Interpretation of forearm bone mineral density

The Tromsø Study

by

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Contents:

1. List of papers

This thesis is based on the following papers, all of which are appended:

I. The Tromsø Study: Artifacts in forearm bone densitometry - Prevalence and effects. Berntsen GKR. Tollan A, Magnus JH, Søgaard AJ, Ringberg T, Fønnebø V. Osteoporosis International, 1999; vol. 10, issue 5. p. 425-437.

II. The Tromsø Study: Determinants of precision in bone densitometry. Berntsen GKR, Fønnebø V, Tollan A, Søgaard AJ, Joakimsen RM, Magnus JH. Journal of clinical epidemiology, In press 2000.

III. The Tromsø Study: A population-based study of forearm bone mineral density by age, in 7620 men and women. Berntsen GKR, Fønnebø V, Tollan A, Søgaard AJ, Magnus JH. Submitted

IV. The Tromsø Study: Prevalence of male and female osteoporosis in a general population Berntsen GKR, Fønnebø V, Søgaard AJ, Njølstad I, Tollan A, Magnus JH. Submitted.

The papers will be referred to by their roman numerals.

2. Introduction

2.1. TROST – TRomsø Osteoporosis STudy

With the highest incidence of hip [1,2], and forearm fractures in the world [3-6], and with evidence of an increasing age-adjusted fracture incidence in the region[7] Scandinavians need to understand the causes of these fractures better. The so-called fragility fractures, i.e. fractures of the hip, forearm or vertebrae due to trauma equivalent to, or less than the fall from standing hight[8], represent a considerable burden both to the individual and society[9].

The Tromsø Osteoporosis Study (TROST) was established in 1993 as a response to the growing awareness of the fragility fracture epidemic. 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.

2.2. Concepts of osteoporosis

Osteoporosis is defined as: "A disease characterised by low bone mass and micorarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk"[10]. This qualitative definition states that osteoporosis is a disease with three main signs: 1) Low bone mass, which refers to the content of bone mineral in the skeleton as measured at selected sites such as the hip, the spine or the forearm with bone densitometry. Bone mass, in this context, is a surrogate measure of bone strength. 2) Micro architectural deterioration of bone tissue refers to the destruction of the lattice network of trabeculae, which contributes considerably to bone strength in the bones that are especially prone to osteoporotic fractures. 3) The increased risk of fracture, which includes both the typical osteoporotic fractures and other fractures.

In the absence of fractures, osteoporosis does not cause pain, loss of function or any other kind of symptom. Fragility fractures, and especially hip-fractures, are however associated with considerable morbidity and mortality. The five years survival rate after hip fracture was about 80% of that expected for people of the same age without fractures[11]. Five-year survival probability decreases dramatically with increasing age at fracture, and is as low as 40% for women who sustained a hip-fracture at 80-84 years as compared to 95% survival probability

for non-fracture cases[12]. One year after a hip fracture, 40% are still not able to walk independently and 60% require assistance with an essential activity of daily life (dressing, bathing, cooking etc.)[9]. Although frail elderly are more prone to hip fracture, the increase in mortality and morbidity after hip-fracture can not be fully explained by the presence of comorbidity[13]. The hip-fracture related morbidity and mortality effects are difficult to prevent once fracture has occurred, which is why prevention of hip fractures is currently seen as the best way to avoid its effects. The five year survival after vertebral fractures was 80% of expected, but vertebral fractures are probably only markers of pre-existing co-morbidity in frail elderly subjects[11]. Incident vertebral fractures are associated with short-term (approximately three months) increases in days with back-pain, limited activity and bedrest[14]. Forearm fractures cause short-term morbidity, herald an increased risk for other osteoporotic fractures[15,16], but are not associated with increased mortality[11].

Thus, the dominating concepts in the field of osteoporosis are that osteoporotic fractures are important causes of morbidity and mortality and that the impact of fractures is best avoided by fracture prevention. Both the original osteoporosis definition and the terms used to designate the associated fractures, i.e. osteoporotic fragility, non-violent and a-traumatic fractures, bear witness of a concept of bone frailty as the early stage and main cause of the symptom of fractures. Riggs took this idea further and stated that "low bone mass is the sine qua non for the occurrence of osteoporosis", and introduced the concept of a fracture threshold, i.e. "a level of bone mass at which non-traumatic fracture begin to occur"[17]. The concept of osteoporosis being more or less equivalent to low bone mass was thus completed.

2.3. Measurement of bone mass - From SPA to DEXA

With this theoretical background, the field of osteoporosis has been largely pre-occupied with various ways of measuring bone mass and bone strength. With the advent of bone densitometry in the early 1960-ies[18] the stage was set for the first non-invasive measurements of bone strength, represented by bone mineral density (BMD). This allowed researchers to examine the relationship between bone strength and fractures in a quantitative manner, and to search for the fracture threshold.

Bone densitometry is a radiographic examination and the BMD result reflects the amount of radiation, which has been absorbed on its way through a defined anatomical site. The

absorption is basically equivalent to the amount of bone mineral present at that site. The first bone densitometers, the Single and Dual Photon Absorptiometric devices (SPA, DPA), used isotopes as their source of radiation. These had a relatively low spatial resolution, scans took a long time to complete (20 min) and the radionucleid source needed replacement from time to time. The advent of x-ray based densitometers in the 1980-ies, Single and Dual Energy X-ray Absorptiometry (SXA or DEXA/ DXA), represented several improvements. The intense, narrow beam of radiation contributed to shortened scan times, enhanced image resolution, improved precision and eliminated the need for source replacements[19].

The single x-ray densitometer sends a single energy beam through the limb and detects how much of the radiation is absorbed by the structures that lie between the x-ray source- and detection-unit. SXA can only be performed at peripheral sites, as the limb needs to be immersed in a water bath, which behaves like a standardised layer of soft tissue during the scan. With an integrated correction for fat mass, the computer is now able to use the x-ray absorption to calculate the amount of bone mineral present. Dual Energy densitometry (DPA and DEXA) can differentiate between soft and bony tissue, whereas the fat mass must still be estimated. This allows the water bath to be omitted and makes it possible for DEXA equipment to measure BMD also at axial and proximal sites such as the spine and the hip.

A two-dimensional grey-scale scan image resembling a radiograph of the forearm is generated on the basis of the absorption pattern. Each pixel represents the estimated bone mass at that particular anatomical point. The image is subsequently analysed by the computer, which identifies bone edges and the anatomical region-of-interest. The forearm regions-of-interest are at present not standardised, whereas all manufacturers define the hip regions-of-interest in the same way. The radiation doses to both the subject and the operator are negligible.

2.4. BMD, bone strength and fracture risk

The BMD measure has been shown to predict both bone strength in cadaver models and fracture risk. In two cadaver studies, where bones were loaded until they broke, the correlation between femoral neck BMD (g/cm^2) and breaking force (kN) was shown to be 0.79[20] and 0.80 between vertebral BMD (g/cm^2) and ultimate vertebral loading (N)[21]. An improved prediction of bone strength can be achieved when measures of bone geometry are added to the BMD-data[22].

Work published by a variety of authors, in many different populations, based on both retrospectively and prospectively collected data, has left no doubt that there is an inverse relationship between BMD and fracture risk. In a meta-analysis by Marshall et. al it was shown that for each standard deviation decrease in BMD, the fracture risk approximately doubled. It also showed that fractures at any location were best predicted by BMD measurements from the same anatomical site, but that no site was superior with respect to prediction of all types of fragility fractures[23] (see Table 1).

Table 1: Relative Risk for fracture pr. standard deviation decrease in age specific BMD, by measurement site and fracture site [23].

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

The relationship between BMD and fracture risk is consistent in predominantly Caucasian female populations across the world. The relative risk for women sustaining any fracture pr. SD decrease in femoral neck BMD was 2.4 in Australia[24], 1.5 in the American SOF study[25], 1.4 in Finland[26] and 1.3 in the Rochester study, USA[27]. The equivalent figures for a SD reduction of the female distal forearm BMD were 2.6[28,29], 1.7[30,31] and 1.1[27] in US-based studies, ranged from 1.5 to 2.7 in Sweden depending on fracture site[32] and was 1.4[33] in Australia. There are few studies on the BMD-fracture relationship in men. A one SD-decrease of hip BMD in men was associated with a two fold increase in risk for any fracture [24] in Australia and a three fold risk for hip-fractures[34] in the Netherlands. There is also a lack of data on the BMD-fracture relationship in non-Caucasian races and in young age groups.

2.5. Recommendations for use of BMD

There has been eagerness in the bone density community to make use of the BMD-test at the individual level, so that persons with an increased risk of fracture could be identified[35]. The

BMD measure was to constitute the basis of a new quantitative and more operational definition of osteoporosis, and a quest for the optimal BMD-threshold, which could identify the osteoporosis population, began. One of the first proposals of an osteoporosis threshold was given by Riggs, who suggested the 90th BMD-percentile for spine- and hip-fracture cases as the threshold[36]. This was, according to Riggs, more or less equivalent to the subsequent WHO-osteoporosis threshold[17]. The WHO-definition has since it was proposed in 1994, become widely accepted[17,37,38], and has later served as a template for two proposed male osteoporosis definitions[39,40].

Several reports have been issued by organisations and experts drawing up guidelines for the use of this new measure of bone strength in the individual and the population setting. With the exception of the National Osteoporosis Foundation (USA) which argues that all women aged >65 should have their BMD measured[41], none of these reports support mass screening programmes of BMD[37,42-45]. However all the reports recommend a case-finding strategy with BMD- measurement in high-risk subjects, often defined as women with one or more selected risk factors for osteoporosis.

Thus, when this thesis was being planned, the use of BMD in the individual setting was on the rise, as most authorities on the subject actively recommended it.

2.6. BMD in the clinical context

Taking the BMD-measure from the epidemiological setting into the individual clinical context is however no straight forward matter. Any epidemiological study is fraught with measurement errors and/ or misclassification of exposure and endpoint variables. As long as these errors are not systematic and the number of participants is large, this will not alter central estimates for groups. However, in the individual setting this is completely another matter. Here any measurement error may have important consequences for the individual. The BMD-patient would rightly expect the clinician to know how a BMD-scan should be evaluated with respect to quality and random measurement error. She would want to know if her BMD-result is normal for her age, and last but not least, she will want to know exactly what the measurement result means and what consequences it may have.

2.6.1. What does the BMD-result mean?

Despite widespread acceptance of BMD-thresholds to identify the osteoporosis population, no researcher has been able to identify a fracture threshold. On the contrary, there is a considerable bone mass overlap between fracture and non-fracture cases[37,43,44,46-48]. In other words, although low bone mass is undeniably linked to an increased fracture risk, bone mass alone cannot identify the future fracture case[44]. Low bone mass seems to be only a component cause, and not a sufficient cause for fracture. In this situation, any BMD-threshold will, depending on where the cut-off is set, inevitably include a proportion of subjects who have low bone mass but who will not experience fractures.

The WHO definition states that women with BMD-values that lie more than 2.5 standard deviations below the female young adult BMD-mean should be considered as osteoporotic. Patients who are diagnosed by this definition will want to know exactly what it means. Will the bones dissolve and crumble spontaneously? Will they sustain a fracture within the next year, or within the next 10-years? Will they suffer from pain? Will they die? Is this a common condition for women/men of their age? The health policy makers also want to know how many women and men are likely to be diagnosed as osteoporotic by these emerging definitions?

Even for the most widely acknowledged osteoporosis definition, the WHO-definition for Caucasian women, some of these questions currently have no answers. The WHO-osteoporosis patient can safely be assured that her bones will neither dissolve nor crumble spontaneously and she will not be in pain or die of osteoporosis unless she sustains a fracture and/ or complications in the course of fracture treatment. However, we found no prospective population-based data on fracture risk in subjects with the WHO-osteoporosis diagnosis.

How common the WHO osteoporosis diagnosis is in the general population, is also an open question. The two population-based studies of osteoporosis prevalence by the WHO-diagnosis, both come from the US. In the NHANES study, between 13-18% of all women aged 50 years or more had osteoporosis at the hip[39] whereas in the Rochester population 35% of all women in the same age group were osteoporotic at the forearm[49]. As both sites predict all osteoporotic fractures with the same strength, it is important that the causes of such a difference between measurement sites are understood[23]. The large prevalence difference raises

the question of whether the Rochester population was more osteoporotic than the NHANES population, or whether forearm osteoporosis is different than hip osteoporosis? The lacks of prevalence studies in other populations and at other sites leave these questions open.

Other osteoporosis definitions have been proposed for men, one by the NHANES study, which is essentially a duplicate of the female WHO definition, using a male reference population, and one by the UK-consensus group on male osteoporosis. The latter includes all men with a BMD-result less than one standard deviation below the age-group BMD mean or 2.5 standard deviations below the young male BMD-mean. The former NHANES definition was applied to both the NHANES and the Rochester populations, yielding osteoporosis prevalences of 19% at the distal forearm and 3-6% at the femoral neck, whereas the UK-consensus group on male osteoporosis's definition to our knowledge has not yet been applied to any population. The short-term fracture risk for these two male osteoporosis definitions is also presently unknown.

2.6.2. BMD-reference ranges

The osteoporosis prevalence dependens on the relative "height" of the young adult BMD mean compared to the rest of the popoulation, and the width standard deviations (SD). Differing prevalences are therefore the result of 1) differing BMD-development by age or 2) different osteoporosis thresholds due to differences in the standard deviations. Thus to understand prevalence differences it would be important to compare BMD by age developments between populations and standard deviations. Comparison of BMD level between populations is not of relevance for osteoporosis prevalence differences, but it would be of interest to determine whether differences in bone strength may explain differences in fracture incidence between populations. However this is currently difficult because of the current lack of standardisation of the BMD unit. BMD-results from densitometers of different brands are not comparable and may vary up to 18%[50-52], whereas results from densitometers of the same brand and type may vary up to 5%[52]. Unless some kind of cross calibration procedure has taken place, only BMD-results from the same densitometer are comparable. This lack of BMD-standardisation explains the use of relative, instead of absolute BMD thresholds, in all the above-mentioned osteoporosis definitions.

By introduction of a BMD golden standard unit, which every densitometer could be judged by, one could achieve comparability. Comparison of BMD-levels between studies, which up to now has been a closed area, would be made possible. However, the mass production of phantoms with standardised absorptiometric qualities has proven difficult. Recently the standardised European Spine and Forearm Phantoms (ESP and EFP) became commercially available[53,54], but the first validation studies on the European Spine Phantom's cross calibration properties were disappointing. The BMD-results for the European Spine Phantom from two different densitometers plotted against each other differed slightly from the plot made on the basis of human spine measurements from the same machines[51]. Humans have unequal distributions of fat-mass around the columna which may be difficult to mimic with a phantom, and which could affect BMD-results[19]. It may therefore be that an equivalent study cross-calibrating BMD-values for the femur or the forearm, where fat distribution is more homogenous, would yield better results. However, such validation studies have, to our knowledge, not yet been performed.

Understanding differences in osteoporosis prevalences must therefore rely on the comparison of BMD distribution by age and sex between populations. However, population-based studies on BMD-development by age, which cover both sexes and a wide range of age groups, are scarce. For both the hip[55-57] and the forearm[57-59] there are three large studies examining the BMD development by age respectively. However, with the exception of the NHANES study which present hip data for all adult age-groups, these studies present results for the middle aged and elderly populations only, thereby limiting the possibility to judge whether the BMD life curve differs between populations and between anatomical sites.

The current lack of BMD-standardisation also makes the question of reference values extremely difficult. On one hand, reference ranges ought to be unbiased and representative for the population at large. On the other hand, the lack of standardisation means that such representative reference values compiled on one densitometer cannot be used on other densitometers unless a cross-calibration procedure has taken place. In real life, the manufacturer have provided each densitometer with a set of reference values, but these are more often than not, far from population-based[60]. Secondarily, centres compile their own reference values, most often by including all subjects who happen to pass through their densitometer, excluding subjects with medication or diseases known to affect the BMD-value.

Thus, both selection biases and calibration differences may cause the same subject to be classified as osteoporotic in one setting, and normal in another.

To summarise, one set of unbiased BMD reference values, which include all adult age groups, have been compiled for the hip. For the forearm no such material, which includes all age groups, has yet been published, although studies of the middle-aged and elderly exist. Even though, these data sets give valuable information on BMD-development by age in the population at large, the lack of BMD-standardisation precludes their use as reference values in the clinical setting.

2.6.3. Is the BMD-result reliable?

Given that the centre compiles its own unbiased reference values and uses current guidelines with caution in their patient evaluations, the BMD-measure may still be very useful in the clinical setting, as long as the BMD-result it self is precise and accurate. All measurement procedures have potential sources of error, and even if every thing is done correctly, measurement variation occurs. Measurement variation which cannot be attributed to any particular cause and which does not change the result in any specific direction is called random measurement error. Errors that are caused by identifiable sources are called artifacts. The effect of the artifact on the BMD-result may be systematic or random. In the former case, the BMD-result is altered in a specific direction, whereas in the latter reproducibility is compromised.

Precision

Precision or reproducibility is the ability of a measurement method to yield the same result for the same individual under comparable circumstances. The importance of precision has long been acknowledged in bone densitometry[61,62] because the expected BMD-changes with time (approximately – 1% pr. year) often lie in the same range as the measurement error. Measures of precision quantifies the size of possible random measurement errors on the BMD-result, and may be expressed as the absolute difference between repeat measurements on the same individuals, or as the intra-individual variation given in standard deviations (SD). To relate these precision measures to the BMD-level, the absolute difference or the SD is often given as a proportion or a percentage of the individual's mean BMD. The latter unit (SD/ BMD mean)*100 is also known as the coefficient of variation or CV.

Judged by the number of studies published, precision for bone densitometry has been extensively studied. The BMD-variation found between two repeat measurements by the same operator on the same day with repositioning between scans (basic precision) as given by the CV is 2-3% for the femoral neck[63-66] and 1-2% for the spine[63,67]. For the forearm, the basic precision given in CVs ranged from 0.8 to 1.7% for the forearm[68-74] and for the calcaneus it ranged from 1.3 to 2.5%[75-77].

However, most of these studies included fifteen or fewer subjects[65,68-71,74,76,77], or they included no subjects aged over 65 years[64,65,68,70,71,73-77], thereby limiting both generalisability and the possibility to study whether subject characteristics, such as sex and age may influence precision in densitometry. Variation in measurement conditions[65,66] and the effect of age[64,66] on precision, were examined in only two studies respectively.

Thus, although the random error of BMD measurement has received much attention, there are still many aspects of precision that need further examination. Especially the precision in elderly subjects, knowledge on how precision is maximised, differences between SXA and DEXA technology with respect to precision and whether special groups have lower precision than others, remain unclear.

Artifacts in bone densitometry

Sources of error that influence the BMD-result may appear in connection with densitometer instability, scan acquisition or scan analysis.

Densitometer fluctuations

Fluctuations in densitometer performance may influence BMD-results, which is why manufacturers recommend monitoring of long-term performance by daily BMD phantom measurements. By identifying changes in the phantom BMD-average and/or -variability over time, it is possible to detect significant changes in densitometer accuracy and/ or precision[78]. Methods of detection range from simple visual inspection of phantom measurement results over time, to formal statistical testing of changes in average phantom BMC and BMD variability with time[78-80]. There is a general agreement that some such quality control measures on long-term performance are required. Judged by the above-mentioned studies, the

formal testing procedures are more sensitive to densitometer fluctuation, but visual inspection is also an adequate technique. Although these studies were performed for DEXA technology, we have no reason to believe that they do not apply to SXA technology also.

Scan acquisition procedures

When a BMD-measurement is performed, the subject is positioned in relation to the densitometer, and the x-ray beam moves in a systematic manner over the anatomical area in question so that the whole region-of-interest is scanned. Movements on the part of the subject, during the scan would lead to distortions of the scan image and lead to errors in measurement of the region-of interest area. Furthermore the moving area would be either omitted or scanned twice, depending on direction of the movement. However, we found no studies or recommendations on the subject of movement artifacts or any description of how movement artifacts might affect the BMD results at any site.

In limb measurements (hip, forearm etc.) rotation of the limb determines the projection of the bony parts on the two-dimensional image. In two scans with different projections, the size of the region-of-interest area would differ, yielding a higher BMD-result for the smaller of the two regions-of-interest. This effect has been documented for the hip[81-84], but we found no studies of positioning / rotation effects on forearm BMD measurements with either SXA or DEXA technology.

Also the size and composition of the area to be scanned may affect its absorptiometric properties. When the scan window was enlarged in a series of vertebral BMD-measurement, increased amounts of fatty tissue were included in the scan, which in turn lowered the BMD result[85] and Hansen et. al. found that inhomogeneous distribution of muscle and/ or fat over the spine had significant impact on spine BMD-results[63]. As the distribution of fat is quite homogenous at the forearm, there is no reason to believe that this is a major source of variability in forearm BMD-measurements, but the issue has so far not been explored.

Scan analysis – identification of region-of-interest

The computer identifies relevant anatomical landmarks and bone edges and suggests a region-of-interest demarcation. The operator should then confirm or alter the region-of-interest until it is in accordance with its definition. Small changes in the region-of-interest may alter the BMD significantly if the area, which is included or excluded, has much lower or higher BMD

than the rest of the region-of-interest. The NHANES study reported a reanalysis of approximately 1/3 of all scans by the quality control centre, but did not report in detail what elicited a reanalysis procedure[66]. We know that choice of vertebrae included in the spine region-of-interest is important, as BMD-results for individual vertebrae may vary up to 25% within the same subject[86]. For the spine, the size of the region-of-interest is of importance, with significant changes in the BMD-value when the amount of soft tissue in the region-of-interest was reduced[63]. Kiel found that two different versions of software produced changes in the region-of-interest identification, which compromised comparability of BMD-results from before and after the software upgrade[87]. At the hip, larger scan windows led the software to include larger portions of the femoral diaphysis in the region-of-interest, which in turn increased the BMD for the total hip[85].

Region-of-interest identification is specific for the differing sites (hip, spine and calcaneus) and in the case of the forearm, the region-of-interest definitions differ between manufacturers also. Therefore, the consistency of region-of-interest identification and the effects of any lack of consistency are aspects, which should be examined for all region-of-interest definitions. We found no studies of errors or variations in region-of-interest placement for the forearm with either DEXA or SXA technology.

2.7. Summary

Although the advocacy for the use of the BMD-measure in a clinical context has been strong, there are several pieces of information that are lacking before the BMD-measure can be taken confidently into every day use. Especially, the understanding of sources of errors in densitometry and how densitometry should be performed to avoid the errors and how errors should be handled if they occur, is still inadequately explored, especially for the forearm and the spine. Although precision with DEXA has been evaluated in a large number of studies, we still lack knowledge on how precision is maximised, which groups need special attention with respect to precision and what the precision is amongst the elderly. Standardised unbiased BMD reference values are still lacking, and the BMD by age pattern in the general population has been inadequately explored for all sites. Finally, there is still uncertainty about the interpretation of BMD-results, as we lack information on what implications the currently proposed osteoporosis definitions will have in a population setting and what fracture risk is linked to the osteoporosis diagnosis in the individual.

3. Aims for this thesis

The main goal was to provide the documentation on the qualities of a cheap and simple method of BMD measurement as a research and/ or clinical tool. This goal can be subdivided into the following tasks, each of which represents one of the enclosed papers:

I. Examine the occurrence and effect of artifacts in a large population-based BMD-scan material.

II. Increase the knowledge of precision with SXA-technology at the forearm and discover what factors might affect this precision.

III. Characterise the BMD-distribution according to age and sex in a general population and establish standardised population-based BMD-reference values for the forearm.

IV. Determine the impact of the currently suggested osteoporosis definitions for men and women in terms of osteoporosis prevalence.

4. Material and Methods

4.1. Setting - The Tromsø Study

The Tromsø study is a population-based multipurpose study, where certain birth cohorts living within the municipality of Tromsø have been invited to four consecutive health surveys (1974, 1979-80, 1985-86 and 1994-95), focusing mainly on cardiovascular and other chronic and lifestyle related diseases. In all these surveys, responders have completed one or two questionnaires, and have had a series of simple clinical measurements, blood- and urine tests performed.

4.2. Subjects

The fourth Tromsø Study health survey started in August 1994 and was concluded in September 1995. All subjects aged 25 years or more were invited to the main survey (Phase I), which covered simple clinical measurements and the completion of two questionnaires. In all 37 582 invitations to take part in the main survey (Phase I) were issued. During the one-year long study, the national register was updated three times with respect to deaths and migrations to and from Tromsø. Yet we received reports by various routes (relatives, post-office etc.) that 2139 of the invitees either died or moved from Tromsø before their scheduled Phase I examination. The eligible population for the main survey was therefore 35 443 subjects, and of these 27 159 (77%) attended the Phase I examination.

A subset was also invited to an extended examination (Phase II) comprising among other things, a TROST examination (see below) which included forearm bone densitometry. All men and women aged 55-74 years and 5-10 % samples in the remaining age groups between 25 and 85 years of age were pre-selected to receive such an invitation. TROST in addition had extra examination capacity, which enabled us to invite all women aged 50-54 years not already included in the 5-10% selections, to the TROST examinations alone. The catchment population of TROST thus included 10 533 pre-selected subjects. 320 subjects had however either died or moved from Tromsø, leaving 10 213 eligible subjects. Of these 9062 subjects attended the main survey (Phase I) and there received their invitation to TROST. 1114 subjects declined to participate which left 7948 subjects (78% of eligible) who were finally included in the TROST study.

The 5-10% selections invited to TROST were composed in the following manner: 1) An original 5% random selection of every 5-year age and sex group younger than 55 years or between 74 and 84 years of age. 2) All male participants of the Family Intervention Study aged less than 55 years (see below). 3) To increase the number of participants in the 40-54 year age group, additional invitations to Phase II were issued to a random selection of men and women in these age groups during spring 1995. For the same reasons, the TROST study also invited an additional random sample of 164 young women, aged 25-35 years, to the TROST examinations alone.

All male participants of the Family Intervention Study (FIS) aged less than 55 years, were invited to the extended examination (Phase II), and constituted up to 70% of certain of 5-year male age strata. 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. The intervention consisted of lifestyle and nutritional advice directed at the index case, his spouse and children[88]. As associations between increased cardiovascular risk and BMD may exist[89], FIS participants were not viewed as representative of the general population with respect to BMD. FIS participants should be neither over- nor under-represented in the final selections, which is why a 5% random selection of the FIS-study participants was included in the TROST study population. "Surplus" FIS participants were excluded from analyses presented as representative of the general population.

There is a discrepancy between the Phase II response rate given above (78%) and that given in paper I (80%). The response analyses made for the first paper were preliminary, and a number of data-set adjustments were performed after paper I had been published. These changes had no impact on the conclusions drawn in paper I, which is why we decided not to publish an erratum on this issue.

4.2.1. The precision sub-studies.

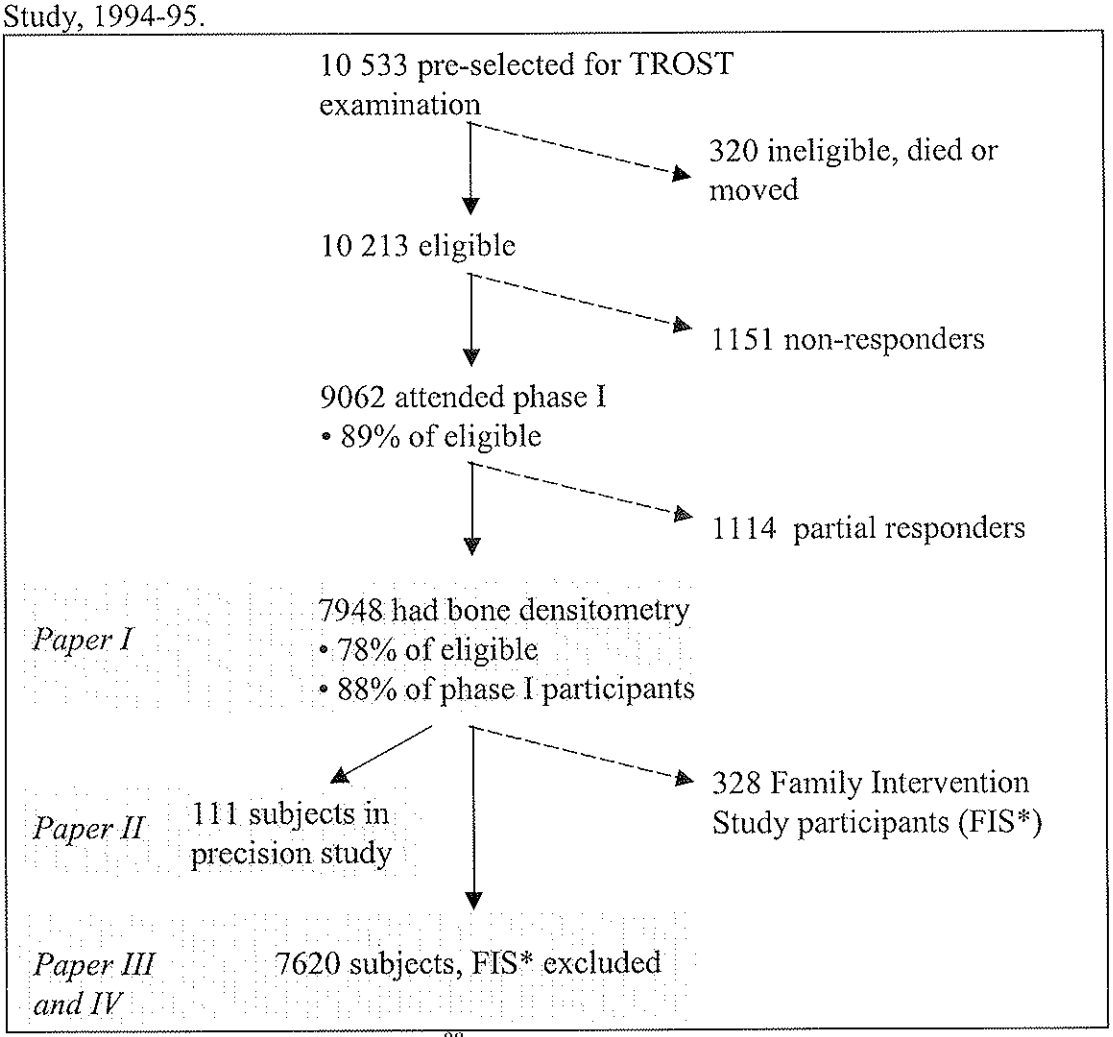
The Tromsø survey performed two precision sub-studies, where the subjects would be measured repeatedly on two different occasions one and three weeks apart respectively. The first survey was performed during autumn 1994, the second during spring 1995. During two short time periods prior to the execution of the precision sub-studies, we intended to

consecutively ask all potential Phase II participants to participate in the precision studies. However, as the precision study included repeated examinations at all five Phase II stations, a full examination took approximately three hours. Subjects who "looked frail" were therefore not asked to participate. Subjects, who declined to participate, were offered an ordinary phase II examination. No record was made of such declinations. In all 111 subjects took part in the two precision sub-studies.

4.2.2. Study populations in each paper:

An overview of the flow of subjects from the entire eligible source population to the separate study populations used in each paper, with the appropriate response rates is given in **Figure 1**.

Figure 1: Flowchart - Inclusion of subjects in the Tromsø Osteoporosis Study (TROST). From the pre-selected TROST study population to the final study population. The Tromsø Study, 1994-95.



*FIS – Family Intervention Study [88]. *Non-responders* attended neither first nor second examination, *partial responders* attended only the first examination.

Paper I: The whole TROST study population (n=7948) was included in the study of artifact prevalence and effects, as we had no reason to believe that FIS-study participants would behave differently than other subjects with respect to artifacts.

Paper II: All precision study participants. FIS subjects were not excluded, as we had no reason to believe that precision among these subjects would differ from that of the general population.

Paper III: The whole TROST study population, with the exclusion of 328 Family intervention study men, which leaves 7620 subjects for analysis. In all 136 distal and 150 ultradistal scans were also excluded due to low quality of the BMD-scan, leaving 7484 distal and 7470 ultradistal scans for analysis.

Paper IV: Identical with paper III.

4.3. Methods

Two information leaflets were provided together with the study invitations to both the main and extended examinations. Participants confirmed that they had understood the nature and objectives of the study by signing a declaration of consent, prior to both the Phase I and II examinations (appendix A). The Regional Committee of Research Ethics and the Norwegian Data Inspectorate approved the study.

A questionnaire accompanied the invitation to the clinical Phase I examination (appendix B). At Phase I, the subjects' blood pressure, heart rate, height and weight were measured, one lead ECG was taken and blood samples were drawn. Every Phase I participant was given a second questionnaire before leaving, and was requested to return it by mail (Appendix C, D).

Phase II consisted of in all five different examination rooms or stations, which each participant should visit. A full Phase II examination could be completed in the course of approximately one hour. The four first stations included a check of the questionnaire information, registration of current medication, measurement of standing and sitting blood pressure, a twelve lead ECG, hip-waist ratio and ultrasound of the internal carotid artery and the abdominal aorta and an approximately 50% random selection of the participants had echocardiography. The TROST examination was at the last and fifth station and included forearm bone mineral density of non-dominant forearm, grip-strength, sub-cutaneous fat

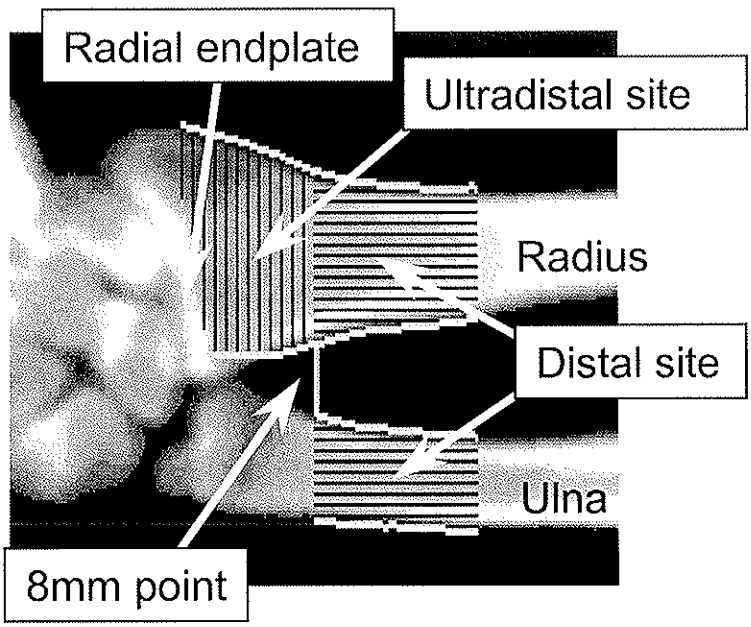
measurements by ultra-red light and blood sampling on all subjects. For subjects aged 70 or more years a balance and a co-ordination test were also administered.

4.3.1. Forearm bone densitometry

Forearm bone densitometry was performed with a device called DTX-100 (Osteometer, Denmark), which uses a single energy x-ray beam (29KeV). The non-dominant forearm was ineligible due to wounds, plaster casts etc. in 1% of the subjects, in which case we measured the dominant arm. During BMD-measurements, the subject held a vertical pole in the densitometer's water basin throughout the scan, which standardised the forearm position, and limited the possibility of rotation and movements. Scan time was approximately five minutes. The importance of non-motion during scan acquisition was stressed, but if movements did occur during a scan, the operator would repeat the scan once or twice if necessary. In September and October 1994, the Quality Control programme disclosed that the instructions to repeat scans on the detection of movement artifacts (see later) were too loose. These guidelines were therefore tightened.

The region-of-interest was automatically identified by the computer as shown in Figure 2. The 8mm point identifies the transition zone between two different segments of the radius.

Figure 2: Normal bone mineral density (BMD) scan image. The hatched areas delineate the two regions-of-interest: the distal and ultradistal sites.



The ultradistal wide part of the radius contains 50-70% trabecular tissue[90]. Whilst the narrower distal site contains only 10-20% trabecular bone. The operators performed manual region-of-interest identification when the automatic routine failed, when the bone edges were wrongly identified, or when the 8mm point was wrongly positioned. The operators were not instructed to evaluate the identification of the radial endplate.

4.3.2. Quality control

All operators took part in a course, which included lectures on the purpose of the BMD-screening, the nature and epidemiology of osteoporosis, BMD-measurements in general, and the specific densitometers to be used in our study. This was followed by supervised sessions where the technicians practised BMD-measurement on each other and on 10 elderly ladies who had agreed to be «pilot-subjects». To counteract boredom with routine duties, the 15 technicians circulated between stations, with a change of duties every two weeks. In order to make up for the frequent changes among the operators, I myself and/ or our principal BMD technician, who did not participate in the circulation scheme, were always present at the TROST-station. We gave advice, supervision and regularly controlled the most recent scans. In addition, posters and booklets containing the densitometry instructions were provided for all technicians.

4.3.3. Long term stability

We adhered to the recommendations of the manufacturer, which consisted of twice daily measurements of an aluminium wedge phantom. Mean BMC phantom results were stable at the same level (3.533g and 3.534g) in both densitometers. The phantom coefficients of variation were also stable at 0.76% and 0.77% until the end of the study on the two densitometers respectively. Phantom results that were outside the ± 1.5% limits of the phantom BMD value should elicit a repeat phantom measurement, and if the second phantom result also was beyond these limits, the manufacturers service department should be contacted. This happened on one occasion (aug-95) when a calibration procedure was executed. Otherwise densitometer performance was stable. Our software did not support data-export of phantom results, which made it difficult to perform formal analyses of densitometer stability as recommended by Lu et al.[80]. The in vivo precision as measured in the precision sub-studies did not change significantly from September 1994 to May 1995.

4.3.4. Precision data

We wanted to investigate the effects of operator change, time between measurements and change of densitometers. The design was as follows: First study, September 1994: At each visit, the first observer (A) performed two scans immediately after one another, thereafter the second observer (B) did a third and, if time permitted, a fourth scan. Repositioning occurred concurrently with observer change. The same pair of observers repeated the same procedure at the second visit, exactly one week later. Second study, May 1995: At each visit observer A performed a scan on one densitometer, thereafter observer B performed a repeat scan on the second densitometer. The same procedure with the same pair of observers was repeated exactly three weeks later.

4.3.5. Scan review

As the Tromsø survey was in progress, we noted that some BMD scans deviated from the ideal as depicted by the manufacturer. We therefore undertook a pilot study, reviewing a random 5% sample of all scans. During this process we developed a classification system for the artifacts observed and re-analysed scans when considered necessary. The ultradistal site is supposed to reflect BMD of a predominantly trabecular site, which is why additional cortical bone should not be included in the region of interest. In the pilot study, 50% of the scans included parts of the radial endplate and a 5% or larger BMD decline was registered in 17% of the reanalysed scans.

As a result of this pilot study, all scans were reviewed by one of three observers. They assessed quality of the scan image, region-of- interest identification and recorded any artifacts present. The observers A and B reviewed 2000 scans of the first 4000 scans each, while observer C reviewed the last 4000 scans alone.

The artifacts were divided in two main categories:

- Image artifacts: Irregularities in the scan image. Subgroups were created according to the cause of the artifact such as movements (movement artifacts) or main structures missing from the scan (Miss artifacts). Movement artifacts were graded as small (grade I), intermediate (grade II) or serious (grade III) according to the anatomical distortion in the BMD scan. The grade III movement artifacts conferred an anatomical distortion, which

compromised identification of anatomical landmarks, and these scans were therefore subsequently excluded from the study material.

- Region-of-interest artifacts: Irregularities in the region-of-interest identification. Subgroups were defined according to the structure that was erroneously identified: i.e. the radial endplate (radial endplate artifact), the bone edges (bone edge artifact) etc. If possible, region-of-interest artifacts were corrected through reanalysis.

To ensure as high a concordance as possible between the reviewers, they performed joint evaluations on parts of the material twice weekly, and discussed difficult cases when appropriate.

Before review the BMD-value was un-calculated in 39 scans and remained so in ten (distal site) and five (ultra-distal site) scans after review. Serious movement artifacts (grade III), region-of-interest outside scan, metallic objects in the region-of-interest or bad quality by other causes led 136 distal and 150 ultradistal scans to be excluded, leaving 7484 distal and 7470 ultradistal scans for analysis. Grade I and II movement artifacts were not excluded, as the anatomical landmarks were sufficiently maintained in these scans to allow analysis, and there was no systematic BMD-deviation introduced by the artifact (paper I).

Reproducibility of scan classification

A 10% random sample of the total material (784 subjects) was selected to be re-reviewed in order to generate reproducibility data on artifact classification. The three observers each reviewed sub-samples previously reviewed by them-selves and sub-samples reviewed by the other two reviewers. The intra- and inter-observer data were generated in parallel with the ordinary scan review.

Agreement on artifact classification was quantified by the kappa statistic at both distal and ultradistal sites for the following questions: Artifact present? Movement artifact present? and Radial endplate artifact present? By the standards presented by Altman[91], all the kappa-values for intra-observer agreement and the distal site inter-observer agreement were either intermediate or good, but at the ultradistal site, observer A differed from both observer B and C, in the judgement of radial endplate artifacts (see Table 2). This is also reflected in the prevalence of radial endplate artifacts by observer, which was 58%, 74% and 80% for

observers A, B and C respectively ($p<0.0001$). The prevalence of movement artifacts did not differ by observer.

Table 2: Reproducibility of scan artifact classification of forearm bone mineral density scans. Kappa values with 95% confidence intervals (CI) of intra- and inter-observer agreement of selected classification units by intra and inter observer pair. The Tromsø Study, 1994-95.

		Distal site		**Ultradistal site**		
	N	OK/ Not OK (95% CI)	Mov Art (95% CI)	OK/ Not OK (95% CI)	Mov Art (95% CI)	Rad EP Art (95% CI)
Intra-observer						
A - A	139	**0.69** (0.52 - 0.85)	**0.70** (0.52 - 0.87)	**0.72** (0.60 - 0.85)	**0.61** (0.38 - 0.84)	**0.72** (0.61 - 0.84)
B - B	142	**0.69** (0.54 - 0.83)	**0.77** (0.64 - 0.91)	**0.61** (0.43 - 0.79)	**0.76** (0.59 - 0.93)	**0.60** (0.45 - 0.74)
C - C	168	**0.85** (0.72 - 0.98)	**0.88** (0.76 - 1.00)	**0.73** (0.57 - 0.89)	**0.87** (0.69 - 1.05)	**0.74** (0.61 - 0.88)
Inter-observer						
A - B	241	**0.71** (0.59 - 0.83)	**0.71** (0.57 - 0.84)	**0.36** (0.25 - 0.47)	**0.80** (0.68 - 0.93)	**0.35** (0.24 - 0.46)
A - C	39	**0.69** (0.36 - 1.01)	**0.69** (0.36 - 1.01)	**0.07** (-0.22 - 0.35)	**0.19** (-0.21 - 0.58)	**0.11** (-0.18 - 0.39)
B - C	55	**0.52** (0.24 - 0.80)	**0.52** (0.20 - 0.84)	**0.71** (0.46 - 0.95)	**1.00** (1.00 - 1.00)	**0.73** (0.52 - 0.93)

Abbreviations: OK-No artifacts in scan, Mov Art – Movment artifact, Rad EP Art – Radial Endplate artifact.

The A-C pair's evaluation of the ultradistal site (Kappa range 0.07 - 0.19) had especially poor agreement. Therefore observer B reviewed this particular sample in 1997 (see Table 3). This revealed that there was a low prevalence of artifacts in this particular sub-sample. This partly explains the Kappa result, which tends to be low when one category in a classification is rare[91]. A and C actually agreed in 64% - 95% of the cases. It also confirmed the systematic tendency for observer A to be more restrictive in the use of the artifact "diagnosis" than observer C.

Table 3: Reproducibility of scan artifact classification. Re-review of the same 39 scans as evaluated in the interobserver B - C test of Table 2, by observer B in 1997. The Tromsø Study, 1994-95.

		Distal site		Ultradistal site		
	N	OK/ Not OK (95% CI)	Mov Art (95% CI)	OK/ Not OK (95% CI)	Mov Art (95% CI)	Rad EP Art (95% CI)
Inter-observer A - C (1995)	39	**0.69** (0.36 - 1.01)	**0.69** (0.36 -1.01)	**0.07** (-0.22 - 0.35)	**0.19** (-0.21 - 0.58)	**0.11** (-0.18 - 0.39)
Inter-observer B-C (1997)	39	**0.69** (0.36 - 1.01)	**0.69** (0.36 - 1.01)	**0.21** (-0.10 - 0.52)	**0.19** (-0.21 - 0.58)	**0.33** (0.05 - 0.60)
Inter-observer A – B (1997)	39	**1.00** (1.00 - 1.00)	**1.00** (1.00 - 1.00)	**0.40** (0.09 - 0.71)	**0.47** (-0.15 - 1.09)	**0.51** (0.23 - 0.79)

Abbreviations: *OK*: No artifacts in scan, *Mov Art*: Movement artifact, *Rad EP Art*: Radial Endplate artifact.

4.3.6. BMD adjustments

The forearm BMD was meant to serve as a surrogate measure of systemic bone strength. We have therefore tried to eliminate the influence of 1) factors that would lead to incorrect ranking with respect to systemic bone strength and 2) non-biologic factors, which are unrelated to bone strength (i.e. systematic differences between densitometers).

Previous fractures in forearm

Distal forearm fracture is associated with BMD-increase at the ultradistal site[92], low BMD at other sites[16,93] and increased risk for fractures[94,95]. Therefore ultradistal BMD in 637 subjects, who reported a distal forearm fracture in the measured hand, was corrected according to the results from a sub-study of fracture and non-fracture cases.

Fracture sub-study

We included 52 fracture cases and 115 age- (same birth year) and sex-matched controls in this sub-study. In order to facilitate the matching procedures, only right-handed subjects were included in the study. Analyses on the effect of handedness on BMD in the 115 controls showed that dominant forearm BMD was 0.004 g/cm^2 ($p=0.032$, paired one sample t-test) and 0.009 g/cm^2 ($p< 0.0001$) higher at the dominant side, for distal and ultradistal sites respectively.

After validation of the fractures by linkage to the medical record, the study included 16 dominant fracture cases linked to 36 controls and 21 non-dominant fracture cases linked to 46 controls. Analyses were stratified by fracture side (dominant / non-dominant side), and matching was retained throughout all analyses. The mean BMD-difference between the dominant and non-dominant hand in controls was compared with the same BMD-difference in fracture cases, by a one-sample paired t-test.

The dominant fractures cases had an ultradistal BMD-difference between the dominant and non-dominant hand of 0.044 g/cm^2, whereas in the controls the difference between hands was only 0.006 g/cm^2 (p=0.0098). In non-dominant fracture cases, the BMD was 0.027 g/cm^2 higher at the non-dominant as compared to the dominant side, whereas the controls had 0.012 g/cm^2 lower BMD at the non-dominant side (p<0001). The BMD-hand difference was not significantly different between cases and controls at the distal site. The average ultradistal BMD increase ascribed to the fracture, (i.e. fracture effect minus effect of hand dominance) was 0.038 g/cm^2 for cases with dominant fracture and 0.039 g/cm^2 for cases with non-dominant fracture. This increase did not depend on sex, time since fracture or BMD-level.

As a consequence of the above-mentioned results, all subjects in the main study population who had reported a distal forearm fracture in the measured arm had their ultradistal BMD-values adjusted down by 0.0039 g/cm^2 or 0.038 g/cm^2, depending on whether dominant or non-dominant hand had been measured.

4.3.7. Standardisation of BMD-values

The European Forearm Phantom (EFP) (QRM-Germany) has recently become commercially available. It has three hydroxyapatite bone imitations (inserts) with differing densities. We performed 20 measurements of each insert on both densitometers and used regression analysis to model the best fitting equation between the given and observed BMD-values[53]. We tested both a linear and a quadratic term in the model. Both terms were significant, but as the R-squared values for the models were similar (R^2 linear model: 0.990, R^2 quadratic model: 0.991) we adhered to the simpler linear model:

- *BMD-EFP = -0.024+1.054 * BMD-observed.*

BMD values were then re-calculated into the new BMD-EFP unit, by use of the above-mentioned formula. Because the EFP-unit is still not universally accepted, we have chosen to present only the BMD-reference data in the new standardised unit. All other results are presented in the original BMD-scale.

Inter-densitometer differences:

There was a systematic BMD-difference between the two densitometers (paper II). To bring the results from the two densitometers to the same scale, BMD values from one densitometer was recalculated to the scale of the other. The BMD-difference increased with BMD-level at both the distal and ultradistal sites. We therefore thought it most correct to use the regression equation model, which would correct the BMD-difference relative to the BMD-value. Both a linear and quadratic model was tested, but the quadratic component was not significant, so we adhered to the following linear equations:

- Distal site: BMD-A =-0.000075+0.980*BMD-B
- Ultradistal site: BMD-A=0.0023+0.965*BMD-B.

The BMD differences found between the two different densitometers in the full data set (n=7948, Distal site: $p=0.0055$, ultradistal site $p < 0.0001$), disappeared after adjustment (Distal: $p= 0.38$, ultradistal: $p= 0.37$).

4.3.8. Other variables

Menopausal status

As we had no access to estradiol, follicular stimulating hormone (FSH) or luteinizing hormone (LH), menopausal status was defined by questionnaire data. The answers to the following questions from the second questionnaire were used (Appendix C,D):

MENSTRUATION	
If you no longer menstruate, how old were you when you stopped having menstruation?	_____ years
If you still menstruate or are pregnant: What date did your last menstruation begin?	day/month/year___ / ___ / ___

Women, who had stopped menstruating over a year ago or were ≥ 55 years, were defined as post-menopausal (n=3631). Women who had stopped menstruating within the last year were

considered peri-menopausal (n=76). Information on cause of menopause (natural or surgical) was not available. Pregnant women and women who were still menstruating and reported a menstruation within the last six months were classified as pre-menopausal (n=647). Menopausal status was left undefined in 204 women due to missing or conflicting values.

Use of hormone replacement therapy (HRT) was determined by the answer to the following question from the second questionnaire:

Do you, or have you ever, used:	Now	Used to	Never:
Oestrogen (tablets or patches)	☐	☐	☐

However, 23% of all women who had answered other questions on reproductive issues had left the HRT question open, but women with missing values on the HRT question were never-the less included in the final analyses. Current and previous HRT-users and women with undefined menopausal status were excluded from all BMD-analyses by menopausal status and by years since menopause.

Medication

The use of certain types of medication, such as hormone replacement therapy, contraceptive pills, vitamin pills, corticosteroid therapy, calcium supplementation, insulin and thyroxin therapy was self-reported by questionnaire. At the extended examination, subjects were also asked to bring along a leaflet specifying their current medication, but only 41% of the participants in phase II actually did so. No validation with respect to the completeness of the medication register was ever performed. Therefore the latter medication registry was only used to supplement the information given by questionnaire.

The "normal" population

By defining a "normal" population, our main goal was to exclude all subjects with diseases and/or medication known to affect BMD. Questionnaire data on diseases and medication were used without any attempt of data validation. This applies to the following disease categories: self-reported gastric surgery, non-insulin dependent diabetes, osteoarthritis, cancer of any form, osteoporosis, and also applies to all medication categories. As a marker of possible renal osteodystrophy we used serum creatinine, which rises above the reference values when at least

50% of renal function has been lost. Similarly a total calcium result above 2.6 mmol/l was regarded as a marker of possible hyper parathyroidism.

4.4. Data management and statistics

With the exception of a few points regarding paper II, the data management and statistical methods used are fully presented in the respective papers.

In paper II we present data on precision for varying measurement situations. In our precision dataset each subject had up to three pairs of available scans that were representative for the measurement situations in question. It is generally acknowledged that any analysis should involve as much of the available data as possible, yet we decided to utilise only the first pair of available scans in our overall analyses of precision.

The advantages of using only the first pair of scans were that the design would be balanced, i.e. every individual contributed only one precision-result to the overall analyses. Thus the 95%-tile would exemplify the range of reproducibility found when two consecutive scans from the same individual are compared. Had we used all available scan-pairs, some subjects would have contributed three pairs, others only one to the individual mean estimate, which was entered into the overall analyses. This would have brought uncertainty of precision estimates down, as each individual precision estimate would be more precise. The 5-95%-tile intervals would thus become tighter, while the central precision estimates would not change appreciably. The 5-95%-tile range could however no longer be used to exemplify the intra-individual BMD-variation found in a given clinical context, because the unbalanced design would not reflect any specific clinical situation. We therefore decided to use only the first available scan pair in overall analyses, so that these results would resemble a possible clinical setting of two consecutive measurements. For the examination of the subject characteristic's effect on precision, we decided to retain all available scan pairs in the analysis in order to gain statistical power.

5. Main results

5.1. Artifacts in forearm bone densitometry - Prevalence and effects

We found that artifacts were common in forearm BMD-scans when scans are obtained with SXA-technology. Artifacts could be sub-classified as either faults in the scan image itself (Image artifacts), or as errors of the analysis of the scan image (Region-of-interest artifacts). The former artifact could not be corrected by any post-scan procedure and should elicit a repeat scan (incorrigible). The latter problem could be eliminated by an operator-guided re-analysis of the scan, aimed at improving the identification of the Region of interest, and was correctable.

At the distal site 15.2% of the scans (n=1213) had one or more artifacts. Reanalysis corrected artifacts in 2.3% thereby leaving 12.9% of the scans with an incorrigible artifact. At the ultradistal site 6539 scans (82.3%) were artifactual, but 76.9% were fully corrected by reanalysis leaving 5.4% of the scans with an incorrigible artifact. Movement by the subjects was the most common cause of image artifacts: 12.6% (distal site) and 4.6% (ultradistal site), The effect of movement artifacts was to decrease reproducibility. The BMD difference between two normal scans was 0.58% of the BMD-level at the distal site, whereas between two scans where one has a movement artifact, the equivalent figure was 0.94% ($p=0.0027$). A computer error caused the large majority of correctable artifacts; an inaccurate identification of the radial endplate, which was present in 72%. This artifact falsely increased the BMD-result. A correction of the region-of-interest led to a mean 3.8% decrease in the BMD-value. Among those who had an inaccurately identified radial endplate the correction led to a 10% increase in the number of subjects defined as osteoporotic by the WHO definition using pre-menopausal BMD mean ($p<0.0001$).

5.2. Determinants of precision in bone densitometry

We wanted to determine whether parts of the measurement process could affect precision and whether subject characteristics, such as age, sex and BMD-level, might influence precision in BMD-measurements.

We found that the individual precision estimates had skewed distributions, which is why results are given in percentiles. Median individual coefficients of variation (CV) for two scans performed one week apart, by two different operators were 0.79% and 0.98% at distal and ultradistal sites respectively, and their concomitant 95% percentiles were 2.2% (distal) and 3.4% (ultradistal). Repositioning was an important determinant of precision, as there was a decrease in reproducibility after repositioning was performed. Neither change of observer nor increased time between measurements seemed to affect precision. Increasing age (p=0.0097) was associated with a decrease in precision, whereas BMD-level and sex was not. The SXA BMD-measurement method was sufficiently precise to establish BMD-level by a single BMD-measurement. The minimal individual percentage BMD-change that can be detected between two single measurements with 95% certainty was 2% and 3% at distal and ultradistal sites respectively. Detection of BMD-changes less than this should rely on multiple repeat measurements at each point in time.

5.3. A population-based study of forearm bone mineral density by age, in 7620 men and women

In this cross sectional study, forearm BMD declined slowly by age (-0.1 percent annually) in both sexes up to 50 years of age. At approximately 50 years of age, the annual BMD-decline increased to -0.6 % (both sites) in men and –1.3 % (distal site) and –1.5 % (ultradistal site) in women. Male BMD-decline was stable throughout senescence, but in women the BMD-decline by age decreased at around 65 years of age to an annual change of –0.7% (distal) and –0.8% (ultradistal). In the late-post-menopause, the BMD decline pr year since menopause seemed to abate, whereas the BMD-decline associated with age was stable throughout senescence also for women.

"Normal" subjects without disease or medication known to affect bone health (n=5179) did not differ from the study population at large with respect to BMD-levels or BMD-distribution with age. The interpretation of change by age in cross-sectional data should be performed with caution, which is why these data should be validated by longitudinal studies.

5.4. Prevalence of male and female osteoporosis in a general population

The objective was to determine the prevalence of female and male osteoporosis in a general population. All currently suggested osteoporosis definitions re-calculate the BMD-value into

number of standard deviations below or above the BMD-mean of a specified reference population. The following osteoporosis definitions were used:

- WHO1: a BMD-result less than 2.5 standard deviations below the *young adult female peak*
- WHO2: a BMD-result less than 2.5 standard deviations below the *pre-menopausal BMD* mean.
- AGE-SPECIFIC: a BMD value less than 1 SD below the age- and sex-specific BMD-mean.
- NHANES: a male version of the WHO definition, i.e. a BMD-value less than 2.5 SD below young adult male BMD.
- UK consensus group on male osteoporosis: a BMD value less than 1 SD below the age- specific male BMD mean or less than 2.5 SD below the young adult male BMD mean.

In all 16%-32% of all women aged 50 years or more were defined as osteoporotic, depending on osteoporosis definition and forearm site. WHO prevalences were higher when the young adult mean was defined as the peak- rather than the pre-menopausal- BMD, and higher at the distal site as compared to the ultradistal site. Of all women aged ≥ 70 years, only 10% had normal BMD according to either of the WHO definitions.

In men, between 1-20% of all men, aged ≥ 50 were defined as osteoporotic again depending on site and definition. The definition that was proposed by the UK-consensus group on male-osteoporosis yielded the highest prevalences. The distal site prevalences were higher than ultradistal prevalences also in men.

Exclusion of subjects with diseases and/ or medication known to affect BMD from the young adult reference populations, did not alter prevalence estimates significantly, but their exclusion from the age- and sex- specific reference groups resulted in a small increase in the AGE-SPECIFIC prevalences for subjects aged over 50 years.

6. Discussion

6.1. Study design

6.1.1. Main study

TROST discussed two possible settings which might fulfil the goals of the study: Either to create a separate survey focused on osteoporosis, in which case we would be free to collect the data we thought appropriate for our research purposes, or to join the fourth survey of the Tromsø Study. We found that the advantages of joining the Tromsø Study outweighed the arguments of a separate osteoporosis survey.

By joining the fourth health survey conducted by the Tromsø Study, we would enjoy high response rates, as the public was well acquainted with, and had previously been faithful to the Tromsø Study. We would also gain access to previously collected data, thereby making prospective studies with BMD as an outcome variable possible already at the conclusion of the fourth health survey. Finally, collaboration with other groups of researchers would hopefully foster a more efficient use of human and economic resources in data collection, and prevent the Tromsø population from becoming exhausted by repeated health surveys by different research groups.

Some decisions made by the Tromsø study were however not optimal for the fulfilment of the osteoporosis study goals. The selection of Phase II subjects should ensure representative data for the adult age-groups of both sexes, and include subjects who had increased probability of becoming either cardiovascular and/ or fracture cases in future follow-up studies. TROST was however, interested in determining the reference ranges for BMD and the prevalence of osteoporosis in the entire adult population, and would have wished to examine larger groups of both young and elderly subjects than was possible to accommodate within the Tromsø study. Furthermore, the osteoporosis study was meant to be a baseline investigation into the causes of osteoporotic fractures. The mean age for female hip fracture patients is 79 years[96]. Had we included larger proportions of the elderly population, the time before follow-up studies could be launched would be shorter.

Osteoporosis examinations

As TROST's measure of bone strength, we chose bone densitometry of the non-dominant forearm with SXA. Forearm BMD measurements predict any fracture in women as well as other measurement sites[23] and may even have a stronger association to male fragility fractures[49]. Measurement of the forearm is easy and readily standardised, multiple measurements in order to enhance precision are feasible and peripheral densitometers are cheaper than Dual Energy X-ray Absorptiometry (DEXA) measurements at axial sites. Single X-ray Absorptiometry (SXA) of the forearm may be a good candidate for any screening based wholly or partly on BMD[97,98], which is why BMD- measurement at the forearm was a good substitute for spine or hip measurements. Undressing, positioning and performance of a hip or spine scan by DEXA took approximately 20 min in 1994, which could not be fitted in together with the other TROST examinations, within our 20-min. time limit.

It was clear, already when this study was planned, that weight bearing and physical activity exert their effects primarily on the bones that are exposed[99,100]. We wanted our BMD-measure to represent systemic bone strength, which was why we chose the non-dominant forearm. This site would be as "clean" of local effects, such as weight bearing and physical activity, as possible. However, physical activity and weight bearing, although acting locally, exert their effects on large parts of the skeleton, and thus contribute to bone strength at important weight bearing sites. Therefore, BMD at sites that are more exposed to either weight bearing and/ or physical activity, such as the calcaneus or the dominant forearm, would probably represent bone strength at weight bearing sites like the hip and spine better than the forearm. By choosing the forearm, our possibilities to study the effects of physical activity and/ or the interactions of physical activity with other variables, may be limited. On the other hand, it may be that the non-dominant forearm BMD will correlate better with systemic determinants of bone mass, than BMD at weight bearing sites. We therefore have a possibility to study such factors without the interference of physical activity and weight bearing.

6.1.2. Precision study

It turned out, during the analyses of the precision data that the effect of repositioning on precision seemed to outweigh those of the other measurement changes. However, as we had not anticipated this, we lacked a study design that could test this hypothesis. Our precision study would have benefited from the inclusion of a set of scans first without repositioning and

thereafter with repositioning between scans, all performed by the same observer. This would have allowed us to examine the effect of repositioning on precision without the concomitant observer change.

6.2. Internal validity

Internal validity depends on whether the results presented are true or valid for the source population[101]. Selection bias, information bias and confounding may threaten the internal validity of an epidemiological study.

6.2.1. Selection bias

Main study population

Descriptive studies rely heavily on representativity with respect to the background population. The study population should therefore ideally be representative of any factor that might influence the outcome of interest. Since many such factors are unknown, the easiest way to ensure representativity is to invite either the entire population in each age- and sex-stratum or representative samples of these strata. Our overall response rate of 78% of the eligible population assures generalisability of results to a majority of the source population. However, the non-responding minority may have qualities that differ substantially from those found in the study population. In this case, the study population will not be representative of the non-responders and therefore not of the general population at large either. It is therefore of interest to discover selection factors, which might influence the descriptive elements in this thesis.

In an effort to characterise response patterns, we compared characteristics for the 10 213 subjects selected to receive a TROST invitation, by response pattern. For 1151 subjects who attended neither examination (non-responders) we had only age and sex data. For 1114 subjects who attended the first, but not the second examination (partial responders) we had data from the first examination and one or two questionnaires, and for the 7948 subjects who attended both examinations (full responders) we had a complete data set. These analyses were stratified by the following age-groups: < 45 (young), 45-64 (middle aged), 65 years and over (elderly), and by sex.

The youngest and oldest subjects were less likely to be full responders than subjects aged 45-74 years, and men were less likely to be full responders than women (see Table 4). Comparisons of partial- and full responders showed that partial responders were more often either very young or old, felt well (no chronic pain), drank and smoked more and exercised less than full responders (see Table 5). There were no indications that full-responders were healthier than partial responders with respect to self-reported disease. Non-responders could, however, still be less healthy than partial- and full responders, which may explain the lower overall response rates among elderly subjects aged > 75 years. Therefore, with the possible exception of subjects aged ≥ 75, where our numbers are few and response rates low, we believe that selection due to disease, does not seriously bias results in this study.

Table 4: Age and sex distribution by response type among 10213 subjects eligible for inclusion in the Tromsø Osteoporosis Study (TROST). *Non-responders* attended neither first nor second examination, *Partial responders* attended only the first examination, whereas *full responders* attended both first and second examinations. The Tromsø study (1994-95).

		Non-responders		Partial responders		Full responders		All
		n	row %	n	row %	n	row %	n
Sex	Women	575	9.9	662	11.4	4558	78.7	5795
	Men	576	13.0	452	10.2	3390	76.7	4418
Age	25-29	83	28.3	61	20.8	149	50.9	293
	30-34	60	20.9	54	18.8	173	60.3	287
	35-39	55	21.3	34	13.2	169	65.5	258
	40-44	33	16.0	27	13.1	146	70.9	206
	45-49	41	10.0	39	9.5	330	80.5	410
	50-54	173	10.2	229	13.5	1298	76.4	1700
	55-59	191	9.4	182	8.9	1666	81.7	2039
	60-64	140	8.2	139	8.2	1424	83.6	1703
	65-69	153	9.0	145	8.5	1400	82.4	1698
	70-74	190	12.8	177	12.0	1113	75.2	1480
	75-79	14	15.2	18	19.6	60	65.2	92
	80-84	18	38.3	9	19.1	20	42.6	47
All		1151	11.3	1114	10.9	7948	77.8	10213

Test for sex*respons-type: Chi: 26.0, $p < 0.001$
Test for age*respons-type: Chi: 359.3, $p<0.001$

Table 5: Selected characteristics of partial and full responders among 9062 participants of the Tromsø Study (1994-95). *Partial responders* were invited to both first and second examination, but attended only the first, whereas *full responders* attended both examinations.

		Women		Men	
		Partial responders	Full responders	Partial responders	Full responders
25-44	n	120	396	56	241
	Age, mean years of age	29.8**	32.2	32.9	32.9
	Alcohol units pr fortnight Median (25-75%-tile)	2.5 (0.0-5.0)	2.0 (0.0 - 4.0)	6.0 (3.0 - 10.0)	4.0 (2.0 - 9.0)
	Chronic disease (%)	5.8	6.3	3.6	7.9
	Cardiovascular disease (%)	0.0	0.3	0.0	2.1
	Poor self reported health (%)	15.8	16.2	7.1	11.2
	Significant chronic pain (%)	7.5	9.6	16.1	12.0
	Daily smoker (%)	45.8	43.2	46.4	38.6
	Sedentary in leisure time (%)	14.2	17.7	17.9	21.2
	Body Mass Index (kg/m^2), mean (SD)	23.1 (3.2)	23.8 (3.7)	25.3 (3.6)	25.2 (2.9)
	Ever user of HRT (%)	0.8	2.0		
45-64	n	344	2741	245	1977
	Age, mean years of age	52.7**	54.0	54.8	55.1
	Alcohol units pr fortnight, median (25-75%-tile)	1.0 (0.0 - 4.0)	1.0 (0.0 - 4.0)	4.0* (0.0 - 9.0)	3.0 (0.0 - 8.0)
	Chronic disease (%)	14.2	12.6	19.2	20.7
	Cardiovascular disease (%)	4.7	4.7	12.2	14.2
	Poor self reported health (%)	46.0	45.4	32.9	38.8
	Significant chronic pain (%)	13.1**	16.7	6.9**	16.0
	Daily smoker (%)	48.5**	34.5	49.4**	36.5
	Sedentary in leisure time (%)	24.1	22.3	29.4*	22.1
	Body Mass Index (kg/m^2), mean (SD)	26.3* (5.2)	25.7 (4.3)	26.7 (3.7)	26.4 (3.3)
	Ever user of HRT (%)	23.0	24.5		

		Women		Men	
		Partial responders	Full responders	Partial responders	Full responders
65-84	n	198	1421	151	1172
	Age, mean years of age	68.7**	67.5	68.1*	67.5
	Alcohol units pr fortnight, median (25-75%-tile)	0.0* (0.0 - 0.0)	0.0 (0.0 - 1.0)	0.0 (0.0 - 4.0)	1.0 (0.0 - 5.0)
	Chronic disease (%)	32.8	29.7	37.7	37.1
	Cardiovascular disease (%)	22.7	17.7	30.5	27.5
	Poor self reported health (%)	54.1	58.2	53.6	47.9
	Significant chronic pain (%)	8.6**	13.2	9.9	11.3
	Daily smoker (%)	33.8*	23.7	39.1*	30.5
	Sedentary in leisure time (%)	46.0**	32.1	32.5*	21.3
	Body Mass Index (kg/m^2), mean (SD)	26.4 (5.4)	26.7 (4.6)	25.2 (3.4)	25.8 (3.6)
	Ever user of HRT (%)	4.5	8.4		

* $p<0.05$, ** $p < 0.001$

Significant chronic pain: Muscle- or joint pain/ stiffness of at least three months continuous duration which affects capacity to perform work. *Alcohol:* Average number of glasses of beer, wine or liquor consumed during a fortnight. *Chronic disease*: Self reported diabetes, angina pectoris, stroke, asthma or myocardial Infarction. *Cardiovascular disease:* Angina pectoris or Myocardial infarction. *Daily smoker*: of pipe, cigarettes or cigars. *Sedentary in leisure time* Less than one-hour pr. week of physical activity in leisure time. *Poor self reported health*: Self reported health reported as either "Poor" or "Not so good". *Ever user of HRT*: Self reported current or previous use of HRT.

The elderly and middle aged partial responders were more often daily smokers (44 vs. 32 percent, $p <0.001$), and were more often sedentary in their leisure time (31 vs. 23 percent, $p < 0.001$) than full responders. Elderly male and female smokers had the largest BMD decrements with 3 and 6 percent lower distal BMD than non-smokers (data not shown), which is in line with previous reports on smoking and BMD[102]. Apart from sedentary elderly men who had 3% lower distal BMD than their active counterparts (data not shown), forearm BMD level did not differ by physical activity in the other middle aged and elderly groups. Judged by these data our mean BMD results may be over-estimated by between 0.3-0.6% in the middle aged and elderly, which by any standard would represent a negligible adjustment of the BMD by age results.

Analyses of the partial responders gave no clues to the cause of the low response rates in the young (<45 years). Previous studies of young non-responders found 'being too busy' and 'perceiving no personal benefit of attending' as important reasons for non-response in the young[103,104]. Such selection-factors would probably not affect the BMD results in this age group.

Precision study population

Movement artifacts

The precision estimates given in paper II are meant to reflect precision in the main study population. However, as we were aware that scans with movement artifacts had lower precision than non-artifactual scans, all subjects with movement artifacts scans were excluded in the precision analyses presented in paper II. These precision estimates may therefore be unrepresentative of precision for the main study population. We therefore reanalysed our precision, now including scans with movement artifacts grade I or II. The analyses were based on scan pairs taken one week or three weeks apart by two different observers on the same densitometer (intermediate term inter-observer precision) and on different densitometers (inter densitometer intermediate term inter-observer precision). Subjects could contribute up to three pairs of scans. A standard deviation (SD) and coefficient of variation (CV) was calculated for each scan pair. All available SDs and CVs for each subject were averaged, so that each individual contributed one mean SD or CV to overall analyses. Precision for measurement on two different densitometers, after adjustment for the inter-densitometer difference, given as the median CV was 1.3% and 1.8% at the distal and ultradistal sites respectively. The results for precision on the same densitometer are given in the table below.

Table 6: BMD-precision by age and measurement site. The estimates are based on BMD scan pairs performed on the same subjects, taken one or three weeks apart by two different observers on the same densitometer. Movement artifacts grade I and II were included. The Tromsø Study, 1994-95.

		Distal site			Ultradistal site		
		n	SD, g/cm^2 (median)	CV, % (median)	n	SD, g/cm^2 (median)	CV, % (median)
Age	25-39	10	0.003	0.5	10	0.004	1.1
	40-54	12	0.005	0.9	12	0.005	1.4
	55-64	37	0.005	1.0	38	0.005	1.3
	65+	11	0.004	0.8	11	0.004	0.9
	All	70	0.004	0.9	71	0.005	1.3

SD-differences between age groups (Kruskal Wallis test), distal site: p= 0.056, ultradistal site: p=0.38.
CV-differences between age groups (Kruskal Wallis test), distal site: p= 0.025, ultradistal site: p= 0.66

As expected, the inclusion of movement artifact scans in the precision data set, led to a slight increase of the overall SD- and CV estimates. As in paper II, precision was shown to be dependent on age in a non-linear fashion at both sites, although this reached significance only at the distal site. Both younger and older subjects had better precision than subjects aged 40-64 years. With these minor changes, the conclusions presented in paper II are considered valid also for BMD precision in the main study population.

Age distribution

In the first precision study, there was both an under-representation of subjects aged 70 years or more, and an over-representation of subjects aged 40 years or less ($p<0.001$) as compared to the main study population. The BMD-level rose from the 55-64 age group to the 65+ age group. This is the opposite of the BMD-development by age found in most other studies on BMD and age (paper III). Thus the decision to invite only subjects who "looked healthy" to the precision study may have produced a selection bias, with an overrepresentation of healthy elderly subjects. Therefore, results from the first precision study may be biased for subjects aged 65 years or more, and should therefore not be generalised to other subjects in this age group. In the second precision study, the age- and sex- distribution did not differ significantly from that of the main study population.

Other variables

BMD-levels, bone width, prevalence of distal forearm fracture, height, weight or body mass index (kg/m^2) were not different from that of the TROST population when controlled for age and sex, in either precision study.

6.2.2. Information bias

BMD measurements

All the major outcome variables in this paper are either BMD-results or derivatives of BMD-results. Although the golden standard for the BMD measure traditionally has been bone ash, in this thesis, the forearm BMD was meant to serve as a surrogate measure of systemic bone strength. Therefore, even though the BMD-measure would be correct with respect to local bone ash and even local bone strength, we have tried to evaluate and if possible eliminate the influence of factors that would lead to incorrect ranking with respect to systemic bone strength. We have also tried to reduce BMD variation caused by non-biologic factors unrelated to bone strength, such as systematic differences between densitometers.

Reproducibility

The overall precision for forearm BMD-results, with and without movement artifacts included, as presented in paper II and in Table 6 was excellent.

Movement artifacts

Movement artifacts decreased precision of the BMD measurement at both the distal and ultradistal sites (paper I). As the movement artifact effect was random, it was not likely to affect the mean estimates in groups. We therefore included subjects who had grade I and II movement artifacts in their scans. However, theoretically the decreased precision of these scans could inflate population standard deviation estimates. To investigate this possibility, we computed a new set of BMD reference values, excluding all subjects with movement artifacts at either distal or ultradistal site. However, neither means nor standard deviations were affected by the exclusions (data not shown).

BMD adjustments

Correction of radial endplate artifact

The radial endplate artifact falsely increased the BMD-result (paper I). In the first 2000 scans, only scans identified as having a region-of-interest artifact were reanalysed. Preliminary analyses of intra- and inter-observer artifact classification were performed when review of the first 2000 scans was complete. We found that the average BMD difference in women, before and after review, was -0.008 g/cm^2 for observer A and –0,012 g/cm^2 for observer B ($p<0.0001$, adjusted for age and BMD). In men, the equivalent figures were –0.013 and –0.016 g/cm^2 for the observers A and B respectively ($p=0.007$, adjusted for age and BMD). These differences were due to differences in scan classification between the observers. Scans that were classified as artifactual and thus reanalysed by one but not the other observer displayed greater BMD-differences, than scans where both observers had identified an artifact and performed a reanalysis.

As the ultradistal site should reflect BMD of a predominantly trabecular site, no additional cortical bone should be added. In the first 2000 scans, observer A classified 493 of 918 scans (53%) as having a radial endplate artifact whereas observer B found the artifact in 653 in 929 scans (70%) ($p<0.0001$). In other words, the classification mode of observer A should have been changed in the direction of observer B's mode, and the first 1000 scans reviewed by observer A ought to be re-reviewed. However, this would have lead to a re-classification of 149 subjects (2 % of study population), whose BMD-result would have been lowered by an average of 4% (paper I). This would on average brought the mean BMD down by 0.08%, which was judged to be of minor importance compared with the delay introduced by re-reviewing the scans, and was therefore not performed.

From then on we decided to reanalyse all scans so that reanalysis was independent of artifact classification. Registration of artifact classification continued as before. After the policy change, the BMD difference before and after review for observers A and B were -0.009 and –0.010 g/cm^2 ($p=0.26$) for women and –0.014 for both observers in men ($p=0.38$).

Adjustment for fracture of the distal forearm

Such a correction depends on correct information of previous forearm fractures. We had however, failed to register which arm (right or left) that had been measured. Therefore, even if

we could validate the forearm fracture from medical record linkage, we would not be able to find out whether he/she had in fact sustained the fracture on the side that was measured.

Joakimsen et al. found that among subjects in the Tromsø population that actually had sustained a forearm fracture, 85% reported the wrist fracture in the questionnaire (under - reporting). He also found that of all self-reported fractures, 9% had not sustained a forearm fracture (over-reporting)[105]. If these figures are applied to our data, approximately 102 subjects would have failed to report their wrist fracture and a total of 159 subjects (2%) of the total population would have a wrong fracture classification.

Assuming that the age and sex distribution of the non-reporters resembles that of the reporters, the highest proportion of under-reporters would be found amongst women aged 70 years or more. In all 22 subjects (3%) in this age group would have failed to report their forearm fracture. A correct adjustment of their BMD-values would bring the group BMD down by 0.0012 g/cm^2, which represents a minor adjustment from 0.262 to 0.261 g/cm^2 (-0.5%). Further misclassification would ensue if subjects did not remember correct fracture side. We found no published studies of this potential problem, which makes it difficult to estimate its significance. We have no indications that fracture over-reporting would be associated with any particular age or sex or BMD-level.

The fracture adjustment entails that the ultradistal BMD of subjects with previous forearm fracture may not be compared directly with the reference ranges presented in paper III, unless effect of the callus is subtracted first.

Densitometer adjustment

We succeeded in correcting the systematic BMD-difference between the densitometers A and B, and this source of variability should thus cause no further concern.

Menopause and HRT

We examined BMD-development by age in post-menopausal women. Misclassification of menopausal status could lead to the inclusion of women with pre-menopausal levels of estrogen in these analyses. Both the questions designed to ascertain menopausal status contain two questions in one. This is unfortunate, as women who are uncertain of their menopausal

status will not be able to reply confidently. This would apply to peri-menopausal women using hormone replacement therapy (HRT), hysterectomised but not oophorectomised women and peri-menopausal women with irregular menstruation.

We had no possibility to exclude women with pre-menopausal estrogen levels due to the two latter causes of uncertainty, but we sought to exclude all ever users of HRT from these analyses. However, the 23% of the women had missing values for the HRT question. Although women who found this question irrelevant or were unfamiliar with the estrogen terminology would be more likely to leave this question open than HRT-users, the women with missing values could also include large proportions of HRT-ever users. We therefore analysed post-menopausal BMD development with and without them. The results were virtually identical (data not shown), which is why we decided that the inclusion of women with missing HRT-values would not bias results and the women could safely be included in the final analyses.

The "normal" population

The reference values are used as a basis of comparison for individual BMD results. We made a point of trying to define a so-called "normal" or "healthy" population in order to examine whether the exclusion of subjects with "unhealthy" bones, would affect reference values. Subjects may have been misclassified according to our chosen definition of "normal", as diseases and medication use was not validated, and information on many factors often included in delimiting the "normal" population, was unavailable to us.

The idea of a correct "normal" and "abnormal" classification depends on a clear concept of what "normal" with respect to bone health is. The diversity of "normal" definitions supplied by previous studies of normal BMD, testifies to the evasiveness of the concept of normality[60,106-113]. The term "normal" includes concepts both of what is common, what is ideal, what is natural for a species and of the distinction between health and diease, and these differing concepts are often contradictory. Our exclusion criteria could be viewed as both as appropriate and inappropriate, depending on what concept or standards that made the basis of the classification. In this light, the possible misclassifications of subjects according to our chosen definition of "normality" becomes very callenging, because the normal definition itself does not reflect a fundamental and universally recognisable difference between individuals.

Reference ranges for recognisable and standardised categories, which can be re-constructed across both time and space, would however be useful to determine whether BMD-levels are within the expected BMD-range. The general population reference ranges for separate race-, sex- and age groups, separate reference values for BMD-development by time since menopause and for women using hormone replacement therapy, and for subjects using corticosteroid therapy would be useful examples.

Fracture adjustment procedure

The fracture adjustment procedure could be regarded as departure from the general population, as any unselected population would include a fraction of previous forearm fracture cases. However, in contrast to the exclusion of subjects to come down to a "normal" population which was criticized above, these subjects were not excluded, but they entered a BMD-value which we considered as more representative of their systemic bone strength than the unadjusted BMD-values.

Distortions of the BMD by age curve

In paper III we explored the BMD distribution by both age and time since menopause. Biases that relate both to BMD-level and to age could theoretically undermine the BMD-age relationship demonstrated in paper III. The radial endplate artifact-, the fracture- and the menopause- misclassifications discussed above all have predilections to certain age groups, but their impact on overall BMD-values were by them selves negligible. The effect of several biases at the same time is difficult to evaluate. However the BMD-life curve was surprisingly robust to the exclusion of more than 2000 "unhealthy" subjects (paper III), even when these exclusions were highly dependent on age. We therefore believe that the above-mentioned biases have negligible effects on the BMD by age curve.

6.2.3. Confounding

When a presumed causal relationship between two variables in reality is fully or partially caused by a third factor, we call this confounding. Thus confounding is not an issue in the presentation of reference material, which is the main issue of this thesis.

Determinants of precision

The age relationship with precision could theoretically be confounded by BMD-level. However, crude analyses of BMD and precision revealed no association between the two. We were not able to exclude this possibility because we had too few subjects to perform analyses stratified both on age and BMD-level. A weak age-precision association has been demonstrated at the distal site in our precision study, but although confounding by BMD-level is unlikely, it could not be ruled out due to small numbers.

6.2.4. Summary - Internal validity

This population-based study had overall high response rates, and results are therefore generalisable to the majority of the subjects in the source population. The low response rates in young and elderly subjects give reason for concern. The non-response in young subjects is probably not related to BMD-levels, or other variables used in this thesis, but non-response among the oldest subjects, may be due to health related issues. We found that smokers and sedentary subjects were under-represented among the full responders, but this would have minor effects on BMD-levels.

Participants of the first precision study aged over 65 years of age are probably not representative of the main study population. The inclusion of movement artifacts in the main study population would be a larger problem among older subjects, as it might threaten associations between BMD and other variables, and/ or augment population standard deviations. However we found no sign of these possible biases affecting our results.

The densitometer adjustment completely removed the systematic difference between densitometers and should cause no further concern. Failure to correct radial endplate artifacts or the effect of callus after forearm fractures could theoretically lead to minor, but insignificant shifts in mean BMD-values. We may unintentionally have included hysterectomised women with intact ovaries, peri-menopausal women with irregular menstruations and post-menopausal HRT-users who failed to report this, in our analyses on post-menopausal BMD-development. These groups would have pre-menopausal estrogen values, in which case BMD-decline by age in post-menopausal women could be slightly underestimated in our study. The post-menopausal BMD by age curves were independent of whether the women who had missing HRT-values were included in the study population or

not. Given the robustness of the BMD-life curve patterns when almost 1/3 of the study population were selectively excluded, it is not likely that the sum of these biases will have significant impact on BMD-by age patterns.

Thus, the results presented in this thesis may not be generalisable to elderly subjects aged > 75 years and precision results are probably not valid for subjects aged 65 years or more. Otherwise, we have found no bias that would seriously undermine the internal validity of the results presented.

6.3. External validity

External validity depends on whether results, which are found to be valid for the source population, also are generalisable to other populations. In the case of prevalence results and reference values, the question of generalisability relies heavily on whether the source population is representative of other populations.

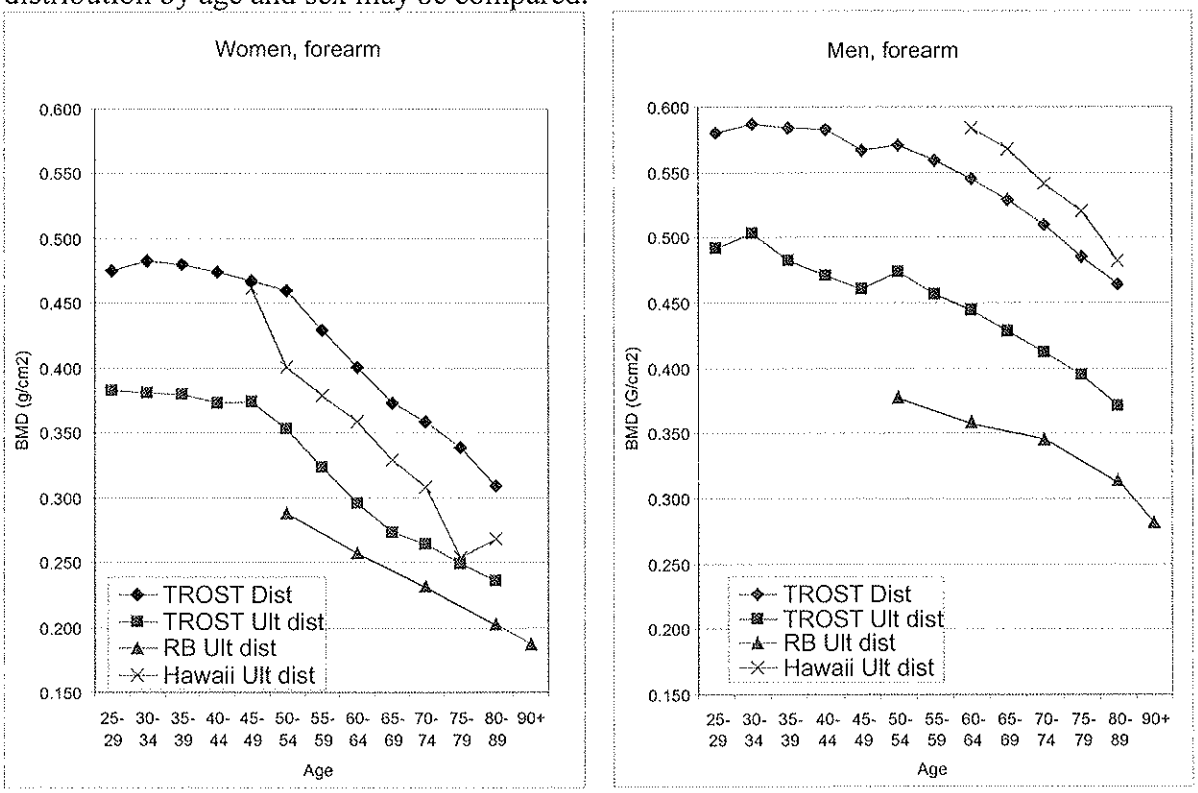
6.3.1. The Tromsø population

The Tromsø population is representative of the Norwegian population at large with respect to age and sex-distribution[114]. It is a largely Caucasian middle-class population which counts 57 000 inhabitants (1998). 46% of the inhabitants work in the tertiary services (public and private sector), and many of these would be associated to The University of Tromsø and the University Hospital, which are the two largest employers in Tromsø[115]. Apart from this, fisheries and commerce represent important sources of income. The city is situated at 69 degrees north, which is approximately 400 km north of the Arctic Circle. The variations in daylight exposure are therefore extreme, as the sun does not rise between 23rd of November and the 21st of January, and does not set between the 21st of May and 23rd of June.

Prevalence of artifacts at the forearm with the methodology used in our study has not been examined elsewhere. Precision measured as coefficients of variation (CV) for repeat scans performed with repositioning at the forearm with SXA is 0.8-1.1%[68-70], which is quite in line with our results of 0.8 and 1.0% for distal and ultradistal sites respectively (paper II). There are currently no comparable BMD data, which can tell us whether BMD levels in Tromsø are different from other populations. The BMD-distribution by age and sex at the forearm is quite similar to that found in other unselected general populations as judged by visual comparison

of BMD by age curves (See Figure 3). These observed no deceleration of BMD-change by age in the late menopause[59], or a small deceleration at the mid radius only[58]. Our osteoporosis prevalences at the forearm are 31%, by the WHO definition (based on peak BMD) when standardised to the US 1990 population at the distal site. This is in accordance with forearm osteoporosis prevalence of 33% as in the Rochester women aged >50 years, by the same definition[49]. The incidence of all fractures in the Tromsø population is lower than in Oslo, the capital of Norway, but higher than in the UK for both men and women[105].

Figure 3: BMD life curves at the forearm in three different populations. BMD units are not standardised between the studies, so BMD-levels cannot be compared, whereas BMD-distribution by age and sex may be compared.



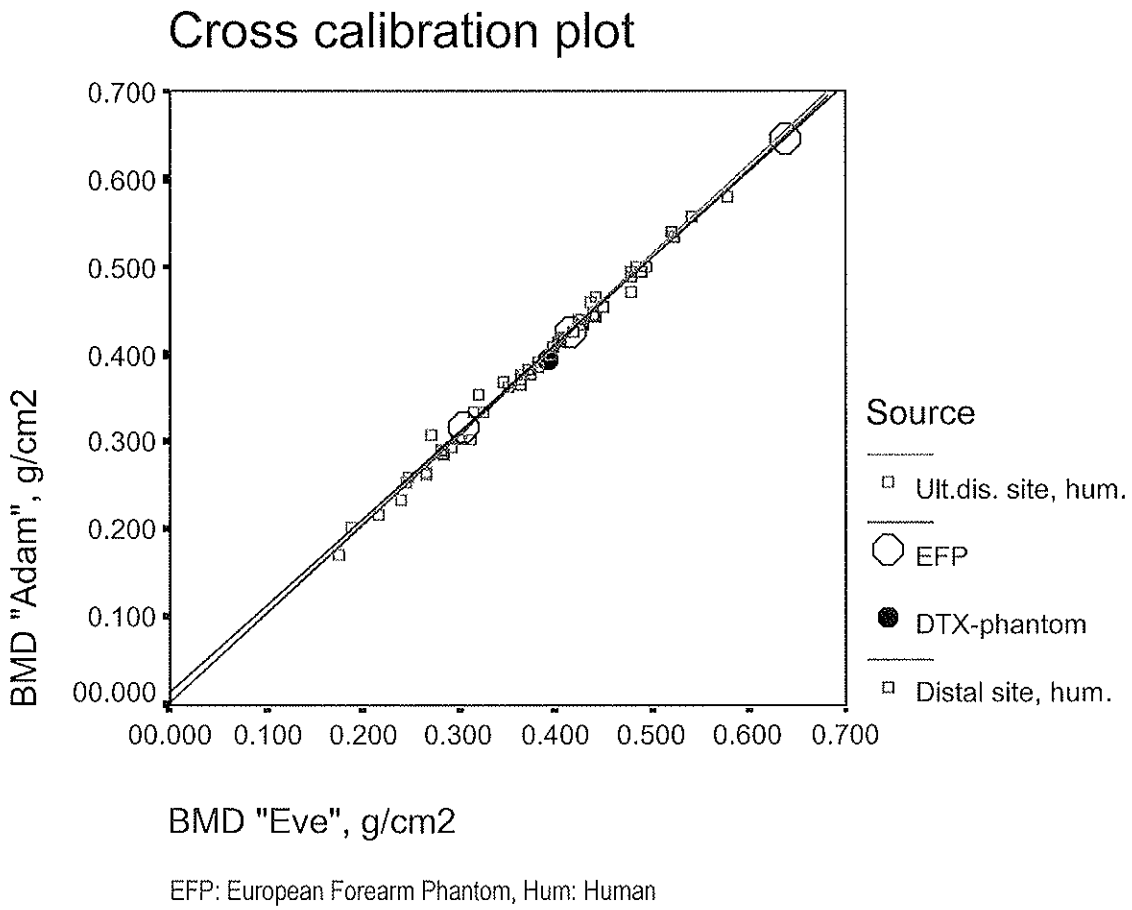
TROST: Tromsø Osteoporosis Study, Norway, Caucasians (paper III)
RB: Rancho Bernardo Study, USA, Caucasian Americans [58]
Hawaii: Kuakini Osteoporosis Study, USA, Asian Americans [59]

6.4. The standardised BMD-unit

Although the European Forearm Phantom has not yet been validated by human cross-calibration studies, we decided to standardise our results to the EFP phantom. Cross calibration with phantoms should ideally give the same result as cross-calibration with

humans. In our own material we compared the cross calibration of BMD-values from our two densitometers and the values produced by the phantoms (Figure 4).

Figure 4: Cross calibration plot for bone mineral density (BMD) results for the two densitometers, nicknamed "Adam and Eve", of the same brand and type used in the Tromsø Osteoporosis Study (TROST). The results of one measurement on each densitometer for every subject, the mean of twenty European Forearm Phantom measurements on each densitometer, and 400 DTX-phantom results from each densitometer, are plotted. The Tromsø Study, 1994-95.



EFP: European Forearm Phantom, Hum: Human

The mean BMD-results from the European Forearm Phantom in the human BMD-range, showed a nice fit with the human regression lines, whereas BMD means for the phantom provided by the manufacturer, the DTX-phantom, deviated slightly. The mean BMD-difference between the two densitometers measured in humans, the EFP and the DTX-phantom were 0.009, 0.009 and 0.001 g/cm^2 respectively. We found that the European Forearm Phantom qualities were superior to those of the DTX-phantom in detecting human BMD-differences between two densitometers of the same brand and type. Whether the EFP

phantom will perform as nicely on densitometers of different brands remains to be determined.

6.5. Significance of results

6.5.1. Scan acquisition procedures

Movement on the part of the subject during a BMD-scan causes movement artifacts. To our knowledge, no other publications have treated this issue in relation to bone-density measurements previously. We demonstrated that movement artifacts had significant effects on the precision of the BMD-result, and that its occurrence should lead to a repeat BMD measurement.

In our study, the movement artifacts were quite common, and the minor artifacts were difficult to eradicate. This finding is probably only generalisable to densitometer settings similar to ours, i.e. 5-min. scans of the forearm immersed in temperate water. Swifter densitometers, densitometers without water baths, and densitometry of less agile anatomical sites, such as the spine or hip, will probably demonstrate lower prevalences of movement artifacts.

6.5.2. Scan analysis – identification of region-of-interest.

A small alteration of the region of interest, so minor that it at first escaped our attention, had significant effects on the final BMD-result. The endplate consists only of cortical bone, and in addition the endplate is scanned on edge so that the BMD is considerably higher in this area than in the rest of the ultradistal site. This is why even minor inclusions of the radial endplate lead to large changes in the BMD for the area, whereas changes of the region-of-interest in areas with homogenous BMD matters little.

Region-of-interest identification is specific for the differing sites (hip, spine and calcaneus) and in the case of the forearm, the region-of-interest definitions differ between manufacturers also. Therefore, the consistency of region-of-interest identification and the effects of any lack of consistency are aspects that should be examined for all region-of-interest definitions.

6.5.3. Cross calibration of densitometers.

We found that the aluminium phantom delivered by the manufacturer did not detect the systematic difference between the densitometers, which was evident when cross-calibration was examined with humans and the European Forearm Phantom.

6.5.4. High precision – so what?

Our precision results for both the distal and ultradistal sites were excellent and in line with that found by other authors for SXA measurements at the forearm. DEXA precision at both the hip (CV: 2-3%) and the spine (CV: 1-2%) are generally lower than at the forearm where both SXA and DEXA precision centre around 1%. With a mean CV of 2.5%, as is common for the femoral neck and a CV of 1% as found in the forearm with SXA, the individual's true BMD value will with 95% certainty lie within an interval which equals 1.96*CV. This would be within a ± 5% interval for the femur and ± 2% interval for the forearm. These intervals equal nearly $^1/_3$ young adult SD (T-score) for the hip[66], whereas the forearm interval equals only $^1/_6{}^{th}$ of a young adult SD (T-score). In other words, the BMD-level is more precisely estimated at the forearm pine than at the hip.

In evaluating the CVs significance for BMD-change, it is necessary to take into account the uncertainty of both the first and second BMD-measurements. The smallest difference, which can be detected between two single BMD-measurements with 95% certainty, is given by the following formulae: $\Delta\% = z * cv\sqrt{(2)}$ [116](appendix E). With a CV of 2.5%, this 95% detection limit will equal ± 7% for the hip, whereas it will be only 3% for the forearm. The expected annual BMD-change of approximately 1% will be detectable after three years with SXA and after 7 years with hip DEXA. These long intervals may be unacceptable to both patients and clinicians in many situations. We therefore suggest that BMD-change should preferably be measured at the forearm with repeated measures at each point in time as this site demonstrates the highest precision.

6.5.5. Determinants of precision

We discovered that repositioning was possibly the most important determinant for precision, as CVs almost doubled when repositioning was introduced. In most cases, it is of minor interest to perform repeated scans without repositioning, but it might be that careful attention

to subject position could reduce the random measurement error. This has been confirmed for the hip, as hip rotation has been shown to affect the BMD result significantly[81 82,83] and a strictly standardised hip-rotation maximised precision in one study[84].

Age is also a possible determinant for BMD-precision. Although this finding was weak in our study, it has been proposed as a precision determinant also by other authors[66,117]. The determination of BMD-precision in elderly subjects urgently needs further examination.

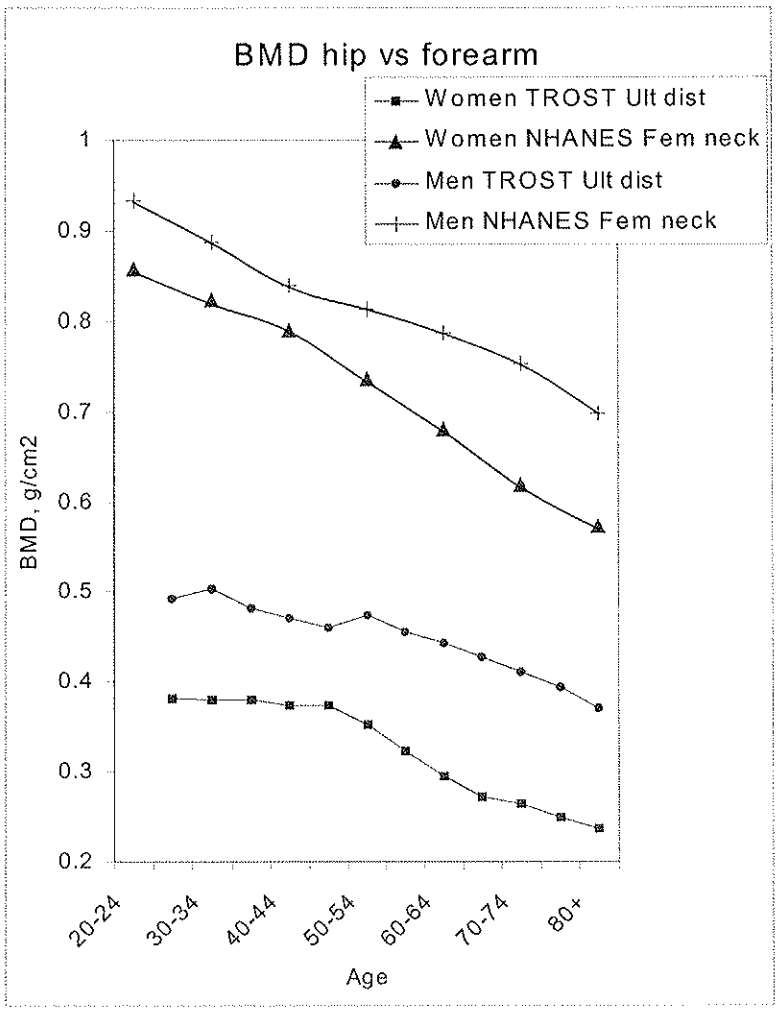
6.5.6. What does BMD development tell us about BMD physiology?

The individual longitudinal BMD development may be quite different from that depicted in a cross-sectional study. The average BMD at any given age is the sum of all individual BMD-developments up to that point. Changes of slope in a cross-sectional BMD curve by age may occur when one age-group develops differently from those born at other times (cohort effect), when a proportion of the individuals change BMD at a slower or swifter pace than other groups, or when most individuals exhibit a parallel BMD-development (tracking). Individual longitudinal BMD-development can only be examined in longitudinal studies with two or more BMD-measurements over time.

With the exception of the BMD-decline associated with menopause in women, the male and female BMD distributions by age were remarkably similar. The same finding was evident for the forearm site in elderly subjects in the Framingham study[57], the Hawaii study[59] and the Rancho Bernardo study[58].

As the BMD decline seems to be comparable and possibly even swifter at the hip than at the forearm (Figure 5)[56,118], the higher osteoporosis prevalences at the forearm can not be attributed to differences in BMD-development by site. However, the young adult standard deviation at the forearm (SD distal forearm: 0.006 g/cm^2) is only half of that found at the hip (SD hip: 0.012 g/cm^2[56]. This results in a relatively higher WHO osteoporosis threshold at the forearm than at the hip, which in turn causes the higher osteoporosis prevalence at this site.

Figure 5: Bone mineral density distribution by sex, age and measurement site. Data from the NHANES study [56] and from the Tromsø Osteoporosis Study (TROST). The Tromsø Study, 1994-95.



It is well known that BMD at different anatomical sites correlate moderately[113]. One possible explanation is that the local BMD is regulated by a combination of local factors such as mechanical loading, weight bearing, micro fractures[119,120], and systemic factors like sex steroids and calcium homeostasis[121,122]. One would expect axial weight bearing sites, which are constantly exposed to mechanical loading, to bear less information on systemic factors such as menopause, than non-weight bearing sites. A study of retired ballet dancers who were exposed to several unfavourable risk factors for osteoporosis such as higher levels of menstrual irregularities and smoking, but still retained a high level of physical activity exemplifies this. The ballet dancers had lower BMD at non-weight bearing sites and similar BMD at weight bearing sites, as compared to age and sex-matched controls[123]. Based on the observed differences between the hip and the forearm as demonstrated in Figure 5, which shows that the menopausal changes are more prominent at the forearm than the hip, we

hypothesise that the forearm site reflects the systemic changes of hormones to a larger extent than the weight bearing sites of the hip and spine.

Why does the BMD-decline that starts at menopause exert different effects in the early and late menopause? Several smaller cross sectional studies of forearm BMD in selected populations also report such a pattern[36,124-127], but the two other population-based studies of forearm BMD observed no equivalent deceleration[59], or a small deceleration at the mid-radius only[58]. Longitudinal studies in selected populations where bone loss levels off 4-10 years after the menopause support the concept of a slowing down of BMD-decline in the late post-menopause[128-131], but further longitudinal studies of this issue is needed to establish whether this is the case and if so, why does the longitudinal BMD-loss decline?

Theories of BMD physiology need to explain 1) the similarities in BMD-development between the two sexes, 2) the differences in BMD-development between weight bearing and non-weight bearing bones, and 3) why the menopausal BMD-decline seems to wane off in the late post-menopause.

6.5.7. The risk diagnosis

As low bone mass causes no symptoms or loss of function in the absence of fractures, the suggested osteoporosis diagnoses are not labels of an ailment, but of an increased risk of fracture – a risk diagnosis. We found that the number of subjects diagnosed as osteoporotic according to the currently proposed definitions were high for all female definitions and also for some of the male definitions. Most striking was the high percentage of osteoporotics amongst women aged 70 years or more. This raises the question of whether such high prevalences are justified? The only way to find out is to examine the foundations for the current diagnostic definitions closely.

The bone mass concept

An osteoporosis prevalence of approximately 30% for women aged 50 years or more, as found at the forearm site in both Rochester and our data, closely matches the female lifetime probability of having any type of fragility fracture (hip, vertebral or forearm)[132]. This similarity between proportions has been used as a justification for the WHO diagnosis cut-off level[133]. This once again exemplifies the underlying "bone-mass-concept" of osteoporosis: if

you find the subjects with low bone strength you will also find the future fracture cases. Osteoporosis is viewed solely in terms of frail bones. Weak bones constitute the early stages of a disease of which fractures are the consequence. However, while BMD unarguably is a strong risk factor for fracture, there is a BMD-overlap between fracture and non-fracture populations [44]. Non-BMD age-related factors account for larger proportions of the age-associated increase in fracture risk than the BMD-decline[34,48]. As long as low bone mass alone confers no symptoms or loss of function, while fractures unarguably do, our focus should be on the causes of fracture, not on low bone mass. It is the fragility fracture that we seek to prevent. Frail bones are of no importance as long as they do not break.

Weak bones + trauma = fracture

Fractures only occur when the bone strength is overcome by a sufficient strain to cause its deformation. Thus the probability of sustaining a strain, most often a trauma that is sufficient to overcome the bone strength must be the other important determinant of fracture. Cummings found that by combining a number of risk factors for hip fracture with tertiles of BMD, he could identify a 6% group of the study-population who sustained 30% of the hip-fractures [48]. The Dubbo project also combined measures of bone strength with risk factors for falls, such as muscle strength and body-sway. Subjects whose composite score was > 6 for these three factors had 2.2-fold (men) and 3.9-fold (women) higher risk for fractures than subjects with a score ≤ 3[24]. A recent paper from the Rotterdam study showed that the inclusion of BMD in the predictive model of hip-fracture only marginally improved, the area under the Receiver operating curve (ROC-curve) (from 0.83 to 0.88, $p=0.04$)[134]. In other words, the osteoporotic fracture cannot be viewed as the result of crumbling and weak bones alone. Rather it is the result of many age-related risk factors, of which the low bone mineral density is only one, and perhaps is even a minor factor compared to combinations of other risk factors. It is obvious that an osteoporosis definition based solely on BMD cannot target the future fracture population with an acceptable degree of sensitivity and specificity. Bone strength and risk for trauma should rather be combined. We have few data that may confirm that the osteoporosis diagnosis does not identify the fracture patients. In the placebo arm of one drug trial, over 80% of the women defined as osteoporotic by the WHO definition suffered no osteoporotic related symptoms (no fractures) during the four year follow-up period[135]. A composite score reflecting absolute fracture risk will probably be a better fracture prediction tool than the current osteoporosis diagnoses.

Benefits and side effects of risk labelling

In this perspective, the high proportions of both men and women, currently diagnosed as osteoporotic is a dilemma. Many of these men and women will never sustain any fragility fracture, yet their lives may very well be changed by the osteoporosis diagnosis. The risk diagnosis is a source of worry. In one study, women who believed that their BMD was below normal limited their physical activity in fear of falling. The measures taken, ranged from limiting daily activities such as grocery shopping to cessation of more recreational activity such as skiing and hiking [136], although this reduction in physical activity actually could increase their fracture risk.

The osteoporosis diagnoses not only labels subjects as having a risk factor for fractures, it also labels them as having a disease. The concept of a disease is associated with frailty, unhealthiness and unpleasant symptoms. Diseases have "a natural course", which left unchecked will lead to a progressively worsened situation for the carrier[137]. Implicit in the disease status is that diseases are the responsibility of health care workers, and not that of the individual who thereby loses influence on the choice of further action. The disease status medicalises the individual at risk. In contrast to this, the concept of risk factors does not include an irrevocably worsening condition, on the contrary risk factors may disappear or get better. Risk factors are more the responsibility of the individual and the asymptomatic nature of the risk factor, as found also in hypertension and hypercholesterolemia, is familiar. Risk factors may well shorten your life, but as long as they give no symptoms, they do not remove the individual from the sphere of the vital and the healthy. Furthermore, the risk factor always points at some undesired outcome, underlining that the point of risk reduction is to prevent the undesired outcome, in this case fractures.

In the absence of fractures, low bone mass fits the concept of a risk factor better than the concept of a disease, as it is a symptom free condition which draws its importance from its relation to fracture risk. By choosing to refer to low bone mass as a risk factor, unnecessary medicalisation may be avoided and attention is not diverted from the prevention of fractures.

Treatment options

If we could treat individuals with low bone mass so that bone loss was arrested and their increased risk of fracture eliminated, the osteoporosis diagnosis, with all its possible side-

effects, might be justified. Of available treatment options for low bone mass, only vitamin D/ calcium and the bisphosphonates have at present a documented preventive effect on fractures[138]. However, vitamin D/ calcium supplements may be given to anyone with a low intake of these two nutrients, without BMD measurement[139]. The effect of alendronate seems to depend on low bone mass, so this is a treatment option for subjects diagnosed as osteoporotic. Although alendronate led to a hip-fracture risk reduction of 50% and 20% in women with and without pre-existing vertebral fractures respectively, the absolute risk reduction was 1% in women with low bone mass and pre-existing vertebral deformities[140], and only 0.2% in women with low bone mass[135]. The possible side effects of alendronate, especially acid related gastrointestinal disease, may also preclude its use in many individuals[141].

If a drug eradicated fragility fractures in the at risk individuals (i.e.low bone mass), this would make us conclude that the low bone mass was a necessary cause of fracture, which if eradicated, would eradicate also the fragility fracture. Although such treatment may hinder further weakening of bones, the above-mentioned evidence of treatment effect does not suggest that fragility fractures will be eradicated. This is because for most subjects it is the combination of low bone mass with trauma, which causes the fractures. With age, both the impact and frequency of falls will increase because individuals become less able to avoid falls, and when they do fall, age-related factors make them less able to break the fall. In addition, one study also suggests that the age-adjusted incidence of falls have increased lately [142]. In the light of increased risk for trauma, the importance of bone mass diminishes. Therefore, even if bone-sparing medication may help reduce fracture risk, these new drugs will not eliminate fragility fractures, nor do their effects justify the current osteoporosis definitions.

The risk diagnosis should be abandoned

To summarise, the currently proposed osteoporosis definitions assign "diagnoses", to subjects who, in the absence of fractures, have no symptoms. These "diagnoses" may not target the future fracture population and they may divert attention from other important risk factors for fractures. Furthermore the osteoporosis "diagnoses" may have unwanted side effects such as medicalisation and decreased physical activity at the individual level. There is at present no documented effective treatment option available for all subjects diagnosed as osteoporotic. It

is therefor at present unclear whether risk identification by the osteoporosis diagnosis has more positive than negative effects for the individual. Osteoporosis definitions based on BMD alone should therefore be abandoned. BMD is an important tool in the assessment of fracture risk, but should be viewed as one of many risk factors, not as a diagnostic entity. Future fracture prevention efforts should be guided by the construction of absolute risk scores, where all relevant risk factors for fracture, including the BMD, are taken into consideration.

7. Further research

The following questions deserve further exploration:

- What is the prevalence of scan-acquisition and scan-analysis errors at other sites and with other techniques than the forearm?
- Is repositioning the main determinant of precision also at other sites?
- Will rigorous repositioning procedures improve precision?
- Is precision poorer in elderly as compared to younger subjects?
- Validation of the standardised European Spine and Forearm Phantoms by human cross-calibration at both the hip and forearm are needed.
- Is BMD-development at the forearm related more to systemic factors and less to local factors than at the weight-bearing sites of the hip, spine and calcaneus?
- Is the change in BMD-decline by age found at around 65-69 years of age a cohort effect, or does it reflect a changing BMD pattern within each individual.
- What is the absolute fracture risk linked to the currently proposed osteoporosis definitions?
- Absolute risk scores for non-vertebral fracture, which combine BMD and risk factors for trauma, need to be developed.

8. Conclusions

Artifacts are common and do exert significant effects on both BMD-level and BMD-precision. Precision at the forearm with SXA is excellent. Repositioning and possibly age are determinants of precision. BMD-distribution by age and sex revealed that male and female BMD-development, with the exception of menopausal bone loss, is quite similar and that the effect of menopause may diminish in the late post-menopause. The prevalence of osteoporosis as defined by the currently proposed female and male osteoporosis definitions yield high prevalences in both sexes. More efficient ways of targeting the future fracture patient are needed.

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Paper I

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Original Article

The Tromsø Study: Artifacts in Forearm Bone Densitometry – Prevalence and Effects

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Abstract. Suboptimal performance of bone densitometer, operator and/or subject may cause artifacts of consequence both for individual patient management and research. The prevalence and effects of such artifacts are largely unknown in densitometry. A cross-sectional population-based study was carried out of artifacts in forearm bone densitometry with single X-ray Absorptiometry (SXA) of the nondominant hand (distal and ultradistal site). After the screening, all scans were reviewed for artifact detection and reanalysis. The effect on the bone mineral density (BMD) result was found by comparing artifactual scans with a reanalyzed version or with normal repeat scans. All women aged 50–74 years, all men aged 55–74 years and 5–10% samples of other age groups aged $\geqslant 25$ years attending the fourth Tromsø health study were invited to have bone densitometry. The response rate from the background population was 80% (n = 7948). Fourteen percent of subjects had a movement artifact at either the distal or ultradistal site. The individual BMD variation was twice as large in scans with a movement artifact (0.94%) compared with normal scans (0.58%) (p = 0.0027). The radial endplate was inaccurately detected in 74% of the scans. Reanalysis of these scans led to a mean 3.8% decrease in the BMD value and an increase in the prevalence of osteoporosis of 10%. Artifacts were thus common, and their effects were clinically relevant in forearm bone densitometry. Artifacts and their effects need to be characterized in other bone densitometry settings also.

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Keywords: Artifacts; BMD; Densitometry; Forearm; Movement artifacts; Region of interest

Introduction

In bone densitometry there is widespread acknowledgement of the importance of the performance of the operator, densitometer and subject in acquiring high-quality bone mineral density (BMD) scans [1]. However the quality control debate has mainly concentrated on densitometer stability and standardization between densitometer brands [2,3]. Wahner et al. [4] found that one-third of 7376 hip scans reviewed needed reanalysis and they also rejected 3.5% of the scans, but the study neither searched for determinants of artifact occurrence nor explored the effect of specific artifacts on the final BMD result. Apart from this work, the extent and effect of artifactual scans in densitometry are largely unknown.

The term 'artifact' is here used to denote any trait in the scan image or scan analysis which departs from the ideal normal scan and which may affect the BMD result. Even the best quality control and standardization programs will not prevent every instance of suboptimal or artifactual scans. We were interested in estimating the occurrence and effects of bone densitometry artifacts in a setting with rigorous quality control (QC). The questions addressed in this article are:

How often do artifacts occur in BMD screening with a rigorous QC program?
Which subjects from the general population are most prone to artifacts?
What is the effect of the artifact on the BMD result?

Is the effect of the artifact dependent on the characteristics of the subject or measurement?

Materials and Methods

Subjects

Bone densitometry was performed on 7948 subjects (57% women, 43% men) recruited from the 1994–95 survey of the Tromsø Study. This is a population-based multipurpose study with focus on lifestyle-related diseases such as atherosclerosis and osteoporosis. Repeated questionnaires and clinical examinations have been administered to certain birth cohorts living in the municipality of Tromsø, Norway, since 1974. In the 1994–95 survey all subjects aged 25 years or more were invited to the main survey. A subgroup consisting of all men aged 55–74 years, all women aged 50–74 years and 5–10% samples of the remaining age groups were selected a priori to receive an invitation to a bone densitometry screening upon arrival at the main survey. Of these subgroups, 80.3% were included in our study. The response rate was lower among subjects <45 years (men, 59%; women, 57%) and >80 years of age (54%). Other age and sex strata had response rates ranging from 77% to 91%. The Regional Committee of Research Ethics and the Norwegian Data Inspectorate approved the study.

Bone Densitometry

We performed bone densitometry of the nondominant forearm, with a single X-ray absorptiometry (SXA) device (DTX-100 Osteometer). In 1% of the subjects, wounds, plaster casts, etc., led to the measurement of the dominant forearm. The arm's position in the water basin of the densitometer was standardized. The subject held a vertical peg during the scan, which limited the possibility for rotation and forearm movements, while the floor of the basin supported the elbow. The importance of avoiding motion during the scan was stressed. However, if movements or other irregularities were detected in the scan image, the operator would repeat the scan once or twice if necessary.

The distal and ultradistal regions of interest (ROI) were detected automatically (Fig. 1). The operators performed a manual ROI identification when the automatic routine failed, when the bone edges were wrongly identified, or when the 8 mm point was wrongly positioned. The ultradistal ROI was supposed to extend up to but not include the radial endplate. The ultradisal ROI was corrected by the operator if the distal border did not touch the radial endplate at all, but was left uncorrected if the line was drawn within or close to the radial endplate.

Long-term stability for the two cross-calibrated densitometers was monitored by measurement of aluminum wedge phantoms twice daily. The phantom

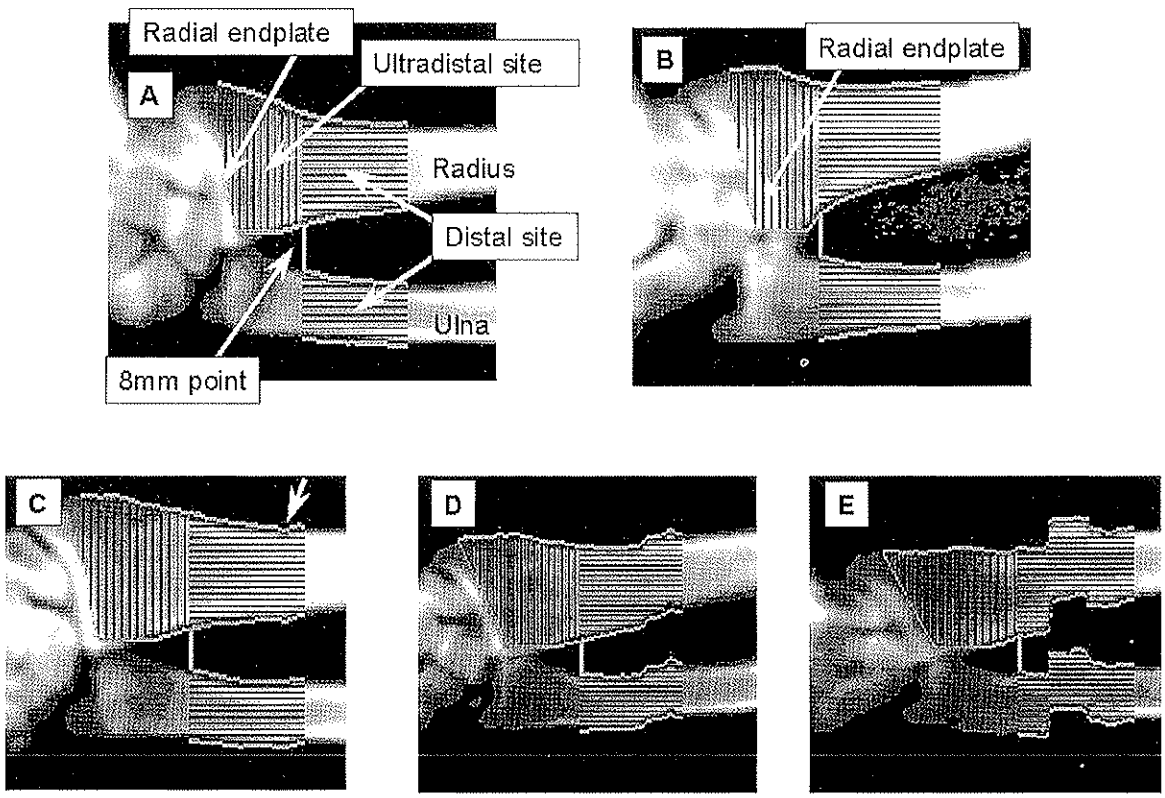

Fig. 1. Example scans from forearm bone densitometry with SXA. **A** Normal scan; **B** example of radial endplate artifact; **C–E** examples of movement artifact (**C** grade I, **D** grade II, **E** grade III).

BMD result for one densitometer was on one occasion measured twice outside the ± 1.5% limits of the calibration value and a calibration procedure was executed at this point. Otherwise densitometer performance was stable throughout the study.

Before the study began, the operators took part in a course, which included lectures on the purpose of the BMD screening, the nature and epidemiology of osteoporosis, BMD measurements in general and the specific densitometers to be used in our study. This was followed by supervised sessions in which the technicians practiced BMD measurement on each other and on 10 elderly ladies who had agreed to be 'pilot subjects'. During the study, posters and booklets containing the densitometry instructions were provided for all technicians. The first author and/or the principal technician were always present at the BMD screening. These performed supervision, gave advice and regularly controlled the most recent scans in order to secure scan quality and aid the 13 other operators. The latter spent 2 weeks each at the BMD screening before circulating to other points in the Tromsø Study program. In September and October 1994, the QC program disclosed that the instructions to repeat scans on the detection of movement artifacts were too loose. These guidelines were therefore tightened and their importance emphasized in November 1994. Otherwise the QC program did not disclose systematic irregularities of any kind during the study.

To evaluate whether artifacts could have an effect on precision we recruited subjects within the main BMD screening for two separate precision studies. A total of 111 subjects, 27–75 years of age, had forearm bone densitometry on two separate occasions (1–3 weeks apart) where repositioning, time between scans, densitometers and/or observer were systematically varied in series of up to eight scans (G. K. R. Berntsen et al., in preparation).

Scan Review

After the screening was completed all scans were reviewed by one of three observers. They assessed quality of the scan image and of the ROI identification and recorded any artifacts present. Observers A, B and C reviewed approximately 2000, 2000 and 4000 scans respectively.

The artifacts were divided into two main categories (Table 1):

1. *Image artifacts*: irregularities in the scan image. Subgroups were created according to the cause of the artifact such as movements (Mov artifacts) or main structures missing from the scan (Miss artifacts). Mov artifacts were graded according to the anatomic distortion in the BMD scan (Fig. 1).
2. *ROI artifacts*: irregularities in ROI identification. Subgroups were defined according to the structure that was erroneously identified, i.e., the radial endplate (Rad EP artifact) (Fig. 1), the bone edges (Bo Edge artifact), etc. If possible, ROI artifacts were corrected through reanalysis.

To insure as high a concordance as possible between the reviewers, they performed joint evaluations on parts of the material twice weekly, and discussed difficult cases when appropriate. Before review the BMD value was uncalculated in 39 scans and remained so in 10 (distal site) and 5 (ultradistal site) scans after review.

Reproducibility of Scan Classification

A 10% random sample of the total material (784 subjects) was selected to be re-reviewed in order to generate reproducibility data on artifact classification. The three observers each reviewed subsamples previously reviewed by themselves and subsamples reviewed by the other two reviewers so that both intra- and inter-observer data were generated. Agreement on artifact classification was quantified by the kappa statistic at both distal and ultradistal sites for the following questions: Artifact present? Mov artifact present? Rad EP artifact present?

We found excellent intra-observer kappa values ranging from 0.60 to 0.88 for all observers at both sites. Inter-observer agreement was good (kappa range 0.36–1.0) for all possible combinations of reviewers, except for the A–C pair's evaluation of the ultradistal site (kappa range 0.07–0.19). There was a low prevalence of artifacts in this particular subsample. This partly explains the kappa result, which tends to be low when one category in a classification is rare [5]. A and C actually agreed in 64–95% of cases. A review of this particular subsample by observer B also revealed a systematic tendency for observer A to be more restrictive in the use of the artifact 'diagnosis' than was observer C.

Data Analysis and Statistics

Prevalence of Artifacts. The determination of artifact prevalence was done in the 'best scan' selection, which included the first normal or the best scan for each subject. Nine percent of the subjects had more than one eligible scan. Prevalence figures are presented as crude percentages of the total material.

Effect of Artifacts on BMD Results. The two most common artifact types, the Rad EP artifact and the Mov artifact, were examined for both systematic shifts in BMD result and nonsystematic effects (increased random variability) on BMD results. Scans with multiple artifacts were excluded from these analyses.

(1) *Systematic effects*. A systematic shift in the BMD result is present when the mean difference between the normal and artifactual scan is different from zero. Specifically the BMD result before and after reanalysis of 5614 scans with an original Rad EP artifact was

compared. In the case of Mov artifact the scans of subjects with a Mov artifact at the distal site (n = 202) and ultradistal site (n = 67) were compared with a normal repeat scan on the same subject. In our analyses the BMD difference is negative when the BMD result of the normal scan is the lower of the two. The BMD difference is expressed in g/cm^2 or in percent of the nonartifactual BMD result (% BMD difference). The BMD difference is normally distributed; thus means and 95% confidence intervals (95% CI) are presented at the group level.

(2) *Nonsystematic, random effects.* High individual BMD variation in artifactual scans as compared with normal scans indicates that the artifact decreases precision. We use the absolute differences between two repeat measurements on each individual (the individual range) as a measure of the individual BMD variation. Specifically for Rad EP artifacts, we compared median individual ranges for two repeat scans in 44 precision study participants before and after their Rad EP artifact was corrected. For Mov artifacts we compared the median individual ranges between two groups:

(a) subjects with two normal repeat scans from the precision substudy (distal site, n = 69; ultradistal site, n = 70);
(b) subjects with one Mov artifact scan and a normal repeat scan from the main study (distal site, n = 202; ultradistal site, n = 67).

The absolute BMD difference can be expressed in g/cm^2 centimeter or as a percentage of the individual BMD level (absolute % BMD difference). The measure has a skewed distribution, which is why medians and percentiles are presented at the group level. Extreme values lie in the right-hand tail of the distributions, thus the 95th percentiles identify the extreme 5% of the data.

Statistics. The SAS software package, v.6.12, was used for both data management and statistical analyses. A p value below 0.01 was considered statistically significant. Associations with skewed continuous dependent variables (absolute BMD difference) were tested with the Kruskal–Wallis chi-squared approximation. Relationships between categorical and continuous normally distributed variables (BMD difference) were tested by the F-test in analysis of variance. Comparisons between two normally distributed, paired variables were examined in a paired one-sample t-test. The Cochrane–Mantel–Haenzel test was used to test associations with categorical dependent variables such as artifact prevalence.

Results

All Artifact Types: Prevalence

At the distal site 15.2% of the scans (n = 1213) had one or more artifacts (Table 1). Reanalysis corrected artifacts in 2.3%, thereby leaving 12.9% of the scans with an uncorrectable artifact. At the ultradistal site 6539 scans (82.3%) were artifactual (Table 1), but 76.9% were fully corrected by reanalysis leaving 5.4% of the scans with an uncorrectable artifact.

Table 1. Distribution of artifacts by measurement site in forearm bone densitometry with SXA, presented as percentages of total (n = 7948).

Artifact type	Distal site (%)	Ultradistal site (%)
Image artifacts		
Mov	12.2	1.9
Miss	–	1.2
ROI artifacts		
8 mm	1.3	0.2
Bo Edg	0.4	3.3
Rad EP	–	70.7
ROI fail	0.1	0.1
Unclassifiable problem	0.4	0.2
Multiple artifacts	0.8	4.7

Image artifact, artifact which flaws the image; *ROI artifact*, inaccurate identification of region of interest (ROI); *Mov*, movement artifact, *Miss*, region of interest partly missed in the scan; *8 mm*, 8 mm point inaccurately identified; *Bo Edg*, Bone edges inaccurately identified; *Rad EP*, radial endplate inaccurately identified; *ROI fail*, failure to identify region of interest.

Mov Artifact

Prevalence. The total Mov artifact prevalence at either distal or ultradistal sites, including scans with other coexisting artifacts, was 14.2% (9.6% distal, 1.5% ultradistal and 3.1% both sites). The prevalence of serious Mov artifacts (grade II/III) decreased from 12% in September/October 1994, via 8% in December 1994 and to a stable 3% from January to September 1995. A grade I artifact was found in 9% of the scans throughout the study period.

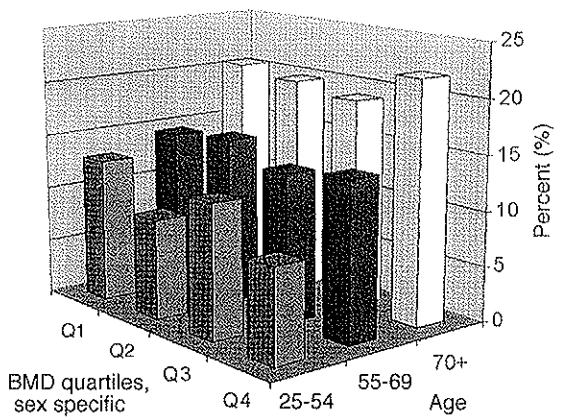

Fig. 2. Prevalence of movement artifacts by age and BMD level in a review of 7948 forearm bone densitometry scans. BMD quartiles are sex-specific; Q1 is the lowest quartile. Cochrane–Mantel–Haenzel tests for association with movement artifact prevalence: (age, adjusted for BMD level): test statistic: 48.0, p<0.001; BMD level, (adjusted for age): test statistic 1.1, p = 0.29.

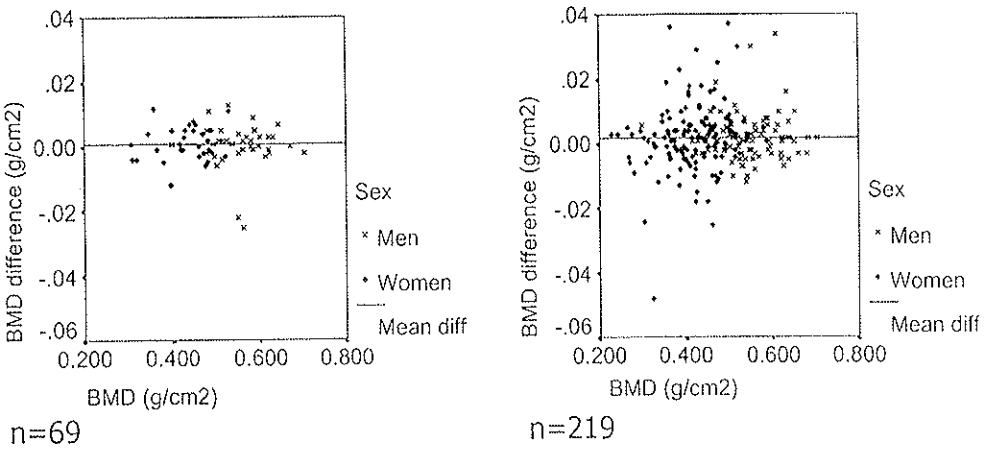

Fig. 3. BMD variation in normal and movement artifact scans (distal site). *Left*: Difference between two normal repeat scans in 69 subjects plotted by the individual BMD mean. *Right*: Difference between two repeat scans in 202 subjects where one has a movement artifact, plotted by the normal BMD result.

Age was an independent predictor of Mov artifact. Prevalence rose from 9% in younger subjects to 20% in the oldest age group. The age association was the same for both sexes and remained strong after adjustment for BMD level (Fig. 2). Neither sex, BMD level nor scan reviewer was an independent predictor of Mov artifact occurrence.

Effects. The effect of Mov artifact was to decrease precision, as illustrated in the Altman plots in Fig. 3. When BMD differences between two normal scans are plotted by their mean BMD level, the differences center on zero in a narrow band (left-hand panel, Fig. 3). When the same is done in 202 subjects with one Mov artifact scan and a normal repeat scan, the differences still center on zero but they are now distributed in a much wider band (right-hand panel, Fig. 3). The median absolute % BMD difference at the distal site was 0.58% for the left-hand plot and 0.94% in the right-hand plot ($p = 0.0027$). At the ultradistal site, the same figures were 0.90% and 1.89% ($p < 0.0001$). The decrease in precision was independent of the grade of the Mov artifact, BMD level, age and sex.

There was a small systematic increase in the normal BMD result as compared with the Mov artifact result at the distal site (BMD difference 0.002, $p = 0.0032$) but not at the ultradistal site (BMD difference –0.004, $p = 0.10$).

Rad EP Artifact

Prevalence. Three of every four scans (74.3%), including those with coexisting artifacts, had a Rad EP artifact. A high BMD level was predictive of a Rad EP artifact in both women ($p = 0.004$) and men ($p < 0.001$) after adjusting for age. Furthermore young age predicted Rad EP artifact in women ($p < 0.001$) but not in men ($p = 0.08$). Scan reviewers A, B and C identified 58%, 74% and 80% of the scans as having a Rad EP artifact respectively ($p < 0.0001$).

Effects. Reanalysis of Rad EP artifact scans led to a drop in BMD in 94% of cases. The normal BMD results were on average 0.012 g/cm^2 ($p < 0.0001$) and 0.017 g/cm^2 ($p < 0.0001$) lower than the artifactual BMD results for women and men respectively. The average % BMD difference was –3.8% for both sexes ($p < 0.001$). The number of subjects with a Rad EP artifact who were diagnosed as osteoporotic (according to WHO criteria [6]) increased from 583 subjects to 649 subjects (+10%) after reanalysis. For subjects without a Rad EP artifact, reanalysis caused only 3 additional subjects to enter the osteoporosis group ($p < 0.0001$).

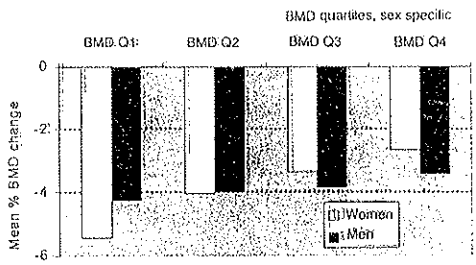

Fig. 4. Mean percentage BMD difference due to reanalysis of 5614 forearm scans with inaccurate radial endplate identification (Rad EP artifact) by BMD level and sex. BMD quartiles are sex-specific; Q1 is the lowest quartile. ANOVA analysis for associations between % BMD change and BMD level, adjusted for age: women: F-statistic 53.8, $p < 0.0001$, men: F-statistic 4.41, $p = 0.0042$.

The % BMD difference was inversely related to BMD level. In particular, women with a low BMD level experienced a large mean % BMD difference (–5.43%) (Fig. 4), and after reanalysis the number of osteoporotic subjects increased by 13% in this group. Neither age nor sex was independently associated with absolute or percentage BMD difference. There was no evidence of any decrease in precision due to reanalysis of these scans.

Discussion

The Mov artifact was found in 14.2% and the Rad EP artifact in 74.3% of all scans. Mov artifacts decreased precision, whereas a correction of the Rad EP artifact led to a systematic decrease in the BMD results.

High Prevalence of Artifacts

Mov Artifacts. We found that despite clear guidelines and rigorous follow-up to avoid Mov artifacts, we were able neither to eliminate the more serious Mov artifacts nor to reduce the occurrence of grade I artifacts. The software's demarcation of the ROI often concealed grade I Mov artifacts. Thus these artifacts were mainly discovered at inspection of a nonshaded scan image during the review. The more serious grade II and III artifacts were, however, easy to detect and should have led to repeat scanning. In the NHANES study roughly 2% of the scans were rejected due to Mov artifacts, which is similar to our grade III Mov artifact prevalence. However, the figures are hardly comparable, as Wahner et al. [4] give no description of the degree of movement that was considered necessary for exclusion. The prevalence of Mov artifacts was highest in the elderly, an important patient group in densitometry. Given the effect of this artifact, it represents a major challenge in high-quality bone densitometry.

Rad EP Artifacts. We felt that reanalysis of a large number of scans with slight differences in radial endplate identification by the operator on site was not a good use of either the operators' time or the QC program. The very high prevalence of the Rad EP artifact was therefore not caused by lax QC procedures, as the operators did comply with their instructions. The low prevalence of other types of ROI artifacts confirms this. The arguments for deferring the handling of this artifact to the review process are summarized below. Firstly, the computer algorithm did in fact identify the radial endplate, but its exact identification of the radial endplate border varied slightly from scan to scan. Often no more than 1 or 2 mm of the cortical radial endplate was included in the lower region of the ROI. Secondly, we were uncertain of both the prevalence and the effect, if any, of this particular inaccuracy. Thirdly, the education and training of 15 observers to identify the radial endplate in a correct and consistent manner would be a large task. Fourthly, such a change of protocol would strain an already tight time schedule at the BMD screening and could also result in decreased precision. Lastly, we felt that reanalysis of the Rad EP artifact scans would be more consistent if performed by as few reviewers as possible.

The proportion of scans with an ROI artifact was high. However, we know from the NHANES study that the original ROIs, as identified automatically and/or by the operator, needed to be reanalyzed in 33% of the hip scans [4]. The SOF study reviewed only scans which had been flagged by the clinic as deviant, or were selected at random or had BMD values outside 4 standard deviations. They reanalyzed 313 hip (4% of the total) and 512 spine (7% of the total) scans in all 7659 subjects in this process [7]. Thus, the need for reanalysis due to deviant ROI identification seems to be common not only at the forearm but also at other sites.

The proportion of scans identified with a Rad EP artifact differed significantly between reviewers. As we had no way of knowing whether we ought to have a high or low threshold for the Rad EP artifact 'diagnosis' we formulated no guidelines for the review of difficult cases. The disagreement between the reviewers probably reflects this lack of guidelines. All three reviewers did, however, identify the Rad EP artifact in a majority of the scans. We conclude that the automatic software algorithm was unable to identify the predefined ROI with confidence. In cases as this we recommend that semiautomatic, interactive software programs allow the operator to define the ROI by visual inspection as a part of the normal BMD measurement procedure.

Bias Considerations. The prevalence of both the Rad EP and the Mov artifact were associated with age, which raises concerns about the lower response rates in subjects aged >80 and <45 years. Nonattenders, especially among the elderly subjects, may have a lower response rate due to disease [8,9], which could theoretically influence artifact prevalence. However, the total number of nonattenders >80 years of age in the a priori selection was 18 subjects, which is too few to alter our overall estimates substantially. In the younger age groups, high mobility, change of address, low preoccupation with health-related issues and difficulties leaving work or children are probably more important causes of nonattendance than disease. We have no reason to believe that young nonattenders would have different artifact prevalences compared with attenders. Therefore, although we have shown some age-related effects in this paper, it is unlikely that the inclusion of these subjects would alter overall estimates substantially.

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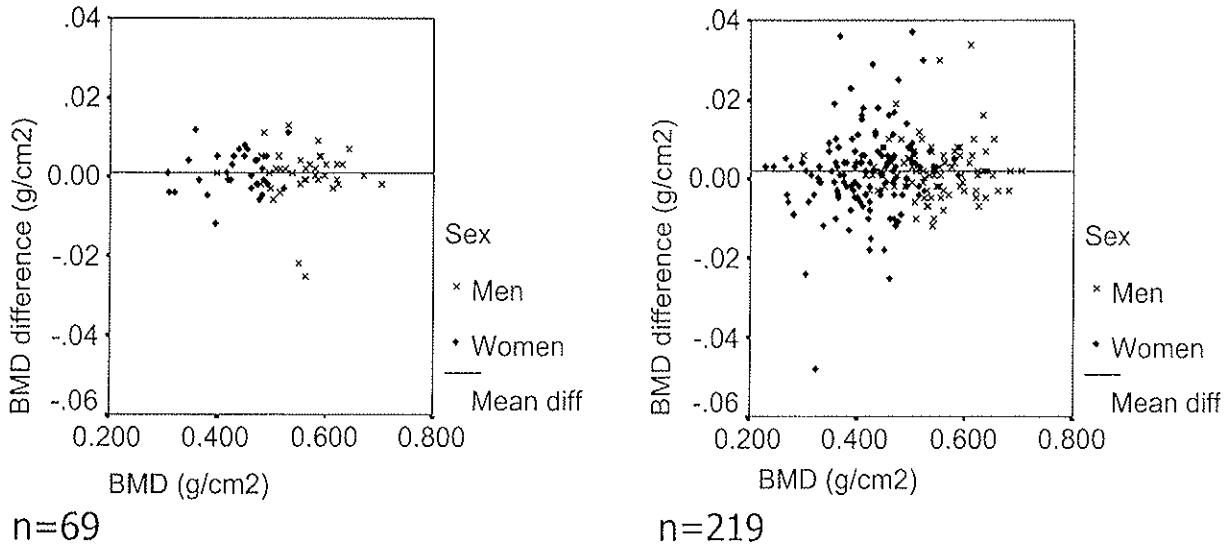

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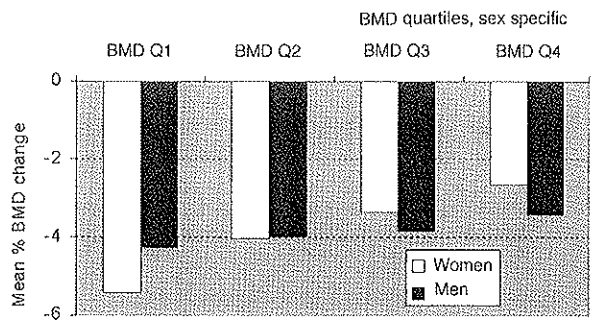

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Mov Artifacts Lower Precision. The general advice in Mov artifact handling up to now has been to discard any definite Mov artifact scan whereas hardly

detectable Mov artifacts are permissible. However, we found that even the slightest movement artifacts decrease precision and this lack of association with the Mov artifact grade was surprising. If the arm moves together with the scanner for one or several cycles, the scanner will either skip or scan the same area twice. This should be of minor importance if the movement is small. We therefore hypothesize that the anatomic distortion in a two-dimensional scan does not reflect the real three-dimensional movement that might have been present.

The precision error in repeat scans with a Mov artifact was roughly double that of normal repeat scans at both sites. This will first and foremost have implications for measurement of a BMD change in patients, where a small decrease in precision seriously undermines the possibility of detecting a real change in BMD (G. K. R. Berntsen et al. in preparation). For the establishment of BMD level, this type of increased imprecision could affect classification of patients who lie close to any predefined cutoff point, but would otherwise be of minor importance. In research, this kind of imprecision would decrease the power of a study to identify associations with BMD [10].

The number of subjects in the control group with normal repeat scans was too small to permit stratification by age, sex and BMD level in the comparison between the two groups. As all three factors are possible confounders, our results need to be confirmed in other studies.

Rad EP Artifact Causes a Systematic Shift in BMD Results. The ultradistal site is designed to yield information about the trabecular tissue at a predominantly trabecular site. This is why the occasional addition of cortical bone within the ROI, such as the radial endplate, is unwanted. Correction of the Rad EP artifact led to a systematic downward shift of the BMD result, equalling roughly 3 years of bone loss. Reanalysis of the scans caused a substantial increase in the number of subjects who were diagnosed as osteoporotic according to the WHO definition, with a larger effect seen in women with a low BMD.

We have shown that a relatively small error in ROI identification may disturb classification of the individual subject's diagnosis, especially if his or her BMD result lies close to the cut off point. Furthermore, such inaccuracies can produce large errors in measurements of BMD change over time. In the research setting, this systematic BMD error, had it been left uncorrected, would have misclassified subjects with the Rad EP artifact relative to those who do not have it, leading to the possibility of decreased statistical power to detect important associations. Depending on the research question, it may even introduce a differential misclassification in certain analyses. We therefore strongly recommend that scans with even slight nonintended inclusions of cortical bone in the ROI should lead to a reanalysis of the scan in both clinical and research settings.

Limitations. Scans with multiple artifacts were excluded from some of the statistical analyses in order to facilitate interpretation of results. It is therefore possible that results regarding associations with artifact prevalence and the description of artifact effects are not applicable to scans with multiple artifacts.

Generalizing Results

The prevalence of movement artifacts in this study can be generalized to any densitometry measurement of the forearm that takes between 3 and 5 min, regardless of densitometer type. The prevalence of the Mov artifact as characterized in this study is at present unknown for other sites and types of equipment. The extent of the problem is probably less with newer and faster equipment, which now largely replaces SXA scanners, but should nevertheless be examined for these newer scanners also. The effects of the movement artifacts can be generalized to any movement artifact at any site, with any type of densitometer equipment.

The magnitude of the ROI artifact problem, and in particular the Rad EP artifact issue, is not readily generalizable to other types of densitometry equipment. However, the high occurrence of ROI artifacts found in our study, and in other large BMD studies at other sites, is disturbing. We hope that this paper may encourage other researchers to characterize artifacts and their effects at other sites and densitometry settings for the good of all practitioners of bone densitometry.

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Paper II

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The Tromsø Study: Determinants of precision in bone densitometry

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The Tromsø Study: Determinants of precision in bone densitometry.

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Studies of precision determinants in bone densitometry are scarce. A total of 111 subjects recruited from the population based multipurpose Tromsø Study (Norway), 27-75 years of age, had repeated forearm bone densitometry (SXA) measurements. Measurement conditions were systematically varied in series up to eight scans. Median coefficients of variation (CV) for two scans performed one week apart, by two different operators were 0.79% and 0.98% at distal and ultradistal sites respectively. The CV distribution was skewed: 5% of the subjects had individual CV's above 2.2% (distal) and 3.4% (ultradistal). Age ($p=0.0097$) and repositioning were important determinants of precision. The SXA BMD-measurement method is sufficiently precise to establish BMD-level. The minimal individual percentage BMD-change that can be detected with 95% certainty was 2% and 3% at distal and ultradistal sites respectively. Detection of BMD-changes less than this should rely on multiple repeat measurements at each point in time.

Key words: Bone mineral density, Precision, SXA, Forearm, Age, Repositioning

Title: The Tromsø Study: Determinants of precision in bone densitometry.

Introduction

Precision can be defined as a test's ability to get the same result with repeated tests on the same individual under comparable circumstances [1]. The importance of precision is widely recognised in measurement of both bone mineral density (BMD)-levels and individual BMD changes [2-4]. Knowledge of precision is especially important in measurements of individual BMD-change as the biological changes are small and may well equal the random measurement error.

Single X-ray Absorptiometry (SXA) of the forearm is a good candidate for any screening based wholly or partly on BMD [5,6]. Forearm BMD measurements predict any fracture in women as well as other measurement sites [7] and may even have a stronger association to male fragility fractures [8]. Measurement of the forearm is easy and readily standardised, multiple measurements in order to enhance precision are feasible and SXA is cheaper than Dual Energy X-ray Absorptiometry (DEXA) measurements at axial sites.

The SXA of the forearm is furthermore thought to be one of the most precise densitometric methods, but this has so far been evaluated by only three authors[9-11]. All three included 15 or fewer women only, thereby limiting the possibilities to study precision in relation to subject or measurement characteristics. It is plausible that subject factors such as age, sex and BMD-level and measurement factors such as densitometer, observer, position etc. could influence precision. Knowledge of precision determinants would help us minimise random measurement error and select patients who need multiple measurements to ensure adequate precision. Yet, despite their importance in the clinical setting, the determinants of BMD-precision are largely unknown.

We feel that the issue of precision in BMD-measurements in general and precision in SXA-densitometers in particular has been inadequately evaluated. Our study was designed to answer the following questions:

1. What is BMD-precision using SXA at the forearm?
2. Do measurement factors such as time between scans, observer and densitometer affect precision?
3. Is precision dependent on subject characteristics such as age, sex or BMD-level ?

Materials and Methods

Subjects

Two separate precision sub-studies were performed in the course of the bone density screening program in the fourth survey (1994-95) of the Tromsø study. This is a population based multipurpose study, where repeated questionnaires and clinical examinations have been administered to certain birth cohorts living in the municipality of Tromsø - Norway since 1974. In the 1994-95 survey, all men and women aged 55 -74 plus 5-10% samples of other age groups who attended the main survey, were invited to an extended examination [12] which included bone densitometry [13]. Subjects who attended the main survey a few weeks ahead of the precision studies and were eligible for the extended examination were consecutively invited to participate in two precision studies. Study 1 was conducted during the 10^{th} and 11^{th} week , and Study 2 during the 37^{th} and 40^{th} week of the 52 week long survey. Subjects were informed they would have repeated examinations in the course of two visits one or three weeks apart.

Precision study design

We performed repeated scans on participants at the non-dominant arm (distal and ultradistal sites), with two SXA-densitometers (DTX-100, Osteometer). The observers switched roles for every second subject, so that each took the observer –A and –B roles described below for 50% of the subjects in both precision studies.

First study: At each visit, the first observer (A) performed two scans immediately after one another, thereafter the second observer (B) did a third and, if time permitted, a fourth scan. Repositioning occurred concurrently with observer change. The same procedure was repeated at the second visit, by the same pair of observers exactly one week later. Two pairs of observers took part, the first pair covered the first two days and the second pair the last three days in each of the two study weeks. In all 497 scans were performed on 79 subjects. No subjects had a full series of eight scans, 72 subjects had seven or six scans, and seven subjects failed to return for their second visit and contributed four or less scans each.
Second study: Only one pair of observers took part. At each visit observer A performed a scan on one densitometer, thereafter observer B performed a repeat scan on the second

densitometer. The same procedure with the same pair of observers was repeated exactly three weeks later. A total of 119 scans were performed on 32 subjects of whom 24 had a full series of four scans and five subjects failed to return for the second visit and contributed only two scans each.

All scans were reviewed for detection of artefacts and only scans completely free of artefacts were included for the distal site, while all normal scans and scans with a corrected identification of the radial endplate were included at the ultradistal site. We have previously shown that movement artefacts decrease precision [13]. We wanted our precision estimates to be independent of movement artefact prevalence, which is why all movement artefacts, also those hardly detectable were excluded. At the distal site, 88 scans (16%) were excluded of which 82% constituted movement artefacts and the remainder erroneous identification of anatomical landmarks. In all 17% of the ultradistal scans were excluded, of which 66% were due to movement artefacts and missing region of interest in the scan, and the remaining were due to incorrect identification of anatomical landmarks other than the radial endplate. After exclusions 103 and 101 subjects were eligible for data analysis of distal and ultradistal precision respectively. Due to the exclusions, all subjects could not contribute to all precision types and the number of subjects contributing to each site and precision type differs. However, no analysis-sub-set had an age, sex or BMD distribution which was significantly different from the total precision study population. Twelve subjects did not return for their second visit, and could therefore only contribute to short-term precision estimates. The sex and age distribution among these twelve did not differ from the total study population.

Densitometer stability and comparability

The long-term performance of the densitometers, both during the main screening and the precision studies was assured by twice daily measurements of an aluminium wedge phantom. Stability was regarded as adequate if phantom measurements were within ±1.5% limits of the calibration value on both densitometers. No calibration procedures or corrections of stability were required during, or between the two precision studies. The mean phantom BMD-results from a total of 30 phantom measurements made during the week of the second precision study were 0.394 g/cm^2 and 0.393 g/cm^2 for each of the two densitometers respectively ($p=0.78$).

Data analysis

The terminology used to describe precision type is presented in Table 1. We calculated a whole range of precision estimates, each reflecting a specific repeat measurement situation. Unless explicitly specified as inter-densitometer estimates, all reported precision estimates are based on scans from the same densitometer for each subject. These are as follows:

- Two scans made immediately after one another without repositioning in between scans by the same observer (Short term intra-observer precision).
- Two scans made by different observers, on the same day with repositioning between them (Short term inter-observer precision)
- Two scans made one week (1st study particpants) or three weeks (2nd study particpants) apart by the same observer. (Intermediate term intra-observer precision)
- Two scans made on two different densitometers by two different observers the same day (Short term inter-densitometer inter-observer precision).
- Two scans made one (1st study particpants) or three weeks (2nd study particpants) apart by two different observers. (Intermediate term inter-observer precision). This precision type represents a common situation in most clinical settings, which is why we chose to examine the effects of subject characteristics on precision and to calculate the clinical consequences of the given precision for this type only.
- Two scans made on two different densitometers by two different observers three weeks apart (Intermediate term inter-densitometer inter-observer precision).

The same subject could have more than one set of scans eligible for a specific precision estimate. In calculating overall precision estimates, we included only the first pair from each individual in each analysis. The 95 percentiles then exemplify the degree of imprecision that can occur between two sequential scans on the same person under the specified circumstances, where the BMD-result is expected to be constant.

To increase power in between group analyses, we entered the mean precision estimate (SD or CV) for each subject in such analyses. The mean was based on results from all available pairs of scans (max. 3) in each individual. The precision of the individual estimates is thus increased, which in turn raises the power of the analysis. Subjects contribute differing numbers of scan pairs (unbalanced design) which makes the 5- and 95 percentiles difficult to

interpret. This is why the 5- and 95 percentiles are not presented for this particular analysis, and why we have adhered to the simpler balanced design in the overall analyses described above.

Describing precision

The following variables describe different aspects of precision:

- The mean difference between two repeat scans reflects the systematic BMD-difference between two measurements. A negative value indicates that the second measurement, or for inter-densitometer difference's, the densitometer A's result is lower than densitometer B's result. The mean of the individual differences with the 95% limits of agreement is presented at the group level [14]. Altman plots give a visual impression of the relationship between BMD-differences and BMD-level [14].
- The individual Standard Deviation (SD) reflects the magnitude of the BMD-change between repeat measurements. As this variable is skewed (Figure 1), median and percentiles for the individual SD is presented at the group level.
- The individual Coefficient of Variation (CV) is the individual SD expressed as a percentage of the individual mean BMD. Again the distribution is skewed (Figure1) thus we present medians and percentiles. This measure reflects change relative to the individual's BMD-level, thus if the SD is similar, the CV will be higher in subjects with a low BMD.
- Distance to BMD-mean. The mean BMD, based on all available BMD results, for each individual is our closest estimate of their true BMD. The difference between the individual's BMD-mean and his/ her single BMD-results is used to identify single BMD-results which deviate more than a predefined clinically relevant unit from the "true" BMD-value.
- Unless otherwise stated, CV and SD estimates all concern BMD-results.

Extreme values of the individual SDs and CVs lie in the right tail of their respective distributions. In order to identify the five- percent of the study population with the lowest precision we therefore supply the 95^{th} percentiles. The addition of the 5^{th} percentile gives the reader a three-point description of every non-normal distribution.

Unadjusted mean BMD-difference revealed a systematic difference between the two densitometers. In order to avoid false inflation of inter densitometer precision estimates due to this systematic difference, BMD values from one densitometer was recalculated to the scale of the other. This was done by use of regression coefficients from best fitting model for the relationship between the individual mean BMD-values from the two densitometers A and B. The equations were:

- Distal site: BMD-A =-0.000075+0.980*BMD-B
- Ultradistal site: BMD-A=0.0023+0.965*BMD-B

The clinical consequences of the precision estimates were evaluated in two different ways:

1) The BMD difference between two scans performed close in time should ideally be zero. We determined the number of subjects where this BMD difference was larger than a clinically relevant BMD-unit. We arbitrarily chose the following units: a ½ T-score unit (the young female SD divided by 2 which is 0.019 g/cm^2 (data not shown) and a three-year bone loss unit which is -0.014 g/cm^2 (1.3% annual bone loss of female mean BMD at age 60-69[15]).
2) Calculating the minimal difference, which represents true biological change with 95% certainty (95% detection limit). This is theoretically given by the following two formulae: $\Delta = \pm 1.96 * s\sqrt{(2)}$ and $\Delta\% = \pm 1.96 * CV\sqrt{(2)}$ [16], where Δ and $\Delta\%$ is the 95% detection limit given in g/cm^2 and percentage difference respectively. S and CV are the estimates of the population's intra-individual mean standard deviation and mean coefficients of variation respectively. We would expect approximately five percent of our subjects to have repeated BMD-measurements that differ more than the 95% detection limits.

Statistics

The SAS software package, v. 6.12 [17,18] was used both for data management and statistical analysis. All means are crude. Difference between paired BMD-results were examined by a paired one-sample t-test. Within subject comparisons of precision estimates were also performed by use of paired one sample t-tests, because the difference between paired SD or CV estimates were, unlike the underlying SD and CV distributions, normally distributed. The skewedness of the SD and CV-variables precludes ANOVA or multiple regression in the analysis of precision determinants, which is why we use the non-parametric Kruskal Wallis chi-square approximation [19] instead. Because multiple tests increases the chances of

committing type I errors, we chose to consider only p-values below 0.01 as statistically significant. In calculation of the number of repeat scans required in a clinical situation to detect a given BMD-change we set probability of type I and II error to 0.05 and 0.20 respectively [20].

Results:

Overall precision

Subject characteristics of precision study participants are given in Table 1. The median CV in the intermediate term, inter observer situation was 0.79% at the distal and 0.98% at the ultradistal site, with the corresponding 95th CV percentiles of 2.2% and 3.4% at the two sites respectively (table 3 and 4).

Using the formulae for the 95% detection limit, we would expect a change of 0.012 g/cm2 and 2.2% between two measurements to represent a true biological change in 95% of the cases (95% detection limit). At the ultradistal site the 95% detection limits were 0.012 g/cm^2 and 2.7%. However 9% (95% Confidence Interval (CI): 4-19%) and 12% (95% CI 5-22%) of the absolute differences between measurements made one or three weeks apart at the distal and ultradistal sites respectively exceeded these 95% detection limits. Of the percentage differences, 3% (Distal, 95% CI 0.4-11%) and 4% (Ultradistal, 95% CI 1-13%) exceeded the 95% percentage detection limits.

One of 130 distal measurements, and none of 132 ultradistal BMD-results of the scans belonging to pairs made on different days by different observers, had a distance to mean of >± ½ T-score. A total of 9% (distal: 95% CI: 4-19 %) and 12% (ultradistal, 95% CI: 5-23 %) had changes exceeding a three-year BMD change.

Precision and measurement factors

Table 3 and 4 provide precision estimates for several different repeat measurement situations. The SD- and CV-values in the first rows, which is the only estimate of precision where subjects were not repositioned, were either significantly lower or borderline significantly lower ($p<0.02$) than those in the last three rows at both measurement sites. Neither SD nor CV estimates of the three last rows were significantly different from each other. The first-row SD and CV estimates were also significantly different from the adjusted inter-densitometer intermediate term precision at both sites. Precision was not significantly different between observers nor between distal and ultradistal measurement sites. With the exception of the unadjusted inter-densitometer precision estimates, no mean BMD-differences were different from zero.

Densitometer change

The short term in vivo results were 0.009 g/cm^2 ($p<0.0001$) and 0.006 g/cm^2 ($p=0.0027$) lower on densitometer A as compared to densitometer B at distal and ultradistal sites respectively (Table 5) The differences between the densitometers equalled 2% of both distal and ultradistal pre-menopausal BMD. The pattern was the same for intermediate term results, but failed to reach statistical significance. When the systematic BMD-difference between the densitometers was corrected, neither CV nor SD-estimates differed from comparable intra-densitometer precision estimates.

Precision and subject characteristics

At the distal site both SD- and CV-estimates were associated with age (Table 6) although the SD-age association was of borderline statistical significance. There were no significant associations between age and precision at the ultradistal site, but the CV estimates exhibit the same age-precision pattern as for the distal site (Table 6). The mean BMD-differences (Figure 2) and SD- and CV estimates were independent of BMD-level (Distal, women: $p = 0.67$, men: $p=0.18$, Ultradistal: women: $p=0.98$, men: $p=0.24$) and sex (SD distal site: women 0.004 vs. men 0.005 g/cm^2 $p=0.054$, ultradistal: women 0.004 vs. men 005 g/cm^2 $p=0.30$).

Discussion.

When measurements are made on different days and by different observers the majority had CV's below 1% at both distal and ultradistal sites. The minimal individual BMD-difference which can be detected with 95% certainty was 0.012 g/cm2 and 2.2% at the distal site and 0.012 g/cm^2 and 2.7% at the ultradistal site. Single BMD-results rarely deviate more than ½ T-score from the individual mean BMD, whereas a BMD-difference between two repeat scans equals a three year bone loss in 10% and 9% of the subjects at distal and ultradistal sites respectively.

Bias considerations

The age-precision relationship was not linear as subjects aged > 65 had both higher BMD-levels and slightly lower SD and CV-estimates than the age group below. This was unexpected and may reflect a selection bias, i.e. that the precision study recruited only the most fit elderly subjects, as participation could be considered both strenuous and tedious.

As we excluded all non-correctable artefacts, such as movement artefacts, our precision estimates are not representative of scans with such artefacts. The effect of movement artefacts on precision has been documented elsewhere [13].

The exclusion of all correctable artefacts (i.e. erroneous identification of region of interest) at the distal site could in theory improve precision estimates, as the effect of scan reanalysis is excluded. However we did not find distal SD's to be significantly lower than ultradistal SD's, where a large part of the scans were reanalysed. We have also shown previously that reanalysis of scans does not alter precision estimates [13].

The "Distance to mean" variable probably underestimates the proportion of subjects with results deviating significantly from the true BMD-value. A BMD-outlier, which lies far away from the true BMD, will move the mean in the same direction as the outlier and away from the true value. This will again affect the "Distance to mean"-value making it smaller than a theoretical "Distance to true BMD" value would have been.

Precision estimates

The median precision estimates were less than 1% at both sites, which is quite satisfactory compared to other BMD-measurement methods [21]. We also did analyses including all available scan pairs for each person. This did not change the central estimates, but led to tighter 5-95 percentiles intervals.

The number of subjects whose absolute BMD-differences exceeded the level which theoretically should represent true biological change with 95% certainty, were higher than the expected 5%. Yet, all matching confidence intervals included the 5% level. Also, the number of subjects with a percentage BMD- change exceeding the 95% detection limits were close to the expected 5%. We therefore conclude that, the 95% detection limit model fitted our data well.

We use measures (SD and CV) which are not normally distributed and therefore present medians and percentiles. This limits comparability with studies presenting means. In the discussion we therefore give the mean SDs and/or CVs for the same age and sex groups as used by other authors. Kelly [10] reports distal site SD and CV of 0.006 g/cm^2 and 1.1 % for nine men and women aged <60, which was close to our results (SD 0.005 g/cm^2, CV 1.0%). Borg's [9] distal CV of 0.83% for 15 men and women aged <50 was near our mean CV (0.62 %). Lin [11] reported a distal CV of 1.1 % for ten women between 20-80 years of age, which was close to our CV (1.3%), whereas ultradistal CV of 2.1% was slightly higher than ours (1.8%). The authors did not present the distributions of individual SDs and CVs, thus this aspect could not be compared.

Densitometer change

There were systematic BMD-differences between densitometers, which were both statistically and possibly clinically significant, whereas the phantom measurements in the same period revealed no such systematic differences. Other authors have also identified systematic measurement error between densitometers of the same brand and type, but these differences were found in vitro [4,21-24], which explains the recommended circulation of a single phantom between densitometers [4] in multicentre trials. Aluminium wedge phantoms may be less suited to mimic the in vivo situation than newer anthopometric phantoms made of hydroxyapatite [25]. We have demonstrated that in vitro comparison may not detect true inter

densitometer bias, therefore inter-densitometer reproducibility should be evaluated both in vitro and in vivo when aluminium wedge phantoms are used. Externally produced reference values for a certain densitometer type and brand may not translate well to the local densitometer either. A possible solution would be to translate both the local densitometer's values and reference values to the scale of a standardised phantom, like the European Forearm Phantom®. Otherwise we suggest clinicians rely on reference values produced on the local densitometer.

The systematic difference between the two densitometers would inflate the inter-densitometer precision. The true inter-densitometer precision can only be evaluated after such systematic differences have been removed. After adjustment, the inter-densitometer precision was comparable to the intra-densitometer precision for the 1st study. We conclude that densitometer change did not affect precision significantly, when systematic differences between densitometers are accounted for. Our adjusted estimates of mean inter densitometer CVs for the distal site (mean CV, short term - 0.9%, longterm 1.4%), were smaller than those of Blake (Spine: 1.4% , Wards triangle 3.2%)[23] and Orwoll (Spine: 2.1-3.3%, Femur: 1.85% - 3.25%)[24], whereas our equivalent ultradistal estimates were in the same range (mean CV, short term: 1.8%, intermediate term: 2.5%).

Repositioning, observer change and different days

The largest and only significant leap between the different precision estimates was found between the first and second rows in Table 3 and 4. This could be due to either repositioning or to observer-change. However, the long-term intra- and inter-observer estimates were not significantly different from each other and precision was also independent of observer. We therefore believe that repositioning of the arm is the most important determinant of precision, and that different operators, time elapsed and change of densitometer only contribute slightly to the random measurement error. Pocock et al also found that hip BMD varied up to 18% from initial value, depending on leg rotation during the scan [26] and Mc Donald [27] found that in vitro CV with SPA depended on repositioning.

Subject characteristics are important for precision

We hypothesise that lower precision among older subjects may be due to a higher frequency of minor undetected movement artefacts in this group. The age-dependent pattern in our study was not linear, but as discussed previously, the five oldest subjects may not be representative for their age group. Why the age-pattern was most clear at the distal site is an open question. Three previous studies support the possible association between age and lower precision in densitometry [21,28,29], although two report this as lower precision among postmenopausal as compared to pre-menopausal women [28,29]. BMD-precision is also lower in elderly hemiplegic patients when compared to younger normals [30]. One study found no age - precision relationship [31].

Determination of BMD-level and BMD change

BMD-level can be determined to the nearest ±½ T-score with only one BMD-measurement with a high degree of certainty. Individual BMD-change should be greater than 2% (distal) and 3% (ultradistal) before it can be reliably detected by two separate measurements, which means that more than two years should elapse before we could expect to detect a BMD-change of 1% pr. year at the distal site in a normal individual. If clinicians would like to detect smaller than 2-3% differences or require a higher than 5% certainty, we would recommend multiple measurements at each point in time. For subjects with a median SD we need only three scans at two points in time to identify a three-year bone loss, whilst for subjects with individual precision estimates exceeding the 95%-level, 9 BMD-measurements would be required at two points in time to detect the three year bone loss.

Conclusions

A single BMD scan is sufficient to establish BMD-**level** to the nearest ± ½ T-score. Detection of an expected individual BMD-**change** less than the 95% detection limits of 2% and 3% at the distal and ultradistal sites respectively, should rely on a minimum of three repeat BMD-scans at each point in time. We hypothesise that strict standardisation of subject positioning may improve precision. Absolute and relative precision may decrease with increasing age of the subject, therefore further research is needed to establish precision estimates in the age groups most commonly seen in densitometry clinics.

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Table 1: Precision terminology.

Type of Precision	**Calculated on the basis of:**
Short-term precision	Same day measurements on the same subject
Intermediate-term precision	Measurements performed one or three weeks apart on the same subject
Int*ra*-observer precision	Measurements by the same observer on the same subject
Int*er*-observer precision	Measurements by two different observers on the same subject
Int*er*-densitometer precision	Measurements on two different densitometers on the same subject.

Table 2: Descriptive variables for participants in first and second study of precision in forearm bone densitometry with SXA. Study 1 and study 2 were performed in the first and second half of a 52 week long BMD screening respectively.

	Study 1	Study 2
N	79	32
Ratio Women/Men	0.9	1.9
Mean age (range)	54.8 (27-70)	64.8 (53-75)
Mean Distal BMD g/cm^2 (SD)	0.492 (0.093)	0.425 (0.081)
Mean Ultradistal BMD g/cm^2 (SD)	0.394 (0.101)	0.331 (0.086)

Table 3: Distal site: Precision in forearm bone mineral density measurements with SXA. Estimates are based on one pairs of scans from each participant. Each pair represents a different measurement situation.

Precision-types		N	Mean diff, g/cm^2 (95% limits of agreement)	Median SD, g/cm^2 (5-95 %-tile)	Median CV (5-95 %-tile)
Short term	Intra observer (1. study - no repositioning)	69	**0.001** (-0.012 ~ 0.013)	**0.002** (0.000 ~ 0.008)	**0.41 %** (0.00 ~ 2.15)
	Inter observer (1. study)	73	**0.002** (-0.015 ~ 0.018)	**0.004** (0.000 ~ 0.011)	**0.71 %** (0.00 ~ 3.03)
Intermediate term	Intra observer (1. & 2. study)	82	**-0.002** (-0.021 ~ 0.017)	**0.004** (0.001 ~ 0.016)	**0.79 %** (0.15 ~ 3.64)
	Inter observer (1. & 2. study)	65	**-0.002** (-0.018 ~ 0.013)	**0.004** (0.001 ~ 0.011)	**0.79 %** (0.12 ~ 2.23)

Terminology: *Mean diff* :Mean BMD difference, *SD*: standard deviation, *CV*: Coefficient of variation. *Short-term precision*: Repeat measurements on same day. *Intermediate-term precision*: Repeat scans on same subject one or three weeks apart. *Intra-observer precision*: Repeat scans on same subject by same observer. *Inter-observer precision*: Repeat scans on same subject by two different observers. Unless otherwise stated there is repositioning between scans.

Table 4: Ultradistal site: Precision in forearm bone mineral density measurements with SXA. Estimates are based on pairs of scans from each participant. Each pair represents a different measurement situation.

Precision-types		N	Mean diff, g/cm^2 (95% limits of agreement)	Median SD, g/cm^2 (5-95 %-tile)	Median CV (5-95 %-tile)
Short-term	Intra observer (1. study - no repositioning)	70	**0.000** (-0.014 ~ 0.016)	**0.003** (0.000 ~ 0.013)	**0.64 %** (0.00 ~ 3.16)
	Inter observer (1. study)	69	**0.003** (-0.020 ~ 0.27)	**0.005** (0.001 ~ 0.016)	**1.15 %** (0.14 ~ 4.69)
Intermediate term	Intra observer (1. & 2. study)	81	**0.000** (-0.019 ~ 0.20)	**0.004** (0.000 ~ 0.014)	**0.97 %** (0.00 ~ 4.27)
	Inter observer (1.& 2. study)	66	**0.000** (-0.018 ~ 0.018)	**0.004** (0.001-0.013)	**0.98 %** (0.15 ~ 3.36)

Terminology: *Mean diff*:Mean BMD difference, *SD*: standard deviation, *CV*: Coefficient of variation. *Short-term precision*: Repeat measurements on same day. *Intermediate-term precision*: Repeat scans on same subject one or three weeks apart. *Intra-observer precision*: Repeat scans on same subject by same observer. *Inter-observer precision*: Repeat scans on same subject by two different observers. Unless otherwise stated there is repositioning between scans.

Table 5: Inter-densitometer precision estimates at distal and ultradistal site based on one pair of scans for each participant, with change of both densitometer and observer between measurements. Unadjusted mean BMD-differences revealed a systematic difference between the two densitometers. This bias was removed by adjusting* BMD-values from both densitometers to the same scale.

			Unadjusted	Adjusted*	
		N	Mean diff (95% Confidence Interval)	Mean diff (95% Confidence Interval)	Median SD (5-95 %-tile)
Distal site	Short term	26	-0.009** (-0.025 ~ -0.007)	0.000 (-0.016 ~ 0.015)	0.003 (0.001 ~ 0.010
	Intermediate term	20	-0.006 (-0.028 ~ -0.015)	0.003 (-0.019 ~ 0.024)	0.005 (0.001 ~ 0.013
Ultradistal site	Short term	25	-0.007** (-0.029 ~ -0.014)	0.002 (-0.020 ~ 0.023)	0.004 (0.002 ~ 0.013
	Intermediate term	25	-0.007 (-0.037 ~ -0.023)	0.002 (-0.028 ~ 0.032)	0.006 (0.001 ~ 0.022

Terminology: *Mean diff* :Mean BMD difference, *SD*: standard deviation, *CV*: Coefficient of variation. *Short-term precision*: Repeat measurements on same day. *Intermediate-term precision*: Repeat scans on same subject three weeks apart.

*Adjusted BMD values were calculated by use of regression coefficients from best fitting model for the relationship between individual mean BMD-values from the two densitometers.

** $p < 0.01$ for mean =0.

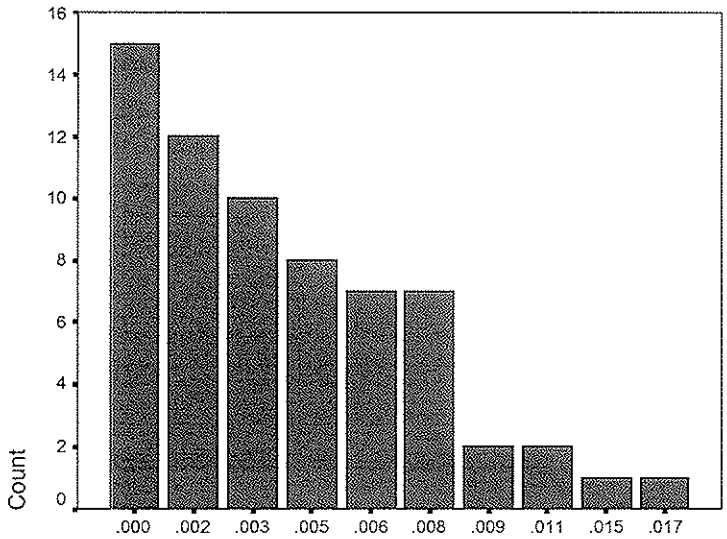
Table 6: Age and precision at distal and ultradistal site. Each participant contributed an individual mean SD/ CV estimate which was based on up to 3 pairs of scans. The paired scans were performed one week apart by two different observers.

	Distal site			Ultradistal site		
Age	N	Median SD, g/cm2	Median CV %	N	Median SD, g/cm2	Median CV %
25-39	10	0.003	0.50	9	0.004	0.96
40-54	12	0.004	0.67	12	0.005	1.22
55-64	36	0.005	1.03	35	0.005	1.31
65+	7	0.003	0.65	10	0.004	0.91
p-value*		p=0.0514	p=0.0097		p=0.9187	p=0.7091

* Between group differences, Kruskal Wallis Chi square test

Figure 1: Distal site: Population distribution of individual Standard deviations (SD) and Coefficients of variation (CV) bone mineral density measurements at the forearm with SXA. SD and CV estimates are based on one pair of scans performed one or three weeks apart by two different observers.

Figure 2: Differences between two bone mineral density (BMD) measurements plotted by their mean. Differences are between pairs of scans performed one or three weeks apart by two different observers.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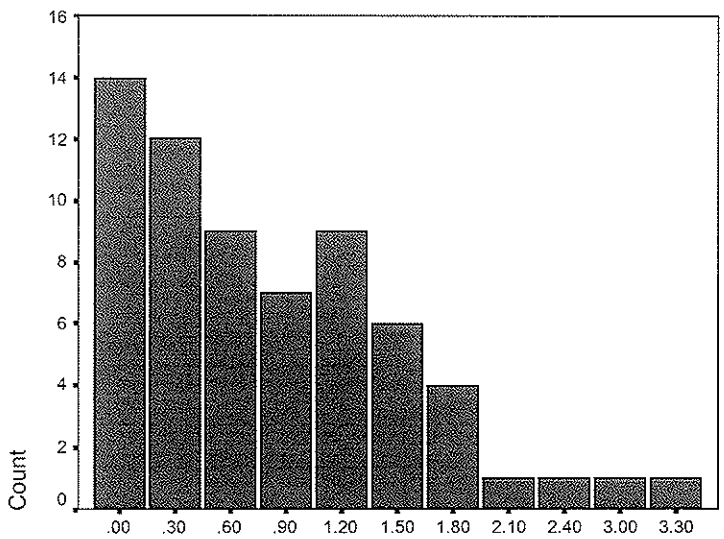
Standard Deviation, g/cm2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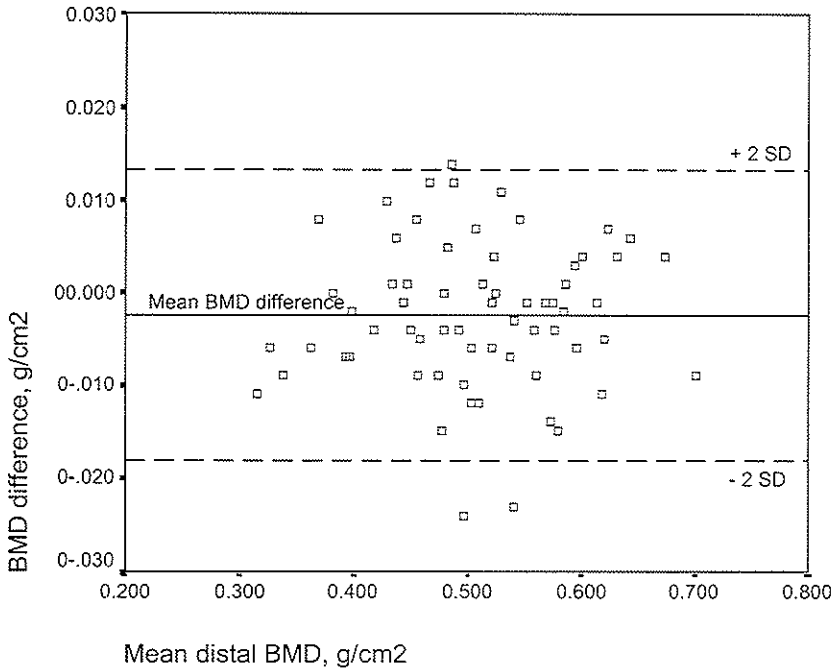
2.40
3.00
3.30
Coefficient of Variation (%)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+ 2 SD
Mean BMD difference
- 2 SD
BMD difference, g/cm2
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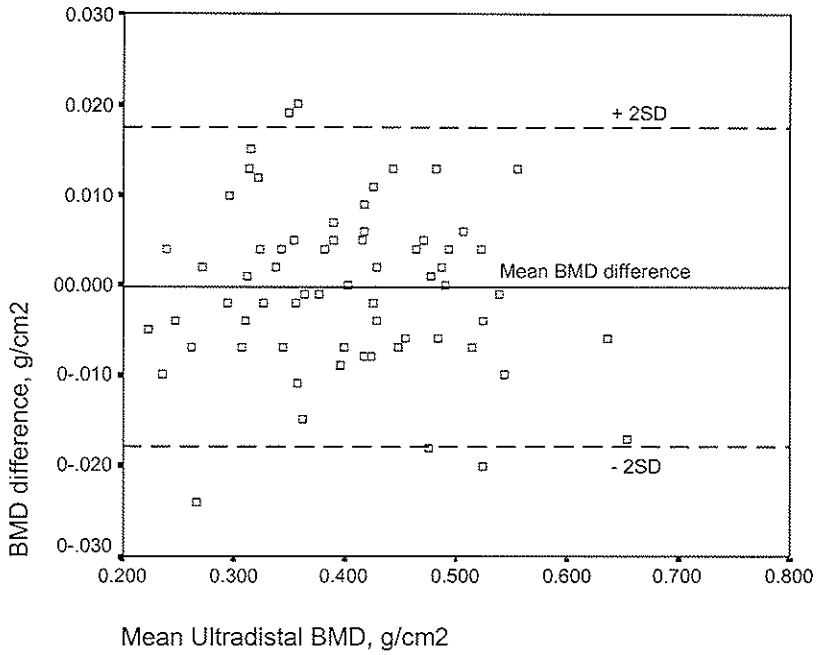
0.300
0.400
0.500
0.600
0.700
0.800
Mean distal BMD, g/cm2


0.030
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Mean BMD difference
- 2SD
BMD difference, g/cm2
0.200
0.300
0.400
0.500
0.600
0.700
0.800
Mean Ultradistal BMD, g/cm2

Paper III

The Tromsø study: A population based study of forearm bone mineral density by age, in 7620 men and women.

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ABBREVIATIONS

BMD – Bone Mineral Density
HRT – Postmenopausal Hormone (estrogen) Replacement Therapy
SD – Standard Deviation
SXA – Single Energy X-ray Absorptiometry
1YAG – One Year Age Group
ΔBMD – Mean BMD difference

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ABSTRACT

Population based studies of adult forearm bone mineral density (BMD) by age are scarce and standardized reference values are lacking. In this cross sectional study, men aged 55-74, women aged 50-74 and representative 5-10 percent samples of remaining age groups between 25-84 years living in Tromsø, Norway, were invited for forearm bone mineral density (BMD) measurement. We measured 3062 men and 4558 women (response rate: 78 percent) by single x-ray absoptiometry at distal and ultradistal forearm sites. Up to age 50, the mean BMD difference was -0.1 percent pr. one year age group in both sexes. After age 50, the mean BMD difference pr. one year age group was -0.6 percent in men, and –1.3 percent (distal) and –1.5 percent (ultradistal) in women. The BMD by age curve was linear for men throughout senescence, but women had a slope change to –0.7 percent (distal) and –0.8 percent (ultradistal) pr. one year age group, from the 65-69 age-group. BMD-levels and BMD by age association in the general population (n=7620) and the population without bone threatening diseases/ medication (n=5179) were similar. Only longitudinal studies can clarify whether cohort effects or longitudinal BMD development patterns explain these cross-sectional results.

Medical Subject Headings:

Adult, Bone density, Cross-sectional studies, Forearm, Men,

Menopause, Reference values, Women, X-ray densitometry

The ability of the forearm bone mineral density (BMD) to predict any fracture in women is believed to be as good as for other measurement sites (1) and wrist BMD has been shown to predict male fragility fractures better than other anatomical sites (2). Forearm Single X-ray Absorptiometry (SXA) is one of the most precise bone densitometric methods (3) and it is easy, readily standardized and cheaper than Dual Energy X-ray Absorptiometry (DEXA) measurements at axial sites. Therefore SXA-measurements of the forearm is a good candidate for any BMD screening (4,5).

Study of the BMD distribution in a general population is needed to compile representative age and sex-specific reference values. Only two studies of forearm BMD in the general population have previously been published, one from a Japanese-American population (6) and the other from an elderly upper middle class retirement community (7). Both studies included only middle aged and elderly subjects. Thus, population-based studies describing the adult life span BMD distribution are wanting.

As BMD-values are not standardized, reference ranges from previous publications are generally not comparable with results from other densitometers (8). To achieve comparability, BMD-results from both densitometers need to be translated to a

common scale. A golden BMD standard, against which all other densitometers can compare their results, has proven difficult to produce and has up to now been lacking for the forearm. Kalender et al. have recently developed the European forearm phantom (9) which is a forearm bone imitation, with a standard bone density. It is currently under evaluation by the International Committee of Standards in Bone densitometry (personal communication, K. Engelke, Feb 1999). No other standardized BMD reference ranges have been presented up to now.

Most presentations of normal BMD-reference ranges are based on highly selected populations believed to be "normal" i.e. subjects without disease or medication known to affect bone health. However, the selection criteria used to define such populations depend on the current and often fleeting views of "normality" with respect to bone health. Such a selection process could have profound effects on reference values and possibly explain reference range disparities between manufacturers (10). To our knowledge a comparison of reference ranges from a general- and a selected population without disease or medication known to affect bone health, have not yet been published.

The aim of this paper is thus to:

- Characterize the forearm BMD distribution by age in a general population.
- Present standardized age- and sex-specific reference values for distal and ultradistal forearm BMD.
- Compare reference ranges derived from a general population and a selected population without diseases or medication known to affect bone health.

MATERIALS AND METHODS

Study population

Bone densitometry was performed on 3062 men and 4558 women recruited from the 1994-95 survey of the Tromsø Study. This is a population-based multipurpose study where all subjects aged 25 years or more living in the municipality of Tromsø were invited to the main survey (Phase I, n=27159). Upon attendance at Phase I the following pre-selected groups were invited to an extended examination (Phase II) which included bone densitometry (n=10 213):

- All men aged 55 –74
- All women aged 50-74
- 5-10 percent samples of the remaining age groups between 25 and 84 years.

Two information brochures were provided together with the study invitations to both the main and extended examinations. Participants signed a declaration of consent prior to both

examinations. The Regional Committee of Research Ethics and the Norwegian Data Inspectorate approved the study.

Of all pre-selected subjects, 78 percent (n=7948) had a bone mineral density measurement. Especially invited male participants of the Family Intervention Study (11) were over-represented in the younger age groups which is why 328 were excluded to avoid over-representation. This left 7620 subjects whose age and sex specific response rates are given in table 1. The study population was dominated by non-Hispanic whites. The majority have a Norwegian ethnic background, and approximately 10-20 percent have Sami, Finnish or Sami/Finnish ethnic background.

Population without disease or medication affecting bone health:

As there is no consensus on which factors should be viewed as a threat to bone health, we applied an aggregate of all exclusion criteria used in larger studies (n>150) which had sought to exclude subjects with diseases and/ or medication affecting bone health (8,10,12-18). We retained any criteria representing *diseases* or *medication* shown to be associated with BMD (table 2) while life-style factors and non-disease conditions such as premature menopause, little physical activity, smoking, excessive weight loss, low body mass index and calcium supplementation were not used as exclusion criteria. We had no

information on anorexia, recent hyper-thyroidism, hypogonadism, oophorectomy, neurological disease, recent immobilization, rickets, adrenal disease or vertebral fractures. The selected subset included 68 percent (n=5179) of the original study population. The proportion with one or more exclusion criteria rose from 5% in 20-29 year olds to 50% among the 70-79 year olds ($p<0.001$) and more women than men were excluded ($p<0.001$) (table 2).

Menopause and use of estrogen.

Women were asked to report whether they still menstruated and if not, their age at menopause. Women who had stopped menstruating over a year ago, or, if menopause data were missing, were ≥ 55 years of age, were defined as post-menopausal (n=3631). Women who had stopped menstruating within the last year were considered peri-menopausal (n=76). Information on cause of menopause (natural or surgical) was not available. The mean, median and 95th percentile age at menopause was 48 years, 49 years and 55 years respectively. Pregnant women and women who were still menstruating and reported a menstruation within the last six months were classified as pre-menopausal (n=647). Menopausal status was left undefined in 204 women due to missing or conflicting values.

A total of 2, 15 and 84 percent of all pre-menopausal and 6, 20 and 74 percent of all post-menopausal women answered that they were previous, current or never users of tablets/ patches containing estrogen (not contraceptives) respectively. We excluded current- and previous estrogen users, and women with undefined menopausal status from analyses by menopausal status. However, 772 women had answered other questions on reproductive issues but left the estrogen question open. Although plausible, we could not be certain that these were estrogen non-users who found the question irrelevant. Therefore, post-menopausal BMD distribution by age was analysed with and without the 772 women with missing estrogen data. The results were virtually identical (data not shown), which is why women with missing estrogen-data were included in the final analyses.

Bone densitometry

Bone densitometry was performed on the non-dominant forearm at distal and ultradistal sites with two Single X-ray Absorptiometric (SXA)-devices (DTX-100 Osteometer). The distal site, which contains 10-20 percent trabecular bone (19), includes both the radius and the ulnae from the 8mm-point (point where the ulnae and radius are separated by 8 mm) and 24 mm proximally. The ultradistal site contains 50-70 percent trabecular bone (19), includes only the radius and stretches from the 8mm point up to the radial endplate. The dominant arm was

measured in 1 percent of the subjects when the non-dominant arm was ineligible due to wounds, plaster casts, etc.

Quality control with respect to precision, long-term stability, detection and correction of artifacts have been described elsewhere (3,20). Briefly, the coefficients of variation (CV) were 0.79 percent and 0.98 percent at the distal and ultradistal sites respectively. All scans were reviewed and if necessary, reanalyzed. Serious movement artifacts, region-of-interest outside scan, metallic objects in the region-of-interest or bad quality by other causes led 136 distal and 150 ultradistal scans to be excluded, leaving 7484 distal and 7470 ultradistal scans for analysis. The systematic BMD-difference between the two densitometers was adjusted before analyses (3).

Standardized BMD-values

The European Forearm Phantom (EFP) (QRM-Germany) had three hydroxyapatite bone imitations (inserts) with differing densities. We performed 20 measurements of each insert on both densitometers and used regression analysis to model the best fitting equation between the given and observed BMD-values (21). We tested both a linear and a quadratic term in the model. Both terms were significant, but as the R-squared values for the models were similar (R^2 linear model: 0.990, R^2

quadratic model: 0.991) we adhered to the simpler linear model:

*BMD-EFP = -0.024+1.054 * BMD-observed.*

Previous fractures in forearm

Distal forearm fracture is associated with BMD-increase at the ultradistal site (22), low BMD at other sites (23,24) and increased risk for fractures (25,26). Therefore ultradistal BMD in 637 subjects who reported a distal forearm fracture in the measured hand, was corrected according to the results from a sub-study of fracture and non-fracture cases. Briefly, 50 subjects with distal forearm fracture were age and sex matched to 115 subjects without fracture. The ultradistal BMD was on average 0.038 g/cm^2 higher on the fracture side in cases as compared to non-cases, whereas there was no effect of fracture on distal BMD.

Data analysis

Plots of BMD life-curve. BMD means for each five-year age and sex stratum were plotted against age to produce BMD life-curves. To dissociate the effects of loss of endogenous estrogen production at menopause from other age-related factors we made an additional plot of mean BMD for each 5-year years since menopause- and 10-year age- stratum for postmenopausal women.

BMD by age curves: The BMD by age curves are described in terms of slope and changes of slope. The slope is calculated in one of two ways: 1) The difference between age-specific BMD means, divided by the number of years between the midpoints of the age-groups in question. For example: BMD differences between two consecutive five year age-groups is divided by five to yield the average BMD-difference pr. one year age group. 2) Each linear segment of the BMD life-curves was also described with linear regression by age. The regression beta-coefficient expresses the mean BMD difference pr. one year of age increase.

Because age is a time-related variable, a description of BMD by age in terms of change pr. year may easily be mistaken for a measure of longitudinal development. We have therefore chosen to use the following terminology: Mean BMD difference (ΔBMD) pr. one year age group (1YAG), i.e. ΔBMD/ 1YAG. The slope is given either as an absolute number or as a percentage of the mean BMD in the youngest age group in the age-span.

Mean BMD differences between age groups were tested by one way analysis of variance. Beta-coefficients were tested for difference to zero by one-sample t-tests and difference between

each other by a partial F-tests. The level of statistical significance was set at p=0.05.

RESULTS

Women

The association between BMD and age in women was non-linear with marked changes of slope around 50-54 years of age and a less marked change at age 65-69 years (figure 1). The BMD by age curve in young adults (25-49 years of age) was slightly negative, but not significantly different from zero at both sites (figure 1, tables 3, 4 and 5). The highest mean BMD-level was found in women aged 30-34 years (distal site), but their values did not differ significantly from other young adult BMD-values before the age of 50.

At 50-54 and 45-49 years of age at distal and ultradistal sites respectively, the association between BMD and age changed so that ΔBMD pr. 1YAG was > -1 percent. From 65-69 years of age the ΔBMD pr. 1YAG decreased to < -1 percent (Table 5). Neither mean BMD-levels, nor BMD by age curves differed significantly between subjects without disease or medication known to affect bone health, and the overall study population (figure 1).

Menopausal status. The ΔBMD pr. 1YAG in pre-menopausal women who had never used HRT was slightly negative, but now differed significantly from zero (distal: -0.11 percent ($p=0.008$), ultradistal: -0.19 percent ($p= 0.0011$). Pre- and peri-menopausal mean BMDs did not differ significantly, but women in their first post-menopausal year had 3.8 percent (distal, $p=0.0008$) and 5.9 percent (ultradistal, $p<0.001$) lower BMD than pre-menopausal women. The mean BMD differences observed between the following five one-years-since menopause-groups, ranged from –0.3 percent to –1.9 percent (distal) and +2.1 to –3.9 percent (ultradistal) .

The ΔBMD pr. five year since menopause groups seemed to diminish in the late post-menopause within all age-strata, whereas average BMD difference between age groups was remarkably constant within all strata of years since menopause (figure 2). However we could not separate the effect of age and years since menopause in a regression analysis, because of the high collinearity between the two variables ($r=0.82$).

Men

Also in men the association between BMD and age was non-linear, with a change of slope around 50-54 years at both sites, although this was most distinct at the distal site (figure 1, table 3 and 4). At the distal site, no age group displayed higher BMD-

levels than others before 50 years, whereas at the ultradistal site, subjects aged 30-34 years had higher BMD-levels. Yet, of all ultradistal BMD means before 50 years, only the 40-44 age group mean was significantly lower ($p=0.017$) than the peak BMD. The ΔBMD pr. 1YAG before 50 years of age was negative and significantly different from zero at both sites, but the ΔBMD pr. 1YAG was much larger at the ultradistal site (table 5).

From 50-54 years of age the ΔBMD pr. 1YAG was -0.6 percent (figure 1, table 3, 4 and 5) at both sites. The slopes of the BMD by age, before and after 50 years of age, were significantly different from one another ($p<0.001$) at the distal site, but of borderline significance at the ultradistal site ($p=0.08$). The ultradistal BMD by age curve could alternatively be viewed as a linear, from the highest BMD level in 30-34 year olds into older age groups. The slopes before and after 50 would be similar ($p=0.71$), and ΔBMD pr. 1YAG from 30 years up would be -0.47 percent (table 5). The BMD development and BMD-levels by age in the sub-population without diseases or medication known to affect bone, were not significantly different from the overall study population (figure 1).

DISCUSSION

Main findings. Forearm BMD association with age was slightly negative (-0.1 percent pr. between one year age-groups) in both sexes up to 50 years of age, after which point the BMD by age slope became clearly negative, with ΔBMD pr. 1YAG of -0.6 percent at both sites in middle aged and elderly men. In middle aged women ΔBMD pr. 1YAG exceeded -1 percent, but decreased to –0.7 percent and –0.8 percent from 65-69 years of age. The effect of time since menopause on BMD-levels seemed to wane off in the late post-menopause. The subset of the study population without disease or medication known to affect bone did not differ from the study population at large with respect to BMD-level or BMD by age associations.

Bias considerations

Cross sectional versus longitudinal BMD-change. The cross sectional estimates of BMD by age associations are not true measures of longitudinal BMD-change. They are vulnerable to both cohort effects and selection bias and patterns of individual BMD-change cannot be discerned. Longitudinal studies provide data on individual BMD-change patterns, but are also prone to selection bias, loss to follow-up and they require repeated measurements that render them costly and time-consuming. Thus cross sectional studies are attractive ways of establishing

BMD-distributions by age, but they should be supplemented with longitudinal studies.

Selection bias. Non-response may generate selection bias, and in our case the BMD by age curves could be distorted if both BMD-level and age were associated with important selection factors. In an effort to characterise response patterns, we compared characteristics for the 10 213 subjects invited to both the first and second examination by response pattern.

For 1151 subjects who attended neither examination (*non-responders*) we had only age and sex data. For 1114 subjects who attended the first, but not the second examination (*partial responders*) we had data from the first examination and one or two questionnaires. For the 7948 subjects who attended both examinations (*full responders*) we had a complete data set. These comparative analyses were stratified by the following age-groups: < 45 (young), 45-64 (middle aged), 65 years and over (elderly), and by sex.

Disease and disability are linked to low BMD (27,28) and non-responders are known to be less healthy than responders (29-31), especially among those >55 years of age (32). However, our full responders were not healthier than partial responders in any age- or sex group, as judged by the self-reported prevalence

of myocardial infarction, stroke, diabetes, angina pectoris and asthma. Non-responders could still be less healthy than partial- and full responders. This may explain the lower response rates in subjects aged > 75 years (table 1).

Smoking and physical activity is known to affect BMD-results (33,34). The elderly and middle aged partial responders were more often daily smokers (44 vs. 32 percent, $p < 0.001$), and were more often sedentary in their leisure time (31 vs. 23 percent, $p < 0.001$) than full responders. Elderly male and female smokers had 3 and 6 percent lower distal BMD than non-smokers (data not shown) respectively, whereas BMD level differed by physical activity only in elderly men in our study (data not shown). These biases may have lead to BMD-over-estimations in the range of 0.3-0.6% in the middle aged and elderly. This is by any standard a negligible adjustment of the BMD by age results.

Analyses of the partial responders gave no clues to the cause of the low response rates in the young (<45 years). Previous studies of young non-responders found 'being too busy' and 'perceiving no personal benefit of attending' as important reasons for non-response in the young (32,35). Such selection-factors would probably not affect the observed associations between BMD and age in this age group.

Misclassification of menopausal status. Hysterectomised women with intact ovaries and estrogen-users who failed to report this, would be classified as post-menopausal even though they have pre-menopausal sex-steroid levels. Such misclassification would mitigate any observed effect of time since menopause on BMD in post-menopausal women.

Other limitations. The study population was dominated by non-Hispanic whites of Norwegian, Sami or Finnish ethnic background. Whether this represents a barrier to comparability with other ethnic groups and /or representativity is currently unknown. BMD distribution by age is quite similar to other unselected populations as judged by visual comparison of BMD curves, but there are currently no data which allow comparisons of BMD levels due to lack of BMD standardisation.

Female BMD-life curve

Young adult female BMD. Most (36-39) but not all (40,41), previously published studies of forearm BMD in self selected and/or healthy populations find no evidence of pre-menopausal bone loss. We found a non-significant decline in analyses of all young women, and a significant decline in analyses restricted to pre-menopausal BMD never users of estrogen. Peri-menopausal estrogen use probably "erases" the BMD-decline in the former

group. We found no age groups with substantially higher BMD-levels than other age-groups, which questions the concept of a pre-menopausal BMD peak. Population based longitudinal studies are required to determine whether BMD does decline in the pre-menopause.

The menopause and post-menopause. The larger BMD differences between women in their first post-menopausal year and pre-menopausal women, with smaller differences between the second to fifth post-menopausal years is supported by other studies (7) and by the current knowledge of estrogens role in bone biology (36,42-44). (14)

The BMD decline by age in the early post-menopause is steeper than the late post-menopause. Several smaller cross sectional studies of forearm BMD in selected populations also report such a pattern (36,38,42,45,46), but the two other population based studies of forearm BMD observed no equivalent changes of slope (6) or a small change at the mid radius only (7). Several explanations could be valid for this observation: 1) An average BMD change identical to the cross-sectional changes. Riggs suggests that a depletion of cancellous bone surface after many years of increased bone loss causes such an average change in bone resorption in the sixth decade (47). 2) If small groups experience large BMD-changes over shorter periods of time,

cross sectional BMD would decline as long as women continue to enter the swift bone loss phase. This is consistent with longitudinal studies where bone loss levels off 4-10 years after the menopause (40,48-50). 3) A cohort effect, where women who are now past 65 years of age generally lose less bone pr. year than younger women.

The observed pattern is still an enigma, and has so far not been satisfactorily explained. Population based longitudinal studies of bone loss coupled with studies of the determinants of such loss are needed.

Male BMD life curve

Young adulthood. The young adult BMD by age slope for the distal site was slightly but significantly negative. Two previous studies of distal BMD in selected populations support this (36,51), while one study found a stable distal BMD (42).

Volumetric ultradistal BMD has been shown to be stable by age up to the age of 50 (46). Our young adult ultradistal curve was quite irregular, with a high peak and a steep decline. The small numbers in the youngest male age groups probably account for the curve irregularity. Furthermore, if the BMD mean for the 30-34 age group is disregarded, the ultradistal young adult curve would become quite similar to the distal curve.

Middle- and old-age. There was a change to a more negative slope in the male BMD by age curve around age 50 at both forearm sites, although the change was not as clear-cut as in women. With the exception of one study (51), other studies of smaller selected populations support this observation (36,42,46,52). The reason for the larger differences is not clear, but the age related decrease in male estrogen levels might play a role (53). The BMD by age slope after 50 is negative and linear at both sites up to the seventh decade. This is comparable to the findings in the population based study of Caucasian men (7), but not of Japanese-American men whose ΔBMD pr. 1YAG was even more negative (>1 percent) after the age of 60 (6).

BMD-development in healthy vs. general populations

Neither the BMD by age association nor BMD-levels in the general population differed significantly from that in subjects without disease or medication known to affect bone health. Considering that over 2000 subjects were excluded, this stability was surprising, as such a systematic selection might be expected to distort results. The explanation may be that the mixture of exclusion factors had no common effect on the BMD, and they therefor to some extent cancelled each other out. This is good news, as we up to now have relied heavily on results from selected groups of so called "normal" subjects.

However the studies which provided our exclusion criteria (8,10,12-18) all applied quite different sets of exclusion criteria effectively rendering the populations incomparable. We fear that the small inconsistencies in our study may be due to a lucky combination of exclusion criteria which cancelled out important effects and that slight changes in the exclusion criteria may produce different results. As long as "normal" and "healthy" with respect to bone status lack operational definitions, we recommend the study of the unselected general population or use of selection criteria that are standardized and easily replicable.

The results presented in this paper bring forth questions that are important for our further understanding of bone biology:

- Does forearm BMD decline in young adult hood in both men and women, and if so why?
- Is the age-related BMD-loss parallel for both men and women when the menopausal BMD-loss is disregarded?
- What mechanism causes the BMD by age curve to become less steep at 65 years of age in women?
- Does BMD development at male trabecular sites differ from that at male cortical sites and female cortical- and trabecular sites?

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TABLE 1: Response rates by age and sex for full participation (attended both first and second examination) among 10 213 eligible subjects to the Tromsø study, 1994-95.

	Women		Men	
	Response (%)	Invited (n)	Response (%)	Invited (n)
25-44 years	64.2	617	56.4	427
45-64 years	81.6	3358	79.3	2494
65-74 years	79.3	1735	78.9	1443
75-84 years	54.1	85	63.0	54
All	78.7	5795	76.7	4418

Difference between age groups (adjusted for sex): $p < 0.001$(Mantel Haenzel)
Difference between sexes (adjusted for age): $p=0.009$ (Mantel Haenzel)

TABLE 2. Exclusion criteria which defined the population without disease or medication known to affect bone health, from the total study population (n=7620) of the Tromsø osteoporosis study, Norway, 1994-95. Each subject may qualify for several exclusion criteria, and may therefore contribute to more than one exclusion category.

	Exclusion criterion	Basis for exclusion	Women (N)	Men (N)
Medication	Current or previous systemic corticosterioid therapy	Self reported current or previous use of systemic steroids	75	40
	Thiazid diuretic	Self reported current use	4	
	Active Vit D3	Self reported current use	3	2
	Treatment for osteoporosis: Fluoride or Calcitonin (no bisfosfonate users registered)	Self reported current use	10	
	Post-menopausal tamoxifen use	Self reported current use	11	
	Hormone Replacement Therapy (HRT)	Self reported current or previous HRT	800	
Diseases	Malabsorption, gastrectomy	Self reported surgery for gastric/ duodenal ulcer	99	140
	Renal bone disease	Increased creatinin (Men >120 µmol/l, Women >100 µmol/l)	83	92
	Non Insulin Dependent Diabetes Mellitus	Self reported diabetes without use of insulin	88	78
	Hyper-parathyroidism	Ca++ values above 2.6 mmol/l	117	39
	Osteoarthritis	Self reported osteoarthritis	231	92
	Current or previous cancer-diagnosis	Self reported cancer	270	134
	Osteoporosis	Self reported diagnosis of osteoporosis	204	11
		Self reported hip fracture	87	60
		Self reported forearm fracture after age 50	303	50

TABLE 3. Mean distal forearm bone mineral density (BMD) and mean BMD differences pr. one year age group for five year intervals. A population based cross sectional study (n=7620) from Tromsø*, Norway, 1994-95. BMD-values are given in standardised European Forearm Phantom units. SD – Standard Deviation. BMD diff – Mean BMD difference.

	Women			**Men**		
Age	N	Mean (SD) g/cm^2	@BMD pr. 1 year age group(%)	N	Mean (SD) g/cm^2	@BMD pr. 1 year age group(%)
25-29	86	0.475 (0.039)		52	0.580 (0.047)	
			0.3 %			0.2 %
30-34	117	0.482 (0.039)		53	0.587 (0.049)	
			-0.1 %			-0.1 %
35-39	103	0.479 (0.047)		69	0.583 (0.042)	
			-0.2 %			0.0 %
40-44	77	0.474 (0.048)		40	0.583 (0.048)	
			-0.3 %			-0.6 %
45-49	105	0.467 (0.047)		75	0.566 (0.051)	
			-0.4 %			0.2 %
50-54	1036	0.460 (0.050)		76	0.571 (0.051)	
			-1.4 %			-0.4 %
55-59	833	0.429 (0.055)		760	0.559 (0.056)	
			-1.4 %			-0.5 %
60-64	699	0.401 (0.061)		701	0.545 (0.061)	
			-1.4 %			-0.6 %
65-69	762	0.373 (0.065)		610	0.529 (0.068)	
			-0.8 %			-0.7 %
70-74	594	0.359 (0.063)		509	0.510 (0.072)	
			-1.2 %			-1.0 %
75-79	55	0.339 (0.070)		54	0.485 (0.092)	
			-1.9 %			-0.9 %
80-84	13	0.309 (0.072)		5	0.464 (0.072)	

*Non-Hispanic white population of Norwegian, Sami or Finnish ethnic background.

TABLE 4: Mean ultradistal forearm bone mineral density (BMD) and mean BMD differences pr. one year age group for five year intervals. A population based cross sectional study (n=7620) from Tromsø*, Norway, 1994-95. BMD-values are given in standardised European Forearm Phantom units. SD – Standard Deviation. BMD diff – Mean BMD difference.

	Women			**Men**		
Age	n	Mean (SD) g/cm2	@BMD pr. 1 year age group(%)	n	Mean (SD) g/cm2	@BMD pr. 1 year age group(%)
25-29	86	0.382 (0.049)		52	0.492 (0.052)	
			-0.1 %			0.5 %
30-34	115	0.381 (0.045)		53	0.504 (0.072)	
			0.0 %			-0.9 %
35-39	104	0.380 (0.049)		70	0.482 (0.054)	
			-0.4 %			-0.5 %
40-44	76	0.374 (0.053)		40	0.471 (0.053)	
			0.0 %			-0.4 %
45-49	102	0.374 (0.046)		76	0.461 (0.066)	
			-1.2 %			0.6 %
50-54	1029	0.353 (0.057)		76	0.474 (0.063)	
			-1.8 %			-0.8 %
55-59	827	0.323 (0.057)		764	0.456 (0.064)	
			-1.8 %			-0.6 %
60-64	698	0.296 (0.062)		703	0.444 (0.066)	
			-1.7 %			-0.7 %
65-69	752	0.273 (0.060)		616	0.429 (0.070)	
			-0.7 %			-0.8 %
70-74	590	0.264 (0.058)		515	0.412 (0.074)	
			-1.2 %			-0.9 %
75-79	52	0.249 (0.060)		54	0.395 (0.095)	
			-1.2 %			-1.2 %
80-84	14	0.236 (0.067)		6	0.372 (0.022)	

*Non-Hispanic white population of Norwegian, Sami or Finnish ethnic background.

TABLE 5. Mean BMD differences pr. one year age groups for linear segments of the BMD by age curve. BMD measurements made at forearm, distal and ultradistal sites. Results broken down by age, sex and measurement site. A population based study (n=7620) in Tromsø*, Norway 1994-95.

	Distal site				Ultradistal site			
	Age	n	@BMD pr. 1 year age group (95% CI) g/cm²	@BMD pr. 1 year age group % change** (95% CI)	Age	n	@BMD pr. 1 year age group (95% CI) g/cm²	@BMD pr. 1 year age group % change** (95% CI)
Women	25-49	488	-0.0005 (-0.001 ~ 0.000)	-0. 11 % (-0.23 ~ 0.01)	25-44	381	-0.0005 (-0.001 ~ 0.000)	-0.13% (-0.37 ~ 0.11)
	50 - 64	2568	-0.0057 (-0.006 ~ -0.005)	-1.25 % (-1.36 ~ -1.15)	45-64	2656	-0.0055 (-0.006 ~ -0.005)	-1.47 % (-1.60 ~ -1.35)
	65+	1424	-0.0033 (-0.004 ~ -0.002)	-0.87 % (-1.18 ~ -0.56)	65+	1408	-0.0019 (-0.003 ~ -0.001)	-0.68 % (-1.03 ~ -0.34)
Men	25-49	288	-0.0008 (-0.002 ~ 0.000)	-0.14% (-0.27 ~ -0.01)	25-49	290	-0.0020 (-0.003 ~ -0.001)	-0.41 % (-0.61 ~ -0.22)
	50+	2714	-0.0033 (-0.004 ~ -0.003)	-0.58 % (-0.65 ~ -0.51)	50+	2733	-0.0030 (-0.003 ~ -0.003)	-0.64 % (-0.73 ~ -0.55)
					30+	2972	-0.0024 (-0.003 ~ -0.002)	-0.47% (-0.52 ~ -0.41)

*Non-Hispanic white population of Norwegian, Sami or Finnish ethnic origin. **Percent of the youngest 5-year-age-group BMD mean within the age segment

FIGURE 1. Mean forearm bone mineral density (BMD, g/cm^2) by age, sex and measurement site in a population based study (n=7620) (right panel) and (right panel) a subset of subjects without disease or medication known to affect bone health (n=5179) from Tromsø*, Norway 1994-95.

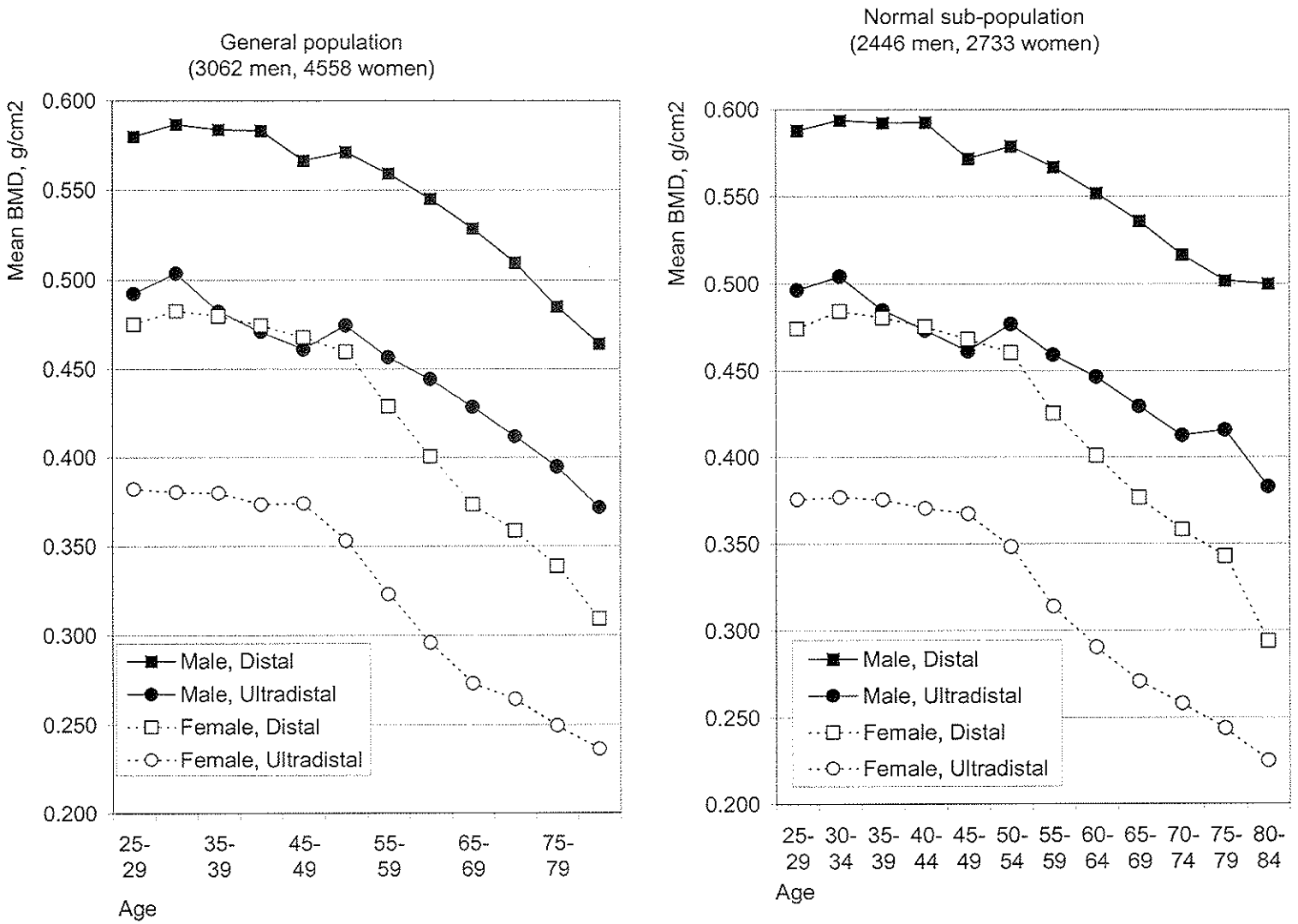
Footnote, figure 1:

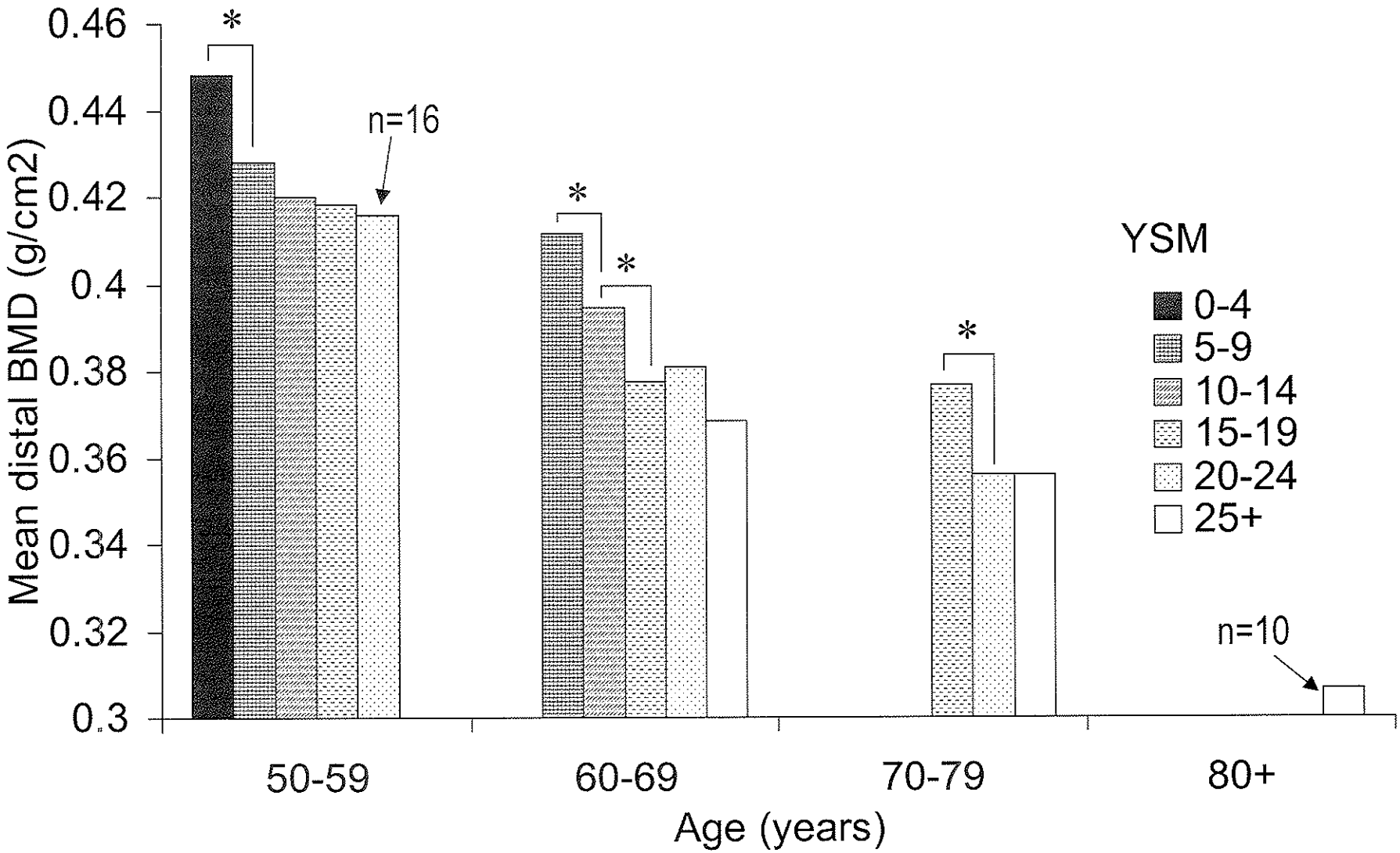
*Non-Hispanic white population of Norwegian, Sami or Finnish ethnic background.

FIGURE 2. Postmenopausal mean distal bone mineral density (BMD, g/cm^2) by age and years since menopause (YSM) in 2530 women from a population based study in Tromsø, Norway 1994-95. All women were post-menopausal and had never used hormone replacement therapy. Columns represent 50 individuals or more, unless otherwise labelled. Columns representing less than ten subjects were excluded due to uncertainty of estimate.

Footnote for figure 2:

- BMD by YSM, linear association, within age strata: 50-59 years: $p<0.0001$, 60-69 years: $p < 0.0001$ and 70-79 years: $p=0.15$.
- Between YSM groups, within age strata: Columns marked with * are significantly different ($p<0.05$) from neighboring columns.
- BMD by age, linear association, within YSM stratum: YSM 5-9: $p=0.043$, YSM 10-14, 15-19 and 20-24: $p < 0.0001$, YSM 25+:$p= 0.0019$


General population
(3062 men, 4558 women)
Mean BMD, g/cm2
0.600
0.550
0.500
0.450
0.400
0.350
0.300
0.250
0.200
Male, Distal
Male, Ultradistal
Female, Distal
Female, Ultradistal
25-29
35-39
45-49
55-59
65-69
75-79
Age
Normal sub-population
(2446 men, 2733 women)
Mean BMD, g/cm2
0.600
0.550
0.500
0.450
0.400
0.350
0.300
0.250
0.200
Male, Distal
Male, Ultradistal
Female, Distal
Female, Ultradistal
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
Age


0.46
0.44
0.42
0.4
0.38
0.36
0.34
0.32
0.3
Mean distal BMD (g/cm2)
*
n=16
*
*
*
n=10
YSM
0-4
5-9
10-14
15-19
20-24
25+
50-59
60-69
70-79
80+
Age (years)

Paper IV

The Tromsø study: Prevalence of male and female osteoporosis in a general population

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Running title: Osteoporosis prevalence

Abstract:

The objective was to determine the prevalence of female and male osteoporosis in a general population. All men aged 55-74, women aged 50-74 and representative 5-10 % samples of remaining age groups between 25 and 84 years, living in a Norwegian municipality were invited to forearm bone densitometry with SXA. In all 3062 men and 4558 women (response rate 78%) took part. We used the WHO-, NHANES study-, UK-consensus group on male osteoporosis- and AGE SPECIFIC- osteoporosis definitions. Osteoporosis prevalences for those aged 50 or more, were 16-32% in women and 1-20% in men, depending on forearm site and osteoporosis definition. In women aged ≥ 70 years, 90% were either osteopenic or osteoporotic according to the WHO definition. The potential benefits of these osteoporosis definitions may be outweighed by medicalisation and increased expenditure of limited health care resources.

Key words:
Osteoporosis, prevalence, men, women, adults, medicalisation, WHO

Introduction

Fragility fractures are associated with significant morbidity and mortality (1) especially in the elderly population (2). Prevention of fractures is currently seen as the most effective way of reducing the impact of osteoporosis. Until recently the osteoporosis definition was qualitative and of little use in a clinical setting (3) which explains the need for a more operational definition. Several definitions have been proposed on the basis of the strong and well-documented relationship between bone mineral density (BMD) and fragility fractures (4).

Due to lack of standardisation of the BMD-unit, all osteoporosis definitions compare BMD-results with the BMD mean in a defined reference population. For Caucasian women, WHO's definition, which defines osteoporosis as a BMD less than 2.5 standard deviations (SD) below the female young adult mean, is widely accepted (3,5,6). Age specific thresholds, where osteoporosis is defined as BMD-values less than 1 SD below the female mean for each age-group are also used by some authors (4) and in clinical contexts (7).

In men, there is yet no broad consensus on an osteoporosis definition. The NHANES study proposed either the same definition as for women (BMD-result less than 2.5 SD below the young adult female BMD) or a male version of the WHO definition (a BMD result less than 2.5 SD below the young adult male BMD) (8). Quite recently the UK consensus group on male osteoporosis suggested that BMD at the hip or spine lower than 2.5 SD below the young adult male BMD or lower than 1 SD below the age-adjusted BMD-mean, should define male osteoporosis (9).

The choice of osteoporosis definition will affect large numbers of individuals and is bound to have implications for both health services and health policies. Yet the consequences of these definitions in a general population is poorly examined. The impact of the WHO definition has been examined in an American general population using the hip measurement site (8)QUOTE, and in a study of 400 Rochester men and women which uses forearm BMD for estimation of WHO osteoporosis prevalence (10). Further data on osteoporosis prevalence in a general population are currently lacking.

BMD and osteoporosis prevalences vary between anatomical sites (11), but no site has been shown superior with respect to prediction of all types of fragility fracture (4). Forearm measurements with SXA are precise, easy to perform and standardise (12), they are cheaper than axial measurements, and wrist BMD has been shown to predict male fragility fractures better than other anatomical sites (10). Forearm BMD may be an attractive choice for any future BMD screening (13,14), which is why the osteoporosis prevalences for this site need to be examined.

The WHO working group states that osteoporosis should be defined relative to the "young adult BMD mean, but it does not define the term "young". As a result, both peak BMD (8) and mean pre-menopausal BMD (15) have served as young adult female BMD. Confusion also exists regarding the use of "normal/ healthy" or general populations in the reference population. Although, the WHO working group does not directly state that the reference population should be "normal/ healthy", they utilise a "healthy" reference group to estimate their expected osteoporosis prevalence. Other authors also differ as to whether their reference populations, include or exclude subjects with bone related diseases and/ or medication (8,16). The effect of these nuances on the final osteoporosis prevalence as estimated by the WHO-, and the closely related NHANES- and UK-consensus criteria, is currently unknown.

In summary the questions addressed in this paper are:

1. What are the prevalences of female and male osteoporosis at the forearm, by current osteoporosis definitions, in a predominantly Caucasian population?
2. Does the choice of young adult female BMD in the WHO-definition, either peak BMD or pre-menopausal BMD, affect prevalence of osteoporosis ?
3. Do the osteoporosis prevalences differ when reference ranges are based on the general population or the "normal" subset of the general population

Methods and Material

Study population

Bone densitometry was performed on 3062 men and 4558 women recruited from the 1994-95 survey of the Tromsø study. This is a population-based multipurpose study of a predominantly Caucasian, middle-class population, living north of the polar circle in Norway with an age and sex distribution representative for the Norwegian population. All subjects aged 25 years or more were invited to the main survey (Phase I, n=27159). All attending men aged 55 -74, women aged 50-74 and pre-selected representative 5-10 % samples of attendants aged between 25 and 84 years were invited to an extended examination (Phase II), which included bone densitometry. In all, 78 % of the subjects selected to receive an invitation were finally included in this study. An information brochure was provided together with the study invitations to both the main and extended examinations. Participants confirmed that they had understood the nature and objectives of the study by signing a declaration of consent prior to the two examinations. The Regional Committee of Research Ethics and the Norwegian Data Inspectorate approved the study.

All age- and sex strata between 45-74 years of age had response rates between 75 - 86%, but lower response rates were observed among subjects aged < 45 years (61%) and subjects aged ≥ 75 years (58%). Men had slightly lower response rates than women (77 vs. 79%, p=0.016). Ten percent of the study population were aged <50, 73 % between 50 and 69 years, and 17 % were aged 70 years or more.

The exclusion criteria, which define the "normal" sub-population, i.e. subjects without bone related diseases and/ or medication, are given in Table 1. They represent an aggregate of exclusion criteria used in other larger studies (n>150) of BMD, in so-called "normal" populations. We had no information on anorexia, recent hyper-thyroidism, hypogonadism, oophorectomy, neurological disease, recent immobilisation, rickets, adrenal disease or vertebral fractures. The "normal" subset included 68% (n=5179) of the original study population.

Bone densitometry

Bone densitometry was performed on the non-dominant forearm at distal and ultradistal sites with two cross-calibrated Single X-ray Absorptiometric (SXA)-devices (DTX-100, Osteometer). In 1% of the subjects, the non-dominant arm was ineligible due to wounds or plaster casts, in which case the dominant arm was measured. The precision as measured by coefficients of variation (CV) were 0.79% and 0.98% at the distal and ultradistal sites respectively (12). In august 1995, increased variability in phantom results for one densitometer led to the execution of a calibration procedure. Otherwise both densitometers were stable. All scans were reviewed and if necessary, reanalysed (17). Serious movement artifacts, region-of-interest outside scan, metallic objects in the region-of-interest or bad quality by other causes led 136 distal and 150 ultradistal scans to be excluded. This left 4480 distal and 4445 ultradistal scans for analysis in women. For men 3004 distal and 3025 ultradistal scans remained for analysis. The systematic BMD-difference between distal forearm fracture and non-fracture cases, and between the two densitometers were adjusted before analyses (12).

Osteoporosis definitions

All osteoporosis definitions are based on recalculation of every BMD-result into number of standard deviations (SDs) above or below the mean BMD of a reference population. The reference populations are either subjects of the same age and sex (Z-score), or a young reference population (T-score). The exact reference population and osteoporosis threshold used by each definition is presented in Table 2. The mean BMDs for the different reference populations were first calculated using all subjects (general population) and thereafter recalculated using only subjects without diseases and/ or medication known to affect BMD ("normal" population). Although the UK-consensus definition was originally intended for axial BMD measurements only (9), we chose to include this definition as it is a combination of the NHANES - and the AGE-SPECIFIC-osteoporosis definitions, neither of which are limited to axial measurement sites. The WHO-definition defines osteopenia as a BMD result between 2.5 and 1 SD below the young female adult mean, and normal BMD as a result higher than 1 SD below the female young adult mean.

Prevalence calculations

Prevalence figures in each sex- and age group are given as percentages of the study population, while overall prevalences for wider age groups (age: 50+ and age:70+) were standardised to the WHO standard European population (18). For the sake of comparison with other authors, we also standardised prevalences to the US 1980 and 1990 census populations (19), in which case the estimate will be followed by the population standard in parenthesis: (US 1980) or (US 1990). Differences between two osteoporosis prevalences are given in absolute numbers and as percentage change relative to the smallest prevalence estimate: $(n_1-n_2)/ n_2)*100$, where n_1 and n_2 are the number of subjects categorised as osteoporotic, by the first and second definition respectively.

Statistics

We calculated 95% confidence intervals (95%CI) of all prevalence estimates using the normal approximation to the binomial distribution (20). Prevalence differences, were tested by use of McNemar's test for paired categorical data (20). Statistical significance was set at the 0.05 level.

Results

Osteoporosis prevalence

Women

The WHO1 prevalence (Table 2) of osteoporosis rose linearly from 10% at the age of 50-59 to 69% at 75 or more years of age at the distal site (Table 3, Figure 1). 32% of all women aged ≥ 50 and 65% of all women ≥ 70 years of age, were defined as osteoporotic by the WHO1 definition (Table 3). The proportion of women who had normal BMD, as defined by either WHO-definition, declined dramatically with age at both sites. Less than half the female population aged ≥ 50 years (36%, 95% CI: 34-37%) were defined as normal (either osteopenic or osteoporotic) by the WHO1 definition, and only 10% (95% CI: 7-12%) of those aged ≥ 70 years were defined as normal (Figure 1). When distal and ultradistal sites were combined, 37% of all women aged 50 or more, had osteoporosis by the WHO1 definition at either site.

The AGE-SPECIFIC osteoporosis prevalences centred around 16% of the population in every age-group as expected (data not shown). The ultradistal prevalences were, with the exception of the AGE-SPECIFIC definition, generally lower than the distal prevalences for all definitions.

Men

There were large differences between prevalence estimates from the different definitions. The UK-consensus definition yielded the highest prevalence estimates, defining 20% of all men aged ≥ 50 years, and 36% of all men ≥ 70 years of age as osteoporotic at the distal site (Table 4). By contrast, the WHO2 definition produced an osteoporosis prevalence of only 2% and 8% of all men aged ≥ 50 and 70 years respectively, at the same site. The AGE-SPECIFIC osteoporosis prevalences centred around 16% of the population in every age-group as expected (data not shown). Also for men, the ultradistal prevalences were lower than the distal prevalences for all definitions applied.

Peak- or Pre-menopausal young adult BMD

The WHO1 prevalence, using the young adult peak BMD as reference, was generally higher than the WHO2 prevalence which used mean pre-menopausal BMD as reference (Table 3 and 5). When the definition of young adult mean was switched from pre-menopausal BMD to peak BMD, the overall prevalence of osteoporosis in the female study population increased from 900 subjects (20%) to 1108 subjects (25%, Table 5), which means an increase of the osteoporotic population of +22% ($p<0.0001$, Mc Nemars test). At the distal site the equivalent prevalence figures were 1083 (24%) and 1193 (26%), which equals an increase in number of osteoporotic individuals of +11% ($p<0.0001$, McNemars test). The same pattern was evident for the male population.

General or "normal"-reference populations

Thresholds based on the "normal" and the general population were virtually identical for the WHO1, WHO2 and NHANES definitions (data not shown). However, the AGE-SPECIFIC osteoporosis thresholds for subjects aged > 50 increased slightly when the reference population was switched from the general population to "normal" subjects (without bone related diseases and/ or medication). For instance, the AGE-SPECIFIC diagnostic threshold at the distal site for women aged 70-74 years, increased from 0.288 g/cm^2 (based on the general population) to 0.293 g/cm^2 ("normal" subjects), and their prevalence of AGE-SPECIFIC osteoporosis increased from 89 (15%) to 109 (18%) which equals a +18% ($p<0.001$, McNemars test) increase in the osteoporotic population. The same pattern applied to both sexes and sites for all age groups above 50 for this particular definition.

Discussion

Main findings:

The WHO1 criteria defined 90% of all women aged 70 years or more as having abnormal BMD-values (osteopenia or osteoporosis). The prevalence of osteoporosis in a population aged ≥ 50 lies between 24-32% for women and 1-20% in men depending on forearm site and choice of osteoporosis definition.

Bias considerations

Selection bias

Although, the Tromsø study has high overall response rates, we were concerned that the low response rates (61%) among those < 45 years, might affect peak BMD and/ or pre-menopausal BMD estimates. We therefore compared 1114 subjects who attended the first examination (Phase I), but failed to attend the second examination, with 7948 subjects who attended both examinations (Phase I+II), with respect to body mass index, ever use of HRT, daily smoking, self evaluated health, self reported prevalence of diabetes, myocardial infarction, angina pectoris, asthma, stroke, chronic pain, physical activity and alcohol consumption. However, none of these factors predicted attendance at the second examination in subjects aged < 45 years. Other studies of young non-responders indicate that 'being too busy' and 'perceiving no personal benefit from attending' are important reasons for non-response in the young (21,22). Such selection factors would probably not affect our young adult BMD level.

The low response rates among elderly (>75 years of age) may be linked to poor health (23-25), in which case we would expect our osteoporosis prevalences to be under estimated for the elderly age groups.

Prevalence in women

The WHO working group estimated an osteoporosis prevalence of 30% by their own definition among all Caucasian post-menopausal women at any site (spine, hip or mid-

radius) (3). Our WHO prevalences at the forearm alone, are approximately 30% for women aged 50 years or more (WHO1: 31%, US 1990), which is in accordance with the findings in the Rochester population of 33% (US 1990) at the wrist in women in the same age group (10). It seems the WHO definition targets a larger part of the female population than was originally intended.

Other authors have pointed out that prevalences differ by skeletal sites (11). We also demonstrate that the choice of young adult mean, affects the number of subjects finally diagnosed as osteoporotic. Even though an increase in overall prevalence from 20% (WHO2) to 25% (WHO1) may seem moderate, this translates into a 22% increase in the absolute numbers of persons in need of appropriate care and follow-up.

The osteopenia and osteoporosis epidemic

The number of women with abnormal bone mass at 70 years or more approaches 90% in our study. NHANES report prevalences of abnormal BMD at the hip in this group around 80% (26). The proportion of women above 80 years of age characterised as normal dwindles to almost zero, when more than one anatomical site is evaluated (15). This represents a dramatic medicalisation of the elderly female population.

The introduction of the osteoporosis epidemic carries the risk of unintentionally stigmatising most elderly women as frail, sick and dependent of the health services. Even though neither the current osteopenia nor the osteoporosis definition were meant to initiate therapy (3), we worry that these definitions may have their own momentum in that direction. Counselling to inform the subject, tests for secondary osteoporosis, BMD-measurements at other anatomical sites, BMD-follow-up measurements, and tests for other risk factors for fracture may follow. When all clinical information is reviewed, intervention is a plausible result of the osteoporosis- and possibly also of the osteopenia "diagnosis". The mere act of assigning the label "Osteoporosis" to an individual could also have side effects. In one study, women who believed that their BMD was below normal, limited their physical activity in fear of falling. The measures taken, ranged from limiting daily activities such as grocery shopping, to stopping more recreational activity such as skiing and hiking (27). The osteoporosis diagnosis has also been shown to be associated with reduced quality of life (28).

Prevalence in men

Looker estimated a hip osteoporosis prevalence of 2-4% (US 1980) of all men aged >50 by the WHO1 criteria, while Melton found 2-3% (US 1990) at the forearm. This is close to our results at the distal and ultradistal site of 2% (WHO1, US 1980). The osteoporosis prevalence is lower at the hip than at the forearm when NHANES criteria are used: Looker reports 3-6% (US 1980) at the hip (8) while Melton found 9% (US 1990) at the total wrist (10), and our estimates were 16% (US 1980) at the distal- and 9% (US 1980) at the ultradistal forearm, for men aged 50 years or more.

The UK-consensus definition of male osteoporosis has to our knowledge not previously been applied to any population. According to their own estimates, 25% of all men would have BMD results at either the hip or the spine below the AGE-SPECIFIC thresholds alone (9), but the group did not estimate the total proportion of men affected by their definition. Their definition is by far the most liberal definition suggested for men, affecting 36% of all men aged ≥ 70 years. Defining 16% of all men aged less than 50 years as osteoporotic is questionable. Although fractures in young men are common, the relationship between BMD and fractures in this group is still poorly examined.

The osteoporosis definition

A diagnosis describes a condition characterised by a symptom, loss of function, or indicates that this will ensue with high probability within foreseeable time limits, if the disease is allowed to follow its natural course. In the case of low bone mass or osteoporosis without fractures, the alleged disease causes neither pain, loss of function nor any other symptom, and the risk of developing symptoms, i.e. fractures, within the first five years after diagnosis is also probably quite low. As we still lack population based data on this point, our best guess comes from the placebo "arm" of a randomised controlled trial, where 81% of the women defined as osteoporotic by the WHO criteria, remained symptom free, i.e. sustained no clinical fractures, during four years of follow-up (29). Nevertheless, the WHO working group insists that osteoporosis should be considered as a symptom free disease (3).

We are concerned that the conversion of a risk factor into a diagnostic entity, produces liberal osteoporosis definitions, which, if fully implemented, will require significant

human, economic and technical resources within the public health services. The definitions' potential benefits must be carefully weighed against possible adverse effects such as medicalization and increased expenditure of already scarce health resources.

We propose that a strict distinction is kept between the many risk factors for fragility fractures (of which osteoporosis is only one) and the clinical outcome or disease, i.e. the fracture. We advise the scientific community to drop the current osteoporosis definitions. Research and prevention should aim at identification of all factors which cause fractures, and try to decrease risk by appropriately targeting the individual risk profile. We suggest that future fracture prevention efforts should be guided by a fracture risk score linked to absolute risk, in both men and women.

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Table1. Exclusion criteria which defined the "normal" sub-population (n=5179) from the total study population (n=7620) of the Tromsø osteoporosis study, Norway, 1994-95.

	Exclusion criterion	Basis for exclusion	Total N *	N - Excluded **
Medication	Current or previous systemic corticosterioid therapy	Self reported current or previous use of systemic steroids	125	41
	Thiazid diuretic	Self reported current use	4	3
	Active Vit D3	Self reported current use	5	-
	Treatment for osteoporosis: Fluoride or Calcitonin (no bisfosfonate users registered)	Self reported current use	10	-
	Post-menopausal tamoxifen use	Self reported current use	11	-
	Hormone Replacement Therapy (HRT)	Self reported current or previous HRT	800	590
Diseases	Malabsorption, gastrectomy	Self reported surgery for gastric/ duodenal ulcer	246	145
	Renal bone disease	Increased creatinin (Men >120 µmol/l, Women >100 µmol/l)	175	97
	Non Insulin Dependent Diabetes Mellitus	Self reported diabetes without use of insulin	168	121
	Hyper-parathyroidism	Ca++ values above 2.6 mmol/l	151	99
	Osteoarthritis	Self reported osteoarthritis	323	183
	Current or previous cancer-diagnosis	Self reported cancer	409	225
	Osteoporosis	Self reported diagnosis of osteoporosis	215	84
		Self reported hip fracture	148	89
		Self reported forearm fracture after age 50	353	188
Combinations	Two or more of diseases or medications mentioned above	Two or more of above criteria fulfilled	-	576
Total excluded				2441

**Total N*: Total number of subjects having the criterion.
***N - excluded*: Number of subjects who were excluded due to that criterion only.

Table 2: Osteoporosis definitions, their thresholds and the populations where they may be applied.

Definition	Threshold for osteoporosis	Reference population	Applied to:
WHO1 (3)	BMD < 2.5 SD below female peak BMD	Female 10-year age group with highest mean BMD	Men and women
WHO2 (3)	BMD < 2.5 SD below mean pre-menopausal BMD	All pre-menopausal women as defined by self report in questionnaire (30)	Men and women
AGE-SPECIFIC	BMD < 1 SD below age- and sex specific BMD mean.	Age groups: 25-30, 30-39, 40-49, 50-59, 60-69, 70-74 and 75+	Men and women
NHANES (8)	BMD < 2.5 SD below male peak BMD	Male 10-year age group with highest mean BMD	Men only
UK-consensus (9)	BMD < 2.5 SD below male peak BMD or < 1 SD below male age specific mean BMD	Either NHANES or AGE SPECIFIC reference population	Men only

SD- Standard deviation of the chosen reference population, BMD- Bone Mineral Density.

Table 3: Women: Prevalence of osteoporosis according to two variants of the WHO-definition in a population based study. The Tromsø study, 1994-95.

	Age groups:	**25-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-74**	**75+**	**50+*** (95% CI)	**70+*** (95% CI)
Distal site	N	86	220	182	1869	1461	594	68	3992	662
	WHO1 (%)	1.2	0.5	0.5	9.6	41.3	60.4	69.1	**31.6** (30.2 - 33.1)	**64.8** (61.1 - 68.5)
	WHO2 (%)	-	0.5	0.5	8.0	37.6	56.6	66.2	**29.0** (27.6 - 30.4)	**61.4** (57.6 - 65.1)
Ultradistal site	N	86	219	178	1856	1450	590	66	3962	656
	WHO1 (%)	0	0.5	1.1	10.2	39.1	52.2	62.1	**29.5** (28.2 - 30.9)	**57.2** (53.3 - 61.0)
	WHO2 (%)	0	0	1.1	7.3	31.6	45.4	56.1	**24.4** (23.1 - 25.70)	**50.7** (48.0 - 53.5)

WHO1: BMD less than 2.5 SD below female peak BMD. ***WHO2***: BMD less than 2.5 SD below female pre-menopausal BMD.
*Standardised to the WHO European population (18)

Table 4: Men: Prevalence of osteoporosis according to differing osteoporosis definitions, in a population based study. The Tromsø study, 1994-95.

	Age groups:	**25-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-74**	**75+**	**50+*** (95% CI)	**70+*** (95% CI)
Distal site	N	52	122	115	836	1311	509	59	2715	568
	WHO1 (%)	0	0	0	0.2	0.9	3.7	13.6	**2.3** (1.8 - 2.7)	**8.6** (6.9 - 10.4)
	WHO2 (%)	0	0	0	0.2	0.8	3.1	13.6	**2.1** (1.7 - 2.6)	**8.4** (6.4 - 10.3)
	NHANES (%)	1.9	0	1.7	6.0	16.2	28.9	42.4	**15.6** (14.2 - 17.0)	**35.6** (31.8 - 39.4)
	UK-consensus (%)	15.4	17.2	13.9	16.1	16.2	28.9	42.4	**20.3** (18.9 - 21.8)	**35.6** (31.8 - 39.4)
Ultradistal site	N	52	123	116	840	1319	515	60	2734	575
	WHO1 (%)	0	0	0	0.4	0.5	2.3	10.0	**2.0** (1.6 - 2.4 %)	**7.8** (6.4 - 9.3)
	WHO2 (%)	0	0	0	0.2	0.4	1.7	8.3	**1.3** (1.0 - 1.7 %)	**5.0** (3.6 - 6.5)
	NHANES (%)	0	0	1.7	2.3	6.5	13.6	20.0	**7.5** (12.5 - 15.1)	**20.1** (16.1 - 24.2)
	UK-consensus (%)	11.5	13	18.1	16.1	14.8	15.1	20.0	**16.7** (15.5 - 18.3)	**20.9** (17.9 - 23.9)

WHO1: BMD less than 2.5 SD below female peak BMD. ***WHO2***: BMD less than 2.5 SD below female pre-menopausal BMD. ***NHANES*** : BMD less than 2.5below male peak BMD. ***UK consensus***: BMD less than 2.5 SD below male peak BMD or less than 1 SD below age- and sex- specific mean BMD.
*Standardised to the WHO European population (18)

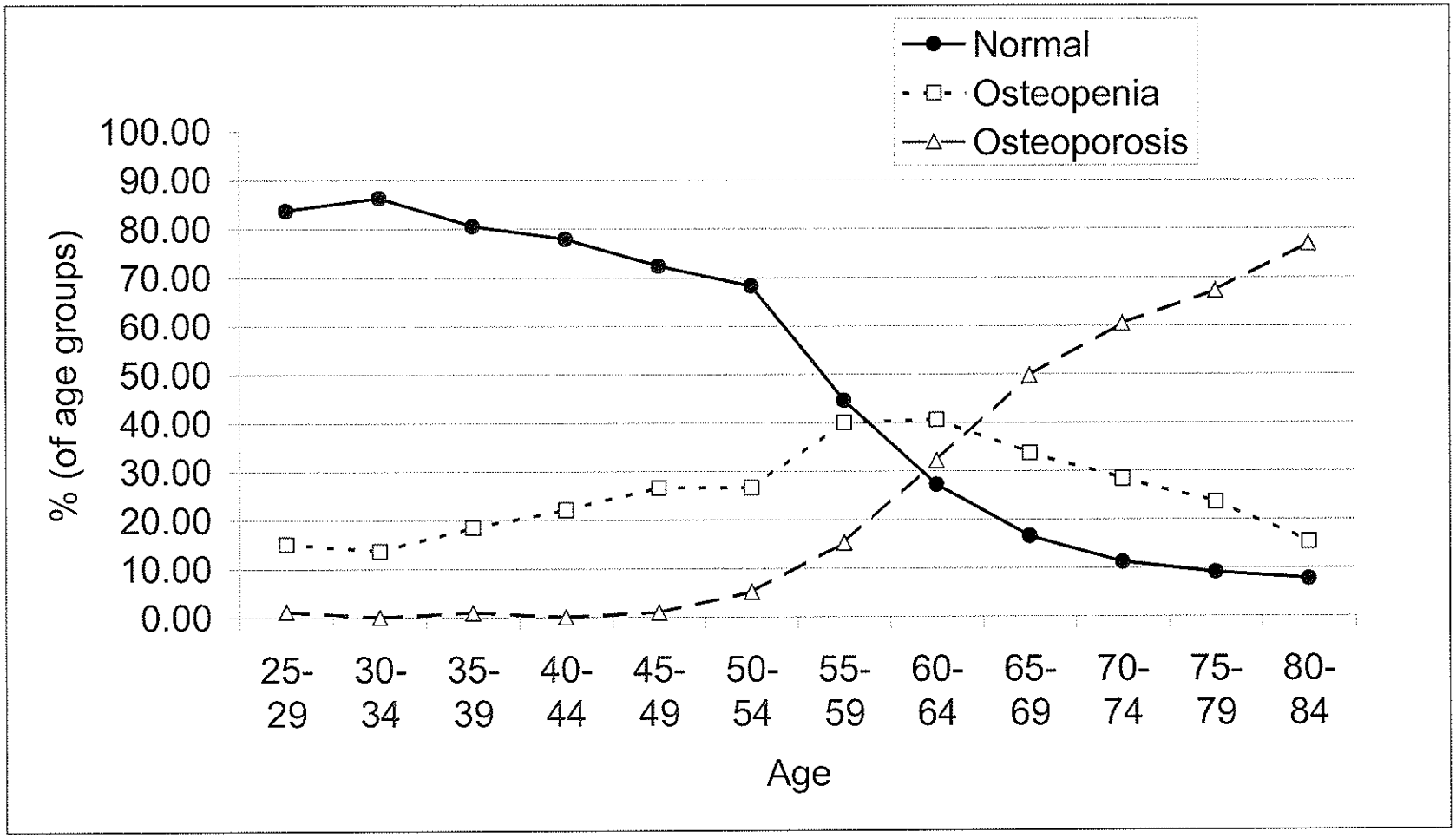
Table 5: Ultradistal site: Change in osteoporosis prevalence according to choice of young adult mean (YAM) in the WHO osteoporosis definition. The Tromsø study, 1994-95.

	Osteoporosis classification by WHO2		
Osteoporosis classification by WHO1	Normal or osteopenia n	Osteoporosis n	Total WHO1
Normal or osteopenia	3337		3337
Osteoporosis	208	900	1108 (25%)*
Total WHO2	3545	900 (20%)*	4445

YAM in WHO1: Female peak BMD. YAM in WHO2: Female pre-menopausal BMD. McNemars test: $p < 0.0001$.
*Prevalence in % of total

Legends

Figure 1: WHO osteoporosis classification at forearm site, in a general female population (n=4480) by age. The diagnostic category prevalences are given in % of age-group, and are mutually exclusive: Normal: BMD higher than 1 standard deviation (SD) below young adult peak BMD, Osteopenia: BMD between 2.5and 1 SD below young adult peak BMD, Osteoporosis: BMD below 2.5 SD below young adult peak BMD. The Tromsø study, 1994-95.


Normal
Osteopenia
Osteoporosis
100.00
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
% (of age groups)
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
Age

Appendix – A:

Information leaflets and declarations of consent

Innbydelse til

HELSEUNDERSØKELSEN

TROMSØ 01 3556 25

Fødselsdato Personnr. Kommune Kretsnr.

Velkommen til helseundersøkelsen i Tromsø!

Helseundersøkelsen kommer nå til Tromsø. Tid og sted for frammøte finner du nedenfor. Du finner også en orientering om undersøkelsen i den vedlagte brosjyren.

Vi ber deg fylle ut spørreskjemaet på baksiden og ta det med til undersøkelsen.

Undersøkelsen blir mest verdifull om frammøtet blir så fullstendig som mulig. Vi håper derfor at du har mulighet til å komme. Møt selv om du kjenner deg frisk, om du er under legebehandling, eller om du har fått målt kolesterol og blodtrykk i den senere tid.

Vennlig hilsen
Kommunehelsetjenesten
Fagområdet medisin, Universitetet i Tromsø
Statens helseundersøkelser

Vi inviterer deg til undersøkelse: onsdag 15.februar 1330 - 1700

Frammøtested: **Elisabeth-senteret, Mellomvn. 50, Tromsø**
(den gamle Kvinneklinikken), tlf. i åpningstiden: 77 64 59 00.

Åpningstider:	**mandag og torsdag**	**kl 12.00 - 19.00**
	tirsdag, onsdag og fredag	**kl 08.30 - 17.00**

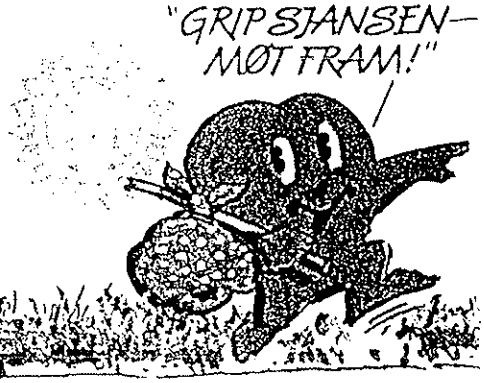
For å kunne avvikle undersøkelsen raskest mulig, inviterer vi et visst antall personer pr. dag. Vi ønsker derfor at så mange som mulig møter innenfor den tiden de får tildelt. Dersom du er forhindret fra å møte i den tiden vi har gitt deg, er du velkommen til undersøkelsen en annen tid, eller en annen dag. Du trenger ikke melde fra til oss hvis du må bytte tid/dag.

Pendlere og andre som bare er hjemme i helgene, kan møte lørdag 11. februar kl 10.00-13.30. Bevegelseshemmede som ikke kan gå i trapper, bes ringe på forhånd for å avtale tid for frammøte.

Egenandelen ved undersøkelsen er kr. 10,-

NB!
Noen uker etter undersøkelsen vil du motta brev med dine egne resultater fra undersøkelsen.

Alle som deltar i Helseundersøkelsen er med i trekningen av en fritt valgt reise for en eller flere personer til en samlet verdi av kr. 10.000,-.



- **Spørreskjema**
- **Spesialundersøkelse.** Alle født mellom 1920-1939, og et utvalg av de øvrige, blir tilbudt en mer omfattende undersøkelse gratis. Hva undersøkelsen omfatter varierer noe, men gir en bedre beskrivelse av hjertet, hovedpulsårens funksjon, åreforkalkning, og tendens til beinskjørhet. Du får time til undersøkelsen ved frammøte.

Spørreskjema

Dette finner du på baksiden av det brevet du har fått. Vennligst fyll ut skjemaet på forhånd og ta det med til undersøkelsen. Dersom enkelte spørsmål er vanskelige å fylle ut, kan du få hjelp når du møter fram.

Om samtykke

Opplysningene om deg blir behandlet strengt fortrolig. De oppbevares og brukes etter regler gitt av Datatilsynet og den forskningsetiske komité for Nord-Norge. For at opplysningene skal brukes i medisinsk forskning, må du samtykke til det. Samtykke er også nødvendig for at din lege skal få resultat av de målinger som gjøres (og som du selv får tilsendt resultat av) og svar du gir på spørreskjemaet som ligger ved dette brevet. Vi ber derfor at du ved frammøte samtykker i:

- at melding om dine resultat sendes til din faste lege, og inngår i din journal hos legen.
- at blodprøven kan brukes til analyser som ledd i medisinsk forskning. Hensikten med slike analyser er å forstå årsak til sykdom.
- at dine resultater kan brukes til medisinsk forskning, ved å sammenholde opplysningene med andre helse- og sykdomsregister (f.eks. kreftregister og dødsårsaksregister) og opplysninger fra de tidligere helseundersøkelsene i Tromsø. Før opplysningene analyseres, blir navn og person-nummer fjernet. Selv om du gir samtykke, kan du senere reservere deg mot bruk av dine resultat.

Etterundersøkelse

Noen av dem som blir undersøkt, blir senere innkalt til egen lege for nærmere kontroll. Trenger du behandling, får du tilbud om det.

Hva koster undersøkelsen ?

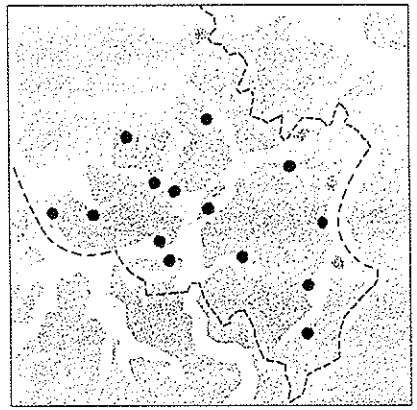
Det er nødvendig med en egenandel ved undersøkelsen. Den er beskjeden i forhold til de totale kostnadene. Beløpets størrelse vil du finne i brevet du nå har mottatt. Spesialundersøkelsen er gratis. Trenger du ny undersøkelse hos egen lege eller ved Regionsykehuset, betaler du vanlig egenandel.

Antrekk

Av hensyn til blodtrykkmålingen ber vi om at du tar på plagg uten ermer eller med korte ermer som ikke strammer. Det er ikke nødvendig å ta av seg på overkroppen.

Steder som får besøk av helseundersøkelsen

- Kaldfjord
- Tromvik
- Lakselvbukt
- Sjursnes
- Breivikeidet
- Fagernes
- Skittenelv
- Ersfjordbotn
- Straumsbukta
- Brensholmen
- Vikran
- Trondjord
- Sjøtun
- Tromsø sentrum



Vel møtt!

Hjertelig hilsen

- Kommunehelsetjenesten
- Fagområdet medisin, Universitetet i Tromsø

Statens helseundersøkelser

Repro & Grafisk AS 389 95 955

Hjertelig velkommen, kjære Tromsøværing

Du er innbudt til den store helseundersøkelsen i Tromsø kommune 1994 - 95

Vi når fram til alle

Vi begynner i de ytre distriktene i kommunen. Her vil undersøkelsen pågå i skolehus og andre lokaler - se opplysningene i innbydelsen som følger dette brevet.
Fra slutten av oktober 1994 til sommeren 1995 vil undersøkelsen foregå i Mellomveien 50 (Elisabeth-senteret; den gamle kvinneklinikken). Vi ser helst at du møter på stedet som er oppført i innbydelsesbrevet.

Hvorfor har du fått tilbudet ?

Fordi vi tilbyr undersøkelsen til alle som er født i 1969 eller tidligere.

Hva er formålet ?

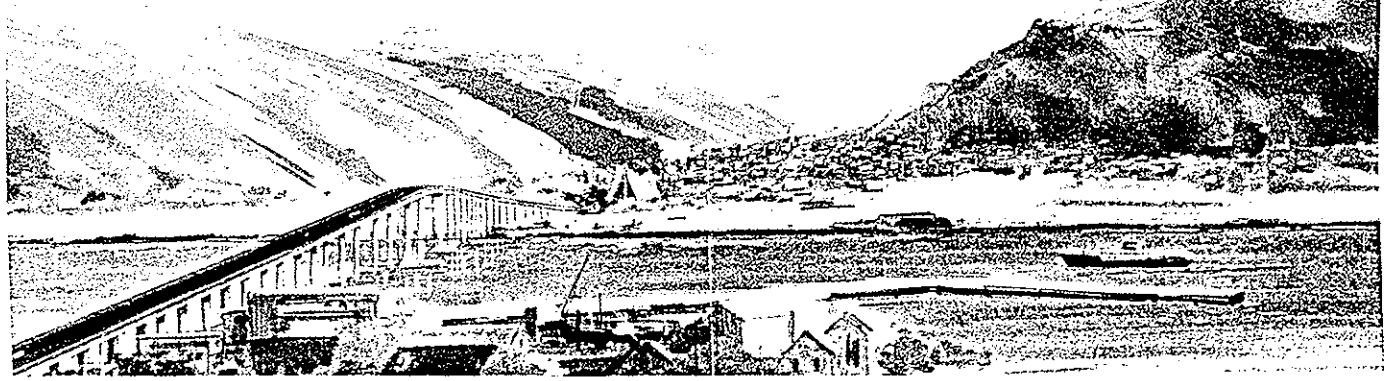
Undersøkelsen er i første rekke rettet mot hjerte-karsykdom, men er også viktig for å få ny viten om andre alvorlige kroniske sykdommer (bl.a. kreft).
Denne gangen vil en i tillegg se spesielt på smertetilstander i muskler og skjelett, blant annet fibromyalgi. Derfor vil noen høsten 1995 bli invitert til en spesialundersøkelse.
Store hjerte-karundersøkelser ble gjort i Tromsø i 1974, 1979-80 og 1986-87. Det var stort frammøte, og det ble funnet en rekke tilfeller av hjerte-karsykdom - som nå får behandling.
Undersøkelsene har også gitt oss viktig kunnskap for å bekjempe disse sykdommene. Den kunnskap vi har fått gjennom de tidligere undersøkelsene, har gjort Universitetet i Tromsø til et av de fremste forskningsmiljøer i verden på hjerte-karsykdommer. Også denne gangen tar vi sikte på å finne personer som har hjerte-karsykdom uten å vite det. Vi vil også gjerne nå dem som har særlig høy risiko, slik at de kan få tilbud om forebygging og andre tiltak som kan hindre at sykdom utvikler seg. Hjerte-karsykdom er fortsatt et av våre største helseproblemer.

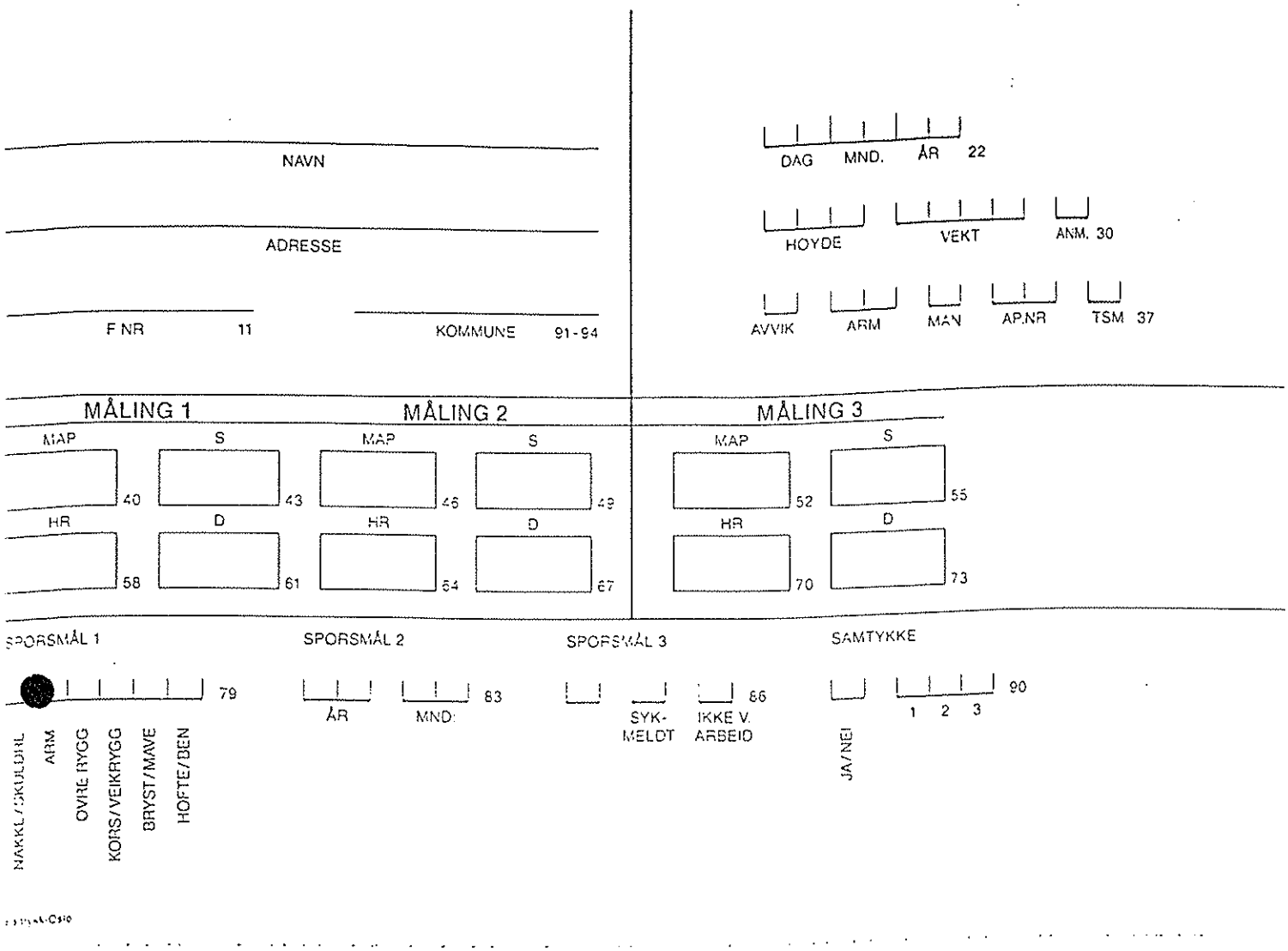
Ikke bare for din egen skyld.....

Undersøkelsen har ikke bare betydning for deg personlig. Det er også viktig at resultatene blir brukt i medisinsk forskning, bl.a. ved at vi sammenholder dem med framtidig forekomst av sykdom. Dermed lærer vi mer om hvordan hjerte-karsykdom, kreft og andre folkesykdommer oppstår og hvordan de kan forebygges. Ved å møte fram er du med i kampen mot disse sykdommene.

Undersøkelsen omfatter

- **Måling av høyde og vekt**
- **Måling av blodtrykk**
- **Blodprøve.** I denne måler vi innholdet av fettstoffer (bl.a. kolesterol), kalk og et leverenzym. Resultatet av disse målingene sendes din lege om du ønsker det. Resultatet av andre prøver blir bare brukt til medisinsk forskning. Prøven blir frosset ned, slik at det senere kan måles andre stoffer om det blir nødvendig for utforskning av sykdom. Før slike målinger blir gjort, blir studien forelagt den forskningsetiske komité for Nord-Norge.
- **EKG** er en undersøkelse som registrerer hjertets aktivitet. Den gjøres på en forenklet måte, og registreringene blir bare brukt til forskning.





SAMTYKKEERKLÆRING

I invitasjonsbrosjyren til Helseundersokelsen i Tromso 1994-95, er jeg orientert om undersokelsens formål. Jeg er kjent med at opplysningene blir behandlet strengt fortrolig og at undersokelsen er godkjent av Datatilsynet og forelagt den forskningsetiske komité for Nord-Norge. Jeg er kjent med at jeg senere kan reservere meg mot bruk av opplysninger om meg.

Jeg samtykker i:

1. at melding om mine resultater sendes til min faste lege.
2. at blodproven oppbevares til senere medisinsk forskning.
3. at mine resultater kan brukes til medisinsk forskning, eventuelt ved å sammenholde opplysningene om meg med opplysninger fra andre helse- og sykdomsregister (f.eks. kreftregister og dodsårsaksregister) og mine data fra de tidligere helseundersokelsene i Tromso.

Vennligst stryk det/de avsnitt du reserverer deg mot.

Tromso, ...

Underskrift

Om samtykke

Opplysningene om deg blir behandlet strengt fortrolig. De oppbevares og brukes etter regler gitt av Datatilsynet og i henhold til norsk lov. Undersøkelsen er anbefalt av den regionale komite for medisinsk forskningsetikk. Dersom det er nødvendig med videre undersøkelse, ber vi deg samtykke i at nødvendige resultater kan sendes din lege eller Regionsykehuset i Tromsø. Vi ber om at du ved fremmøte samtykker i:

- ✗ at melding om dine resultater sendes til din lege eller Regionsykehuset i Tromsø dersom du trenger videre undersøkelse eller behandling.
- ✗ at dine resultater kan brukes til medisinsk forskning, ved å sammenholde opplysningene med andre helse- og sykdomsregistre og opplysninger fra de tidligere helseundersøkelsene i Tromsø. Før opplysningene analyseres, blir navn og person-nummer fjernet.
- ✗ at blodprøven kan oppbevares og brukes til medisinsk forskning.
- ✗ at Helseundersøkelsen i Tromsø kan kontakte deg senere med forespørsel om å delta i undersøkelser.

Selv om du gir samtykke, kan du senere reservere deg mot bruk av dine resultat.

Spesialundersøkelsen

er en del av Helseundersøkelsen i Tromsø og arrangeres av Universitetet i Tromsø, Fagområdet Medisin, i samarbeid med Regionsykehuset i Tromsø

UNIVERSITETET I TROMSØ

Bruk av medisin

For å tolke resultatene ønsker vi opplysning om medisinbruk den siste uka. Vennligst angi navn, styrke og dose på alle medisiner som du bruker. Dersom du er i tvil om utfylling, ta med medisinene. Vi vil da kunne hjelpe deg.

Medisin-navn	Styrke	Dose

Hjertelig velkommen

SPESIALUNDERSØKELSEN '94-95

Du er innbudt til spesial-undersøkelsen i Tromsø

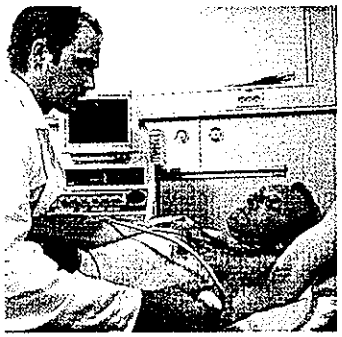
GRAFISK AS, TROMSØ

DU ER INNBUDT TIL SPESIALUNDERSØKELSEN

Helseundersøkelsen i Tromsø inviterer noen av deltakerne til en gratis spesialundersøkelse.

Spesialundersøkelsen

Spesialundersøkelsen benytter avanserte apparater som lager bilder av blodårer og hjertet og gir informasjon om kroppens beinvev og fettmengde. Det benyttes ikke røntgenstråler, men ultralyd eller lysbølger som reflekteres til et lite apparat som holdes mot huden (se bildet). Disse undersøkelsene medfører ikke stikk eller smerter og har ingen kjente bivirkninger. Spesialundersøkelsen omfatter også blodprøve, urinprøve og hjerte-aktivitet (EKG).



Hvorfor har du fått tilbudet?

Vi har ikke mulighet til å gi alle spesial-undersøkelse. Vi inviterer alle menn og kvinner født mellom 1920 og 1939 og noen tilfeldig utvalgte fra andre aldersgrupper.

Hva er formålet?

Mange sykdommer utvikler seg gradvis over lang tid uten at personen selv er klar over det. Med avanserte metoder er det mulig å påvise forandringer på et tidlig stadium. I enkelte tilfeller kan forebygging og behandling iverksettes før sykdommene utvikler seg. I andre tilfeller vet vi ikke sikkert hva forandringene betyr og videre forskning er nødvendig. Spesialundersøkelsen er derfor et unikt tilbud som ikke bare har betydning for deg personlig. Ved at resultatene blir brukt i medisinsk forskning får vi økt kunnskap om hvordan sykdommer oppstår og hvordan de kan forebygges og behandles.

Spesialundersøkelsen omfatter

✓ Ultralyd av blodårer og hjertet

Alle får undersøkt halspulsårer og hovedpulsåren i mageregionen. Dette gir opplysning om åreforkalkning og innsnevringer eller utposninger av årene. Halvparten får også undersøkt hjertets form og funksjon.

✓ Måling av beintetthet og kroppens fettmengde

Opplysningene vil benyttes til å undersøke risiko for beinskjørhet (osteoporose) og brudd, og om det er en sammenheng mellom kroppsfett og sykdom.

✓ EKG

Dette er en utvidet registrering av hjerteaktivitet som også gir informasjon om hjertesykdom.

✓ Urinprøve

I urinprøvene måles eggehvite (protein) og et annet stoff (kreatinin) som forteller om nyrefunksjon. Resultatet blir sikrere ved at urinen fra tre forskjellige dager undersøkes.

✓ Blodprøve og blodtrykk

I blodprøven undersøkes fettstoffer og stoffer som forteller om nyrefunksjon, stoffskifte (kalk og sukker) og blodlevring. Prøven blir frosset ned, slik at den senere kan brukes i utforsking av sykdom.

✓ Videre oppfølging

- Dersom vi mener at du trenger videre undersøkelse eller behandling, får du tilbud om det.
- Enkelte kan senere bli forespurt om å komme til ny undersøkelse som ledd i forskning.

Praktiske opplysninger

Sted og tid
Undersøkelsen foregår i 2.etasje av Elisabeth-senteret - den gamle kvinneklinikken (Mellomveien 50) - altså i etasjen over Tromsø-undersøkelsen. Undersøkelsen tar 1 til 1,5 time og er gratis.

Vi håper du kan benytte den avtalte time.
Dato og klokkeslett står i brosjyren.
Dersom du må bytte time, ber vi om at du gir beskjed på telefon 77 64 59 00.

Urinprøve
Du har fått utlevert tre uringlass merket 1, 2 og 3. Vi ønsker at du de siste tre dagene før spesial-undersøkelsen lager en morgen-urinprøve i hvert glass. Du har altså fått ett glass for hver morgen. Legg merke til følgende:

1. Vennligst uriner en liten mengde urin i toalettet før du tar av urin til prøven. Siste morgenprøve lages den dag du møter til undersøkelsen.
2. Påfør dato på hvert av uringlassene.
3. Det er en fordel om prøvene kan stå kjølig.
4. Lever alle tre glassene når du møter til undersøkelsen.

Bruk av medisin
På neste side ber vi deg notere hvilke medisiner du har brukt den siste uka. Dette kan ha betydning når vi skal tolke resultatene.

Påkledning
Av hensyn til blodtrykksmålingen ber vi om at du tar på plagg som ikke strammer på armen. Ved undersøkelse av hjertet er det nødvendig å ta av seg på overkroppen. Ved undersøkelse av hovedpulsåren må klær trekkes noe ned slik at huden i mageregionen blir bar.

TILBUD OM UNDERSØKELSE AV BENSKJØRHET

Alle kvinner mellom 50 og 54 år i Tromsø kommune får i forbindelse med Helse-undersøkelsen i Tromsø tilbud om en tilleggsundersøkelse - nemlig undersøkelse av **benskjørhet**. I 50-årsalderen gjennomgår de fleste kvinner store hormonelle endringer. Som en følge av dette skjer det også et forholdsvis stort bentap. Dette er normalt, men hos noen er denne nedgangen i bentetthet større enn hos andre. Lav bentetthet **kan** være en risiko for senere benbrudd. Vi vet ikke hvorfor bentapet skjer raskere hos noen enn hos andre - og vi har ikke gode metoder til å finne ut hvem disse kvinnene er. Tromsø-undersøkelsen vil prøve å finne svar på dette.

Vi håper du vil møte til den timen du har fått - og dermed delta i verdens største undersøkelse av benskjørhet. For å finne svarene på hva som er **årsaker** til benskjørhet - og senere brudd i lårhals, undersarm og ryggsøyle, er det viktig at nettopp **DU** møter.
Hvis du ligger spesielt lavt i bentetthet, vil du sommer/høst 1995 få tilbud om ny undersøkelse og samtale.

Undersøkelsen er gratis, smertefri og helt uten risiko. Den tar ca. 5 minutter. I tillegg ønsker vi å ta en blodrøve. Undersøkelsen skjer i 2. etasje i **Gamle** Kvinneklinikken - nåværende Elisabeth-senteret. Dersom du må bytte time el.l ber vi om at du gir beskjed på telefon 77 64 59 00.

Med vennlig hilsen

Institutt for samfunnsmedisin, Universitetet i Tromsø
Regionsykehuset i Tromsø

SPESIALUNDERSØKELSEN '94-95

SAMTYKKE-ERKLÆRING

I invitasjonsbrosjyren til Spesialundersøkelsen i Tromsø 1994-95 er jeg orientert om undersøkelsens formål. Jeg vet at opplysningene blir behandlet strengt fortrolig og at undersøkelsen er godkjent av Datatilsynet og anbefalt av den regionale komite for medisinsk forskningsetikk. Jeg vet at jeg senere kan reservere meg mot bruk av opplysninger om meg.

Vennligst kryss av for det/de avsnitt du reserverer deg mot.

Jeg samtykker i:

☐ at melding om mine resultater sendes til min lege eller Regionsykehuset i Tromsø dersom jeg trenger videre undersøkelse eller behandling.

☐ at mine resultater kan brukes til medisinsk forskning, ved å sammenholde opplysningene med andre helse- og sykdomsregistre og opplysninger fra de tidligere helseundersøkelser i Tromsø.

☐ at blodprøven kan oppbevares og brukes til medisinsk forskning.

☐ at Helseundersøkelsen i Tromsø kan kontakte meg senere med forespørsel om å delta i undersøkelser.

Tromsø, ...

Dato Underskrift

Appendix – B:

First questionnaire, Norwegian and English

Innbydelse til

HELSEUNDERSØKELSEN

Fødselsdato Personnr. Kommune Kretsnr.

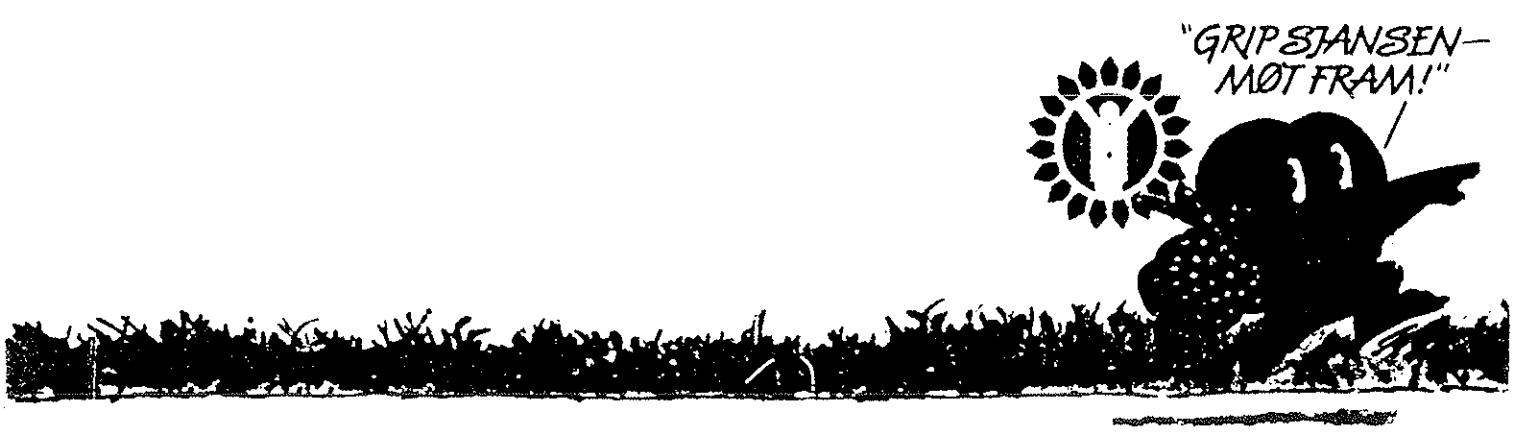
Velkommen til helseundersøkelsen i Tromsø!

Helseundersøkelsen kommer nå til Tromsø. Tid og sted for frammøte finner du nedenfor. Du finner også en orientering om undersøkelsen i den vedlagte brosjyren.

Vi ber deg fylle ut spørreskjemaet på baksiden og ta det med til undersøkelsen.

Undersøkelsen blir mest verdifull om frammøtet blir så fullstendig som mulig. Vi håper derfor at du har mulighet til å komme. Møt selv om du kjenner deg frisk, om du er under legebehandling, eller om du har fått målt kolesterol og blodtrykk i den senere tid.

Vennlig hilsen
Kommunehelsetjenesten
Fagområdet medisin, Universitetet i Tromsø
Statens helseundersøkelser



HELSE

Hvordan er helsen din nå? *Sett bare ett kryss.*

Dårlig	12	1
Ikke helt god		2
God		3
Svært god		4

Har du, eller har du hatt:

		JA	NEI	Alder første gang
Hjerteinfarkt	13			år
Angina pectoris (hjertekrampe)	16			år
Hjerneslag/hjerneblødning	19			år
Astma	22			år
Diabetes (sukkersyke)	25			år

Bruker du medisin mot høyt blodtrykk?

Nå	28	1
Før, men ikke nå		2
Aldri brukt		3

Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende? 29 — JA / NEI

Har du de siste to ukene følt deg:

		Nei	Litt	En god del	Svært mye
Nervøs og urolig?	30				
Plaget av angst?	31				
Trygg og rolig?	32				
Irritabel?	33				
Glad og optimistisk?	34				
Nedfor/deprimert?	35				
Ensom?	36				
		1	2	3	4

RØYKING

Røykte noen av de voksne hjemme da du vokste opp? 37 — JA / NEI

Bor du, eller har du bodd, sammen med noen dagligrøykere etter at du fylte 20 år? 38 — JA / NEI

Hvis "JA", hvor mange år tilsammen? 39 — Antall år

Hvor lenge er du vanligvis daglig tilstede i røykfylt rom? 41 — Antall timer

Sett 0 hvis du ikke oppholder deg i røykfylt rom.

Røyker du selv:

		JA	NEI
Sigaretter daglig?	43		
Sigarer/sigarillos daglig?	44		
Pipe daglig?	45		

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? 46 — Antall år

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? 48 — Antall sigaretter

Hvor gammel var du da du begynte å røyke daglig? 52 — Alder år

Hvor mange år tilsammen har du røykt daglig? 54 — Antall år

MOSJON

Hvordan har din fysiske aktivitet i fritiden vært det siste året? *Tenk deg et ukentlig gjennomsnitt for året.*
Arbeidsvei regnes som fritid.

		Timer pr. uke: Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)*	56				
Hard fysisk aktivitet *(svett/andpusten)*	57				
		1	2	3	4

KAFFE

Hvor mange kopper kaffe drikker du daglig?
Sett 0 hvis du ikke drikker kaffe daglig.

Kokekaffe	58	Antall kopper
Annen kaffe	60	Antall kopper

ALKOHOL

Er du total avholdsmann/-kvinne? 62 — JA / NEI

Hvor mange ganger i måneden drikker du vanligvis alkohol? *Regn ikke med lettøl.*
Sett 0 hvis mindre enn 1 gang i mnd. 63 — Antall ganger

Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av to uker? 65
Regn ikke med lettøl.
Sett 0 hvis du ikke drikker alkohol.

Øl	Vin	Brennevin
glass	glass	glass

FETT

Hva slags margarin eller smør bruker du vanligvis på brødet? *Sett ett kryss.*

Bruker ikke smør/margarin	71	1
Meierismør		2
Hard margarin		3
Bløt (soft) margarin		4
Smør/margarin blanding		5
Lettmargarin		6

UTDANNING/ARBEID

Hvilken utdanning er den høyeste du har fullført?

Grunnskole, 7-10 år, framhaldsskole, folkehøgskole	72	1
Realskole, middelskole, yrkesskole, 1-2-årig videregående skole		2
Artium, øk.gymnas, allmennfaglig retning i videregående skole		3
Høgskole/universitet, mindre enn 4 år		4
Høgskole/universitet, 4 år eller mer		5

Hva slags arbeidssituasjon har du nå?

Lønnet arbeid	73	
Heltids husarbeid	74	
Utdanning, militærtjeneste	75	
Arbeidsledig, permittert	76	

Hvor mange timer lønnet arbeid har du i uka? 77 — Antall timer

Mottar du nå noen av følgende ytelser?

Syketrygd (sykmeldt)	79	
Attføring	80	
Uførepensjon	81	
Alderspensjon	82	
Sosialstøtte	83	
Arbeidsløshetstrygd	84	

SYKDOM I FAMILIEN

Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? 85 — JA / NEI / VET IKKE

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

Translation based on translations by Kevin McCafferty and Anne Clancy

HEALTH SURVEY INVITATION

"This is your chance"

Date of birth Social security No.

Municipality Electoral ward No.

Welcome to the Tromsø Health Survey!

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

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

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

Yours sincerely,

Municipal Health Authorities

Faculty of Medicine - University of Tromsø

National Health Screening Service

"This is a real opportunity — Take it!"

Your own health

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

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

Do you have, or have you ever had:

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

Do you take medicine for high blood pressure?

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

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

YES ☐ NO ☐

Have you in the last two weeks felt:

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

Smoking

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

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

YES ☐ NO ☐

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

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

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

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

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

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

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

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

Exercise

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

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

Coffee

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

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

Alcohol

Are you a teetotaler? YES ☐ NO ☐

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

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

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

Fat

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

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

Education/work

What is the highest level of education you have completed?

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

What is your current work situation?

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

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

Do you receive any of the following benefits?

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

Illness in the family

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

YES	NO	DON'T KNOW
☐	☐	☐

Appendix – C:

Second questionnaire for subjects aged < 70 years, Norwegian and English

Helseundersøkelsen i Tromsø

Hovedformålet med Tromsøundersøkelsene er å skaffe ny kunnskap om hjerte-karsykdommer for å kunne forebygge dem. I tillegg skal undersøkelsen øke kunnskapen om kreftsykdommer og andre alminnelige plager som f.eks. allergier, smerter i muskulatur og nervøse lidelser. Vi ber deg derfor svare på noen spørsmål om forhold som kan ha betydning for risikoen for disse og andre sykdommer.

Skjemaet er en del av Helseundersøkelsen som er godkjent av Datatilsynet og av Regional komite for medisinsk forskningsetikk. Svarene brukes bare til forskning og behandles strengt fortrolig. Opplysningene kan senere bli sammenholdt med informasjon fra andre offentlige helseregistre etter de regler som Datatilsynet og Regional komite for medisinsk forskningsetikk gir.

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

Det utfylte skjema sendes i vedlagte svarkonvolutt. Portoen er betalt.

På forhånd takk for hjelpen!

Med vennlig hilsen

Fagområdet medisin
Universitetet i Tromsø **Statens helseundersøkelser**

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

Jeg ønsker ikke å besvare spørreskjemaet ..... 17 ☐

Dag Mnd År

...to for utfylling av skjema: ..... 18 ...../...../.....

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?

..... 24 - 28

Hvis du ikke bodde i Norge, oppgi land i stedet for kommune.

Hvordan var de økonomiske forhold i familien under din oppvekst?
- Meget gode ..... 29 ☐
- Gode ..... ☐
- Vanskelige ..... ☐
- Meget vanskelige ..... ☐

Hvor mange av de første 3 årene av ditt liv
- bodde du i by? ..... 30 _____ år
- hadde dere katt eller hund i hjemmet? ..... 31 _____ år

Hvor mange av de første 15 årene av ditt liv
- bodde du i by? ..... 32 _____ år
- hadde dere katt eller hund i hjemmet? ..... 34 _____ år

BOLIG

Hvem bor du sammen med?

Sett ett kryss for hvert spørsmål og angi antall.		Ja	Nei	Antall
Ektefelle/samboer	36	☐	☐	
Andre personer over 18 år	37	☐	☐	_____
Personer under 18 år	40	☐	☐	_____

Hvor mange av barna har plass i barnehage? ..... 43 _____

Hvilken type bolig bor du i?
- Enebolig/villa ..... 45 ☐ 1
- Gårdsbruk ..... ☐ 2
- Blokk/terrasseleilighet ..... ☐ 3
- Rekkehus/2-4 mannsbolig ..... ☐ 4
- Annen bolig ..... ☐ 5

Hvor stor er din boenhet? ..... 46 _____ m^2

I omtrent hvilket år ble boligen bygget? ..... 49 _____

		Ja	Nei
Er boligen isolert etter 1970?	53	☐	☐
Bor du i underetasje/kjeller?	54	☐	☐
Hvis "Ja", er gulvbelegget lagt på betong?	55	☐	☐

Hvordan er boligen hovedsakelig oppvarmet?
- Elektrisk oppvarming ..... 56 ☐
- Vedfyring ..... ☐
- Sentralvarmeanlegg oppvarmet med:
  - Parafin ..... ☐
  - Elektrisitet ..... ☐

		Ja	Nei
Er det heldekkende tepper i stua?	60	☐	☐
Er det katt i boligen?	61	☐	☐
Er det hund i boligen?	62	☐	☐

ARBEID

Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive ditt arbeid?
- For det meste stillesittende arbeid? ..... 63 ☐ 1
  (f.eks. skrivebordsarbeid, montering)
- Arbeid som krever at du går mye? ..... ☐ 2
  (f.eks. ekspeditørarb., lett industriarb., undervisning)
- Arbeid hvor du går og løfter mye? ..... ☐ 3
  (f.eks. postbud, pleier, bygningsarbeid)
- Tungt kroppsarbeid? ..... ☐ 4
  (f.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)

Kan du selv bestemme hvordan arbeidet ditt skal legges opp?
- Nei, ikke i det hele tatt ..... 64 ☐ 1
- I liten grad ..... ☐ 2
- Ja, i stor grad ..... ☐ 3
- Ja, det bestemmer jeg selv ..... ☐ 4

		Ja	Nei
Har du skiftarbeid, nattarbeid eller går vakter?	65	☐	☐

Har du noen av følgende yrker (heltid eller deltid)?

Sett ett kryss for hvert spørsmål.		Ja	Nei
Sjåfør	66	☐	☐
Bonde/gårdbruker		☐	☐
Fisker		☐	☐

EGNE SYKDOMMER

Har du noen gang hatt:
Sett ett kryss for hvert spørsmål. Oppgi alderen ved hendelsen.
*Hvis det har skjedd flere ganger, hvor gammel var du **siste** gang?*

	Ja	Nei	Alder
Lårhalsbrudd 69	❑	❑	_____
Brudd ved håndledd/underarm 72	❑	❑	_____
Nakkesleng (whiplash) 75	❑	❑	_____
Skade som førte til sykehusinnleggelse 78	❑	❑	_____
Sår på magesekken 81	❑	❑	_____
Sår på tolvfingertarmen 84	❑	❑	_____
Magesår-operasjon 87	❑	❑	_____
Operasjon på halsen 90	❑	❑	_____

Har du eller har du hatt:
Sett ett kryss for hvert spørsmål.

	Ja	Nei
Kreftsykdom 93	❑	❑
Epilepsi (fallesyke)	❑	❑
Migrene	❑	❑
Kronisk bronkitt	❑	❑
Psoriasis	❑	❑
Benskjørhet (osteoporose) 98	❑	❑
Fibromyalgi/fibrositt/kronisk smertesyndrom	❑	❑
Psykiske plager som du har søkt hjelp for	❑	❑
Stoffskiftesykdom (skjoldbruskkjertel)	❑	❑
Sykdom i leveren	❑	❑
Nyrestein 103	❑	❑
Blindtarmsoperasjon	❑	❑
Allergi og overfølsomhet		
Atopisk eksem (f.eks. barneeksem)	❑	❑
Håndeksem	❑	❑
Høysnue	❑	❑
Matvareallergi 108	❑	❑
Annen overfølsomhet (ikke allergi)	❑	❑

Hvor mange ganger har du hatt forkjølelse, influensa, "ræksjuka" og lignende siste halvår? ....110 _____ ganger

	Ja	Nei
Har du hatt dette siste 14 dager? 112	❑	❑

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene:
Kryss av for "Ingen" hvis ingen av slektningene har hatt sykdommen.

	Mor	Far	Bror	Søster	Barn	Ingen
Hjerneslag eller hjerneblødning 113	❑	❑	❑	❑	❑	❑
Hjerteinfarkt før 60 års alder 119	❑	❑	❑	❑	❑	❑
Kreftsykdom 125	❑	❑	❑	❑	❑	❑
Astma 131	❑	❑	❑	❑	❑	❑
Mage/tolvfingertarm-sår 137	❑	❑	❑	❑	❑	❑
Benskjørhet (osteoporose) 143	❑	❑	❑	❑	❑	❑
Psykiske plager 149	❑	❑	❑	❑	❑	❑
Allergi 155	❑	❑	❑	❑	❑	❑
Diabetes (sukkersyke) 161	❑	❑	❑	❑	❑	❑
– alder da de fikk diabetes 167	___	___	___	___	___	___

SYMPTOMER

	Ja	Nei
Hoster du omtrent daglig i perioder av året? 177	❑	❑
Hvis "Ja":		
Er hosten vanligvis ledsaget av oppspytt? 178	❑	❑
Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste år? 179	❑	❑
Har du hatt episoder med piping i brystet? 180	❑	❑
Hvis "Ja", har dette oppstått:		
Sett ett kryss for hvert spørsmål.		
Om natten 181	❑	❑
Ved luftveisinfeksjoner	❑	❑
Ved fysiske anstrengelser	❑	❑
Ved sterk kulde	❑	❑
Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste år? 185	❑	❑

Hvor ofte er du plaget av søvnløshet?
- Aldri, eller noen få ganger i året ....186 ❑ 1
- 1-2 ganger i måneden ❑ 2
- Omtrent en gang i uken ❑ 3
- Mer enn en gang i uken ❑ 4

Hvis du er plaget av søvnløshet i perioder, når på året er du mest plaget?
- Ingen spesiell tid ....187 ❑ 1
- Særlig i mørketiden ❑ 2
- Særlig i midnattsoltiden ❑ 3
- Særlig vår og høst ❑ 4

	Ja	Nei
Har du det siste året vært plaget av søvnløshet slik at det har gått ut over arbeidsevnen? 188	❑	❑

Hvor ofte er du plaget av hodepine?
- Sjelden eller aldri ....189 ❑ 1
- En eller flere ganger i måneden ❑ 2
- En eller flere ganger i uken ❑ 3
- Daglig ❑ 4

Hender det at tanken på å få alvorlig sykdom bekymrer deg?
- Ikke i det hele tatt ....190 ❑ 1
- Bare i liten grad ❑ 2
- En del ❑ 3
- Ganske mye ❑ 4

BRUK AV HELSEVESENET

Hvor mange ganger har du siste året, på grunn av egen helse eller sykdom, vært:
*Sett **0** hvis du **ikke** har hatt slik kontakt.*

	Antall ganger siste år
Hos vanlig lege/legevakt 191	_____
Hos psykolog eller psykiater	_____
Hos annen legespesialist utenfor sykehus	_____
På poliklinikk 197	_____
Innlagt i sykehus	_____
Hos bedriftslege	_____
Hos fysioterapeut 203	_____
Hos kiropraktor	_____
Hos akupunktør	_____
Hos tannlege 209	_____
Hos naturmedisiner (homøopat, soneterapeut o.l.)	_____
Hos håndspålegger, synsk eller "leser"	_____

LEGEMIDLER OG KOSTTILSKUDD

Har du det siste året periodevis brukt noen av de følgende midler daglig eller nesten daglig?
Angi hvor mange måneder du brukte dem.
*Sett **0** hvis du **ikke** har brukt midlene.*

Legemidler
- Smertestillende ....215 ____ mnd.
- Sovemedisin .... ____ mnd.
- Beroligende midler .... ____ mnd.
- Medisin mot depresjon ....221 ____ mnd.
- Allergimedisin .... ____ mnd.
- Astmamedisin .... ____ mnd.

Kosttilskudd
- Jerntabletter ....227 ____ mnd.
- Kalktabletter eller benmel .... ____ mnd.
- Vitamin D-tilskudd .... ____ mnd.
- Andre vitamintilskudd ....233 ____ mnd.
- Tran eller fiskeoljekapsler .... ____ mnd.

Har du de siste 14 dager brukt følgende legemidler eller kosttilskudd?
*Sett **ett** kryss for **hvert** spørsmål.*

	Ja	Nei
Legemidler		
Smertestillende medisin 237	☐	☐
Febersenkende medisin	☐	☐
Migrenemedisin	☐	☐
Eksemsalve	☐	☐
Hjertemedisin (ikke blodtrykksmedisin)	☐	☐
Kolesterolsenkende medisin 242	☐	☐
Sovemedisin	☐	☐
Beroligende medisin	☐	☐
Medisin mot depresjon	☐	☐
Annen nervemedisin	☐	☐
Syrenøytraliserende midler 247	☐	☐
Magesårsmedisin	☐	☐
Insulin	☐	☐
Tabletter mot diabetes (sukkersyke)	☐	☐
Tabletter mot lavt stoffskifte (thyroxin)	☐	☐
Kortisontabletter 252	☐	☐
Annen medisin	☐	☐
Kosttilskudd		
Jerntabletter	☐	☐
Kalktabletter eller benmel	☐	☐
Vitamin D-tilskudd	☐	☐
Andre vitamintilskudd 257	☐	☐
Tran eller fiskeoljekapsler	☐	☐

VENNER

Hvor mange gode venner har du som du kan snakke fortrolig med og gi deg hjelp når du trenger det? ....259 ____ gode venner
Tell ikke med de du bor sammen med, men ta med andre slektninger!

Hvor mange av disse gode vennene har du kontakt med minst en gang i måneden? ....261 ____

	Ja	Nei
Føler du at du har nok gode venner? 263	☐	☐

Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?
- Aldri, eller noen få ganger i året ....264 ☐ 1
- 1-2 ganger i måneden .... ☐ 2
- Omtrent en gang i uken .... ☐ 3
- Mer enn en gang i uken .... ☐ 4

KOSTVANER

Hvis du bruker smør eller margarin på brødet, hvor mange skiver rekker en liten porsjonspakning vanligvis til? Vi tenker på slik porsjonspakning som du får på fly, på kafé o.l. (10-12 gram).

Den rekker til omtrent ....265 ____ skiver

Hva slags fett blir vanligvis brukt til **matlaging** (ikke på brødet) i din husholdning?
- Meierismør ....266 ☐
- Hard margarin .... ☐
- Bløt (Soft) margarin .... ☐
- Smør/margarin blanding .... ☐
- Oljer ....270 ☐

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis?
Sett ett eller to kryss!

	Loff	Fint brød	Kneip-brød	Grov-brød	Knekke-brød
Brødtypen ligner mest på:	☐ 271	☐	☐	☐	☐ 275

Hvor mye (i **antall** glass, kopper, poteter eller brødskiver) spiser eller drikker du vanligvis **daglig** av følgende matvarer?
*Kryss av for **alle** matvarene.*

	0	Færre enn 1	1-2	3-4	5-6	Mer enn 6
Helmelk (søt eller sur) (glass) 276	☐	☐	☐	☐	☐	☐
Lettmelk (søt eller sur) (glass)	☐	☐	☐	☐	☐	☐
Skummet melk (søt eller sur) (glass)	☐	☐	☐	☐	☐	☐
Te (kopper)	☐	☐	☐	☐	☐	☐
Appelsinjuice (glass)	☐	☐	☐	☐	☐	☐
Poteter 281	☐	☐	☐	☐	☐	☐
Brødskiver totalt (inkl. knekkebrød)	☐	☐	☐	☐	☐	☐
Brødskiver med						
– fiskepålegg (f.eks. makrell i tomat)	☐	☐	☐	☐	☐	☐
– magert kjøttpålegg (f.eks. skinke)	☐	☐	☐	☐	☐	☐
– fetere kjøttpålegg (f.eks. salami)	☐	☐	☐	☐	☐	☐
– gulost 286	☐	☐	☐	☐	☐	☐
– brunost	☐	☐	☐	☐	☐	☐
– kaviar	☐	☐	☐	☐	☐	☐
– syltetøy og annet søtt pålegg	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Hvor mange **ganger i uka** spiser du vanligvis følgende matvarer?
*Kryss av for **alle** matvarene.*

	Aldri	Færre enn 1	1	2-3	4-5	Omtrent daglig
Yoghurt 290	☐	☐	☐	☐	☐	☐
Kokt eller stekt egg	☐	☐	☐	☐	☐	☐
Frokostblanding/havregryn o.l.	☐	☐	☐	☐	☐	☐
Middag med						
– rent kjøtt	☐	☐	☐	☐	☐	☐
– pølser/kjøttpudding/-kaker	☐	☐	☐	☐	☐	☐
– feit fisk (f.eks. laks/uer) 295	☐	☐	☐	☐	☐	☐
– mager fisk (f.eks. torsk)	☐	☐	☐	☐	☐	☐
– fiskeboller/-pudding/-kaker	☐	☐	☐	☐	☐	☐
– grønnsaker	☐	☐	☐	☐	☐	☐
Majones, remulade o.l.	☐	☐	☐	☐	☐	☐
Gulrøtter 300	☐	☐	☐	☐	☐	☐
Blomkål/kål/brokkoli	☐	☐	☐	☐	☐	☐
Epler/pærer	☐	☐	☐	☐	☐	☐
Appelsiner, mandariner o.l.	☐	☐	☐	☐	☐	☐
Sukkerholdige leskedrikker	☐	☐	☐	☐	☐	☐
Sukkerfrie («Light») leskedrikker	☐	☐	☐	☐	☐	☐
Sjokolade	☐	☐	☐	☐	☐	☐
Vafler, kaker o.l. 307	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

ALKOHOL

Hvor ofte pleier du å drikke	øl?	vin?	brennevin?
Aldri, eller noen få ganger i året	☐	☐	☐ 1
1-2 ganger i måneden	☐	☐	☐ 2
Omtrent 1 gang i uken	☐	☐	☐ 3
2-3 ganger i uken	☐	☐	☐ 4
Omtrent hver dag	☐	☐	☐ 5
	308		310

Omtrent hvor ofte har du i løpet av siste år drukket alkohol tilsvarende minst 5 halvflasker øl, en helflaske vin eller 1/4 flaske brennevin?

- Ikke siste år ..... 311 ☐ 1
- Noen få ganger ..... ☐ 2
- 1 - 2 ganger per måned ..... ☐ 3
- 1 - 2 ganger i uken ..... ☐ 4
- 3 eller flere ganger i uken ..... ☐ 5

I omtrent hvor mange år har ditt alkoholforbruk vært slik du har svart i spørsmålene over? ..... 312 _____ år

SLANKING

Omtrent hvor mange ganger har du bevisst prøvd å slanke deg? Sett **0** hvis ingen forsøk.

- før 20 år ..... 314 _____ ganger
- senere ..... 316 _____ ganger

Hvis du har slanket deg, omtrent hvor mange kilo har du på det meste gått ned i vekt?

- før 20 år ..... 318 _____ kg
- senere ..... 320 _____ kg

Hvilken vekt ville du være tilfreds med (din "trivselsvekt")? ..... 322 _____ kg

UFRIVILLIG URINLEKKASJE

Hvor ofte har du ufrivillig urinlekkasje?

- Aldri ..... 325 ☐ 1
- Ikke mer enn en gang i måneden ..... ☐ 2
- To eller flere ganger i måneden ..... ☐ 3
- Ukentlig eller oftere ..... ☐ 4

Dine kommentarer:

BESVARES BARE AV KVINNER

MENSTRUASJON

Hvor gammel var du da du fikk menstruasjon første gang? ..... 326 _____ år

Hvis du ikke lenger har menstruasjon, hvor gammel var du da den sluttet? ..... 328 _____ år

Når du ser bort fra svangerskap og barselsperiode, har du noen gang vært blødningsfri i minst 6 måneder? ..... 330 Ja ☐ Nei ☐

Hvis "Ja", hvor mange ganger? ..... 331 _____ ganger

Hvis du fremdeles har menstruasjon eller er gravid:

Hvilken dato startet din siste menstruasjon? ..... 333 dag/ mnd/ år ___/___/___

Bruker du vanligvis smertestillende legemidler for å dempe menstruasjonsplager? ..... 339 Ja ☐ Nei ☐

SVANGERSKAP

Hvor mange barn har du født? ..... 340 _____ barn

Er du gravid nå? ..... 342 Ja ☐ Nei ☐ Usikker ☐

Har du i forbindelse med svangerskap hatt for høyt blodtrykk og/eller eggehvite (protein) i urinen? ..... 343 Ja ☐ Nei ☐

Hvis "Ja", i hvilket svangerskap?

	Svangerskap Første	Senere
For høyt blodtrykk 344	☐	☐
Eggehvite i urinen 346	☐	☐

Hvis du har født, fyll ut for hvert barn barnets fødselsår og omtrent antall måneder du ammet barnet.

Barn:		Fødselsår:	Antall måneder med amming:
1	348	_____	_____
2		_____	_____
3	356	_____	_____
4		_____	_____
5	364	_____	_____
6		_____	_____

PREVENSJON OG ØSTROGEN

Bruker du, eller har du brukt:	Nå	Før	Aldri
P-pille (også minipille) 372	☐	☐	☐
Hormonspiral	☐	☐	☐
Østrogen (tabletter eller plaster) 374	☐	☐	☐
Østrogen (krem eller stikkpiller)	☐	☐	☐
	1	2	3

Hvis du bruker p-pille, hormonspiral eller østrogen; hvilket merke bruker du nå?

376 .....

Hvis du bruker eller har brukt p-pille:

Alder da du begynte med P-piller? ..... 380 _____ år

Hvor mange år har du tilsammen brukt P-piller? ..... 382 _____ år

Dersom du har født, hvor mange år brukte du P-piller før første fødsel? ..... 384 _____ år

Hvis du har sluttet å bruke P-piller:

Alder da du sluttet? ..... 386 _____ år

Takk for hjelpen! Husk å postlegge skjemaet idag!

Helseundersøkelsen i Tromsø

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

Based on translations by K. McCafferty and A. Clancy

TROMSØ HEALTH SURVEY

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

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

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

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

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

National Health
Screening Service

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

I do not wish to answer the questionnaire. ☐

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

CHILDHOOD/YOUTH

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

_____

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

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

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

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

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

HOME

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

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

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

What type of home do you live in?

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

How big is your home? _____ m2

Approximately what year was your home built? _____

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

What is the main source of heat in your home?

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

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

WORK

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

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

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

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

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

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

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

YOUR OWN ILLNESSES

Have you ever had:

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

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

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

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

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

_____ times

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

YES	NO
☐	☐

ILLNESS IN THE FAMILY

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

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

SYMPTOMS

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

How often do you suffer from sleeplessness?
- Never, or just a few times a year ☐
- 1-2 times a month ☐
- Approximately once a week ☐
- More than once a week ☐

If you suffer from periods of sleeplessness, what times of the year does it affect you most?
- No particular time of year ☐
- Especially during the dark winter months ☐
- Especially during the midnight sun period ☐
- Especially in spring and autumn ☐

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

How often do you suffer from headaches?
- Seldom/Never ☐
- Once a month or more ☐
- Once a week or more ☐
- Every day ☐

Does the thought of getting a serious illness ever worry you?
- Not at all ☐
- Only a little ☐
- Some ☐
- Very much ☐

USE OF HEALTH SERVICES

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

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

MEDICATION AND DIETARY SUPPLEMENTS

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

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

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

Medicines	YES	NO
Painkillers	☐	☐
Antipyretic drugs (to reduce fever)	☐	☐
Migraine drugs	☐	☐
Eczema cream/ointment	☐	☐
Heart medicine (not blood pressure)	☐	☐
Lipid lowering drugs	☐	☐
Sleeping pills	☐	☐
Tranquilizers	☐	☐
Antidepressants	☐	☐
Other drugs for nervous conditions	☐	☐
Antacids	☐	☐
Gastric ulcer drugs	☐	☐
Insulin	☐	☐
Diabetes tablets	☐	☐
Thyroxin tablets (for metabolic disorder)	☐	☐
Cortisone tablets	☐	☐
Other medicine(s)	☐	☐
Dietary supplements	**YES**	**NO**
Iron tablets	☐	☐
Calcium tablets or bonemeal	☐	☐
Vitamin D supplement	☐	☐
Other vitamin supplements	☐	☐
Cod liver oil or fish oil capsules	☐	☐

FRIENDS

How many good friends do you have whom you can talk confidentially with and who give you help when you need it? _____ good friends
Do not count people you live with, but do include other relatives!

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

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

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

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

DIET

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

A catering portion is enough for about _____ slices.

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

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

What kind of bread (bought or home-made) do you usually eat? *Tick one or two boxes!*
The bread I eat is most similar to

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

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

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

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

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

ALCOHOL

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

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

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

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

WEIGHT REDUCTION

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

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

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

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

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

URINARY INCONTINENCE

How often do you suffer from urinary incontinence?

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

Your comments:

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

Tromsø Health Survey

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

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

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

Apart from pregnancy and after giving birth, have you ever stopped having menstruation for 6 months or more? YES ☐ NO ☐

If "Yes", how many times? _____ times

If you still menstruate or are pregnant:

What date did your last menstruation begin?

day/month/year ___ / ___ / ___

Do you normally use painkillers to relieve period pains? YES ☐ NO ☐

PREGNANCY

How many children have you given birth to? _____ children

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

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

If "Yes", during which pregnancy?

	First	Later
High blood pressure	☐	☐
Proteinuria	☐	☐

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

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

CONTRACEPTION AND OESTROGEN

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

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

_____

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

Age when you began taking the pill? _____years

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

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

If you have stopped taking the pill:

Age when you stopped? _____years

Appendix – D:

Second questionnaire for subjects aged ≥ 70 years, Norwegian and English

Helseundersøkelsen i Tromsø

for dem som er 70 år og eldre.

Hovedformålet med Tromsøundersøkelsene er å skaffe ny kunnskap om hjerte-karsykdommer for å kunne forebygge dem. De skal også øke kunnskapen om kreftsykdommer og alminnelige plager som f.eks. allergier, smerter i muskulatur og nervøse lidelser. Endelig skal de gi kunnskap om hvorledes den eldste delen av befolkningen har det. Vi ber deg derfor svare på spørsmålene nedenfor.

Skjemaet er en del av Helseundersøkelsen som er godkjent av Datatilsynet og av Regional komite for medisinsk forskningsetikk. Svarene brukes bare til forskning og behandles strengt fortrolig. Opplysningene kan senere bli sammenholdt med informasjon fra andre offentlige helseregistre etter de regler som Datatilsynet og Regional komite for medisinsk forskningsetikk gir.

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

Det utfylte skjema sendes i vedlagte svarkonvolutt. Portoen er betalt.

På forhånd takk for hjelpen!

Med vennlig hilsen

Fagområdet medisin
Universitetet i Tromsø — Statens helseundersøkelser

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

Jeg ønsker ikke å besvare spørreskjemaet ..... 17 ☐

Dag Mnd År

Dato for utfylling av skjema: ..... 18 ...../...../.....

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?

..... 24-28

Hvis du ikke bodde i Norge, oppgi land i stedet for kommune.

Hvordan var de økonomiske forhold i familien under din oppvekst?

- Meget gode ..... 29 ☐ 1
- Gode ..... ☐ 2
- Vanskelige ..... ☐ 3
- Meget vanskelige ..... ☐ 4

Hvor gamle ble dine foreldre?

- Mor ble ..... 30 _____ år
- Far ble ..... 32 _____ år

BOLIG

Hvem bor du sammen med?

Sett ett kryss for hvert spørsmål og angi antall.	Ja	Nei	Antall
Ektefelle/samboer 34	☐	☐	
Andre personer over 18 år 35	☐	☐	_____
Personer under 18 år 38	☐	☐	_____

Hvilken type bolig bor du i?

- Enebolig/villa ..... 41 ☐ 1
- Gårdsbruk ..... ☐ 2
- Blokk/terrasseleilighet ..... ☐ 3
- Rekkehus/2-4 mannsbolig ..... ☐ 4
- Annen bolig ..... ☐ 5

Hvor lenge har du bodd i boligen du bor i nå? ..... 42 _____ år

	Ja	Nei
Er boligen tilpasset til dine behov? 44	☐	☐
Hvis "Nei", er det problemer med:		
Plassen i boligen 45	☐	☐
Ujevn, for høy eller for lav temperatur 46	☐	☐
Trapper 47	☐	☐
Toalett 48	☐	☐
Bad/dusj 49	☐	☐
Vedlikehold 50	☐	☐
Annet (spesifiser) 51	☐	☐

Ønsker du å flytte til en eldrebolig? ..... 52 ☐ ☐

TIDLIGERE ARBEID OG ØKONOMI

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

- For det meste stillesittende arbeid? ..... 53 ☐ 1
  (f.eks. skrivebordsarbeid, montering)
- Arbeid som krever at du går mye? ..... ☐ 2
  (f.eks. ekspeditørarbeid, husmor, undervisning)
- Arbeid hvor du går og løfter mye? ..... ☐ 3
  (f.eks. postbud, pleier, bygningsarbeid)
- Tungt kroppsarbeid? ..... ☐ 4
  (f.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)

Har du hatt noen av følgende yrker (heltid eller deltid)?

Sett ett kryss for hvert spørsmål.	Ja	Nei
Sjåfør 54	☐	☐
Bonde/gårdbruker 55	☐	☐
Fisker 56	☐	☐

Hvor gammel var du da du ble pensjonert? ..... 57 _____ år

Hva slags pensjon har du?

- Minstepensjon ..... 59 ☐
- Tilleggspensjon ..... 60 ☐

Hvordan er din økonomi nå?

- Meget god ..... 61 ☐ 1
- God ..... ☐ 2
- Vanskelig ..... ☐ 3
- Meget vanskelig ..... ☐ 4

HELSE OG SYKDOM

Er helsen din blitt forandret det siste året?
- Ja, dårligere ..... 62 ☐ 1
- Nei, uforandret ..... ☐ 2
- Ja, bedre ..... ☐ 3

Hvordan synes du at helsen din er nå i forhold til andre på samme alder?
- Mye dårligere ..... 63 ☐ 1
- Litt dårligere ..... ☐ 2
- Omtrent lik ..... ☐ 3
- Litt bedre ..... ☐ 4
- Mye bedre ..... ☐ 5

EGNE SYKDOMMER

Har du noen gang hatt:
Sett ett kryss for hvert spørsmål. Oppgi alderen ved hendelsen. Hvis det har skjedd flere ganger, hvor gammel var du siste gang?

	Ja	Nei	Alder
Lårhalsbrudd 64	☐	☐	_____
Brudd ved håndledd/underarm 67	☐	☐	_____
Nakkesleng (whiplash) 70	☐	☐	_____
Skade som førte til sykehusinnleggelse 73	☐	☐	_____
Sår på magesekken 76	☐	☐	_____
Sår på tolvfingertarmen 79	☐	☐	_____
Magesår-operasjon 82	☐	☐	_____
Operasjon på halsen 85	☐	☐	_____

Har du eller har du hatt:
Sett ett kryss for hvert spørsmål.

	Ja	Nei
Kreftsykdom 88	☐	☐
Epilepsi (fallesyke)	☐	☐
Migrene	☐	☐
Parkinsons sykdom	☐	☐
Kronisk bronkitt	☐	☐
Psoriasis 93	☐	☐
Benskjørhet (osteoporose)	☐	☐
Fibromyalgi/fibrositt/kronisk smertesyndrom	☐	☐
Psykiske plager som du har søkt hjelp for	☐	☐
Stoffskiftesykdom (skjoldbruskkjertel)	☐	☐
Sykdom i leveren 98	☐	☐
Gjentatt, ufrivillig urinlekkasje	☐	☐
Grønn stær	☐	☐
Grå stær	☐	☐
Slitasjegikt (artrose)	☐	☐
Leddgikt 103	☐	☐
Nyrestein	☐	☐
Blindtarmsoperasjon	☐	☐
Allergi og overfølsomhet		
Atopisk eksem (f.eks. barneeksem)	☐	☐
Håndeksem	☐	☐
Høysnue 108	☐	☐
Matvareallergi	☐	☐
Annen overfølsomhet (ikke allergi)	☐	☐

Hvor mange ganger har du hatt forkjølelse, influensa, "ræksjuka" og lignende siste halvår? 111 ____ ganger

	Ja	Nei
Har du hatt dette de siste 14 dager? 113	☐	☐

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene:
Kryss av for "Ingen" hvis ingen av slektningene har hatt sykdommen.

	Mor	Far	Bror	Søster	Barn	Ingen
Hjerneslag eller hjerneblødning 114	☐	☐	☐	☐	☐	☐
Hjerteinfarkt før 60 års alder 120	☐	☐	☐	☐	☐	☐
Kreftsykdom 126	☐	☐	☐	☐	☐	☐
Høyt blodtrykk 132	☐	☐	☐	☐	☐	☐
Astma 138	☐	☐	☐	☐	☐	☐
Benskjørhet (osteoporose) 144	☐	☐	☐	☐	☐	☐
Slitasjegikt (artrose) 150	☐	☐	☐	☐	☐	☐
Psykiske plager 156	☐	☐	☐	☐	☐	☐
Alderdomssløvhet 162	☐	☐	☐	☐	☐	☐
Diabetes (sukkersyke) 168	☐	☐	☐	☐	☐	☐
– alder da de fikk diabetes 174	__	__	__	__	__	

SYMPTOMER

	Ja	Nei
Hoster du omtrent daglig i perioder av året? 184	☐	☐
Hvis "Ja":		
Er hosten vanligvis ledsaget av oppspytt? 185	☐	☐
Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste år? 186	☐	☐
Har du hatt episoder med piping i brystet? 187	☐	☐
Hvis "Ja", har dette oppstått:		
Sett ett kryss for hvert spørsmål.		
Om natten 188	☐	☐
Ved luftveisinfeksjoner	☐	☐
Ved fysiske anstrengelser	☐	☐
Ved sterk kulde 191	☐	☐
Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste år? 192	☐	☐
Har du gått ned i vekt siste året? 193	☐	☐
Hvis "Ja":		
Hvor mange kilo? 194	_____	

Hvor ofte er du plaget av søvnløshet?
- Aldri, eller noen få ganger i året ..... 196 ☐ 1
- 1-2 ganger i måneden ..... ☐ 2
- Omtrent en gang i uken ..... ☐ 3
- Mer enn en gang i uken ..... ☐ 4

Hvis du er plaget av søvnløshet i perioder, når på året er du mest plaget?
- Ingen spesiell tid ..... 197 ☐ 1
- Særlig i mørketiden ..... ☐ 2
- Særlig i midnattsoltiden ..... ☐ 3
- Særlig vår og høst ..... ☐ 4

	Ja	Nei
Pleier du å ta en lur på dagen? 198	☐	☐
Føler du at du vanligvis får nok søvn?	☐	☐

Er du plaget av:	Nei	Litt	I stor grad
Svimmelhet 200	☐	☐	☐
Dårlig hukommelse	☐	☐	☐
Kraftløshet	☐	☐	☐
Forstoppelse 203	☐	☐	☐

Hender det at tanken på å få alvorlig sykdom bekymrer deg?

- Ikke i det hele tatt ..... 204 ❑
- Bare i liten grad ..... ❑
- En del ..... ❑
- Ganske mye ..... ❑

LEGEMLIGE FUNKSJONER

Klarer du selv disse gjøremålene i det daglige uten hjelp fra andre?	Ja	Med noe hjelp	Nei
Gå innendørs i samme etasje 205	❑	❑	❑
Gå i trapper	❑	❑	❑
Gå utendørs	❑	❑	❑
Gå ca. 500 meter	❑	❑	❑
Gå på toalettet	❑	❑	❑
Vaske deg på kroppen 210	❑	❑	❑
Bade eller dusje	❑	❑	❑
Kle på og av deg	❑	❑	❑
Legge deg og stå opp	❑	❑	❑
Spise selv	❑	❑	❑
Lage varm mat 215	❑	❑	❑
Gjøre lett husarbeid (f.eks. oppvask)	❑	❑	❑
Gjøre tyngre husarbeid (f.eks. gulvvask)	❑	❑	❑
Gjøre innkjøp	❑	❑	❑
Ta bussen	❑	❑	❑

	Ja	Vanskelig	Nei
Kan du høre vanlig tale (evt. med høreapparat)? 220	❑	❑	❑
Kan du lese (evt. med briller)? 221	❑	❑	❑

Er du avhengig av noen av disse hjelpemidlene?

	Ja	Nei
Stokk 222	❑	❑
Krykke	❑	❑
Gåstol (rullator)	❑	❑
Rullestol	❑	❑
Høreapparat	❑	❑
Trygghetsalarm 227	❑	❑

BRUK AV HELSEVESENET

For mange ganger har du siste året, på grunn av egen helse eller sykdom, vært:
Sett 0 hvis du ikke har hatt slik kontakt.

	Antall ganger siste år
Hos vanlig lege/legevakt 228	
Hos psykolog eller psykiater	
Hos annen legespesialist utenfor sykehus	
På poliklinikk 234	
Innlagt i sykehus	
Hos fysioterapeut	
Hos kiropraktor 240	
Hos akupunktør	
Hos tannlege	
Hos fotterapeut 246	
Hos naturmedisiner (homøopat, soneterapeut o.l.)	
Hos håndspålegger, synsk eller "leser"	

Har du hjemmehjelp?	Ja	Nei
Privat 252	❑	❑
Kommunal	❑	❑

Har du hjemmesykepleie? ..... ❑ ❑

Er du fornøyd med helse- og hjemmetjenesten i kommunen?	Ja	Nei	Vet ikke
Prinsippet med fast lege 255	❑	❑	❑
Hjemmesykepleien	❑	❑	❑
Hjemmehjelpen	❑	❑	❑

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

- Trygg ..... 258 ❑ 1
- Ikke trygg ..... ❑ 2
- Svært utrygg ..... ❑ 3
- Vet ikke ..... ❑ 4

LEGEMIDLER OG KOSTTILSKUDD

Har du det siste året periodevis brukt noen av de følgende midler daglig eller nesten daglig?
Angi hvor mange måneder du brukte dem.
Sett 0 hvis du ikke har brukt midlene.

Legemidler

- Smertestillende ..... 259 _____ mnd.
- Sovemedisin ..... _____ mnd.
- Beroligende midler ..... _____ mnd.
- Medisin mot depresjon ..... 265 _____ mnd.
- Allergimedisin ..... _____ mnd.
- Astmamedisin ..... _____ mnd.
- Hjertemedisin (ikke blodtrykksmedisin) ..... 271 _____ mnd.
- Insulin ..... _____ mnd.
- Tabletter mot diabetes (sukkersyke) ..... _____ mnd.
- Tabletter mot lavt stoffskifte (thyroxin) ..... 277 _____ mnd.
- Kortisontabletter ..... _____ mnd.
- Midler mot forstoppelse ..... _____ mnd.

Kosttilskudd

- Jerntabletter ..... 283 _____ mnd.
- Vitamin D-tilskudd ..... _____ mnd.
- Andre vitamintilskudd ..... _____ mnd.
- Kalktabletter eller benmel ..... 289 _____ mnd.
- Tran eller fiskeoljekapsler ..... _____ mnd.

FAMILIE OG VENNER

Har du nær familie som kan gi deg hjelp og støtte når du trenger det? 293	Ja ❑	Nei ❑

Hvis "Ja": Hvem kan gi deg hjelp?

- Ektefelle/samboer ..... 294 ❑
- Barn ..... ❑
- Andre ..... ❑

Hvor mange gode venner har du som du kan snakke fortrolig med og gi deg hjelp når du trenger det? ..297 ____ gode venner
Tell ikke med dem du bor sammen med, men ta med andre slektninger!

	Ja	Nei
Føler du at du har nok gode venner? 299	❑	❑

Føler du at du hører med i et fellesskap (gruppe av mennesker) som stoler på hverandre og føler forpliktelse overfor hverandre (f.eks. i politisk parti, religiøs gruppe, slekt, naboskap, arbeidsplass eller organisasjon)?

- Sterk tilhørighet ..... 300 ❑ 1
- Noe tilhørighet ..... ❑ 2
- Usikkert ..... ❑ 3
- Liten eller ingen tilhørighet ..... ❑ 4

Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?

- Aldri, eller noen få ganger i året ..... 301 ❑ 1
- 1-2 ganger i måneden ..... ❑ 2
- Omtrent en gang i uken ..... ❑ 3
- Mer enn en gang i uken ..... ❑ 4

KOSTVANER

Antall

Hvor mange måltider spiser du vanligvis daglig (middag og brødmåltid)? ..... 302 _____

Hvor mange ganger i uken spiser du varm middag? ..... 304 _____

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis?

Sett ett eller to kryss.

	Loff	Fint brød	Kneip-brød	Grov-brød	Knekke-brød
Brødtypen ligner mest på:	❑ 306	❑	❑	❑	❑ 310

Hva slags fett blir til vanligvis brukt til *matlaging* (ikke på brødet) i din husholdning?

- Meierismør ..... 311 ❑
- Hard margarin ..... ❑
- Bløt (Soft) margarin ..... ❑
- Smør/margarin blanding ..... ❑
- Oljer ..... 315 ❑

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

Kryss av for alle matvarene.

	Ingen	Mindre enn 1	1-2	3 og mer
Melk alle sorter (glass) 316	❑	❑	❑	❑
Appelsinjuice (glass)	❑	❑	❑	❑
Poteter	❑	❑	❑	❑
Brødskiver totalt (inkl. knekkebrød) ...	❑	❑	❑	❑
Brødskiver med				
– fiskepålegg (f.eks. makrell i tomat)	❑	❑	❑	❑
– gulost	❑	❑	❑	❑
– kaviar 322	❑ 1	❑ 2	❑ 3	❑ 4

Hvor mange ganger i uka spiser du vanligvis følgende matvarer?

Kryss av for alle matvarene.

	Aldri	Sjeldnere enn 1	1	2 og mer
Yoghurt 323	❑	❑	❑	❑
Kokt eller stekt egg	❑	❑	❑	❑
Frokostblanding/havregryn o.l.	❑	❑	❑	❑
Middag med				
– rent kjøtt	❑	❑	❑	❑
– feit fisk (f.eks. laks/uer)	❑	❑	❑	❑
– mager fisk (f.eks. torsk) 328	❑	❑	❑	❑
– grønnsaker (rå eller kokte)	❑	❑	❑	❑
Gulrøtter (rå eller kokte)	❑	❑	❑	❑
Blomkål/kål/brokkoli	❑	❑	❑	❑
Epler/pærer	❑	❑	❑	❑
Appelsiner, mandariner o.l. 333	❑ 1	❑ 2	❑ 3	❑ 4

TRIVSEL

Hvordan trives du med å bli gammel - alt i alt?

- Godt ..... 334 ❑ 1
- Ganske bra ..... ❑ 2
- Opp og ned ..... ❑ 3
- Dårlig ..... ❑ 4

Hvordan ser du på livet fremover?

- Lyst ..... 335 ❑ 1
- Ikke så verst ..... ❑ 2
- Nokså bekymret ..... ❑ 3
- Mørkt ..... ❑ 4

BESVARES BARE AV KVINNER

MENSTRUASJON

Hvor gammel var du da du fikk menstruasjon første gang? ..... 336 _____ år

Hvor gammel var du da menstruasjonen sluttet? ..... 338 _____ år

SVANGERSKAP

Hvor mange barn har du født? ..... 340 _____ barn

Hvis du har født, fyll ut for hvert barn barnets fødselsår og omtrent antall måneder du ammet barnet.
Hvis du har født mer enn 6 barn, noter fødselsår og antall måneder med amming for dem nederst på siden.

Barn:	Fødselsår:	Antall måneder med amming:
1	342 _____	_____
2	346 _____	_____
3	_____	_____
4	_____	_____
5	358 _____	_____
6	_____	_____

Har du i forbindelse med svangerskap hatt for høyt blodtrykk og/eller eggehvite (protein) i urinen? ..... 366 Ja ❑ Nei ❑

Hvis "Ja", i hvilket svangerskap?

	Svangerskap Første	Senere
For høyt blodtrykk 367	❑	❑
Eggehvite i urinen 369	❑	❑

ØSTROGEN-MEDISIN

Bruker du, eller har du brukt, østrogen-medisin?

	Nå	Før	Aldri
Tabletter eller plaster 371	❑	❑	❑
Krem eller stikkpiller 372	❑	❑	❑

Hvis du bruker østrogen, hvilket merke bruker du nå?

..... 373

Dine kommentarer:

Takk for hjelpen! Husk å postlegge skjemaet idag!

Helseundersøkelsen i Tromsø

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

Based on translations by Kevin McCafferty and Anne Clancy.

TROMSØ HEALTH SURVEY for the over 70s

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

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

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

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

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

National Health
Screening Service

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

I do not wish to answer the questionnaire. ☐

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

CHILDHOOD/YOUTH

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

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

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

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

How old were your parents when they died?

- Mother _____ years
- Father _____ years

HOME

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

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

What type of home do you live in?

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

How long have you lived in your present home? _____years

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

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

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

PREVIOUS WORK AND FINANCIAL SITUATION

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

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

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

	YES	NO
Driver	☐	☐
Farmer	☐	☐
Fisherman	☐	☐

How old were you when you retired? _____ years

What kind of pension do you have?

- Basic state pension ☐
- Additional pension ☐

How is your current financial situation?

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

HEALTH AND ILLNESS

Has your state of health changed in the last year?

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

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

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

YOUR OWN ILLNESSES

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

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

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

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

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

Have you had any of these in the last two weeks?
YES ☐ NO ☐

ILLNESS IN THE FAMILY

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

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

SYMPTOMS

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

How often do you suffer from sleeplessness?

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

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

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

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

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

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

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

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

BODILY FUNCTIONS

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

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

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

Are you dependent on any of the following aids?

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

USE OF HEALTH SERVICES

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

*Tick **0** if you have **not** had such contact*

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

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

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

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

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

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

MEDICATION AND DIETARY SUPPLEMENTS

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

Medication:

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

Dietary supplements:

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

FAMILY AND FRIENDS

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

If "Yes", who can give you help?

Spouse/partner	☐
Children	☐
Others	☐

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

_____good friends

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

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

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

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

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

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

DIET

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

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

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

The bread I eat is most similar to

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

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

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

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

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

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

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

WELL BEING

How content do you generally feel with growing old?

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

What is your view of the future?

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

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

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

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

PREGNANCY

How many children have you given birth to? _____children

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

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

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

If "Yes", during which pregnancy?

	Pregnancy First	Later
High blood pressure	☐	☐
Proteinuria	☐	☐

OESTROGEN

Do you, or have you ever used oestrogen:

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

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

_____

Your comments:

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

Appendix – E :

BMD-change and precision

Is the observed BMD-change between two measurements at two points in time, larger than changes which may be ascribed to the random measurement error?

The uncertainty of both measurements must be taken into consideration. As the individual BMD-results at both points in time have a normal distribution, the comparison of two single BMD-results from the same subject, is equivalent to the two sample t-test situation, with n=1 in each sample. Using the formulae for the two sample t-test we get:

$$z = \frac{\overline{x_1} - \overline{x}_2 / \overline{x_1}}{s\sqrt{\left(1/n_1 + 1/n_2\right)}} \Leftrightarrow z = \frac{x_1 - x_2}{s\sqrt{\left(1/1 + 1/1\right)}} \Leftrightarrow z = \frac{\Delta}{s\sqrt{(2)}} \Leftrightarrow \Delta = z * s\sqrt{(2)}$$

$$z = \frac{\overline{x_1} - \overline{x}_2}{s\sqrt{\left(1/n_1 + 1/n_2\right)}} \Leftrightarrow z = \frac{\left(\overline{x_1} - \overline{x}_2 / \overline{x}\right) * 100}{\left(s\sqrt{\left(1/n_1 + 1/n_2\right)} / \overline{x}\right) * 100} \Leftrightarrow z = \frac{\Delta\%}{cv\sqrt{\left(1/1 + 1/1\right)}}$$

$$\Leftrightarrow z = \frac{\Delta\%}{cv\sqrt{(2)}} \Leftrightarrow \Delta\% = z * cv\sqrt{(2)}$$

Thus we derive the simple formulae of $\Delta = z * s\sqrt{(2)}$ and[114], where Z is the standard normal deviate equivalent to a chosen two sided probability, and S and CV are estimates of the population mean of the individual SD and coefficients of variation respectively. If Z is set equal to the 5% probability limit of 1.96, the Δ and the Δ% will equal the smallest BMD-difference which can be detected with 95%-certainty. BMD changes that are smaller will have a more than 5% probability of occurring due to measurement error alone.

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

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