Clinical and laboratory aspects of vitamin D in relation to type 2 diabetes and osteoporosis

Results from the Tromsø Study and two randomized clinical trials

by

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Contents

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Norsk sammendrag – Norwegian summary

Det har vært økende interesse rundt mulige helsegevinster ved å øke vitamin D-nivået i befolkningen. I data fra Tromsøundersøkelsen studerte vi sammenhengen mellom vitamin D-nivå i blodet og risiko for senere å utvikle type 2 diabetes hos totalt 6119 personer. Risikoen var omtrent doblet blant den fjerdedelen som hadde lavest vitamin D-nivå sammenlignet med den fjerdedelen som hadde høyest nivå. Dette kunne hovedsakelig forklares ved at de med lavest vitamin D-nivå også hadde høyere kroppsmasseindex.

Når vi deretter sammenlignet 52 personer med høye og 108 personer med lave vitamin D-nivåer, fant vi gunstigere nivåer av sukker og fett i blodet hos de med høye vitamin D-nivåer. Allikevel var det ingen bedring av disse verdiene i gruppen med lave vitamin D-nivåer etter å ha gitt vitamin D i høy dose (ca 150 mikrogram eller 6000 Internasjonale Enheter per dag) sammenlignet med placebo i seks måneder. I en annen studie sammenlignet vi standard dose vitamin D (800 Internasjonale Enheter) med slik høydose vitamin D hos 297 kvinner med redusert beintetthet. Begge dosene bedret eller opprettholdt beintettheten uten noen sikker forskjell mellom gruppene. Våre arbeider gir derfor ikke grunnlag for å anbefale bruk av vitamin D i høye doser. Ytterligere studier er nødvendige for å avklare det ideelle nivået av vitamin D.

Videre har vi påvist at røyking kan påvirke målemetoder for vitamin D, noe som er viktig å være oppmerksom på i utvikling og kvalitetssikring av slike metoder.

English summary

There has been a large interest in possible beneficial health effects of increasing the vitamin D (as measured by 25-hydroxyvitamin D (25(OH)D)) levels in the population. Data from the Tromsø Study were used to assess the relation between serum 25(OH)D levels and the risk of subsequent type 2 diabetes in 6119 participants. This risk was approximately doubled in the lowest serum 25(OH)D quartile as compared to the highest quartile. This could to a large extent be explained by higher body mass index in the lowest quartile.

When thereafter comparing 52 persons with high and 108 persons with low serum 25(OH)D levels, we found more beneficial levels of glucose and lipid measures in those with high serum 25(OH)D levels. However, there was no improvement in the same measures in the low serum 25(OH)D group after six months supplementation with high dose vitamin D (approximately 150 mikrogram or 6000 international units/day) as compared to placebo. In another study, we compared one year treatment with standard dose of vitamin D (800 international units) with the same high dose vitamin D among 297 women with reduced bone mineral density. Both doses improved or maintained bone mineral density with no differences between the groups. These results do not support the use of vitamin D in such high doses. Further studies are needed to assess the ideal level of serum 25(OH)D.

We have further demonstrated that smoking might interfere with 25(OH)D laboratory analyses. This is important to consider in developing and validating such methods.

List of papers

1) Grimnes G, Almaas B, Eggen AE, Emaus N, Figenschau Y, Hopstock L, Hutchinson MS, Methlie P, Mihailova A, Sneve M, Torjesen P, Wilsgaard T, Jorde R. Effect of smoking on the serum levels of 25-hydroxyvitamin D depends on the assay employed. *Eur J Endocrinol* 2010;163:339-48

2) Grimnes G, Emaus N, Joakimsen RM, Figenschau Y, Jenssen T, Njølstad I, Schirmer H, Jorde R. Baseline serum 25-hydroxyvitamin D concentrations in the Tromsø Study 1994-95 and risk of developing type 2 diabetes mellitus during eleven years of follow-up. *Diabet Med* 2010;27:1107-15

3) Grimnes G, Figenschau Y, Almås, B, Jorde R. Vitamin D, insulin secretion, sensitivity and lipids – the results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique. (In Press, *Diabetes*)

4) Grimnes G, Joakimsen RM, Figenschau Y, Torjesen P, Almås B, Jorde R. The effect of high dose vitamin D on bone mineral density and bone turnover markers in postmenopausal women with low bone mass – a randomized controlled one-year trial. (In press, *Osteoporos Int*)

Abbreviations

ANCOVA: analysis of covariance

ANOVA: analyses of variance

BMD: bone mineral density

BMI: body mass index

CI: confidence interval

CT: computer tomography

CTX-1: C-terminal telopeptid of type 1 collagen

CV: coefficient of variation

d: day

DBP: vitamin D binding protein

DEXA: dual X-ray absorptiometry

ECLIA: electrochemiluminescence immunoassay

FFA: free fatty acid

FGF-23: fibroblast growth factor 23

GC: gas chromatography

h: hour

HbA_{1c}: glycated haemoglobin

HOMA-IR: insulin resistance from the homeostasis model assessment

HPLC: high performance liquid chromatography

HR: hazard ratio

IDS: Immuno Diagnostic System

IPAQ: International Physical Activity Questionnaire

ISI: insulin sensitivity index

IU: international units

LC: liquid chromatography

MET: metabolic equivalent

min: minute

MS: mass spectrometry

OPG: osteoprotegerin

OR: odds ratio

PTH: parathyroid hormone

P1NP: N-terminal propeptid of type 1 procollagen

RANK/ RANKL: receptor activator of nuclear factor-kappa B/ RANK ligand

RCT: randomized controlled trial

RIA: radioimmunoassay

RR: relative risk

SD: standard deviation

TG: triglyceride

UVB: ultraviolet B

VDR: vitamin D receptor

w: week

$1,25(OH)_2D$: 1,25-dihydroxyvitamin D

$24,25(OH)_2D$: 24,25-dihydroxyvitamin D

25(OH)D: 25-hydroxyvitamin D

1. Introduction

This thesis originated from an interest in the ancient hormone vitamin D, which has attained a lot of focus the last couple of decades as a possible multifunctional and important contributor to health, and especially in the context of chronic lifestyle-related diseases. Thus, vitamin D deficiency has been associated with osteoporosis, cardiovascular disease, diabetes, cancer, autoimmune diseases and depression – to mention a few [1]. In general, a person's vitamin D level (measured as 25-hydroxyvitamin D (25(OH)D)) is a product of ultraviolet B (UVB) radiation from the sun, and to a less degree, from food. Our vitamin D status is therefore vulnerable to modern lifestyle with less physical activity and outdoor time, at the same time as overweight, contributing to vitamin D deficiency, increases. Many of the same lifestyle choices predispose both for vitamin D deficiency as well as for many diseases associated with vitamin D deficiency. Therefore, there are huge methodological challenges in defining whether vitamin D deficiency has a causal role in the development of these diseases. Thus, the key question is: Will increased vitamin D levels in the general population decrease the burden of chronic lifestyle related diseases, or is a high vitamin D level nothing but a marker of a healthy lifestyle?

Through the longitudinal, multi-purposed and population-based Tromsø Study, we had the opportunity to analyze serum 25(OH)D in sera stored from the 4th Tromsø Study in 1994-1995, and to relate the 25(OH)D levels to subsequent occurrence of type 2 diabetes in an observational study. Results from such observational studies are important as hypothesis generators, but can not be used as final evidence for causal relations between vitamin D deficiency and the studied diseases. To go further, we also invited participants from the 6th Tromsø Study in 2008 based on their serum 25(OH)D measurements to study how these levels related to the regulation of glucose and lipid metabolism. Finally, we randomized the

participants with low serum 25(OH)D levels to receive either vitamin D or placebo for six months and then performed a new examination to see if and how the supplementation affected the measurements. As we were faced with laboratory difficulties regarding serum 25(OH)D measurements which were previously not described, a methodological validation study was necessary to perform.

Although focusing on a different chronic disease – osteoporosis – the last study included in this thesis also dealt with the question whether the vitamin D levels seen today, and accordingly, the recommended intake, are adequate for optimal health. Including postmenopausal women with low bone mineral density (BMD) and randomizing them to standard or high dose of vitamin D, the objective of the study was to see whether high dose was better than standard dose in improving BMD and reducing bone turnover.

The thesis will present these studies in detail, and try to discuss and integrate the methodological challenges and the findings into the current state of knowledge in the extensive field of vitamin D research.

1.1 Vitamin D

Vitamin D is a lipophil secosteroid that exists in two forms; ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) [2]. These two forms differ in one double-binding and one methyl group. While vitamin D_2 is found in vegetable sources like mushrooms, vitamin D_3 can be found in animal sources like fat fish, cod liver oil, egg yolk and fortified food like dairy products [1]. Vitamin D supplements might contain both forms, although in Norway, vitamin D_3 is almost exclusively used in over-the-counter vitamin D supplements.

Importantly, the body itself has the ability to produce vitamin D_3, when UVB radiation (wavelength 290-315 nm) reaches preformed 7-dehydrocholesterol in the skin. Previtamin D_3 is then formed, which under normal temperature conditions isomerizes to form vitamin D_3 [3]. The

relative importance of the different vitamin D sources differs in and between populations due to different climatic conditions, cultural practices and dietary habits [4]. In Tromsø, located at 69°N, sufficient UVB radiation for dermal vitamin D production is only available from the mid of March to the end of September [5]. However, the use of sunbeds, sunny holidays and supplementation like cod liver oil, together with a traditionally high intake of marine food, might counteract the lower dermal production [6]. Serum 25(OH)D levels have demonstrated high heritability, which seems to be at least as important as environmental factors in explaining variance in serum 25(OH)D levels [7]. Thus, genome wide association studies have identified polymorphisms in genes coding for proteins involved in cholesterol metabolism (7-dehydrocholesterol reductase), vitamin D hydroxylation (CYP2R1) and transport (vitamin D binding protein (DBP)) as important determinants of serum 25(OH)D levels [8].

In the body, vitamin D is rapidly 25-hydroxylated in the liver to either 25-hydroxyvitamin D_2 ($25(OH)D_2$) or 25-hydroxyvitamin D_3 ($25(OH)D_3$) (referred to as 25(OH)D if the distinction is of no importance). This enzymatic process is poorly regulated [9], but seems to be of first order magnitude when the substrate concentration is low (serum vitamin D below 15 nmol/L, corresponding to 25(OH)D below 80-100 nmol/L), and zero order above (higher substrate concentrations) [10]. Thus, excess vitamin D_3 has been widely believed to be sequestered and stored in adipose tissue [1,2], which also might explain a consistently described inverse relation between body mass index (BMI) and serum 25(OH)D [11,12]. However, in a recently published study using vitamin D_3 50,000 IU/week (w), resulting in final serum 25(OH)D of 125 nmol/l, the authors estimated that less than one fifth of the administered vitamin D_3 actually was sequestered in fat tissue, indicating that most of it was metabolically consumed [13]. The half-life of 25(OH)D is two - three weeks, and because of its stability, and its reflection of vitamin D from all sources, this metabolite is currently regarded the most suitable biomarker for a person's vitamin D status [9].

Activation of 25(OH)D requires further hydroxylation to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). This hydroxylation occurs mainly in the kidneys, where the enzyme, 1-alfa-hydroxylase, is under tight control from parathyroid hormone (PTH), which upregulates the process, and fibroblast growth factor 23 (FGF-23) which downregulates it [9]. The main stimulus for this regulation is the serum concentration of ionized calcium, which, when low, increases PTH secretion from the parathyroid glands. The resulting increase in $1,25(OH)_2D$ leads to increased gastrointestinal and renal calcium absorption, as well as mobilization of calcium from bone through increased osteoclast activation. Also, gastrointestinal phosphate absorption is increased. Likewise, high serum $1,25(OH)_2D$ and phosphate levels stimulate release of FGF-23 from osteocytes and osteoblasts, which through downregulation of 1-alfa hydroxylase and increasing transformation of $1,25(OH)_2D$ to the less active form 24,25-dihydroxyvitamin D ($24,25(OH)_2D$), diminish calcium absorption and also increases phosphaturia. These processes ensure the body with serum calcium levels within narrow physiological ranges, providing stable extracellular calcium available for intracellular calcium, important particularly for nerve and muscle function, as well as optimal conditions for normal bone homeostasis and blood coagulation [14].

Activation of vitamin D does not only occur in the kidneys. The enzyme 1-alfa-hydroxylase is present in numerous other tissues and cells, providing opportunities for extrarenal hydroxylation. This hydroxylation is not regulated by PTH, but by local growth factors and cytokines [9], and it is believed that sufficient substrate, 25(OH)D, is of greater importance there than in the kidneys, where PTH drives $1,25(OH)_2D$ production across a broad range of 25(OH)D levels, and only at low substrate levels begins to diminish [15]. Locally produced $1,25(OH)_2D$ does probably not enter the circulation in large amounts, but works locally in an autocrine or paracrine manner [9]. Thus, the local $1,25(OH)_2D$ levels are probably better reflected by serum 25(OH)D than by serum $1,25(OH)_2D$, which in addition has a short

half-life (2-4 hours (h)) [2]. The importance of this system is however highly unsettled, as is its regulation [9].

Vitamin D in all forms is transported in blood coupled to DBP. This protein's affinity is stronger to 25(OH)D than to the active form $1,25(OH)_2D$. The effect of vitamin D on the target cells are mediated through the vitamin D receptor (VDR), where the affinity is opposite, being much stronger to $1,25(OH)_2D$. VDR is a member of the steroid receptor family, and as such, acts as a ligand-activated transcription factor [9]. A vitamin D responsive element is found in many genes involved mainly in bone and calcium metabolism, inflammation, and cell growth and differentiation [16], and it has been reported that vitamin D affects the transcription of more than 200 genes, either directly or indirectly [1]. There are also evidence for non-genomic rapid effects of $1,25(OH)_2D$ which seem to involve other receptors, but the nature and significance of these receptors are not completely understood [9].

The different vitamin D metabolites are finally catabolized to several compounds that are excreted via the biliary and renal system, among them calcitroic acid and lactones [1,2]. The regulation of the first step in this process, 24-hydroxylation of either 25(OH)D or $1,25(OH)_2D$, is tightly regulated in a reciprocal way of 1-alfa hydroxylase [9]. Fig 1 shows vitamin D_3 synthesis, activation, and catabolism.

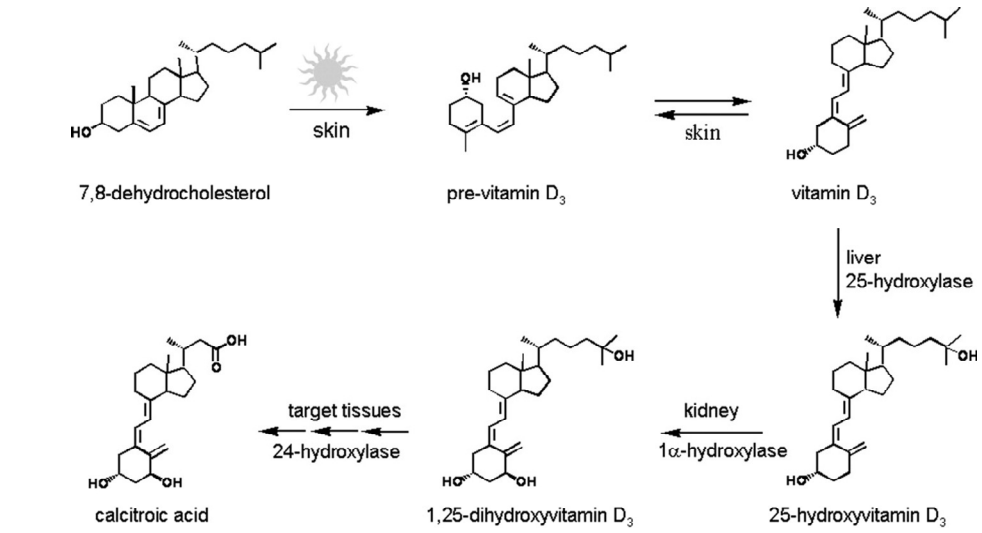

Fig. 1 Vitamin D_3 synthesis, activation, and catabolism[9]. Used with permission.

1.2 Vitamin D levels

The definition of an optimal vitamin D status remains a challenge. Roles of biomarkers in nutritional surveillance can be divided into markers of supply, markers of function, markers of intermediate endpoint or markers of disease [17]. Serum 25(OH)D is regarded the most suitable marker of supply. However, there is no international consensus regarding reference range for serum 25(OH)D concentrations, neither for how this range should be defined. Setting a reference range using population based cutoffs of 5 and 95% will depend on the general vitamin D status in that particular population, and will not necessarily reflect the physiological normal range. A more historical approach has been to assume that the body's physiology is adapted to an outdoor life with abundant UVB exposure [18]. Thus, mean serum levels of outdoor workers like farmers or lifeguards have been used as a proxy of a "natural" serum 25(OH)D level, ranging from 135 to 163 nmol/l [19].

As a functional outcome, several authors have studied the inverse relation between serum 25(OH)D and PTH. The level where serum PTH stops decreasing has been suggested as the threshold for sufficiency. Notably, this approach has not given consistent results, as this threshold has been reported somewhere from 25 nmol/l [20] to 110 nmol/l [21]. Differences in calcium intake between the study populations and methodological problems with PTH and 25(OH)D measurements might explain some of this discrepancy. Also, in spite of low serum 25(OH)D levels, a substantial portion of patients may have a "blunted" PTH response and conversely lower serum calcium levels. The mechanism and significance of this is not clear, but low intracellular magnesium levels have been suggested as a possible mechanism [22].

Using intermediate endpoints for diseases like BMD, insulin sensitivity, or markers of innate immunity is complex, as these endpoints are affected by a number of factors other than vitamin D. The index disease of vitamin D deficiency, rickets in children and osteomalacia in adults, are seldom seen when serum 25(OH)D exceeds 20 nmol/l [23]. However, rickets in children with higher vitamin D levels have been reported in the state of calcium deficiency [24,25]. The prevalence of rickets can nonetheless be regarded an index of severe vitamin D deficiency in a population.

Definition of degrees of vitamin D sufficiency from the Norwegian guidelines from 2006 is shown in Table 1. The aim of the guidelines is to achieve a serum 25(OH)D level above 50 nmol/l in as many as possible with nobody below 25 nmol/l [26]. To ensure that adequate levels are achieved in the general population, a vitamin D intake of at least 300 IU for those aged 2-60 years, and 400 IU for those younger than two years or older than 60 years, is recommended [26]. It should be noted that other authors define levels below 75-80 nmol/l as insufficient [2,27].

Table 1 Threshold values for vitamin D status

25(OH)D in serum or plasma	Description
>50 nmol/l*	sufficient
25-50 nmol/l	suboptimal
12.5-25 nmol/l	deficiency
<12.5 nmol/l	severe deficiency

* Serum 25(OH)D should not exceed 200 nmol/l for a longer period of time.

Slightly modified from Meyer HE et al (2006) National Nutrition Council [26]. Used with permission.

1.3 Vitamin D measurements

Being highly hydrophobic and tightly protein-bound, measuring serum 25(OH)D is challenging [28,29]. Furthermore, an assay should ideally measure both the 25(OH)D_2 and 25(OH)D_3 forms, especially in populations where supplementation and fortification consist of both. Several methods are available today, and they can mainly be divided into two main groups: immunoassays and chromatographic methods [28]. Both depends on the separation between the DBP and the 25(OH)D molecule. In the immunoassays, an antibody will then recognize 25(OH)D, and the quantification relies on some sort of enzymatic, radioactive or electrochemilumnicent marker coupled to the antibody. These methods might be more or less fully automated, which make high-throughput possible. However, their ability to recognize the two forms 25(OH)D_2 and 25(OH)D_3 differs, and the methods are prone to performance changes over time [29]. The chromatographic methods use either gas chromatography (GC) or high performance liquid chromatography (HPLC), which again can be coupled to a mass spectrometry (MS) method. The advantages of these methods are higher accuracy with no cross-reactions, and 25(OH)D_2 may easily be separated from 25(OH)D_3. However, the equipment is expensive, it requires trained and experienced personnel, and through-put is much lower than for the automated immunoassays [28].

A general problem with serum 25(OH)D measurements is the lack of international standardization with the use of a common global calibrator, which makes results from different studies difficult to compare directly [29]. This adds to the confusion regarding defining thresholds for optimal serum 25(OH)D levels. Several attempts are being made to improve the quality and comparability of these measurements [29,30].

Validation of serum 25(OH)D assays is usually performed by comparing with other available methods, as there is no generally accepted gold standard method [29]. This is usually done irrespective of the characteristics of the blood donors [31-33]. Own preliminary results from the 4th Tromsø Study surprisingly showed higher serum 25(OH)D levels in smokers than in non-smokers, which was not consistent with prevailing literature [34-36]. Smoking increases risk of both osteoporosis [37] and diabetes [38]. With the possible influence smoking may have on serum 25(OH)D measurements, it is therefore an important factor to consider in studies on these diseases, and also in the validation of the assays used for determining serum 25(OH)D.

1.4 Type 2 diabetes

The prevalence of type 2 diabetes is increasing worldwide, with an estimated doubling of persons with the disease from year 1995 to year 2025 [39]. As a chronic condition, type 2 diabetes contributes to increased risk of microvascular and macrovascular complications including cardiovascular disease [40]. Thus, the disease has both individual costs through decreased quality of life and huge economical costs for the society.

The development of type 2 diabetes is considered a result of increased peripheral insulin resistance combined with decreased insulin secretion from the beta-cells in pancreas [40]. While the body's capacity for insulin secretion is predominantly genetically determined, the insulin resistance is considered mainly a result of lifestyle [41,42], with central obesity, inactivity, aging, overeating and increased levels of free fatty acids (FFA) being the main risk factors [39]. Thus,

we are born with different vulnerability for insulin resistance, which explains why some might tolerate obesity without developing type 2 diabetes through a compensatory increase in insulin secretion, while others do not have this ability. Nonetheless, increased insulin resistance leads to slightly increased blood glucose values within the normal range, which over time may damage the beta cells in a phenomenon called glucotoxicity [39,40]. A similar phenomenon, called lipotoxicity, is a result of increased levels of FFA, which originate from insulin resistant adipocytes [40]. This results in a diminished beta cell mass over time, leading to a decrease in the insulin secretory capacity.

1.5 Vitamin D and type 2 diabetes

In vitro and animal studies have revealed several aspects of diabetes development that might be affected by vitamin D. First, both VDR and 1-alfa-hydroxylase are present in beta cells, allowing local $1,25(OH)_2D$ production and function [43,44]. Secondly, a VDR responsive element on the human insulin gene promoter has been identified [45]. Accordingly, several [46-49], but not all [50] experimental studies have provided evidence for an independent role of vitamin D in the insulin secretory capacity of the beta cells, suggesting that vitamin D affects glucose-mediated insulin secretion rather than fasting insulin levels [47,48]. In vitro, $1,25(OH)_2D$ has been reported to increase the expression of the insulin receptor and enhance insulin-mediated glucose transport [51], indicating a role also in insulin sensitivity. Finally, the systemic inflammation accompanying insulin resistance and diabetes development might also be dampened by vitamin D through several mechanisms [52].

Human observational studies have predominantly supported these experimental results. In a prospective study of more than 83,000 women in the Nurses' Health Study, those with the highest intake of vitamin D as well as calcium experienced a 33% decrease in subsequent risk of diabetes [53]. In studies based on serum measurements, thereby including also sun-derived

vitamin D, inverse associations between serum 25(OH)D and measures of glucose levels [54-59], insulin resistance [56,58-62] and diabetes [63-66] have been reported.

With few exceptions [53,56,65,67], these studies have been cross-sectional, excluding temporality as an evidence of causality. There have also been few properly designed intervention trials, and as recently reviewed, the results are conflicting [68]. Limitations of the studies include small samples, lack of proper control groups, short intervention periods, indirect measurements of insulin sensitivity, in addition to heterogeneity regarding dosing regimens [68]. As some of the data originate from post hoc analyses of osteoporosis intervention trials, the effect of vitamin D might be hard to separate from the effect of calcium.

1.6 Bone metabolism

The skeleton is a highly metabolic tissue which provides the best compromise between strength and stability (stiffness) on one hand, as opposed to functional mobility on the other hand. Other tasks are protection of internal organs, production of blood cells in the bone marrow, and it also constitutes the body's main store of different minerals like calcium and phosphate. The skeletal tissue consists of principally three different cell types; bone-resorbing osteoclasts, and bone forming osteoblasts, which when surrounded by mineralized connective tissue finally become osteocytes; all offering important tasks in maintaining a functioning skeleton. The extracellular matrix consists predominantly of the mineral calciumhydroxyapatite and type 1 collagen. There are two types of bone tissue, cortical (compact) bone which is found especially in the shafts of the long bones and the surface of flat bones, and trabecular (cancellous) bone which is located in vertebrae, in the end of long bones and the inner part of flat bones [69].

The skeleton is undergoing lifelong renewal in form of dynamic bone remodelling. During ten years, the adult skeleton is completely remodelled [70]. The remodelling process follows a certain pattern in the osteon (the functional unit of cortical bone), where bone resorption, performed by osteoclasts, is followed by osteoid production by the osteoblasts. This

is governed by an orchestra of endocrine, neuronal and local factors, where the osteocytes exert a major role in defining where and when bone remodelling should take place. Central in this process is the osteoprotegerin (OPG)/receptor activator of nuclear factor-kappa B ligand (RANK)/RANK ligand (RANKL) system, where RANKL released from the osteoblasts reacts with the receptor RANK at the osteoclast precursor and induce osteoclast formation and activation, leading to bone resorption. OPG, on the other hand, acts as a soluble decoy receptor, where binding to RANKL inhibits osteoclast stimulation [70]. Bone resorption is followed in time and space by bone formation, where osteoid is laid down by the osteoblasts [69]. Finally, the osteoid is mineralized in two stages; early mineralization, which occurs within a few days, and secondary mineralization which may take more than six months [71].

After increasing bone mass through childhood and adolescence, a peak bone mass is reached in early adult life (20-30 years). Bone resorption and formation are thereafter balanced, resulting in minimal cortical bone loss until menopause in women, and until 60 years in men [72]. Trabecular bone loss is reported to start as early as in the third decade in both sexes, and in addition accelerates during perimenopause in women [73]. Sex steroids have proapoptotic effects on osteoclasts but antiapoptotic effects on osteoblasts and osteocytes, accordingly, menopause leads to an imbalance between bone resorption and formation [69,70,72]. Together with decreased calcium absorption from the gut and reabsorption in the kidneys, this accounts for lower mineral content and bone strength [74]. As women in general obtain a lower peak bone mass in young adulthood, and experience a larger loss due to the influence of rapid sex steroid hormone loss, these factors explain why osteoporosis is regarded a women's disease. However, osteoporosis may also affect men, as illustrated by data from Sweden showing that almost one out of two women and one out of four men will experience an osteoporotic fracture throughout life [75].

Presently, the diagnosis of osteoporosis depends on BMD measurements, where a T-score (standard deviations (SD) above or below the mean of healthy young women) ≤ -2.5 defines osteoporosis, and a T-score ≥ -1.0 is regarded as normal. Those in between are defined as having osteopenia [76].

1.7 Vitamin D and osteoporosis

In addition to its role of providing calcium to the mineralization of bone, $1,25(OH)_2D$ is also involved locally in several steps of the bone turnover process. The exact role of $1,25(OH)_2D$ in bone is, however, complex and not fully understood [71]. Both the enzyme 1-alfa-hydroxylase and the VDR are present in bone cells [77], and in vitro experiments suggest a role of $1,25(OH)_2D$ in enhancing the coupling and communication between osteoclasts and osteoblasts [78]. In vitro experiments have also demonstrated that treatment with $1,25(OH)_2D$ reduces impairment of human osteoblast functions during aging [79], and that locally produced $1,25(OH)_2D$ is important in differentiation of osteoblasts from human marrow stromal cells [80]. By inducing RANKL, $1,25(OH)_2D$ further stimulates osteoclast formation and differentiation; the latter down-regulating bone resorption [78]. Also, by increasing OPG secretion from mature osteoblasts, bone resorption is inhibited [81]. Although very high doses of $1,25(OH)_2D$ increase bone resorption in vitro, physiological doses are believed to have the opposite effect by inhibiting PTH-induced bone resorption [82].

Still, the role of vitamin D in osteoporosis is controversial. Vitamin D together with calcium is generally considered first line therapy for people at risk of osteoporotic fractures [83]. A positive association between vitamin D intake and/or serum 25(OH)D levels and BMD has been reported in several studies [84-88]. However, no association was found in other populations [89-91]. The reasons for this discrepancy remain unclear. It has been suggested that in a population with generally good vitamin D and calcium status, vitamin D does not play a major role in bone

health [90,91], although in some of the studies showing an association, mean serum 25(OH)D concentrations were generally high (102 nmol/L in women and 109 nmol/L in men) [86,88].

Similarly, cohort studies have not established a consistent association between basal serum 25(OH)D levels and later fracture risk. Thus, no association was seen in some studies [90,92], while two longitudinal American studies reported higher risk of hip fracture with lower baseline serum 25(OH)D levels [93,94]. A third study reported no association between hip fracture risk and serum 25(OH)D levels, while lower serum $1,25(OH)_2D$ was associated with an increased risk of hip fracture [95].

Results from clinical studies on the effect of vitamin D on fracture risk are also conflicting, with some finding an effect [96-98], and others not [99-101]. Several meta-analyses have been published on the effect of vitamin D with or without calcium supplementation on the risk of fracture [102,103]. Although with some methodological differences, one may conclude that vitamin D given alone does not prevent fractures, while vitamin D combined with calcium has a modest fracture reducing effect. The interpretation of the results has been complicated by problems with low compliance to medication, the use of vitamin D_2 which might be less potent than vitamin D_3 [13], and low vitamin D dosages (400 international units (IU)/d). Thus, studies reaching a mean 25(OH)D level >75nmol/l, which requires dosages of at least 7-800 IU/d, show a significant effect on hip fracture, with a relative risk (RR) (95% confidence interval (CI)) of 0.74 (0.61-0.88) compared to placebo [104].

2. Aims of the thesis

The overall aim of the thesis was to explore the relation between serum 25(OH)D and metabolic disorders in order to elucidate whether higher levels of serum 25(OH)D could have beneficial health effects. Specifically, the aims of the subprojects were to:

- Validate 25(OH)D measurement methods with special emphasize on the effect of smoking. (Paper I)
- Study the association between serum 25(OH)D levels at baseline and incident type 2 diabetes during 11 years of follow-up in a population-based study. (Paper II)
- Compare insulin sensitivity, secretion and lipid profiles between subjects with sufficient and insufficient levels of serum 25(OH)D, and to assess whether supplementation with vitamin D in the insufficient group affects these measures. (Paper III)
- Study whether high dose of vitamin D is better than standard dose of vitamin D in improving BMD and bone turnover markers in postmenopausal women with low BMD. (Paper IV)

3. Study population and methods

3.1 Study populations

3.1.1 Papers I-III

The data and/or inclusion of participants to the studies described in Paper I-III originated from the Tromsø Study. This population-based ongoing study started in 1974 in order to explore the reasons for the high cardiovascular mortality among men in Northern Norway. Since then, the study has expanded to include both genders, and a broad multipurpose approach has been applied, opening for research on a number of life-style related diseases [105]. Table 2 shows examination years, age groups included, and attendance rates.

In the 4th Tromsø Study, performed in 1994-95, all individuals living in the municipality of Tromsø aged 25 years or older were invited to participate. A total number of 27,158 persons attended the first visit, providing an attendance rate of 77% among eligible inhabitants. All men aged 55-74 years, all women aged 50-74 years, and a sample of 5-10% of the remaining age groups between 25 and 84 years were invited to undergo a more extensive clinical examination (second visit), and 7965 persons, or 78% of those invited, attended [105]. All participants who attended this second visit had a blood sample taken and stored, and these sera were thawed and analyzed for 25(OH)D during spring 2008.

The 6th Tromsø Study was performed in 2007-8 and the following groups were invited: those who participated in the second phase of the fourth survey (1994-95), a random 10% sample of subjects 30-39 years old, all subjects 40-42 and 60-87 years old, and a random 40% sample of subjects 43-59 years old, In total, 19,762 subjects were invited to the 6th Tromsø Study, and 12,984 subjects (65.7%) attended [105]. Serum 25(OH)D was measured in all participants.

Table 2 The Tromsø Study; examination year, age groups included and attendance rate. Number of subjects (N) and mean age in the six different surveys are given according to gender and attendance

		Men					Women				
			Attendees		Non-attendees			Attendees		Non-attendees	
	Age group	% attendance	N	Age	N	Age	% attendance	N	Age	N	Age
Tromsø 1 (1974)	20-49	74.4	6595	33.7	2271	30.2	-				
Tromsø 2 (1979-80)	20-54 [a]	73.8	8477	35.7	3004	31.3	81.8	8144	32.9	1815	28.7
Tromsø 3 (1986-87)	12-67 [b]	71.7	10,963	37.6	4318	32.5	79.0	10,863	35.4	2882	29.9
Tromsø 4 (1994-95)	25-97	69.6	12,865	46.6	5615	40.9	74.9	14,293	47.2	4785	44.1
Tromsø 5 (2001-02)	30-89	75.7	3511	59.9	1125	46.0	80.8	4619	59.4	1098	50.8
Tromsø 6 (2007-08)	30-87	62.9	6054	57.5	3571	54.5	68.4	6930	57.5	3207	58.1

[a] 20-49 in women. [b] All men aged 20-61 and women aged 20-56 were invited

Slightly modified from Jacobsen BK (2011) Int J Epidemiol [105]. Used with permission.

In Paper I we included all participants with valid serum 25(OH)D measurements and available data on smoking from the 4th Tromsø Study. We also included randomly selected participants from the 6th Tromsø Study who accepted an invitation to participate in a validation study of vitamin D measurements. Based on self-reported smoking data in the Tromsø Study questionnaire, they were regarded current smokers (defined as a person reporting smoking at least 5 cigarettes per day (d)) or non-smokers (defined as never smoked, or more than five years since quitted smoking), and a similar number of smokers and non-smokers were included.

In Paper II we included participants in the 4th Tromsø Study with valid serum 25(OH)D and glycated haemoglobin (HbA_{1c}) measurements in the baseline examination at the Tromsø Study 1994-95. Participants with baseline $HbA_{1c} \geq 6.5\%$, those who reported or were registered with diabetes at baseline, were registered as moved before baseline, or had missing information on any of the variables used in the models (BMI, physical activity and smoking), were excluded from the analyses.

In Paper III we invited participants from the 6th Tromsø Study based on their serum 25(OH)D measurements to a follow-up study. The analyses from the validation study in Paper I were ongoing during the inclusion period, and we therefore chose not to invite smokers to avoid interference with the results. Participants with serum 25(OH)D between the 5-10 percentile (low serum 25(OH)D, cases) or between the 80-95 percentiles (high serum 25(OH)D, controls), were invited, and low or high serum 25(OH)D levels were confirmed in new serum samples before inclusion. BMI is inversely associated with serum 25(OH)D [12] and also a main contributor to insulin sensitivity [39]. To avoid confusion on whether a difference between cases and controls were dependent on differences in BMI only, participants were invited based on BMI data, age and gender from the 6th Tromsø Study in order to achieve a fairly equal distribution between cases and controls. There was, however, no head-to-head

matching. Exclusion criteria were diabetes mellitus, acute myocardial infarction or stroke last 12 months, cancer last five years, steroid use, serum creatinine ≥ 130 μmol/l (males) or ≥ 110 μmol/l (females), possible primary hyperparathyroidism (plasma PTH >5.0 pmol/l combined with serum calcium >2.50 mmol/l), sarcoidosis, systolic blood pressure >175 mmHg or diastolic blood pressure >105 mmHg. Pregnant or lactating women, and women in fertile age (<50 years) reporting no use of contraception, were not included.

3.1.2 Paper IV

In Paper IV, we included 50-80 years old postmenopausal women with a T-score ≤-2.0 in total hip or lumbar spine (L2-4). The participants should not have used hormone replacement therapy or other therapy affecting bone remodelling during the last 12 months before enrolment. Further exclusion criteria were use of steroids, renal stone disease, systolic blood pressure >175 mm Hg or diastolic blood pressure >105 mm Hg, serum creatinine >110 μmol/l, suspected primary hyperparathyroidism (serum calcium >2.55 mmol/l; serum calcium >2.50 mmol/l combined with plasma PTH >5.0 pmol/l; or serum calcium >2.45 mmol/l combined with plasma PTH >7.0 pmol/l), or chronic diseases like ischemic heart disease, diabetes, granulomatous disease or cancer.

Participants were recruited from the outpatient clinic; through advertisement; and from other completed clinical studies where BMD was measured. These other studies included the 6th Tromsø Study; the NATTO Study (studying the effect of vitamin K on bone loss) [106]; and the ACUFLASH Study (studying the effect of acupuncture on menopausal symptoms) [107].

3.2 Measurements

3.2.1 Questionnaires

Self-administrated questionnaires were filled out in all the Tromsø Study surveys. In Paper I and II we used the following questions regarding smoking: "Do you smoke cigarettes daily?" (yes/no), "For previous or current smokers: How many cigarettes do you, or did you smoke daily? (handrolled + factory made)", and "If you currently smoke, or have smoked before, how many years in all have you smoked daily?". We also used the smoking variable "If you previously smoked daily, how long is it since you stopped (years)?" Subjects answering yes to "Do you smoke a pipe daily?" or "Do you smoke cigars/cigarillos daily?" were coded as current smokers. In Paper III, the question "Do you/did you smoke daily" was used to exclude current smokers (ticking "yes, now") from being invited.

Data on physical activity used in Paper I and II was registered in the 4th Tromsø Study through the following questions: 1."Light activity (not sweating or out of breath): How has your physical activity in leisure time been during the last year? Think of your weekly average for the year. Time spent going to work count as leisure time (h/w)." 2. "Vigorous physical activity (sweating/out of breath): How has your physical activity in leisure time been during the last year? Think of your weekly average for the year. Time spent going to work count as leisure time (h/w)." The response alternatives for both questions were as follows: 1 = none, 2 = <1 h, 3 = 1-2 h, 4 = 3 h or more. In Paper I, the main purpose was to adjust for outdoor time. The answers were therefore recoded into 0-1-2-3 h, and a physical activity score was calculated by adding together hours of light and vigorous physical activity/w. In Paper II, we wanted to adjust for both outdoor time and the effect of physical activity on diabetes development, and each hour of vigorous activity was therefore given a double score compared to each hour of light activity, up to a maximum of nine points.

Data on physical activity used in Paper III as a proxy for outdoor time was obtained through the following question in the 6th Tromsø Study: "Exercise and physical exertion in leisure time. If your activity varies much, for example between summer and winter, then give an average. The questions refer only to the last twelve months." The following response categories were possible: level 1: reading, watching television, or engaging in sedentary activities; level 2: at least 4 h a week walking, bicycling, or engaging in other types of physical activity; level 3: at least 4 h a week exercising to keep fit and participating in recreational athletics; and level 4: regular, vigorous training or participating in competitive sports several times a week.

In Paper I and II, vitamin D supplementation was defined as use of cod liver oil (yes/no) and/or multivitamins containing vitamin D (yes/no). In Paper III, data on fat fish intake was self-reported using the following alternatives: 1: 0-1 times/month; 2: 2-3 times/month; 3: 1-3 times/w; 4: 4-6 times/w; and 5: 1-2 times/d. The following variables were in addition registered at screening: Medical history, current medication use, use of cod liver oil last year (whole year every day; whole year, not daily; winter every day; or winter, not daily), other supplements (name), sunny holidays last three months, times using sunbeds last year, number of glasses of milk and sandwiches with cheese/d, and servings of yoghurt/w. Women were asked if they had regular menstruation, and accordingly; use of contraception or year of menopause. Due to content of nut oil in the study medication, all participants were asked specifically if they had experienced nut allergy.

In Paper IV the following information was obtained at screening: Medical history, current medication use, nut allergy, previous use of estrogen and bisphosphonates, current or previous smoking, year of menopause, times using sunbed last year, sunny holidays the previous 12 months and time spent outdoor during the period of possible UVB-mediated vitamin D production in the skin at the study location (69ºN) [5]. Hence, the participants were

asked about mean time spent outdoor between 10 AM and 3 PM in March-April and September, and between 8 AM and 8 PM in May-August. At baseline the participants filled in a food frequency questionnaire [108] and a questionnaire on physical activity (International Physical Activity Questionnaire (IPAQ), short last 7 days self-administered format) [109]. Thus, intakes of calcium and vitamin D were calculated, and physical activity was transformed to metabolic equivalent (MET)-minutes (min)/w and IPAQ categories according to IPAQ guidelines.

3.2.2 The end point registry

In Paper II we used data on diabetes from the Tromsø Study's endpoint registry. The University Hospital of North Norway is the only hospital in Tromsø, and admissions to other hospitals are unlikely because of long distances. The Tromsø Study is therefore able to follow attendants who have taken part in the surveys with regard to incident cases of several endpoints, which includes cardiovascular disease, diabetes and non-vertebral fractures. Adjudication of first-ever cases of these conditions is performed by independent endpoint committees, and each case is reviewed separately [105]. Emigration from the municipality or from Norway and date of death are registered by the National Population Register of Norway. A detailed description of definition and ascertainment of type 2 diabetes is presented in Paper II.

3.2.3 Physical measurements

Height and weight were measured wearing light clothing and no shoes. Height was rounded to the nearest 0.5 cm, and weight in kg was recorded with one decimal.

3.2.4 Blood samples

Serum 25(OH)D was measured in sera from the 4th and 6th Tromsø Study by an electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics®, Mannheim, Germany), using an automated clinical chemistry analyser (Modular E170, Roche Diagnostics®, Mannheim, Germany) [31]. The total analytical coefficient of variation (CV) for the 25(OH)D_3 assay was 7.3% as recorded by measuring a donor control (65.0 nmol/L) consecutively during the analytical period using a quality management programme (QM™, Tieto Enator, Helsinki, Finland). This was in accordance with the total analytic precision of ≤7.8% as reported by the producer. The cross-reactivity with 25(OH)D_2 was <10% and the lower detection limit was 10 nmol/L. The sera from the 4th Tromsø Study had been stored frozen at -70ºC. Serum 25(OH)D levels have been demonstrated to be stable in spite of multiple freeze-thaw cycles [110].

In Paper I, the main purpose was to validate the ECLIA method against other available methods. In addition to ECLIA, we therefore used two liquid chromatography (LC)-MS/MS methods, one HPLC method and two different radioimmunoassay methods (RIA) (DiaSorin and Immuno Diagnostic Systems (IDS)) in a substudy. One of these LC-MS/MS methods, developed at the Hormone Laboratory, Haukeland University Hospital, Bergen, Norway was also used when analyzing baseline and final serum 25(OH)D levels in Paper III and IV. This method includes extraction of serum with n-hexane:isopropanol and injection into an isocratic HPLC system coupled with a MSciex API 3000 mass spectrometer (Carlsbad, CA, USA) equipped with an electrospray source. There is no known interference from other substances, including no cross-reaction with vitamin 25(OH)D_2.

Bone turnover markers and 1,25$(OH)_2$D used in Paper IV were analysed at the Hormone Laboratory, Oslo University Hospital. The bone resorption marker C-terminal telopeptid of type 1 collagen (CTX-1) was measured in serum by an enzyme-linked

immunosorbent assay (IDS, Herlev, Denmark), reference range for postmenopausal women was <1.35 µg/l according to the producer. The bone formation marker N-terminal propeptid of type 1 procollagen (P1NP) in serum was measured by RIA (Orion Diagnostics, Espoo, Finland); reference range for postmenopausal women was 16-96 µg/l according to the producer. $1,25(OH)_2D$ was measured by RIA (DiaSorin, Stillwater, MN, USA); reference range 42-169 pmol/l.

The other laboratory analyses were performed consecutively at the Department of Medical Biochemistry at the University Hospital of North Norway. The only exception was plasma PTH from the 4th Tromsø Study (used in Paper I and II), which was measured in thawed stored samples in a subgroup (47%) in 2001 using an automated clinical chemical analyser (Immulite 2000, Siemens Healthcare Diagnostics, Los Angeles, CA, USA), with a reference range of 1.1-6.8 pmol/L (≤50 years) and 1.1-7.5 pmol/L (>50 years). The laboratory methods for the other analyses used are described in Paper I-IV.

3.2.5 Hyperglycemic clamp

Insulin sensitivity and secretion were measured in Paper III as previously described using a three-hour hyperglycemic clamp technique [60,111,112]. Under a standardized steady state hyperglycemic condition where plasma glucose is held constantly at 10 mmol/l, measures of total (hepatic and peripheral) insulin sensitivity are provided. The insulin sensitivity index (ISI) is calculated as the amount of glucose infused (mg x kg^{-1} x min^{-1}) divided by the mean serum insulin level during the last hour of the clamp (120-180 min). The results correspond well with the "gold standard" euglycemic clamp technique [111]. In addition, the method provides a measure of beta-cell function or insulin secretion, which is not obtained through the euglycemic clamp technique. First-phase insulin secretion is calculated as the serum insulin area under curve during the first ten minutes of the clamp, and second phase as the

area under the curve during the last hour of the clamp. A more detailed description of the hyperglycemic clamp method is given in Paper III.

Other methods of assessing insulin sensitivity and beta cell function include modeling based on fasting glucose and insulin levels. Although not a planned endpoint, we chose to analyze insulin resistance from the homeostasis model assessment (HOMA-IR) in order to compare our results with others [113] (HOMA-IR=fasting serum insulin (mIU/ml) x fasting plasma glucose (mmol/l)/22.5) [114].

3.2.6 BMD

BMD was measured in Paper IV using dual X-ray absorptiometry (DEXA) (GE Lunar Prodigy, Lunar Corporation, Madison, WI, USA) at the following sites: dual hip, lumbar spine and total body. We used the mean of the left and right hip measurements for analyses. For participants with metallic implant in one hip, the measurement from the eligible hip was used in the analyses. The scanner was calibrated daily against the standard calibration block supplied by the manufacturer (aluminium spine phantom), and these measurements showed no drift throughout the study. In a quality study of 30 volunteers of different gender and ages, and both with and without osteoporosis, BMD scanning was performed twice the same day by two different technicians. The CV was <1.0% at both the total hip and the spine.

3.3 Interventions

3.3.1 Vitamin D doses and safety

At the time of the study planning, most intervention studies on vitamin D had used doses ranging from 4-800 IU/d. Based on the considerations outlined in section 1.2, much attention was drawn towards the use of higher doses which would be more similar to the natural

supplies from UVB-radiation in a traditional outdoor life. Being outdoor with easy clothing a sunny summer day will after a short time induce the production of 10-20,000 IU of vitamin D_3 in the skin [115]. Conversely, safety studies using graded doses of 0 – 10,000 IU/d given for five winter months resulted in serum 25(OH)D changes from -11 nmol/l to +158 nmol/l, and no signs of toxicity [116]. Based on reviews of vitamin D safety, no harm would be expected with doses up to 10,000 IU/d [117,118], or below serum 25(OH)D levels of 374-700 nmol/l [1,117,118]. Our research group performed a pilot study before starting the intervention studies, where seven healthy group members were supplemented with 40,000 IU/w (equaling 5700 IU/d) for six months. A slight reduction in serum PTH was seen, and no hypercalcemias or adverse events were registered (data not published). This dose was therefore selected for the intervention studies, and measurements of serum calcium and creatinine were performed throughout the studies for safety monitoring.

3.3.2 Study medication

In Paper III, the participants with low serum 25(OH)D levels were randomized to receive capsules of 20,000 IU vitamin D_3 to be taken twice weekly, or identical looking placebo capsules. In Paper IV, which was a study among women with reduced BMD, all the participants were given a daily supplement of 800 IU vitamin D_3 and 1000 mg calcium. This is standard treatment for osteoporosis, and also commonly used in the placebo groups in clinical trials in this particular patient group [119]. In addition, the treatment group was given capsules of 20,000 IU vitamin D_3 to be taken twice a week. In total this constituted an average daily dose of 6500 IU. The placebo group received identical looking placebo capsules.

In both the intervention studies, the participants received a calendar as an aid to remember to take the study medication. In Paper III, phone calls from the study nurse at one and three months were used to assure that the study medication was taken as planned. The

participants brought the remaining study medication at the final six month's visit for counting. In Paper IV, a study visit every third month was performed, and compliance was checked as the participants brought their remaining study medication to be counted at each visit. For the participants living far from the hospital, this control was performed by phone from the study nurse, and these participants brought all their remaining study medication to be counted at the final twelve month's visit.

3.3.3 Randomization

The randomization was performed by the central randomization unit at the Clinical Research Center, University Hospital of North Norway, using block-randomization with various block-sizes. In Paper IV, stratification based on current smoking and previous use of bisphosphonates was included to ensure an equal distribution of these characteristics between the treatment and placebo groups. In both studies, the randomization numbers with treatment allocations were provided directly to the hospital pharmacy where the medication boxes were prepared and delivered each participant at baseline by the study nurse. In summary, both studies were randomized, double blind clinical trials; neither the participants nor the staff performing the examinations nor the researchers knew the randomization status of the participants during the study.

3.3.4 Follow-up and safety

The participants in both intervention studies were asked to stop any vitamin D supplements at baseline, and in Paper IV, also calcium supplements. Generally, sunbed use was discouraged, and persons taking sunbed regularly were not included. Limited sunbed use before special occasions was not an exclusion criterion, but the study medication should be temporarily

stopped if using sunbed or if going on a sunny holiday. In Paper IV, the basic calcium and vitamin D supplements should however be continued.

Adverse events were asked for and registered through a phone call from the study nurse at one and three months, as well as at the final visit at six months in Paper III. In Paper IV, adverse events were registered at the visits every third month. Blood for serum calcium, ionized calcium, PTH, phosphate and creatinine were sampled and analyzed. This was done at the local health center for participants living far from the hospital, and the samples were mailed to the University Hospital of North Norway. Thus, all samples were analysed at the same laboratory. Exclusion criteria with special relevance to vitamin D were predefined. Participants with serum calcium >2.80 mmol/l should be excluded, and participants with serum calcium in the range 2.60 – 2.80 mmol/l should be retested and excluded if still above 2.60 mmol/l.

3.4 Power calculations and statistics

Statistical methods and power calculations (for the intervention studies) are described in detail in Papers I-IV.

In general, all tests were done two-sided, and a significance level was set at 0.05. Normal distribution of the variables was assessed by visual inspection of histograms, and log-transformation resolved non-normality so that parametric statistical tests could be used. Seasonal adjustment is of high importance when examining serum 25(OH)D levels. In Paper I and II, such adjustment was done using dummy variables for each month when assessing serum 25(OH)D as a continuous variable. To address possible non-linear associations between baseline serum 25(OH)D levels and later type 2 diabetes in Paper II, we also constructed quartiles of serum 25(OH)D levels within each month before pooling them together [120] (closer discussed in section 5.2.3).

In Paper I, comparison between the different smoking subgroups were made using Chi square tests or analyses of variance (ANOVA) using the Bonferroni correction. General linear models were used to compare estimates adjusted for confounders. To assess the effect of amount of smoking on serum 25(OH)D levels, the variables number of cigarettes smoked/d, years of smoking, and years since smoke cessation were grouped into categories, followed by analyses of linear trends using general linear models. When the six different serum 25(OH)D methods were compared with regard to smoking, a linear mixed model was used.

In Paper II, we used the Cox regression model in the main analyses. Smokers and non-smokers were evaluated separately, and adjustments for number of cigarettes and years of smoking were performed in the smokers. In addition, the possible confounders age, sex, BMI, and physical activity were included in the final models. To further study the effect modification of BMI, we performed analyses stratified by BMI quartiles. There will inevitably be some degree of uncertainty regarding the year of diagnosis for the diabetes cases. For participants with unknown year of diabetes diagnosis, a year midway in the observation time was imputed for the main analyses, and sensitivity analyses with these participants excluded were also performed. In addition, we performed logistic regression with diagnosis of diabetes (yes or no) as dependent variable to study whether the year of diagnosis affected the results.

Participants with high and low levels of serum 25(OH)D in Paper III were compared with independent t-tests or chi-square tests for continuous or categorical variables, respectively. General linear models were used to compare estimates adjusted for possible confounders. Also, baseline characteristics of participants randomized to treatment versus placebo in Papers III and IV, were compared with independent t-tests or chi-square tests. Changes in outcome variables from baseline to final examination in the treatment and placebo groups were compared using independent t-tests. In Paper III we also studied the treatment

effect by using analysis of covariance (ANCOVA) models with log-transformation of baseline and final outcome values; allowing us to adjust for baseline differences and present the relative effects of the treatment compared to placebo [121].

In the two intervention studies, the analyses were performed both as per-protocol and intention-to-treat analyses, with the last observation carried forward.

3.5 Ethics

All the participants provided a written informed consent prior to the examinations. The studies were recommended by the Regional Committee for Medical and Health Research Ethics, North Norway, and approved by the Norwegian Data Inspectorate. The intervention studies were also approved by the Norwegian Medicines Agency, and registered at ClinicalTrials.gov (NCT00809744 (Paper III) and NCT00491920 (Paper IV)).

4. Summary of results

Paper I

In this paper, the main finding was an interference between the ECLIA (Roche) assay for serum 25(OH)D measurements and smoking. In the 6932 participants included from the 4th Tromsø Study where ECLIA was used, smokers had more than 20 nmol/l higher serum 25(OH)D levels than non-smokers, with former smokers slightly above never smokers (never smokers 51±17 nmol/l; former smokers 54±17 nmol/l; and current smokers 72±17 nmol/l, *p* for difference <0.01). A dose-response relationship between smoking and serum 25(OH)D levels was evident, with serum 25(OH)D levels increasing with number of cigarettes and years smoked in current smokers and decreasing with years since smoking cessation in former smokers. In the validation studies where serum 25(OH)D levels were measured in 54 smokers and 53 non-smokers, the ECLIA (Roche) method was significantly different from the five other methods in finding higher levels in smokers. The results indicate that smoking interferes with the serum 25(OH)D measurement in a dose-dependent manner using this particular immunoassay. The mechanisms are not known and further exploration is needed.

Paper II

In this paper, non-smokers (n=4157) and smokers (n=1962) in the 4th Tromsø Study were assessed separately due to the interference between smoking and serum 25(OH)D measurements discovered in Paper I. In both groups, baseline serum 25(OH)D levels in 1994 were inversely associated with risk of subsequent diabetes during 11 years of follow-up, so that the risk of developing type 2 diabetes was approximately doubled in the lowest versus the highest quartile of serum 25(OH)D when adjusting for age and gender. Hazard ratios (HRs) (95% CI) were for non-smokers 1.89 (1.25-1.88), and for smokers 2.68 (1.18-6.06).

Accordingly, each 10 nmol/l increase in serum 25(OH)D led to a 14-15% decreased risk of developing type 2 diabetes (HR (95% CI) for non-smokers 0.86 (0.78-0.95) and for smokers 0.85 (0.74-0.98)) when serum 25(OH)D was assessed as a continuous variable. Further adjustment for BMI attenuated the risk estimates in both models so they were no longer significant. Thus, BMI-adjusted HRs (95% CI) for lowest vs highest serum 25(OH)D quartile were for non-smokers 1.40 (0.91-2.14) and for smokers 1.50 (0.64-3.55). Accordingly, for each 10 nmol/l increase in serum 25(OH)D, BMI-adjusted HRs (95% CI) were for non-smokers 0.95 (0.86-1.05) and for smokers 0.96 (0.83-1.12). However, stratified analyses according to quartiles of BMI showed both in smokers and non-smokers still a statistical significant decreased risk of developing type 2 diabetes with increasing serum 25(OH)D levels in the leanest BMI quartile (BMI <23.2 kg/cm^2), with a 38-44% risk reduction per 10 nmol/l increase in serum 25(OH)D, indicating a possible protective effect of vitamin D independent of BMI. As there were low numbers of cases in this quartile, these results must be interpreted with caution.

Paper III

In this paper, we compared measures of glucose and lipid metabolism between otherwise healthy adults with low and high serum 25(OH)D levels (40.3±12.8 nmol/l (mean±SD) (n=108) and 85.6±13.5 nmol/l (n=54), respectively). Subjects with low levels had significantly higher HbA_{1c} (5.55±0.35 versus 5.37±0.36%, p<0.01), and triglyceride (TG) levels (geometric mean 1.07 versus 0.89 mmol/l, p=0.03), and lower ISI (geometric mean 0.13 versus 0.17 μmol x min^{-1} x kg^{-1} x pmol^{-1}, p=0.04) than those with high levels. Physical activity differed between the two groups, and adjustment for this possible confounding factor removed the significant difference between the groups regarding ISI and TG, but not HbA_{1c}. However, in a subsequent randomized double-blinded placebo-controlled trial (RCT) in 104

participants with low serum 25(OH)D levels, six months supplementation with high dose vitamin D_3 did not lead to improvements in any of these measures as compared to placebo. Although not significant from the placebo group, fasting glucose and HbA_{1c} increased in the supplemented group. In the 94 participants completing the study, achieved serum 25(OH)D levels were 142.7±25.2 and 42.9±17.3 nmol/l in the treatment and placebo group, respectively. Reasons for not completing the study were medical reasons (n=2), consent withdrawal (n=1), technical problems (n=3), lost to follow-up (n=3) and death (n=1). Numbers of adverse events were similar in the two groups, and no hypercalcemias were observed. One participant in the placebo group died of unknown reasons.

In spite of confirming previous observational findings of an inverse relationship between serum 25(OH)D and measures of metabolic dysregulation in the case-control study, the findings from the RCT did not support a causal role of vitamin D in this regard. The interpretation of the results might however be limited due to short follow-up time and the dose used, as the resultant serum 25(OH)D level was higher in the treated group than in the controls at baseline. The ideal serum 25(OH)D level may therefore have been exceeded.

Paper IV

In this paper, we found that one year treatment with high dose vitamin D_3 administrated with calcium was not better than standard dose of vitamin D_3 in improving or maintaining BMD in 297 postmenopausal women with reduced BMD. Both treatments led to marginal improvements in BMD at the hip, and maintenance of BMD at the femoral neck, spine and total body. Serum 25(OH)D increased from 71±23 (mean±SD) to 185±34 and from 71±22 to 89±17 nmol/l in the high and standard dose vitamin D group, respectively. Although not adjusted for multiple comparisons, predefined subgroup analyses indicated a better effect of standard dose at certain measurement sites in persons with osteopenia rather than

osteoporosis, and with serum PTH levels below the median (4.8 pmol/l). Bone turnover markers were reduced in both groups, but the bone formation marker P1NP was more reduced in the standard dose group (-10.7±14.2 µg/l in the high dose group, and -14.3±15.4 µg/l in the standard dose group, $p<0.05$). As the reduction in both resorption and formation markers were associated with an increase in BMD, this might indicate that the standard dose was the more efficient. Twenty-two participants did not complete the study (medical reasons, n=15; consent withdrawal, n=8). The results were similar when analyzed per-protocol as intention-to-treat. The number of adverse events did not differ significantly between the treatment groups, although the number of transient hypercalcemias (as defined by serum calcium >2.60 mmol/l) was non-significantly higher in the high dose group (nine versus four). Both baseline serum 25(OH)D levels and calcium intake were higher than expected from the general population, and we cannot exclude that high dose vitamin D would have had another effect in vitamin D deficient women. However, as a maintenance treatment in vitamin D replete women with low BMD, high dose vitamin D can not be recommended.

5. General discussion

This thesis combines data from epidemiological observational studies, one methodological study and two intervention studies. All these approaches are prone to limitations which might affect the validity of the findings. Internal validity refers to whether the findings are true for the population studied, while external validity refers to whether the findings also applies to populations not studied. Both types of validity are challenged by two categories of errors, namely random errors and systematic errors.

5.1 Random errors

Random errors refer to imprecision in measurement, data processing or calculation, which might decrease the precision in the estimates, and reduce reproducibility [122]. Although not possible to eradicate completely, these are best prevented through a continuous focus on quality all the way through the research process. This includes optimizing the study design and the inclusion of adequately sized study samples. Further, statistical tools are used to minimize the impact of these errors.

A statistical type 1 error denominates reporting a difference which is not real. To avoid that, strict statistical criteria are predefined to assess when a finding should be regarded significant. We have in the papers included in this thesis, set the significance level at 0.05, which means that a $p<0.05$ leads to rejection of the null hypothesis. According to the normal distribution, one in 20 non-significant findings will by chance turn out significant. Hence, the more statistical comparisons performed, the greater the chance will be for reporting a false significant finding. This implies that when multiple comparisons are performed, the results must be interpreted carefully [123].

In Paper IV, we had predefined certain strata of participants for subgroup analyses; namely participants with baseline serum 25(OH)D or PTH below or above the median, age below or above 65 years, and with or without osteoporosis in the hip or L2-4. We found significant differences in the effects of high dose vitamin D treatment on BMD in participants with T-score >-2.5 in L2-4 and in participants with plasma PTH below the median (4.8 mmol/l), where standard treatment was better at the femoral neck and total hip, respectively. The a priori selection of strata reduces the chance of type 1 errors. However, in total 40 comparisons were made, and the number of significant findings were therefore as expected through the statistical distribution. A possible interpretation is therefore that this was nothing but random findings without significance. However, the direction of the estimates - although not significant - was also the same at the other measurement sites. In addition, the results were paralleled by what we found for bone turnover markers, increasing the validity of the findings. Nonetheless, this illustrates why such results must be interpreted carefully, and that they can be regarded hypothesis-generating rather than evidence of causality.

A type 2 error denominates not finding a difference which is real. This might happen if the number of participants included in a study is too small or the drop-out rate higher than expected. Adequately sized study samples will prevent this kind of error.

Paper I and II were based on data from the Tromsø Study, which included large number of participants, minimizing the risk of type 2 errors. In Paper I, we also included 53 non-smokers and 54 smokers in order to study the effect of smoking on the measurement methods. This was a pragmatic number based on what is commonly included in that kind of studies and what was practically possible. Also – if we could not find a difference between the methods with this study size, the effect could probably be regarded of little practical importance. However, the effect of smoking was evident, which had implications also for Paper II and III (See also section 5.2.1). In Paper II, the power was thus restricted due to the

need of stratifying by current smoking. We found that those in the lowest quartile of serum 25(OH)D both in smokers and non-smokers, had higher HR of developing type 2 diabetes when adjusted for age and sex only. After adjustment for BMI, the estimates were attenuated and no longer significant. Still, there was a 40-50% increased risk in the lowest serum 25(OH)D quartile, with the confidence intervals including 1.0. The number of participants and events were very similar to those reported from a Finnish study [67], who reported similar findings – an attenuation of estimates and loss of significance after adjustment for BMI. Later, the same research group published a new paper where the cohort from the first study was extended to include also a second cohort, more than doubling the numbers of participants and events. This time, the findings were significant also after adjustment for BMI, however, only in men (HR (95% CI) for developing type 2 diabetes 0.28 (0.10-0.81)) [65]. This could suggest that the power in our study was limited to discover a consistent association independent of confounding factors.

In Paper III, the study sample size in the RCT was based on power calculations using the results from a previous work from our research group [60]. In that study, which failed to find a difference in ISI between 15 persons with secondary hyperparathyroidism and 15 controls, there was a significant difference in ISI between persons with serum 25(OH)D above and below the median. This difference was, however, greater than the difference we found in the case-control part of Paper III, thus, one could suspect that the present study was underpowered. Notably, the study size was similar to two other recently published studies which did find an effect on insulin sensitivity of vitamin D supplementation [113,124], and the direction of the estimates did not favor vitamin D treatment above placebo in our study. Further, the study efficacy was maximized through the strict inclusion criteria to limit confounding and control the distribution by age, gender and BMI. Thus, we find it unlikely that we should have missed a positive effect of vitamin D treatment on insulin sensitivity due

to the study size. The discrepancy regarding results might rather reflect differences in study population characteristics or resulting serum 25(OH)D levels, as discussed in section 6.2.

The number of participants in Paper IV was also based on power calculations prior to the study. These calculations had to be recalculated during the inclusion period owing to problems with obtaining the planned number during the available timeframe, as described more closely in Paper IV. The study was not powered to detect differences in the subgroup analyses, underscoring the need of interpreting those results carefully.

For both the intervention studies, the rates of non-completion were low. This increases the internal validity of the findings.

5.2 Systematic errors

Systematic errors, which might result in incorrect estimates and thereby reduce the validity of the findings, can be discussed in terms of selection bias, information bias, and confounding.

5.2.1 Selection bias

Selection bias is present when individuals have different probability of being included in the study sample according to the exposure or the outcome [125].

In Paper I and II, data was based on participants in the 4th Tromsø Study. This was a large study including both men and women in a wide age range. Volunteers in population-based studies have been reported to be more interested in health issues; hence they could represent a healthier population compared to non-participants. High attendance rates, approximating nearly 80% in both visits of the Tromsø Study, reduce the risk of selection bias and increase the external validity. However, the attendance rate was lower in the youngest and oldest age groups, as only 52% and 54% of the invited among 25-34 years and 75-84 years old subjects, respectively, attended the second phase of the study [126]. Serum 25(OH)D tends to

decrease with age, while incidence of type 2 diabetes increases. This could therefore introduce a selection bias towards nil, underestimating the association between serum 25(OH)D and subsequent type 2 diabetes. This is, however, speculative, and previous reports from the Tromsø Study did not find any significant differences regarding self-reported health between participants who only attended the first visit and participants attending both the first and second visits [126].

The inclusion of participants in Paper III was restricted to non-smokers only, as we at that time had not yet concluded the analyses in Paper I. Thus, we can not tell whether the results also apply to smokers. Smoking increases the risk of diabetes [38], but if there is an interaction between smoking and serum 25(OH)D level and insulin sensitivity, is not known.

5.2.2 Information bias

Information bias results from a systematic tendency for individuals selected for inclusion in the study to be erroneously placed in different exposure/outcome categories, thus leading to misclassification [125]. This misclassification can be differential or non-differential, depending on whether the degree of misclassification of exposure is dependent on the outcome or not. While non-differential misclassification tends to weaken true associations, the direction of the bias when differential misclassification occurs is difficult to predict [125].

There are many sources of information bias, and one of them relevant to these studies is recall bias regarding self-reporting on exposure or confounding variables of life-style like smoking, physical activity, sun seeking behavior and food and supplementation use. In Paper I, the main exposure variable was smoking habits. It is well known that under-reporting of smoking might occur, and also, a tendency to round to nearest five or ten when answering questions on amount of smoking has been shown [127]. This is clearly illustrated in Fig. 2 and 3, where we see self-reported years of smoking and number of cigarettes smoked in the

population included in Papers I and II. This influences precision when these variables are used in the analyses, and is one important reason for stratifying smokers and non-smokers in Paper II where there was such a clear dose-response relationship between amount of smoking and serum 25(OH)D levels using the ECLIA (Roche) method.

Smoking status was extremely important in the validation part of Paper I, where 54 smokers and 53 non-smokers were included based on self-reporting in the 6th Tromsø Study questionnaire. In order to increase study efficacy, we chose to include smokers who reported to smoke on average at least five cigarettes daily, and we also wanted non-smokers to have been without smoking during the last five years before inclusion. These data were rechecked through a new questionnaire at examination. We therefore consider it unlikely that misclassification of smoking status has occurred.

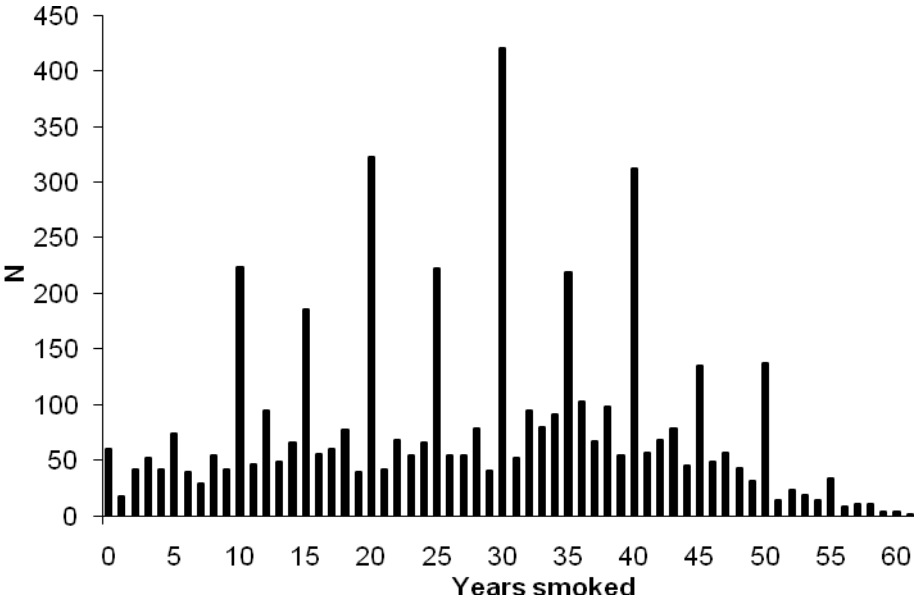

Fig. 2 Self-reported years of smoking in 4773 former or current smokers in the 4th Tromsø Study.

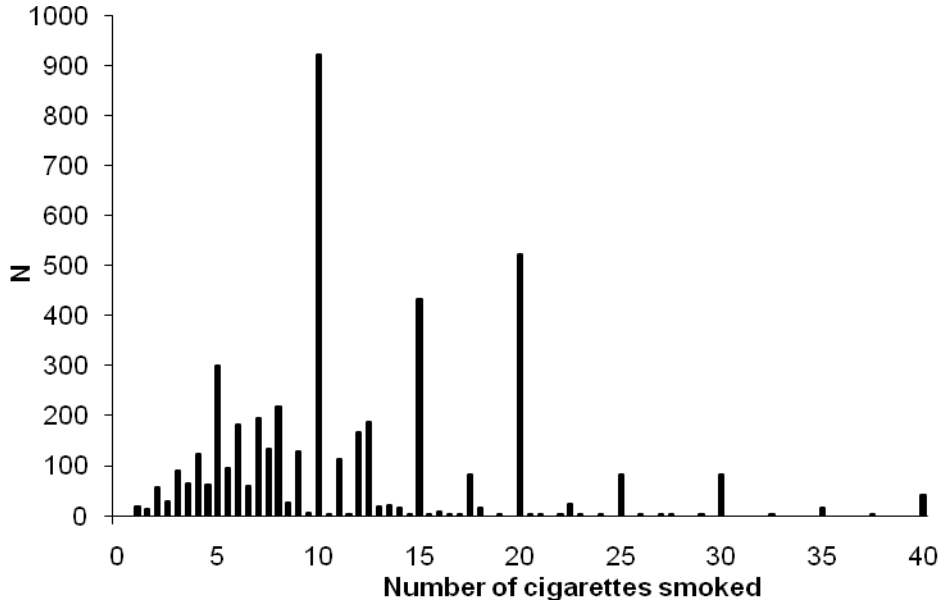

Fig. 3 Self-reported number of cigarettes smoked in 4713 former or current smokers in the 4th Tromsø Study. Participants smoking more than 40 cigarettes/d (n=26) were excluded in order to increase readability.

Other life-style related exposures prone to information bias are self-reported physical activity and food intake. Validated data on self-reported physical activity was used in all four papers, assessed from the questionnaire used in the 4th (Papers I and II) [128] and 6th [129] surveys in the Tromsø Study (Paper III), and an international validated questionnaire tool (IPAQ) [109] in Paper IV. The correlation between self-reported physical activity and objective measures of physical activity or fitness was reported to be from low to moderate, with correlation coefficients in the range of 0.11-0.46 [109,128,129].

The correlation coefficient between self-reported intake of different nutrients in the food-frequency questionnaire and weighed records, was reported to be better (0.44-0.66), however, vitamin D intake from the food-frequency questionnaire was overestimated as compared to weighed records, and less than half of the participants were correctly placed in quartiles of vitamin D and calcium intake based on self-reports [108]. These limitations in self-reports should therefore be kept in mind. However, as the participants in the Tromsø Study

filled out their questionnaires when entering the 4th Tromsø Study, not knowing their serum 25(OH)D level or later diabetes status, any misclassification would be expected to be non-differential, diluting the findings.

The diabetes registry used in Paper II was based on journal screening of participants who reported to have diabetes in the questionnaire in the 4th, 5th or 6th Tromsø Study or had a HbA_{1c} >6.5% at any of the surveys. In addition, the participant list was linked to diabetes-related discharge diagnosis in the digital patient records at the University Hospital of North Norway. Since the hospital provides the only laboratory in the municipality, the diabetes registration committee also had HbA_{1c} measurements taken by the general practitioners available when validating the possible cases. Still, some cases might have been missed due to the limitation of the registry to include only hospital based journals. We expect that to be a non-differential misclassification, diluting the observed associations. One could however speculate that since lower serum 25(OH)D levels are associated with a number of diseases, the risk of getting in touch with health services and having a measurement of serum glucose or HbA_{1c} would be greater in those with low serum 25(OH)D levels, increasing their chance of having a type 2 diabetes detected. If so, this would be a differential misclassification, which might have led to a bias away from nil, resulting in falsely elevated HRs. However, we anticipate the magnitude of such a misclassification to be low.

Also, the data could include persons already having diabetes without knowing it at baseline in the 4th Tromsø Study 1994-95, and these persons could in theory have lower serum 25(OH)D levels owing to deteriorated health and less outdoor time. The time lag in diagnosing the diabetes would then give the false impression that low serum 25(OH)D levels were evident before the diabetes was established, introducing a bias away from nil. This phenomenon is also called reversed causation. In addition to excluding participants with self-

reported or registered diabetes at baseline, we therefore also excluded everyone with a baseline serum HbA_{1c} >6.5%, regardless of later diabetes diagnosis.

In Paper III, we chose to invite participants in the 5-10 and 80-95 percentiles of serum 25(OH)D measured in the 6th Tromsø Study. Since there was considerable time span between the participation in the 6th Tromsø Study and the inclusion in the present study (median 13 months), low or high serum 25(OH)D levels were confirmed at screening before inclusion, using the same laboratory method (ECLIA, Roche) as in the 6th Tromsø Study. As this method later was withdrawn, we chose to measure baseline and six months serum 25(OH)D with LC-MS/MS, both done in frozen samples. This resulted in a change in vitamin D status so that one participant with low serum 25(OH)D in the 6th Tromsø Study and at screening was classified as a case when actually having a high serum 25(OH)D level at baseline. As the participant had consistently low serum 25(OH)D levels during considerable time before inclusion, the impact of an increase during the last weeks before the clamp would probably be of minor importance. It has been reported that an effect of vitamin D supplementation on insulin sensitivity needs more than three months to be evident [113], and exclusion of this participant did not change the results.

5.2.3 Confounding

The term confounding refers to when a non-causal association between a given exposure and an outcome is observed as a result of a third variable associated with both the exposure and the outcome [125]. Confounding is more likely to occur in observational than in experimental epidemiology. By the means of random allocation, the subsamples of the study population are expected to be comparable with regard to the distribution of both known and unknown confounders. In observational studies, multivariate analyses and stratification are the analytic tools that are used to control for confounding effects and to assess effect modification [125].

Thus, in Paper I, the results from the 4th Tromsø study, showing that smokers had higher levels of serum 25(OH)D than non-smokers, could have been a result of confounding factors like differences in BMI, dietary habits, use of supplementation or outdoor time. This was adjusted for, and the results remained very similar. In theory, the differences could still be a result of residual confounding, although the magnitude of the differences in serum 25(OH)D levels between smokers and non-smokers made this unlikely. However, the results were confirmed in the validation study, with the comparison with five other methods clearly showing that the difference found was restricted to the particular assay used in the Tromsø Study.

The seasonal variation in serum 25(OH)D levels offers an extra challenge regarding adjustment in observational studies. This is solved in different ways, from adjusting for season dichotomized in summer and winter, to splitting the year in three, four, six, or in each month. A simulated model has shown that stratifying participants for instance in quartiles based on serum 25(OH)D levels, and thereafter adjusting for season in one way or another, might result in a bias away from nil [120]. The authors suggested stratification within each month, with subsequent pooling of strata. This seems logic, as a person with serum 25(OH)D level of 60 nmol/l might be in the upper quartile in January, but in one of the lower in August. Accordingly, this method was chosen in Paper II.

Confounding by other factors is a more challenging issue in Paper II and in the case-control part of Paper III. The increased HRs of developing type 2 diabetes observed in the participants in the lowest serum 25(OH)D quartile after adjustment for the near obligatory confounders age and sex, were attenuated and turned non-significant after adjustment for BMI. There is a clear inverse association between serum 25(OH)D levels and BMI [12], which is believed to be due to storage and sequestration of vitamin D in fat tissue [11], although increased clearance resulting from the proinflammatory state associated with obesity might

also contribute [2]. However, obesity has also been suggested to result from vitamin D deficiency [130], and in that case, BMI would be an intermediate step between serum 25(OH)D and type 2 diabetes, and not a confounder. If so, it should not be adjusted for. Intervention studies have not supported this hypothesis [131,132], supporting the need of adjusting for BMI. As discussed in section 5.1, the lack of significance after this adjustment could also be the result of lack of power. When analyses were performed stratified by BMI quartiles, we still found an inverse association between serum 25(OH)D and risk of developing type 2 diabetes in the leanest group, indicating that differences in BMI could not fully explain the higher risk of type 2 diabetes with lower serum 25(OH)D levels observed in the main analyses. Importantly, it has been argued that adjustment for BMI is less appropriate than adjustment for fat mass as obtained by DEXA or computer tomography (CT) [62]. These measures were however not available to us.

In the case-control part of Paper III, participants with low serum 25(OH)D levels had lower ISI and higher TG and HbA_{1c} levels than the participants with high serum 25(OH)D levels. To avoid confounding by age, sex and BMI, the inclusion procedure included balancing the two groups in regard of these variables. However, there was other differences between the groups that could both be associated with serum 25(OH)D levels and the outcomes, such as physical activity, fat fish intake and supplementation use. Thus, after adjusting for physical activity, the two groups did not differ in TG and ISI anymore; however, the difference in HbA_{1c} was still significant.

Although a number of variables fulfil the criteria of being a confounder, one caveat is that if we could fully adjust for all exposure variables that affected serum 25(OH)D levels, the remaining difference between cases and controls would in theory approach nil and only represent the genetic variations in serum 25(OH)D levels. Thus, the chance of finding a difference would be markedly reduced, and it is therefore not evident that such adjustment

should be performed. Nonetheless, as we found no effect of supplementation with vitamin D_3 as compared to placebo, a causal relationship was not established.

5.3 External validity

The generalisability of the study findings depends on whether the source population is representative also of other populations. The population of Tromsø is regarded not substantially different from the Norwegian population with respect to age and sex distribution [133]. However, the geographic location at 69ºN will impact the amount and variation of UVB exposure [5]. As long as we have used the biomarker 25(OH)D, which includes both vitamin D intake and UVB mediated production, the associations between measured serum levels and health outcomes should not be influenced by that. In contrast, studies including only vitamin D intake, might be less valid as they do not take into account UVB exposure.

The recruitment procedure to the BMD study might have favored participants with especially high health interest and behavior. This is supported by the observation that the intake of calcium and vitamin D was higher than expected from the general Norwegian population [134]. Accordingly, baseline serum 25(OH)D was also substantially higher (71 ± 23 nmol/l) than the levels found in 1712 never smoking women between 50 and 80 years in the 4th Tromsø Study, where serum 25(OH)D was 50 ± 16 nmol/l (data not published). We can therefore not rule out that the results would have been different in a more vitamin D-deplete population.

In the clamp study, recruitment was based on serum 25(OH)D levels only, and persons with impaired glucose tolerance or diabetes mellitus were excluded. As such, the study can be regarded as an attempt of defining the role of vitamin D deficiency for glucose metabolism in the general population. Inclusion of at risk participants might therefore have yielded other results, as shown by others [113,124]. Although our study was not powered for subgroup analyses,

the directions of the estimates gave no indication of different results in the subgroups of high BMI or high HOMA-IR – both regarded as indices of insulin resistance. The inconsistency in results between these studies may therefore also have other explanations, like ethnicity.

It is a common problem of RCTs that the characteristics of the population included not necessarily reflect the characteristics of the population at risk seen in the real world, limiting the external validity of the findings [135]. Both Paper III and IV had strict exclusion criteria, both for safety reasons and for avoiding interference with the results from comorbidity that might have affected the outcome. This means that the results not necessarily can be applied to more heterogeneous populations. This is most relevant for Paper IV, as Paper III must be regarded an experimental study of healthy participants.

6. Implications and further research

6.1 Smoking and 25(OH)D assays

We have shown that smoking might interfere with serum 25(OH)D measurements, a finding that as far as we are concerned, has not previously been reported. According to the producer, this method was widely used in clinical practice in several countries, where overestimation of serum 25(OH)D levels in smokers must have occurred. This is concerning, since smokers also have increased risk of osteoporotic fractures [37], thus, diagnosis and treatment of vitamin D insufficiency would be of specific importance. In addition, studies reporting use of this assay should be interpreted carefully, as misclassification regarding vitamin D status in smokers is likely to occur. The method is now withdrawn.

We do not know the exact mechanism(s) for this interference, and this would also be very challenging to explore as there are more than 4000 substances present in cigarette smoke [136]. Until the mechanisms are clarified we can therefore not rule out that such interference also might affect other types of analyses and assays. We therefore suggest particular attention to be paid to this problem when analyses are being developed and validated.

6.2 Vitamin D, metabolic disturbances and type 2 diabetes

Consistent with other observational studies [54-64,137,138], we have observed that vitamin D insufficient persons have lower insulin sensitivity and higher HbA_{1c} than vitamin D sufficient controls. In accordance with others [65-67], we have also demonstrated an inverse association between serum 25(OH)D concentrations and the risk of developing type 2 diabetes, which to a large extent seems to be mediated through differences in BMI.

However, associations found in observational studies can not be interpreted as evidence of causality, and there is inconsistency in the literature as there are several studies

which do not report such relations [139,140]. In contrast, an effect on the metabolic parameters in RCTs using vitamin D supplementation, would strongly support a causal role of vitamin D insufficiency in metabolic disturbances. Notably, we found no beneficial effect of supplementation on these endpoints in the intervention trial, which makes a causal relation between vitamin D insufficiency and diabetes less likely.

The results of the intervention study are consistent with other recently published studies. Using low vitamin D doses, and in combination with calcium, no effect on diabetes during seven years of follow-up was observed in more than 33,000 women in the Women's Health Initiative as compared to placebo (HR (95% CI) 1.01 (0.94-1.10)) [141]. Likewise, in the RECORD trial, there was no effect of vitamin D supplementation with or without calcium on development of diabetes in more than 5000 older persons during a follow-up period of 2.5 years (odds ratio (OR) (95% CI) in intention-to-treat analyses: 1.11 (0.77-1.62), and in per-protocol analyses: 0.68 (0.40-1.16)) [142]. The results of these two studies, which originally were designed for skeletal purposes, have been questioned as vitamin D doses used and compliance may have been too low. However, also studies using high dose treatment (40,000 IU/w, or 100,000 or 200,000 IU as one single dose) have failed to improve glycemic control in 36 and 61 already diabetic patients [143,144], and similarly did 100,000 IU given twice not improve insulin sensitivity or fasting glucose in vitamin D insufficient persons without diabetes [145]. The last study was small (n=33), had no control group, and was limited by short duration (four weeks).

As there has been considerable interest in vitamin D insufficiency as an explanation for the increasing prevalence of type 2 diabetes, our results are therefore important, indicating that there is no need for changing the recommendations of vitamin D intake in the general population. However, there is still a need for more studies including participants with both high risk of diabetes and established vitamin D insufficiency. Adequately powered long-term

studies with diabetes as an endpoint should be performed before drawing a final conclusion. We cannot preclude that the serum 25(OH)D level achieved in the intervention study was above the ideal level for glucose metabolism, assuming an U-shaped relation between glucose dysregulation and serum 25(OH)D levels. Although speculative, such an association has recently been suggested by others [140], and has also been observed in relation to frailty [146], some types of cancer [147], and mortality [148]. Finally, the results may be different in other populations, as significant effects of supplementation on insulin sensitivity recently have been reported in South-Asians in particular [113,124].

Serum lipid levels are associated with both insulin resistance and cardiovascular disease [149]. Consistent with reports from other studies, we found lower TG levels in participants with high serum 25(OH)D levels [64,137,138]. However, supplementation with high dose vitamin D_3 to those with low serum 25(OH)D levels did not affect the TG levels, or any other lipid measurements. This is in accordance with most other intervention studies [113,124,144,150-152], although one study found a concomitant reduction in TG levels and an increase in low density lipoprotein levels after one year of daily supplementation with 3332 IU vitamin D_3 [132]. A limitation with these studies, including ours, is that the participants were not included based on presence of hyperlipidemia or hypertriglyceridemia; thus, RCTs using vitamin D in participants with such traits should be performed.

6.3 Vitamin D and BMD

Our results suggest that high and standard dose vitamin D are equally efficient in improving or maintaining BMD in mainly vitamin D-replete postmenopausal women with reduced BMD, and that bone turnover markers were more reduced using standard dose, indicating that this dose was the most effective. To be interpreted with care, the subgroup analyses indicating better effect of standard dose on BMD in those with higher baseline BMD and lower PTH,

should prompt alertness when using high dose vitamin D for any purpose. Again, the results add support to the current guidelines where a daily intake of 800 IU vitamin D is recommended to persons with osteoporosis [83].

One important limitation of the study is the use of the intermediate endpoint BMD instead of the clinical relevant endpoint fracture. BMD has been shown to predict fracture with the same strength as hypertension predicts stroke, and better than serum cholesterol predicts coronary heart disease [153], but still, BMD forms only one component of bone strength and fracture risk. Recently, the use of BMD as an intermediate endpoint in calcium studies (with or without vitamin D) was questioned [154]. Vitamin D has been shown to reduce risk of falling [155], which might represent another mechanism for fracture reduction not reflected by BMD changes.

Several authors argue that a serum 25(OH)D level >50 nmol/l is sufficient for bone health [71,83]. It is therefore interesting that even with a higher than expected baseline level of 70 nmol/l, and with an already sufficient calcium intake, serum PTH decreased substantially in both groups, bone turnover was reduced, and BMD was maintained or slightly increased. This might indicate that a serum level of at least 90 nmol/l (as achieved in the standard dose group) is more beneficial than lower levels. However, consistent with other studies of vitamin D_3 and calcium supplementation [97,98,156-158], the BMD gain was small, and the clinical importance uncertain. Similarly, our research group found no differences between high dose vitamin D_3 (40,000 IU/w), intermediate dose (20,000 IU/w) or placebo regarding BMD or bone turnover markers when given to 312 overweight or obese participants coadministrated with calcium 500 mg/d, and the changes in BMD after 12 months were only marginal [159]. Another study including 71 patients with multiple sclerosis, reported no difference in bone loss in those given 20,000 IU/w vitamin D_3 and 500 mg/d calcium versus calcium alone for 96 weeks [160]. In contrast, in 45 nursing home residents with a baseline serum 25(OH)D of 28.5 ± 10.8

nmol/l, BMD at the hip increased 23% after one year supplementation with cholecalciferol 5000 IU/d, resulting in a serum 25(OH)D of 125.6 ± 38.8 nmol/l [161]. This impressive increase might have been due to mineralization of osteoid caused by osteomalacia.

It could be argued that the duration of our study (one year) was too short for finding an effect on BMD. However, when bone turnover is reduced by vitamin D treatment, the secondary mineralization, which usually takes about six months to complete, will improve, by which the proportion of bone with high mineral content increases. This effect will for the greatest part be seen during the first year of therapy [71]. Accordingly, in the Amsterdam Vitamin D Study, where 400 IU vitamin D_3 or placebo was given to 348 women >70 years, BMD in the femoral neck increased 1.9% in the first study year and only additional 0.2% the next year [158]. Also, a positive effect on lumbar spine BMD in 240 Danish women treated with 1000 mg calcium and 560 IU vitamin D/d versus placebo for two years was mainly seen during the first year [156]. Inclusion in our study of a substantial proportion of participants already using vitamin D and calcium supplementation might therefore have diluted an effect. We found similar results when these subjects were excluded, although the study was not powered for such subgroup analyses.

Consistent with previous meta-analyses [102,103], two recently published meta-analyses [162,163] found no fracture reduction whatever vitamin D dose used when given alone (RR (95% CI) 1.01 (0.92-1.12)) [163], while there was a modest fracture reduction of vitamin D irrespective of dose when given together with calcium (RR (95% CI) 0.92 (0.86-0.99)) [163]. Both meta-analyses underscored the need for intervention trials using high doses. Our study, combined with the results from a recently published Australian study showing an increase in fracture rates in participants randomized to an annual dose of 500,000 IU cholecalciferol for 3-5 years as compared to placebo [164], do not support the use of high doses in populations with increased risk of osteoporotic fractures, neither alone nor with calcium.

Interestingly, VDR polymorphisms might modify the effect of vitamin D supplementation on BMD [165]. As materials for genetic analyses were collected in both intervention studies, this can be studied more closely in the future.

6.4 Vitamin D doses, achieved serum 25(OH)D levels, and safety

In the two intervention trials, there were similar numbers of adverse events in both the treatment and the placebo groups. Although not statistically significant, there were more hypercalcemias in the high than in the standard dose group in the BMD study, while no hypercalcemias were observed after six months in the clamp study. This most likely reflects the impact of concomitant calcium supplementation, and not so much achieved serum 25(OH)D levels, as there was such cases both in the standard dose group (achieved serum 25(OH)D level 89 nmol/l), and the high dose group (achieved level 185 nmol/l) in the BMD study, but not in the treatment group in the clamp study (achieved level 142 nmol/l). Also, hypercalcemias in the BMD study occurred at a wide range of serum 25(OH)D concentrations, as shown in Table 3.

The ionized calcium concentration, which shows free calcium regardless of the amount of binding protein, was also measured in the BMD study, and after an initial increase, the levels stabilized with no statistically significant differences between the standard and high dose groups (Fig. 4).

Other complications related to vitamin D toxicity results from longstanding hypercalciuria or hypercalcemia, leading to kidney stones or vascular and soft tissue calcifications [166]. One participant in the high dose group in the BMD study experienced back pain and hematuria during an angiography with a percutaneous cardiac intervention procedure, and although no calcifications were seen on a CT taken thereafter, the diagnosis can not be excluded. There was one case of unstable angina pectoris in the standard dose

group, and two cases of transient ischemic attack in the high dose group in the BMD study, both occurring early (after two and five months in the trial, measured serum 25(OH)D were then 146 and 150 nmol/l, respectively, serum calcium in normal range). We find it unlikely that these events should be related to the study medication, however, concern has recently been raised towards a possible increased risk of cardiovascular morbidity when using calcium supplements, with or without vitamin D supplementation [167].

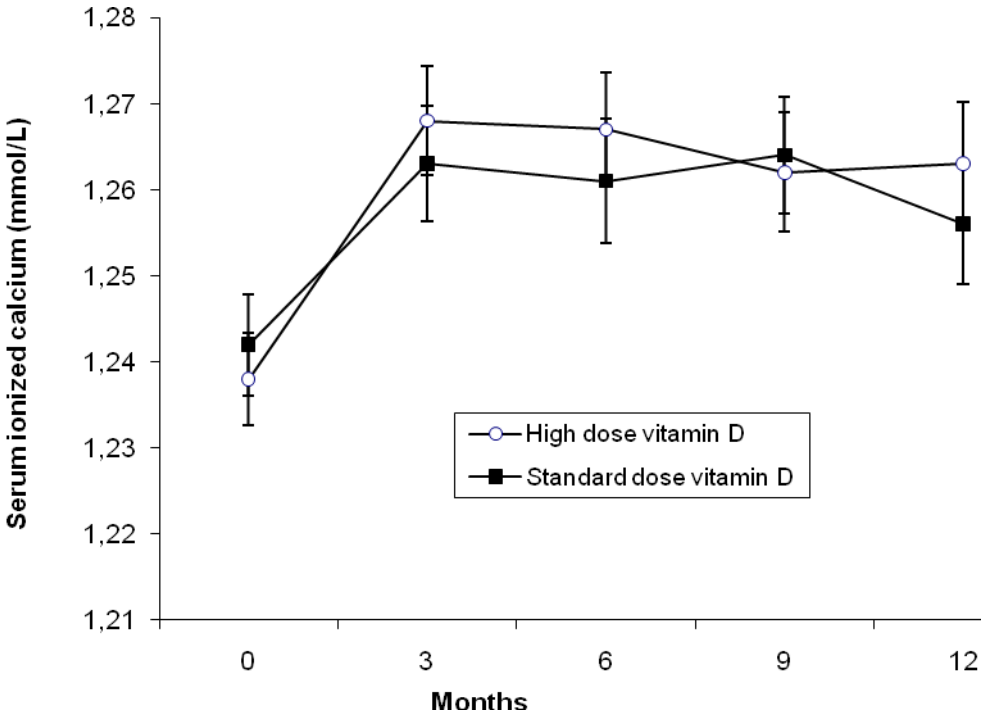

Fig. 4 Serum ionized calcium levels at baseline, 3, 6, 9 and 12 months in 149 participants receiving high dose vitamin D_3 (6500 IU/d) and 148 participants receiving standard dose (800 IU/d). There were no significant differences in serum ionized calcium levels between the groups at any time point.

Table 3 Characteristics at screening and at event of participants with serum calcium >2.59 mmol/l during the study.

Characteristics at screening					Treat-ment [a]	Event characteristics					Retest value Serum-calcium (mmol/l)	Actions [b]
Age (years)	BMI (kg/cm^2)	Serum calcium (mmol/l)	Plasma PTH (pmol/l)	Serum 25(OH)D (nmol/l)		Month	Serum calcium (mmol/l)	Serum ionized calcium (mmol/l)	Plasma PTH (pmol/l)	Serum 25(OH)D (nmol/l)		
51	25.4	2.34	3.5	61	HD	3	2.77	.	1.3	188	2.39	E
66	26.2	2.29	3.7	59	HD	3	2.63	1.31	2.5	144	2.56	C
56	24.8	2.45	6.2	45	HD	3	2.61	1.33	2.9	178	2.45	C
60	30.1	2.25	5.6	92	HD	6	2.72	1.34	2.9	203	2.46	C
55	21.8	2.20	3.5	64	SD	6	2.65	1.34	1.3	101	2.51	C
65	22.5	2.43	6.2	82	HD	6	2.63	1.36	3.3	190	2.54	C
69	26.4	2.45	.	50	SD	6	2.62	1.38	3.0	88	2.45	C
67	27.4	2.35	8.5	37	SD	6	2.62	1.39	3.7	64	2.40	C
68	28.6	2.44	8.3	35	HD	6	2.60	.	6.3	137	2.42	C
57	23.9	2.45	4.4	48	HD	12	2.63	1.33	3.7	175	.	F
67	28.5	2.31	10.2	26	SD	12	2.62	1.40	3.9	91	2.57	F
61	29.2	2.49	4.0	107	HD	12	2.62	1.34	2.8	256	2.39	F
66	32.5	2.45	2.9	52	HD	12	2.61	1.31	1.9	204	2.28	F

HD; high dose, SD; standard dose, E; excluded, C; continued in study, F; finished the study.

Further, the doses of vitamin D_3 used in the intervention trials were substantially higher than those used in most clinical settings. The same dose (40,000 IU/w) and an intermediate dose (20,000 IU/w) have been used in a one year study of overweight and obese participants [131]. When comparing the participants receiving vitamin D_3 in the three studies as shown in Table 4, we find an increase in serum 25(OH)D of 0.55-0.90 nmol/l for each microgram vitamin D_3 given. This is quite similar to previous reports [116,168], which also have shown that the increase in serum 25(OH)D level will be higher in those starting out low, and lower in those starting out high [168]. Therefore, it might seem surprising that the increase in serum 25(OH)D per given microgram vitamin D_3 was exactly the same in the vitamin D replete participants in the BMD study as in the vitamin D deplete participants in the clamp study. This might be explained by a higher BMI in the clamp study, as higher doses will be needed to achieve the same serum 25(OH)D levels in obese than in non-obese subjects [12]. This is consistent with the lower increase in the overweight study in spite of starting out with intermediate serum 25(OH)D levels (Table 4). Of importance is probably also the addition of calcium supplementation in the BMD study, as calcium is believed to have a vitamin D sparing effect (and vice versa). Thus, higher $1,25(OH)_2D$ resulting from higher serum PTH in response to low calcium, increases 25(OH)D turnover and vice versa [71].

As seen from the SDs of achieved serum 25(OH)D level in Fig. 5, the variation was large even if the same dose was given. This is also observed by others [168]. It might very well be that a more relevant approach in future intervention studies using vitamin D would be to define the serum 25(OH)D targets to be achieved rather than the vitamin D doses to be used. This would of course be more costly and time-consuming, as consecutively serum 25(OH)D measurements followed by individual dose-adjustments would be necessary. Also, the need for standardized and precise serum 25(OH)D analyses is obvious. However, if the objective is to answer the still unsettled question what the ideal serum 25(OH)D level for multiple health

outcomes is, we find that to be the most appropriate approach. Reasonable serum 25(OH)D targets in such studies, based on own and others' findings, would be for instance 50-60 nmol/l, 75-90 nmol/l and 110-125 nmol/l.

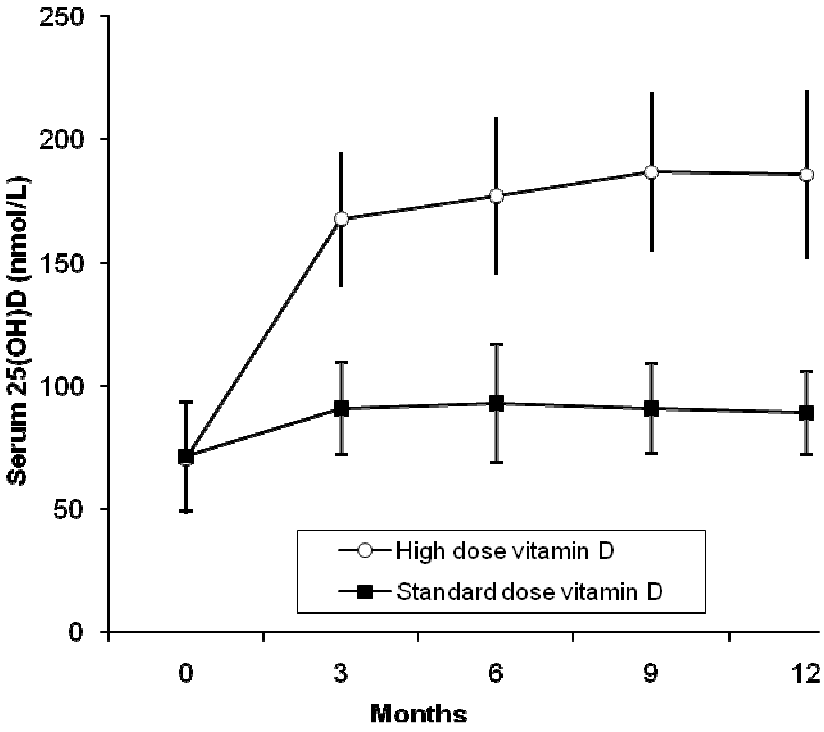

Fig. 5 Serum 25(OH)D (mean and SD) at baseline, 3, 6, 9 and 12 months in 149 participants receiving high dose cholecalciferol (6500 IU/d) and 148 participants receiving standard dose (800 IU/d). There was a significant difference in serum 25(OH)D levels between the groups at 3, 6, 9 and 12 months ($p<0.01$).

Table 4 Some characteristics of participants receiving high dose vitamin D_3

	BMD study (Paper IV)		Clamp study (Paper III)	Overweight study [131]	
	High dose	Standard dose		High dose	Medium dose
N	135	140	49	114	104
Intervention length (months)	12	12	6	12	12
Average daily vitamin D dose (IU (µg))	6500 (162.5)	800 (20)	5700 (142.5)	5700 (142.5)	2850 (71.3)
Calcium supplementation	1000 mg	1000 mg	0	500 mg	500 mg
BMI (kg/cm^2)	24.9 ± 3.4	24.6 ± 3.3	27.2 ± 3.1	34.6 ± 3.9	34.1 ± 3.6
Age (years)	62.8 ± 7.8	63.4 ± 6.9	51.5 ± 8.8	47.7 ± 11.1	48.8 ± 11.8
Proportion women (%)	100	100	45	59	62
Baseline serum 25(OH)D (nmol/l)	71 ± 23[a]	71 ± 22[a]	42 ± 14[a]	61 ± 21[b]	58 ± 22[b]
Final serum 25(OH)D (nmol/l)	186 ± 34[a]	89 ± 17[a]	143 ± 25[a]	140 ± 35[b]	101 ± 21[b]
Baseline PTH (pmol/l)	5.0 ± 1.6	5.1 ± 1.7	6.1 ± 1.4	5.1 ± 1.6	5.5 ± 1.8
Final PTH (pmol/l)	3.8 ± 1.1	4.5 ± 1.5	5.1 ± 1.3	4.2 ± 1.5	4.7 ± 1.7
Baseline serum calcium (mmol/l)	2.36 ± 0.09	2.36 ±0.07	2.26 ± 0.07	2.30 ± 0.11	2.32 ± 0.11
Final serum calcium (mmol/l)	2.38 ± 0.09	2.36 ± 0.09	2.26 ± 0.07	2.30 ±0.08	2.30 ± 0.07
Delta[c] serum 25(OH)D (nmol/l)/dose (microgram/d)	0.71	0.90	0.71	0.55	0.60

[a] measured by LC-MS/MS, [b] measured by RIA (DiaSorin), [c]final serum 25(OH)D level minus baseline level

A recently released report from Institute of Medicine in the US, has concluded that there are no yet proven benefits of achieving a certain amount of vitamin D except for bone health. Importantly, based on several reports on U-shaped associations between serum 25(OH)D levels and adverse health outcomes, they concluded that higher serum levels than 125 nmol/l should be avoided [166]. This is in contrast to previous safety reviews, where levels have been assumed to be safe up to 375-750 nmol/l [2,117,118,169,170]. Interestingly, the report also suggests an upper limit of 4000 IU/d, implying that this dose, although not generally recommended, can be considered to be safe for anyone. From Table 4 we must assume that such a dose would inevitable lead to serum 25(OH)D levels >125 nmol/l in several of the participants. Nonetheless, taken together, and with the limitations discussed in the previous chapters, our results do not give any support for raising the serum 25(OH)D levels higher than 90 nmol/l.

7. Concluding remarks

The results presented in this thesis illustrate that there are still important methodological challenges in the assessment of a person's vitamin D status. Extensive work for international standardization of 25(OH)D measurements is ongoing, and will hopefully improve the basis of decision-making regarding recommendations of vitamin D intake in the population. Although a huge number of observational studies, including ours, report associations between higher serum 25(OH)D levels and beneficial health outcomes, these studies do not provide sufficient evidence for increasing the intake. Our results from the intervention trials do not challenge the current recommendations regarding vitamin D intake or levels in the general population or in persons with increased risk of osteoporotic fractures. Further carefully designed intervention studies, preferably using serum 25(OH)D targets, are however needed before we can conclude regarding vitamin D intake – for whom, when and how much.

Errata

Paper I

The following erratum has been published (Eur J Endocrinol 2010;163:965):

The authors and the journal apologise for errors in the Introduction section of this paper published in the European Journal of Endocrinology 2010 vol 163 pp 339–348. Lines 11–14 of the Introduction section should read as follows: “This reflects the amount of vitamin D ingested from food (ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3)) and the amount of vitamin D produced in the skin during ultraviolet B (UVB) exposure (vitamin D_3).”, and not as published.

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Paper I

Paper II

Paper III

Paper IV

Appendix A

Questionnaires from the 4th Tromsø Study

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

EGEN 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

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 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 ❑
- 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	❑ 308	❑	❑ 1
1-2 ganger i måneden	❑	❑	❑ 2
Omtrent 1 gang i uken	❑	❑	❑ 3
2-3 ganger i uken	❑	❑	❑ 4
Omtrent hver dag	❑	❑	❑ 5 310

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

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 ❑

Dato for utfylling av skjema: ..... 18 Dag ...../ Mnd ...../ År .....

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	_____ kg	

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

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 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

Hvor mange måltider spiser du vanligvis daglig (middag og brødmåltid)? ..... 302 _____ Antall

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

Appendix B

Questionnaire from the 6th Tromsø Study

Tromsø-undersøkelsen

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Du kan ikke bruke komma, bruk blokkbokstaver.

2007 – 2008 KONFIDENSIELT

HELSE OG SYKDOMMER

1 **Hvordan vurderer du din egen helse sånn i alminnelighet?**

- ☐ Meget god
- ☐ God
- ☐ Verken god eller dårlig
- ☐ Dårlig
- ☐ Meget dårlig

2 **Hvordan synes du at helsen din er sammenlignet med andre på din alder?**

- ☐ Mye bedre
- ☐ Litt bedre
- ☐ Omtrent lik
- ☐ Litt dårligere
- ☐ Mye dårligere

3 **Har du eller har du hatt?**

	Ja	Nei	Alder første gang
Hjerteinfarkt	☐	☐	
Angina pectoris *(hjertekrampe)*	☐	☐	
Hjerneslag/hjerneblødning	☐	☐	
Hjerteflimmer *(atrieflimmer)*	☐	☐	
Høyt blodtrykk	☐	☐	
Beinskjørhet *(osteoporose)*	☐	☐	
Astma	☐	☐	
Kronisk bronkitt/emfysem/KOLS	☐	☐	
Diabetes	☐	☐	
Psykiske plager *(som du har søkt hjelp for)*	☐	☐	
Lavt stoffskifte	☐	☐	
Nyresykdom, unntatt urinveisinfeksjon	☐	☐	
Migrene	☐	☐	

4 **Har du langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer?**

☐ Ja ☐ Nei

5 **Hvor ofte har du vært plaget av søvnløshet de siste 12 måneder?**

- ☐ Aldri, eller noen få ganger
- ☐ 1-3 ganger i måneden
- ☐ Omtrent 1 gang i uken
- ☐ Mer enn 1 gang i uken

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

	Ikke plaget	Litt plaget	Ganske mye	Veldig mye
Plutselig frykt uten grunn	☐	☐	☐	☐
Føler deg redd eller engstelig	☐	☐	☐	☐
Matthet eller svimmelhet	☐	☐	☐	☐
Føler deg anspent eller oppjaget	☐	☐	☐	☐
Lett for å klandre deg selv	☐	☐	☐	☐
Søvnproblemer	☐	☐	☐	☐
Nedtrykt, tungsindig	☐	☐	☐	☐
Følelse av å være unyttig, lite verd	☐	☐	☐	☐
Følelse av at alt er et slit	☐	☐	☐	☐
Følelse av håpløshet mht. framtida	☐	☐	☐	☐

BRUK AV HELSETJENESTER

7 **Har du i løpet av de siste 12 måneder vært hos:** Hvis JA; Hvor mange ganger?

	Ja	Nei	Ant ggr
Fastlege/allmennlege	☐	☐	
Psykiater/psykolog	☐	☐	
Legespesialist utenfor sykehus *(utenom fastlege/allmennlege/psykiater)*	☐	☐	
Fysioterapeut	☐	☐	
Kiropraktor	☐	☐	
Annen behandler *(homøopat, akupunktør, fotsoneterapeut, naturmedisiner, håndspålegger, healer, synsk el.l)*	☐	☐	
Tannlege/tannpleier	☐	☐	

8 **Har du i løpet av de siste 12 måneder vært på sykehus?**

	Ja	Nei	Ant ggr
Innlagt på sykehus	☐	☐	
Konsultasjon ved sykehus uten innleggelse;			
Ved psykiatrisk poliklinikk	☐	☐	
Ved annen sykehuspoliklinikk	☐	☐	

9 **Har du gjennomgått noen form for operasjon i løpet av de siste 3 årene?**

☐ Ja ☐ Nei

BRUK AV MEDISINER

10 **Bruker du, eller har du brukt, noen av følgende medisiner?** (Sett ett kryss for hver linje)

	Aldri brukt	Nå	Før	Alder første gang
Medisin mot høyt blodtrykk	☐	☐	☐	
Kolesterolsenkende medisin	☐	☐	☐	
Medisin mot hjertesykdom	☐	☐	☐	
Vanndrivende medisin	☐	☐	☐	
Medisin mot beinskjørhet *(osteoporose)*	☐	☐	☐	
Insulin	☐	☐	☐	
Diabetesmedisin *(tabletter)*	☐	☐	☐	
Stoffskiftemedisinene Thyroxin/levaxin	☐	☐	☐	

11 **Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner?** (Sett ett kryss pr linje)

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende på resept	☐	☐	☐	☐
Smertestillende reseptfrie	☐	☐	☐	☐
Sovemidler	☐	☐	☐	☐
Beroligende medisiner	☐	☐	☐	☐
Medisin mot depresjon	☐	☐	☐	☐

12 **Skriv ned alle medisiner – både de med og uten resept – som du har brukt regelmessig i siste 4 ukers periode.** (Ikke regn med vitaminer, mineraler, urter, naturmedisin, andre kosttilskudd etc.)

Får du ikke plass til alle medisiner, bruk eget ark.

VED FRAMMØTE vil du bli spurt om du har brukt antibiotika eller smertestillende medisiner de siste 24 timene. Om du har det, vil vi be om at du oppgir preparat, styrke, dose og tidspunkt

FAMILIE OG VENNER

13 **Hvem bor du sammen med?** (Sett kryss for hvert spørsmål og angi antall)

	Ja	Nei	Antall
Ektefelle/samboer	☐	☐	
Andre personer over 18 år	☐	☐	
Personer under 18 år	☐	☐	

14 **Kryss av for de slektninger som har eller har hatt**

	Foreldre	Barn	Søsken
Hjerteinfarkt	☐	☐	☐
Hjerteinfarkt før fylte 60 år	☐	☐	☐
Angina pectoris *(hjertekrampe)*	☐	☐	☐
Hjerneslag/hjerneblødning	☐	☐	☐
Beinskjørhet *(osteoporose)*	☐	☐	☐
Magesår/tolvfingertarmsår	☐	☐	☐
Astma	☐	☐	☐
Diabetes	☐	☐	☐
Demens	☐	☐	☐
Psykiske plager	☐	☐	☐
Rusproblemer	☐	☐	☐

15 **Har du nok venner som kan gi deg hjelp når du trenger det?**

☐ Ja ☐ Nei

16 **Har du nok venner som du kan snakke fortrolig med?**

☐ Ja ☐ Nei

17 **Hvor ofte tar du vanligvis del i foreningsvirksomhet som for eksempel syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?**

☐ Aldri, eller noen få ganger i året
☐ 1-2 ganger i måneden
☐ Omtrent 1 gang i uken
☐ Mer enn en gang i uken

ARBEID, TRYGD OG INNTEKT

18 **Hva er din høyeste fullførte utdanning?** (Sett ett kryss)

☐ Grunnskole, framhaldsskole eller folkehøyskole
☐ Yrkesfaglig videregående, yrkesskole eller realskole
☐ Allmennfaglig videregående skole eller gymnas
☐ Høyskole eller universitet, mindre enn 4 år
☐ Høyskole eller universitet, 4 år eller mer

19 **Hva er din hovedaktivitet?** (Sett ett kryss)

☐ Yrkesaktiv heltid
☐ Yrkesaktiv deltid
☐ Arbeidsledig
☐ Hjemmeværende
☐ Pensjonist/trygdet
☐ Student/militærtjeneste

20 **Mottar du noen av følgende ytelser?**

- ☐ Alderstrygd, førtidspensjon (AFP) eller etterlattepensjon
- ☐ Sykepenger (er sykemeldt)
- ☐ Rehabiliterings-/attføringspenger
- ☐ Uføreytelse/pensjon, hel
- ☐ Uføreytelse/pensjon, delvis
- ☐ Dagpenger under arbeidsledighet
- ☐ Overgangstønad
- ☐ Sosialhjelp/-stønad

21 **Hvor høy var husholdningens samlede bruttoinntekt siste år?** Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende.

- ☐ Under 125 000 kr
- ☐ 125 000-200 000 kr
- ☐ 201 000-300 000 kr
- ☐ 301 000-400 000 kr
- ☐ 401 000-550 000 kr
- ☐ 551 000-700 000 kr
- ☐ 701 000 -850 000 kr
- ☐ Over 850 000 kr

22 **Arbeider du utendørs minst 25 % av tiden, eller i lokaler med lav temperatur, som for eksempel lager-/industrihaller?**

- ☐ Ja
- ☐ Nei

FYSISK AKTIVITET

23 **Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt?**

- ☐ For det meste stillesittende arbeid *(f.eks. skrivebordsarbeid, montering)*
- ☐ Arbeid som krever at du går mye *(f.eks ekspeditørarbeid, lett industriarbeid, undervisning)*
- ☐ Arbeid der du går og løfter mye *(f.eks postbud, pleier, bygningsarbeider)*
- ☐ Tungt kroppsarbeid

24 **Angi bevegelse og kroppslig anstrengelse i din fritid. Hvis aktiviteten varierer meget f eks mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året.** (Sett kryss i den ruta som passer best)

- ☐ Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse
- ☐ Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uken *(her skal du også regne med gang eller sykling til arbeidsstedet, søndagsturer med mer)*
- ☐ Driver mosjonsidrett, tyngre hagearbeid, snømåking e.l. *(merk at aktiviteten skal vare minst 4 timer i uka)*
- ☐ Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka

25 **Hvor ofte driver du mosjon?** (Med mosjon mener vi at du f.eks går en tur, går på ski, svømmer eller driver trening/idrett)

- ☐ Aldri
- ☐ Sjeldnere enn en gang i uken
- ☐ En gang i uken
- ☐ 2-3 ganger i uken
- ☐ omtrent hver dag

26 **Hvor hardt mosjonerer du da i gjennomsnitt?**

- ☐ Tar det rolig uten å bli andpusten eller svett.
- ☐ Tar det så hardt at jeg blir andpusten og svett
- ☐ Tar meg nesten helt ut

27 **Hvor lenge holder du på hver gang i gjennomsnitt ?**

- ☐ Mindre enn 15 minutter
- ☐ 15-29 minutter
- ☐ 30 minutter – 1 time
- ☐ Mer enn 1 time

ALKOHOL OG TOBAKK

28 **Hvor ofte drikker du alkohol?**

- ☐ Aldri
- ☐ Månedlig eller sjeldnere
- ☐ 2-4 ganger hver måned
- ☐ 2-3 ganger pr. uke
- ☐ 4 eller flere ganger pr.uke

29 **Hvor mange enheter alkohol** (en øl, et glass vin, eller en drink) **tar du vanligvis når du drikker?**

- ☐ 1-2
- ☐ 3-4
- ☐ 5-6
- ☐ 7-9
- ☐ 10 eller flere

30 **Hvor ofte drikker du 6 eller flere enheter alkohol ved en anledning?**

- ☐ aldri
- ☐ sjeldnere enn månedlig
- ☐ månedlig
- ☐ ukentlig
- ☐ daglig eller nesten daglig

31 **Røyker du av og til, men ikke daglig?**

- ☐ Ja
- ☐ Nei

32 **Har du røykt/røyker du daglig?**

- ☐ Ja, nå
- ☐ Ja, tidligere
- ☐ Aldri

33 **Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet?**

Antall år ☐☐

34 **Hvis du røyker daglig nå eller har røykt tidligere: Hvor mange sigaretter røyker eller røykte du vanligvis daglig?**

Antall sigaretter ☐☐

35 **Hvor gammel var du da du begynte å røyke daglig?**

Antall år ☐☐

36 **Hvor mange år til sammen har du røykt daglig?**

Antall år ☐☐

37 **Bruker du, eller har du brukt, snus eller skrå?**

- ☐ Nei, aldri
- ☐ Ja, men jeg har sluttet
- ☐ Ja, av og til
- ☐ Ja, daglig

KOSTHOLD

38 **Spiser du vanligvis frokost hver dag?**

☐ Ja ☐ Nei

39 **Hvor mange enheter frukt og grønnsaker spiser du i gjennomsnitt per dag?** (Med enhet menes f.eks. en frukt, glass juice, potet, porsjon grønnsaker)

Antall enheter ☐☐

40 **Hvor mange ganger i uken spiser du varm middag?**

Antall ☐☐

41 **Hvor ofte spiser du vanligvis disse matvarene?**
(Sett ett kryss pr linje)

	0-1 g pr. mnd	2-3 g pr.mnd	1-3 g pr.uke	4-6 g pr.uke	1-2 g pr. dag
Poteter	☐	☐	☐	☐	☐
Pasta/ris	☐	☐	☐	☐	☐
Kjøtt *(ikke kvernet)*	☐	☐	☐	☐	☐
Kvernet kjøtt *(pølser, hamburger o.l)*	☐	☐	☐	☐	☐
Grønnsaker, frukt, bær	☐	☐	☐	☐	☐
Mager fisk	☐	☐	☐	☐	☐
Feit fisk *(f.eks.laks, ørret, makrell, sild, kveite,uer)*	☐	☐	☐	☐	☐

42 **Hvor mye drikker du vanligvis av følgende?**
(Sett ett kryss pr. linje)

	Sjelden/ aldri	1-6 glass pr. uke	1 glass pr. dag	2-3 glass pr. dag	4 glass el. mer pr. dag
Melk, kefir, yoghurt	☐	☐	☐	☐	☐
Fruktjuice	☐	☐	☐	☐	☐
Brus/leskedrikker med sukker	☐	☐	☐	☐	☐

43 **Hvor mange kopper kaffe og te drikker du daglig?**
(sett 0 for de typene du ikke drikker daglig)

	Antall kopper
Filterkaffe	☐☐
Kokekaffe/presskanne	☐☐
Annen kaffe	☐☐
Te	☐☐

44 **Hvor ofte spiser du vanligvis fiskelever?**
(For eksempel i mølje)

☐ Sjelden/aldri ☐ 1-3 g i året ☐ 4-6 g i året
☐ 7-12 g i året ☐ Oftere

45 **Bruker du følgende kosttilskudd?**

	Daglig	Iblant	Nei
Tran, trankapsler	☐	☐	☐
Omega 3 kapsler *(fiskeolje,selolje)*	☐	☐	☐
Kalktabletter	☐	☐	☐

SPØRSMÅL TIL KVINNER

46 **Er du gravid nå?**

☐ Ja ☐ Nei ☐ Usikker

47 **Hvor mange barn har du født?**

Antall ☐☐

48 **Hvis du har født, fyll ut for hvert barn: fødselsår og vekt samt hvor mange måneder du ammet.**
(Angi så godt som du kan)

Barn	Fødselsår	Fødselsvekt i gram	Ammet ant.mnd
1	☐☐☐☐	☐☐☐☐	☐☐
2	☐☐☐☐	☐☐☐☐	☐☐
3	☐☐☐☐	☐☐☐☐	☐☐
4	☐☐☐☐	☐☐☐☐	☐☐
5	☐☐☐☐	☐☐☐☐	☐☐
6	☐☐☐☐	☐☐☐☐	☐☐

49 **Har du i forbindelse med svangerskap hatt for høyt blodtrykk?**

☐ Ja ☐ Nei

50 **Hvis Ja, i hvilket svangerskap?**

☐ Første ☐ Senere

51 **Har du i forbindelse med svangerskap hatt protein (eggehvite) i urinen?**

☐ Ja ☐ Nei

52 **Hvis Ja, i hvilket svangerskap?**

☐ Første ☐ Senere

53 **Ble noen av disse barna født mer enn en måned for tidlig (før termin) pga. svangerskapsforgiftning?**

☐ Ja ☐ Nei

54 **Hvis Ja, hvilke(t) barn**

Barn 1	Barn 2	Barn 3	Barn 4	Barn 5	Barn 6
☐	☐	☐	☐	☐	☐

55 **Hvor gammel var du da du fikk menstruasjon første gang?**

Antall år ☐☐

56 **Bruker du for tiden reseptpliktige legemidler som påvirker menstruasjonen?**

P-pille, hormonspiral eller lignende ☐ Ja ☐ Nei
Hormonpreparat for overgangs-alderen ☐ Ja ☐ Nei

VED FRAMMØTE vil du få utfyllende spørsmål om menstruasjon og eventuell bruk av hormoner. Skriv gjerne ned på et papir navn på hormonpreparater du har brukt, og ta det med deg. Du vil også bli spurt om din menstruasjon har opphørt og eventuelt når og hvorfor.

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Appendix C

International Physical Activity Questionnaires (IPAQ)

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRES

IPAQ: SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health-related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken in 12 countries (14 sites) across 6 continents during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages. IPAQ is suitable for use in regional, national and international monitoring and surveillance systems and for use in research projects and public health program planning and evaluation. International collaboration on IPAQ is on-going and an international prevalence study is under development.

Using IPAQ

Worldwide use of the IPAQ instruments for monitoring and research purposes is encouraged.

It is strongly recommended, to ensure data quality and comparability and to facilitate the development of an international database on health-related physical activity, that

- no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments,
- if additional questions on physical activity are needed they should follow the IPAQ items,
- translations are undertaken using the prescribed back translation methods (see website)
- new translated versions of IPAQ be made available to others via the web site to avoid duplication of effort and different versions in the same language,
- a copy of IPAQ data from representative samples at national, state or regional level be provided to the IPAQ data storage center for future collaborative use (with permission) by those who contribute.

More Information

Two scientific publications presenting the methods and the pooled results from the IPAQ reliability and validity study are due out in 2002.

More detailed information on the IPAQ process, the research methods used in the development of the IPAQ instruments, the use of IPAQ, the published papers and abstracts and the on-going international collaboration is available on the IPAQ web-site.

www.ipaq.ki.se

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

IPAQ: SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS

NOTE: EXAMPLES OF ACTIVITIES MAY BE REPLACED BY CULTURALLY RELEVANT EXAMPLES WITH THE SAME METS VALUES (SEE AINSWORTH *ET AL*., 2000).

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. This is part of a large study being conducted in many countries around the world. Your answers will help us to understand how active we are compared with people in other countries.

The questions are about the time you spent being physically active in the last 7 days. They include questions about activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Your answers are important.

Please answer each question even if you do not consider yourself to be an active person.

THANK YOU FOR PARTICIPATING.

In answering the following questions,

- **vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder that normal.

- **moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder that normal.

1a. During the last 7 days, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling,?

Think about *only* those physical activities that you did for at least 10 minutes at a time.

_____ **days per week** ⇨

or

☐ **none**

1b. How much time in total did you usually spend on one of those days doing vigorous physical activities*?*

_____ **hours** _____ **minutes**

2a. Again, think *only* about those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ **days per week** ⇨

or

☐ **none**

2b. How much time in total did you usually spend on one of those days doing moderate physical activities*?*

_____ **hours** _____ **minutes**

3a. During the last 7 days, on how many days did you **walk** for at least 10 minutes at a time? This includes walking at work and at home, walking to travel from place to place, and any other walking that you did solely for recreation, sport, exercise or leisure.

_____ **days per week** ⇨

or

☐ **none**

3b. How much time in total did you usually spend walking on one of those days*?*

_____ **hours** _____ **minutes**

The last question is about the time you spent sitting on weekdays while at work, at home, while doing course work and during leisure time. This includes time spent sitting at a desk, visiting friends, reading traveling on a bus or sitting or lying down to watch television.

4. During the last 7 days, how much time in total did you usually spend *sitting* on a **week day?**

____ **hours** _____ **minutes**

This is the end of questionnaire, thank you for participating.

Appendix D

Food frequency questionnaire

HVA SPISER DU?

I dette skjemaet spør vi om dine spisevaner slik de er nå.
Vi er klar over at kostholdet varierer fra dag til dag. Prøv derfor så godt du kan å gi et "gjennomsnitt" av dine spisevaner. Der du er usikker, anslå svaret.

Skjemaet skal leses av en maskin, og det er derfor viktig at du setter et tydelig kryss i avmerket rute.

Riktig markering er slik: ☒

Bruk helst svart eller blå kulepenn (ikke rød).
Bløt blyant kan også brukes, men marker da ekstra tydelig.

Av hensyn til den maskinelle lesingen pass på at arkene ikke blir brettet.

Alle svar vil bli behandlet strengt fortrolig.

Eksempel på utfylling av spørsmål 1.

Kari Nordmann spiser daglig 5 skiver brød og ett knekkebrød. Hun spiser vanligvis kneippbrød, men i helgene blir det en del loff. I tillegg spiser hun ett knekkebrød hver dag. Hun fyller ut første spørsmål slik:

1. Hvor mye brød pleier du å spise?

Legg sammen det du bruker til alle måltider i løpet av en dag.
(1/2 rundstykke = 1 skive, 1 baguett = 5 skiver, 1 ciabatta = 4 skiver)

	Antall skiver pr. dag													
	0	1/2	1	2	3	4	5	6	7	8	9	10	11	12+
Fint brød (loff, baguetter, fine rundstykker o.l.)	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Mellomgrovt brød (lys helkorn, lys kneipp, lys hj.bakt o.l.)	☐	☐	☐	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐
Grovt brød (fiberkneipp, mørk kneipp, mørkt hj. bakt o.l.)	☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Knekkebrød (kavring, grov skonrok o.l.)	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Sum skiver pr. dag = 6
Antall skiver pr. uke: 6 x 7 = 42. Tallet brukes i spørsmål 5.

1. HVOR MYE BRØD PLEIER DU Å SPISE?

Legg sammen det du bruker til alle måltider i løpet av en dag.
(1/2 rundstykke = 1 skive, 1 baguett = 5 skiver, 1 ciabatta = 4 skiver)

	Antall skiver pr. dag													
	0	1/2	1	2	3	4	5	6	7	8	9	10	11	12+
Fint brød (loff, baguetter, fine rundstykker o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Mellomgrovt brød (lys helkorn, lys kneipp, lys hj.bakt o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grovt brød (fiberkneipp, mørk kneipp, mørkt hj. bakt o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Knekkebrød (kavring, grov skonrok o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Sum skiver pr. dag = ___
Antall skiver pr. uke: ___ x 7 = ___. Tallet brukes i spørsmål 5.

2. HVA PLEIER DU Å SMØRE PÅ BRØDET?

Merk av både for hverdag og helg, selv om du bruker det samme.

Hverdager		Lørdager, søndager
☐	Bruker ikke	☐
☐	Smør (meierismør)	☐
☐	Bremykt	☐
☐	Brelett	☐
☐	Soft-, soyamargarin (pakke, beger)	☐
☐	Solsikke	☐
☐	Oliven	☐
☐	Vita	☐
☐	Olivero	☐
☐	Omega	☐
☐	Soft light	☐
☐	Vita lett	☐
☐	Annen margarin	☐

3. OM DU BRUKER FETT PÅ BRØD, HVOR MYE BRUKER DU?

En porsjonspakning på 12 g rekker til antall skiver

1 ☐
2 ☐
3 ☐
4 ☐
5 ☐

4. MELK SOM DRIKK

(1 glass = 1,5 dl)

	Drikker sjelden/ ikke	Antall glass pr. dag: 1/2	1	2	3	4	5	6	7	8+
Helmelk, søt, sur	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lettmelk, søt, sur	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lettmelk, ekstra lett	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Skummet melk, søt, sur	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

5. PÅLEGGSSORTER

Bruk sum skiver pr. uke fra spørsmål 1.

Til antall skiver pr. uke

	0	1/2	1	2-3	4-5	6-7	8-14	15-21	22-28	29-35	36+
Brun ost, prim	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Hvit ost, helfet, 27% fett (Jarlsberg, Norvegia o.l., smøreost; eske, tube)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Hvit ost, halvfet, 16% fett (Jarlsberg, Norvegia o.l. smøreost; eske, tube)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Ost med mer enn 27% fett (kremoster, Normanna, Ridderost)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	0	1/2	1	2-3	4-5	6-7	8-14	15-21	22-28	29-35	36+
Leverpostei, vanlig	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Leverpostei, mager	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Servelat, vanlig	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lett servelat, kalverull, kokt skinke, okserull o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Salt pølse, spekepølse (fårepølse, salami o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	0	1/2	1	2-3	4-5	6-7	8-14	15-21	22-28	29-35	36+
Kaviar	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Makrell i tomat, røkt makrell	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sardiner, sursild, ansjos o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Laks, ørret	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Reker, krabbe	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	0	1/2	1	2-3	4-5	6-7	8-14	15-21	22-28	29-35	36+
Syltetøy, marmelade, frysetøy	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Honning, sirup, sjokolade-, nøttepålegg	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	0	1/2	1	2-3	4-5	6-7	8-14	15-21	22-28	29-35	36+
Grønnsaker som pålegg (agurk, tomat o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Frukt som pålegg (banan, eple o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Salater med majones	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Majones på smørbrød	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

6. EGG

Antall pr. uke

	0	Mindre enn 1	1	2	3-4	5-6	7	8+
(kokt, stekt, eggerøre, omelett)	☐	☐	☐	☐	☐	☐	☐	☐

7. FROKOSTGRYN, GRØT OG YOGHURT

Svar enten pr. måned eller pr. uke. <1 betyr sjeldnere enn 1 gang.

	Gang pr. måned					Gang pr. uke						Mengde pr. gang			
	0	<1	1	2	3	1	2-3	4-5	6-7	8+		1	11/2	2	3+
Havregryn,kornblandinger (4-korn, usøtet müsli o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Cornflakes, puffet ris, havrenøtter o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Havregrøt	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7 ☐
Sukker til frokostgryn, grøt	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ts)	1 ☐	2 ☐	3-4 ☐	5+ ☐
Yoghurt, naturell, frukt	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(beger)	1/2 ☐	1 ☐	11/2 ☐	2+ ☐
Lettyoghurt	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(beger)	1/2 ☐	1 ☐	11/2 ☐	2+ ☐
Go'morgen yoghurt, inkl. müsli	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(beger)	1/2 ☐	1 ☐	11/2 ☐	2+ ☐
Melk søt, sur på gryn, grøt og dessert	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	3/4 ☐	1 ☐	2 ☐	3+ ☐

8. KAFFE OG TE

(1 kopp kaffe = 1,2 dl 1 kopp te = 2 dl)

	Drikker ikke/ikke daglig	Antall kopper pr. dag							
		1/2	1	2	3-4	5-6	7-8	9-10	11+
Kaffe, kokt	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kaffe, traktet, filter	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kaffe, pulver (instant)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kaffe, koffeinfri	☐	☐	☐	☐	☐	☐	☐	☐	☐
Te	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nypete, urtete	☐	☐	☐	☐	☐	☐	☐	☐	☐

	Antall teskjeer eller biter pr. kopp					
	0	1/2	1	2	3	4+
Sukker til kaffe	☐	☐	☐	☐	☐	☐
Sukker til te	☐	☐	☐	☐	☐	☐
Kunstig søtstoff til kaffe eller te	☐	☐	☐	☐	☐	☐
Fløte til kaffe	☐	☐	☐	☐	☐	☐

9. ANDRE DRIKKER

Svar enten pr. måned eller pr. uke. < 1 betyr sjeldnere enn 1 gang. Merk at porsjonsenhetene er forskjellige. 1/3 liter tilsvarer en halvflaske øl og 2/3 liter tilsvarer en helflaske.

	Gang pr. måned					Gang pr. uke						Mengde pr. gang						
	0	<1	1	2	3	1	2-3	4-5	6-7	8+		1/2	1	2	3	4	5+
Vann	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Appelsinjuice	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Annen juice, most, nektar	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Saft, solbærsirup m. sukker	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Saft, kunstig søtet	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Brus, Cola, Solo o.l. med sukker	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/4 ☐	1/3 ☐	1/2 ☐	2/3 ☐	1 ☐	11/2+ ☐
Brus, Cola, Solo o.l. kunstig søtet	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/4 ☐	1/3 ☐	1/2 ☐	2/3 ☐	1 ☐	11/2+ ☐
Farris, Selters, Soda o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/4 ☐	1/3 ☐	1/2 ☐	2/3 ☐	1 ☐	11/2+ ☐
Alkoholfritt øl, vørterøl, lettøl	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/4 ☐	1/3 ☐	1/2 ☐	2/3 ☐	1 ☐	11/2+ ☐
Pilsnerøl	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/4 ☐	1/3 ☐	1/2 ☐	2/3 ☐	1 ☐	11/2+ ☐
Vin	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐
Brennevin, likør	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(1 dram =4cl)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐

10. MIDDAGSRETTER

Vi spør både om middagsmåltidene og det du spiser til andre måltider. Tell til slutt sammen antall retter du har merket av for å se om summen virker sannsynlig. En "dl" tilsvarer omtrent mengden i en suppeøse. Med "ss" menes en spiseskje.

	Gang pr. måned										Mengde pr. gang					
	0	<1	1	2	3	4	5-6	7-8	9+		1/2	2/3	1	11/2	2+
Kjøttpølse, medisterpølse	☐	☐	☐	☐	☐	☐	☐	☐	☐	(kjøttpølse)	☐	☐	☐	☐	☐
											1	2	3	4	5+
Hamburger, karbonader o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐
											1	2	3	4	5+
Grill- og wienerpølse	☐	☐	☐	☐	☐	☐	☐	☐	☐	(pølse)	☐	☐	☐	☐	☐
Hamburger-, pølsebrød, lomper	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Kjøttkaker, medisterkaker, kjøttpudding	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Kjøttdeigretter (saus eller gryte med kjøttdeig, lasagne o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Taco (med kjøtt og salat)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Pastaretter	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐

	Gang pr. måned										Mengde pr. gang					
	0	<1	1	2	3	4	5-6	7-8	9+		1/8	1/4	1/2	3/4	1+	
Pizza (500-600 g)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(pizza)	☐	☐	☐	☐	☐	
											1/2	1	11/2	2	21/2+	
Biff (alle typer kjøtt)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐	
											1/2	1	11/2	2	21/2+	
Koteletter (lam, okse, svin)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐	
											1-2	3-4	5-6	7-8	9+	
Stek (lam, okse, svin)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	☐	☐	☐	☐	☐	
											1-2	3-4	5-6	7-8	9+	
Stek (elg, hjort, reinsdyr o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	☐	☐	☐	☐	☐	
Gryterett med helt kjøtt, frikassè, fårikål o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐	
Lapskaus, suppelapskaus, betasuppe	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐	
											1-2	3-4	5-6	7-8	9+	
Bacon, stekt flesk	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	☐	☐	☐	☐	☐	
											1/4	1/3	1/2	3/4	1+	
Kylling, høne	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐	
											1-2	3-4	5-6	7-8	9+	
Leverretter	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	☐	☐	☐	☐	☐	
	0	<1	1	2	3	4	5-6	7-8	9+		1	2	3	4	5+	
Fiskekaker, fiskepudding, fiskeboller	☐	☐	☐	☐	☐	☐	☐	☐	☐	(kake)	☐	☐	☐	☐	☐	
											1-2	3-4	5-6	7-9	10+	
Fiskepinner	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐	
											1	2	3	4	5+	
Torsk, sei, hyse (kokt)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐	
											1	2	3	4	5+	
Torsk, sei, hyse (stekt, panert)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐	
											1	2	3	4	5+	
Sild (fersk, speket, røkt)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(filet)	☐	☐	☐	☐	☐	
											1/2	1	11/2	2	3+	
Makrell (fersk, røkt)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(filet)	☐	☐	☐	☐	☐	
											1	2	3	4	5+	
Laks, ørret (sjø, oppdrett)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	☐	☐	☐	☐	☐	
Fiskegryte, -grateng, suppe med fisk	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐	
											1	2	3	4	5+	
Reker, krabbe	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl, renset)	☐	☐	☐	☐	☐	
	0	<1	1	2	3	4	5-6	7-8	9+		1-2	3-4	5-6	7-8	9+	
Risgrøt, annen melkegrøt	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	☐	
											1-2	3-4	5-6	7-8	9+	
Pannekaker	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐	
Suppe (tomat, blomkål, ertesuppe o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐	
Vegetarrett, vegetarpizza, grønnsaksgrateng, -pai	☐	☐	☐	☐	☐	☐	☐	☐	☐	(bit/dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐	
	0	<1	1	2	3	4	5-6	7-8	9+		1/2	1	11/2	2	21/2+	
Brun/hvit saus	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	☐	
Smeltet margarin, smør til fisk	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐	
											1	2	3	4	5+	
Bearnaisesaus o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐	
											1	2	3	4	5+	
Majones, remulade	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐	
											1	2	3	4	5+	
Ketchup	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐	

11. POTETER, RIS, SPAGHETTI, GRØNNSAKER

Svar enten pr. måned eller pr. uke. < 1 betyr sjeldnere enn 1 gang.
Disse spørsmålene dreier seg først og fremst om tilbehør til middagsretter, men spiser du for eksempel en rå gulrot eller salat til lunsj, skal det tas med her.

	Gang pr. måned					Gang pr. uke						Mengde pr. gang				
	0	<1	1	2	3	1	2-3	4-5	6-7	8+						
Poteter, kokte	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Pommes frites, stekte poteter	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Potetmos, -stuing, gratinerte poteter	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Ris	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Spaghetti, makaroni, pasta	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Gulrot	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	11/2 ☐	2 ☐	3+ ☐
Hodekål	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skalk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Kålrot	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Blomkål	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(bukett)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Brokkoli	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(bukett)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Rosenkål	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Grønnkål	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Løk	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Spinat, andre bladgrønns.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Sopp	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Avocado	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/4 ☐	1/2 ☐	3/4 ☐	1 ☐	11/4+ ☐
Paprika	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(strimmel)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Tomat	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	11/2 ☐	2 ☐	3+ ☐
Tomatbønner, bønner/linser	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Mais	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Erter, frosne grønnsak-blandinger	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Salatblandinger	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Dressing	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1/2 ☐	1 ☐	2 ☐	3 ☐	4+ ☐
Rømme	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1/2 ☐	1 ☐	2 ☐	3 ☐	4+ ☐

Hvor mange ganger om dagen spiser du vanligvis grønnsaker utenom grønnsakene du spiser til middag? 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5+ ☐

12. TYPE FETT TIL MATLAGING

Smør/margarin	Oljer
☐ Smør (meierismør)	☐ Olivenolje
☐ Bremykt	☐ Soyaolje
☐ Melange, Per	☐ Maisolje
☐ Soft-, soyamargarin (pakke, beger)	☐ Solsikkeolje
☐ Solsikke	☐ Valnøttolje
☐ Oliven	☐ Andre oljer
☐ Annen margarin	

13. FRUKT

Svar enten pr. måned eller pr. uke. < 1 betyr sjeldnere enn 1 gang.

	Gang pr. måned					Gang pr. uke						Mengde pr. gang			
	0	<1	1	2	3	1	2-3	4-5	6-7	8+		1/2	1	2	3+
Eple	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐
Appelsin, mandarin, grapefrukt	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐
Banan	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐
Druer	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(klase)	☐	☐	☐	☐
Eksotisk frukt (kiwi, mango)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐
Annen frukt (fersken, pære m.v.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐
Jordbær, bringebær (friske, frosne)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Blåbær	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Multer	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐

Hvor mange frukter spiser du vanligvis pr. dag? 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9+ ☐

14. DESSERT, KAKER, GODTERI

Svar enten pr. måned eller pr. uke. < 1 betyr sjeldnere enn 1 gang.

	Gang pr. måned					Gang pr. uke					Mengde pr. gang				
	0	<1	1	2	3	1	2-3	4-5	6-7	8+					
Hermetisk frukt, fruktgrøt	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Puddinger (sjokolade, karamell o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4+ ☐
Is (1 dl=1 pinne=1 kremmerhus)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4+ ☐
Boller, julekake, kringle	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4+ ☐
Skolebrød, skillingsbolle	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4+ ☐
Wienerbrød, -kringle o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4+ ☐
Smultring, formkake	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4+ ☐
Vafler	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(plate)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Sjokoladekake, bløtkake, annen fylt kake	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Søt kjeks, kakekjeks (Cookies, Bixit, Hob Nobs)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-2 ☐	3-4 ☐	5-6 ☐	7+ ☐
Sjokolade (60 g)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(plate)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Drops, lakris, seigmenn o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-2 ☐	3-4 ☐	5-6 ☐	7+ ☐
Smågodt (1 hg = 100g)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(hg)	1/2 ☐	3/4 ☐	1 ☐	11/2+ ☐
Potetgull (1 pose 100g=7 dl)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7+ ☐
Annen snacks (skruer, crisp, saltstenger, lettsnacks o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7+ ☐
Peanøtter, andre nøtter (1 pose 100g = 4 never)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(neve)	1 ☐	2 ☐	3 ☐	4+ ☐

15. KOSTTILSKUDD (bs = barneskje, ts = teskje)

	Hele året	Bare vinterhalvåret	Gang pr. uke: 0	<1	1	2-3	4-5	6-7	Mengde pr. gang
Tran	☐	☐	☐	☐	☐	☐	☐	☐	1 ts ☐ 1 bs ☐ 1 ss ☐
Trankapsler	☐	☐	☐	☐	☐	☐	☐	☐	kapsler 1 ☐ 2+ ☐
Fiskeoljekapsler	☐	☐	☐	☐	☐	☐	☐	☐	kapsler 1-2 ☐ 3-4 ☐ 5-6 ☐ 7+ ☐
Multipreparater									
Sanasol	☐	☐	☐	☐	☐	☐	☐	☐	bs 1 ☐ 2 ☐ 3 ☐ 4+ ☐
Biovit	☐	☐	☐	☐	☐	☐	☐	☐	bs 1 ☐ 2 ☐ 3 ☐ 4+ ☐
Vitaplex	☐	☐	☐	☐	☐	☐	☐	☐	tablett 1 ☐ 2 ☐ 3 ☐ 4+ ☐
Kostpluss	☐	☐	☐	☐	☐	☐	☐	☐	tablett 1 ☐ 2 ☐ 3 ☐ 4+ ☐
Vitamineral	☐	☐	☐	☐	☐	☐	☐	☐	tablett 1 ☐ 2 ☐ 3 ☐ 4+ ☐
Annet	☐	☐	☐	☐	☐	☐	☐	☐	tablett 1 ☐ 2 ☐ 3 ☐ 4+ ☐

Hvis annet, hvilket?.....

Jernpreparater										
Ferro C	☐	☐	☐	☐	☐	☐	☐	☐	tablett	1 ☐ 2 ☐ 3 ☐ 4+ ☐
Hemofer	☐	☐	☐	☐	☐	☐	☐	☐	tablett	1 ☐ 2 ☐ 3 ☐ 4+ ☐
Duroferon Duretter	☐	☐	☐	☐	☐	☐	☐	☐	tablett	1 ☐ 2 ☐ 3 ☐ 4+ ☐
Annet	☐	☐	☐	☐	☐	☐	☐	☐	tablett	1 ☐ 2 ☐ 3 ☐ 4+ ☐

Hvis annet, hvilket?.....

B-vitaminer	☐	☐	☐	☐	☐	☐	☐	☐	tablett	1 ☐ 2 ☐ 3 ☐ 4+ ☐
C-vitamin	☐	☐	☐	☐	☐	☐	☐	☐	tablett	1 ☐ 2 ☐ 3 ☐ 4+ ☐
D-vitamin	☐	☐	☐	☐	☐	☐	☐	☐	tablett	1 ☐ 2 ☐ 3 ☐ 4+ ☐
E-vitamin	☐	☐	☐	☐	☐	☐	☐	☐	tablett	1 ☐ 2 ☐ 3 ☐ 4+ ☐
Folat (folsyre)	☐	☐	☐	☐	☐	☐	☐	☐	tablett	1 ☐ 2 ☐ 3 ☐ 4+ ☐
Kalktabletter	☐	☐	☐	☐	☐	☐	☐	☐	tablett	1 ☐ 2 ☐ 3 ☐ 4+ ☐
Fluortabletter	☐	☐	☐	☐	☐	☐	☐	☐	tablett	1 ☐ 2 ☐ 3 ☐ 4+ ☐
Annet	☐	☐	☐	☐	☐	☐	☐	☐	tablett	1 ☐ 2 ☐ 3 ☐ 4+ ☐

Hvis annet, hvilket?.....

16. NÅR SPISER DU PÅ HVERDAGER?

HOVEDMÅLTIDER som frokost, formiddagsmat, middag, kvelds.

Omtrent klokken

6	8	10	12	14	16	18	20	22	24	2	4
☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐

MELLOMMÅLTIDER som kaffe, frukt, godteri, snacks m.v.

Omtrent klokken

6	8	10	12	14	16	18	20	22	24	2	4
☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐

17. MENER DU SVARENE I SPØRRESKJEMAET GIR ET BRUKBART BILDE AV KOSTHOLDET

Ja ☐ Nei ☐

Er det matvarer/produkter du regelmessig bruker, og som ikke er nevnt i skjemaet?

.....

.....

18. ER DU FORNØYD MED KROPPSVEKTEN DIN SLIK DEN ER NÅ?

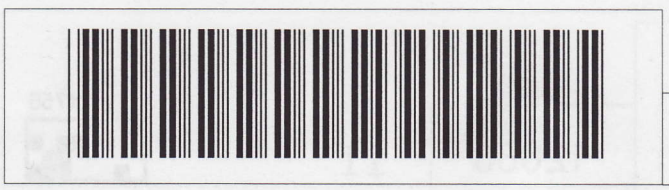
- ☐ Ja
- ☐ Nei, jeg ønsker å slanke meg
- ☐ Nei, jeg ønsker å legge på meg

19. KJØNN

Mann ☐ Kvinne ☐

Vennligst se etter at du har svart på alle spørsmål.

Takk for innsatsen!



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