Vitamin D and its implication on inflammation and genomics. The data from the Tromsø study and the U.S. National Health and Nutrition Examination Survey

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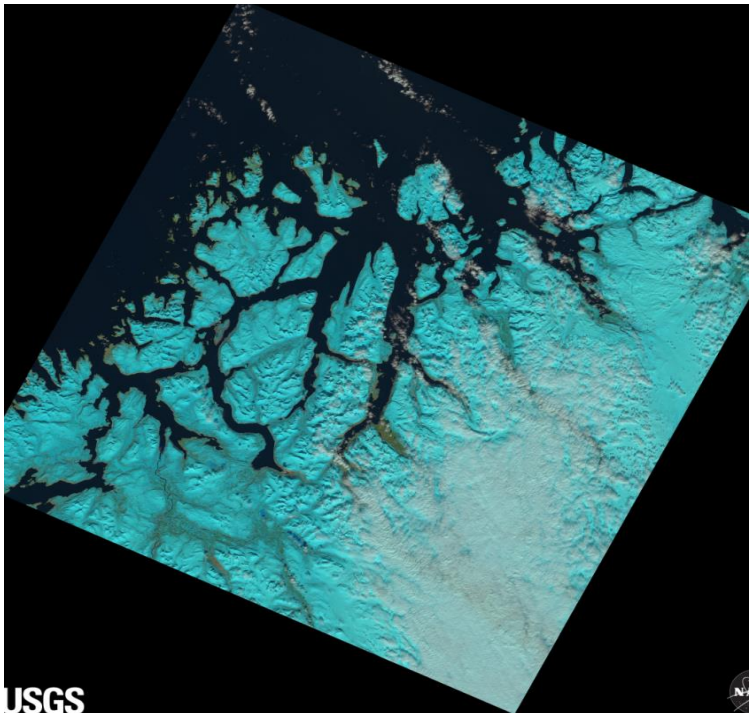

The front page is decorated with the satellite image over the Tromsø-region in Norway from June 2017. Data is the courtesy of the U.S. Geological Survey.

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Acknowledgments

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Norsk sammendrag

Det har vært en økende interesse for vitamin D sin rolle i patogenese av inflammasjonsrelaterte sykdommer, metabolske forstyrrelser, hjertekarsykdommer og cancer. Mange observasjonsstudier har antydet en sammenheng mellom redusert vitamin D nivå og økt risiko for disse sykdommene. Vårt mål var å undersøke denne sammenhengen i to store observasjonsstudier: den norske Tromsøundersøkelsen og den amerikanske NHANES (National Health and Nutrition Examination Survey), samt at vi har gjennomført to randomiserte studier (RCTer) for å vurdere om vitamin D tilskudd kan virke positivt på inflammasjonsmarkører. I Tromsøundersøkelsen (Tromsø 6) fant vi at redusert nivå av serum 25-hydroxyvitamin D (25(OH)D) var assosiert med høyere verdier av high-sensitive CRP (hs-CRP). Dessverre kunne vi ikke bekrefte kausal sammenheng i en RCT som gikk over 5 år, hvor vi testet om høy dose vitamin D (20 000 IU cholecalciferol per uke) kunne redusere serum hs-CRP. I en annen RCT hvor vi inkluderte overvektige personer, ble deltagerne delt i tre grupper og ble randomisert til enten høy dose cholecalciferol (40 000 IU per uke), cholecalciferol i dose 20 000 IU per uke eller placebo; og deretter fulgt i ett år. Vi fant at interleukin 6 verdiene falt, men tumor necrosis factor α og hs-CRP ikke ble redusert. Vi fant heller ingen effekt på insulinresistens.

Data fra NHANES ble brukt for å studere assosiasjon mellom serum 25(OH)D og leukocyte telomere lengde (LTL). Forkortningen av telomere lengden er assosiert med genetisk predisposisjon for carcinogenese og tidlig aldring. Vi inkluderte 4260 menn og kvinner i ulike aldersgrupper og fant en positiv og selvstendig assosiasjon mellom serum 25(OH)D og LTL hos personer i aldersgruppen 40-59 år. Dette funnet støtter hypotesen om at redusert vitamin D status kan være assosiert med forøket risiko for kreft og andre aldersrelaterte sykdommer.

Avslutningsvis, våre data indikerer at det er en assosiasjon mellom reduserte verdier av serum 25(OH)D og øket nivå av inflammasjonsmarkører og markører for carcinogenese og aldring.

Funnene lot seg ikke med sikkerhet bekrefte i intervensjonsstudiene og den klinisk betydning av vitamin D i forebygging av inflammasjonsrelaterte og metabolske sykdommer er ikke avklart.

English summary

There are several observational studies, suggesting an association between decreased vitamin D status and increased risk of cardiovascular diseases, metabolic and autoimmune diseases, and certain types of cancer. The relation between serum 25-hydroxyvitamin D (25(OH)D) and proinflammatory cytokines and some markers of carcinogenesis is still unknown and it is yet not established if supplementation with cholecalciferol reduces these markers. We used data from Tromsø study and from the U.S. National Health and Nutrition Examination Survey (NHANES) to study the association between 25(OH)D and proinflammatory cytokines and leukocyte telomere length (a marker of carcinogenesis and aging).

In the observational study based on 10.118 non-smokers from the sixth Tromsø study we found a significant negative association between serum 25(OH)D and high-sensitive CRP (hs-CRP). However, in a smaller cohort of subjects with prediabetes (n=511), there were no significant correlations between serum 25(OH)D and hs-CRP. Moreover, 5 years supplementation with 20 000 IU cholecalciferol per week did not result in significant reduction in serum hs-CRP levels, as compared with subjects receiving placebo. In another RCT, 1 year supplementation with 20 000 IU or 40 000 IU cholecalciferol, resulted in lowering of interleukin 6 (IL-6), but not hs-CRP and tumor necrosis factor-α. In another large observational study, based on NHANES cycles 2001-2002, we demonstrated the significant positive association between serum 25(OH)D and LTL, but only in middle-aged adults (e.g. age 40-59 years). The findings were independent of other risk factors for LTL shortening (e.g. age, race/ethnicity, BMI, intake of sugars and calories, physical activity, etc). These findings might provide the biological plausibility on vitamin Ds action on carcinogenesis and other ager-related conditions.

In conclusion, the results of our study indicate an association between serum 25(OH)D levels and levels of certain proinflammatory cytokines and markers of carcinogenesis and aging, but

supplementation with cholecalciferol for as long as 5 years, did not show a beneficial effect of vitamin D. It means that the clinical impact of the associational findings remains unclear.

List of presented papers

1. Julia Beilfuss,Vivian Berg, Monica Sneve, Rolf Jorde, Elena Kamycheva. Effects of a one-year supplementation with cholecalciferol on interleukin-6, tumor necrosis factor-alfa and insulin resistance in overweight subjects. Cytokine 60 (2012) 870-874, doi:10/1016/j.cyto.2012.07.032

2. Julia Beilfuss, Rolf Jorde, Elena Kamycheva. High-sensitivity CRP is associated with serum 25-hydroxyvitamin D levels, but is not affected by 5-year supplementation with cholecalciferol. Submitted BMC Nutrition 29.05.17

3. Julia Beilfuss, Carlos A Camargo Jr., Elena Kamycheva. Serum 25-Hydroxyvitamin D has a modest Positive association with leucocyte telomere length in middle-aged US adults. Journal of Nutrition 147 (2017) 514-520, doi:10.3945/jn.116.244137

Abbreviations

BMI	Body mass index
CVD	Cardiovascular disease
CYP2R1	Cytochrome P450, family 2, subfamily R, polypeptide 1
CYP24A1	Cytochrome P450, family 24, subfamily A, polypeptide 1
DBP	Vitamin D binding protein
ELISA	Enzyme-linked immunosorbent assay
IBD	Inflammatory bowel disease
IL-6	Interleukin 6
GI	Gastrointestinal
HbA_1c	Glycated hemoglobin
Hs-CRP	High-sensitive C-reactive protein
HOMA-IR	Homeostasis model assessment of insulin resistance
LC-MS/MS	Liquid chromatography-tandem mass spectrometric assay
LTL	Leukocyte telomere length
MAPK	Mitogen activated protein kinase
mRNA	Messenger ribonucleic acid
MS	Multiple sclerosis
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHANES	National Health and Nutrition examination survey
OGTT	Oral glucose tolerance test
PTH	Parathyroid hormone
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor kB ligand
RCT	Randomized controlled trial
STAT3	Signal transducer and activator of transcription 3
TNF-α	Tumor necrosis factor alpha
TLRs	Toll like receptors
T1DM	Diabetes mellitus type 1

T2DM	Diabetes mellitus type 2
TGF-β	Transforming growth factor beta
TERT	Telomerase reverse transcriptase
VDR	Vitamin D receptor
WHO	World Health Organization
QUICKI	Quantitative insulin-sensitivity check index
25(OH)D	25-hydroxyvitamin D
1,25(OH)2D	1,25-dihydroxyvitamin D

1. Introduction

The rates of metabolic diseases, such as obesity and type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD) and cancer have reached pandemic levels and these diseases are on the top of leading causes of mortality worldwide [1]. That's why it is not surprising, that in the past decades, we have seen increased scientific interest in the study of the pathogenesis of metabolic diseases, inflammatory conditions, cancer, aging processes and possible ways to prevent them.

Vitamin D insufficiency is one of several factors that have been recently linked to these conditions, even though the main primary role of vitamin D has always been to maintain the healthy bone metabolism, and vitamin D insufficiency and deficiency was only mentioned in prevention of rickets and osteomalacia.

Vitamin D deficiency has been associated with increased risks of systemic connective tissue diseases like rheumathoid arthritis, systemic lupus erythematosus [2], inflammatory bowel diseases, such as Crohns disease [3] and ulcerative colitis [4] and some malignancies [5]. Similar associations apparently also exist for infections [6], mortality in critically ill patients [7] and all-cause mortality [8, 9].

The findings in these observational studies are, of course, not proof of causality. Large randomized-controlled trials (RCTs) with metabolic and/or inflammatory diseases and malignancies as primary outcomes are needed to find out if the correction of vitamin D status is beneficial in the prevention of these diseases, and if the decreased levels of serum 25-hydroxyvitamin D (25(OH)D) have a causal role in the pathogenesis of these diseases and conditions. Is the association between serum 25(OH)D and these diseases solely mediated by environmental factors (e.g. geographic latitude, sun exposure, intake of fatty fish, etc), or are

there some vitamin D mediated genomic changes involved? Will vitamin D supplementation (and in that case with which target level of serum 25(OH)D and for how long a time period) prevent occurrence and progression of metabolic diseases, inflammatory conditions and malignancies? These questions are yet to be answered, and the present thesis is hopefully a humble step towards some conclusions.

We used two large population-based surveys: the Tromsø Study and the U.S. National Health and Nutrition Examination Survey (NHANES) to study if there are associations between serum 25(OH)D levels and markers of inflammation (such as, interleukin 6 (IL-6) and high-sensitive C–reactive protein (hs-CRP)) and some markers of cancer (leukocyte telomere length (LTL)). Results from these observational studies generate many important hypotheses, but cannot be used as a final evidence for causal relationship between serum 25(OH)D and inflammation and cancer. We have therefore also performed two RCTs in order to find out if the supplementation with cholecalciferol (vitamin D3) affects the levels of these important biomarkers.

1.1 **Vitamin D**

Vitamin D is a fat soluble vitamin that exists in two forms; ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) that differ from each other with one double-binding and one methyl group [10, 11]. Vitamin D is mostly produced endogenously in the skin or obtained through the diet from fatty fish like salmon, mackerel, tuna, cod liver oil and vitamin D supplementation [5].

Upon solar ultraviolet B exposure, 7-hydrocholesterol in the skin is converted to previtamin D3 [12]. Previtamin D3 undergoes heat-induced membrane-isomerization to vitamin D3 [13]. Vitamin D3 produced in the skin, along with vitamin D2 and D3 obtained through the diet are transported to the liver, bound to the vitamin D Binding Protein (DBP), where the 25-

hydroxylation process occurs with the help of 25-hydroxylase (CYP2R1); and 25(OH)D, the major measured vitamin D metabolite, is synthetized [5]. 25-hydroxyvitamin D is an inactive metabolite and it undergoes further hydroxylation by 1 alfa-hydroxylase to turn into the biologically active metabolite 1,25 dihydroxyvitamin D (1,25(OH)2D) [14]. The 1 alfa-hydroxylase activity in the kidneys is auto-regulated by parathyroid hormone (PTH), which is in turn regulated through a negative feedback mechanism in the parathyroid glands depending on the calcium and phosphate levels in the serum. The main function of 1,25(OH)2D is maintaining the calcium and phosphorus homeostasis and accordingly promoting the bone health. 1,25(OH)2D stimulates increased calcium absorption in the gut, reduced excretion of calcium in the kidneys and increased calcium desorption from bone, which result in increased serum calcium. High serum calcium levels lead to stimulated production of fibroblast growth factor 23 from the bone cells, which in its feedback down-regulates 1 alfa-hydroxylase activity and thereby reducing secretion of 1,25(OH)2D and depleting serum calcium levels [15]. Regarding the choice of intervention time in our present and future RCTs it is worth mentioning that the half-life of 25(OH) D is two-three weeks and 1,25(OH)2D is 2-4 hours [15]. However, it is still not completely understood how and where 25(OH)D is stored [13]. Since half-life time for 25(OH)D is much longer, the serum concentrations of this inactive metabolite are usually used when we refer to "vitamin D status".

It was recently found that 1 alfa-hydroxylase is also produced in other tissues, then kidneys, but it is not regulated by PTH. Probably it is regulated by local tissue cytokines and growth factors and therefore, 1,25 (OH)2D production is small and dependent on the amount of available 25(OH)D [16].

One may ask why we call vitamin D a "vitamin"? Why don't we call it a "hormone"? 1,25(OH)2D is according to existing definitions a genuine lipophilic hormone. It has its target tissues (e.g. enterocytes), it is transported to target tissues bound to DBP, a protein with

specific qualities [17] and the action in target tissues (e.g. enterocytes) is mediated through the vitamin D receptor (VDR). Furthermore, there are also not bound fractions of circulating 25(OH)D. Less then 1 % of total amounts of vitamin D metabolites are circulating as free steroids. So, we can see that vitamin D possesses all the propensities of a conventional hormone. This fact makes it even more interesting and tempting to explore novel effects of this phenomenal vitamin.

Now some facts about VDR. Receptors are essential in normal hormone functioning. VDR is present in the most tissues and cells in the human body [16, 18]. That is consistent with our hypothesis of vitamin D`s role in extraskeletal health. The main physiologic function of VDR is promoting calcium and phosphorus absorption in enterocytes in the small intestine, through the interaction with 1,25(OH)2D [11] . Furthermore, through the interaction between VDR and 1,25(OH)2D in bone cells, immature preosteoclasts are converted to mature osteoclasts [19]. The mature osteoclasts stimulate the desorption of calcium and phosphorus from the bone (bone resorption) and hence repletion of serum calcium. In the kidneys, 1,25(OH)2D through VDR stimulates calcium reabsorption from the glomerular filtrate. Moreover, VDRs were also found in other tissues and organs (with no obvious physiological function of mineral balance maintaining), such as central nervous system, vascular smooth muscles, prostate cells, epithelial cells in breast glands, blood cells and tissue macrophages [16, 18]. 1,25(OH)2D was demonstrated to be synthetized in these tissues as well, according to available levels of circulation 25(OH) [5, 16].

The biological actions of 1,25(OH)2D are mainly divided into two types: genomic and non-genomic. The main effect of 1,25(OH)2D, the maintaining of calcium homeostasis, is a genomic action. Briefly, genomic effects are mediated through regulation of transcription of genes in the target cells, which is facilitated by the VDR, a ligand activated transcription system [15]. There are estimated to be 200 to 2000 genes that have a vitamin D response

element or that are influenced indirectly, possibly by epigenetics, to control a substantial amount of genes across the genome [20]. The majority of regulated genes are related to calcium metabolism, but several other biological actions are considered. For example, inhibiting cellular proliferation, inducing terminal differentiation, inhibiting angiogenesis, stimulating macrophage cathelicidin production, stimulating insulin production, inducting apoptosis, inhibiting renin production [5, 21].

1,25(OH)2D has also non-genomic effects, but the mechanism of this is not fully understood. It is well documented that 1,25(OH)2D can exert rapid actions at the cellular level, independently of gene expression. Non-genomic effects include the opening of ion channels, the induction of second messenger's molecule, such as mitogen activated protein kinases (MAPK), secretion of hormones (e.g. insulin), mediating the effects of growth factors and cytokines by altering either their cytosolic signaling pathways or the activity of their target transcription factors [22].

The biochemical elaborations and physiological actions described above provide quite solid plausible biological mechanisms for the hypothesis that vitamin D is involved in a number of nonskeletal health related outcomes.

1.2 What are the optimal (sufficient) serum 25(OH)D levels?

It is an essential question. The answer depends on what we want to prevent/cure? Alternatively, what effect do we want to receive? Still today, after many decades with massive vitamin D research, we basically know only one thing: the approximate levels of serum 25(OH)D in order to prevent rickets and/or osteomalacia (serum 25(OH)D >20 nmol/L). Internationally, there is no consensus on what levels of vitamin D that should be considered optimal regarding general health and potential extraskeletal effects [23, 24]. In our

clinical practice we follow the Nordic nutritional recommendations: serum 25(OH)D<25 nmol/l is considered deficiency, levels from 25- to 50 nmol/l suboptimal, and >50 nmol/l to be optimal levels of serum 25(OH)D [25].

These recommendations were proposed based on current knowledge of an inverse association between serum PTH and serum 25(OH)D. Previous studies demonstrated that serum PTH achieved plateau levels (steady-state) in subjects with serum levels of 25(OH)D between 20 and 40 ng/ml (multiply with ~2,5 to convert to nmol/L) [26-28].

It is important to point out that to current date it is unknown what is the highest (or lowest) optimal level of serum 25(OH)D in order to prevent extraskeletal health outcomes. The increasing amount of published RCTs has not contributed to any consensus. It is worth mentioning, that there are studies with hard end-points such as mortality, cardiovascular mortality and cancer risk indicating that serum 25(OH)D levels as high as >100 nmol/l might be beneficial [23, 29, 30]. On the other hand, the U-shaped association between serum 25(OH)D levels and extraskeletal outcomes has recently been described [31-34]. U-shaped (or sometimes also called J-shaped) association means that adverse/non-desirable effects on health are recorded in subjects with both extremely low and extremely high serum 25(OH)D. This emerging evidence is hard to ignore and this uncomfortable fact leaves us at the point where we started: what are the optimal serum 25(OH)D levels?

Levels of serum 25(OH)D and the importance of the different vitamin D sources are dependent on different factors. One of most important sources of vitamin D is the epidermal production in the skin under sunlight exposure. The minimal erythema dose of UV radiation leading to the amount of vitamin D produced in the skin is equivalent to ingesting between 10.000 and 25.000 IU of cholecalciferol [11]. Skin production of vitamin D depends on a variety of factors like skin pigmentation, age, clothing coverage and topical application of sunscreen. An alteration in the zenith angle of the sun caused by a change in latitude, season

of the year. Above and below latitudes of approximately 33º, vitamin D3 synthesis in the skin is very low or absent during most of the winter [11, 12, 35, 36]. In North Norway (69 º North) sufficient UVB radiation for dermal vitamin D production is only available from the middle of March to the end of September [37].

Enteral intake of vitamin D containing foods and supplements is one of the most important sources of vitamin D in Norway in general and in North Norway in particular. Normally, an affordable Norwegian diet seldom contains enough vitamin D [38] to meet the requirements of 400 IU/day suggested by the Nordic Nutrition Recommendation working group [39]. Institute of Medicine of the National Academies recommends intake of 400-600 IU vitamin D daily, which is assumed to be associated with a predicted mean circulating 25(OH)D level of 59 nmol/L in all age groups [40].

Intake of vitamin D supplements is therefore recommended and encouraged. Supplementation could be administered daily, weekly, monthly, or every 4 months to sustain serum 25(OH)D concentration >50 nmol/L [5].

What else may influence serum 25(OH)D levels? It is of course important to mention genetic variations in cholesterol metabolism, which have been shown to affect the production of vitamin D3 by limiting the amount of available 7- dehydrocholesterol [41]. Genetic differences in the VDR is associated with low serum 25(OH)D levels with potential clinical outcomes [41-44]. Genetic mutation of the cyp24p1 reduces the catabolism of 25(OH)D and 1,25(OH)2D and may lead to infantile hypercalcemia [45].

Moreover, diseases and conditions affecting the gastrointestinal (GI) tract (e.g. celiac disease, malabsorption, Crohn`s disease of small intestine, post-bariatric surgical conditions with affected anatomy and physiology of the GI tract, elderly population with swallowing

difficulties) may lead to substantially decreased absorption of orally consumed vitamin D [46-48].

1.3 Vitamin D and extraskeletal health. Metabolic disorders and inflammation

Recent meta-analyses and systematic review studies indicate that vitamin D insufficiency is associated with higher risk of all elements of the metabolic syndrome like cardiovascular disease [49, 50], hypertension [51], obesity, insulin resistance [52, 53] and T2DM [54] .

Vitamin D`s possible cardioprotective propensities and anti-inflammatory effects are suggested by the recent *in vitro* studies in which low 25(OH)D levels influenced the activity of macrophages and lymphocytes in atherosclerotic plaques and thus promoting chronic inflammation in the artery wall [55]. Moreover, the *in vitro* results indicate that 1,25(OH)2D inhibited foam cell formation and, hence, stimulated angiogenesis in endothelial colony-forming, and the mechanisms behind that are most likely an elevation in vascular endothelial growth factor expression and pro-matrix metalloproteinase-2 activity [56]. Since arterial plaques and endothelial dysfunctions are among the most documented causes of CVD (e.g. myocardial infarction, angina, stroke and arterial insufficiency in lower extremities (claudication intermittens)), altered vitamin D status may have a plausible biological mechanism in CVD, according to the studies cited above. Furthermore, low serum 25(OH)D levels may contribute to an increased risk of CVD through hypertension (another well-known risk factor of CVD) because low serum 25(OH)D levels have been associated with an increased activation of the renin-angiotensin system, and thus contributing to elevated blood pressure [57, 58]. However, interventional studies with vitamin D supplementation have not shown any beneficial effect on the cardiovascular risk factors [59, 60].

According to recent *in vivo* studies insufficient vitamin D status is suggested to impact glucose tolerance and type 2 diabetes through various mechanisms [61, 62]. The VDR and 1-alfa-hydroxylase are present in the pancreatic β-cell [63]. Stimulation of pancreatic islets in animal models demonstrate increased insulin secretion after addition of 1,25(OH)2D to the culture medium [64, 65]. Another potential explanation for these findings is VDR responsive action on the human insulin gene promoter [66]. Active vitamin D metabolite may also modulate β-cells growth and differentiation [54]. The vast majority of observational studies have supported these experimental results [67-69], but not all [70]. However, the well accepted conclusion of these studies is that genetic polymorphisms of VDR, enzymes responsible for vitamin D conversions into the active metabolite, and VDP may predispose to T2DM [65]. Altered metabolic profile in general, and insulin resistance in particular may also be exaggerated because of chronic inflammation, due to possible effects of insufficient vitamin D status on proinflammatory cytokines like IL-6 and TNF-α, and low grade inflammation markers, such as hs-CRP [71]. However, a Mendelian randomization study on vitamin D and CRP did not find evidence for a causal relationship [72].

The association between low serum 25(OH)D concentrations and decreased insulin sensitivity was found to be stronger in overweight individuals than in normal-weight individuals [73]. The storage of vitamin D in fat tissues may result in insufficient vitamin D bioavailability for influencing pancreatic β-cell function or activating VDRs, thereby increasing the risk of adverse glycemic outcomes [68]. Moreover, the clinical importance of proinflammatory cytokines-metabolic disease association (and that the association exists per se) has been demonstrated in weight loss intervention studies, where obese subjects showed reduction in IL-6 and TNF-α concentrations along with corresponding improvement of the metabolic profile after the bariatric surgery [74].

Furthermore, IL-6 is produced not only by T lymphocytes but also by adipocytes and increased production of IL-6 inhibits adiponectin gene expression in cultured adipocytes [75]. Adiponectin has been suggested to have anti-atherogenic and anti-inflammatory propensities, it is also considered to have beneficial effects on glucose metabolism and lower levels of adiponectin are associated with insulin resistance and metabolic syndrome [76, 77]. Deranged levels of IL-6 may therefore contribute to endothelial dysfunction, thus playing an important role in the development and progress of CVD and metabolic conditions (e.g obesity and T2DM). Similar properties have been described for TNF-α which has even been called an "adipokine", and in addition to possible production of cytokines in the adipocytes, there is also an infiltration of adipose tissue with inflammatory cells like macrophages [78, 79].

As mentioned above, observational findings are by no means proof of causality. To date, there are only few RCTs with T2DM and other metabolic disorders as primary outcomes and cholecalciferol as the treatment arm. Interestingly, those studies have as yet failed to demonstrate any beneficial effect on glucose metabolism, insulin resistance [80, 81] and on prevention of T2DM [82, 83].

1.4 **Vitamin D and extraskeletal health. Immune system**

We mentioned previously that the impact of vitamin D in inflammation might play a role in the development and progress of metabolic conditions. Interestingly, the association between vitamin D status and immune-mediated conditions like infections [84], autoimmune and allergic diseases [85] has also been well-studied during the past few decades. Three important discoveries, that were made in the last 25 years, suggesting the potential role of vitamin D and its active metabolite 1,25(OH)2D in the modulating of immune response are particularly worth mentioning. Firstly, the discovery of the VDR presence in activated human

inflammatory cells [86], secondly, the ability of 1,25(OH)2D to inhibit T-cell proliferation [87] and at last, but not in the least, the ability of disease activated macrophages to produce 1,25(OH)2D [88].

Vitamin D and innate immunity.

Innate immunity (also called non-specific immunity or in-born immunity) is the immune responses not specific to a particular pathogen. The innate immunity consists of a group of specific proteins, receptors and phagocytic cells that recognize the conserved features of pathogens and could be quickly activated in order to destroy the pathogens. The main pathway in innate immune response is the activation of toll like receptors (TLRs) in polymorphonuclear cells, such as monocytes and macrophages [89]. Involvement of vitamin D in this pathway has recently been described. Thus, pathogen/invader activates TLR signaling pathway in macrophages, which leads in turn to the transcriptional induction of VDR and CYP27B expression. Circulating 25(OH)D binds to plasma DBP, then enters macrophages and is converted to 1,25(OH)2D by mitochondrial CYP27B, and can retain VDR in the cell [90]. Once bound to VDR, 1,25(OH)2D is able to act as a transcriptional factor leading to the induction of cathelicidin synthesis, one of the antimicrobial peptides [91]. Incorporation into phagosomes containing internalized pathogen/invader enables cathelicidin to function as an antibacterial agent. As well as upregulating cathelicidin expression, macrophage synthesis of 1,25(OH)2D can also facilitate negative autoregulation, firstly via increased expression of the feedback enzyme CYP24A, and secondly via downregulation of TLR expression [90].

Vitamin D and adaptive immunity.

Adaptive immunity, as opposed to innate, responds to a specific pathogen/invader (bacteria, viral agents, fungi). Adaptive immunity “remembers” previous encounters with the invading

agent and destroys them when they attack again. Adaptive immune responses, again unlike innate responses, are rather slow on the primary exposure to invader/pathogen, as specific clones of T and B lymphocytes have to be activated and expand. Macrophages and mature dendritic cells (DCs) can induce both T lymphocyte mediated and B lymphocyte mediated immunity by internalizing and processing invaders/pathogens. Macrophages and mature DCs also express the vitamin D-activating enzyme CYP27B and hence are able to synthetize 1,25(OH)2D from inactive metabolite, 25(OH)D [92]. In turn, 1,25(OH)2D synthesized this way can act on activated B lymphocytes and activated T lymphocytes, which express abundant VDR. Moreover, 1,25(OH)2D inhibits differentiation of DCs and decreases T lymphocytes proliferation and activation by increase of the synthesis in the Th2 cells of anti-inflammatory cytokines IL-10, IL-4, IL-5 and inhibiting the synthesis in the Th1 cells of proinflammatory cytokines IL-2, IFN-γ and TNF -α [92, 93]. Due inhibition of Th1 cells vitamin D might be involved in the prevention of several autoimmune diseases such as multiple sclerosis (MS), rheumatoid arthritis (RA), type 1 diabetes (T1DM) and inflammatory bowel disease (IBD) [94]. Dysregulation of Th2 cells may in turn lead to development of allergic diseases, including asthma, allergic rhinitis and atopic dermatitis [90, 95].

B lymphocytes play a key role in adaptive immunity through the production of antibodies towards specific antigens. The vast majority of pathogens/invaders are able to express antigens (proteins and polysaccharides, and less frequently lipids), which in turn are triggers for the activation of B lymphocytes and adaptive immunity. B lymphocytes express the VDR and CYP27B1 event under non-activated (so-called resting) condition. Exposure of B lymphocytes to 1,25(OH)2D results in upregulation of VDR and CYP24A1 at the mRNA level [90]. *In vivo* studies revealed that active metabolite of vitamin D inhibits the generation of plasma cells and controls antibody expansion [96]. Moreover, 1,25(OH)2D inhibits the secretion of IgA, IgG, IgM, IgE from stimulated B cells *in vitro* [97].

To summarize in short, there is a body of evidence that vitamin D is a biologically plausible mechanism in both innate and adaptive immunity; and insufficient vitamin D status might therefore influence the development and progress of such clinically relevant outcomes as infections, autoimmune diseases, allergies, and even malignancies, especially colorectal, liver and lung cancers [98, 99].

1.5 Vitamin D and extraskeletal health. Carcinogenesis and aging

Recent observational studies indicate that vitamin D deficiency is associated with increased incidence and prevalence of several types of malignancies [8, 100, 101]. Carcinogenesis is undoubtedly a multifactorial process, with involvement of the immune system, genomic changes/mutations, increased inflammation and so on [102, 103]. The interaction between inflammation and tumorigenesis is significant and present in very early stages; and also could be promoted to further carcinogenesis by genetic alterations [99]. Key factors in cancer-related inflammation are transcriptions factors as NF-kappa B (NF-kB), activator of transcription 3 (STAT3) and major proinflammatory cytokines such as IL-1β, IL-6,IL-23 and TNF-α [99].

Genetic alterations that cause tumorigenesis include the activation of various types of oncogenes like members of RAS and MYC family by mutation [104, 105], the inactivation of tumor-suppressor genes [99] and chromosomal rearrangement and shortening of telomere length. It has been recently established that telomere shortening plays an essential role in genomic instability, which in turn lead to carcinogenesis and malignant diseases [106, 107].

Telomeres are repetitive nucleotide sequences located at the ends of chromosomes, telomeres do not participate in DNA replication or RNA synthesis. The main function of telomeres is to prevent nucleolytic degradation and recombinations occurrence [106, 108]. Telomeres

become shorter under each cell cycle (mitosis) and when a sufficient number of telomeres become critically short, apoptosis and cellular aging will be triggered with cell death as the inevitable result. Telomerase, a cellular enzyme, protects telomeres and maintains telomere length at equilibrium. Telomere dysfunction and disrupted genomic integrity are therefore the main genomic factors leading to aging and death at the cellular level [107, 109]. What about clinical consequences? Recent studies demonstrate that telomere shortening is frequently associated with higher risk of several age related diseases and conditions, such as CVD [110], different types of malignancies [111, 112] and last, but not least, dementia [113, 114].

Interestingly, both the telomere shortening process and increased telomerase activity are present in tumor cells, which is constantly in the uncontrolled mitosis; thus it is tempting to suggest that telomere dysfunction may not be only hallmark of cell aging but also one of the plausible mechanisms leading to unlimited cell proliferation and eventually tumorigenesis [107].

In a research setting, it is usual to measure the telomere lengths in the blood cells, for instance, in leukocytes. It is considered the most convenient method, which does not involve unnecessary discomfort in the study participants, except for venous blood sampling. It is worth mentioning that with the appropriate laboratory method and reagents, one can measure telomere length in other cells than leukocytes, for instance in the epithelium; but in the setting of observational studies when the aim is to examine a substantial number of subjects, analysis of leukocyte telomere length (LTL) is used most frequently.

Age is, of course, a well-established factor associated with telomere shortening. However, age is a non-modifiable factor and for us, clinicians, there is little to do when dealing with aging patients. Another non-modifiable factor, known to be associated with shorter telomeres is a non-Hispanic white race/ethnicity [115], to which the majority of the Scandinavian population belong. Luckily, according to recent studies, there are other modifiable factors which may

influence telomere length. Environmental factors, dietary factors, such as increased energy consumption and the intake of high-sugar foods have been linked to shorter telomeres [116]. Thus, modifying t conditions and factors such as poor diet, overweight and obesity, one may prevent exaggerated telomere shortening [117-119]. Vitamin D insufficiency is one of these modifiable factors associated with increased age related disease, including premalignancies and cancer [8, 100, 101]. It has recently been linked to shorter LTL and we found it worth exploring further.

Among other mechanisms, which might involve vitamin D in tumorigenesis, NF-κB signaling pathway is worth mentioning. Thus, there is an evidence from the *in vitro* studies that 1,25(OH)2D may downregulate the NF-κB pathway and as a result lead to decreased proliferation of malign cells [120, 121]. Moreover, the possible antiproliferative effect of vitamin D might also be multifactorial; due to an effect on many genes that in turn regulate active proteins and pathways, such as E2F transcription factors, cyclin-dependent kinase activity, c-myc expression, transforming growth factor beta (TGF-β) signaling pathway, and prostaglandin signaling [122]. And finally, active metabolite of vitamin D has been shown to reduce the expression of telomerase reverse transcriptase (TERT), hence mitigating the telomerase activity, which is frequently elevated in the most of malignant cells [123].

1.6 **Summary**

The rates of CVD, metabolic diseases and malignancies have indeed reached the pandemic levels [124], especially in the industrialized countries with rapidly aging populations and tremendously augmenting health costs. Though the vast majority of risk factors are well established, and the healthcare funds are generous in the western countries, the prevalence of these diseases is escalating and there is emerging evidence that there are other risk factors

associated with these conditions. Altered vitamin D status (e.g. insufficient levels of serum 25(OH)D) is suggested be one of them. Through mediating the inflammation processes and influencing the human genome, vitamin D status might be involved in the development of clinically significant outcomes, such as CVD, obesity, T2DM and even carcinogenesis. Many questions remain to be answered, based on the findings from large observational studies and/or meta-analyses. After many years of a "vitamin D research rush" we still don't know whether trying to increase serum 25(OH)D (and in that case, to what point) by means of high doses of cholecalciferol supplementation or solar exposure will give us clinically relevant health benefits.

Our scientific work combines both epidemiological ways to study the relationship between the exposure and the outcome, observational and interventional. We hope that we would be able to approach some answers.

2 Aims of the study

The overall objective of this thesis is to investigate the association between serum 25(OH)D levels and some biomarkers of health related outcomes (e.g. inflammation and carcinogenesis). We have tried to investigate the possible associations from both perspectives: observational (with the use of large population-based studies) and causal (with the use of RCTs).

This dissertation consists of three independent projects/three papers. We used the Tromsø study and the U.S. NHANES as observational studies and the RCT studies. We used ancillary studies to the RCTs with metabolic diseases as primary outcomes (obesity and T2DM). These were performed earlier.

Briefly, the aims of the subprojects were:

- to investigate the association between serum 25(OH)D concentrations and levels of proinflammatory cytokines IL-6 and TNF-α in overweight subjects
- to investigate the effect of vitamin D (cholecalciferol) supplementation on proinflammatory cytokines IL-6 and TNF-α in overweight subjects
- to investigate association between serum 25(OH)D concentrations and hs-CRP, as a marker of low grade inflammation
- to investigate if the supplementation with cholecalciferol reduces the serum concentration of hs-CRP during 5-year intervention
- to examine the association between serum 25(OH)D concentrations and LTL, as a marker of carcinogenesis and aging.

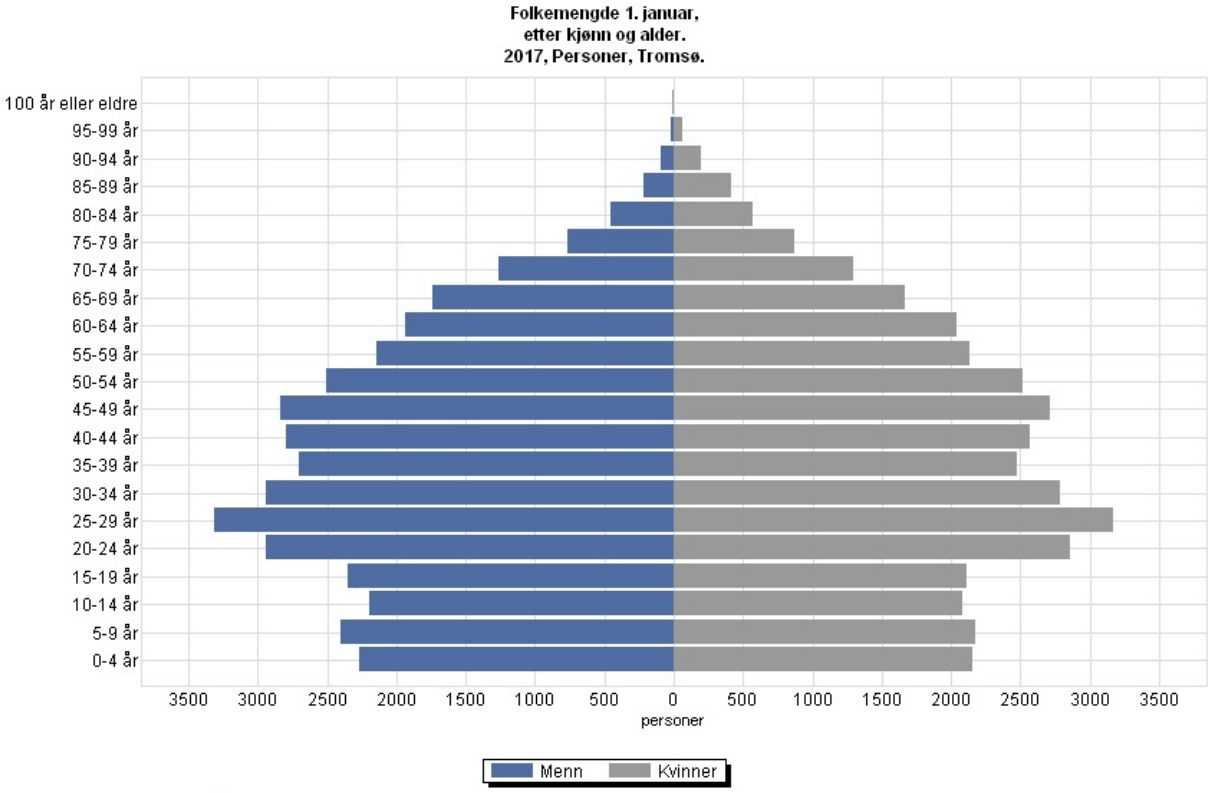
3 Methodological highlights and considerations

A detailed descriptions of study designs, inclusion and exclusion criteria, intervention period, endpoints, physical and laboratory measurements and statistical tools are available in the individual papers. In this paragraph, we will try to give a brief description of the study population with an emphasis on the unique methods and analyses used in this work. The short-comings of ours studies will also be described in detail below.

3.1 Observational study. The Tromsø Study, paper II

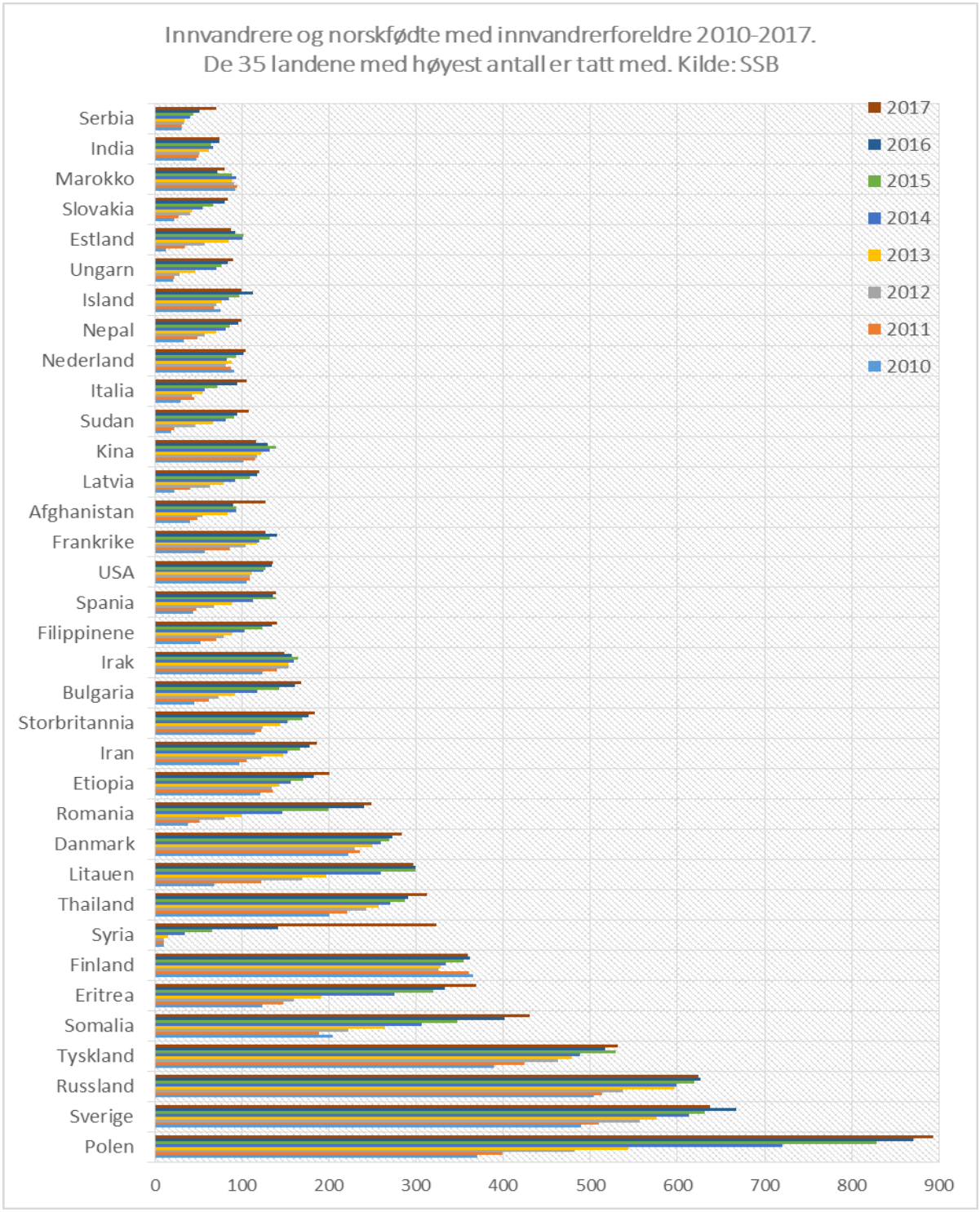
The municipality of Tromsø (Tromsø 69°40′58″N 18°56′34″E) is situated at the northern coast of Norway (Picture 1). The population has increased annually with approximately 1000 inhabitants during past decade, and the present population (per 01.01.2017) is 74.541 inhabitants [125]. The demographics is presented in Figure 1.

Figure 1. The demographics of the Municipality of Tromsø. Data presentation is the courtesy of Central Bureau of Statistics.



The population of the municipality of Tromsø is composed predominantly of subjects of Norwegian origin, in addition to a certain percentage of subjects of Sámi ancestry. Among foreign nationals or citizens of foreign decent, Polish, Swedish, Russian, German and Somali are represented , Figure 2.

Figure 2. The distribution of foreign nationalities in the Municipality of Tromsø. Data presentation is the courtesy of Central Bureau of Statistics.



The Tromsø Study is a longitudinal population-based study, conducted by the University of Tromsø in cooperation with the National Health Service, with the first survey in 1974. It is the largest population-based study in North Norway. It was designed to investigate lifestyle factors related to CVD in males. The main original objective was to find out the cause of the high prevalence of CVD in Northern Norwegian men and if there were some ways to prevent further increment [126]. The following surveys have also included women and other clinical outcomes such as endocrinological, neurological, dermatological, gastrointestinal and psychological diseases have also been investigated, and a wide array of possible causes and confounders have been included [127].

We used the data from the sixth Tromsø Study. The sixth Tromsø study was performed in 2007 - 2008, and 9.625 men and 10.137 women, aged 30-87 years were invited to participate. All invited subjects received the information brochure (Appendix 1) and the questionnaire (Appendix 2). Among those, 6054 men and 6930 women attended the study, creating the participation rate of 62,9% and 68,4%, respectively.

At the first visit, the participant's medical histories were collected and they had a brief clinical examination (height and weight, blood pressure, waist and hip circumferences, as well as one blood sample was drawn). The participants were also asked to complete an additional questionnaire (Appendix 3). They were allowed to take the questionnaire home, complete it there, and return it by mail in the enclosed envelope. The blood samples, which were drawn at the examination, was later analyzed for serum 25(OH)D, Hba1c and hs-CRP.

Since the serum 25(OH)D assay discrepancy for smokers versus non-smokers was early demonstrated [128], only non-smokers were included in our study (n=10.118).

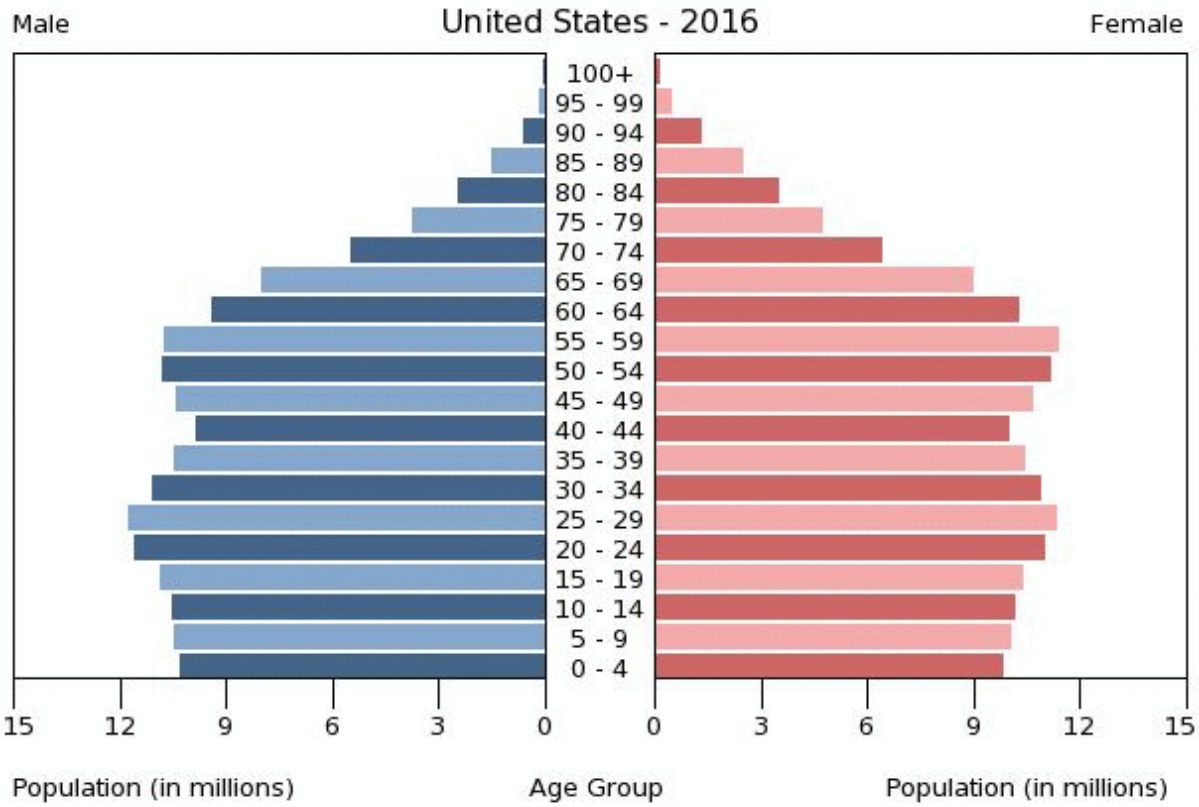
One of the main limitations in our observational study was that we were not able to cross check with patient records the self-reported data on whether the subjects were using

nonsteroidal anti-inflammatory drugs (e.g. NSAIDS) or had any active inflammatory conditions (e.g. infection, latent autoimmune disease). This data could be important, since the outcome of our observational study is the association between serum 25(OH)D and inflammatory biomarkers. Moreover, we did not have access to the data on physical activity, which is also an important factor, while investigating exposure-outcome association regarding inflammation. However, we feel that excluding smokers added strength to our study as we eliminated smoking as a confounder in the investigation of the association between serum 25(OH)D and hs-CRP.

3.2 Observational Study. The U.S. National Health and Nutrition examination Survey (NHANES). Paper III

NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States. The background and historic facts are available at *https://www.cdc.gov/nchs/nhanes/about_nhanes.htm*. The survey is unique in that it combines interviews and physical examinations. NHANES is a major program of the National Center for Health Statistics (NCHS), and a part of the Centers for Disease Control and Prevention (CDC), which has the main responsibility to produce vital, and health statistics for the US government. The demographics of the US is presented in Figure 3.

Figure 3. The demographics of the US per 31.12.2016. The data presentation is the courtesy of the U.S. Census Bureau.



The population distribution by race/ethnicity is demonstrated in Table 1.

Table 1. The population distribution by race/ethnicity in the U.S. Data presentation is the courtesy of the Henry J. Kaiser Family foundation. Timeframe 2015.

Race/ethnicity	% of total population
Non-Hispanic white	61
Non-Hispanic black	12
Hispanic	18
Asian	6
American Indian/Alaska Native	1
Native Hawaiian/other Pacific Islander	0
Multiracial (two or more races/ethnicities)	2
Total	100

The US population is undoubtedly very diverse. This diversity is not only reflected by several races/ethnicities, but also in wealth and poverty levels and extreme social inequality. The U.S. Census Bureau's poverty threshold for a family with two adults and one child was $19,078 in 2015. Figure 4 demonstrates the distribution of poverty rates in the U.S.

Figure 4. Distribution of poverty by race/ethnicity. Data is the courtesy of Federal Safety Net.

	All Americans In Category (Millions)	Americans In Poverty (Millions)	Poverty Rate
White, not Hispanic	195.5	17.8	9.1%
Black	41.6	10.0	24.1%
Asian	18.2	2.1	11.4%
Hispanic, any race	56.8	12.1	21.4%

The NHANES program began in the early 1960s and has been performed as a series of studies focusing on different populations and/or health outcomes. In 1999, the survey became a continuous program and the focus changed more towards a variety of health and nutrition measurements to meet the emerging needs of the society and the healthcare system. In brief, the NHANES interview includes demographic, socioeconomic, dietary, and health-related questions. The examination component consists of medical, dental, and physiological measurements, as well as laboratory tests administered by highly trained medical personnel.

The main objective of NHANES is to determine the prevalence of major diseases and risk factors for diseases. Information received during the survey will be used to assess nutritional

status and its association with health promotion and disease prevention. NHANES findings are also the basis for national standards for measurements of height, weight, and blood pressure. Data from this survey are available for public access for researchers worldwide (*https://www.cdc.gov/nchs/nhanes/index.htm*) and is widely used in epidemiological studies and health sciences research. A quick search on *https://www.ncbi.nlm.nih.gov/pubmed/* reveals that NHANES based studies embrace over 30.000 publications. The strategies of the National Center for Health Statistics in general and NHANES program in particular help to develop adequate public health policy, direct and design healthcare programs and services, and expand the current health knowledge not only for the US population, but also for humanity as a whole.

NHANES data is unique and represents the epidemiological state-of-the-art. The main difference from other large epidemiological studies (for instance our local Tromsø study) is that the data are obtained by using a complex, multistage probability-sampling design to select participants, representative of the civilian, non-institutionalized U.S. population. The continuous NHANES refers to the 2-years cycles of data produced since 1999. Basically, it is the mathematically computed sample, composed of approximately 10.000 subjects per cycle, which is representative for the entire US population. In other words, the computed sample is demographically, ethnically and income-wise more or less similar to the total population of the U.S. (see figures 3 and 4, and Table 1). The details of this complicated sample estimation and weighting are available on *https://wwwn.cdc.gov/nchs/data/series/sr02_159.pdf.* The representativeness of the samples and great user-friendly public accessibility are the huge advantages of NHANES. However, we need to mention some minor limitations. Firstly, all of the dietary data, including intake of diary products, dietary supplements and the data on physical activity are self-reported. The same limitation affects the variable family income,

which was not cross-checked with tax reports. Secondly, self-reported diseases are not cross-checked with patient records.

The continuous NHANES refers to the 2-years cycles of data produced since 1999. In paper II we used the data from the continuous NHANES cycles 2001-2002. An overview of this cycle is presented in Appendix 4. This particular cycle oversampled low-income persons aged 60 years and over, persons of Hispanic, and non-Hispanic black race/ethnicity to obtain more accurate estimates in these populations. All respondents of this cycle aged ≥20 years were asked to provide DNA samples and consented specifically to future genetic research. Files providing genetic data were made available for public access in November 2014. There are some issues regarding methodological assessment of DNA and LTL in NHANES, which we feel need clearer acknowledgment here. DNA for LTL analyses was extracted from whole blood and stored at -80 °C using standardized procedures. The LTL assay was performed in the laboratory of Dr. Elisabeth Blackburn at the University of California, San Francisco, using the quantitative polymerase chain reaction (qPCR) method to measure telomere length relative to standard reference DNA (T/S ratio). The conversion from T/S ratio to kilobase pair (kb pair) was calculated based on a comparison of telomeric restriction fragment length from Southern blot analysis and T/S ratios using DNA samples from the human diploid fibroblast cell line IMR90 at different population doublings. The formula to convert the T/S ratio to kb pair was (3.274 + 2.413 × (T/S)). Since qPCR was not considered the gold standard of telomere length measuring, Cawthon [129] compared the standard method Southern blot and qPCR in 2002. In this study on 95 individuals, he found a strong correlation between these two very different approaches: correlation coefficient, r^2, for the relationship of T/S ratio (from qPCR approach) to mean terminal restriction fragment (TRF) length (from Southern blot approach) was 0.6777, and the *P* value was 1.4914×10^{-24}.

3.3 Interventional study. Tromsø vitamin D and obesity trial. Paper I

Our work presented in Paper I is the ancillary study to the main 1-year RCT, Tromsø vitamin D and obesity trial. In this RCT, high dose vitamin D supplementation was tested against placebo and the primary end-point was weigh loss. Males and females 21-70 years old, with BMI between 28.0 and 47.0 kg/m² were recruited by advertisements in local newspapers and from the ambulatory department of internal medicine at the University Hospital of North Norway [130]. The study was registered at ClinicalTrials.gov (NCT00685594). The exclusion criteria were serum calcium >2.55 mmol/L, serum creatinine >129 μmol/L (men) and >104 μmol/L (women). If serum calcium was 2.50-5.55 mmol/L, a measurement of serum PTH below 5.0 pmol/L was required. Other exclusions criteria were: known diabetes, active cancer or cancer diagnosed in the past five years, kidney stones, stroke or coronary heart disease in the past 12 month, pregnant or lactating women, women below 50 years without adequate contraception, planning a trip to a sunny location in the study period. Included subjects were required to withdraw from any current supplementation with calcium and/or vitamin D (including cod liver oil). Four hundred forty five subjects met the inclusion criteria and 332 subjects fulfilled the intervention. The participants were randomized into three groups: DD group (two capsules of 20.000 IU cholecalciferol, per week), DP group (one capsule of 20.000 IU cholecalciferol and one capsule of placebo, per week), and PP group (two capsules of placebo per week). They were all given supplementation with calcium 500 mg daily throughout the 1-year intervention period. Body measurements, estimates of insulin sensitivity (fasting insulin, HOMA-IR and QUICKI), as well as serum 25(OH)D, cytokines and h-s CRP were measured at baseline and at the end of intervention. The delta values were calculated to determine the changes (positive or negative) during the 1-year intervention.

The main short-coming of this ancillary work is that the primary end point was weigh loss and not the reduction of inflammation. The study was powered according to the primary end

point-weight loss. The inclusion criteria was therefore overweight and obese subjects and our results might not be applicable to the slimmer population. Moreover, we did not measure the cytokines in the intervals in between the baseline and the end of intervention, hence we could have missed the transient effects. And finally, all three groups received calcium supplementation, thus the potential effect of "pure" vitamin D supplementation

is most likely missed.

3.4 Interventional study. Tromsø vitamin D and T2DM trial. Paper II

Our work presented in paper II is the ancillary work to the 5-year RCT, Tromsø vitamin D and T2DM trial. In this trial, it was investigated whether high dose vitamin D supplementation has any effect on the prevention of T2DM. A more detailed description is available elsewhere [83]. Briefly, subjects for this study were recruited mainly from the sixth Tromsø study, the methodological considerations for which were described in detail above. Eligibility criteria were: age 21-80 years and impaired fasting glucose (IFG) (fasting glucose >6.0 mmol/L and < 7.0 mmol/L) and/or impaired glucose tolerance (IGT). IGT was defined as 2-hours serum glucose >7.7 mmol/L and <11.1 mmol/L on oral glucose tolerance test (OGTT) with 75 g glucose combined with a fasting glucose < 7.0 mmol/L. The exclusion criteria were: a history of coronary infarction, angina pectoris, stroke, sarcoidosis, cancer in the preceding 5 years, renal stones, nut allergies or reduced kidney function (serum creatinine >125 μmol/L in men and 105 μmol/L in women). Use of weight reducing drugs or antidepressant medications, pregnancy and lactation were also exclusion criteria, and females < 50 years and not using adequate birth control. The study was registered at ClinicalTrials.gov (NCT00243256).

All participants were randomized into two groups: high dose vitamin D supplementation (1 capsule with cholecalciferol 20,000 IU per week) or identical-looking placebo capsule containing arachis oil per week. The medications were provided for six months with all necessary information about intake of one capsule per each week. The subjects were not allowed to take vitamin D supplements (including cod liver oil) exceeding 400 IU per day.

To keep all investigators blinded, all data were sent directly to the hospital's Clinical Research Unit where the data files were merged and coupled to the randomization code. The follow-up period was 5 years. The variables of interest for the present study were recorded each 12 month. Delta values for hs-CRP were calculated for each year of intervention.

4 Main results

Paper I *Effects of a 1-year supplementation with cholecalciferol on interleukin-6, tumor necrosis factor-alpha and insulin resistance in overweight and obese subjects.*

In Paper I our aim was to examine the association between serum 25(OH)D and some proinflammatory cytokines (e.g. IL-6, TNF-α and hs-CRP) and if there is an effect of a 1 – year supplementation with high dose cholecalciferol on these cytokines. The study was an ancillary study to another RCT where weight loss was the main primary outcome. The subjects enrolled in this study were therefore overweight and obese.

At baseline, serum 25(OH)D was significantly negatively associated with the measure of insulin resistance (HOMA-IR), adjusted for gender and smoking status, indicating that higher levels of 25(OH)D is associated with better insulin sensitivity (e.g. with an increase in serum 25(OH)D by 1 nmol/L, HOMA-IR was reduced by 0.10). No statistical significant

associations were seen between serum 25(OH)D and levels of IL-6 and TNF-α, however the associations direction between serum 25(OH)D and levels of IL-6 was negative (linear regression coefficient of -0.09).

There were no significant differences between the subjects in the DD, DP and PP groups before intervention. When DD and DP groups were analyzed together, there were still no differences in baseline values (BMI, serum 25(OH)D, PTH, hs-CRP, IL-6, TNF-α, and insulin resistance measures HOMA-IR and QUICKI).

After 1-year intervention, serum 25(OH)D increased and serum PTH levels decreased as expected in DD and DP groups as compared to PP group. Except for this finding, there were no significant changes in delta values for cytokines and insulin resistance measures in these three groups. However, after combining the DD and DP groups in one vitamin D group, the latter had a pronounced, but not statistically significant ($P = 0.08$) decrease in IL-6 and an elevation of hs-CRP at the end of the study when compared to the PP group. Neither measures of insulin resistance, nor TNF-α were influenced by a 1-year vitamin D supplementation. We concluded that vitamin D supplementation over a 1-year period had a lowering effect on a proinflammatory cytokine IL-6. However, the clinical impact is scarce since there was no corresponding effect on insulin sensitivity and other proinflammatory cytokines.

Paper II *High-sensitivity CRP is associated with serum 25-hydroxyvitamin D levels, but is not affected by 5-year supplementation with cholecalciferol.*

In paper II our aim was to investigate the association between serum 25(OH)D and hs-CRP in the large observational study, the sixth Tromsø study, and in the smaller cohort of subjects with prediabetes. In the total study population of the sixth Tromsø study (n=10118), there was a significant negative correlation between serum 25(OH)D and hs-CRP, resulting in a Pearson

correlation coefficient *r* of −0.05 (P=0.001). In the linear regression model, after adjusting for age, sex, BMI, HbA_1c and waist circumference, a 1 nmol/L increment in serum 25(OH)D resulted in a 0.02 mg/L decrease in hs-CRP (P=0.03). As there were significant interactions between BMI, serum 25(OH)D and sex, we performed a sex-stratified analysis. When analysing the genders separately, the negative association was statistically significant only in the women, resulting in a Pearson correlation coefficient *r* of −0.06 (P=0.001) and a β coefficient of −0.03 (P=0.03). In a smaller cohort of subjects with prediabetes (n=511), there were no significant correlations between serum 25(OH)D and hs-CRP. However, in a multiadjusted linear regression model there was a negative but not statistically significant association between serum 25(OH)D and hs-CRP, adjusted for age, sex, BMI, HbA_1c and smoking, resulting in decrease in hs-CRP with 0.06 mmol/L with each increase of serum 25(OH)D by 1 nmol/L.

Furthermore, these subjects with prediabetes were randomized to either 20 000 IU cholecalciferol per week or placebo and followed up for 5 years. At baseline, there were no differences between the vitamin D group and the placebo group with regard to age (68±8 years and 68±9 years, respectively) and sex (63% males and 60% females, respectively). There was also no difference in vitamin D supplement use (n=87 [34.0%] in the vitamin D group versus n=92 [36.1%] in the placebo group). The effect of intervention was studied by the analysing differences between delta values of hs-CRP for each year of intervention and with the logistic regression model, with hs-CRP decrease (yes/no dichotomous variable) and type of intervention(cholecalciferol/placebo) as a predictor, adjusted for age, sex, BMI, HbA_1c and smoking status at baseline). There were no significant differences between the vitamin D and placebo groups in delta values of hs-CRP during any part of the 5-year intervention. Interestingly, in contrary to what was expected, vitamin D intervention was associated with an increased odds ratio for delta hs-CRP of >0 for each year of intervention;

however, the statistical significance of this observation was only seen for delta values at the second year.

Paper III *Serum 25-Hydroxyvitamin D has a modest positive association with leucocyte telomere length in middle-aged US adults.*

In Paper III our aim was to examine the association between serum 25(OH)D and LTL. LTL was measured in 4260 participants of different age groups. Three age groups were defined: young adults 20-39 years, middle-aged adults 40-59 years and older adults ≥60 years. There were no differences in serum 25(OH)D concentration between age groups. All of the age groups differed significantly in LTL, with the longest LTLs in adults aged 20-39 years. Only women aged ≥60 years had significantly longer LTL than men of the same age; otherwise, there were no significant differences in LTL according to sex in those aged 20–39 and 40–59.

In the whole study population, age and BMI had significant negative associations with LTL when adjusted for sex, race/ethnicity, serum 25(OH)D, total energy and sugar intakes, calcium intake, socioeconomic status, consumption of milk and supplements, and physical activity. Thus, an increase in age by one year was associated with 0.02 ± 0.001 kb pair shorter LTL ($P < 0.001$), and an increase in BMI by 1 kg/m^2 was associated with 0.01 ± 0.002 kb pair shorter LTL ($P=0.02$). Furthermore, in the same multiple adjusted model, female sex was associated with 0.09 ± 0.03 kb pair longer LTL ($P=0.02$) as compared to male sex, and non-Hispanic black race/ethnicity was associated with 0.10 ± 0.05 kb pair longer LTL ($P=0.049$) as compared to non-Hispanic white race/ethnicity. Serum 25(OH)D concentrations had no significant association with LTL in the whole population.

In age group stratified multivariate analyses, age was the only significant negative predictor of LTL in each age group. Regarding serum 25(OH)D, only middle-aged adults

demonstrated a subtle, but statistically significant, positive association between serum 25(OH)D and LTL after adjustments for age, sex, race/ethnicity, BMI, total energy and sugar intakes, calcium intake, socioeconomic status, consumption of milk and supplements, and physical activity . An increase in serum 25(OH)D concentration by 10 nmol/L was associated with 0.03 ± 0.01 kb pair longer LTL in the unadjusted model and with 0.03 ± 0.01 kb pair longer LTL in the multiple adjusted model. After sex stratification of the age group 40–59 years, and after the multiple adjustments for other factors, the 25(OH)D–LTL association remained positive and statistically significant in both sexes (β of 0.03, P= 0.04 and β of 0.03 P= 0.02, for men and women respectively).

Moreover, middle-aged participants with serum 25(OH)D concentrations considered optimal (25(OH)D ≥ 50 nmol/L) demonstrated significantly longer LTL than their counterparts with serum 25(OH)D concentrations < 50 nmol/L (5.90 ± 0.05 kb pair versus 5.78 ± 0.05 kb pair, respectively, P = 0.03). When serum 25(OH)D was entered into the multivariate regression model as a dichotomous variable (< 50 nmol/L and ≥ 50 nmol/L) and adjusted for age, sex, race/ethnicity, BMI, and other factors, participants with serum 25(OH)D concentrations ≥ 50 nmol/L had 0.13 ± 0.04 kb pair longer LTL compared to their counterparts with serum 25(OH)D concentrations < 50 nmol/L (P = 0.01).

5 General discussion of the main results

Vitamin D, metabolic syndrome and inflammation.

Overweight is a risk for all-cause mortality [131] and has become a pandemic in the last decades of the 20th century [132].

Chronic inflammation and proinflammatory cytokines CRP, IL6, TNFα are tightly associated with metabolic conditions like obesity, insulin resistance, endothelial dysfunction and CVD [133, 134] . Patients with T2DM also demonstrate deranged inflammatory profile with overproduction of certain proinflammatory cytokines [135].

Reduced concentrations of serum 25(OH)D and inadequate vitamin D status has recently been linked to proinflammatory conditions, such as metabolic syndrome [136] , CVD and atherosclerosis [137], insulin resistance and overweight [138, 139]. A body of evidence from associational studies has stimulated the further interventional research on vitamin D and prevention of these conditions.

In Paper I we found a strong association between cytokines and metabolic syndrome parameters at the baseline of the RCT. This is consistent with results from earlier observational studies [140-143]. No significant correlation was found between proinflammatory cytokines and vitamin D, which is partly opposite to findings from some other studies. For instance, Peterson et al. studied 69 healthy women, aged 25-82 years with a wide range of serum 25(OH)D concentration, due to recruitment from both high and low sun exposed populations. In this study, the authors found that TNF-α was inversely related to serum 25(OH)D, while no significant association was found between serum 25(OH)D and other proinflammatory cytokines (CRP, IL-10 and IL-6)[144]. It is interesting to note that mean serum 25(OH) D in our study was lower than mean serum 25(OH)D in women from UV low-exposed population in Peterson`s study (54.3 nmol/l versus 74.4 nmol/L, respectively), and certainly lower then mean serum 25(OH)D in women from UV high-exposed population (126 nmol/L). At the same time in Peterson`s study serum levels of TNF-α differed significantly between groups according to serum 25(OH)D status, and the high UV-exposure group had significantly lower serum TNF-α levels than the low UV-exposure group (0.79 pg/ml versus 1.22 pg/ml, respectively). Interestingly, our subjects had mean serum

TNF-α levels even higher than those from the low UV-exposure group in Peterson's study (1.53 pg/ml), which might be explained by our subjects' overweight which is proinflammatory per se.

In the RCT we found that vitamin D supplementation over a 12 month period had a lowering effect on IL-6, but no effect TNF-α or hs-CRP. Our findings are opposite to some other interventions, in which a beneficial effect of vitamin D supplementation on proinflammatory cytokines, TNF-α, IL-6 and IL-10 was described [143, 145, 146]. However, these studies were performed in highly selected groups of patients with type II diabetes, end stage kidney disease and colorectal adenoma. These diseases have more pronounced inflammation and adverse immune response, as compared to an otherwise healthy overweight population in our RCT.

Despite evidence of IL-6 involvement in glucose metabolism [142] and findings of lowering of IL-6 under supplementation with vitamin D in previous RCTs [143] , we didn't demonstrate any favorable effect of decreased of IL-6 during cholecalciferol supplementation on insulin sensitivity. Most likely the potential effects on insulin sensitivity could be mitigated by the fact that metabolic disturbances and inflammatory changes were not severe enough to be clinically significant.

An unexpected finding in our paper I is increased hs-CRP after 12 months supplementation with high dose cholecalciferol. Interestingly, a similar finding is also present in our paper II. This is hard to explain. A possible explanation might be the parallel stimulation of protein synthesis (including acute-phase proteins) in the liver under the cholecalciferol treatment, and CRP is a protein which is predominantly synthesized in the liver [75]. Its worth mentioning that the similar finding in our paper II was only statistically significant after the second year of intervention and was further mitigated during the continued intervention. This finding is not entirely consistent with other studies [147, 148], and most likely due to chance.

In Paper II we demonstrated a significant negative correlation between serum 25(OH)D and hs-CRP in the general non-smoking population in our observational study. The association was highly significant in females only after gender stratification. However, regarding our prediabetes RCT population, we did not find any significant association between serum 25(OH)D levels and serum levels of hs-CRP. The supplementation with 20 000 IU cholecalciferol per week during 5 years period did not lead to any lowering effect on hs-CRP. Moreover, as mentioned above, after second year of intervention receiving the cholecalciferol treatment was associated with almost 50 % increased odds ratio of getting increased hs-CRP values.

Some observational and interventional studies, unlike ours, show significant negative association between vitamin D and hs-CRP, and lowering effect of cholecalciferol on hs-CRP, but mostly in subjects with other proinflammatory conditions like cardiovascular disease, obesity and in the elderly [149-151]. Interestingly, this relationship was than stronger in those with lower levels of serum 25(OH)D or in those with higher serum levels of hs-CRP [152-156]. This discrepancy can be explained by possibly higher expression of proinflammatory cytokines in vitamin D deficient subjects.

The lack of an intervention effect in our paper II is not very unexpected, however, in regard to our study population. At baseline there was no significant association between serum 25(OH)D and hs-CRP, while the direction of the association was nevertheless inverse. It is important to remember that study populations for our observational study and our RCT study were quite different. The RCT population included subjects with prediabetes and hence ongoing inflammation, though otherwise healthy. The drawback of the majority of RCTs is that they recruit highly specific populations with one or several diseases/conditions, on which we try to intervene. In our RCT the target population included subjects with prediabetes and the primary outcome was T2DM. One may therefore speculate that if the study population had

been composed of generally healthy subjects from Tromsø municipality and the primary outcome was lowering of proinflammatory cytokines, the result might have been different.

Summarizing, there is an association between serum 25(OH)D levels and proinflammatory cytokines (hs-CRP) in the North Norwegian general population. A population with more or less optimal serum 25(OH)D levels (~50 nmol/L). However, long-term supplementation with high dose cholecalciferol in a vitamin D sufficient population, but with present metabolic conditions (e.g. obesity or prediabetes) does not lead to decrease in proinflammatory cytokines (Il-6, TNF-α and hs-CRP). Thus, the effect of cholecalciferol treatment on metabolic conditions with deranged inflammatory profile is uncertain and most likely minimal, if present at all.

Vitamin D and Leukocyte Telomere Length

Previous observational studies indicate that vitamin D deficiency is associated with increased incidence and prevalence of age-related diseases, such as CVD, cancer and autoimmune diseases [11, 18, 58] . Moreover, findings from the observational studies are supported by recent genetic research [157]. It is well established that telomeres shortening play an important role in carcinogenesis and are crucial for aging at cellular level [106]. Several studies from the past decade demonstrate that telomere shortening (for instance measured as LTL) is significantly associated with higher risk of CVD, dementia and inflammatory diseases [107, 110, 158] .

Our study supports current knowledge on the associations between LTL and age, LTL and race/ethnicity on many points. However, our findings of the positive and significant association serum 25(OH)D-LTL in middle-aged adults were only in partially consistent with existing research. Thus, in the study based on Northern Finland Birth Cohort 1966, there was no significant association between serum 25(OH)D and LTL [159]. All of the participants in

the Finnish study were 31 years old at the time of the study, and the small age range could be a possible explanation for the discrepancy between their results and ours.

Other studies that found no association between serum 25(OH)D and LTL, were the studies by Julin et al.[160] and Liu at al.[161]. However, these studies were performed on highly selected populations and did not represent wide samples of participants across all age groups in human adulthood and diversity in race/ethnicities.

To our knowledge, only one of these observational studies on white women with an average age of 59 years [162] found a significant positive association between serum 25(OH)D and LTL, and results that were similar to ours. In this study the highest quartile of serum 25(OH)D (median concentration of 103 nmol/L) was associated with an almost 60% increased odds of higher LTL compared with the lowest quartile (median serum 25(OH)D concentration of 38 nmol/L).

We also found significant associations between LTL and age, sex and BMI and these findings support knowledge about telomere shortening during aging, shorter telomeres in men than women and shorter telomeres in obese persons.

Thus, our observational findings may be interpreted in two ways. Firstly, the genomic instability associated with decreased serum 25(OH)D levels may start in younger adulthood and targeting the sufficient/optimal vitamin D status, may prevent accelerating of the LTL shortening. Another interpretation may come from the perspective of an inverse causality. Thus, one can speculate that middle-aged persons with optimal vitamin D status have in general better health, lower incidence of chronic conditions and subsequently have lower inflammation rate and oxidative stress, which are crucial determinants of shorter LTL [163, 164].

With regard to vitamin D`s role in carcinogenesis, it is undoubtedly difficult to provide proof causality even though evidence from several upcoming RCTs show lower incidents of some cancer types under supplementation with vitamin D [165, 166]. Neither of these studies have incidence of malignant diseases as a primary outcome, the occurrence of malignancies were registered as secondary outcomes. Future studies are indeed needed to determine the effect of vitamin D in the prevention of malignancies. Nevertheless, we feel that our findings are important as they strongly support the biological plausibility of the latter hypothesis.

6 Conclusions and future opportunities

Our findings are partly consistent with other studies regarding a relation between serum 25(OH)D levels and markers of inflammation, carcinogenesis and aging.

- there is no statistical significant associations between serum 25(OH)D and levels of IL-6 and TNF-α in the overweight and obese subjects at the baseline of RCT, however the associations direction between serum 25(OH)D and levels of IL-6 is inverse
- cholecalciferol supplementation (20 000 IU/weekly or 40 000 IU/weekly) tends to decrease the levels of IL-6 and does not affect TNF-α levels in overweight and obese subjects
- there is a significant negative association between serum 25(OH)D concentrations and hs-CRP (a marker of low grade inflammation) in the non-smoking general population and this relation is independent of other factors. However, in subjects with prediabetes, there is no such significant association at the baseline of RCT
- supplementation with cholecalciferol (20 000 IU/weekly during 5 years) does not reduce the serum concentration of hs-CRP

- there is a significant positive association between serum 25(OH)D concentrations and LTL (a marker of carcinogenesis and aging) in middle-aged adults in the U.S.

The observational studies were based on different populations, north Norwegian and American, which strengthens the legitimacy and eligibility of our findings. However, two of the RCTs which we performed and analyzed could not support the hypothesis that vitamin D supplementation can have a positive effect on inflammation markers. The main conclusion of this thesis is therefore that deranged vitamin D status is associated with increased levels of proinflammatory cytokines and marker of carcinogenesis and aging LTL, but since the beneficial effect of cholecalciferol supplementation was not evident, clinical importance and implication of this association is most likely scarce.

The results of some large RCTs on the effect of vitamin D on clinically relevant outcomes have started to be published [167]. To our knowledge, the only clinical outcome which is demonstrated to be improved by high dose cholecalciferol supplementation is muscle strength, and as a result reduced fall frequency in the elderly [168]. The other extraskeletal benefits of vitamin D are yet to be confirmed. The different dosages of cholecalciferol and different administration intervals are also examined in ongoing studies. It might be also interesting to investigate if enteral cholecalciferol administration is equal in regard to biological and clinical effect as vitamin D received through skin as a result of UV radiation. To our knowledge, there are no ongoing RCTs focusing on this issue. However, it could be difficult to obtain the necessary permits from the ethics committees, as it would involve solar exposure. Future investigations are needed to establish the further extraskeletal clinical impact of vitamin D.

7 References

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Appendix 1

Tromsø 6
- en del av Tromsøundersøkelsen

Vil du være med i den 6. Tromsøundersøkelsen?

» viktig forskning
» undersøkelse av egen helse
» forebygging av helseproblemer

Hva er Tromsøundersøkelsen?

Tromsøundersøkelsen er et stort forskningsprosjekt. Opplysninger som samles inn skal brukes til å gi oss kunnskap som kan bedre menneskers helse.

Den første Tromsøundersøkelsen ble gjennomført allerede i 1974, og dette er den sjette i rekken. Et viktig mål med undersøkelsen er å få kunnskap om hvorfor noen blir syke mens andre beholder god helse gjennom livet.

Visste du at ..?

Den som deltar på Tromsøundersøkelsen får også en enkel undersøkelse av sin egen helse.

Hva forskes det på i Tromsøundersøkelsen?

Tromsøundersøkelsen gjennomføres først og fremst for å kunne øke kunnskapen om de store folkehelseproblemene og forhold som påvirker disse, blant annet:

- Hjerte- og karsykdommer
- Lungesykdommer (f.eks. KOLS)
- Diabetes
- Stoffskiftesykdommer
- Kreftsykdommer
- Psykiske plager
- Demens
- Muskel- og skjelettplager

Undersøkelsen vil også bli benyttet til forskning om bruk og effekter av legemidler, trivsel, livskvalitet, livsstil, døgnrytme, smerter, sosial ulikhet, fysisk aktivitet, kosthold, bruk av helsetjenester og alternativ behandling. Det vil også bli undersøkt om miljøgifter kan påvises i blodet og om disse innvirker på helsa.

Videre vil det bli gjort forskning på kvinnesykdommer, sykdommer i fordøyelsesorganer, allergi, nyrer og urinveier, nervesystemet, sanseorganer og hud. Det vil også bli forsket på arbeidsuførhet som følge av disse sykdommene eller tilstandene. En del av prosjektene vil spesielt undersøke samspillet mellom arv, miljø, sykdom og helse. Til slike prosjekter vil det bli hentet ut DNA (arvestoff) fra blodprøvene.

Det er allerede planlagt mange forskningsprosjekter som skal benytte data fra Tromsøundersøkelsen. Du vil finne en liste over disse på vår internettside:

http://www.tromso6.no

Vil du delta?

Ved å delta på Tromsøundersøkelsen er du med på å bidra til forskning om hvordan sykdom kan forebygges og behandles, hva som fremmer god helse, og hva som er årsak til helseproblemer.

Hvorfor spør vi deg?

Alle som møtte til spesialundersøkelsene i Tromsøundersøkelsen i 1994 og 2001, og et tilfeldig uttrukket utvalg av personer som er over 30 år og som er innbyggere i Tromsø kommune, blir spurt om å delta.

Alle er viktige!

Hver deltaker er like viktig, enten du er ung eller gammel, frisk eller syk. Det har vært stort frammøte til de tidligere Tromsøundersøkelsene. Godt oppmøte er viktig for gode forskningsresultater. Det er en styrke for forskningen at de som har vært med i tidligere Tromsøundersøkelser møter fram på nytt.

Frivillig

Det er frivillig å delta. Det vil ikke få noen konsekvenser for deg dersom du ikke deltar eller velger å trekke deg fra undersøkelsen på et senere tidspunkt. Du må ikke gi noen begrunnelse dersom du ønsker å trekke deg fra undersøkelsen.

Visste du at ..?

Du kan delta på Tromsøundersøkelsen selv om det er deler av undersøkelsen du ikke ønsker å være med på.

Din helse

Cirka fire uker etter undersøkelsen vil du få et brev med resultatene fra målinger av kolesterol og blodtrykk. Dersom det er nødvendig, vil du bli anbefalt å ta kontakt med din fastlege. Det blir ikke gitt rutinemessig tilbakemelding om resultater av andre blodprøver eller målinger.

Dersom resultatet av prøvene viser at det er nødvendig med oppfølging av lege eller henvisning til spesialist, vil du bli orientert om det. Ved behov for henvisning til spesialist, vi vil sørge for at slik henvisning blir sendt.

Du kan reservere deg mot å få vite resultatene av prøvene dine. Men hvis et prøveresultat er slik at det er nødvendig med rask legebehandling, vil du uansett bli kontaktet.

Tromsøundersøkelsen er gratis. Trenger du videre undersøkelse / oppfølging av fastlegen eller i spesialisthelsetjenesten, betaler du vanlig egenandel.

Slik foregår undersøkelsen

Sammen med dette informasjonsskrivet ligger det et ark med praktiske opplysninger og beskjed om hvor og når du kan møte fram. Her står også åpningstidene for undersøkelsen. Hvis du vil delta og den foreslåtte tiden ikke passer, kan du komme en annen dag. Du trenger ikke melde fra om dette på forhånd.

Unngå før undersøkelsen

For at resultatene skal bli mest mulig korrekt, er det en fordel om du avstår fra alkohol og smertestillende medisiner 12 timer før undersøkelsen.

Påkledning

Vekt og høyde, liv- og hoftevidde måles med lett påkledning, men uten sko. For at det skal gå raskt å måle blodtrykk, er det en fordel om du har plagg som ikke strammer over armen og benet. Ha gjerne et kortermet plagg innerst.

Spørreskjema

Sammen med denne brosjyren har du fått et spørreskjema som du skal fylle ut og ta med til undersøkelsen. Hvis du er i tvil om hvordan du skal svare på et eller flere av spørsmålene, lar du det stå åpent. Personalet på undersøkelsen hjelper deg da med utfyllingen om du ønsker det.

Utfylte svar i spørreskjema er like viktig for forskningen som resultater fra blodprøver og undersøkelser.

Regelmessig bruk av legemidler

Ved frammøte til undersøkelsen vil du bli intervjuet om hva slags legemidler du har brukt regelmessig de siste fire ukene, og om noen av de legemidlene du har brukt siste 24 timer. Navn på legemidler du bruker fast kan besvares i skjemaet på forhånd. Ta gjerne med deg legemidlene du bruker ved frammøte til undersøkelsen.

Undersøkelser

Når du møter fram, vil kvalifisert helsepersonell veilede deg gjennom undersøkelsen og svare på spørsmål. Du vil bli intervjuet og få utlevert et nytt spørreskjema med en frankert svarkonvolutt. Spørreskjemaet kan også besvares mens du er tilstede på undersøkelsen, og du vil kunne få hjelp underveis. Hver enkelt undersøkelse varer bare noen minutter. Totalt vil undersøkelsen vare cirka en time.

De måler høyde, vekt, hoftevidde og livvidde, de måler blodtrykket og tar blodprøve av deg. I tillegg vil følgende undersøkelser bli gjort:

- Beintetthetsmåling (måling av beinmasse) i den ene armen med svake røntgenstråler. Målingene brukes til å undersøke risiko for beinskjørhet og brudd.
- Bakterieprøve fra nese og hals fra om lag halvparten av deltagerne, for å se etter gule stafylokokker, en bakterie som normalt finnes på hud og slimhinner hos mennesker, men som i enkelte tilfeller kan forårsake alvorlige infeksjoner. Prøven gjøres med fuktet vattpensel.
- Smerteølsomhet som måler hvordan kroppen reagerer på smerte. Du blir bedt om å holde hånden i isvann i opptil 1 minutt. Underveis registreres blodtrykk og du angir hvor mye smerte du kjenner. Du kan ta hånden ut av vannet før tiden er ute hvis det blir for ubehagelig.
- Hårprøve. Vi vil be om å få noen hårstrå for å undersøke forekomsten av spormetaller som kvikksølv.
- Fysisk aktivitet og kosthold. Vi planlegger at utvalgte deltakere vil bli bedt om å registrere fysisk aktivitet (aktivitetsmålere som skritttellere og lignende) og kosthold i en periode.

Blodprøver

Blodet fordeles på fem glass, men til sammen utgjør det ikke mer enn 45 milliliter, som er mindre enn en tidel av det en blodgiver gir. For de aller fleste vil det være tilstrekkelig med ett stikk. Disse analysene blir gjort:

- Måling av kolesterol og andre fettstoffer, blodsukker, blodlegemer, stoffskifteprøver, hormoner, markører for betennelsesreaksjoner, allergi, mage- og tarmfunksjon, lever- og nyrefunksjon samt muskel- og beinmarkører.
- DNA (arvestoff) vil bli lagret til bruk i forskningsprosjekter som er omtalt i denne brosjyren og som kartlegger sammenhengen mellom arv og miljø, sykdom og helse. DNA vil ikke bli brukt til andre formål enn forskning.
- Miljøgifter, blant annet sporstoffer, spormetaller og organiske stoffer. Forekomsten i blodet skal sammenlignes med tilsvarende målinger i andre befolkninger. Forskere vil studere om miljøgifter kan påvirke helsa vår.

Spesialundersøkelsen

Når første del av Tromsøundersøkelsen er gjennomført, kan du bli forespurt om å delta i en eller flere deler av Spesialundersøkelsen noen uker senere. Over halvparten vil bli spurt om dette. Hele Spesialundersøkelsen vil vare cirka en time, og

varigheten vil være avhengig av hvor mange deler du blir spurt om å være med på. Ved oppmøte til Spesialundersøkelsen vil det bli tatt ny blodprøve som skal brukes til samme formål som beskrevet for første del av undersøkelsen. Deler av blodprøven blir frosset ned for senere bruk i forskning som er beskrevet i denne brosjyren.

Hvilke undersøkelser gjøres i Spesialundersøkelsen?

- Ultralyd av blodårene (arteriene) på halsen. Undersøkelsen gjøres for å se etter forkalkninger og innsnevringer av årene. Undersøkelsen kartlegger også blodforsyningen til hjernen.
- Ultralyd av hjertet gjøres for å undersøke hjertets form og funksjon.
- Måling av beintetthet i rygg/hofte og kroppens fettmengde. Målingene brukes til å undersøke risiko for beinskjørhet og brudd, og for studier om sammenhengen mellom kroppsfett, beinmasse og brudd.
- Fotografering av øyebunn. Fotografiet vil vise tilstanden for blodkarene i øyet som også sier noe om blodkarene i kroppen. Ved øyestasjonen tas fotografi av øyebunnen din. Deltagerne får en øyedråpe i hvert øye en tid før fotografering for at pupillene skal utvide seg. Dette kan svi noe og synet kan forbigående bli noe uklart. Effekten går gradvis over, og etter en time er den borte. I tillegg vil det gjøres en enkel synstest som du vil få svar på umiddelbart.
- Tester av hukommelse gjøres ved hjelp av enkle spørsmål og omfatter også evne til gjenkjenning av ord og grad av fingerbevegelighet.
- EKG og blodtrykk. EKG er en registrering av hjerterytmen som også kan gi informasjon om hjertesykdom. Ved registrering festes ledninger til kroppen. Blodtrykket måles både på overarmen og ved ankelen.
- Pusteprøve. Dette er en enkel undersøkelse av lungefunksjonen. Du skal puste så hardt du klarer gjennom et munnstykke. Hvor mye luft som blåses ut pr. sekund, er et mål på lungefunksjonen din.
- Ny bakterieprøve fra nese og hals. Prøven utføres på samme måte som i første del av undersøkelsen.
- Urinprøve. Du vil bli bedt om å avlevere urinprøver fra de tre siste dagene før spesialundersøkelsen. Du gis alt nødvendig utstyr. Urinen blir lagret til bruk i forskning som er beskrevet i denne brosjyren.

For å sikre høy kvalitet på forskningsdata ønsker vi å undersøke et lite utvalg som møter til undersøkelsen to ganger med circa en ukes mellomrom. De som er aktuelle vil bli forespurt om dette ved frammøte.

Nye prosjekter

Noen deltakere vil i ettertid bli spurt om å delta i videre undersøkelser. Hvis dette gjelder deg, vil du få en forespørsel i posten. Du er ikke forpliktet til å delta selv om du har deltatt i andre deler av Tromsøundersøkelsen. Omtale av alle delprosjektene finner du på nettsiden vår:

http://www.tromso6.no

Forsikring og finansiering

Deltakere i Tromsøundersøkelsen er forsikret gjennom Norsk Pasientskadeerstatning.

Tromsøundersøkelsen er finansiert av Universitetet i Tromsø, Helse Nord HF samt ulike forskningsfond.

Etikk, personvern og sikkerhet

Du kan være trygg på at informasjon som gis til Tromsøundersøkelsen vil bli behandlet med respekt for personvern og privatliv, og i samsvar med lover og forskrifter. Alle medarbeidere som jobber med undersøkelsen har taushetsplikt. Opplysningene som samles inn vil bare bli brukt til godkjente forskningsformål.

Alle opplysninger om deltakere vil bli lagret på datamaskin. Navn og personnummer blir fjernet og erstattet med en kode. Kodenøkkelen oppbevares separat og kun noen få, autoriserte medarbeidere har tilgang til denne.

Den enkelte forsker får ikke tilgang til opplysninger som gjør det mulig å identifisere enkeltpersoner. Hver enkelt deltaker har en rett til å vite hvilke opplysninger som er lagret om en selv.

For alle prosjekter kreves det at prosjektlederen tilhører en kompetent forskningsinstitusjon.

Tromsøundersøkelsen har konsesjon fra Datatilsynet og er godkjent av Regional komité for medisinsk forskningsetikk, Nord-Norge.

Sammenstilling med andre registre

Opplysninger om deg fra den sjette Tromsøundersøkelsen kan bli knyttet sammen med opplysninger fra tidligere Tromsøundersøkelser. For enkelte prosjekter kan det være aktuelt å sammenstille opplysninger om deg med opplysninger fra barn, søsken, foreldre og besteforeldre hvis disse har deltatt i Tromsøundersøkelsen.

For spesielle forskningsprosjekter kan det være aktuelt å sammenstille informasjon fra Tromsøundersøkelsen med nasjonale helseregistre som Reseptregisteret, Medisinsk fødselsregistrer, Kreftregisteret, Norsk pasientregister og Dødsårsaksregisteret, og andre nasjonale registre over sykdommer som det forskes på i Tromsøundersøkelsen.

I tillegg kan det være aktuelt å innhente helseopplysninger fra primær- og spesialisthelsetjenesten til bruk i forskning på sykdommer og helseproblemer som er nevnt i denne brosjyren, for eksempel hjerte-karsykdom, diabetes og beinbrudd. I slike tilfeller innhentes nytt samtykke, eller annen type godkjenning (dispensasjon fra taushetsplikten).

Informasjon fra Tromsøundersøkelsen kan også bli sammenstilt med registre ved Statistisk sentralbyrå, for eksempel om miljø, befolkning, utdanning, inntekt, offentlige ytelser, yrkesdeltakelse og andre forhold som kan ha betydning for helsa.

Slike sammenstillinger krever noen ganger forhåndsgodkjenning av offentlige instanser, for eksempel Regional komité for medisinsk forskningsetikk, Datatilsynet eller NAV.

Bruk av innsamlede data i framtiden

Data fra Tromsøundersøkelsen vil kun bli brukt til forskning og vil ikke kunne brukes til andre formål.

Opplysninger og prøver som du gir, blir oppbevart på ubestemt tid til bruk i forskning til formål som nevnt i denne brosjyren. I noen tilfeller kan det bli aktuelt å gjøre analyser av blodprøver ved forskningsinstitusjoner i utlandet. Hvis dette gjøres, vil det skje i en slik form at våre utenlandske samarbeidspartnere ikke kan knytte prøvene opp mot deg som person.

Hva som er aktuelle problemstillinger i medisinsk forskning forandrer seg hele tiden. I framtiden kan data bli brukt i forskningsprosjekter som i dag ikke er planlagt, forutsatt at det er i samsvar med gjeldende lover og forskrifter. For alle slike nye prosjekter kreves det at prosjektet er godkjent av Regional komité for medisinsk forskningsetikk og Datatilsynet.

Tromsøundersøkelsen informerer om nye forskningsprosjekter på: http://www.tromso6.no
Her kan du også lese om forskningsresultatene fra Tromsøundersøkelsen. Forskningsresultater vil ellers bli publisert i internasjonale og nasjonale tidsskrifter, på faglige konferanser og møter. Det vil ikke være mulig å identifisere enkeltpersoner når forskningsresultatene offentliggjøres.

Samtykke

Hvis du vil delta i den sjette Tromsøundersøkelsen, må du gi skriftlig samtykke til dette. Personalet på Tromsøundersøkelsen vil kunne gi mer informasjon om undersøkelsen, og kan svare deg dersom du har spørsmål i forbindelse med samtykket.

Det er viktig å vite at selv om du sier ja til dette nå, kan du senere ombestemme deg. Du kan når som helst etter undersøkelsen trekke ditt samtykke tilbake. Allerede innsamlede data blir lagret videre, men kan ikke lenger knyttes til deg som person, og dine data vil ikke bli brukt i nye forskningsprosjekter. Du kan be om at blodprøven din blir ødelagt.

Hvis du vil trekke tilbake ditt samtykke, henvend deg til:

Tromsøundersøkelsen, Inst. for samfunnsmedisin
Universitetet i Tromsø
9037 Tromsø
telefon: 77 64 48 16
telefaks: 77 64 48 31
e-post: tromsous@ism.uit.no
internett: www.tromso6.no

Hvis vi i framtiden ønsker å forske på nye spørsmål som ikke er beskrevet i denne brosjyren, kan det bli nødvendig å be deg om et nytt samtykke.

Vil du delta?

Følgende tekst er en kopi av dokumentet du blir bedt om å signere når du møter fram til undersøkelsen:

Samtykke til bruk av helseopplysninger i forskning - den 6. Tromsøundersøkelsen

I brosjyren jeg har fått tilsendt, har jeg lest om undersøkelsens innhold og formål, og jeg har hatt mulighet til å stille spørsmål. Jeg samtykker herved i å delta i undersøkelsen [dato/signatur].

Tromsø-
undersøkelsen

Tromsøundersøkelsen
Institutt for samfunnsmedisin, Universitetet i Tromsø
9037 TROMSØ
telefon: 77 64 48 16
telefaks: 77 64 48 31
epost: tromsous@ism.uit.no
internett: www.tromso6.no

www.GnistDesign.no

Appendix 2

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 3

Tromsø 6

- en del av Tromsøundersøkelsen

SLIK FYLLER DU UT SKJEMAET:

Skjemaet vil bli lest maskinelt, det er derfor viktig at du krysser av riktig:

☒ Riktig

☑ Galt

☒ Galt

■ Om du krysser feil, retter du ved å fylle boksen slik

Skriv tydelige tall 1 2 3 4 5 6 7 8 9 0

7 | 4 Riktig

7 | 4 Galt

Bruk kun sort eller blå penn, bruk ikke blyant eller tusj

1. BESKRIVELSE AV DIN HELSETILSTAND

Vis hvilke utsagn som passer best på din helsetilstand i dag ved å sette ett kryss i en av rutene utenfor hver av de fem gruppene nedenfor:

1.01 **Gange**

- ☐ Jeg har ingen problemer med å gå omkring
- ☐ Jeg har litt problemer med å gå omkring
- ☐ Jeg er sengeliggende

1.02 **Personlig stell**

- ☐ Jeg har ingen problemer med personlig stell
- ☐ Jeg har litt problemer med å vaske meg eller kle meg
- ☐ Jeg er ute av stand til å vaske meg eller kle meg

1.03 **Vanlige gjøremål** (f.eks. arbeid, studier, husarbeid, familie- eller fritidsaktiviteter)

- ☐ Jeg har ingen problemer med å utføre mine vanlige gjøremål
- ☐ Jeg har litt problemer med å utføre mine vanlige gjøremål
- ☐ Jeg er ute av stand til å utføre mine vanlige gjøremål

1.04 **Smerte og ubehag**

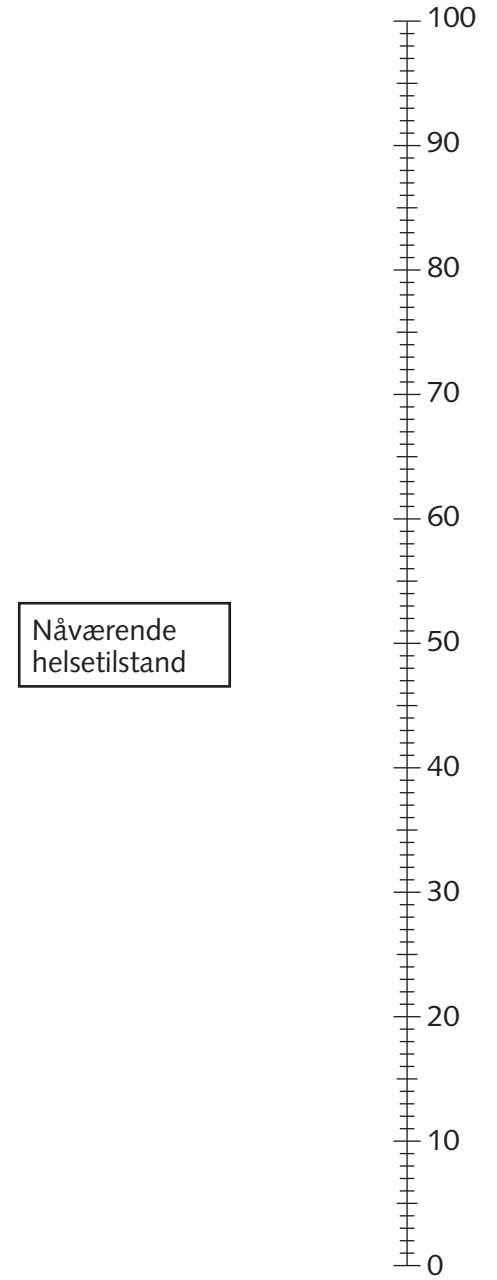
- ☐ Jeg har verken smerte eller ubehag
- ☐ Jeg har moderat smerte eller ubehag
- ☐ Jeg har sterk smerte eller ubehag

1.05 **Angst og depresjon**

- ☐ Jeg er verken engstelig eller deprimert
- ☐ Jeg er noe engstelig eller deprimert
- ☐ Jeg er svært engstelig eller deprimert

1.6 For at du skal kunne vise oss hvor god eller dårlig din helsetilstand er, har vi laget en skala (nesten som et termometer), hvor den beste helsetilstanden du kan tenke deg er markert med 100 og den dårligste med 0. Vi ber om at du viser din helsetilstand ved å trekke ei linje fra boksen nedenfor til det punkt på skalaen som passer best med din helsetilstand.

Best tenkelige helsetilstand



Verst tenkelige helsetilstand

2. OPPVEKST OG TILHØRIGHET

2.01 **Hvor bodde du da du fylte 1 år?**

- ☐ I Tromsø *(med dagens kommunegrenser)*
- ☐ I Troms, men ikke i Tromsø
- ☐ I Finnmark fylke
- ☐ I Nordland fylke
- ☐ Annet sted i Norge
- ☐ I utlandet

2.02 **Hvordan var de økonomiske forhold i familien under din oppvekst?**

- ☐ Meget gode
- ☐ Gode
- ☐ Vanskelige
- ☐ Meget vanskelige

2.03 **Hvilken betydning har religion i ditt liv?**

- ☐ Stor betydning
- ☐ En viss betydning
- ☐ Ingen betydning

2.04 **Hva regner du deg selv som?** (Kryss av for ett eller flere alternativ)

- ☐ Norsk
- ☐ Samisk
- ☐ Kvensk/Finsk
- ☐ Annet

2.05 **Hvor mange søsken og barn har du/har du hatt?**

Antall søsken ..... ☐☐

Antall barn ..... ☐☐

2.06 **Lever din mor?**

☐ Ja ☐ Nei

Hvis NEI: hennes alder ved død ..... ☐☐

Lever din far?

☐ Ja ☐ Nei

Hvis NEI: hans alder ved død ..... ☐☐

2.07 **Hva var/er den høyeste fullførte utdanning til dine foreldre og din ektefelle/samboer?**
(sett ett kryss i hver kolonne)

	Mor	Far	Ektefelle/ samboer
Grunnskole 7-10 år, 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)	☐	☐	☐

3. TRIVSEL OG LIVSFORHOLD

3.01 **Nedenfor står tre utsagn om tilfredshet med livet som et hele. Deretter står to utsagn om syn på din egen helse. Vis hvor enig eller uenig du er i hver av påstandene ved å sette et kryss i rubrikken for det tallet du synes stemmer best for deg.** (sett ett kryss for hvert utsagn)

	Helt uenig	1	2	3	4	5	6	7	Helt enig
På de fleste måter er livet mitt nær idealet mitt		☐	☐	☐	☐	☐	☐	☐	
Mine livsforhold er utmerkede		☐	☐	☐	☐	☐	☐	☐	
Jeg er tilfreds med livet mitt		☐	☐	☐	☐	☐	☐	☐	
Jeg ser lyst på min framtidige helse		☐	☐	☐	☐	☐	☐	☐	
Ved å leve sunt kan jeg forhindre alvorlige sykdommer		☐	☐	☐	☐	☐	☐	☐	

3.02 **Nedenfor står fire utsagn om syn på forhold ved din nåværende jobb, eller hvis du ikke er i arbeid nå, den jobben du hadde sist** (sett ett kryss for hvert utsagn)

	Helt uenig	1	2	3	4	5	6	7	Helt enig
Arbeidet mitt er for belastende, fysisk eller følelsesmessig		☐	☐	☐	☐	☐	☐	☐	
Jeg har tilstrekkelig innflytelse på når og hvordan arbeidet mitt skal utføres		☐	☐	☐	☐	☐	☐	☐	
Jeg blir mobbet eller trakassert på arbeidsplassen min		☐	☐	☐	☐	☐	☐	☐	
Jeg blir rettferdig behandlet på arbeidsplassen min		☐	☐	☐	☐	☐	☐	☐	

3.03 **Jeg opplever at yrket mitt har følgende sosiale status i samfunnet:** (dersom du ikke er i arbeid nå, tenk på det yrket du hadde sist)

- ☐ Meget høy status
- ☐ Ganske høy status
- ☐ Middels status
- ☐ Ganske lav status
- ☐ Meget lav status

3.04 **Har du over lengre tid opplevd noe av det følgende?** (sett ett eller flere kryss for hver linje)

	Nei	Ja, som barn	Ja, som voksen	Ja, siste år
Blitt plaget psykisk, eller truet med vold	☐	☐	☐	☐
Blitt slått, sparket eller utsatt for annen type vold	☐	☐	☐	☐
Noen i nær familie har brukt rusmidler på en slik måte at dette har vært til *bekymring* for deg	☐	☐	☐	☐

Dersom du har opplevd noen av disse forholdene, hvor mye plages du av dette nå?

☐ Ingen plager ☐ Noen plager ☐ Store plager

4. SYKDOMMER OG PLAGER

4.01 **Har du i løpet av den siste måneden følt deg syk eller hatt en skade?**

☐ Ja ☐ Nei

Hvis JA: har du i den samme perioden?
(sett ett kryss for hver linje)

	Ja	Nei
Vært hos allmennlege/fastlege	☐	☐
Vært hos spesialist	☐	☐
Vært på legevakt	☐	☐
Vært innlagt i sykehus	☐	☐
Vært hos alternativ behandler *(kiropraktor, homøopat eller lignende)*	☐	☐

4.02 **Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste året?**

☐ Ja ☐ Nei

4.03 **Blir du tungpustet i følgende situasjoner?**
(sett ett kryss for hvert spørsmål)

	Ja	Nei
Når du går hurtig på flatmark eller svak oppoverbakke	☐	☐
Når du spaserer i rolig tempo på flatmark	☐	☐
Når du vasker deg eller kler på deg	☐	☐
Når du er i hvile	☐	☐

4.04 **Hoster du omtrent daglig i perioder av året?**

☐ Ja ☐ Nei

Hvis JA: Er hosten vanligvis ledsaget av oppspytt?

☐ Ja ☐ Nei

Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste årene?

☐ Ja ☐ Nei

4.05 **Hvor ofte er du plaget av søvnløshet?**
(sett ett kryss)

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

Hvis du er plaget av søvnløshet månedlig eller oftere, når på året er du mest plaget?
(sett ett eller flere kryss)

☐ Ingen spesiell tid
☐ Mørketida
☐ Midnattsoltida
☐ Vår og høst

4.06 **Har du i de siste par ukene hatt vansker med å sove?**

☐ Ikke i det hele tatt
☐ Ikke mer enn vanlig
☐ Heller mer enn vanlig
☐ Mye mer enn vanlig

4.07 **Har du de siste par ukene følt deg ulykkelig og nedtrykt (deprimert)?**

☐ Ikke i det hele tatt
☐ Ikke mer enn vanlig
☐ Heller mer enn vanlig
☐ Mye mer enn vanlig

4.08 **Har du i de siste par ukene følt deg ute av stand til å mestre dine vanskeligheter?**

☐ Ikke i det hele tatt
☐ Ikke mer enn vanlig
☐ Heller mer enn vanlig
☐ Mye mer enn vanlig

4.09 **Nedenfor ber vi deg besvare noen spørsmål om din hukommelse:** (sett ett kryss for hvert spørsmål)

	Ja	Nei
Synes du at din hukommelse har blitt dårligere?	☐	☐
Glemmer du ofte hvor du har lagt tingene dine?	☐	☐
Har du problemer med å finne vanlige ord i en samtale?	☐	☐
Har du fått problemer med daglige gjøremål som du mestret tidligere?	☐	☐
Har du vært undersøkt for sviktende hukommelse?	☐	☐

Hvis JA på minst ett av de fire første spørsmålene ovenfor: Er det et problem i hverdagen?

☐ Ja ☐ Nei

4.10 **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?** (sett ett kryss i hver linje)

	Ikke plaget	En del plaget	Sterkt plaget
Nakke, skuldre	☐	☐	☐
Armer, hender	☐	☐	☐
Øvre del av ryggen	☐	☐	☐
Korsryggen	☐	☐	☐
Hofter, ben, føtter	☐	☐	☐
Andre steder	☐	☐	☐

4.11 **Har du vært plaget med smerter og/eller stivhet i muskler og ledd i løpet av de siste 4 ukene?** (sett ett kryss i hver linje)

	Ikke plaget	En del plaget	Sterkt plaget
Nakke, skuldre	☐	☐	☐
Armer, hender	☐	☐	☐
Øvre del av ryggen	☐	☐	☐
Korsryggen	☐	☐	☐
Hofter, ben, føtter	☐	☐	☐
Andre steder	☐	☐	☐

4.12 **Har du noen gang hatt:**

	Ja	Nei	Alder siste gang
Brudd i håndledd/ underarm?	☐	☐	
Lårhalsbrudd?	☐	☐	

4.13 **Har du fått stilt diagnosen slitasjegikt av lege?**

☐ Ja ☐ Nei

4.14 **Har eller har du hatt noen av følgende:**

	Aldri	Litt	Mye
Nikkelallergi	☐	☐	☐
Pollenallergi	☐	☐	☐
Andre allergier	☐	☐	☐

4.15 **Har du opplevd ufrivillig barnløshet i mer enn 1 år?**

☐ Ja ☐ Nei

Hvis JA, skyldtes dette:

	Ja	Nei	Vet ikke
Forhold hos deg selv?	☐	☐	☐
Forhold hos partneren?	☐	☐	☐

4.16 **I hvilken grad har du hatt følgende plager i de siste 12 måneder?**

	Aldri	Litt	Mye
Kvalme	☐	☐	☐
Halsbrann/sure oppstøt	☐	☐	☐
Diare	☐	☐	☐
Treg mage	☐	☐	☐
Vekslende treg mage og diare	☐	☐	☐
Oppblåsthet	☐	☐	☐
Smerter i magen	☐	☐	☐

4.17 **Hvis du har hatt smerter i eller ubehag fra magen siste året:**

	Ja	Nei
Er disse lokalisert øverst i magen?	☐	☐
Har du hatt plagene så ofte som 1 dag i uka eller mer de siste 3 måneder?	☐	☐
Blir plagene bedre etter avføring?	☐	☐
Har plagene sammenheng med hyppigere eller sjeldnere avføring enn vanlig?	☐	☐
Har plagene noen sammenheng med løsere eller fastere avføring enn vanlig?	☐	☐
Kommer plagene etter måltid?	☐	☐

4.18 **Har du noen gang hatt:**

	Ja	Nei	Alder siste gang
Sår på magesekken	☐	☐	
Sår på tolvfingertarmen	☐	☐	
Magesår-operasjon	☐	☐	

4.19 **Til kvinnen: Har du spontanabortert?**

☐ Ja ☐ Nei ☐ Vet ikke

Hvis JA, antall ganger

4.20 **Til mannen: Har din partner noen gang spontanabortert?**

☐ Ja ☐ Nei ☐ Vet ikke

Hvis JA, antall ganger

4.21 **Bruker du glutenfri diett?**

☐ Ja ☐ Nei ☐ Vet ikke

4.22 **Har du fått stilt diagnosen Dermatitis Herpetiformis (DH)?**

☐ Ja ☐ Nei ☐ Vet ikke

4.23 **Har du fått stilt diagnosen cøliaki på bakgrunn av en vevsprøve fra tynntarmen tatt under en undersøkelse der du svelget en slange (gastroskopi)?**

☐ Ja ☐ Nei ☐ Vet ikke

4.24 **Har du egne tenner?**

☐ Ja ☐ Nei

4.25 **Hvor mange amalgamfyllinger har du/har du hatt?**

☐ 0 ☐ 1-5 ☐ 6-10 ☐ 10+

4.26 **Har du vært plaget av hodepine det siste året?**

☐ Ja ☐ Nei

Hvis NEI, gå til del 5, kosthold

4.27 **Hva slags hodepine er du plaget av?**

☐ Migrene ☐ Annen hodepine

4.28 **Omtrent hvor mange dager per måned har du hodepine?**

☐ Mindre enn 1 dag
☐ 1-6 dager
☐ 7-14 dager
☐ Mer enn 14 dager

4.29 **Er hodepinen vanligvis:**
(sett et kryss for hver linje)

	Ja	Nei
Bankende/dunkende smerte	☐	☐
Pressende smerte	☐	☐
Ensidig smerte *(høyre eller venstre)*	☐	☐

4.30 **Hvor sterk er hodepinen vanligvis?**

☐ Mild *(hemmer ikke aktivitet)*
☐ Moderat *(hemmer aktivitet)*
☐ Sterk *(forhindrer aktivitet)*

4.31 **Hvor lenge varer hodepinen vanligvis?**

☐ Mindre enn 4 timer
☐ 4 timer – 1 døgn
☐ 1-3 døgn
☐ Mer enn 3 døgn

4.32 **Dersom du er plaget av hodepine, når på året er du plaget mest?** (sett ett eller flere kryss)

☐ Ingen spesiell tid
☐ Mørketida
☐ Midnattsoltida
☐ Vår og/eller høst

4.33 **Før eller under hodepinen, kan du da ha forbigående:**

	Ja	Nei
Synsforstyrrelse? *(takkede linjer, flimring, tåkesyn, lysglimt)*	☐	☐
Nummenhet i halve ansiktet eller i hånden?	☐	☐
Forverring ved moderat fysisk aktivitet	☐	☐
Kvalme og /eller oppkast	☐	☐

4.34 **Angi hvor mange dager du har vært borte fra arbeid eller skole siste måned på grunn av hodepine:**

Antall dager ☐☐

5. KOSTHOLD

5.01 **Hvor ofte spiser du vanligvis følgende?** (sett ett kryss i hver linje)

	0-1 g per mnd	2-3 g per mnd	1-3 g per uke	Mer enn 3 g per uke
Ferskvannsfisk *(ikke oppdrett)*	☐	☐	☐	☐
Saltvannsfisk *(ikke oppdrett)*	☐	☐	☐	☐
Oppdrettsfisk *(laks, røye, ørret)*	☐	☐	☐	☐
Tunfisk *(fersk eller hermetisert)*	☐	☐	☐	☐
Fiskepålegg	☐	☐	☐	☐
Skjell	☐	☐	☐	☐
Den brune innmaten i krabbe	☐	☐	☐	☐
Hvalkjøtt/sel/kobbekjøtt	☐	☐	☐	☐
Innmat fra rein eller elg	☐	☐	☐	☐
Innmat fra rype	☐	☐	☐	☐

5.02 **Hvor mange ganger i året spiser du/spiste du vanligvis følgende?** (antall ganger)

	Som voksen	I din barndom
Mølje *(Antall ganger i året)*	☐☐	☐☐
Måsegg *(Antall egg i året)*	☐☐	☐☐
Reinsdyrkjøtt *(Antall ganger i året)*	☐☐	☐☐
Selvplukket sopp og bær *(blåbær/tyttebær/multe) (Antall ganger i året)*	☐☐☐	☐☐☐

5.03 **Hvor mange ganger i måneden spiser du hermetiske matvarer (fra metallbokser)?**

Antall ☐☐

5.04 **Bruker du vitaminer og/eller mineraltilskudd?**

☐ Ja, daglig ☐ Iblant ☐ Aldri

5.05 **Hvor ofte spiser du?**

	Aldri	1-3 g per mnd	1-3 g per uke	4-6 g. per uke	1-2 g. per dag	3 g. per dag eller mer
Mørk sjokolade	☐	☐	☐	☐	☐	☐
Lys sjokolade/melkesjokolade	☐	☐	☐	☐	☐	☐
Sjokoladekake	☐	☐	☐	☐	☐	☐
Andre søtsaker	☐	☐	☐	☐	☐	☐

5.06 **Hvis du spiser sjokolade, hvor mye pleier du vanligvis å spise hver gang?**
Tenk deg størrelsen på en Kvikk- Lunsj sjokolade, og oppgi hvor mye du spiser i forhold til den.

¼	½	1	1 ½	2	Mer enn 2
☐	☐	☐	☐	☐	☐

5.07 **Hvor ofte drikker du kakao/varm sjokolade**

Aldri	1-3 g per mnd	1-3 g per uke	4-6 g. per uke	1-2 g. per dag	3 g. per dag eller mer
☐	☐	☐	☐	☐	☐

6. ALKOHOL

6.01 **Hvor ofte har du <u>det siste året</u>:**

	Aldri	Sjeldnere enn månedlig	Månedlig	Ukentlig	Daglig, eller nesten daglig
Ikke klart å stoppe og drikke alkohol når du først har begynt?	☐	☐	☐	☐	☐
Ikke klart å gjøre det som normalt forventes av deg fordi du har drukket?	☐	☐	☐	☐	☐
Trengt en drink om morgenen for å få komme i gang etter en rangel?	☐	☐	☐	☐	☐
Følt skyld eller anger etter at du har drukket?	☐	☐	☐	☐	☐
Ikke klart å huske hva som skjedde kvelden før på grunn av at du hadde drukket?	☐	☐	☐	☐	☐

	Aldri	Ja, men ikke det siste året	Ja, det siste året
6.02 **Har du eller andre noen gang blitt skadet på grunn av at du har drukket?**	☐	☐	☐
Har en slektning, venn, lege, eller annet helsepersonell vært bekymret for din drikking, eller foreslått at du reduserer inntaket?	☐	☐	☐

7. VEKT

7.01 **Har du ufrivillig gått ned i vekt <u>siste 6 måneder</u>?**

☐ Ja ☐ Nei

Hvis JA: Hvor mange kilo? ☐☐

7.02 **Anslå din vekt da du var 25 år gammel:**

Antall hele kg ☐☐☐

7.03 **Er du fornøyd med vekta di nå?**

☐ Ja ☐ Nei

7.04 **Hvilken vekt ville du være tilfreds med (din trivselsvekt):**

Antall kg ☐☐☐

8. LØSEMIDLER

8.01 **Hvor mange timer i uka driver du med følgende <u>fritids- eller yrkesaktiviteter:</u>**
Bilreparasjoner/lakkering, keramikkarbeid, maling/lakkering/løsemidler, frisør, glassmester, elektriker (Sett 0 om du ikke driver med slike fritids eller yrkesaktiviteter)

Antall timer per uke i gjennomsnitt ☐☐

8.02 **Bruker du hårfargemidler?**

☐ Ja ☐ Nei

Hvis JA, hvor mange ganger per år? ☐☐

9. BRUK AV HELSETJENESTER

9.01 **Har du noen gang opplevd at sykdom er blitt mangelfullt undersøkt eller behandlet, og at dette har gitt alvorlige følger?**

- ☐ Ja, det har rammet meg selv
- ☐ Ja, det har rammet en nær pårørende *(barn, foreldre, ektefelle/samboer)*
- ☐ Nei

Hvis JA, hvor mener du årsaken ligger? (sett ett eller flere kryss):

- ☐ hos fastlege/allmennlege
- ☐ hos legevaktslege
- ☐ hos privatpraktiserende spesialist
- ☐ hos sykehuslege
- ☐ hos annet helsepersonell
- ☐ hos alternativ behandler
- ☐ hos flere på grunn av svikt i rutiner og samarbeid

9.02 **Har du noen gang følt deg overtalt til å godta undersøkelse eller behandling som du selv ikke ønsket?**

☐ Ja ☐ Nei

Hvis JA, mener du dette har hatt uheldige helsemessige følger?

☐ Ja ☐ Nei

9.03 **Har du noen gang klaget på behandling du har fått?**

- ☐ Har aldri vært aktuelt
- ☐ Har vurdert å klage, men ikke gjort det
- ☐ Har klaget muntlig
- ☐ Har klaget skriftlig

9.04 **Hvor lenge har du hatt din nåværende fastlege/annen lege?**

- ☐ Mindre enn 6 måneder
- ☐ 6 til 12 måneder
- ☐ 12 til 24 måneder
- ☐ Mer enn 2 år

9.05 **Ved siste legebesøk hos fastlegen, snakket legen(e) til deg slik at du forsto dem?** Svar på en skala fra 0 til 10, hvor 0=de var vanskelige å forstå og 10=de var alltid enkle å forstå

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

9.06 **Hvordan vil du karakterisere behandlingen eller rådgivingen du fikk siste gang du var hos lege?** Svar på en skala fra 0 til 10, hvor 0= meget dårlig behandling og 10 = meget god behandling

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

9.07 **Har du i løpet av de siste 12 måneder opplevd at det har vært vanskelig å bli henvist til spesielle undersøkelser (som røntgen eller liknende) eller til spesialist-helsetjenesten (privatpraktiserende spesialist eller ved sykehus)?**

- ☐ Ikke aktuelt
- ☐ Intet problem
- ☐ Noe problem
- ☐ Stort problem

9.08 **Har du i løpet av de siste 12 måneder opplevd at det er vanskelig å bli henvist til fysioterapeut, kiropraktor eller liknende?**

- ☐ Ikke aktuelt
- ☐ Intet problem
- ☐ Noe problem
- ☐ Stort problem

9.09 **Alt i alt, har du opplevd at det er vanskelig eller enkelt å bli henvist til spesialisthelse-tjenesten?**

- ☐ Ikke aktuelt
- ☐ Meget vanskelig
- ☐ Noe vanskelig
- ☐ Rimelig enkelt
- ☐ Meget enkelt

9.10 **Har du i løpet av de siste 12 måneder vært til undersøkelse eller behandling i spesialist-helsetjenesten?**

☐ Ja ☐ Nei

Hvis JA, snakket legen(e) til deg slik at du forstod dem? Svar på en skala fra 0 til 10, hvor 0=de var vanskelige å forstå og 10=de var alltid enkle å forstå

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

9.11 **Hvordan vil du karakterisere behandlingen eller rådgivningen du fikk siste gang du var hos spesialist?** Svar på en skala fra 0 til 10, hvor 0=meget dårlig og 10=meget god

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

9.12 **Har du noen gang før 2002 gjennomgått en operasjon på sykehus eller spesialist-klinikk?**

☐ Ja ☐ Nei

9.13 **Har du i løpet av de siste 12 måneder brukt urtemedisin , naturmidler eller naturlegemidler?**

☐ Ja ☐ Nei

9.14 **Har du i løpet av de siste 12 måneder brukt meditasjon, yoga, qi gong eller thai chi som egenbehandling?**

☐ Ja ☐ Nei

10. BRUK AV ANTIBIOTIKA

10.01 **Har du brukt antibiotika i løpet av de siste 12 måneder?** (all penicillinliknende medisin i form av tabletter, mikstur eller sprøyter)

☐ Ja ☐ Nei ☐ Husker ikke

Hvis JA, hva fikk du behandling mot? Har du tatt flere antibiotikakurer, sett ett kryss for hver kur.

	Kur 1	Kur 2	Kur 3	Kur 4	Kur 5	Kur 6
· Urinveisinfeksjon *(blærebetennelse, blærekatarr)*	☐	☐	☐	☐	☐	☐
· Luftveisinfeksjon *(øre-, bihule- hals- eller lungebetennelse, bronkitt)*	☐	☐	☐	☐	☐	☐
· Annet	☐	☐	☐	☐	☐	☐
Antall dagers antibiotika kur						

Hvordan skaffet du deg antibiotikakuren? Har du tatt flere kurer, sett ett kryss for hver kur.

Etter resept fra lege/tannlege	☐	☐	☐	☐	☐	☐
Uten kontakt med lege/uten resept:						
· Kjøp direkte fra apotek i utlandet	☐	☐	☐	☐	☐	☐
· Kjøp gjennom Internett	☐	☐	☐	☐	☐	☐
· Rest fra tidligere kur tilgjengelig hjemme	☐	☐	☐	☐	☐	☐
· Fått av familie/venner	☐	☐	☐	☐	☐	☐
· Andre måter	☐	☐	☐	☐	☐	☐

10.02 **Har du antibiotika hjemme?**

☐ Ja ☐ Nei

Hvis JA, er dette etter avtale med lege for å behandle kronisk eller hyppig tilbakevendende sykdom?

☐ Ja ☐ Nei

Hvis Nei, hvordan skaffet du deg dette legemiddelet? (Flere kryss er mulig)

- Kjøpt direkte fra apotek i utlandet ☐
- Kjøpt over Internett ☐
- Rest fra tidligere kur ☐
- Fått av familie/venner ☐
- Andre måter ☐

10.03 **Kan du tenke deg å bruke antibiotika uten å kontakte lege først?**

☐ Ja ☐ Nei

Hvis JA, hvilke tilstander vil du i så fall behandle? (Flere kryss mulig)

- Forkjølelse ☐
- Hoste ☐
- Bronkitt ☐
- Halsbetennelse ☐
- Bihulebetennelse ☐
- Feber ☐
- Influensa ☐
- Ørebetennelse ☐
- Diaré ☐
- Blærebetennelse ☐
- Andre infeksjoner ☐

11. DIN DØGNRYTME

Vi vil stille deg noen spørsmål som handler om dine søvnvaner.

11.01 **Har du hatt skiftarbeid de tre siste månedene?**

☐ Ja ☐ Nei

11.02 **Antall dager i løpet av uken hvor du ikke kan velge fritt når du vil sove (f.eks arbeidsdager)?**

0 1 2 3 4 5 6 7

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Da går jeg til sengs klokken ..... ☐☐:☐☐

Jeg gjør meg klar til å sove klokken ..... ☐☐:☐☐

Antall minutter jeg trenger på å sovne ..... ☐☐

Jeg våkner klokken ..... ☐☐:☐☐

Ved hjelp av: ☐ Vekkeklokke ☐ annen ytre påvirkning *(støy, familie etc)* ☐ av meg selv

Antall minutter jeg trenger på å stå opp ..... ☐☐

11.03 **Antall dager i løpet av uken hvor du fritt kan velge når du vil sove** (f.eks helger eller fridager)

0 1 2 3 4 5 6 7

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Da går jeg til sengs klokken ..... ☐☐:☐☐

Jeg gjør meg klar til å sove klokken ..... ☐☐:☐☐

Antall minutter jeg trenger på å sovne ..... ☐☐

Jeg våkner klokken ..... ☐☐:☐☐

Ved hjelp av: ☐ Vekkeklokke ☐ annen ytre påvirkning *(støy, familie etc)* ☐ av meg selv

Antall minutter jeg trenger på å stå opp ..... ☐☐

12. HUD OG HUDSYKDOMMER

12.01 **Hvor ofte dusjer eller bader du vanligvis?** (sett ett kryss)

- ☐ 2 eller flere ganger daglig
- ☐ 1 gang daglig
- ☐ 4-6 ganger per uke
- ☐ 2-3 ganger per uke
- ☐ 1 gang per uke
- ☐ sjeldnere enn 1 gang per uke

12.02 **Hvor ofte vasker du vanligvis hendene med såpe i løpet av en dag?** (sett ett kryss)

- ☐ 0 ganger
- ☐ 1-5 ganger
- ☐ 6-10 ganger
- ☐ 11-20 ganger
- ☐ Mer enn 20 ganger

12.03 **Har du noen gang fått antibiotikakur (penicillin og liknende medisin) på grunn av en hudlidelse, for eksempel betent eksem, kviser, leggsår som ikke vil gro, tilbakevendende verkebyll?**

☐ Ja ☐ Nei

Hvis JA, hvor mange ganger i gjennomsnitt per år fikk du antibiotika i den perioden du var mest plaget (sett ett kryss)

☐ 1-2 ☐ 3-4 ☐ Mer enn 4 ganger

12.04 **Har du eller har du noen gang hatt følgende hudlidelser?** (sett ett kryss for hver linje)

	Ja	Nei
Psoriasis	☐	☐
Atopisk eksem (barneeksem)	☐	☐
Tilbakevendende håndeksem	☐	☐
Tilbakevendende kviser over flere måneder	☐	☐
Legg- eller fotsår som ikke ville gro i løpet av 3-4 uker	☐	☐

Hvis JA på spørsmål om legg-og/eller fotsår, har du leggsår i dag?

☐ Ja ☐ Nei

12.05 **Har du ofte eller bestandig noen av følgende plager?** (sett ett kryss for hver linje)

	Ja	Nei
Hevelse i ankler og legger, særlig om kvelden	☐	☐
Åreknuter	☐	☐
Eksem (rødt, kløende utslett) på leggene	☐	☐
Smerter i beina når du går, men som forsvinner når du står stille	☐	☐

12.06 **Har du noen gang fått følgende diagnoser av lege?** (sett ett kryss for hver linje)

	Ja	Nei
Psoriasis	☐	☐
Atopisk eksem	☐	☐
Rosacea	☐	☐

12.07 **Har du tilbakevendende store kviser/ verkebyller som er ømme/smertefulle og som ofte tilheler med arr på følgende steder?** (sett ett kryss for hver linje)

	Ja	Nei
Armhulene	☐	☐
Under brystene	☐	☐
Magefolden/navlen	☐	☐
Rundt kjønnsorganet	☐	☐
Rundt endetarmsåpningen	☐	☐
Lyskene	☐	☐

Hvis JA, har du noen gang oppsøkt lege på grunn av verkebyller?

☐ Ja ☐ Nei

Hvis JA, fikk du da noen av følgende behandlinger? (sett ett kryss for hver linje)

	Ja	Nei
Antibiotika salve/krem	☐	☐
Antibiotika tabletter	☐	☐
Kirurgisk åpning/tømming	☐	☐
Større kirurgisk inngrep med fjerning av hud	☐	☐
Kirurgisk laserbehandling	☐	☐

Oppfølgingsspørsmål

INFORMASJON TIL OPPFØLGINGSSPØRSMÅL

De neste sidene med spørsmål skal ikke besvares av alle. Dersom du har svart ja på ett eller flere av spørsmålene under, ber vi deg om å gå videre til oppfølgingsspørsmål om emnet eller emnene du har svart ja på. De fire første emnene er fra det første spørreskjemaet og det siste spørsmålet er fra dette skjemaet.

Vi har for enkelhetsskyld markert emnene med ulike farger slik at du lett skal finne frem til de spørsmålene som gjelder for deg.

Dersom du svarte JA på at du har: langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer, ber vi deg svare på spørsmålene på side 19 og 20. Margen er markert med grønn.

Dersom du svarte JA på at du har gjennomgått noen form for operasjon i løpet av de siste 3 årene, ber vi deg svare på spørsmålene på side 21 og 22. Margen er markert med lilla.

Dersom du svarte JA på at du arbeider utendørs minst 25% av tiden, eller i lokaler med lav temperatur, som for eksempel lager/industrihaller, ber vi deg svare på spørsmålene på side 23. Margen er markert med rød.

Dersom du svarte JA på at du har brukt reseptfrie smertestillende medisiner, ber vi deg svare på spørsmålene på side 24. Margen er markert med orange.

Dersom du svarte JA på at du har eller noen gang har hatt plager med hud (som psoriasis, atopisk eksem, legg- eller fotsår som ikke vil gro, tilbakevendende håndeksem, kviser eller verkebyll), ber vi deg svare på spørsmålene på side 25. Margen er markert med gul.

Har du svart **NEI** på disse fem spørsmålene, er du ferdig med besvarelsen din. Spørreskjemaet returneres i svarkonvolutten du fikk utlevert på undersøkelsen. Portoen er allerede betalt.

Skulle du ønske å gi oss en skriftlig tilbakemelding om enten spørreskjema eller Tromsøundersøkelsen generelt, er du hjertelig velkommen til det på side 26.

Har du noen spørsmål, kan du ta kontakt med oss på telefon eller på e-post. Du finner kontaktinformasjon på baksiden av skjemaet. **TUSEN TAKK** for at du tok deg tid til undersøkelsen og til å svare på spørsmålene fra oss.

13. OPPFØLGINGSSPØRSMÅL OM SMERTE

Du svarte i det første spørreskjemaet at du har langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer. Her ber vi deg beskrive de smertene litt nærmere.

13.01 **Hvor lenge har du hatt disse smertene?**

Antall år..... ☐☐ måneder..... ☐☐

13.02 **Hvor ofte har du vanligvis disse smertene?**

- ☐ Hver dag
- ☐ En eller flere ganger i uken
- ☐ En eller flere ganger i måneden
- ☐ Sjeldnere enn 1 gang i måneden

13.03 **Hvor er det vondt?** (Kryss av for alle steder der du har langvarige eller stadig tilbakevendende smerter)

- ☐ Hode/ansikt
- ☐ Kjeve/kjeveledd
- ☐ Nakke
- ☐ Rygg
- ☐ Skulder
- ☐ Arm/albue
- ☐ Hånd
- ☐ Hofte
- ☐ Lår/kne/legg
- ☐ Ankel/fot
- ☐ Bryst
- ☐ Mage
- ☐ Underliv/kjønnsorganer
- ☐ Hud
- ☐ Annet sted

13.04 **Hva mener du er årsaken til smertene?** (Kryss av for alle kjente årsaker)

- ☐ Ulykke/akutt skade
- ☐ Langvarig belastning
- ☐ Kirurgisk inngrep/operasjon
- ☐ Skiveutglidning *(prolaps)*/lumbago
- ☐ Nakkesleng *(whiplash)*
- ☐ Migrene/hodepine
- ☐ Slitasjegikt *(artrose)*
- ☐ Leddgikt
- ☐ Bechterews sykdom
- ☐ Fibromyalgi
- ☐ Angina pectoris *(hjertekrampe)*
- ☐ Dårlig blodsirkulasjon
- ☐ Kreft
- ☐ Nerveskade/nevropati
- ☐ Infeksjon
- ☐ Helvetesild
- ☐ Annen årsak *(beskriv under)*
- ☐ Vet ikke

Beskriv annen årsak:

.....

13.05 **Hvilke former for behandling har du fått for smertene?** (Kryss av for alle typer smertebehandling du har mottatt)

- ☐ Ingen behandling
- ☐ Smertestillende medisiner
- ☐ Fysioterapi/kiropraktikk
- ☐ Behandling ved smerteklinikk
- ☐ Operasjon
- ☐ Smerteskole/avspenning/psykoterapi
- ☐ Akupunktur
- ☐ Alternativ behandling *(homøopati, healing, aromaterapi, m.m.)*
- ☐ Annen behandling

13.06 **På en skala fra 0 til 10, der 0 tilsvarer ingen smerte og 10 tilsvarer den verst tenkelige smerten du kan forestille deg:**

Hvor sterke vil du si at smertene vanligvis er?	Ingen smerte	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Verst tenkelige smerte
Hvor sterke er smertene når de er på sitt sterkeste?	Ingen smerte	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Verst tenkelige smerte
I hvor stor grad påvirker smertene søvnen din?	Påvirker ikke	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Umulig å få sove
I hvor stor grad hindrer smertene deg i å utføre vanlige aktiviteter hjemme og i arbeid?	Påvirker ikke	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Kan ikke gjøre noe

14. OPPFØLGINGSSPØRSMÅL OM OPERASJON

I det første spørreskjemaet svarte du at du har gjennomgått en operasjon i løpet av de siste 3 årene.

14.01 **Hvor mange operasjoner har du totalt gjennomgått de siste 3 årene?**

Antall ..... ☐☐

Nedenfor ber vi deg beskrive operasjonen. Dersom du har gjennomgått flere operasjoner i løpet av de siste 3 årene gjelder disse spørsmålene den siste operasjonen du gjennomgikk.

14.02 **Hvor i kroppen ble du operert?** (Dersom du samtidig ble operert flere steder i kroppen, settes flere kryss)

Operasjon i hode/nakke/rygg
- · Hode/ansikt ☐
- · Nakke/hals ☐
- · Rygg ☐

Operasjon i brystregionen
- · Hjerte ☐
- · Lunger ☐
- · Bryster ☐
- · Annen operasjon i brystregionen ☐

Operasjon i mage/underliv
- · Mage/tarm ☐
- · Lyskebrokk ☐
- · Urinveier/kjønnsorganer ☐
- · Galleblære/galleveier ☐
- · Annen operasjon i mage/underliv ☐

Operasjon i hofte/ben
- · Hofte/lår ☐
- · Kne/legg ☐
- · Ankel/fot ☐
- · Amputasjon ☐

Operasjon i skulder og arm
- · Skulder/overarm ☐
- · Albue/underarm ☐
- · Hånd ☐
- · Amputasjon ☐

14.03 **Bakgrunn for operasjonen:**
- Akutt sykdom/skade ☐
- Planlagt ikke-kosmetisk operasjon ☐
- Planlagt kosmetisk operasjon ☐

14.04 **Hvor ble du operert?**
- Sykehuset i Tromsø ☐
- Sykehuset i Harstad ☐
- Annet offentlig sykehus ☐
- Privat klinikk ☐

14.05 **Hvor lenge er det siden du gjennomgikk operasjonen?**

Antall år ..... ☐☐ måneder ..... ☐☐

14.06 **Har du nedsatt følsomhet i et område nær operasjonsarret?**

☐ Ja ☐ Nei

14.07 **Er du overfølsom for berøring, varme eller kulde i et område nær operasjonsarret?**

☐ Ja ☐ Nei

14.08 **Kan lett berøring av klær, dusj og lignende fremkalle ubehag/smerte?**

☐ Ja ☐ Nei

14.09 **Hvis du hadde smerter på operasjonsstedet før du ble operert, har du samme type smerte nå?**

☐ Ja ☐ Nei

14.10 **Smerte fra operasjonsstedet:** Svar på en skala fra 0 til 10, hvor 0=ingen smerte og 10=verst tenkelige smerte

Hvor sterke smerter hadde du fra operasjonsstedet før operasjonen.....	Ingen smerte	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Verst tenkelige smerte
Hvor sterke smerter har du vanligvis fra operasjonsstedet nå.....	Ingen smerte	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Verst tenkelige smerte
Hvor sterke smerter har du nå fra operasjonsstedet når smertene er på det sterkeste.....	Ingen smerte	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Verst tenkelige smerte

15. OPPFØLGINGSSPØRSMÅL OM ARBEID I KALDT KLIMA

I det første spørreskjemaet svarte du ja på at du arbeidet i kaldt klima. Her er noen oppfølgingsspørsmål vi håper du vil svare på.

15.01 **Fryser du på jobb?**

☐ Ja, ofte
☐ Ja, noen ganger
☐ Nei, aldri

15.02 **Hvor lenge har du vært utsatt for kalde omgivelser under 0°C sist vinter?**

Fritid/hobby *(timer/uke)* ..... ☐☐
Arbeid *(timer/uke)* ..... ☐☐
Utendørs, godt kledd *(timer/uke)* ..... ☐☐
Utendørs, tynnkledd *(timer/uke)* ..... ☐☐
Innendørs, uten oppvarming *(timer/uke)* ..... ☐☐
I kalde omgivelser, med våte klær *(timer/uke)* ..... ☐☐
Kontakt med kalde gjenstander/ verktøy *(timer/uke)* ..... ☐☐

15.03 **Hvilken omgivelsestemperatur forhindrer deg i å:**

	Under °C
Arbeide utendørs	☐☐
Trene utendørs	☐☐
Utføre andre aktiviteter utendørs	☐☐

15.04 **Har du hatt forfrysninger siste 12 måneder, med blemmer, sår eller skader i huden?**

☐ Ja ☐ Nei

Hvis JA, hvor mange ganger? ..... ☐☐

15.05 **Har du opplevd kløe og/eller utslett i forbindelse med kulde?**

☐ Ja ☐ Nei

15.06 **Har du i løpet av de siste 12 måneder vært involvert i ulykke som krevde medisinsk behandling der kulde var en viktig faktor?**

	Ja	Nei
På arbeid	☐	☐
I fritiden	☐	☐

15.07 **Opplever du noen av følgende symptomer mens du oppholder deg i kalde omgivelser? I så fall, ved hvilken temperatur oppstår symptomene?**

	Ja	Nei	Under °C
Pusteproblemer	☐	☐	☐☐
Pipende pust	☐	☐	☐☐
Slim fra lungene	☐	☐	☐☐
Brystsmerter	☐	☐	☐☐
Forstyrrelse i hjerterytmen	☐	☐	☐☐
Nedsatt blodsirkulasjon i hender/føtter	☐	☐	☐☐
Synsforstyrrelse *(kortvarig/ forbigående)*	☐	☐	☐☐
Migrene *(kortvarig/forbigående)*	☐	☐	☐☐
Hvite fingre *(kortvarig/ forbigående)*	☐	☐	☐☐
Blå, blå-røde fingre *(kortvarig/forbigående)*	☐	☐	☐☐

15.08 **Hvordan påvirker kalde omgivelser og kulderelaterte symptomer din yteevne?**

	Nedsatt	Uforandret	Forbedret
Konsentrasjon	☐	☐	☐
Hukommelse	☐	☐	☐
Fingerfølsomhet *(følelse)*	☐	☐	☐
Fingerferdighet *(motorikk)*	☐	☐	☐
Kontroll av bevegelse *(for eksempel skjelving)*	☐	☐	☐
Tungt fysisk arbeid	☐	☐	☐
Langvarig fysisk arbeid	☐	☐	☐

16. BRUK AV RESEPTFRIE SMERTESTILLENDE LEGEMIDLER

I det første spørreskjemaet svarte du at du hadde brukt reseptfrie smertestillende legemidler de siste 4 ukene. Her er noen oppfølgingsspørsmål vi håper du vil svare på.

16.01 **Hvilke typer reseptfrie smertestillende legemidler har du brukt?**

Paracetamol: *(Pamol, Panodil, Paracet, Paracetamol, Pinex)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter, stikkpiller)..... ☐☐

Acetylsalisylsyre: (*Aspirin,Dispril, Globoid)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter)..... ☐☐

Ibuprofen: *(Ibumetin, Ibuprofen, Ibuprox, Ibux)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter, stikkpiller)..... ☐☐

Naproksen: *(Ledox, Naproxen)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter)..... ☐☐

Fenazon med koffein: *(Antineuralgica ,Fanalgin Fenazon-koffein, Fenazon-koffein sterke)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter)..... ☐☐

16.02 **Mot hvilke plager bruker du reseptfrie smertestillende midler: (**Flere kryss er mulig)

- ☐ Hodepine
- ☐ Menssmerter
- ☐ Migrene
- ☐ Ryggsmerter
- ☐ Muskelsmerter/leddsmerter
- ☐ Tannsmerter
- ☐ Annet

16.03 **Mener du å ha opplevd bivirkninger av noen av legemidlene?** (sett ett kryss for hver linje)

	Ja	Nei
Paracetamol	☐	☐
Acetylsalisylsyre	☐	☐
Ibuprofen	☐	☐
Naproksen	☐	☐
Fenazon med koffein	☐	☐

16.04 **Hvor pleier du å kjøpe slike legemidler?**

- ☐ Apotek
- ☐ Dagligvare
- ☐ Bensinstasjon
- ☐ Utenlands
- ☐ Internett

16.05 **Kombinerer du behandlingen med bruk av reseptbelagte smertestillende midler?**

☐ Ja ☐ Nei

17. OPPFØLGINGSSPØRSMÅL OM HUDSYKDOMMER

På side 15 i dette spørreskjemaet svarte du at du har eller har hatt en hudsykdom. Her er noen oppfølgingsspørsmål vi håper du vil svare på.

Svar på en skala fra 0 til 10, der 0 tilsvarer ingen plager og 10 tilsvarer verst tenkelige plager. Dersom du svarte JA på at du har eller har hatt:

Ingen plager 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelige plager

17.01 **Psoriasis**
- Hvor mye plaget er du av din psoriasis i dag? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
- Hvor mye plaget er du av din psoriasis når den er som verst? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

17.02 **Atopisk eksem**
- Hvor mye plaget er du av ditt atopiske eksem i dag? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
- Hvor mye plaget er du av ditt atopiske eksem når det er som verst? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

17.03 **Håndeksem**
- Hvor mye plaget er du av ditt håndeksem i dag? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
- Hvor mye plaget er du av ditt håndeksem når det er som verst? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

17.04 **Kviser**
- Hvor mye plaget er du av dine kviser i dag? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
- Hvor mye plaget er du av dine kviser når de er som verst? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

17.05 **Verkebyller**
- Hvor mye plaget er du av dine verkebyller i dag? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
- Hvor mye plaget er du av dine verkebyller når de er som verst? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

17.06 **Her er en liste over faktorer som kan tenkes å utløse eller forverre verkebyller, kryss av for hva du synes gjelder for deg:**

	Ja	Nei
Stress/psykisk påkjenning	☐	☐
Trange/tette klær	☐	☐
Menstruasjonssyklus	☐	☐
Svangerskap	☐	☐
Annet	☐	☐

17.07 **Hvor mange utbrudd av verkebyller har du vanligvis i løpet av ett år?** (sett ett kryss)

☐ 0-1 ☐ 4-6
☐ 2-3 ☐ Mer enn 6

17.08 **Hvor gammel var du da du fikk verkebyller første gang?**

☐ 0-12 år ☐ 26-35 år
☐ 13-19 år ☐ 36-50 år
☐ 20-25 år ☐ Over 50 år

17.09 **Dersom du ikke lenger har verkebyller, hvor gammel var du da plagene forsvant?**

☐ 0-12 år ☐ 26-35 år
☐ 13-19 år ☐ 36-50 år
☐ 20-25 år ☐ Over 50 år

TILBAKEMELDING

Skulle du ønske å gi oss en skriftlig tilbakemelding om enten spørreskjema eller Tromsøundersøkelsen generelt, er du hjertelig velkommen til det her:

Takk for hjelpen!

LUNDBLAD MEDIA AS · FOTO: TORGER GRYTA

Tromsø-undersøkelsen

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Appendix 4

National Health and Nutrition Examination Survey

Overview

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Center for Health Statistics

Introduction

The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews and physical examinations. NHANES is a major program of the National Center for Health Statistics (NCHS). NCHS is part of the Centers for Disease Control and Prevention (CDC), U.S. Public Health Service, and has the responsibility for producing vital and health statistics for the Nation.

The NHANES program began in the early 1960's and has been conducted as a series of surveys focusing on different population groups or health topics. In 1999, the survey became a continuous program that will have a changing focus on a variety of health and nutrition measurements to meet emerging needs. The survey examines a nationally representative sample of about 5,000 persons each year. These persons are located in counties across the country, 15 of which are visited each year.

The NHANES detailed interview includes demographic, socioeconomic, dietary, and health-related questions. The examination component consists of medical and dental examinations, physiological measurements, and laboratory tests administered by highly trained medical personnel.

Findings from this survey will be used to determine the prevalence of major diseases and risk factors for diseases. Information will be used to assess nutritional status and its association with health promotion and disease prevention. NHANES findings are also the basis for national standards for such measurements as height, weight, and blood pressure. Data from this survey will be used in epidemiological studies and health sciences research, which help develop sound public health policy, direct and design health programs and services, and expand the health knowledge for the Nation.

Survey Content

As in past health examination surveys, data will be collected on the prevalence of chronic conditions in the population. Estimates for previously undiagnosed conditions, as well as those known to and reported by survey respondents, are produced through the survey. Such information is a particular strength of the NHANES program.

Risk factors, those aspects of a person's lifestyle, constitution, heredity, or environment that may increase the chances of developing a certain disease or condition, will be examined. Smoking, alcohol consumption, sexual practices, drug use, physical fitness and activity, weight, and dietary intake will be studied. Data on certain aspects of reproductive health, such as use of oral contraceptives and breastfeeding practices, also will be collected.

The diseases, medical conditions, and health indicators to be studied include:

- Anemia
- Cardiovascular disease
- Diabetes and lower extremity disease
- Environmental exposures
- Equilibrium
- Hearing loss
- Infectious diseases and immunization
- Kidney disease
- Mental health and cognitive functioning
- Nutrition
- Obesity

- Oral health
- Osteoporosis
- Physical fitness and physical functioning
- Reproductive history and sexual behavior
- Respiratory disease (asthma, chronic bronchitis, emphysema)
- Sexually transmitted diseases
- Skin diseases
- Vision

The sample for the survey is selected to represent the U.S. population of all ages. Special emphasis in the current NHANES will be on adolescent health and the health of older Americans. To produce reliable statistics for these groups, adolescents 15–19 and persons 60 and older are oversampled for the survey. African Americans and Mexican Americans are also over-sampled to enable accurate estimates for these groups.

Several important areas in adolescent health, including nutrition and fitness and other aspects of growth and development, will be addressed. Since the United States has experienced dramatic growth in the number of older people during this century, the aging population has major implications for health care needs, public policy, and research priorities. NCHS is working with public health agencies to increase the knowledge of the health status of older Americans. NHANES has a primary role in this endeavor.

In the examination, all participants visit the physician who takes their pulse or blood pressure. Dietary interviews and body measurements are included for everyone. All but the very young have a blood sample taken and see the dentist. Depending upon the age of the participant, the rest of the examination includes tests and procedures to assess the various aspects of health listed above. Usually, the older the individual, the more extensive the examination. Some persons who are unable to come to the examination center may be given a less extensive examination in their homes.

Survey Operations

Health interviews are conducted in respondents' homes. Examinations are performed in specially-designed and equipped mobile examination centers, which travel to survey locations throughout the country. The survey team consists of a physician, dentist, medical and health technicians, dietary and health interviewers. A large staff of trained bilingual interviewers conducts the household interviews.

An advanced computer system using high-end servers, desktop PCs, and wide-area networking collects and processes all of the NHANES data, nearly eliminating the need for paper forms and manual coding operations. This system allows interviewers to use notebook computers with electronic pens. The staff at the mobile exam center can automatically transmit data into data bases through such devices as digital scales and stadiometers. Touch-sensitive computer screens let respondents enter their own responses to certain sensitive questions in complete privacy. Survey information is available to NCHS staff within 24 hours of collection, which will enhance the capability of collecting quality data and will increase the speed with which results are released to the public.

In each location, local health and government officials are notified of the upcoming survey. Households in the survey receive a letter from the NCHS Director to introduce the survey. Local media may feature stories about the survey.

NHANES is designed to facilitate and encourage participation. Transportation is provided to and from the examination center and participants receive compensation. A report of medical and dental findings is given to each participant. All information collected in the survey is kept strictly confidential. Privacy is protected by public laws.

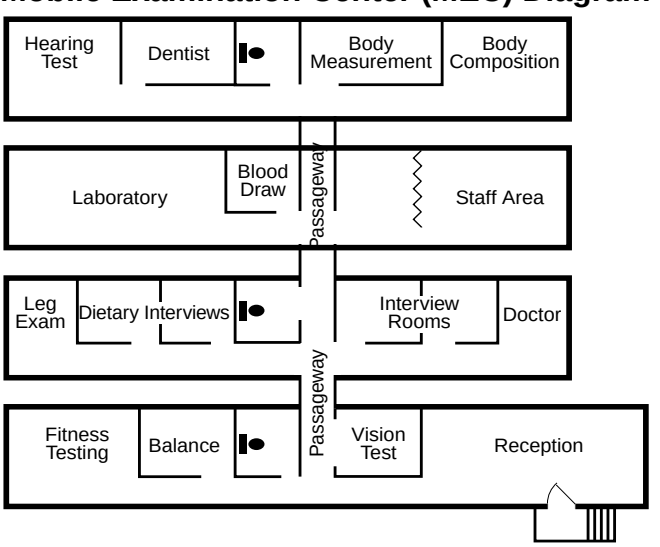
Uses of the Data

Information from NHANES is made available through an extensive series of publications and articles in scientific and technical journals. For data users and researchers throughout the world, survey data are available on easy-to-use CD-ROMS and personal computer diskettes. In the future, data will be widely distributed on the World Wide Web.

Research organizations, universities, health care providers, and educators will benefit from survey information. Primary data users are the U.S. Public Health Service agencies that collaborated in the design and development of the survey. The National Institutes of Health, the Food and Drug Administration, and CDC are among the agencies that rely upon NHANES to provide data essential for the implementation and evaluation of program activities. The U.S. Department of Agriculture and NCHS cooperate in planning and reporting dietary and nutrition information from the survey.

NHANES' partnership with the U.S. Environmental Protection Agency allows continued study of the many important environmental influences on our health.

Mobile Examination Center (MEC) Diagram



NHANES' record of important accomplishments is made possible by the thousands of Americans who have participated.

- Past surveys have provided data to create the growth charts used nationally by pediatricians to evaluate children's growth. The charts have been adapted and adopted worldwide as a reference standard—and have recently been updated using the latest NHANES figures.

- Blood lead data were instrumental in developing policy to eliminate lead from gasoline and solder in food and soft drink cans. Recent survey data indicate the policy has been even more effective than originally envisioned, with a decline in elevated blood lead levels of more than 70% since the 1970's.

- Overweight prevalence figures have led to the proliferation of programs emphasizing diet and exercise, stimulated additional research, and provided a means to track trends in obesity.

- Data have continued to indicate that undiagnosed diabetes is a significant problem in the United States. Efforts by Government and private agencies to increase public awareness, especially among minority populations, have been intensified.

These are just a few examples of what survey findings have meant. The current program promises continuing contributions and some new initiatives.

- Information collected in this survey will help the Food and Drug Administration decide if there is a need to change vitamin and mineral fortification regulations for the Nation's food supply.

- The national programs to reduce hypertension and cholesterol levels continue to depend on NHANES data to steer education and prevention programs toward those at risk and to measure success in curtailing risk factors associated with heart disease, the Nation's number one cause of death.

- New measures of physical fitness will further our understanding of its role in health and enhance the analysis of relationships between exercise and obesity and disease.

Because NHANES is now an ongoing program, the information collected will contribute to annual estimates in some topic areas included in the survey. For small population groups and less prevalent conditions and diseases, data must be accumulated over several years to provide adequate estimates. The new continuous design also allows increased flexibility in survey content.

Results of NHANES will benefit people in the United States in important ways. Facts about the distribution of health problems and risk factors in the population give researchers important clues to the causes of disease. Information collected from the current survey will be compared with information collected in previous surveys. This will allow health planners to detect the extent various health problems and risk factors have changed in the U.S. population over time. By identifying the health care needs of the population, government agencies and private sector organizations can establish policies and plan research, education, and health promotion programs that will help improve present health status and prevent future health problems.

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For more information about the National Health and Nutrition Examination Survey you may visit the NHANES web site at: www.cdc.gov/nhanes

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