by analysis of variance. Tracking between the first and second measurements was assessed by using Pearson’s correlation coefficient. We further divided BMD values measured at baseline and at follow-up into four quartiles, the highest categorized as position 1 and the lowest as position 4 in both studies. The values from both studies were categorized respectively, and each subject’s position in both studies was compared. The distribution of quartile BMD positions at baseline according.
### TABLE 3. Annual bone mineral density changes in participants in the Tromsø IV (1994–1998) and Tromsø V (2001) longitudinal studies, Norway, comparing age groups by sex

<table>
<thead>
<tr>
<th>Age group</th>
<th>No.</th>
<th>Change (mg/cm²)</th>
<th>95% CI</th>
<th>Annual change (%)</th>
<th>ANOVA p value</th>
<th>No.</th>
<th>Change (mg/cm²)</th>
<th>95% CI</th>
<th>Annual change (%)</th>
<th>ANOVA p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–29</td>
<td>56</td>
<td>0.44</td>
<td>−0.2 to 1.1</td>
<td>0.11</td>
<td>0.047</td>
<td>35</td>
<td>1.39</td>
<td>0.4 to 2.4</td>
<td>0.43</td>
<td>0.003</td>
</tr>
<tr>
<td>30–34</td>
<td>75</td>
<td>0.38</td>
<td>−0.1 to 0.8</td>
<td>0.06</td>
<td>0.44</td>
<td>75</td>
<td>0.44</td>
<td>−0.1 to 1.0</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>35–39</td>
<td>72</td>
<td>−0.16</td>
<td>−0.6 to 0.3</td>
<td>−0.05</td>
<td>0.04</td>
<td>73</td>
<td>−0.04</td>
<td>−0.8 to 0.79</td>
<td>−0.01</td>
<td></td>
</tr>
<tr>
<td>40–44</td>
<td>70</td>
<td>−0.31</td>
<td>−0.8 to 0.2</td>
<td>−0.07</td>
<td>0.05</td>
<td>69</td>
<td>−0.55</td>
<td>−1.3 to 0.2</td>
<td>−0.13</td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–29</td>
<td>24</td>
<td>0.91</td>
<td>−0.1 to 1.9</td>
<td>0.16</td>
<td>0.000</td>
<td>24</td>
<td>0.44</td>
<td>−1.1 to 2.0</td>
<td>0.10</td>
<td>0.250</td>
</tr>
<tr>
<td>30–34</td>
<td>29</td>
<td>0.17</td>
<td>−0.5 to 0.8</td>
<td>0.03</td>
<td>0.40</td>
<td>29</td>
<td>−0.40</td>
<td>−1.4 to 0.6</td>
<td>−0.08</td>
<td></td>
</tr>
<tr>
<td>35–39</td>
<td>43</td>
<td>−0.78</td>
<td>−1.4 to −0.2</td>
<td>−0.13</td>
<td>0.05</td>
<td>44</td>
<td>−1.05</td>
<td>−2.0 to −0.1</td>
<td>−0.21</td>
<td></td>
</tr>
<tr>
<td>40–44</td>
<td>45</td>
<td>−0.98</td>
<td>−1.4 to −0.5</td>
<td>−0.16</td>
<td>0.09</td>
<td>45</td>
<td>−0.50</td>
<td>−1.3 to 0.3</td>
<td>−0.09</td>
<td></td>
</tr>
</tbody>
</table>

* CI, confidence interval; ANOVA, analysis of variance.

To the different loss groups was assessed with chi-square testing, Fisher's exact test.

To assess the cohort effect, we extracted four comparable cohort groups comprising persons aged 33–35 and 43–45 years in 1994 and those aged 33–35 and 43–45 years in 2001. BMD level for the relevant cohort groups was compared by independent two-sample t-test. The statistical analysis was performed with SPSS software, version 11 (SPSS, Inc., Chicago, Illinois). A p value of <0.05 was regarded as statistically significant.

### RESULTS

#### Comparison of responders and nonresponders

Data for the first study in Tromsø IV were compared for nonresponders, partial responders, and full responders. The analysis gave no indication of any differences between the two groups (43). After Tromsø V, we could use baseline characteristics from Tromsø IV to compare participants lost to follow-up with those who attended both studies. The results from the analysis are displayed in table 1.

#### Changes in BMD

The general characteristics at baseline of those who participated in both studies are displayed in table 2 according to 5-year age groups. Changes in BMD in both sexes according to 5-year age groups are shown in table 3 and figure 1.

At the distal site, BMD change was predicted by baseline age ($p < 0.001$) but not by sex ($p = 0.089$). There was no significant interaction between baseline age and sex ($p = 0.127$). For every 5-year increase in age, the BMD-change estimate declined by 0.1 percentage points. Before peak bone density was attained, growth was reduced by 0.1 percentage points for every 5 years. After peak bone density was achieved, bone loss increased by 0.1 percent every 5 years. Peak bone density was attained by age 36 years in women and by age 34 years in men (figure 2).

At the ultradistal site, BMD change was predicted by sex ($p = 0.038$), and a linear association was found between baseline age and BMD change in women ($p = 0.005$). In men, the linear BMD change estimate was not significantly different from zero.

#### FIGURE 1. Annual percentage changes in bone mineral density (BMD), with 95% confidence intervals, at the distal site (top) and the ultradistal site (bottom), by age in women and men in Norway, Tromsø IV (1994–1998) and Tromsø V (2001) studies. Norway. Trends: $p = 0.003$, for women and $p < 0.001$ for men at the distal site, and $p = 0.001$ for women and $p = 0.048$ for men at the ultradistal site.

different from zero ($p = 0.239$). A smaller BMD change in the age group 40–44 years compared with the previous age groups indicated a possible nonlinear association at the ultradistal site for men; therefore, test of linear interaction between age and sex was not assessed.

In women, the BMD change estimate at the ultradistal site declined by $-0.15$ percentage points for every 5-year increase in age. Before peak bone density was attained by age 38 years, growth was reduced by 0.15 percentage points for every 5 years. After peak bone density was achieved, bone loss increased by 0.15 percentage points for every 5 years (figure 2).

One man in the age group 25–29 years and one in the age group 40–44 years had an annual loss of $-0.013$ g/cm² and an annual increase of $0.008$ g/cm², respectively. Excluding these outliers did not alter the lack of association between age and BMD change at the ultradistal site ($p = 0.061$) for men (figure 2).

**Changes in area and BMAD**

BMD is size dependent, and BMD changes may reflect changes in size rather than in mineral content. We therefore calculated area and BMAD changes, and the results are given in table 4. The area declined slightly and similarly at the distal site, and it increased slightly and similarly in the two sexes at the ultradistal site. Changes in BMAD followed the same pattern as BMD changes in both sexes at the distal forearm site and was negatively predicted by age ($p = 0.001$) but not by sex ($p = 0.16$).

**"Losers," "nonlosers," and "gainers"**

Table 5 displays the distribution of "losers," "nonlosers," and "gainers" for both sexes. The distribution of quartile BMD positions at baseline was not significantly different between loss groups. At both sites and in both sexes, BMAD followed the same pattern as BMD, declining in "losers" and increasing in "gainers," whereas the area increased significantly in "losers" and declined in "gainers" (figure 3).

**Tracking and cohort effects**

The correlations between the BMD measurements in the two studies were high and were similar for the two sexes:

<table>
<thead>
<tr>
<th>Distal site</th>
<th>Ultrasound site</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>No.</td>
<td>Mean</td>
<td>95% CI*</td>
<td>Annual change (%)</td>
<td>p-value</td>
<td>No.</td>
<td>Mean</td>
<td>95% CI*</td>
</tr>
<tr>
<td>Area (mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–29</td>
<td></td>
<td>36</td>
<td>-0.036</td>
<td>-0.10 to 0.03</td>
<td>-0.05</td>
<td>0.93</td>
<td>36</td>
<td>0.014</td>
<td>-0.15 to 0.16</td>
</tr>
<tr>
<td>30–34</td>
<td></td>
<td>75</td>
<td>-0.038</td>
<td>-0.09 to 0.04</td>
<td>-0.06</td>
<td>0.66</td>
<td>75</td>
<td>0.144</td>
<td>0.06 to 0.24</td>
</tr>
<tr>
<td>35–39</td>
<td></td>
<td>72</td>
<td>-0.058</td>
<td>-0.10 to 0.01</td>
<td>-0.07</td>
<td>0.73</td>
<td>73</td>
<td>0.267</td>
<td>0.10 to 0.44</td>
</tr>
<tr>
<td>40–44</td>
<td></td>
<td>70</td>
<td>-0.023</td>
<td>-0.09 to -0.02</td>
<td>-0.07</td>
<td>0.88</td>
<td>69</td>
<td>0.275</td>
<td>0.11 to 0.44</td>
</tr>
<tr>
<td>BMC (mg/cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–29</td>
<td></td>
<td>33</td>
<td>0.11</td>
<td>-0.05 to 0.26</td>
<td>0.17</td>
<td>0.54</td>
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</tr>
<tr>
<td>30–34</td>
<td></td>
<td>66</td>
<td>0.09</td>
<td>-0.01 to 0.19</td>
<td>0.14</td>
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<tr>
<td>35–39</td>
<td></td>
<td>69</td>
<td>0.02</td>
<td>-0.06 to 0.13</td>
<td>0.03</td>
<td></td>
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<tr>
<td>40–44</td>
<td></td>
<td>63</td>
<td>0.01</td>
<td>-0.06 to 0.11</td>
<td>0.01</td>
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<td></td>
</tr>
<tr>
<td>Area (mm²)</td>
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<tr>
<td>25–29</td>
<td></td>
<td>24</td>
<td>-0.052</td>
<td>-0.14 to 0.04</td>
<td>0.16</td>
<td>0.06</td>
<td>24</td>
<td>0.030</td>
<td>0.07 to 0.59</td>
</tr>
<tr>
<td>30–34</td>
<td></td>
<td>29</td>
<td>-0.024</td>
<td>-0.09 to 0.06</td>
<td>0.03</td>
<td>0.10</td>
<td>29</td>
<td>0.192</td>
<td>-0.14 to 0.34</td>
</tr>
<tr>
<td>35–39</td>
<td></td>
<td>43</td>
<td>-0.042</td>
<td>-0.11 to 0.03</td>
<td>-0.13</td>
<td>0.06</td>
<td>44</td>
<td>0.063</td>
<td>-0.15 to 0.28</td>
</tr>
<tr>
<td>40–44</td>
<td></td>
<td>45</td>
<td>-0.047</td>
<td>-0.11 to 0.02</td>
<td>-0.16</td>
<td>0.23</td>
<td>45</td>
<td>0.233</td>
<td>-0.01 to 0.46</td>
</tr>
<tr>
<td>BMC (mg/cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–29</td>
<td></td>
<td>24</td>
<td>3.22</td>
<td>-5.97 to 13.01</td>
<td>0.09</td>
<td>0.001</td>
<td>24</td>
<td>17.16</td>
<td>-2.16 to 32.17</td>
</tr>
<tr>
<td>30–34</td>
<td></td>
<td>29</td>
<td>-1.29</td>
<td>-7.39 to 4.63</td>
<td>-0.03</td>
<td>0.11</td>
<td>29</td>
<td>1.31</td>
<td>-12.42 to 14.84</td>
</tr>
<tr>
<td>35–39</td>
<td></td>
<td>43</td>
<td>-1.14</td>
<td>-6.32 to -6.48</td>
<td>-0.04</td>
<td>0.01</td>
<td>44</td>
<td>3.75</td>
<td>-14.75 to 17.17</td>
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<tr>
<td>40–44</td>
<td></td>
<td>45</td>
<td>-12.58</td>
<td>-17.49 to -7.68</td>
<td>-0.28</td>
<td>0.20</td>
<td>45</td>
<td>6.20</td>
<td>-6.08 to 18.46</td>
</tr>
<tr>
<td>BMAD (mg/cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–29</td>
<td></td>
<td>24</td>
<td>0.15</td>
<td>-0.02 to 0.20</td>
<td>0.02</td>
<td>0.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–34</td>
<td></td>
<td>29</td>
<td>0.04</td>
<td>-0.07 to 0.15</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–39</td>
<td></td>
<td>43</td>
<td>-0.06</td>
<td>-0.16 to 0.07</td>
<td>-0.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–44</td>
<td></td>
<td>45</td>
<td>-0.08</td>
<td>-0.16 to 0.01</td>
<td>-0.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* BMC, bone mineral content; BMAD, bone mineral apparent density; CI, confidence interval; ANOVA, analysis of variance.

distal and ultrade bilateral sites for women: r = 0.97 and r = 0.93, respectively (p < 0.001). The correlations in area and BMC were also high at the distal site: r > 0.97 for both sexes. At the ultrade bilateral site, the correlations between area measurements were r = 0.88 for women and r = 0.86 for men, and the correlations between BMC measurements were r = 0.74 for women and r = 0.60 for men.

For both sexes, 75–80 percent kept their quartile BMD position from the first to the second survey, whereas 10–13 percent either lost or gained one position at the distal site. This loss or gain was evenly distributed from all original quartile positions. A similar pattern was seen at the ultrade bilateral site: 72–73 percent kept their quartile position, 11–12 percent lost one quartile, and 12–14 percent gained one quartile, also from all quartile positions. Two percent—four women—lost two quartiles, all from the highest quartile. From the analysis, we concluded that only those who were close to the quartile "borders" changed positions, and the changes occurred in any direction. As such, the degree of tracking was extremely high for both sexes before middle age.

The BMD levels of the different cohort groups are shown in Table 6. No significant differences in BMD levels between the compared cohort groups (p > 0.5) were observed.

<table>
<thead>
<tr>
<th></th>
<th>Losing (&gt; -3.48%)</th>
<th>Not losing (≤ -3.48%)</th>
<th>Gaining (&gt; -3.48%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. or mean</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Distal site: women (n = 253)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMC change (cm²)</td>
<td>0.007</td>
<td>7</td>
<td>-0.022 to 0.042</td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.022 to 0.042</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Distal site: men (n = 141)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMC change (cm²)</td>
<td>0.007</td>
<td>7</td>
<td>-0.022 to 0.042</td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.022 to 0.042</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ultradistal site: women (n = 253)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMC change (cm²)</td>
<td>0.017</td>
<td>7</td>
<td>0.039 to 0.315</td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.013 to 0.364</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ultradistal site: men (n = 142)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMC change (cm²)</td>
<td>0.022</td>
<td>7</td>
<td>-0.028 to 0.072</td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.038 to 0.072</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CI, confidence interval; BMC, bone mineral content.
† Difference between groups, p < 0.001, analysis of variance (ANOVA).
‡ Difference between groups, p < 0.05, ANOVA.
§ Difference between groups not significant, ANOVA.

**DISCUSSION**

The main finding from this population-based longitudinal study is that BMD changes at the distal forearm, as measured by ultrasound, are smaller compared to changes at the proximal site in the same population. The results are consistent with previous studies that have shown a smaller rate of change at the distal forearm compared to the proximal site.

One of the strengths of this study is its longitudinal design, allowing for the assessment of changes over a longer period of time. The findings have implications for the interpretation of BMD measurements and the assessment of osteoporosis in clinical practice.
energy x-ray absorptiometry. Men aged 22–39 and 40–59 years had an annual BMD increase of 0.4 and 0.24 percent, respectively, at the mid-distal radius (39). Age-stratified analysis was not presented. No longitudinal results from the ultradistal radius are reported for young men.

Our findings of bone loss starting at the distal forearm site in the third decade of life are in contrast to Chapurlat et al. (31) and Khosla et al. (39) reporting no loss in the comparable age groups. This discrepancy might be influenced by differences in machine performance, length of follow-up, or variations in the population. Our study has its strengths, with the longest follow-up, high response rates, and strict quality control routines. The coefficient of variation reported in the study by Khosla et al. is 2.1 percent compared with our 0.9 percent (43). However, our study was based on a Scandinavian population that, together with North-American Whites, is known to have the highest incidence of forearm, proximal humerus, and hip fractures (51–55). The discrepancy in findings might therefore represent true population differences, which should be studied further.

Eighty-five percent of the total bone in the body is cortical, and it is relatively most abundant in the long bone shafts of the appendicular skeleton (56). With the distal site containing mainly cortical and the ultradistal site mainly trabecular bone (57), both types can be studied as at the distal forearm. Because of the different environments of the bone cells, decline in trabecular bone mass is thought to begin earlier than cortical bone mass (56). An earlier and greater bone loss would therefore be expected at the ultradistal site. However, opinions differ regarding this issue (56), and our findings are in concordance with recent studies from other comparable sites. Bainbridge et al. (36), who followed a cohort of 614 women aged 24–44 years over 6 years, reported an annual bone loss of –0.3 percent beginning by the mid-twenties at the femoral neck (75 percent cortical bone), with no evidence of early bone loss at the lumbar spine (>50 percent cancellous bone) (36).

BMD changes did not differ significantly at the distal site when the two sexes were compared. At the ultradistal site, the trend regarding change was significant in women but not in men, with women gaining significantly in the age group 25–29 years. The main impact of estrogen deficiency is on trabecular bone (58). Because this study comprised mostly premenopausal women whose sex hormone levels are expected to be high, it was actually not surprising to find that the youngest women, those aged 25–29 years, gained a significant amount of BMD at the ultradistal forearm site (table 3, figures 1 and 2).

An annual loss of –0.1 percent over 10 years indicates a loss of approximately 1 percent from peak value, before the more extensive loss starts at middle age in women. As stated by Riis (59), this loss might not be of any clinical relevance, and the degree of tracking in BMD measurements is high. Tracking of a characteristic is defined as the ability to maintain the same position within a distribution over time (60, 61) or the ability to predict future values from earlier

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**TABLE 8.** Cohort-effect analysis of the bone mineral density (g/cm²) of participants in the Tromsø IV (1994–1995) and Tromsø V (2001) longitudinal studies, Norway

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean</td>
<td>SD</td>
<td>No.</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal site</td>
<td>52</td>
<td>0.488</td>
<td>0.042</td>
<td>27</td>
</tr>
<tr>
<td>Ultradistal site</td>
<td>52</td>
<td>0.562</td>
<td>0.050</td>
<td>27</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal site</td>
<td>12</td>
<td>0.575</td>
<td>0.045</td>
<td>18</td>
</tr>
<tr>
<td>Ultradistal site</td>
<td>12</td>
<td>0.469</td>
<td>0.066</td>
<td>16</td>
</tr>
</tbody>
</table>

* SD, standard deviation.

measurements (62, 63). Despite the high degree of tracking, there was some interindividual variation in both sexes, with 6.7%–7% losing more than 3.46% of their BMD in 6 years (more than 0.5% annually). This represents a substantial amount of early bone loss, which might lead to an early increased fracture risk (64). It is interesting to note that the area (in centimeters squared) increased significantly in "looters" compared with "guiners," which might represent a physiologic compensation of periosteal apposition resulting in an increased area that seeks to preserve bone strength (18, 23, 65, 66).

We observed no cohort effect when measurements from similar age groups in the studies were compared, indicating that BMD changes can be derived from cross-sectional studies in this age group. This observation is in contrast to that of Melton (67), who argued that cross-sectional data tend to overestimate bone loss rates observed longitudinally in many sites, and to our own cross-sectional data that indicated higher bone loss rates in both sexes at both forearm sites (43). In conclusion, changes in BMD in the age group 25–44 years are significantly explained by age, but not by sex. The degree of tracking between measurements is high, but a clinically significant group of both women and men experience bone loss before middle age. However, the observed loss might be compensated for by an increase in area, which preserves bone strength. This effect needs to be explored further in other populations.

ACKNOWLEDGMENTS
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Conflict of interest: none declared.

REFERENCES


Paper III
Longitudinal Changes in Forearm Bone Mineral Density in Women and Men Aged 45–84 Years: The Tromso Study, a Population-based Study

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2 University Hospital of Tromsø, Tromsø, Norway.

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The aim of this study was to describe changes in bone mineral density in Norwegian women and men aged 45–84 years in a population-based, longitudinal study. Bone mineral density (g/cm²) was measured at distal and ulnar distal forearm sites with single x-ray absorptiometric devices in 3,169 women and 2,197 men at baseline in 1994–1995 and at follow-up in 2001 (standard deviation, 0.4 years). The mean annual bone loss was −0.56% and −0.4% in men and −0.9% and −0.8% in women not using hormone replacement therapy at the distal and ulnar distal sites, respectively. In men, age was a negative predictor of bone mineral density change at both sites. Women not using hormone replacement therapy had the highest bone loss at the ulnar distal site 1–5 years after menopause. The correlation between the two measurements was high: r = 0.90 in women and r = 0.96 and r = 0.93 in men for the distal and ulnar distal sites, respectively. More than 70% kept their quartile positions, indicating a high degree of tracking of bone mineral density measurements. Although the study population live above the polar circle, the rate of bone loss was not higher at the distal and ulnar distal forearm sites compared with that of other cohorts.

Bone density; densitometry; follow-up studies; forearm; longitudinal studies; men; women

Abbreviations: HRT, hormone replacement therapy; SD, standard deviation; TROST, Tromso Osteoporosis Study.

Osteoporotic fractures in both sexes constitute a major health problem with substantial morbidity and cost (1, 2). The causation of fracture is complex, but bone fragility is an important contributor to fracture risk (3). Bone mineral density is a good surrogate measure of bone strength, predicting 60–70% of its variation (4). A strong relation between bone mineral density level and the probability of fracture has been documented (5). Bone mineral density in the elderly is a function of the amount of bone gained during growth and the amount of bone lost during aging (6, 7). Bone loss estimates derived from cross-sectional studies may be subject to cohort effects, and longitudinal studies provide the best foundation for precise estimations of bone loss (8, 9).

Bone mineral density changes in women through menopause (10–14) and in old age (15–22) have been described through longitudinal, population-based surveys. These changes in men are, however, not extensively explored longitudinally in population-based samples (23–25). Studies, based on representative samples, comprising both sexes from the same population are even more rare, and those existing are from elderly populations (26–30). Longitudinal, population-based studies describing bone mineral density changes in both sexes from middle age into old age are therefore still lacking.

The Tromso Osteoporosis Study (TROST) is part of the Tromso Study in northern Norway. With a follow-up of more than 6 years, TROST has obtained repeated bone mineral density measurements from the distal and ulnar distal forearm sites of 3,169 women and 2,197 men aged 45–84 years. The aim of this study was to describe and compare

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variations in bone mineral density changes in women and men from middle into old age. With the long follow-up, we also wanted to study the degree of tracking of bone mineral density measurements by assessing how well the second measurement was predicted by the first.

MATERIALS AND METHODS

Study participants

The Tromsø Study is a longitudinal, population-based, multipurpose study that focuses on lifestyle-related diseases (31). It was initiated in 1974 (Tromsø I), with the surveys repeated in 1979–1980, 1986–1987, and 1994–1995; the fifth survey was performed in 2001 (Tromsø V). In 1994–1995 (Tromsø IV), TROGST had bone density measured on a total of 7,311 subjects (4,522 women and 2,789 men) aged from 45 to 84 years. These numbers corresponded to 80 and 79 percent of the invited women and men, respectively. In 2001, the 6,755 persons still alive and still living in Tromsø were invited for another examination. Bone densitometry was performed on a total of 5,366 subjects (3,169 women and 2,197 men), which corresponds to 80 and 78 percent of the invited women and men, respectively. The follow-up examination therefore included 61 and 55 percent of the women and men originally invited in 1994. The mean age at baseline in 1994 was 60 (standard deviation (SD), 7.4) years and 61 (SD, 7.2) years for the participating women and men, respectively. The mean follow-up time was 6.5 (SD, 0.4) years. The participants signed a declaration of consent prior to both examinations. The Regional Committee of Research Ethics recommended the study, with approval by the Norwegian Data Inspectorate.

Comparison of responders with nonresponders

Data for the first study, Tromsø IV, were compared for nonresponders, partial responders, and full responders. For nonresponders, we had only age and sex data; for partial responders, we had data from the first part of the examination in addition to one of two questionnaires; and for full responders, we had a complete data set. The analysis gave no indication for any differences among the groups (32). After Tromsø V, we could use baseline characteristics from Tromsø IV to compare participants who attended both studies with those lost to follow-up, because either they missed participating for unknown reasons or they were ineligible (deceased or moved out of town). Comparisons of the three groups are displayed in table 1. Participants attending both studies were younger and taller, had a lower body mass index (women), and had better self-perceived health. They also smoked less and had a higher bone mineral density at both forearm sites.

Measurements

Bone densitometry was performed in both surveys at the distal and ulnar distal sites of the forearm with two single x-ray absorptiometric devices (DTX-100; Osteometer MedTech, Inc., Hawthorne, California). The distal site includes both the radius and the ulna from the 8-mm point (where the ulna and radius are separated by 5.5 mm) and 24 mm proximally. The ulnar distal site includes only the radius and stretches from the 8-mm point up to the radial endplate. The nondominant arm was measured except when it was ineligible because of wounds, plaster casts, and so on.

In both studies, by use of the same protocol, participants were allocated to the two densitometers depending on accessibility. Quality control with respect to precision and correction of artifacts in Tromsø IV was reported previously (33, 34). In the second survey, Tromsø V, one of the two densitometers had a major repair, and the x-ray tube had to be replaced on both densitometers during the survey. Quality control routines, using the European forearm phantom (QRM GmbH, Möhrendorf, Germany), revealed that one of the machines measured at a higher bone mineral density level before the x-ray tube replacement than the other one did, the mean difference being 0.005 g/cm² (35). The European forearm phantom data were used to adjust the differences in densitometer measurement level. The internal variation of each machine was studied by both coefficient of variation, which is equal to the standard deviation/mean × 100, and comparison of the European forearm phantom measurement levels at different time periods and was found to be satisfactory, with a mean coefficient of variation of 0.9 percent measured with the European forearm phantom (35).

All scans were reviewed and reanalyzed, and the results from Tromsø IV have been described previously (34). The scans from Tromsø V were analyzed by four technicians, one of whom also did the analysis in Tromsø IV. To test for reliability, we obtained three intraobserver tests (each technician compared with himself/herself) and three interobserver tests (each technician compared with the other technicians). Each pair corrected a minimum of 27 and a maximum of 127 similar scans. We missed one intraobserver test and one interobserver test feasibility, with one technician testing 275 (5 percent) of the scans. At the distal site, there were no significant differences among the technicians with respect to bone mineral density, either in intraobserver or in interobserver testing. At the ulnar distal site, there were significant differences among the technicians with respect to bone mineral density in two of the three intraobserver tests and in two of the three interobserver tests. From these tests, we could derive that one of the technician's measurements was approximately 0.001 g/cm² lower than the others. This would entail an effect of less than 1 percent on the annual bone loss estimates (g/cm²) and reduce the estimates of percentage of change by 0.02 percentage points. We also compared annual change estimates (g/cm²), and they were not significantly influenced (P > 0.29) at any site (analysis of variance). We therefore decided not to do any correction of the data. After exclusion of invalid scans, which were due mostly to excessive movement artifacts, there remained 3,093 and 3,050 repeated measurements for women and 2,150 and 2,100 measurements for men at the distal and ulnar distal sites, respectively.
TABLE 1. Comparison of participants lost to follow-up (participating in Tromsø IV only) with those who participated in both the Tromsø IV (1994–1995) and Tromsø V (2001) longitudinal studies, Norway

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Participating in the Tromsø IV and Tromsø V studies (mean (SD) or %)</th>
<th>Participating only in the Tromsø IV Study (mean (SD) or %)</th>
<th>Participating only in the Tromsø V Study (mean (SD) or %)</th>
<th>p value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>56.9 (7.4)</td>
<td>52.6 (8.2)</td>
<td>65.7 (7.9)</td>
<td>0.021</td>
</tr>
<tr>
<td>Height, cm</td>
<td>162 (6.2)</td>
<td>161 (6.5)</td>
<td>160 (6.6)</td>
<td>0.021</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.0 (11.5)</td>
<td>68.8 (13.4)</td>
<td>67.2 (13.3)</td>
<td>0.105</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.9 (4.2)</td>
<td>26.5 (5.0)</td>
<td>25.2 (5.1)</td>
<td>0.029</td>
</tr>
<tr>
<td>Present smokers, %</td>
<td>29.3</td>
<td>34.2</td>
<td>43.1</td>
<td>0.0015</td>
</tr>
<tr>
<td>Smoking, years</td>
<td>25.4 (12.3)</td>
<td>27.5 (13.6)</td>
<td>33.0 (14.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Self-perceived health &quot;good,&quot; %</td>
<td>52.8</td>
<td>45.1</td>
<td>31.6</td>
<td>0.0015</td>
</tr>
<tr>
<td>Baseline distal BMD, g/cm²</td>
<td>0.668 (0.27)</td>
<td>0.635 (0.27)</td>
<td>0.576 (0.28)</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline ultradistal BMD, g/cm²</td>
<td>0.309 (0.07)</td>
<td>0.296 (0.07)</td>
<td>0.233 (0.07)</td>
<td>0.001</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>56.9 (7.2)</td>
<td>52.7 (8.1)</td>
<td>65.9 (7.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175 (6.6)</td>
<td>174 (6.8)</td>
<td>174 (7.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60.5 (11.7)</td>
<td>79.4 (12.5)</td>
<td>79.6 (14.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.2 (5.2)</td>
<td>26.1 (5.6)</td>
<td>25.9 (4.2)</td>
<td>0.399</td>
</tr>
<tr>
<td>Present smokers, %</td>
<td>31.4</td>
<td>40.7</td>
<td>41.2</td>
<td>0.0015</td>
</tr>
<tr>
<td>Smoking, years</td>
<td>29.9 (13.4)</td>
<td>34.1 (13.9)</td>
<td>36.7 (13.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Self-perceived health &quot;good,&quot; %</td>
<td>61.6</td>
<td>54.2</td>
<td>39.7</td>
<td>0.0015</td>
</tr>
<tr>
<td>Baseline distal BMD, g/cm²</td>
<td>0.541 (0.06)</td>
<td>0.327 (0.07)</td>
<td>0.514 (0.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline ultradistal BMD, g/cm²</td>
<td>0.442 (0.07)</td>
<td>0.432 (0.07)</td>
<td>0.418 (0.08)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Participating in the Tromsø IV and Tromsø V studies: 3,169 women and 2,197 men; participating only in the Tromsø IV Study but eligible for the Tromsø V Study: 761 women and 608 men; participating only in the Tromsø IV Study and ineligible for the Tromsø V Study: 212 women and 344 men.

1. SD, standard deviation; ANOVA, analysis of variance; BMD, bone mineral density.
2. Died of cancer.
3. Chi-square testing.
4. Invasive scans excluded.

Other measurements

Height and weight were measured to the nearest centimeter and half kilogram. The participants wore light clothing without shoes. Body mass index was calculated as weight in kilograms divided by the square of the height in meters.

Questionnaires

Two self-administered questionnaires were filled in by the participants in Tromsø IV, one before entering the study and the other during the study, in which the participants provided data on different lifestyle variables at baseline. We used data on smoking status and self-perceived health to assess possible selection bias. Women's meniscal status at baseline was also derived from answers to the questionnaires. Women using hormone replacement therapy (HRT) were classified as "HRT users." Women who were aged more than 44 years, were not using HRT, and were either pregnant or had a time from the last menstrual period of less than 180 days were classified as "premenopausal." Women who were aged more than 44 years, were not using HRT, were not pregnant, and had a time from the last menstrual period of between 180 and 364 days were classified as "perimenopausal." Women who were aged more than 44 years, were not using HRT, and had a time from the last menstrual period of 1 year or more were classified as "postmenopausal." When information about meniscus was lacking completely and meniscal status could not be determined, meniscal status was defined as "missing." For further classification of HRT use in the period of follow-up, we have used information provided from questionnaires in Tromsø IV.

Statistical analysis

Bone mineral density measurements from intra- and interobserver testing were compared by use of a one-sample paired t test. Change in bone density was estimated by calculating the difference between measurements from
TABLE 2. Annual bone mineral density changes in mg/cm² and percentage (%) with 95% confidence intervals in men and women (not using hormone replacement therapy), according to 5-year age group, the Tromsø IV (1984–1995) and Tromsø V (2001) longitudinal studies, Norway

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>No.</th>
<th>Annual bone mineral density changes</th>
<th>No.</th>
<th>Annual bone mineral density changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mg/cm²</td>
<td>95% confidence interval</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men, distal site</td>
<td></td>
<td>Women, distal site</td>
</tr>
<tr>
<td>45–49</td>
<td>186</td>
<td>-1.49</td>
<td>-1.84, -1.14</td>
<td>-0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–54</td>
<td>184</td>
<td>-1.54</td>
<td>-1.83, -1.25</td>
<td>-0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55–59</td>
<td>605</td>
<td>-1.92</td>
<td>-2.12, -1.73</td>
<td>-0.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–64</td>
<td>525</td>
<td>-2.70</td>
<td>-2.96, -2.43</td>
<td>-0.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–69</td>
<td>394</td>
<td>-3.24</td>
<td>-3.50, -2.99</td>
<td>-0.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–74</td>
<td>275</td>
<td>-3.77</td>
<td>-4.21, -3.34</td>
<td>-0.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75+</td>
<td>10</td>
<td>-3.59</td>
<td>-5.04, -2.04</td>
<td>-0.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2,150</td>
<td>-2.55</td>
<td>-2.83, -2.24</td>
<td>-0.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tromsø V and Tromsø IV. This total estimate was divided by the length of each participant's follow-up time to calculate the annual changes that are presented by 5-year age groups as mg/cm² and percent, with 95 percent confidence intervals. Regression analysis was used to investigate how age and sex predicted changes in bone mineral density. The difference in annual bone loss rates in women according to reported HRT use in the follow-up period and years since menopause was analyzed by use of analysis of variance, applying the Bonferroni correction.

To investigate the variation of changes in bone mineral density and to identify possible "fast losers," we used the annual lesion and bone mineral density to categorize the participants into groups of "losers," "nonlosers," and "gainers" through calculation of the minimal difference, which represents the true biologic change with 95 percent certainty (95 percent detection limit). It is theoretically given by the following formula: A percent = z x coefficient of variation x q/2 (36). The median coefficient of variation estimated on our material was for an intermediate term between two measurements of 1.25 and 1.66 percent at the distal and ulnar/distal sites, respectively (33). Persons with an annual loss or gain of more than ±3.46 percent were categorized as true "gainers/losers" at the distal site. At the ulnar/distal site, the equivalent 95 percent detection limit was ±5.14 percent.

Tracking was assessed by use of Pearson's correlation coefficient and correlation with ranking of the variables. We divided values for bone mineral density measured at baseline and at follow-up into four quartiles, the highest quartile being categorized as position 1 and the lowest quartile being categorized as position 4. The values from both studies were categorized, respectively, and each participant's positions in both studies were compared.

The statistical analysis was performed by use of SPSS, version 11.0, software (SPSS, Inc., Chicago, Illinois). A p value of less than 0.05 was regarded as statistically significant.

RESULTS

Changes in bone mineral density by age

Annual changes in bone mineral density according to 5-year age groups in men and in women reporting no HRT use in the follow-up period are displayed in table 2 and in figure 1. In men, the rate of bone mineral density loss was associated with age at both sites (p < 0.001), with an increase in the rate of loss of approximately 0.2 percent per 10-year increase in age (beta = -0.02). In women, a smaller bone mineral loss rate in the age group 45–49 years compared with the older age groups indicated a possible nonlinear association at both sites. The test of linear interaction between age and sex was therefore not assessed.

Bone mineral density changes in women

The highest rate of bone loss was seen in women who were not using HRT and in women who had stopped using

Am J Epidemiol 2008;163:441–449
HRT during the follow-up period (table 3). The differences between the groups also remained significant \( p < 0.001 \) at both sites after adjustment for age. Among postmenopausal women not using HRT, the highest bone loss rates were seen in the period 1–5 years after menopause at the ultradistal site (table 4) \( p > 0.001 \) and also, when adjusting for age, with the same trend at the distal site \( p = 0.005 \). Women reporting to be premenopausal at baseline and not using HRT in the period of follow-up had bone mineral density loss rates at the ultradistal site that were not significantly different from those of women 1–3 and 4–5 years after menopause. At the distal site, their bone mineral density loss rates were not significantly different from those of any other group (table 4).

**Fast losers**

Among women not using HRT, 1 percent \( n = 16 \) were losing more than −3.6 percent annually at the distal site. Their mean age was 62.0 (SD, 8.6) years. Nine of these women were in the lowest bone mineral density quartile at baseline, and in the second survey they were all in the lowest bone mineral density quartile. Only three men lost more than −3.6 percent annually at the distal site. At the ultradistal site, only three women lost more than −5.14 percent annually.

**Tracking of bone mineral density measurements**

The correlations in the measurements between the two studies are significant \( p < 0.001 \) and high at the distal and ultradistal sites, respectively, in men \( r = 0.96 \) and \( r = 0.95 \) and in all women \( r = 0.93 \) and \( r = 0.90 \). Including only women reporting no HRT use, the correlation coefficient is \( r = 0.94 \) and 0.91 at the distal and ultradistal sites, respectively. The ranked correlation is slightly less but also high.

Among men, 79 and 75 percent keep their quartile position from the first to the second survey, and 10 and 12 percent either lose or gain one position, from all quartiles, at the distal and ultradistal sites, respectively. Among all the women, 74 and 70 percent keep their quartile position, whereas 12 and 14 percent either lose or gain one or two quartile positions at the distal and ultradistal sites, respectively. A similar pattern is seen also when only the women not using HRT are included in the analyses; 75 and 69 percent of the women keep their quartile position, 14 and 16 percent lose, and 10 and 11 percent gain one position at the

**TABLE 3. Annual bone mineral density changes in mg/cm² and percentage (%) with 95% confidence intervals in women, according to reported hormone replacement therapy use in the follow-up period, the Tromso IV (1994–1995) and Tromso V (2001) longitudinal studies, Norway**

<table>
<thead>
<tr>
<th>Hormone replacement therapy status</th>
<th>No.</th>
<th>Mean age (years)</th>
<th>Mean bone mineral density changes</th>
<th>95% confidence interval</th>
<th>%</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not using</td>
<td>1,685</td>
<td>61.23</td>
<td>−3.73</td>
<td>−3.61, −3.66</td>
<td>−0.93</td>
<td>−0.98, −0.89</td>
</tr>
<tr>
<td>Stopped using</td>
<td>174</td>
<td>56.28</td>
<td>−3.56</td>
<td>−4.58, −2.34</td>
<td>−0.91</td>
<td>−1.03, −0.77</td>
</tr>
<tr>
<td>Started using</td>
<td>251</td>
<td>55.98</td>
<td>−1.00</td>
<td>−1.43, −0.57</td>
<td>−0.32</td>
<td>−0.94, −0.11</td>
</tr>
<tr>
<td>Using</td>
<td>278</td>
<td>56.97</td>
<td>−0.46</td>
<td>−0.80, −0.12</td>
<td>−0.10</td>
<td>−0.18, −0.02</td>
</tr>
<tr>
<td>Ultradistal site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not using</td>
<td>1,684</td>
<td>61.22</td>
<td>−2.67</td>
<td>−2.67, −2.47</td>
<td>−0.84</td>
<td>−0.91, −0.77</td>
</tr>
<tr>
<td>Stopped using</td>
<td>174</td>
<td>56.28</td>
<td>−3.54</td>
<td>−4.18, −2.91</td>
<td>−1.05</td>
<td>−1.22, −0.85</td>
</tr>
<tr>
<td>Started using</td>
<td>250</td>
<td>56.05</td>
<td>0.39</td>
<td>−0.21, 0.99</td>
<td>0.37</td>
<td>0.01, 0.54</td>
</tr>
<tr>
<td>Using</td>
<td>285</td>
<td>55.84</td>
<td>0.05</td>
<td>−0.41, 0.51</td>
<td>0.08</td>
<td>−0.08, 0.24</td>
</tr>
</tbody>
</table>

*Am J Epidemiol 2006;163:441–449*
TABLE 4. Bone mineral density changes in mg/cm² and percentage (%) with 95% confidence intervals in women not using hormone replacement therapy who were classified according to menopausal status and years since menopause, the Tromsø IV (1994-1995) and Tromsø V (2001) longitudinal studies, Norway

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Mean age (years)</th>
<th>Mean bone mineral density changes</th>
<th>95% confidence interval</th>
<th>%</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>mg/cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopause</td>
<td>106</td>
<td>50.10</td>
<td>-3.57</td>
<td>-5.77, -1.37</td>
<td>-0.85</td>
<td>-1.01, -0.69</td>
</tr>
<tr>
<td>1-5 years since menopause</td>
<td>142</td>
<td>53.56</td>
<td>-4.84</td>
<td>-5.55, -4.13</td>
<td>-1.11</td>
<td>-1.26, -0.94</td>
</tr>
<tr>
<td>6-10 years since menopause</td>
<td>101</td>
<td>55.09</td>
<td>-4.47</td>
<td>-5.17, -3.76</td>
<td>-1.00</td>
<td>-1.24, -0.93</td>
</tr>
<tr>
<td>&gt;10 years since menopause</td>
<td>270</td>
<td>57.72</td>
<td>-3.73</td>
<td>-4.12, -3.34</td>
<td>-0.91</td>
<td>-1.01, -0.82</td>
</tr>
<tr>
<td>Distal site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopause</td>
<td>106</td>
<td>50.10</td>
<td>-4.99</td>
<td>-5.41, -3.77</td>
<td>-1.05</td>
<td>-1.47, -1.03</td>
</tr>
<tr>
<td>1-5 years since menopause</td>
<td>139</td>
<td>53.98</td>
<td>-4.60</td>
<td>-5.36, -3.93</td>
<td>-1.26</td>
<td>-1.59, -1.11</td>
</tr>
<tr>
<td>6-10 years since menopause</td>
<td>100</td>
<td>55.12</td>
<td>-3.18</td>
<td>-3.96, -2.46</td>
<td>-1.03</td>
<td>-1.26, -0.80</td>
</tr>
<tr>
<td>&gt;10 years since menopause</td>
<td>286</td>
<td>57.69</td>
<td>-2.49</td>
<td>-2.93, -2.05</td>
<td>-0.97</td>
<td>-0.93, -0.86</td>
</tr>
<tr>
<td>Distal site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopause</td>
<td>106</td>
<td>50.10</td>
<td>-4.99</td>
<td>-5.41, -3.77</td>
<td>-1.05</td>
<td>-1.47, -1.03</td>
</tr>
<tr>
<td>1-5 years since menopause</td>
<td>139</td>
<td>53.98</td>
<td>-4.60</td>
<td>-5.36, -3.93</td>
<td>-1.26</td>
<td>-1.59, -1.11</td>
</tr>
<tr>
<td>6-10 years since menopause</td>
<td>100</td>
<td>55.12</td>
<td>-3.18</td>
<td>-3.96, -2.46</td>
<td>-1.03</td>
<td>-1.26, -0.80</td>
</tr>
<tr>
<td>&gt;10 years since menopause</td>
<td>286</td>
<td>57.69</td>
<td>-2.49</td>
<td>-2.93, -2.05</td>
<td>-0.97</td>
<td>-0.93, -0.86</td>
</tr>
</tbody>
</table>

DISCUSSION

The main findings from this population-based survey are that the mean annual bone mineral density loss in men aged 45-84 years is less than -0.5 and 0.4 percent, negatively predicted by age, at the distal and ultradistal sites, respectively. In women not using HRT, the equivalent bone mineral density changes are -0.9 and -0.8 percent. There is a high degree of tracking in bone mineral density measurements.

Two of the strengths of this study are its long follow-up and a high attendance rate of more than 70 percent in both studies. The single x-ray absorptiometric measurement of the distal forearm is thought to be one of the most precise densitometric methods (33, 37-39), and we had densitometer performance strictly controlled in both studies. Although fracture risk is best predicted by bone mineral density measurements from the same anatomic site, no site is superior with respect to prediction of all types of fragility fractures (5). When central dual x-ray absorptiometry is not available, peripheral bone mineral density measurement can be used to assess fracture risk at both peripheral and central sites (5, 40, 41), and they still constitute a valuable tool for the diagnosis of osteoporosis (42).

Irrespective of high response rates, nonresponse may generate selection bias. As displayed in table 1, participants lost for follow-up in general seem to be less healthy or having a less healthy lifestyle than those who participated in both studies. As smoking status is associated with greater bone loss rates (43) and low self-perceived health might indicate a greater degree of comorbidity (44), we possibly have some "healthy selection bias" in the material. Similar findings are observed in other longitudinal studies within the field. In a prospective osteoporosis study in Rochester, Minnesota, nonrespondents were less healthy than were full respondents (45). In the Framingham Osteoporosis Study, cohort members without longitudinal data were more likely to be older, to have a lower mean baseline bone mineral density, and to have lower physical activity scores, and they were less likely to have reported good health (30). The Rotterdam Study also reported selection in favor of the more mobile and healthy population with probably lower rates of bone loss, and loss to follow-up was most likely related to illness, so that true progression was probably underestimated (28). Despite possible selection bias, with the high attendance rates, we do feel confident that the results from our study are comparable to other population-based studies in the field.

At the forearm site, we have the possibility of comparing age-related changes of both trabecular and cortical bone, as the distal site contains mainly cortical and the ultradistal site contains mainly trabecular bone (46). We have compared our results with findings from other longitudinal, population-based studies on bone mineral density changes, limited to studies with data from the distal and ultradistal radius. Annual percentages of decline of approximately 1.0 percent were seen at the distal and proximal radius in previous studies of 1,000 Japanese-American postmenopausal women aged 55-74 years (15, 16, 18) and of 271 White women aged 55-80 years (17). The loss rates in both of these studies are slightly higher at the distal site than that in our cohort for the concurrent age groups. In men, we observed an increasing rate of bone loss at the distal site with increasing age, from about -0.30 percent per year at ages 45-59 years to 0.75 percent per year at ages 70-74 years. Similar trends were seen in a large study of Japanese-American men aged 51-82 years (23, 24) and in the Mayo Clinic study of the Rochester, Minnesota, population (23, 24). The Framingham longitudinal study reported annual loss rates of -1.2 and -0.9
percent at the distal radius and of −1.0 and −0.5 percent at the ulnar site in elderly women and men (aged 67–95 years) (30). These rates are slightly higher than those in our cohort at similar age groups. In summary, despite difficulties in comparing studies, the population of Tromsø living above the Arctic Circle does not seem to have higher bone loss rates than do other comparable populations.

Because of the different environments of the bone cells, decline in trabecular bone mass is thought to begin earlier than that in cortical bone mass, which is thought to occur increasingly after the age of 40 years and to be mainly age related (47). Our findings of bone mineral density development in the age group 45–84 years are supportive of this concept. In men, with age being a negative predictor of bone mineral density changes at both sites, the loss rates are higher at the distal than at the ulnar site. In women not using HRT, the ulnar site bone loss rates decrease from −1.3 percent in the age group 50–54 years to −0.6 percent in the age group 63–69 years, indicating that the most dramatic trabecular bone loss in women had occurred before that age. This is also supported by the findings of highest bone loss rates in women 1–5 years after menopause, findings which are comparable to those of Guthrie et al. (12) and Alhborg et al. (48), who studied bone loss in relation to menopause in a longitudinal study of more than 16 years (healthy volunteers).

Tracking of a characteristic is defined as the ability to maintain the same position within a distribution over time (49, 50) or as the ability to predict future values from earlier measurements (51). As such, the term “tracking” is used to describe the extent of predictability or relative constancy that a measurable characteristic may have in a group of individuals observed over repeated observations (52). A number of methods may be used (53), and we used both the Pearson correlation coefficient and the comparison of quartile position between the two studies. Our findings are comparable to the findings of Sowers et al. (17) and Alhborg et al. (48) and, therefore, supportive of those of Gilmore and Nelson (54), who indicate that the morphologic traits that contribute to the strength of bone track throughout life, with values remaining in the same position relative to population percentiles. The high degree of tracking also indicates that one bone mineral density measure expresses a person’s bone mineral density level and, as such, supports the notion that, except for patients with expected rapid bone loss or on bone mass treatment, there are rarely indications for frequent repeated bone mass measurements (55–59).

Notwithstanding the high degree of tracking, there is interindividual variation in bone loss estimates illustrated through both the confidence intervals and the distribution of participants into different “loss groups.” As we used the notion of “minimal detectable difference,” persons losing more than −3.14 percent annually at the distal site were identified as “fast losers.” 1 percent of the women not using HRT, in the study of Sowers et al. (17), 30 percent of women aged 55–80 years lost at least 2 percent annually; the equivalent rate in our study would be 12.5 percent. We found, however, as did Sowers et al. and Nguyen et al. (60), that the rates of bone loss were not generally associated with baseline bone mineral density (or quartile positions).

In conclusion, our study is one of the first to describe bone mineral density changes in a longitudinal, population-based study comprising both sexes from the age of 45 years to well above 80 years. The frequency of fractures appears to be increasing in many countries (61), but the incidence of fractures varies (62). The Scandinavian countries, together with North America, have the highest incidence of hip and forearm fractures in the world (63, 64). Even if the study represents a northern population, the observed bone loss rates are not greater than those observed in other comparable populations.

ACKNOWLEDGMENTS
Conflict of interest: none declared.

REFERENCES


Paper IV
Cross-calibration in densitometry; can in vitro replace in vivo measures?
The NOREPOS Study

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Abstract:

**Background:** Determination of bone mineral density (BMD) level and changes requires high-precision densitometry techniques. BMD measurements from different densitometers are not easily comparable. The purpose of this study was to investigate the agreement of densitometry between two types of densitometer phantoms and human measurements.

**Methods:** Bone densitometry was performed on the distal forearm with five similar SXA-devices on 17 persons with a wide variation in BMD level, bone size and body mass index (BMI). Each person was measured three times after full repositioning. Repeated measurements were also performed using equipment specific aluminium forearm phantoms (AFP) provided by the manufacturer, and the European forearm phantom (EFP) of semi-anthropomorphic calcium-hydroxyapatite. Data was analysed by pairwise comparison between densitometers, in addition to metaanalyses of the pairwise difference.

**Results:** One of the five densitometers measured at a higher level than the other four densitometers. Compared to AFP, there was better agreement between EFP and in vivo measurements, but EFP tended to overestimate the difference between the densitometers measurement level.

**Conclusions:** In vivo measurements remain the most valid tool for detection of densitometer differences. Densitometer performances are better captured by phantoms of calcium-hydroxyapatite than by aluminium phantoms. For follow-up and comparative studies, phantoms of calcium-hydroxyapatite are recommended for daily quality assessments.
Introduction

Osteoporotic fractures constitute a major health problem with substantial morbidity and costs [1,2]. The causation of fracture is complex, but bone fragility is an important contributor to fracture risk [3]. Bone mineral density (BMD) is a good surrogate measure of bone strength [4], and a strong relationship between BMD level and the probability of fracture has been documented [5]. Fracture risk differs between populations [6-8], but there are few studies comparing BMD levels across populations because the measurements are not easily comparable. BMD levels may vary as much as 18% between densitometers from different producers, and 5% between densitometers of the same make and model [9]. Differences large enough to be clinically relevant may therefore occur even among devices from the same manufacturer [9].

Comparison of BMD measurement between populations is usually done by cross-calibrations of densitometers to a common scale by using standardized phantom measurements. This is a poorly documented praxis, and it is generally agreed that in vivo cross-calibration is the best [10,11] representing the gold-standard for calibration. Cross-calibration based on human measurements alone provides equivalency among the instruments in use, but could imply a lack of accuracy as we do not know which instrument is closest to the true value.

Conflicting results have been reported by few studies comparing human and phantom measurements. Genant, using the European Spine Phantom (ESP), concluded that in vivo and in vitro were comparable [10], and so did Pearson using ESP, the Bona Fide Phantom and the GE Lunar Aluminium Spine Phantom.
Blake, using the ESP and the Hologic Phantom, found however a significant mismatch between in vivo and in vitro cross calibration results [12].

Peripheral BMD measurements are associated with fracture risk at both peripheral and central sites [5,13-15]. Single x-ray absorptionmetry (SXA) of the forearm has high precision, accuracy, ease of use, low radiation doses and moderate cost [16-21]. In a six-year longitudinal study, using two SXA devices, quality assessment procedures indicated that two types of phantoms identified changes in densitometer performance differently. The European Forearm phantom (EFP) (QRM-Germany) predicted BMD changes observed in a large population sample, whereas the equipment specific Aluminium Forearm Phantom (AFP) did not [22]. The aim of this study was to compare agreement between two phantoms (EFP and AFP) and in vivo densitometry of the distal forearm in a cross-calibration study.

Materials and methods

Study design and materials

The Norwegian Epidemiological Osteoporosis Studies (NOREPOS) comprise four large population-based multipurpose studies in the cities of Oslo (the Oslo Health Study, HUBRO, 2000-2001), Bergen (the Hordaland Health Study, HUSK, 1998 – 99), Tromsø (The Tromsø Study/Tromsø Osteoporosis Study, TROST, 1994-95 – 2001) and the county of Nord-Trøndelag (the Nord-Trøndelag Health Study, HUNT, 1995-1997) [23]. In 2003 the five SXA-devices (DTX-100; Osteometer MedicTech, Inc., Hawthorne, California) formerly used in TROST [24-26], HUNT [27] and HUBRO [28] were brought together for a cross-calibration study.
Volunteers were recruited among employees at the University of Tromsø (UiTØ). In order to represent a wide range of characteristics which could influence BMD, initial selection of subjects was based on age, height, and weight as surrogates for bone mass, bone size and BMI. 20 participants underwent a preliminary DXA examination of total hip and were included into the study according to variation in BMD levels and bone size measured by DXA (total hip) and variation in BMI. The chosen range of variation was provided through a large population sample (TROMSØ V) with use of the three tertiles within the borders of the fifth and 95 percentile in the upper and lower part of the distribution. As displayed in Table 1, we had a total of 9 categories, and participants were included until a minimum of 3 participants fitted into each category. Each participant contributed to three categories. Finally a total of 17 participants were included into the study.

Informed consent was obtained from all participants. The regional Committee of Medical Research Ethics recommended, and the Norwegian Data Inspectorate approved the study.

Human measurements

Bone densitometry was performed at the distal and ultradistal forearm sites on the five similar SXA-devices of the non-dominant arm. The distal site includes both the radius and ulna from the 8 mm-point (the point at which the ulna and radius are separated by 8 mm) and 24 mm proximally. The ultradistal site includes only the radius and stretches from the 8-mm point up to the radial endplate. Each of the 17 participants had three measurements done on each densitometer with full repositioning between each measurement. One trained technician performed the BMD measurements from the same protocol formerly used in NOREPOS sub-
studies [28]. All scans were reviewed and reanalysed according to a rigorous quality control protocol [29]. Only measurements from the distal site are presented as the ultradistal measurements followed the same pattern.

**Phantom measurements**

From November 2003 to February 2004 measurements were performed regularly on all densitometers with the equipment specific AFP provided by the manufacturer, and the EFP [30-32] which is a semianthropomorphic phantom, comprising three hydroxyapatite bone imitations with different densities within the human range, 0.662 g/cm² (high), 0.415 g/cm² (medium) and 0.314 g/cm² (low). To keep the EFP in position for SXA measurements, a device was specially constructed in plastic. All EFP scans were analysed by the same person according to protocol using the special calculation option in the densitometer’s software.

**Statistical analysis**

Short term precision error (σₚ) for each device with 95% confidence interval was estimated from the repeated measurements of the individuals. Coefficients of repeatability (CR) for each device were calculated by \( \sqrt{\frac{\text{CV}^2}{100}} \cdot \sigma_p \). We expect 95% of all differences (in absolute value) between two measurements on the same individual at the same machine to be less than the machine’s CR value. The precision error is expressed by standard deviation and CV.

Evaluation of agreement between pairs of devices was performed by Bland-Altman analyses of the in vivo measurements [33]. Differences between means did not vary systematically over the range of BMD values and normal distribution
assumption was valid, no transformation of the original data was necessary. The smallest detectable differences (SDD) [34] comparing measurements from machine i and machine j were calculated by the formula: 

\[ SDD_{ij} = 1.96 \cdot \sqrt{\frac{\sigma_i^2}{n_i} + \frac{\sigma_j^2}{n_j}} \]

The SDD is an estimate of the magnitude of inter-machine differences (absolute value) which is likely to occur when the same individuals are measured by two different machines. Computing an interval of length SDD around the mean difference in BMD between the two machines considered gave the limits of agreement (LOA) which cover about 95% of the differences observed on the actual material. If the interval is small enough and has no clinical importance, the two devices being investigated may be interchanged [33].

A meta-analysis approach was used in order to make a statistical comparison of in vivo data and phantom data with respect to the ability to identify differences in mean BMD between pairs of densitometers [35;35]. Difference in mean BMD between two densitometers was scaled or standardised by the pooled standard deviation from the repeated measurements for each individual in the in vivo material. The standardised mean difference expresses the size of the machine differences for each individual relative to the variability observed for each individual. Hedges' adjustments to correct for small sample bias were applied to the standardised difference in mean BMD [35]. Further the standardised difference in mean BMD between the two densitometers were weighted by the inverse variance method giving a pooled estimate of the difference in mean for all individuals in the in vivo measurements. The weights used in the inverse variance method are the reciprocals of the squared standard error of the standardised
difference. This method minimises the variability of the pooled estimate [35]. The pooled estimate of standardised difference in mean was calculated for all 10 pairs of densitometer based on the in vivo measurement. A similar procedure was applied on the phantom measurements. Finally the pooled estimate of standardised difference in mean of human and EFP measurements were compared by a Student T test.

Results

Human measurements

Seven participants were male, and the mean BMD level of the 17 participants was 491.3 mg/cm² (SD 90.6 mg/cm²), with a range of variation from 269 to 619 mg/cm². The mean bone size was 34.7 mm² (SD 4.03 mm²), with a range of variation from 29.0 to 42.0 mm². The mean BMI was 26.08 kg/m² (SD 3.21 kg/m²), with a range of variation from 22.2 to 34.2 mm². BMD levels measured by the different densitometers are displayed in table 2 and the BMD differences from pair wise comparison between the densitometers in table 3. The measurement levels of four of the densitometers were similar, the mean BMD difference varying from 0 to 2.25 mg/cm². The fifth densitometer, SXA 3, reported BMD at a higher level compared to the other densitometers, with a mean difference varying between 5.53 and 7.78 mg/cm² (table 3).

Phantom measurements

Descriptive statistics from the phantom measurements according to the different densitometers are displayed in table 4. The AFP measurements indicated that
SX A 1 and 2 measured at an equal, but lower BMD level than SX A 3, 4 and 5. The AFP did not "recognise" SX A 3 to measure at a higher BMD level than SX A 4 and 5. The EFP measurements at the low density level, followed the same pattern as AFP. The EFP measurements at the mid density level, indicated a greater variance in BMD level between the densitometers, with SX A 3 measuring at the highest density level. The EFP measurements at the high density level, indicated, as the human measurements, that SX A 3 measured higher density. Although the mid and high density level reflected the densitometer differences measured in vivo, some heterogeneity in the estimated differences among the levels of the EFP phantom were present.

A presentation of the pooled estimate of the standardised difference in mean for each pair wise combination of the densitometers based on human and EFP measurements is shown in figure 1 and table 5. The figure illustrate what is also seen in table 5; the human measurements indicated different measurement levels only in the densitometer combinations involving SX A 3, that is in four out of ten combinations. The direction of the differences was captured by the EFP in all four combinations, and by the AFP in three of four combinations. There were six combinations where the human measurements indicated no difference between the densitometer's measurement levels. The AFP indicated that the measurement level differed in five of these six combinations whereas the EFP followed the pattern of the human measurements. The differences between densitometers captured by the EFP followed the direction of the differences indicated by the human measurements in eight of 10 densitometer combinations, the differences were however overestimated in two of the combinations involving SX A 3 (SX A1-
SX3 and SXA2 - SXA3). From the tables and the figure we can conclude that the differences in densitometers’ measurement level in direction were generally captured by the EFP, the magnitude of the differences however tended to be overestimated.

Comparison of in vivo data and phantom data

Results of the meta-analyses are presented in Table 5. The phantom measurements showed differences between all pairs of densitometers, while in vivo measurements identified significant differences for 4 out of the 10 pairs using 5% significance level. Comparing the pooled standardised mean differences estimated by in vivo data and phantom measurements showed that even if significant difference between pairs of densitometers are detected by each data set, there are significant difference in magnitude.

Discussion

In this cross-calibration study there was a better agreement between EFP and in vivo measurements compared to AFP. The EFP measurements followed the direction of the human measurements, however tending to overestimate the magnitude of differences in measurement level.

The strength of this study is the possibility to compare phantom measurements with human measurements (or in vivo) from a wide variety of BMD levels, measurements over a number of days giving the opportunity to estimate repeatability, and measurements of all densitometers performed by the same
technician and location [11]. Initially we planned only to see how well the EFP revealed possible densitometer differences. As the results of our longitudinal study indicated that the EFP and AFP measurements predicted densitometer differences differently [36], we also included AFP measurements into this study. Because that was not planned initially, we only had daily AFP measurements available. Ideally the AFP measurements should have been performed in the same manner as the EFP measurements.

Genant et al tested standardised phantoms (the ESP, the European spine phantom prototype, the standard phantoms of Hologic, Lunar and Norland) with respect to similarity of results compared to humans on three types of DXA systems and concluded that area, BMC, and BMD values obtained on the three different systems were not directly comparable. The ESP demonstrated data that were very close to the patient data. After applying standardization formulas, the absolute average differences in patient’s BMD between the three systems were significantly reduced [10]. Pearson et al compared three types of phantoms used for cross-calibration with in vivo cross-calibration (the Bona Fide Phantom, the ESP and the GE Lunar Aluminium Phantom) of two DXA systems, and reported no significant differences between the in vitro and in vivo calibration. The Bona Fide Phantom performed best compared to the human measurements, although the in vitro cross-calibrations were not significantly different from one another [11]. Pearson emphasised the importance of collecting data over a period of time to include day to day variation in densitometer performance [11], and recommended the use of calcium hydroxyapatite phantoms for cross-calibration of different DXA systems.
In a longitudinal study where a Hologic QDR-2000 was upgraded to a QDR-2000plus, the new scanner was carefully cross-calibrated with the Hologic spine phantom, which is anthropomorphic in shape, and composed of calcium hydroxyapatite, but only represents a single density level [12]. The accuracy of this cross-calibration was checked by in vivo scans of patients in addition to the ESP. Blake reported that the in vivo study showed a significant mismatch between the two systems with systematic errors exceeding 2% at five out of 10 scan sites studied. The results from the ESP lay closer to the in vivo data than the Hologic spine phantom, but still the mismatch revealed was greater than anticipated. Blake therefore emphasised the importance of performing in vivo cross-calibration studies whenever DXA systems are replaced. The full explanation of the difference between phantom and in vivo cross-calibration between two systems is not clear [12].

Our study is based on SXA technology, but our findings are in concordance with Blake's; even if anthropomorphic phantoms perform better than aluminium phantoms, in vitro cannot fully replace in vivo cross-calibration. The implication of our findings is, as other authors have concluded, that clinically relevant differences in measurement level may occur between densitometers of the same make and model [9,37]. In cross-sectional, single- or multi-centre studies, using different densitometers, in vivo cross-calibration still remain the best option to secure comparability of human BMD measured on different densitometers. If in vivo cross-calibration is not possible, like in longitudinal studies, in vitro cross-calibration with anthropomorphic phantoms can replace human measurements, but
one should be aware of influence on precision. Important differences in
measurement level between densitometers, as well as changes in densitometer
performance (due to maintenance, upgrading, long term drift etc) [38], might not
be detected by aluminium phantoms, which are the phantoms provided by the
manufacturers and usually integrated into the daily scanning procedures. In
longitudinal or multi-centre studies where in vivo cross-calibrations are not
obtainable, we recommend daily measurements with anthropomorphic phantoms
of calcium hydroxyapatite in tissue-equivalent plastic on all participating
densitometers in order to evaluate the stability of and differences in measuring
levels of densitometers.

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and Rehabilitation, Norwegian Osteoporosis Association, the Research Council of
Norway and AstraZeneca, Norway.

Reference List


14 Suppl 3, S13-S18.


Ref Type: Serial (Book, Monograph)


Table 1. Categories for inclusion of participants to the SXA cross-calibration study, the Norwegian Epidemiological Osteoporosis Studies

<table>
<thead>
<tr>
<th>BMD total hip (g/cm²)</th>
<th>Bone size (mm²)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N*</td>
<td>N*</td>
<td>N*</td>
</tr>
<tr>
<td>0.680 – 0.861</td>
<td>4</td>
<td>29.8 – 33.5</td>
</tr>
<tr>
<td>0.862 – 0.995</td>
<td>8</td>
<td>33.6 – 37.4</td>
</tr>
<tr>
<td>0.996 – 1.202</td>
<td>5</td>
<td>37.5 – 42.6</td>
</tr>
</tbody>
</table>

* A total of 17 persons included, one person could contribute to more than one category.

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Table 2. Results for 5 SXA densitometers in vivo. BMD at distal site (mg/cm²) of 17 subjects with 3 repeated measurements, the Norwegian Epidemiological Osteoporosis Studies

<table>
<thead>
<tr>
<th>Machine m_i; i=1..5</th>
<th>Mean BMD (mg/cm²)</th>
<th>σᵦ (short term precision error) (mg/cm²)</th>
<th>CV (%)</th>
<th>95% Confidence interval of σᵦ (mg/cm²)</th>
<th>Coefficient of repeatability (CR): 1.96*1.96 σᵦ (mg/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SXA1</td>
<td>491.08</td>
<td>5.84</td>
<td>1.2 %</td>
<td>4.97, 8.31</td>
<td>16.19</td>
</tr>
<tr>
<td>SXA2</td>
<td>489.92</td>
<td>4.57</td>
<td>0.9 %</td>
<td>3.89, 6.50</td>
<td>12.67</td>
</tr>
<tr>
<td>SXA3</td>
<td>496.61</td>
<td>4.16</td>
<td>0.8 %</td>
<td>3.54, 5.92</td>
<td>11.53</td>
</tr>
<tr>
<td>SXA4</td>
<td>489.92</td>
<td>2.99</td>
<td>0.6 %</td>
<td>2.54, 4.26</td>
<td>8.29</td>
</tr>
<tr>
<td>SXA5</td>
<td>488.82</td>
<td>5.20</td>
<td>1.1 %</td>
<td>4.42, 7.39</td>
<td>14.41</td>
</tr>
<tr>
<td>All machines</td>
<td>491.27</td>
<td>4.65</td>
<td>0.9 %</td>
<td>3.91, 4.75</td>
<td>12.89</td>
</tr>
</tbody>
</table>
Table 3. Pairwise comparison of BMD (mg/cm²) differences in vivo. Mean BMD, SDD (Smallest detectable difference) and LOA (Limits of agreement) for 17 individuals with 3 repeated measurements, the Norwegian Epidemiological Osteoporosis Studies

<table>
<thead>
<tr>
<th>Pairs of SXA machines</th>
<th>Mean difference ( \sigma_{m_i,m_j} )</th>
<th>SDD ( \frac{\sigma_{m_i}^2 + \sigma_{m_j}^2}{2} )</th>
<th>LOA Lower</th>
<th>LOA Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>SXA1-SXA2</td>
<td>1.16</td>
<td>7.41</td>
<td>14.53</td>
<td>-13.37</td>
</tr>
<tr>
<td>SXA1-SXA3</td>
<td>-5.53</td>
<td>7.17</td>
<td>14.05</td>
<td>-19.58</td>
</tr>
<tr>
<td>SXA1-SXA4</td>
<td>1.16</td>
<td>6.56</td>
<td>12.86</td>
<td>-11.70</td>
</tr>
<tr>
<td>SXA1-SXA5</td>
<td>2.25</td>
<td>7.82</td>
<td>15.32</td>
<td>-13.06</td>
</tr>
<tr>
<td>SXA2-SXA3</td>
<td>-6.69</td>
<td>6.18</td>
<td>12.11</td>
<td>-18.80</td>
</tr>
<tr>
<td>SXA2-SXA4</td>
<td>0</td>
<td>5.46</td>
<td>10.70</td>
<td>-10.70</td>
</tr>
<tr>
<td>SXA2-SXA5</td>
<td>1.10</td>
<td>6.92</td>
<td>13.56</td>
<td>-12.46</td>
</tr>
<tr>
<td>SXA3-SXA4</td>
<td>6.69</td>
<td>5.12</td>
<td>10.04</td>
<td>-3.35</td>
</tr>
<tr>
<td>SXA3-SXA5</td>
<td>7.78</td>
<td>6.66</td>
<td>13.05</td>
<td>-5.26</td>
</tr>
<tr>
<td>SXA4-SXA5</td>
<td>1.10</td>
<td>6.00</td>
<td>11.75</td>
<td>-10.65</td>
</tr>
</tbody>
</table>

Table 4. Descriptive statistics (mean ± sd) of phantom measurements (mg/cm²) where n=number of repeated measurements, the Norwegian Epidemiological Osteoporosis Studies

<table>
<thead>
<tr>
<th>Phantom</th>
<th>True BMD</th>
<th>SXA Machine 1 (n=37)</th>
<th>SXA Machine 2 (n=37)</th>
<th>SXA Machine 3 (n=37)</th>
<th>SXA Machine 4 (n=37)</th>
<th>SXA Machine 5 (n=37)</th>
<th>Precision error ( \hat{\sigma} ) (mg/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFP</td>
<td>314</td>
<td>288.1 ± 2.3</td>
<td>286.6 ± 2.0</td>
<td>290.7 ± 1.9</td>
<td>290.2 ± 1.9</td>
<td>290.9 ± 2.5</td>
<td>2.12</td>
</tr>
<tr>
<td></td>
<td>415</td>
<td>395.5 ± 1.6</td>
<td>392.1 ± 1.6</td>
<td>398.5 ± 2.1</td>
<td>394.5 ± 2.0</td>
<td>397.7 ± 2.1</td>
<td>1.86</td>
</tr>
<tr>
<td></td>
<td>662</td>
<td>632.1 ± 2.4</td>
<td>632.4 ± 4.1</td>
<td>637.3 ± 1.5</td>
<td>631.8 ± 1.8</td>
<td>631.9 ± 1.9</td>
<td>2.50</td>
</tr>
<tr>
<td>AFP</td>
<td>3.535 g</td>
<td>392.6 ± 1.7</td>
<td>392.2 ± 1.7</td>
<td>394.5 ± 1.1</td>
<td>394.4 ± 1.2</td>
<td>395.3 ± 0.9</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>(n=13)</td>
<td>(n=14)</td>
<td>(n=13)</td>
<td>(n=13)</td>
<td>(n=12)</td>
<td>(n=12)</td>
<td></td>
</tr>
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</table>
Table 5. Meta-analyses of pair wise differences in BMD (mg/cm²). Pooled estimate of the standardised difference in mean, 95% CI of the pooled estimate and Student T-test statistics testing inequality in machine difference identified by in vivo and EFP measurements. In vivo measurements of 17 individuals and phantom measurements at 3 levels, the Norwegian Epidemiological Osteoporosis Studies.

<table>
<thead>
<tr>
<th>Pairs of SXA machines</th>
<th>Pooled estimate of standardised difference in mean</th>
<th>95% CI of pooled estimate</th>
<th>T-test statistics (In vivo-EFP)</th>
<th>Two-sided p-value</th>
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<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SXA1-SXA2</td>
<td></td>
<td></td>
<td>In vivo</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EFP</td>
<td>1.14</td>
</tr>
<tr>
<td>SXA1-SXA3</td>
<td></td>
<td></td>
<td>In vivo</td>
<td>-0.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EFP</td>
<td>-6.54</td>
</tr>
<tr>
<td>SXA1-SXA4</td>
<td></td>
<td></td>
<td>In vivo</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EFP</td>
<td>0.42</td>
</tr>
<tr>
<td>SXA1-SXA5</td>
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<td></td>
<td>In vivo</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EFP</td>
<td>-1.29</td>
</tr>
<tr>
<td>SXA2-SXA3</td>
<td></td>
<td></td>
<td>In vivo</td>
<td>-0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EFP</td>
<td>-8.53</td>
</tr>
<tr>
<td>SXA2-SXA4</td>
<td></td>
<td></td>
<td>In vivo</td>
<td>-0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EFP</td>
<td>-0.96</td>
</tr>
<tr>
<td>SXA2-SXA5</td>
<td></td>
<td></td>
<td>In vivo</td>
<td>-0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EFP</td>
<td>-0.66</td>
</tr>
<tr>
<td>SXA3-SXA4</td>
<td></td>
<td></td>
<td>In vivo</td>
<td>1.38</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>EFP</td>
<td>2.16</td>
</tr>
<tr>
<td>SXA3-SXA5</td>
<td></td>
<td></td>
<td>In vivo</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EFP</td>
<td>0.78</td>
</tr>
<tr>
<td>SXA4-SXA5</td>
<td></td>
<td></td>
<td>In vivo</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EFP</td>
<td>-1.09</td>
</tr>
</tbody>
</table>
Fig 1. Pooled mean differences for all 10 pairs of densitometers. In vivo data, EFP measurements and AFP measurements, the Norwegian Epidemiological Osteoporosis Studies
Appendix 1

First questionnaire, Tromsø IV, 1994-95
Velkommen til helseundersøkelsen i Tromsø!

Helseundersøkelsen kommer nå til Tromsø. Tid og sted for frammøte finner du nedenfor. Du finner også en ordnering om undersøkelsens i den vedlagte brønsyrer.

Vi har glemt å spørre jentene på busstenen og ta det med til undersøkelsen.


Vennlig hilsen
Kommunehelsetjenesten
Fagområdet medisin. Universitetet I Tromsø
Statens helseundersøkelser

"GRIP SJÅNSEN - MOT FRAM!"
Dør
Ikke
Svelg
Hjerneskad.
Angine perforere (fjær)
Hjerneslag
Asthma
Diabetes melitusa
Bruker du noen medisiner med blodtryksnedtur?
Ja
Nei
Før, men ikke nå
Adr drukk

Nemm og urkelig?
Plaget av angst?
Ting og rolig?
Innlegg?
Glad og optimistisk?
Sentrer kan

Sett 0 hvis du ikke oppholder deg i roligfyllt om.

Sigaret røykt?
Sigaret- og sigare tørrig?
Pipe røykt?

Hvordan mange sigaretter røykte til tids, eller
røykte du regelmessig røykt?
Hvor gammalt var du da du oppytte til
røykte daglig?
Hvor mange årligč i åring har du røykt
daglig?
Appendix II

Second questionnaire for subjects aged < 70 years.
Tromsø IV, 1994-95
Helseundersøkelsen i Tromsø

Hovedformålet med Tromsøundersøkelsene er å skaffe kunnskap om helse-kvadrantmåter for å kunne forebygge sos. I tillegg skal undersøkelsen skape kunnskap om kreftsykdommer og andre alvorlige plager som eks. allergier. Skader i muskelarbeid og nærvær i arbeid er. Vi ber deg torte svare på noen spørsmål om forhold som kan ha betydning for risikoen for disse og andre sykdommer.

Skiknet er et av Tromsøundersøkelsene som er gitt avavtalt av Detallavtalen og av Regional komité for medisinsk forskningsrett. Operatør har skrevet sin til forskning og behandling av strimg. Opplysningene kan senere bli sammenholdt med information fra andre offentlige helseregister eller de regler som Detallavtalen og Regional komité for medisinsk forskningsrett gir.

Hvis du er i tvil om hva du skal svare, sett kryss i den rute som du synes passer best.

Del utskrift skiknet ved vedlegg av särskilt. Posten er betalt.

På forhånd takk for hjelpen!

Med vennlig hilsen

Fagområdet medicin

Univeristet i Tromsø

Statens helseundersøkelser

Hva du ikke ønsker å besvar spørsmålene, sett kryss i rute under og ber burde skiknet. Da slutter du tilbake.

Jeg ønsker ikke å delta i spørsmålene.

I dag med Ar.

Du ser ut til å være av ekstra.

OPPVÆKST

I høvelen kom manide du da du tyle 1 år?

Hva du ikke bevege i utgangspunktet, også i maskins for kommandør.

Hvem har de ekstraer foret for hjemmefor medisinsk tidligere diagnose?

Menneske gutter

Børn

Voksne

Menneske-gutter

Hva trenger du de første 15 årene av livet?

- Boddes du, by?
- Hva sto du, ellev kloster i hjemmet?

Hva trenger du de første 15 årene av livet?

- Boddes du, by?
- Hva sto du, ellev kloster i hjemmet?

ARBEID

Hva du er i et overdrevet eller avlantet arbeid, hvordan vil du beskrive dette arbeidet?

Først mest tilfelleende arbeid?

(ekse. børnemadrhus, inntakning)

Arbeid som krever at du går mye?

(ekse. personverk, i fjellidet i undervisning)

Arbeid hvor du går og kletter mye?

(ekse. børnemadrhus, personverk)

Tang i klopesfet?

(ekse. skomaster, langt fra detsag, langt i bygde)

Kan du selv bestemme hvordan arbeidet slik skal legges opp?

Ja, ikke i det hele tatt

I et gres

Ja, aldri gres

Ja, det bestemmer jeg selv

Hva du stikkor, skinnsidd eller går velter?

Hvor du nærer ut folkepenget jekt (heltid eller deltid)

Hva er sann i det avspenner?

Stadig

Stedse/tid/fortidere

Frisier
### SYMPTOMER

<table>
<thead>
<tr>
<th>Symptome</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Husten, snakkesleng</td>
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<tr>
<td>Svalhet, øyeblikk</td>
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<td>Blod i bukken</td>
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<td>Øyeblækking</td>
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<td>Hodepine</td>
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<tr>
<td>Sunnfall</td>
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<tr>
<td>Fuktighet i buken</td>
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<td>Vred eller koselig</td>
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<tr>
<td>Får man nattmer</td>
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<td>Får man aftenmer</td>
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<td>Får man dagmer</td>
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</table>

### SYMPTOM I FAMILIEN

<table>
<thead>
<tr>
<th>Symptome</th>
<th>Ja</th>
<th>Nei</th>
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</thead>
<tbody>
<tr>
<td>Husten, snakkesleng</td>
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<td>Blod i bukken</td>
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<td>Øyeblækking</td>
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<td>Hodepine</td>
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<td>Sunnfall</td>
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<td>Fuktighet i buken</td>
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<td>Vred eller koselig</td>
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<td>Får man nattmer</td>
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<td>Får man aftenmer</td>
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<td>Får man dagmer</td>
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</table>

### BRUK AV HELSEVESENET

<table>
<thead>
<tr>
<th>Symptome</th>
<th>Ja</th>
<th>Nei</th>
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</thead>
<tbody>
<tr>
<td>Husten, snakkesleng</td>
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<tr>
<td>Svalhet, øyeblikk</td>
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<td>Blod i bukken</td>
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<tr>
<td>Øyeblækking</td>
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<td>Hodepine</td>
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<td>Sunnfall</td>
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<td>Fuktighet i buken</td>
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<td>Vred eller koselig</td>
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<tr>
<td>Får man nattmer</td>
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<tr>
<td>Får man aftenmer</td>
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<tr>
<td>Får man dagmer</td>
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</tbody>
</table>
ALKOHOL

Hver eneste skolet du å drukke? er det livet? ikke? ukjent?
Alkohol, eller noen til ganger i året ...
1-2 ganger i måneden ...
Ovenfor 1 gang i måneden ...
2-3 ganger i uke ...
Ovenfor 3 ganger i uke ...

Selv om du har ikke drukket alkohol, kan det være farlig å bruke alkohol i løpet av en periode av tid.

SLUMNING

Gjør du noe heftigt fysisk trening på hver dag?

Så lenge du ikke har sommer ...

Hvor mange timer slumber du ...
1-3 timer ...
4-5 timer ...
6-7 timer ...

Hva er kroppen din mest 

SVÆRERIKT

Hvor mange timer har du tidligere ...

Først ...

Så lenge ...

Selv om det er svært viktig å ha viss sværet ...

UGJØR VEL MED 

Hva slutter du at det er viktig å gjøre?

Avslør ...

Vekst ...

Bruker du ikke ...

FEKS, TILBEHØR

Bruker du, eller har du brukt ...

Hvordan ...

Hvor mange ...

PREVENSIAN OG ASTROGEN

Bruker du, eller har du brukt ...

Hva slutter du at det er viktig å gjøre?

Avslør ...

Vekst ...

Bruker du ...

Hvor mange ...

Hva slutter du at det er viktig å gjøre?

Avslør ...

Vekst ...

 Bergen leveres til Fidelity

Takk for hjelpen! Husk å pålegge skjemaet i dag!
Appendix III

Second questionnaire for subjects aged > 70 years,
Tromsø IV, 1994-95
Helseundersøkelsen i Tromsø
for dem som er 70 år og eldre.

Hovedformålet med Helseundersøkelsene er å skewe ny
kunnskap om hjerter- og karsykdommer før å kunne forebygge
dem. De skal også øke kunnskapen om kroflaksydommer og
almunne plager som f.eks. allergier, smerte i
muskel eller nervøse lidelser. Endelig skal de gi
kunnskap om hvorledes den eldste delen av befolkningen
har det. Vi bør derfor være på sørømtige nedenfor.

Skjemaet er en del av Helseundersøkelsen som er
godkjent av Datatilsynet og av Regional komité for
medisinsk forskningsstelkk. Svarene brukes bare til
forskning og behandles strengt forfølgelig. Opplysningene
can senere bli sammenholdt med informasjon fra andre
offentlige helseinstitutter etter de regler som Datatilsynet
og Regional komité for medisinsk forskningsstelkk gir.

Hvis du er i tvil om hva du skal svare, sett kryss i den
ruben som du synes passer best.

Det utfylte skjema sendes i vedlagt svarkonglom.
Porten er beskat.

På forhånd takk for hjelpen!

Med venlig hilset

Fagområdet medisin
Universitetet i Tromsø
Statens helseundersøkelse

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss i ruten
under og returner skjemaet. Da slipper du gurrling.

Jeg ønsker ikke å besvare spørreskjemaet.

Dato for utfylling av skjema: 

Feltet er obligatorisk.

I hvilken kommunen bodde du da du fylte 1 år?

Hva de ikke bodde i Norge, oppgir land i stedet for kommune.

Hvordan var de økonomiske forhold i familien under din
oppekst?

Mest gode
God
Vanskelig
Mest vanskelig

Hvor gamle ble dine forfølgere?

Mer ble 
Før ble 

Bolle

Hvem bor du sammen med?
Slett å kryss før hvert spørsmål og angi antall.

Ektefelle/samboer
Andre personer over 18 år
Personer under 18 år

Hvilken type bobil har du?

Enебobil/ville
Gårdsbilk
Blokkterrænaselighet
Rokkstus: 2-4 mannsbobil
Ann en bobil

Hvor lenge har du bodd i boligen du bor i nå?

Er bobilen tilpasset til dine behov?

Hvis "Nei", er det problemer med:

Plassen i bobilen
Ujevn for høy eller for lav temperatur
Trapper
Toalett
B Walsh
Vedlikehold
Ann en (spesiell)

Ønsker du å flytte til en eldbobil?

TILSTÅELSE OG EKSEMPLER

Hvordan vil du beskrive det arbeidet du hadde de siste 5-10
årene før du ble pensjonist?

Før det møde stilleslitative arbeid?
Arbeid som krever at du går mye?
Arbeid hvor du gør og løfter mye?
Tang innsatsarbeid?

Har du hatt noen av følgende yrker
[heitt eller dødelig]

Sjå i
Bonde/gårdbruker
Fisker

Arbeid hvor gamle var du da du ble pensjonert?

Møget god
God
Vanskelig

Vanskelig

Tillegspensjon

Hvor lang er din åkonomi nå?

Mest god
God
Vanskelig
Mest vanskelig
**SYKDOMME I FAMILIEN**

<table>
<thead>
<tr>
<th>Symptomer</th>
<th>Ja</th>
<th>Nei</th>
<th>Alder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kryss av for de slektingene som har eller har hatt noen av sykdommen?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hjemmeleg eller hjemmebladning...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyttelekt kedumålt for 50 åres alder...</td>
<td></td>
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<tr>
<td>Høyttalere...</td>
<td></td>
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<tr>
<td>Astma...</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Benkesjøtt (osteoporose)...</td>
<td></td>
<td></td>
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<tr>
<td>Stjertjegikl (artrose)...</td>
<td></td>
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<tr>
<td>Psykiske planer...</td>
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<tr>
<td>Aldersdomsbevegelse...</td>
<td></td>
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</tr>
<tr>
<td>Diabetes (sukkerens)...</td>
<td></td>
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<tr>
<td>- alder da di fikk diabetes...</td>
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</tbody>
</table>

**SYMPTOMER**

<table>
<thead>
<tr>
<th>Husler du om trening daglig i perioden av året?</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hvis &quot;ja&quot;, har du denne oppslutningen?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Om det,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ved høytemperatur...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ved fysiske arveflekker...</td>
<td></td>
<td></td>
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<tr>
<td>Ved sterk kold...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Har du mørket anfalt med plutselig endring i pulsen eller hjerteffekten siste året?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hvis &quot;ja&quot;, hvor mange kilo?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hvor ofte er du plaget av sovnlust?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldri, eller noen få ganger i året...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 ganger i måneden...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Om trening en gang i uken...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mer enn en gang i uken...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hvis du er plaget av sovnlust i perioden, når på året er du mest plaget?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ingen spesiell tid...</td>
<td></td>
<td></td>
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<tr>
<td>Særleg i mørktiden...</td>
<td></td>
<td></td>
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<tr>
<td>Særleg i midnattstiden...</td>
<td></td>
<td></td>
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<tr>
<td>Særleg vek og haast...</td>
<td></td>
<td></td>
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</tbody>
</table>

**ER DU PLAGET AV**

<table>
<thead>
<tr>
<th>Symptomer</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sikre...</td>
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<tr>
<td>Dypt...</td>
<td></td>
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<tr>
<td>Såvel...</td>
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<tr>
<td>Førstegang...</td>
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</tbody>
</table>

**HVER MANGE GANGER HAR DU HATT FORKJÆRLIGHETER?**

<table>
<thead>
<tr>
<th>Forblir...</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;røksykka&quot; og lignende siste halvår?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Her du hatt dette de siste 14 døgn?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hender det at tankek på å få alvorlig sykdom</td>
<td>Ja</td>
<td>Nei</td>
</tr>
<tr>
<td>---------------------------------------------</td>
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<td>------</td>
</tr>
<tr>
<td>bekymrer deg?</td>
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<td></td>
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<tr>
<td>ikke i det hele tatt</td>
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<tr>
<td>bare i liten grad</td>
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<tr>
<td>en del</td>
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<tr>
<td>ganske mye</td>
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</table>

**LEGEMELIGE FUNKSJONER**

<table>
<thead>
<tr>
<th>Klarer du selv disse gjennomførtene i det daglige uten hjelp fra andre?</th>
<th>Ja</th>
<th>Med noe hjelp</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Går innemmeder i samme etasje</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Går i toget</td>
<td></td>
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<tr>
<td>Går utendørs</td>
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<tr>
<td>går ca. 500 meter</td>
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<tr>
<td>går på toaletter</td>
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<tr>
<td>Vask deg på kroppen</td>
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<tr>
<td>Bade eller dusje</td>
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<tr>
<td>Kne på og av deg</td>
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<tr>
<td>Legge deg og stå opp</td>
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<tr>
<td>Spise selv</td>
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<tr>
<td>Legge varm mat</td>
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<tr>
<td>Gjøre tett husværd (f.eks. oppvask)</td>
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<tr>
<td>Gjøre tyngre husværd (f.eks. pulvovask)</td>
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<tr>
<td>Gjøre inngjøringsystem</td>
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<tr>
<td>Ta busen</td>
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</tbody>
</table>

**Kan du bare vanlig tele (ev. med helseapparat)?**

<table>
<thead>
<tr>
<th>(ev. med helseapparat)?</th>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can du lese (ev. med briller)?</td>
<td></td>
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</table>

**Er du avhengig av noen av disse hjelpemidlene?**

<table>
<thead>
<tr>
<th>Stoff</th>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stykke</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Krykke</td>
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<td></td>
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<tr>
<td>Gassel (rallator)</td>
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<tr>
<td>Rolfestol</td>
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<td></td>
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<tr>
<td>Horreaparal</td>
<td></td>
<td></td>
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<tr>
<td>Tryggelsalarm</td>
<td></td>
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</tbody>
</table>

**BRUK AV HELSEVÆSNET**

<table>
<thead>
<tr>
<th>hvordan mange ganger har du i siste året, på grunn av egen sykdom</th>
<th>Antall ganger</th>
</tr>
</thead>
<tbody>
<tr>
<td>sett i hvis du ikke har hatt slik kontakt, siste år</td>
<td></td>
</tr>
<tr>
<td>Hos vanlig lege/negevekk</td>
<td>121</td>
</tr>
<tr>
<td>Hos psykolog eller psykater</td>
<td></td>
</tr>
<tr>
<td>Hos annen legespesialist utenfor sykehus</td>
<td></td>
</tr>
<tr>
<td>På poliklinikje</td>
<td></td>
</tr>
<tr>
<td>Innlegt i sykehus</td>
<td></td>
</tr>
<tr>
<td>Hos fysioterapeut</td>
<td></td>
</tr>
<tr>
<td>Hos kiropraktor</td>
<td></td>
</tr>
<tr>
<td>Hos akupunktør</td>
<td></td>
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<tr>
<td>Hos tannlege</td>
<td></td>
</tr>
<tr>
<td>Hos tetterapeut</td>
<td></td>
</tr>
<tr>
<td>Hos naturalmedisiner (hamaoppat, samferipat o.l.)</td>
<td></td>
</tr>
<tr>
<td>Hos håndspålegger, synsk eller &quot;fleser&quot;</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Er du fornøyd med helse- og helsefjernelsest i kommunen?</th>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prinsippet med test lege</td>
<td>158</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hjemmesykeplassen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hjemmelhjelp</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Er du trygg på at du kan få hjelp av helse- og helsefjernelsest hvis du trenger det?**

<table>
<thead>
<tr>
<th>Trygg</th>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ikke trygg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Svært uttrygg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vet ikke</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**LEGEMIDLER OG KOSTTILSKUDD**

<table>
<thead>
<tr>
<th>Hvor mange dager er det siste året perioder i bruk av disse legemidlene?</th>
<th>702</th>
<th>1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sømmestilleffende</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sovemiddels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beroendelegende</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicin mot depresjon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergimiddels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asamidels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hjertemidels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Ikke høytrykkssosialmedicin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tablettene mot diabetes (sukkorsyke)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tablettene mot lavt stoffskifte (thyroxin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tablettene mot fett stoffskifte (thyroxin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korsettablettene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miljordiagnosticer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kosttillskudd</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ERDIGTEK**

<table>
<thead>
<tr>
<th>Var du mer familie som kan gi deg hjelp og støtte når du trenger det?</th>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hvis &quot;Ja&quot;; Hvor kan gi deg hjelp?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ektefelle/sambær</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andre</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hvor mange gode vennner har du som du kan snakke gode førstelig med og gi deg hjelp når du trenger det?</th>
<th>300</th>
<th>1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tell ikke om dem du bør sammen med, noen få med andre slektninger!</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FAMILIEN OG VENNER**

<table>
<thead>
<tr>
<th>Feller du at du har nok gode vennner?</th>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feller du at du har nok gode vennner?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feller du at du harer med i et felleskap (gruppe av mennesker) som stoler på hverandre og lever forpliktelser overfor hverandre (f.eks. i politisk parti, religiøs gruppe, slekt, nasjonal, arbeidsplass eller organisasjon)?</th>
<th>100</th>
<th>1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterk tilhørighet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nøy tilhørighet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unikert</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liten eller ingen tilhørighet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. sykehus, idrettslag, politiske lag, religiøse eller andre foreninger?
- Aldri, eller noen få ganger i året ...
- 1-2 ganger i måneden ...
- Omtrent en gang i uken ...
- Mer enn en gang i uken ...

Hvor mange manndager spiser du vanligvis daglig (middag og brødmotte)? ...

Hvor mange ganger i uken spiser du vanligvis daglig?

Hva slag type brød (kjept eller hjemmebakt) spiser du vanligvis?
- Sort alt eller to kryss ...
- Fløt ...
- Knækbrød ...
- Grubbred ...
- Knøkkelbrød ...

Barndypen ligner mest på ...

Hva slags flett blir til vanligvis brukt til matlaging (ikke på brødet) i din husholdning?
- Metterismer ...
- Hard margarin ...
- Blant (Soft) margarin ...
- Smeer/margarin blanding ...
- Oljer ...

Hvor mye (i antall glass, poteter eller brødskiver) spiser/drikker du vanligvis daglig av følgende matvarer?

Kryss av for alle matvarer.

<table>
<thead>
<tr>
<th>Ingredienser</th>
<th>Mindre</th>
<th>Middel</th>
<th>1-2</th>
<th>3 og mer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melk alle sorter (glass)</td>
<td>50%</td>
<td>50%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Apelsin/jice (glass)</td>
<td></td>
<td></td>
<td>80%</td>
<td>30%</td>
</tr>
<tr>
<td>Poteter</td>
<td></td>
<td></td>
<td>50%</td>
<td>30%</td>
</tr>
<tr>
<td>Brødskiver totalt (inkl. knøkkelbrød)</td>
<td></td>
<td></td>
<td>80%</td>
<td>30%</td>
</tr>
<tr>
<td>Brødskiver med</td>
<td></td>
<td></td>
<td>80%</td>
<td>30%</td>
</tr>
<tr>
<td>- fiskålelegg (f.eks. makrell i tomat)</td>
<td></td>
<td></td>
<td>80%</td>
<td>30%</td>
</tr>
<tr>
<td>- gullost</td>
<td></td>
<td></td>
<td>80%</td>
<td>30%</td>
</tr>
<tr>
<td>- kaviar</td>
<td></td>
<td></td>
<td>80%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Hvor mange ganger i uke spiser du vanligvis følgende matvarer?

Kryss av for alle matvarer.

<table>
<thead>
<tr>
<th>Ingredienser</th>
<th>Aldri</th>
<th>1 og mer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoghurt</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Kokt eller stekt egg</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Friskostblanding/havregryn o.l.</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Middag med</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- fisk (f.eks. makrell)</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>- mager fisk (f.eks. borsk)</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>- grønnsaker (rå eller kokte)</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Grønnt (rå eller kokte)</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Sauerkraut/skokkoli</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Epler/pærer</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Applesiner, mandariner o.l.</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Hvordan trives du med å bli gammel - alt i alt?
- Gott ...
- Ganske bra ...
- Opp og ned ...
- Dårlig ...

Hvordan ser du på livet fremover?
- Lyk ...
- Ikke så ver ...
- Nekks bekymret ...
- Mørkt ...

BESVARES BARE AV KVINNER

MEISTRASJON

Hvor gammel var du da du fikk menstruasjon første gang?

Hvor gammel var du da menstruasjonen sluttet?

SVANGERSKAP

Hvor mange barn har du fødd?


Barn: | Fødselsår: | Antall måneder |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>300</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>300</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>300</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>300</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>300</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>300</td>
<td>9</td>
</tr>
</tbody>
</table>

Hvis du i forbindelse med svangerskap halte for høy blodtrykk og/eller eggelhile (protein) i urinen?
- Ja ...
- Nei ...

Hvis "Ja", i hvilket svangerskap?

Svangerskap: Forhånd: Selvare:

For høy blodtrykk ...

Eggelhile i urinen ...

HISTROGEN-MEDISIN

Bruker du, eller har du brukt, astrogen-medisin?
- Yes ...
- No ...

Tabletter eller pølster ...

Ihv du bruker astrogen, hvilket merke bruker du nå?
Appendix IV

First questionnaire,
Tromsø V, 2001
Personlig innbydelse
## 1. EGEN HELSE

1. Hvordan er helsen din nå? (Skriv hele ditt kryss)
   - Dårlig
   - Ikke hatt god
   - God
   - Uværet god

2. Har du, eller har du blitt?
   - Astma
   - Hypans
   - Kronisk brennemmer
   - Diabetes (sukkerløske)
   - Beskyttet (astenforresse)
   - Fibromyalgi/kronisk smerte
   - Psikiske plager som du har sett hjelp for
   - Hjertesatellit
   - Angina pectoris (hjerteinfarkt)
   - Fierceinfarkt (hjerteskade)

3. Andre plager
   - Plusselig frykt uten grunn
   - Feber og rodd eller anpassing
   - Målhet eller svimmelhet
   - Feber og besvissel eller oppgjøret
   - Litt for å kunde deg selv
   - Forblir avfødt og et blitt
   - Faste av døde ekstremt, trummis
     - Jung i 1, 2, 3

## 3. ANMELD PLAGET

3. Bruk av helsetjenester
   - Hvor mange ganger skratt du skrive 2 hundre lar av det (Skriv helt for hver døgn)
     - Astma
     - Børnliv
     - Psykologisk
     - Poliklinik
     - Annen specialist
     - Legemliften
     - Sykevård
     - Hjerneskade
     - Fysioterapeut
     - Kiropraktor
     - Tannlege
     - Alternativer behandlet

## 5. OPPVEKST OG TILHÖRIGHET

6. Anskr av vekt da du er 25 år gammel
### 7. MAT OG DRIKKER

<table>
<thead>
<tr>
<th>7.1</th>
<th>Hvor ofte spiser du vanligvis disse matvariene?</th>
<th>Antall høye trimm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frukter, baer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gist (olle typer)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pøsteret</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kjære grønnsaker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ris grønnsaker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fett fisk (fiske, øst, makrell, sel)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7.2</th>
<th>Hva slags fisk bruker du oftest? (Svart om kryss på listen)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7.3</th>
<th>Bruker du følgende kosttilskudd?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Træsk, tørrkost, råksalat, jalapeno</td>
</tr>
<tr>
<td></td>
<td>Vitamintabletter, mineralvann, kost</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7.4</th>
<th>Hvor mye dricker du vanligvis av løsgrøt (Svart om kryss på listen)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Helmet, kaffe, yoghurt,</td>
</tr>
<tr>
<td></td>
<td>Laskande, kafe, lekyoghurt,</td>
</tr>
<tr>
<td></td>
<td>Sjokolade melk (kaffel)</td>
</tr>
<tr>
<td></td>
<td>Elska kaffemelk</td>
</tr>
<tr>
<td></td>
<td>Friskkaffe</td>
</tr>
<tr>
<td></td>
<td>Suve</td>
</tr>
<tr>
<td></td>
<td>Frullan, Frullan melk</td>
</tr>
<tr>
<td></td>
<td>Cobo-koffe, Cobo kaffemelk</td>
</tr>
<tr>
<td></td>
<td>Amrine brushekk (kaffemelk)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7.5</th>
<th>Drinker du vanligvis brushekk? (Svart om kryss på listen)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uten sukker</td>
</tr>
</tbody>
</table>

### 8. ROYKING

<table>
<thead>
<tr>
<th>8.1</th>
<th>Hvor lenge er det vanligvis daglig tilstått i royktrykket?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antall høye trimm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8.2</th>
<th>Royst etter ord av de vakene hjemme, du vil lekke opp?</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8.3</th>
<th>Hvor lenge er det i begge, som er med,</th>
<th>Antall høye trimm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>har noen dagligrykter etter at de fylte 20 år?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8.4</th>
<th>Hvis du røyker daglig, har du rokt i</th>
<th>Antall høye trimm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>flere gang?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8.5</th>
<th>Hvis du har rokt daglig tidligere, har</th>
<th>Antall høye trimm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lenge er det i de som du slutet?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8.6</th>
<th>Hvis du har rokt daglig tidligere, har</th>
<th>Antall høye trimm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lenge er det i de som du slutet?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8.7</th>
<th>Hvis du har rokt daglig tidligere, har</th>
<th>Antall høye trimm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lenge er det i de som du slutet?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8.8</th>
<th>Hvor mange dagligvæsker røyker du?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antall høye trimm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8.9</th>
<th>Hvor mange dagligvæsker røyker du?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antall høye trimm</td>
</tr>
</tbody>
</table>

### 9. UTDANNING OG ARBEID

<table>
<thead>
<tr>
<th>9.1</th>
<th>Hvor mange år skoleang</th>
<th>Antall høye trimm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>har du gjennomført?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9.2</th>
<th>Er du i inntektsregulering?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ja, totalet i 2</td>
</tr>
<tr>
<td></td>
<td>Ja, filter i 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9.3</th>
<th>Bestemte ytvagslapper: (Svart om kryss på listen)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Der udefra innenlegerende inntekter i lengst til</td>
</tr>
<tr>
<td></td>
<td>de sist 12 måneder. (F.eks. regnskapsleder,</td>
</tr>
<tr>
<td></td>
<td>administers, bank,</td>
</tr>
<tr>
<td></td>
<td>dagerverfører e.l.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9.4</th>
<th>Hvor mange ytvagslapper har du? (Svart om kryss på listen)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antall høye trimm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9.5</th>
<th>Ytvagslapper: (Svart om kryss på listen)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antall høye trimm</td>
</tr>
</tbody>
</table>

| 9.6 | Arbeidsd, har du i ditt hoved yrke?
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Særlig med</td>
</tr>
<tr>
<td></td>
<td>familiedel</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9.7</th>
<th>Mener du at du er i fare for å miste ditt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>anslagsrettet arbeid?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9.8</th>
<th>Sykepenger</th>
<th>Antall høye trimm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arbeidsganger</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9.9</th>
<th>Alderstrøg, tarifspensjon (AFP) eller</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>etterlønnspensjon</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9.10</th>
<th>Rehabiliterings-</th>
<th>Antall høye trimm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tar iftoppspensjon</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>9.11</th>
<th>Utbypensjon (tredel eller delvik)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>9.12</th>
<th>Dagspenger under arbeidsdighet?</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>9.13</th>
<th>Socialhjelp-støtte</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>9.14</th>
<th>Overgangsfondet for øvrige forstørre</th>
</tr>
</thead>
</table>
10. MOSJON OG FYSISK AKTIVITET

10.1: Hvordan har din fysiske aktivitet i helheten vært det siste året?

- T
- F

T: Tilknyttet
F: Ikke tilknyttet

10.2: Arbeider du i en yrke som kræver hard fysisk aktivitet?

- Nei
- Ja

10.3: Arbeider du i en yrke som krever sanntidsarbeid?

- Nei
- Ja

10.4: Har du noen anfallsformer?

- Nei
- Ja

10.5: Har du noen mentale anfallsformer?

- Nei
- Ja

11. FAMILIE OG VENNER

11.1: Bør du sammen med en familie? (Ja/Nei)

- Ja
- Nei

11.2: Hvor mange grader har du?

Antall grader

11.3: Hvor mange foreldre, brødre eller søsken har du?

Antall

11.4: Hvor mange foreldre, brødre og søsken har du?

Antall

11.5: Får du at du kan påvirke det som skjer i familien?

Ja: Ja

12. SYKDOM I FAMILIEN

12.1: Har en eller flere av dine foreldre eller søskener

- Hipertoneri
- Diabetes
- Kræft
- Skjær
- Egna

12.2: Hvis noen av disse sykdommene er det vært noen av disse sykdommene?

- Sist krevnet
- Krevnet
- Krevnet
- Krevnet
- Krevnet

13. BRUK AV MEDISINER

13.1: Bruker du?

- Nei
- Ja

13.2: Hvor ofte har du i løpet av de siste 4 uker bruket følgende medicin?

Antall

13.3: Hvor lenge har du i løpet av de siste 4 uker

- Helt sikkert
- Usikkert
- Usikkert

14. RESTEN AV SKJEMMA SKAL BARE BESVARES AV KVINNER

14.1: Hvor gammel var du da du fikk menstruasjon eller første gang?

- Alder i år

14.2: Hvor mange bar

- Bar
- Bar
- Bar

14.3: Hvor mange barn har du?

Antall

14.4: Hvor mange barn har du?

Antall

14.5: Bruker du eller har du bruket

- Nei
- Ja

14.6: Hvordan bruker du

- Nei
- Ja

14.7: Hvor lenge har du bruket dette?

- Nei
- Ja

14.8: Hvor lenge har du bruket dette?

- Nei
- Ja

14.9: Hvor lenge har du bruket dette?

- Nei
- Ja
Appendix V

Second questionnaire for subjects aged < 70 years,
Tromsø V, 2001
Tilleggspsormå til helseundersøkelsen i Troms og Finnmark 2001-2002

Hovedformålet med Helseundersøkelsen er å skaffe ny kunnskap om helse- og lekeksamom for å kunne forebygge dem. I tillegg skal undersøkelsen øke kunnskapen om helsesystemer og påvirke fakta allergier, smerte i muskulatur og nærvær i liden. Vi ber derfor svarer på noen spørsmål om forhold som kan ha betydning for risikoen for disse og andre sykdommer. Skjemaet er en del av Helseundersøkelsen som er godkjennt av Datastyre og foretaget av Regionalt komité for medisinsk forskningspolitikk. Svarene brukes bare til forskning og behandles strengt fortrolig.

1. LOKALMILJØ OG BOLIG

1.1 I hvilken kommune bodde du de fire årene? (Hvis du ikke bodde i Norge, oppgi hvilket land i stedet for kommunen)

1.2 Hvilken type bolig bor du i? (Sett bare ett kryss)
- Enehåusbolig/villa
- Gårdsbolig
- Blockhus/leilighet
- Rikshus
- Institusjonsselskapbolig
- Annen bolig

1.3 Hvor stor er din boenshet? (Kvadratbrutto)

1.4 Er du plagent av? (Sett ett kryss for hver ågegruppe)
- Fukt, trekk eller kolde i din bolig
- Andre forster for dårlig inneklimate
- Trafikkstøy (for eksempel et fly)
- Annen støy (bordfart, byggemess e.l.)
- Naboløy
- Dårlig støy
- Luftforurensning fra trafikk
- Luftforurensning fra ved- oljefyring, fabrikk e.l.

1.5 Hvilket hjemmespråk hadde dine besteforeldre? (Kryss av ett eller flere alternativer)

2. LØNNET OG ULØNNET ARBEID

2.1 Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive ditt arbeid? (Sett bare ett kryss)
- Arbeid som krever at du går mye
- Arbeid med håndverk og håndverksarbeidene
- Tungt kroppsarbeid

2.2 Kan du selv bestemme hvordan arbeidet ditt (lønnet eller ulønnet) skal legges opp? (Sett bare ett kryss)

2.3 Hør du skiltarbeid, nattarbeid eller går vækter?
Tilføyte: TOBÅKK

3.1 Røyker du?
   Ja, daglig
   Ja, av og til
   Nei, aldri

Hvis Ja, av og til?
   Hva røyker du?
   Sigaretter
   Pippe
   Sigarettetabak

3.2 Har du brukt, eller bruker du snus daglig?
   Ja, nå
   Ja, tidligere
   Aldri

Hvis Ja, hvor mange år har du til sammen brukt snus?

Tilføyte: ALKOHOL

4.1 Er du totalavholdsmann/kvinne?

4.2 Hvor mange ganger i måneden drikker du vanligvis alkohol?
   Ansigt ganger
   (Hvis ikke med feltet Sett 0 hvis mindre enn 1 gang i måneden)

4.3 Hvor mange ganger er det med vin eller brennvin?
   (Hvis ikke med feltet Sett 0 hvis du ikke drukner alkohol)

4.4 I enhver av dem hvor mange år har du ditt alkoholforbruk vært slik at du har svart i spørsmålene ovenfor?

4.5 Har du i en eller flere perioder de siste 5 årene drukket så mye alkohol at det har hatt innvirkning på yrkeslivet eller sosialt?
   Ja
   Nei

Tilføyte: MAT OG KOSTTILSKUDD

5.1 Spiser du vanligvis frøkast hver dag?

5.2 Hvor mange ganger i uken spiser du vanligvis middag?

5.3 Hvor mange ganger i uken spiser du vanligvis kveldens spise?

5.4 Bruker du følgende kosttilskudd?

6.1 Gjør du i tillegg noen forskjell på å drikke kaffeavsett?

6.2 Hvilken avleden er du tilsprent med i forhold til sitt livsstilbeskrivelse?

Tilføyte: SYKDOMMER OG SKADER

7.1 Har du noen gang hatt:
   Slett åt kysa før hvert spisemål. Oppgi også alderen ved hendelsen. Hva har du sykt mest av?

   Alkoholisk skade som førte til sykehjemstjeneste
   JA NEI

   Antikvitt
   JA NEI

   Magstort
   JA NEI

   Magstort operasjon
   JA NEI

   Operasjon på hansen
   JA NEI

   Prostatitis operasjon
   JA NEI

7.2 Har du eller har du hatt?
   (Søtt åt kysa forskjell på hvert spisemål)
   Kreftsykdom
   JA NEI

   Psoriasis
   JA NEI

   Sjukdomslatsteilt (sykdomsmellomstilt)
   JA NEI

   Grønn stor
   JA NEI

   Grå stor
   JA NEI

   Sjukdomsart (artrose)
   JA NEI

   Krokatate lunge
   JA NEI

   Husstrømminger i håndflaten
   JA NEI

   Nystein
   JA NEI

   Brennmarksoperasjon
  JA NEI

   Blodoperasjon
   JA NEI

   Operasjonstilbehandling for utviklingsløse
   JA NEI

   Epilepsi
   JA NEI

   Poliomyelit (Polio)
   JA NEI

   Parkinsons sykdom
   JA NEI

   Menopauze
   JA NEI

   Leggse
   JA NEI

   Allergi og allergi overforbruket
   JA NEI

   AlkopISK oksam (f.eks. barnekebak)
   JA NEI

   Håndtekk
   JA NEI

   Matvareallergi
   JA NEI

   Annen overfølsomhet (Usikkert allergi)
   JA NEI

7.3 Har du hatt forkjojelse, influensa, "røkkejuka" eller lignende syte de siste 14 dager?

7.4 Har du forskjelt av de siste 3 uker vært forkjølt, eller hatt influenza, bronkitt, lungebetennelse, beseivtebetennelse eller annen lufteinfeksjon?

7.5 Har du noen gang hatt bronkitt eller lungebetennelse?

7.6 Har du i løpet av de siste 2 årene vært forkjølt, eller hatt influenza, bronkitt, lungebetennelse eller annen lufteinfeksjon?

7.7 Har du noen gang hatt bronkitt eller lungebetennelse?
T8. SYMPTOMER

8.1 Har du de siste to ukene følt deg: (Sett et kryss for hvert spørsmåls) ja nej

- Nervøs og urolig
- Plaget av angst
- Trygg og rolig
- Irritabel
- Glad og optimistisk
- Nellor/deprimert
- Ensom

8.2 Hoster du omtrent daglig i perioder av året?
   Ja nej

8.3 Har du hatt episoder med piping i brystet?
   Ja nej

8.4 Får du smerter i tyrkkesgalen når du går?
   Ja nej

8.5 Bør du turgjuten i følgende situasjoner?
   (Sett et kryss for hvert spørsmål)

- Når du går hurtig på flatmark
- Når du spiser i rolig tempo på flatmark
- Når du vækker deg eller klar på dag
- Når du er i tvil

8.6 Må du stoppe på grunn av tung pass
   Ja nej

8.7 Har du i løpet av det siste året vært pløyet med smerter og/eller svært i muskler og lading som har vært i minst 3 måneder sammenhengende?
   Ja nej

8.8 Hvor ofte er du pløyet av søvnløshet?
   (Sett et kryss for hvert spørsmål)

- Aldri
- 1-2 ganger i måneden
- Omsetten 1 gang i uken
- Mer enn en gang i uken

8.9 Hvis du er pløyet av søvnløshet mange dager eller hyppigere, når på året er du magt pløyet?
   Ingen spesiell tid
   Samtidig i mønsterorden
   Samtidig i midnattstiden
   Samtidig vår og sommer

8.10 Har du det siste året vært pløyet av søvnløshet slik at det har gått ut over arbeidsveien?
   Ja nej

8.11 Piler du sove om dagen?

8.12 Hvor ofte har du uhyrlig urinlækasje?
   Aldri
   Ikke mer enn en gang i måneden
   To eller flere ganger i måneden
   Usærlig eller ofte

8.13 Kan du gå ned 10 trapperrinn uten å holde deg i tine (f.x. å gjenlende)
   Ja nej

8.14 Bruker du bryllene?

8.15 Bruker du hørevurdering?

8.16 Hva tror du er hukommelsesforstyrrelser?
   (Sett et kryss for hvert spørsmål)

8.17 Tror du at du er mer trygg?

T9. MEDISINER

9.1 Bruker du, eller har du brukt noen av følgende medisiner?

- Medisin mot osteoporose (bensklofet)
- Tabletter mot suksesssyke
- Tabletter mot lavt stofsløse (thyoxin)

9.2 Bruker du noen medisin som du får som sprøyte (injeksjon)?
   Ja nej

Hvis JA: Oppgi navn på medisinen (til sprøyte):
(ett navn pr. linje):
## Sykdom i familien

10.1 Kryss av for de slettingene som har eller har hatt nøden av sykdomsmerker. (Sett kryss for hver linje)
- Hjerteriskt (så på hjertet)
- Anginapectoris (hjertespærre)
- Høyt blodtrykk
- Udødel hovedskaerle i mage
- Maget-kæmpeformede i mage
- Lirhasabudd
- Psykiske plager
- Allergier
- Skinnepigement (Osleres)
- Aldersmerker

10.2 Hvor mange søskenn og barn har du?
- Brødrene
- Søstrene
- Barn

## Hvis det er tilfelle

10.3 Fører sykdom e.i. hos noen i nær familie til å du vanligvis utfører ekstra omsorgsarbeid?
- JA
- NEI
- EVNT. aldri ved dokt.

10.4 Hvor lenge har du hjemmedjelp eller hjemmestykkelse?
- JA, NEI
- EVNT. aldri ved dokt.

10.5 Lever din mor?
- JA
- NEI
- EVNT. aldri ved dokt.

10.6 Lever din far?
- JA
- NEI
- EVNT. aldri ved dokt.

## Mobiltelefon

11.1 Disponerer du (eller leverer du管理制度) mobiltelefon?
- JA, har til en
- JA, er av og til
- NEI

Hvis JA:
- Hva bruker du mobiltelefonen til, og hvor ofte bruker du den? (Sett kryss for hver linje)

<table>
<thead>
<tr>
<th>Aktiviteter per dag</th>
<th>Sj eller Bar</th>
<th>1-25</th>
<th>2-3</th>
<th>3-4</th>
<th>5</th>
<th>6+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samleriar...</td>
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<td></td>
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<td></td>
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<tr>
<td>Teknologier...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anmerkninger...</td>
<td></td>
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</tr>
</tbody>
</table>

## Resten besvares bare av kvinner

12.1 Hvis du har føtt barn, tylt ut hvart barns fødselsår, og hvor mange måneder du anmette før fødselen.

**Hvis du ikke anmet, skriv 0**

<table>
<thead>
<tr>
<th>Barn</th>
<th>Fødselsår</th>
<th>Med anmerking</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12.2 Hvis du fremdeles har menstruasjon eller er gravide:
- Hvilkene dato startet din siste menstruasjon?
  - Dag: NEI
  - Måned: NEI
  - År: NEI

12.3 Hvis du ikke længer har menstruasjon; hvorfor mistet du menstruasjonen? (Sett et kryss)
- Den stoppet av seg selv: JA
- Operasjon på tarmen: NEI
- Opererte bon begge eggstokkene: NEI
- Amner grunn (f.eks. strålning, gallerarbeid): NEI

12.4 Bruker du eller har du brukt magoptegnende og bladmjøl (tabletter eller plakker)?

Hvis JA:
- Hvor gammel var du da du begynte med magoptegnende og bladmjøl?
  - JA
  - NEI

Hvis du har sluttet å bruke magoptegnende og bladmjøl:
- Hvor gammel var du da du sluttet med magoptegnende og bladmjøl?
  - JA
  - NEI

12.5 Bruker du eller har du brukt p-piller?

Hvis JA:
- Hvor gammel var du da du begynte med p-piller?
  - JA
  - NEI

12.6 Når du ser barn fra egne skap og børnepermitted, har du noen gang vært bladningsfri i minst 6 måneder?

Hvis JA:
- Hvor mange ganger?
  - JA
  - NEI

12.7 Hvor lang tid vi anbefaler stroppingstiden for deg nå?
- Jeg har ikke god tilbladninger (i slekt)/
  - JA
- Jeg har regelmessige bladninger:
  - NEI
- Jeg har unødvendige bladninger:
  - NEI

12.8 Da du var i 25-28 årsalderen, hvor mange dager...?

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Veh sos</th>
<th>dager</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Pålikkelig selve bladningstiden om tre
der mange dager hvor gang?

Hvor mange dager var det vanligvis mellom starten på to bladninger?

**Takk for hjelpen!**
Husk å postlege skjemaet i dag!
Appendix VI

Second questionnaire for subjects aged > 70 years, Tromsø V, 2001
Helse-undersøkelsen

Personlig innbydelse
## EGENHÆLSE

*Hvordan er helsen din nå? (Sett bare ett kryss)*

<table>
<thead>
<tr>
<th>Dårlig</th>
<th>Ikke helt god</th>
<th>God</th>
<th>svært god</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Har du eller har du haft?:  
- Astma 
- Kronisk bronkittisemfys 
- Diabetes (sukkerstyrke) 
- Benet 
- Fibromyalgi 
- Hemmefinn 
- Psykiske plager du har søkt hjelp for

## EURILLAGER

Under finner du en liste over ulike problemer. Har du opplevd noe av dette den siste uken (til og med i dag)? (Sett ett kryss for hver linje)

- Plutselig frykt men grunn
- Folk deg redd eller angestig
- Matte eller overmøhlet
- Folk deg ampent eller oppjåret
- Litt for å klare deg selv
- Søvnsommer
- Nedtrykt, tungsindig
- Føles av og til vara unytlig, lite ved
- Føles av og til av en liten skål
- Føles av høpløshet mt. trumdla

## TENNER, MUSKEL OG SJELETT

*Hvor mange tanner har du mistet eller brukt? Antall tanner (se bort fra melotoner og visdomsvenner)*

Har du vært plaget med smertet og/eller skikten i muskler og ledd i løpet av de siste 4 uker?

- Nækknokkel
- Armmer, hender
- Over del av ryggen
- Korset
- Hovrer, ben, fotter
- Andre slemmer

Har du noen gang haft:
- Brudd i håndled eller armen?
- Lønnsbrudd?

## SYKDOMMENHÆLSE

*Har en eller flere av dine foreldre eller søsknene haft?*

- Hjertekartet (sår på hjertet) eller angina pectoris (hjertekramp)?

*Kryss for de skittningenene som har eller har haft noen av sykdommene: (Sett kryss for hver linje)*

*Hjernetjekking eller hjernekramp vagt*  
- Mer  
- Færre  
- Smerter  
- Deuser  
- Desværre av denne*

*Asma*  
- Mer  
- Færre  
- Smerter  
- Desværre av denne*

*Kreftsykdom*  
- Mer  
- Færre  
- Smerter  
- Desværre av denne*

*Diabetes (sukkerstyrke)*  
- Mer  
- Færre  
- Smerter  
- Desværre av denne*

Hvis noen skittningen har diabetes, i hvilken alder til de diabetes (hvis før olva, flere søsknene, før opp som fell det tidligst i livet):

- Vel på, 
- Mors alder 
- Fars alder 
- Søskne alder 
- Barnealder

## MOSJON OG FYSISK AKTIVITET

*Hvordan har din fysiske aktivitet vært det siste året?*  
- Takk deg av likvidt gjennomsnitt for året.  
- Besøk begge samfunnene.

**Timer pr. uke**

- Ingen
- Under 1
- 1-2
- 3 og mer

## VÆKT

Anslatt din vækt da du var 25 år gammel:  

- heime
### E7. UTDANNING

Hvor mange år skolegang har du gjennomført? Antall år
(Ta med alle åt du har gått på skole eller studert)

### E8. MATERIØRIKKE

Hvor ofte spiser du vanligvis gress matvarer?
(Sett å kres i hvert felle)

<table>
<thead>
<tr>
<th>Gress varer</th>
<th>1 g pr. måned</th>
<th>1,5 g pr. måned</th>
<th>2 g pr. måned</th>
<th>2,5 g pr. måned</th>
<th>3 g pr. måned</th>
<th>3,5 g pr. måned</th>
<th>4 g pr. måned</th>
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<tbody>
<tr>
<td>Frukt, bær</td>
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<tr>
<td>Grønt (alle typer)</td>
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<tr>
<td>Kuòte grønnsaker</td>
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<td>☐</td>
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<tr>
<td>På grønnsaker og grønt</td>
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<tr>
<td>Fest fisk (føle, laks, ore, ost)</td>
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<td>Brølker</td>
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</tbody>
</table>

### E9. RØYKING

Hvor lenge er du vanligvis daglig?
Tilsette i et røykkytt rom? Antall time

### E10. FUNKSJON OG TRYGGHET

Hvis du har røykt daglig tidligere, hvor lenge er det siden du slutet? Antall år

Hvis du har røykt daglig tidligere, hvor lenge er det siden du slutet? Antall år

Hvis du har røykt daglig tidligere, hvor lenge er det siden du slutet? Antall år

Hvis du har røykt daglig tidligere, hvor lenge er det siden du slutet? Antall år

### E11. FUNKSJON OG TRYGGHET

Vil du følge deg trygg ved å følge stene på livsfølge i nærområdet der du bor?

En: Lit utrygg

Svart utrygg

Ja

Nei

### E12. FUNKSJON OG TRYGGHET

Når det gjelder farlighet, syn og hørsl, kan du:
(Sett å kres for hver linje)

<table>
<thead>
<tr>
<th>Linje</th>
<th>Problemer</th>
<th>Med lit problemer</th>
<th>Med store problemer</th>
<th>Nei</th>
</tr>
</thead>
</table>

### E13. FUNKSJON OG TRYGGHET

Her du på grunn av vanlige helseproblemer vansker med å: (Sett å kres for hver linje)

### E14. FUNKSJON OG TRYGGHET

Beveg deg rundt i egen bolig?.....

Kunne deg ut av boligen på egen hånd?.....

Delte i foreningsliv eller andre friidrettstvitter?.....

Bruke offentlige transportmidler?.....

Uttøre nødvendige daglige øvning?.....
E11. BRUK AV HELSETJENESTER

Hvor mange ganger har du søkt hjelp fra en helsefaglig person i de siste 12 månedene?

Ingen
1-2 ganger
4 eller flere
Ja
Nei
Tilbakebetaling.

E12. FAMILIE OG VEDEMER

Bør du en kjære?:
Ja
Nei
Institusjon/bolig/lokkspis?:
Ja
Nei
Ektefelle/samboer?:
Ja
Nei
Andre personer?:
Ja
Nei

E13. OPPVEKST OG TILHØRIGHET

Hvor lenge har det samlet bodd i fylket?

1 år
2 år
4 år
Ja
Nei
Tilbakebetaling.

E14. BRUK AV MEDISINER

Medicin er en medisiner.

Bruker du?
Ja
Nei
Vet ikke

E15. RESTEN AV SKJENET SKAL BARE BESVARE AV KVINNER

Har du noen gang brukt P-piller?
Ja
Nei
Tilbakebetaling.
1. Bidrag til belysning av medisinske og sosiale forhold i Finnmark fylke, med særlig vekt på forholdene blant finskattede i Sør-Varanger kommune. 
   **Av Anders Forsdahl, 1976. (nytt opplag 1990)**

   **Av Anders Forsdahl, 1977.**

   **Av Jan-Ivar Kvanme og Trond Haider, 1979.**

   **Av Olav Helge Førde og Dag Steinar Thelle, 1979.**

5. D. Reform i distriktshelsetjenesten III: Hypertensjon i distriktshelsetjenesten. 
   **Av Jan-Ivar Kvanme, 1980.**


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

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

   **Av Toralf Hasvold, 1984.**

    **Av Georg Høyen, 1986.**

    **Av Bjarne Koster Jacobsen, 1988.**

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


   Av Vinjar Fønnebø, 1992.

22. D. Aspects of breast and cervical cancer screening. 

   Av Roar Johnsen, 1992.


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


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


50. D. Environmental and occupational exposure, life-style factors and pregnancy outcome in arctic and subarctic populations of Norway and Russia. 

50B. 
   Окружающая и профессиональная экзопиация, факторы стиля жизни и исход беременности у населения арктической и субарктической частей Норвегии и России 
   Юн Ойвинн Одлан, 2000


52. D. Ultrasound assessed carotid atherosclerosis in a general population. The Tromsø Study. 


54. D. The South Asian cataract management study. 

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


57. D. Individual fatty acids and cardiovascular risk factors. 

58. 
   Finnmarkundersøkelserne 


61. D. Studies in perinatal care from a sparsely populated area. 


64. D. Ill health in two contrasting countries. 

   Av Tom Wilsaard, 2002.

   Av Odd Nilssen, Alexei Kalinin, Tormod Brenn, Maria Averina et al., 2003.


68. D. Persistent organic pollutants in human plasma from inhabitants of the artic. 

69. D. Aspects of women’s health in relation to use of hormonal contraceptives and pattern of child bearing. 

70. Pasienterfaringer i primærlegetjenesten før og etter fastlegereformen. 

71. D. Vitamin D security in northern Norway in relation to marine food traditions. 


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

74. D. Det skapende mellomrommet i møtet mellom pasient og lege. 

76. D. Characteristics and prognosis of long-term stroke survivors. The Tromsø Study.  
Av Torgeir Rønstad, 2004

77. D. Withdrawal and exclusion. A study of the spoken word as means of understanding schizophrenic patients.  
Av Geir Fagerjord Lorentz, 2005.

78. "Søkelys på safunnsmedisinene." Evaluering av kommunal samfunnsmedisinsk legetjeneste, offentlig legefag og de forebyggende oppgaver i Fastlegeordningen.  
Av Betty Pettersen og Roar Johnsen, 2005.

1. Prosjekt egenmelding Kristiansand kommune.  
Evaluering av kontrollert intervansforsøk i stor skala, med utvidet rett til egenmelding i kombinasjon med økt og formalisert samhandling mellom arbeidstaker og arbeidsplasen ved sykefravær.  

80. D. Abdominal aortic aneurysms: Diagnosis and epidemiology. The Tromsø study.  
Av Kulbir Singh, 2005.

Av Maria Averina, 2005.

82. D. Exposure to exogenous hormones in women: risk factors for breast cancer and molecular signature.  
Av Vanessa Dumeaux, 2005.

Av Stein Harald Johnsen, 2005.

84. D. Risk Factors For Fractures In Tromsø. The Tromsø Study.  

85. D. The quality and use of two health registries in Russia. The Arkhangelsk Cancer Registry and the Kola Birth Registry  
Качество и использование двух медицинских регистров в России. Архангельск регистр рака и Колский регистр родов  
Av Arild Vaktskjold, 2005.

86. D. Haemoglobin, anemia and haematological malignancies.  
87. D. The sick-listed – an under-recognised resource in handling sickness absence.

De som er merket med D er doktorgradsarbeid.
De som er merket med * har vi dessverre ikke flere eksemplar av.