

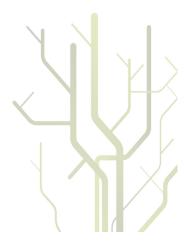
FACULTY OF HEALTH SCIENCES DEPARTMENT OF COMMUNITY MEDICINE

INCIDENCE AND RISK FACTORS FOR TYPE 2 DIABETES IN A GENERAL POPULATION. The Tromsø Study.



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List of papers

This thesis based on the following papers, referred to in the text with their Roman numerals;

- I. Josepha Joseph, Johan Svartberg, Inger Njølstad, Henrik Schirmer. Incidence of and risk factors for type 2 diabetes in a general population. The Tromsø Study. Scand J of Public Health, 2010;38 (7):768-775.
- II. Josepha Joseph, Johan Svartberg, Inger Njølstad, Henrik Schirmer. Change in cardiovascular risk factors in relation to diabetes status. The Tromsø Study.
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- III. Josepha Joseph, Johan Svartberg, Inger Njølstad, Henrik Schirmer. Risk factors of type 2 diabetes in groups stratified according to Metabolic Syndrome. A 10-year follow-up of The Tromsø Study. European J Epidemiology 2010 Dec 28th online.

Abbreviations

BMI Body Mass Index

CVD Cardiovascular Disease

CI Confidence Interval

CV Coefficient of Variation

HDL High Density Lipoprotein

HbA_{1c} Glycated Haemoglobin A_{1c}

HR Hazard Ratio

LDL Low Density Lipoprotein

LTPA Leisure-Time Physical Activity

PH Proportional Hazard

RR Relative Risk

ROC Receiver Operating Characteristics

SD Standard Deviation

TC Total Cholesterol

VIF Variation Inflation Factor

WHO World Health Organization

Introduction

Background

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces (1). There are mainly two types of diabetes; Type 1 diabetes is immune-mediated and requires daily administration of insulin. The other common type is type 2 diabetes and characterized by insulin resistance or relative insulin deficiency (1,2). Type 2 diabetes is the most common form and comprises of 90% of people with diabetes around the world (1). The prevalence of type 2 diabetes rates continue to increase with increasing number of patients at risk of serious diabetes-related complications. Having type 2 diabetes increase the risk of a myocardial infarction two times and the risk of suffering a stroke two to four times. It is also a leading cause of blindness, limb amputation and kidney failure (1,3-5). Although trials of secondary prevention after myocardial infarction show as good or better short term effect of interventions in patients with diabetes as in patients without, patients with diabetes have not had a similar reduction in longer-term case fatality rates of cardiovascular disease (CVD) (6). Population based studies of CVD risk factor trends among subjects with and without diabetes show differing trend in disfavour of those with diabetes (7). Studies of adherence to guidelines for CVD prevention targets in patients with diabetes in general practice have shown that only 13% reach all the targets (8). Previous studies have found appropriate lifestyle intervention and/or drug treatment are effective in delaying or preventing both diabetes and its complications (9-12). Accordingly, simple, sensitive and acceptable tools for identification of subjects at risk are warranted.

Epidemiology of type 2 diabetes

The world prevalence of diabetes in 2010 among adults aged 20-79 years is estimated to 6.4%, affecting 285 millions adults (13). Between 2010 and 2030, there is an expected 70% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries (13). Each year more than 231,000 people in the United states and more than 3,96 million people worldwide die from diabetes and its complications (2). This number is expected to increase by more than 50 percent over next decade (1). Estimated global healthcare expenditures to treat and prevent diabetes and its complications is at least 376 billion US Dollar (USD) in 2010. By 2030, this number is projected to exceed some 490 billion USD (14). These costs are mainly due to treatment of concomitant CVD (15). It has been shown in several studies that a clustering of features, such as high plasma glucose, obesity, dyslipidemia (high triglyceride and total cholesterol levels low high density lipoprotein (HDL) cholesterol levels and hypertension, referred to as insulin resistance or the metabolic syndrome, is a marker of increased risk for the development of type 2 diabetes as well as for CVD (16,17). Environmental and lifestyle factors are the main causes of the dramatic increase in type 2 diabetes prevalence (18-20). Genetic factors probably identify those most vulnerable to these changes. Further more, studies have shown certain ethnic groups to be more susceptible to developing diabetes than others (21,22).

Aetiology of type 2 diabetes

Type 2 diabetes results from an imbalance between insulin sensitivity and insulin secretion. Both longitudinal and cross-sectional studies have demonstrated that the earliest detectable abnormality in type 2 diabetes is an impairment of the body's ability to respond to insulin. Impaired insulin action is observed in several tissues e.g., skeletal muscle, adipose tissue and the liver. It leads to increased insulin secretion from the pancreas to overcome impaired insulin action. Compensatory hyperinsulinemia maintains glucose level within normal

range, but in individual at high risk of developing diabetes, beta cells function eventually declines and leads to the development of impaired glucose tolerance and eventually overt diabetes mellitus (23-25).

Risk factors for type 2 diabetes

Many studies have elaborated the associations between several risk factors and the risk of type 2 diabetes. Body mass index (BMI), lipids, hypertension, smoking, physical inactivity, low education, dietary patterns, family history, and recently also specific genes are the most frequently documented risk factors for type 2 diabetes (26-32).

BMI

Many longitudinal studies have reported that increased BMI is a strong risk factor for type 2 diabetes (27,33-36). A strong positive association between obesity and type 2 diabetes is found both in men (33,36-38), and women (27,33,36,39). Obesity is associated with increased risk of developing insulin resistance and type 2 diabetes. In obese individuals adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors involved in the development of insulin resistance. When insulin resistance is accompanied by dysfunction of the beta cells, the following fall in insulin secretion results in failure to control blood glucose level leading to type 2 diabetes. Many genes interact with the environment leading to obesity and in some also to diabetes. Many genes have been shown to be involved in determining the whole range of BMI in a population, with each gene only explaining a few hundred grams difference in body weight (40). Genes responsible for obesity and insulin resistance interact with environmental factors such as increased fat/ calorie intake and decreased physical activity resulting in the development of obesity and insulin resistance followed ultimately by the development of type 2 diabetes (41,42).

Lipids

Unfavourable blood lipids has been reported as a risk factor for type 2 diabetes by several prospective studies (27,28,33,35,36,43). An inverse relationship between HDL cholesterol and risk of type 2 diabetes have been documented in several of these (27,28,35,43). Some prospective studies found low HDL cholesterol to be a stronger risk factor for type 2 diabetes in women only (35,44). Only one previous study measuring non-fasting triglycerides found an independent risk of type 2 diabetes connected to elevated triglyceride levels (36). High plasma triglycerides and low plasma HDL cholesterol levels are both seen in the insulin resistance syndrome, which is a prediabetic state (16,17), suggesting that nonfasting triglycerides and HDL cholesterol levels reflect the degree of insulin resistance. The mechanisms suggested are increased circulating levels of free fatty acids due to increased insulin levels and increased chylomicron-assembly and secretion in the gut, the latter process being a result of localized insulin resistance in the intestine. Cross sectional studies have shown that high BMI is associated with a higher level of total cholesterol and unfavourable lipids pattern, with low concentrations of HDL cholesterol and high triglycerides concentrations (45-47). Longitudinal studies have shown BMI change over time to be positively associated with changes in total cholesterol, triglycerides, and low density lipoprotein (LDL) cholesterol and negatively associated with HDL cholesterol change (48,49). Apart from triglycerides, all these lipids have been shown to convey diabetes risk independently of BMI, but how they interact have been little studied.

Hypertension

Previous prospective and case control studies have shown that hypertension progression is an independent predictor of type 2 diabetes (34,50-52). Several possible factors are likely causes of the association between type 2 diabetes and hypertension. Endothelial dysfunction could be one of the common pathophysiological pathways explaining the strong association

between blood pressure and incident type 2 diabetes. Studies have shown that markers of endothelial dysfunction are associated with new-onset of diabetes (53,54), and endothelial dysfunction is closely related to blood pressure and hypertension (55). Markers of inflammation such as C-reactive protein have been consistently related to incident of type 2 diabetes (56), and to increasing blood pressure levels (57), suggesting that inflammation might be another explanatory factor for the association between blood pressure, the metabolic syndrome, and incident type 2 diabetes (58). Finally, insulin resistance could be another potential link between blood pressure levels and the incidence of type 2 diabetes (59). In addition evidence from cross sectional and cohort studies suggests a strong relation between blood pressure and BMI and risk of type 2 diabetes (46-48,60). Although studies show that blood pressure increases with increasing BMI, the risk of type 2 diabetes associated with hypertension is independent of BMI and BMI change. A causal relationship between hypertension and type 2 diabetes is further strengthened by a recent randomized clinical trial study showing a 14% reduction of risk of diabetes in subjects with glucose intolerance by allocation to 5 year treatment with valsartan, an angiotensin II blocker with antihypertensive properties (61).

Smoking

Several prospective studies reported that current smoking is a risk factor for developing type 2 diabetes (19,62-65). Recently, a meta- analysis including 25 prospective studies showed that current smoking was associated with a 44% increased risk of diabetes (66). The association between smoking and type 2 diabetes was stronger for heavy smokers \geq 20 cigarettes/day compared with light smokers or former smokers (66-68). In addition some studies found an increased risk of type 2 diabetes the first 2-3 years after smoking cessation (62,63), with a risk in the ARIC study equalling the

smokers first after 12 years (63). Smoking leads to insulin resistance and inadequate compensatory insulin secretion response (69-71). This could be due to a direct effect of nicotinic or other components of cigarette smoke on beta cells of the pancreas as suggested by the association of cigarette smoking with chronic pancreatitis and pancreatic cancer (72). Also, some studies suggest that heavy smokers with evidence of increased systemic inflammation who gain substantial in weight after quitting, are at high risk of developing type 2 diabetes (63,73). However over longer follow up, smoking cessation is associated with a reduction in risk of developing type 2 diabetes (74).

Physical inactivity

Longitudinal studies have found physical inactivity to be a strong risk factor for type 2 diabetes (36,75-78). Prolonged television watching as a surrogate marker of sedentary lifestyle, was reported to be positively associated with diabetes risk in both men and women (79-81). Moderate and vigorous physical activity was associated with a lower risk of type 2 diabetes (37,75,82). Evidence from clinical trials which included physical activity as a integral part of life style interventions suggested that onset of type 2 diabetes can be prevented or delayed as a result of successful lifestyle interventions that included physical activity as a part of this interventions (9-11,83). Physical activity plays an important role in delaying or prevention of development of type 2 diabetes in those at risk both directly by improving insulin sensitivity and reducing insulin resistance, and indirectly by beneficial changes in body mass and body composition (84-86).

Low education

Previous prospective studies have examined the association between educational attainment and the incidence of diabetes and found that low education is significant predictor of type 2 diabetes (26,87,88). In a cross sectional study of National Population Health Survey found that people with less than high school diploma were almost twice as likely to report having diabetes as those with a bachelor degree or more (89). Another cross sectional study from the National Health Interview Survey found that women with low education had a higher prevalence of diabetes than the better educated. Furthermore, the association varied by race / ethnicity and gender, with Whites, Hispanics and women exhibiting a stronger association between education and diabetes than blacks and men (90). A recent cross sectional study found that type 2 diabetes risk was higher in the least educated who were obese and inactive compared to the more educated (91). These studies suggest that educational attainment promote an interest in own health and acquisition of knowledge that strongly influence people's ability to reduce risk by successfully adopting a healthier life style.

Dietary pattern

An important life style factor associated with the development of type 2 diabetes is dietary habits. Positive association have been reported between the risk of type 2 diabetes and different patterns of food intake (92-95). Higher dietary glycemic index has been consistently associated with elevated risk of type 2 diabetes in prospective cohort studies (95,96). The relative risk (RR) for type 2 diabetes highest to the lowest glycemic index was; for quintiles 1–5, respectively: 1, 1.15, 1.07, 1.27, and 1.59 (*P* for trend 0.001), whereas cereal fiber intake was associated with a decreased risk for quintiles 1–5, respectively: 1, 0.85, 0.87, 0.82, and 0.64 (*P* for trend 0.004), (95).

A prospective study found that regular consumption of white rice is associated with an increased risk of type 2 diabetes whereas replacement of white rice by brown rice or other whole grains was associated with a lower risk (93). A review which included 19 studies, "On diet and risk of type 2 diabetes: the role of fat and carbohydrate" concluded that a higher intake of polyunsaturated fat and long- chain n.3 fatty acid is beneficial, where as higher intake of saturated fat and trans fat adversely affects glucose metabolism and insulin resistance (97). Another prospective study found higher consumption of butter, potatoes and whole milk to be associated with increased risk of type 2 diabetes. Higher consumption of fruits and vegetable was associated with reduced risk of type 2 diabetes (98). The possible mechanisms suggested are that insoluble fibre intake was consistently associated with improved insulin sensitivity and decreases risk of type 2 diabetes (99,100). Furthermore large observational studies have suggested an association between low vitamin D status or low vitamin D intake and increased incidence of type 2 diabetes (101,102). The suggested mechanisms are that vitamin D deficiency may contribute to beta cell dysfunction, insulin resistance and inflammation that may result in type 2 diabetes. The effect of dietary habits has in all these studies been shown to be independent of BMI change.

Genetics

Several studies have found that genetic components plays an important role in pathogenesis of type 2 diabetes (18,103-105). Several prospective studies and cross sectional studies have reported that positive family history among first degree relatives confers an increased risk of type 2 diabetes and the risk is greater when both parents are affected (103,104,106,107). A study on twins have demonstrated that concordance estimate for type 2 diabetes is high in monozygotic compared to dizygotic and the rate increases with duration of follow up (108). Also, diabetes prevalence varies substantially among different ethnic groups (18), and this observation of substantial variation of disease prevalence across ethnic groups that share a

similar environment, supports the idea that genetic factors contribute to disease predisposition (109). Data from multiple laboratories support that genetic factors predispose to development of type 2 diabetes by reducing insulin sensitivity and insulin secretion which deteriorate in parallel in most human type 2 diabetes cases (109-111). Recent studies have identified variants in 11 genes (TCF7L2, PPARG, FTO,KCNJ11, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1, and HHEX) to be significantly associated with the risk of type 2 diabetes independently of other clinical risk factors and variants in 8 of these genes were associated with impaired beta-cell function (32). Among these genes expressed in pancreatic cells and involved in impairment of insulin secretion, the transcription factors 7-like 2 (TCF7L2), is the locus with the highest risk of type 2 diabetes (HR 1.5) (32,112-114). This corresponds to an attributable risk of 25%, due to an average single allele frequency 18-30% in Northern Europeans (112). Still the value of genetic information decreased by duration of follow up and eventually only increases the receiver operating characteristics (ROC) achieved by clinical risk factors from 0.74 to 0.75 (p <0.0001), (32). So far genetic information is of interest for research purposes only.

Risk scores for type 2 diabetes

A simple, sensitive and acceptable screening tool is vital in early identification and intervention of type 2 diabetes. Because fasting blood glucose tests are invasive, time consuming, and requires fasting status and/or glucose ingestion, several attempts have been made to assess the diabetes risk according to diabetes risk factors such as age, obesity, blood lipids, blood pressure, smoking, physical inactivity, diet, family history of diabetes, history of intermediate hyperglycaemia, and gestational diabetes, etc. A review of tools for predicting risk of type 2 diabetes in daily practice concluded that the Finnish Diabetes Risk Score (FINDRISC) was the most useful as it had the highest ROC area (ROC 87%) when validated in other populations and was independent of blood sampling or other invasive

tests (115). A recent study on early detection of type 2 diabetes mellitus in Chinese and Indian adult populations found age, obesity and family history of diabetes to be moderately discriminative for early detection of diabetes with only an ROC of 62% in men and 64% in women (116,117), clearly showing the need for screening tools incorporating more risk factors.

Aims of the thesis

The main aim of this thesis was to explore different risk factors for type 2 diabetes in the population of Tromsø, with the main focus being:

- To determine the incidence of type 2 diabetes in a Norwegian population.
- To determine gender specific impact of lipids on the risk of type 2 diabetes independent of BMI.
- To investigate the changes in cardiovascular risk factors in relation to of type 2 diabetes status over time from 1994 to 2008 and to what degree targets in prevention guidelines were reached.
- To evaluate whether diabetes risk in subjects with low metabolic score were more
 likely to be detected by other risk factors than the metabolic factors BMI, lipids and
 hypertension.

Material and methods

Study design

This is a large population-based observational study. Due to the prospective design of this study, the risk factors included were measured and classified before the occurrence of diabetes.

Study population

The population-survey in Tromsø has comprised the cohorts presented in table 1. The target cohort of the present thesis comprises the 27158 persons who attended the fourth survey in 1994/95. At that time all residents of the Tromsø municipality born 1969 or earlier were invited to the phase 1 of the fourth survey. Among 37559 persons invited, 2139 persons died or moved before their scheduled phase 1 examination. The eligible population was therefore 35420 persons, and 73% of those invited attended the phase I examination of the survey and answered the relevant questionnaires. This is the population studied in paper I and paper III. A subgroup of 6820 from phase 1 attended a second examination (phase 2) a few weeks after the main Tromsø IV survey and this gave additional baseline information on waist circumference in paper III. In 2001/02, 10353 were invited to the Tromsø V survey. A total of 8130 subjects attended the survey. Of these, 7191 were followed from the 1994 survey. This enabled us to evaluate the change in risk factors from 1994 to 2001 in paper III. In 2007/2008, 19762 subjects were invited to the Tromsø VI survey and a total of 12984 attended. Among these, 10327 had also attended the 1994 survey. These subjects were the basis for analysis of change in cardiovascular risk factors in relation to diabetes status from 1994 to 2008 in paper II.

Table 1: The Tromsø Study 1974-2008

Study year	Study's name	Number of participants	Age group	Attendance rates
1974	Tromsø I	6595 men	20-49	74%
1979-80	Tromsø II	16621 men and women	20-54	78%
1986-87	Tromsø III	21826 men and women	12-67	76%
1994-95	Tromsø IV	27158 men and women	25-97	73%
2001-02	Tromsø V	8130 men and women	30-89	79%
2007-8	Tromsø VI	12984 men and women	30-87	66%

A total of 40,051 different people have participated in at least one of the studies, while 15,157 have participated on three or more occasions (www.tromsostudy.com or www.tromsoundersokelsen.no).

Data from questionnaire and examinations

Questionnaires printed on the reverse side of letters of invitation were distributed to the eligible population in each Tromsø survey (Appendix A-D). In the fourth survey (1994/1995) two sets of questionnaires were handed out; the second one with different versions for those above and below 70 years of age (appendix A-C). The first one was printed on the reverse side of a letter of invitation, while the second one was handed out at the health examination to be returned by mail.

The first questionnaire was checked for inconsistency by a trained nurse at the health examination, and it included questions on disease and symptoms, habits with respect to leisure-time physical activity (LTPA), diet, smoking, coffee consumption and work related issues. The second questionnaire included questions on health condition, earlier disease, disease in the family, use of medication and health service, marital status, education level and more thorough questions on diet and LTPA. The second questionnaire differed for

those younger or older than 70 years with more focus on activity of daily living and cognitive function in the elderly (appendix B-C).

Physical inactivity was defined as less than 3 hours per week of light activity in leisure time without sweating or dyspnoea. Moderate LTPA was defined as 3 hours or more of light activity or 1-2 hours of hard LTPA per week which caused sweating or dyspnoea. Hard LTPA was defined as a hard activity with sweating or becoming out of breath for 3 hours or more per week.

Educational level was defined as having completed 1: primary and secondary-school, 2: high school or vocational school 1-4 years, 3: university less than 4 years and 4: 4 years or more.

Family history of diabetes was reported as first degree family members, i.e. parents or siblings, with a history of diabetes.

Smoking status was ascertained as current, previous or never smoker.

Height and weight was measured at screening with light clothing without shoes, BMI was computed as kg/m².

Blood pressure was recorded in the sitting position after two minutes' rest by the use of an automatic blood pressure measurement device (Dinamap Vital Signs Monitor, Waukesha, US). Three recordings were taken at 2-minute intervals, and the mean of the two last readings were used in the analysis. The participants were considered to have hypertension if he or she had systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or reported being on antihypertensive medication.

Non-fasting blood samples were collected from an antecubital vein, serum prepared by centrifugation after one hour respite at room temperature, and analyzed at the Department of Clinical Chemistry, University Hospital of North Norway. Serum total cholesterol and triglycerides were analyzed by enzymatic colorimetric methods and commercially available

kits (CHOD-PAP for cholesterol and GPO-PAP for triglycerides: Boeringer Mannheim). Serum HDL-cholesterol was measured after precipitation of lower-density lipoproteins with heparin and manganese chloride. The coefficients of variation (CV) for total cholesterol 1.1%, triglycerides 2.6% and for HDL cholesterol 4.4% respectively. Determination of glycated haemoglobin (HbA_{1c}) in EDTA whole blood was based on an immunoturbidometric assay (UNIMATES, F. Hoffmann-La Roche AG: Basel, Switzerland). The CV for HbA_{1c} was less than 5%.

Registration of exposure variables

Data form questionnaires and examinations used to define exposure variables in each paper depending on the main aim of the corresponding analysis.

Paper I:

Using information collected from questionnaires and examinations, the risk factors included in this paper were age, BMI, diastolic and systolic blood pressure, total cholsterol, serum triglycerides, HDL cholesterol, treatment for hypertension, smoking habits, leisure-time physical activity, educational level and family history of diabetes.

Paper II:

In paper II the focus was on change in BMI, lipids, blood pressure, smoking and glucose control (HbA $_{1c}$). LDL cholesterol (LDL-C) was calculated by means of the Friedewald formula if the triglyceride concentration was <4.5 mmol/l (118). 138 cases were found to have triglycerides >4.5 mmol/l and were excluded from LDL-C calculation. For estimation of adherence to current guidelines the national guidelines from 1995 and 2000 (same cut off values) were used with HbA $_{1c}$ < 7.5%, blood pressure \leq 140/85mmHg, total cholesterol/HDL cholesterol (TC/HDL-C) ratio <4 TC < 6.5 mmol/l (119). To estimate the challenge facing clinicians today, the guidelines from the American diabetes association was used with blood

pressure <130/80 mmHg, LDL-C <2.5 mmol/l and HbA1c <7% (120), deviating only from national guidelines with regards to blood pressure(≤135/80 mmHg).

Paper III

In paper III the metabolic syndrome was defined according to a modified version of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) (121), in which the metabolic syndrome is present when three or more of the following criteria are fulfilled.

- 1. Hypertension; blood pressure ≥130/85mmHg and /or antihypertensive medication.
- 2. Hypertriglyceridemia; fasting serum triglycerides > 1.70 mmol/L.
- 3. Low HDL cholesterol, < 1.03mmol/L (men), <1.29 mmol/L (women).
- 4. Central obesity; waist circumference > 102 cm (men), >88 cm (women).
- 5. Fasting plasma glucose \geq 6.1 mmol/L.

Because waist circumference measurements were available only for a subset of participants, BMI was used instead of waist circumferences as suggested as a possible alternative in other studies (122,123). In this analysis, the cut - off values for BMI were calculated as the mean BMI values in men and women with waist circumference of 102 and 88 cm, respectively. Accordingly, BMI >28.3 kg/m² for men and >27.0 kg/m² for women were used. The last criterion of fasting plasma glucose was not available and was not included in the analysis.

The other risk factors included in this paper were age, total cholesterol, family history of type 2 diabetes, smoking, physical inactivity and educational level.

A subgroup of 6820 who met for a second visit a few weeks after the main survey, gave additional baseline information on waist circumference. In 2001, 7191 of the original cohort of the 1994/95 survey participated in the fifth Tromsø survey. This enabled us to evaluate the change in risk factors from 1994 to 2001.

Follow up and case identification of type 2 diabetes

Possible cases of diabetes mellitus were identified through self-reported diabetes in questionnaires or Hb_{Alc}>6.5% in the health surveys 1994/95 or 2001 and 2008, and through linkage of the Tromsø Study participant list to diabetes related discharge diagnoses in the digital patient records at the only local hospital (ICD- 9 codes 250, 357.2, 362.0, 583.8, 648.0, 648.8, 790.2, ICD-10 codes E10 -E14, O24 and R73). Some cases of hospital confirmed diabetes, but with no diabetes-related discharge diagnosis, were detected through our adjudication process for cardiovascular diseases. We validated all possible cases of diabetes by checking their medical records. Cases were classified as having no diabetes, type 1 or type 2 diabetes, based on glucose measurements if they had non fasting glucose \geq 11.1 mmol/l, fasting glucose > 7.0 mmol/l, 2 hour glucose load \geq 11.1 mmol/l or Hb_{A1c} ≥7.0% in the hospital laboratory database or recorded use of insulin or oral anti-diabetic drugs (124). C-peptide measurement was the common method at the hospital during the follow-up period to differentiate between type 1 diabetes and type 2 diabetes, while glutamic acid decarboxylase antibody (anti-GAD) measurements were performed in a minority of cases. Follow up ended December 31st, 2005. In paper II the cases were followed from the screening in 1994 to the screening in 2008 to estimate the change in risk factor levels.

Statistical analysis

To determine the risk of type 2 diabetes for different risk factors, Hazard ratios (HR) were calculated using Cox' proportional hazard (PH) model in the SPSS software (version 17.0, SPSS Inc., Chicago, IL, USA). The Cox model is a robust model that gives good estimate of regression coefficients, hazard ratios and adjusted survival curves which closely approximate the results for the correct parametric model (125). In paper I & III, for each participant, person-years of follow-up were accrued from the date of enrolment through the

date a type 2 diabetes-events was diagnosed, the date the participant died or officially moved from the municipality of Tromsø, or through the end of the study period, December 31st 2005. Total length of follow up was 258571 person-years of follow-up. The proportional hazard model assumes a constant hazard ratio over time, or equivalently, a hazard for one individual that is proportional to the hazard for any other individual, where the proportionality constant is independent of time. Satisfaction of PH assumption was assessed for type 2 diabetes risk predictors using the graphical approach. Log-log survival curves of independent variables above mentioned were parallel and this indicates that the PH assumption is satisfied. All proportional hazard models were adjusted for possible confounders which might be associated with both exposure and effect variables. Point estimates for HR are presented for 1 standard deviation (SD) change for continuous variables. The Variation Inflation Factor (VIF) showed low multicollinearity (<4 for all independent variables) (126). Interaction terms of all possible combination of two or more causes that might modify one another were introduced in the models to determine the necessity for interaction terms in final models. Data are presented stratified by sex. Confidence interval 95% (CI 95%) was estimated and the significance level was chosen at p<0.05. In paper I, Incidence rates were calculated by dividing the number of incident cases by person years in each age group. Age specific incidence was calculated by direct standardization with the use of World Health Organization (WHO) European Standard Population (127). In all three papers, base line differences in means between groups were tested using by age-adjusted general linear models. Differences in proportions were tested with logistic regression adjusted for age. In paper II, changes were calculated as difference between examinations in 2007-2008 and 1994-1995 and differences in change between groups tested with general linear model or logistic regression where appropriate.

Main results

Paper I: Incidence of and risk factors of type 2 diabetes in a general population

The study is based on 12431 men and 13737 women aged 25 to 98 years, attending the Tromsø Study in 1994, followed through 2005, and who did not have diabetes when entering the study. A total of 522 validated incident type 2 diabetes cases were registered, during a median follow-up 10.8 years, 308 among men and 214 among women. The age standardized incidence rate was higher in men than in women, 2.6 (95%CI 2.32-2.90) and 1.6 (95%CI 1.40-1.83) per 1000 person years, respectively. In multivariate survival analysis, age, BMI, triglycerides, HDL cholesterol, hypertension, family history of diabetes, low education and smoking were independent predictors of type 2 diabetes in both genders p<0.05. Total cholesterol and lack of leisure-time physical activity were independent predictors in men only. We found an interaction between HDL cholesterol and triglyceride levels, (p<0.001), and between triglyceride levels and a positive family history of diabetes (p=0.04). These interactions were independent of BMI. A positive family history combined with triglycerides in the highest tertile and BMI > 25 kg/m² conveyed a 10 year risk of type 2 diabetes of 10% (95%CI 8-12%) vs 0.2% (95%CI 0.08-0.31%) for the lowest risk group.

Paper II: Change in cardiovascular risk factors in relation to diabetes status.

The study is based on 10327 subjects who attended the Tromsø Study in 1994 and were screened again in 2007/2008. There were 49 prevalent cases, and 392 incident cases of type 2 diabetes were diagnosed between 1994 and 2008. Incident and prevalent cases of type 2 diabetes significantly decreased in HDL-C and increased in triglycerides, BMI, and antihypertensive treatment during 14 years of follow-up. Incident and prevalent cases of type 2 diabetes had decreasing levels of HDL-C total TC, blood pressure and increasing levels of triglycerides, BMI, and antihypertensive treatment. Despite decreasing blood pressure, more than 73% of the treated cases had blood pressure above 135/80 at end of follow up.

Similarly, less than 35% of incident cases using statins had LDL-C below the recommended threshold value of 2.5 mmol/l. Despite greater relative reduction in cardiovascular risk factors among people with type 2 diabetes compared to those without, treatment targets were met in less than 50% of subjects with type 2 diabetes. Fourteen percent reached the combined targets for glucose, blood pressure and LDL-C control.

Paper III: Risk factors for type 2 diabetes in groups stratified according to criteria of metabolic syndrome.

The study is based on 1298 men and 13695 women, attending the Tromsø Study in 1994, followed through 2005, and who did not have diabetes when entering the study. A total of 492 validated incident type 2 diabetes cases were registered. For those fulfilling ≥3 metabolic score criteria, increasing age, BMI, triglycerides, hypertension and a family history of diabetes were independent predictors. Of these risk factors age, BMI, hypertension and triglycerides predicted type 2 diabetes more strongly in subjects with low metabolic score. The risk associated with a positive family history was unaffected by metabolic score. In the low risk group with low metabolic score, smoking, low education and in men also inactivity, significantly improved prediction. Adding these non metabolic risk factors increased correct classification significantly (ROC area increased from 77.2% to 87.1%, p <0.0001). In this study one half of the incident cases of type 2 diabetes were missed by using high metabolic score for risk prediction.

General discussion

Methodological considerations

Validity

The aim of an epidemiological study is to be both valid and reliable and to avoid random and systematic error. The validity has two different aspects. A measurement is valid if it measures what it is suppose to measure. This validity can be divided into an internal and an external validity. Internal validity is the degree to which the results of a study are correct for the sample of people being studied. External validity refers to whether the results from the study can be applied to other populations who were not actually studied (128). In epidemiological research, two broad types of errors afflict studies; systematic errors and random errors. Systematic error can also be termed as bias and cofounding. Different type of bias can distort the estimation of an epidemiologic measure of interest and retract both the internal and external validity. Random error can affect the reliability of the measurement and precision of estimate (129).

Random error

Random error is the chance of non-reproducibility of a study finding. It can result in weakening of a true association or inability of finding an association between exposure and effect variables. Precision (lack of random error) can be improved by increasing the size of the study and efficiency of the study by modifying its design (129). The large size of this study reduces sampling error and therefore increases precision. Moreover, the study efficiency is improved with the proper allocation of subjects into study groups using all the available information of the data.

Random error was addressed by statistical inference. Estimation of the associated relative risk and its confidence interval were calculated. Hypotheses were tested at the 0.05 alpha

level with 95% confidence intervals. The null hypothesis was rejected if the chance of a random finding was less than 5% (p value < 0.05). Otherwise the null hypothesis was retained and the analysis reported as non-significant. By applying this significance level on the tests, Type I errors, which represent the possibility of rejecting null hypothesis that are true, are avoided. Although the avoidance of Type I error increase the likelihood of Type II error, which represent the possibility of not rejecting a null hypothesis when it is false, the large study size and a long follow-up time in this study minimize the chance of Type II error.

Systematic errors (bias and confounding)

Selection bias

Selection bias occurs in the procedures used to select individuals to be studied (130;131). This type of bias occurs if there are systematic differences in the exposure status and disease status between those who participated and those who do not participate in the study. The potential for selection bias is limited with 73% of the eligible population included in this study. Apart from age (born 1969 or earlier), there were no defined criteria for those invited to the fourth survey. Figure 1 show the percentages of attendance by age groups among men and women respectively. The lowest attendance rate were among those less than 40 years and those older than 75 years, with attendance rates of 67% and 71% among men and 76% and 74% among women. We have no possibility to explore differences between responders and non responders. Previous findings from the Tromsø study showed agreeable result between individuals who returned and did not return second questionnaire (132).

100 ■ Men 80 □ Women 60 % 40 20 35 45 50 55 60 65 70 75 85 30 40 80

Age groups

Figure 1: Percentage of attendance by age groups among men and women

Information bias

Information bias can occur whenever there exist errors or misclassifications in the measurement of subjects, but the consequences of the errors are different, depending on whether the distribution of errors for one variable depends on the actual value of other variables (129). Misclassification of discrete variables can be of two types: Differential misclassifications are errors that depend on the values of other variables; i.e. systematic errors, and non-differential misclassifications are errors that do not depends on other variables; i.e. random errors. Variables used in paper I - paper III as categorical variables smoking, hypertensive treatment, lipids treatment, physical inactivity, family history of diabetes and education level could lead to a recall bias since they were only self-reported. But as this information is obtained prior to development of disease recall bias is minimized. As these categorical variables all are subject to change over time this is most like to introduce a random error weakening the associations found. We have no indication of

serious errors of the other cardiovascular risk factors that are used in all three papers such as blood pressure, serum lipids and BMI. Serum lipids were measured in a non-fasting state. The value of triglycerides may depend on the time since last meal (133). However when we adjusted for time since last meal in the multivariable analysis it had no effect on the estimates of interest.

Confounding and interaction

A definition of confounding is confusion, or mixing of effects which implies that the effect of an exposure variable mixed together with effect of other variables leads to a bias (130). Confounding exists if meaningfully different interpretations of the relationship of interest result when an extraneous variable or a covariate is ignored or included in the data analysis. With a large number of independent risk factors for type 2 diabetes risk, it is certain that some of these risk factors will have some degree of associations. The association between the exposure and effect variables might be distorted by an extraneous factor(s) which is/are associated with the effect (diabetes risk) in both exposed and unexposed groups leading to mixing of effects or confounding. There are ways of avoiding or adjusting for confounding. In our analysis we stratified on possible confounders such as age and sex or we included all possible confounding variables as covariates and adjusted in the linear or multivariate models. Separate from confounding, some extraneous factors can also have a modification on the effect of an exposure. This effect modification or interaction; difference in effect of one factor according to the level of another factor, can have direct biological and public health relevance. Therefore interaction terms (exposure variable multiplied by possible effect modifier) were introduced to the models to assess any significant differences between models with and without the interaction term. In paper I we found significant independent interactions between HDL cholesterol and triglycerides, p<0.001 and between family history of diabetes and triglycerides (p=0.04). The increased risk conveyed by decreasing

HDL cholesterol increased by increasing triglyceride levels and more so at high BMI levels. This interaction was most prominent in women. We did not find any interaction between BMI and dyslipidemia in any form, but in men we found an interaction between family history and increased BMI (p<0.0001). Of the interactions with family history of diabetes, the interaction with triglyceride levels was most prominent A positive family history in those with BMI≤25 kg/m² conveyed the same risk as BMI >25kg/m² and a negative family history of diabetes. The risk increased with increasing triglyceride levels and positive family history and increased BMI >25 kg/m². The absolute risk of type 2 diabetes over 10 years increased from 0.1% (95% CI 0.04–0.3) to 10.1% (95% CI 7.4–13.7) in women and from 0.3% (95% CI 0.1–0.7) to 10.3% (95% CI 7.8–12.5) in men, respectively.

External validity

The external validity of the study refers to the generalization of the internally valid results for the source populations to other populations. The population in this study is representative of the Norwegian and Scandinavian population, as it is largely a middle-class Caucasian population. To assess the statement of more universal association we have to gather information from different populations. In the Tromsø Study we assessed associations between cardiovascular risk factors and type 2 diabetes. Other studies and other study population have addressed these associations, may be not in the same sub groups and with the same range of risk factors as the present results. It is important to compare result between different populations. Association between risk factors may vary due to differences in dietary habits, ethnic differences and genetic variation or other characteristics. Although the participation in the Tromsø Study is not statistically representatives for the population of Norway, we believe that the inferences drawn from study could be generalized to the Norwegian population. In Tromsø the incidence of cardiovascular disease, education, and lifestyles is in accordance with data from other parts

of Norway (134). A relative high proportion of population in the municipality of Tromsø comprises a homogeneous set of individuals, although a few of the inhabitants are of Sami or Finnish origin, 3 and 7% respectively (as reported in Tromsø III).

Implications for public health practice

This study is one of few studies which included several risk factors such as family history of type 2 diabetes, lipids and blood pressure as well as life style risk factors. As shown in paper I and paper III, high BMI is an important risk factor for type 2 diabetes. Public health approaches such as promoting healthier eating practice and active lifestyle to stop increase or even reduce BMI would successfully prevent type 2 diabetes. This could be implemented by health education through media as well as in clinical and primary care settings. In the latter prevention could be targeted to those at highest risk by screening of family history, smoking and physical activity habits in addition to simple measurements of blood pressure and non-fasting triglycerides. Helping patients with smoking cessation and prevention or treatment of hypertension also will prevent the more prevalent lung and cardiovascular diseases.

In paper II risk factor levels are shown to be high in subjects with type 2 diabetes despite the favourable changes in blood pressure and total cholesterol over time. Consequently a substantial number of patients do not reach treatment targets. Clinicians need to adhere more strictly to treatment guidelines. As weight loss and physical activity affects both lipids, blood pressure and glucose control non-pharmacological treatment could increase fulfilment of treatment targets.

In paper III the use of fixed criteria of metabolic syndrome to target subjects at risk of developing missed 50% of the cases indicating a need for a wider approach to diabetes prevention. Incorporating low education, smoking and a family history of type 2 diabetes, improved risk classification significantly to levels matching FINDRISC.

Conclusions

- A total of 522 validated incident type 2 diabetes cases were registered, during a median follow-up 10.8 years, 308 among men and 214 among women. The age standardized incidence rate was higher in men than in women, 2.6 (95%CI 2.32-2.90) and 1.6 (95%CI 1.40-1.83) per 1000 person years, respectively.
- Age, BMI, triglycerides, HDL cholesterol, hypertension, family history of diabetes, low education and smoking were independent predictors of type 2 diabetes in both genders and in addition also total cholesterol and lack of physical activity in men.
- Unfavourable levels of HDL cholesterol and in triglycerides, BMI, and hypertension were seen in diabetes cases during 14 years of follow-up. Despite a reduction in both blood pressure and total cholesterol among people with diabetes, treatment targets were met in less than 50% of subjects. This might explain why coronary disease patients with type 2 diabetes have a worse long term prognosis than patients without type 2 diabetes.
- In early detection of type 2 diabetes, the use of metabolic syndrome criteria miss more than 50% of cases. Therefore screening tools acknowledging a wider range of risk factors need to be adopted in early detection of diabetes. We suggest in addition to BMI, physical inactivity and age to incorporate smoking and non-fasting triglycerides (as an early marker of insulin resistance) in these risk scores.

Further research

1. Further research should focus on primary prevention by health education in primary and secondary care settings on life style factors such as food intake, smoking, physical activity, reducing obesity and early detection of lipids, blood pressure as well as early screening of those who have family history of diabetes and test the effect of different educational programme in prevention of diabetes.

- 2. Risk scores including non-fasting triglycerides should be tested against the FINDRISC in a new dataset to answer whether the inclusion of lipids improves case detection. Cut off values for low risk, need for prevention and possible undiagnosed diabetes should be established by evaluating the risk score against oral glucose testing and HbA_{1c}. The first two cut off values i.e. low risk and need for prevention, need to be established in a prospective follow up study. The latter; cut off for undiagnosed diabetes, is best established in a cross sectional study.
- 3. More follow up studies should be done to assess the benefits of different treatment modalities on control of hyperglycaemia as well as on other cardiovascular risk factors such as blood pressure and lipids in diabetes patients to prevent further CVD and other complications. Especially the focus should be on assessing the effect of non-pharmacological interventions based on healthy lifestyle such as increased physical activity, smoking cessation, weight loss and a healthy dietary pattern.
- 4. More studies are needed in understanding of how genetic variation contributes to disease within populations. This will require a simultaneous acquisition of detailed genetic and environmental (life-style) data from very large population cohorts. So far large endeavours like the DECODE study (135), have increased our understanding of the mechanisms behind development of type 2 diabetes, but clinically useful information is still lacking.

Erratum

Paper I

The *p* values were mistyped in abstract and main text

The corrected version as follows:

Abstract

In multivariate survival analysis, age, body mass index (BMI), triglycerides, high-density lipoprotein (HDL) cholesterol, hypertension, family history of diabetes, low education and smoking were independent predictors of T2DM in both genders (p<0.05). Total cholesterol and lack of leisure-time physical activity were independent predictors in men only. We found an interaction between HDL cholesterol and triglyceride levels (p<0.001) and between triglyceride levels and a positive family history of diabetes (p=0.04).

Result

We did not find any interaction between BMI and dyslipidemia in any form, but in men we found an interaction between family history and increased BMI (p<0.0001). Of the interactions with family history of diabetes, the interaction with triglyceride levels was most prominent.

Discussion

For men, a positive family history interaction with BMI caused elevated risk for elevated BMI also at low triglyceride levels (p<0.0001).

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HEALTH SURVEYInvitation



Date of birth

Social security No.

Municipality

Electoral ward No.

Welcome to the Tromsø Health Survey!

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

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

The more people take part in the survey, the more valuable its results will be. We hope, therefore, that

you will be able to come. Attend even if you feel healthy, if you are currently receiving medical treatment, or if you have had your cholesterol and blood pressure levels taken recently.

Yours sincerely,

Municipal Health Authorities

y of Medicine University of Tree

Municipal Health Authorities
Faculty of Medicine - University of Tromsø
National Health Screening Service



YOUR OWN HEALTH	EXERCISE
What is your current state of health? Tick one box only.	How has your physical activity in leisure time been during this
Poor 12 1	last year? Think of your weekly average for the year.
Not so good2	Time spent going to work counts as leisure time.
Good	Hours pr. week
Very good 4	Light activity (not None Less than 1 1-2 3 or more
Do you have or have you ever had:	sweating/out of breath) 56
bo you have, of have you ever had.	Hard activity (sweating/
Myocardial infarction 13	out of breath)57
Angina pectoris	1 2 3 4
Stroke/ brain haemorrhage 19	COFFEE
Asthma 22 years	How many cups of coffee do you drink daily?
Diabetes 25 years	Put 0 if you do not drink coffee daily. Cups
Diubeles	Boiled coffee 58
Do you take medicine for high blood pressure?	Other coffee 60 Cups
Currently 28 1	Officer Coffice
Before, but not now	ALCOHOL
Never used	Are you a teetotaler? 62 Yes No
Have you during the last year suffered from pains	How many times a month do you normally drink alcohol? Do not count low-alcohol beer.
and/or stiffness in muscles and joints that have	Times I
lasted continuously for at least 3 months?	Put 0 if less than once a month 63
	How many glasses of beer, wine or spirits do you
Have you in the last two weeks felt:	normally drink in a fortnight? 65 Beer Wine Spirits
Very	Do not count low-alcohol beer. Glasses Glasses Glasses
No A little A lot much	Put 0 if less than once a month.
Nervous or worried? 30	FAT CONTROL OF THE STATE OF THE
Anxious?31	What kind of maraarine or butter do you normally use on
Secure and calm?32	Bread? Tick one box only.
Irritable? 33	Don't use butter/margarine 71
Happy and optimistic? ₃₄	Butter
Down/depressed? 35	Hard margarine 3
Lonely? 36	Putter/managine bland
1 2 3 4	Light resuments
SMOKING	6
	EDUCATION/WORK
you were growing up?	What is the highest level of education you have completed?
you wate growing op	7-10 vears primary, folk high school
Do vou now. or have vou previously. lived	Technical school, vocational school,
with daily smokers after your 20 th birthday? ³⁸	1-2 years high secondary school
Years	A-levels/High secondary school
If "YES", for how many years in all? 39	(3-4 years)
How many hours a day do you normally spend	College/university, less than 4 years 4
in smoke-filled rooms? 41	College/university, 4 or more years
Put 0 if you do not spend time in smoke-filled rooms.	What is your current work situation?
	Paid work 73
Do you yourself smoke:	Full-time housework 74
Cigarettes daily? 43	Education, military service 75
Cigars/ cigarillos daily? 44	Unemployed, on leave
Cigars/ cigarillos daily? 44 Pipe daily? 45	How many hours of paid work do you have per 77 No. of
Pipe daily? 45	How many hours of paid work do you have per 77 No. of hours
	How many hours of paid work do you have per 77 No. of hours Do you receive any of the following benefits?
Pipe daily? 45 If you previously smoked daily, how long Is it since you stopped? 46 Years	How many hours of paid work do you have per 77 No. of hours
Pipe daily? If you previously smoked daily, how long Is it since you stopped? If you smoke daily at the moment, or	How many hours of paid work do you have per week? Do you receive any of the following benefits? Sickness benefit (sick leave)
Pipe daily? If you previously smoked daily, how long Is it since you stopped? If you smoke daily at the moment, or have smoked before?	How many hours of paid work do you have per week? Do you receive any of the following benefits? Sickness benefit (sick leave) 79 Rehabilitation benefit 80 Disability pension 81 Old-age pension 82
Pipe daily? If you previously smoked daily, how long Is it since you stopped? If you smoke daily at the moment, or have smoked before? How many cigarettes do you smoke/	How many hours of paid work do you have per week? Do you receive any of the following benefits? Sickness benefit (sick leave) 79 Rehabilitation benefit 80 Disability pension 81 Old-age pension 82 Social welfare benefit 83
Pipe daily? If you previously smoked daily, how long Is it since you stopped? If you smoke daily at the moment, or have smoked before? How many cigarettes do you smoke/ did you smoke per day? 45 Years Years	How many hours of paid work do you have per week? Do you receive any of the following benefits? Sickness benefit (sick leave) 79 Rehabilitation benefit 80 Disability pension 81 Old-age pension 82
Pipe daily? If you previously smoked daily, how long Is it since you stopped? If you smoke daily at the moment, or have smoked before? How many cigarettes do you smoke/ did you smoke per day? How old were you when you began	How many hours of paid work do you have per week? Do you receive any of the following benefits? Sickness benefit (sick leave) 79 Rehabilitation benefit 80 Disability pension 81 Old-age pension 82 Social welfare benefit 83
Pipe daily? If you previously smoked daily, how long Is it since you stopped? If you smoke daily at the moment, or have smoked before? How many cigarettes do you smoke/ did you smoke per day? How old were you when you began smoking daily? Age years	How many hours of paid work do you have per week? Do you receive any of the following benefits? Sickness benefit (sick leave) 79 Rehabilitation benefit 80 Disability pension 81 Disability pension 82 Social welfare benefit 83 Unemployment benefit 84 Disability Pension 85 Rehabilitation benefit 85 Rehabilitation benefit 86 Rehabilitation benefit 87 Rehability Pension 88 Rehabilitation benefit 88 Rehability Pension 82 Rehability Pension 82 Rehability Pension 84 Rehability Pension 85 Rehability Pension 86 Rehability Pension 87 Rehability Pension 88 Rehability Pension
Pipe daily? If you previously smoked daily, how long Is it since you stopped? If you smoke daily at the moment, or have smoked before? How many cigarettes do you smoke/ did you smoke per day? How old were you when you began	How many hours of paid work do you have per week? Do you receive any of the following benefits? Sickness benefit (sick leave) 79 Rehabilitation benefit 80 Disability pension 81 Old-age pension 82 Social welfare benefit 83 Unemployment benefit 84

展畫

Tromsø Health Survey

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

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

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

The completed form should be sent to us in the enclosed prepaid envelope.

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine University of Tromsø

growing up?

National Health Screening Service

Date Month Year

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

I do not wish to answer the questionnaire.

Date for filling in this form:18/

CHILDHOOD/YOUTH_	
What Norwegian municipality did you live in at the age of 1	year?
If you did not live in Norway, give country of residence instead of mu	24 -

How was your family's economic situation while you were

Very good 29 Good Difficult Very difficult

For how much of the first three years of your life	
- did you live in a town/city?30 _	Years
- did your family have a cat or dog in the home?31 _	Years

For how much of the first 15 years of your life	
- did you live in a town/city?32	Years
- did your family have a cat or dog in the home?34	Years

HOME (STATE OF THE STATE OF THE	Alatran
Who do you live with? Tick once for each item and give the number of persons. Yes No Spouse/partner Other persons over 18 years 37 Persons under 18 years 40	Numbe
How many of the children go to kindergarten?	43
What type of home do you live in? Villa/ detached house 45 1 Farm 2 Flat / apartment 3 Terraced / semi-detached house 45 Other 5	
How big is your home?46 _	m
Approximately what year was your home built?49	
Yes Has your home been insulated after 1970?53	No
Do you live on the bottom floor/cellar level?54 ☐ If "YES", is the floor laid on concrete?55 ☐	
What is the main source of heat in your home? Electric heating Wood-burning stove Central heating system using: Paraffin Electricity Yes Do you have fitted carpets in the living room? Is there a cat in your home? Is there a dog in your home?	No .
WORK	Sen, No.
If you have paid or unpaid work, which statement describes your work best? I am mainly seated while working (e.g., at a desk/assembly work) My work requires a lot of walking (e.g., shop assistant, light industrial work, teaching) My work entails a lot of walking and lifting (e.g., postman/woman, nurse, building work) I do heavy physical work (e.g., forestry, heavy agricultural/construction work)	
Variation In the Indiana Incident	No
Tick one box only for each item. Priver Driver 66	No

Fisherman

TOOK OWN ILLINESSES		1000	STWPTOWS		EXECUTE:
Have you ever had:				Yes	No
Tick one box only for each item. Give your age at the tim If you have had the condition several times, how old were y	e. ou la	st time?	Do you cough approximately every day of the year?177 If "Yes":		
	No	Age	Is your cough productive ?178	3	
Hip fracture69 🖵		Age	Have you had this kind of cough for as long as		
Wrist/forearm fracture	5		3 months in each of the last two years?	9 🔲	
Whiplash 75 🔲	ō		Have you had a said do of what said of in your shoot?		
Injury requiring hospital admission	5		Have you had periods of wheezing in your chest?180 If "Yes", has this occurred:		_
Gastric ulcer	ō		Tick one box only for each item.		
Duodenal ulcer 84 🖵	ō		At night181		
Gastric/duodenal ulcer surgery	ō		In connection with respiratory infections		
Throat/ neck surgery			In connection with physical exertion In connection with very cold weather		
Have you you ever had, or do you still have: Tick one box only for each item.	Yes	No	Have you noticed cudden changes in your pulse		_
Cancer			or heart rhythm in the last year?		
Epilepsy	_		How often do you suffer from sleeplessness?		
Migraine			Never, or just a few times a year	1	
Chronic bronchitis			1-2 times a month		
Psoriasis		<u>-</u>	Approximately once a week	. 🛄 3	
Osteoporosis 98			More than once a week	4	
Fibromyalgia/fibrositis/chronic pain syndrome			If you suffer from periods of sleeplessness, what times of the year does it affect you most?		
Psychological problems for which you have sought help			No particular time of year187		
Thyroid disease			Especially during the dark winter months	D 2	
Liver disease			Especially during the midnight sun period	. 🔲 3	
Kidney disease 103			Especially in spring and autumn		
Appendectomy			Have you in the last year suffered from sleeplessness	Yes	No
Allergy and hypersensitivity:			to the extent that it has affected your ability to work?		
Atopic eczema (e.g., childhood eczema)					
Hand eczema			How often do you suffer from headaches?		
Hay fever			Seldom/never		
Food allergy108			Once a month or more Once a week or more	-	
Other hypersensitivity (not allergy)			Every day		
How many times have you had a cold, influenza (flue),			Does the thought of getting a serious illness ever		
vomiting/diarrhoea, or similar in the last six months? _	_tim	ies	worry you?	-	
	Yes	No	Not at all	-	
Have you had any of these in the last two weeks?112		INU	Only a little		
mave you mad any or these in the last two weeks:112	_		Some Very much		
ILLNESS IN THE FAMILY	som	olsdiA	very much	- 4	
Tick the appropriate box for relatives that have,			USE OF HEALTH SERVICES	mmo	rivolitica)
or have ever had the following illnesses: Tick "None" if none of your relatives have had the cond	ition	. 1	How many visits have you made during the past year		
			due to your own health or illness?	Numl	ber of tin
Mother Father Brother Si	ster C	hild None	Tick 0 if you have not had such contact		past yea
Stroke or brain haemorrhage 📑 🔲 🖳 🖵					
Myocardial infarction before age 60 $_{119}$ \square \square \square	,		To a general practitioner (GP)/ Emergency GP		
Cancer125			Psychologist or psychiatrist		
Asthma asthma			Other medical specialist (not at a hospital) Hospital out-patient clinic	107	
Gastric/ duodenal ulcer137			Hospital admission	191	
Osteoporosis143 🔲 🔲 🔲	Į,		Medical officer at work		
Psychological problems149	Į,		Physiotherapist	203	
Allergy155	Ţ		Chiropractor		
Diabetes161 🔲 🔲 🔲	Į		Acupuncturist		
- age when they got			Dentist Alternative medical practitioner /hemogeneth fact report		
diabetes167			Alternative medical practitioner (homoeopath, foot zone the Healer, faith healer, clairvoyant		

MEDICATION AND DIETARY SUPPLEMENTS DIET Have you during the past year used any of the following If you use butter or margarine on your bread, how many slices does a small catering portion normally cover? By this, we mean the medicines every day or almost daily? Indicate how many months you used them. portion packs served on planes, in cafés, etc. (i.e., 10-12g) Put **0** for items you have **not** used. A catering portion is enough for about _______ Medications slices215 **Painkillers** mths Sleeping pills Tranquilizers mths What kind of fat is normally used in cooking mths (not on the bread) in your home? Antidepressants ______mths Butter Allergy drugs _____mths Asthma drugs _____mths mths What kind of bread (bought or home-made) do you usually eat? White bread brown Ordinary brown Coarse brown Calcium tablets or bonemeal mths Vitamin D supplement _____mths Other vitamin supplements ______ mths Crisp bread Cod liver oil or fish oil capsules _____mths The bread I eat is most similar to 275 Have you in the last 14 days used the following How much (in number of glasses, cups, potatoes or slices) do you medicines or dietary supplements? usually eat or drink daily of the following foodstuffs? Tick one box only for each item. No Medicines Tick one box for **each** foodstuff. Less More 0 than 1 1-2 3-4 **Painkillers** 5-6 than 6 Full cream milk (fresh or soured) (glasses) Antipyretic drugs (to reduce fever) Semi-skimmed milk (low-fat) Migraine drugs (fresh or soured) (glasses) Eczema cream/ointment Heart medicine (not blood pressure) Lipid lowering drugs Sleeping pills Tranquilizers Antidepressants Skimmed milk (fresh or soured) (glasses) 0000 Tea (cups) Orange juice (glasses) Potatoes 281 Slices of bread in total Other drugs for nervous conditions Antacids Gastric ulcer drugs Insulin Diabetes tablets (incl. crisp-bread) Slices of bread with - fish (e.g., mackerel in tomato sauce) - lean meat Thyroxin tablets (for metabolic disorder) (e.g., ham) Cortisone tablets Other medicine(s) - fat meat (e.g., salami) - cheese (e.g. Gouda/ Norvegia) ..286 🔲 Dietary supplements - brown cheese Iron tablets Calcium tablets or bonemeal Vitamin D supplement Other vitamin supplements - smoked cod caviare - jam and other sweet spreads 🖵 How many times per week do you normally eat the following foodstuffs? Cod liver oil or fish oil capsules Tick a box for all foodstuffs listed. Never Less approximately 2-3 than 1 1 everyday Boiled or fried egg Breakfast cereal / not mod 000 FRIENDS 00 Breakfast cereal/ oat meal, etc. How many good friends do you have whom you can talk good For dinner confidentially with and who give you help when you259 ____ _friends - meat need it? Do not count people you live with, - sausage/meatloaf/ meatballs but do include other relatives! - fat fish (e.g., salmon/redfish) 295 🔲 - lean fish (e.g., cod) How many of these good friends do you have contact with at least once a month? - fishballs/fishpudding/fishcakes 🔲 - vegetables Mayonnaise, remoulade Carrots Cauliflower/cabbage/ broccoli 🔲 How often do you normally take part in organised gatherings, e.g., sewing circles, sports clubs, political meetings, religious or other associations? Apples/pears Oranges, mandarins Sweetened soft drinks Never, or just a few times a year 1-2 times a month Approximately once a week Sugar-free ("Light") soft drinks Chocolate

Chocolate Waffles, cakes, etc.307

More than once a week

ALCOHOL	TO BE ANSWERED BY WOMEN ONLY
How often do you usually drink beer? wine? Spirits?	MENSTRUATION
Never, or just a few times a year 1-2 times a month Approximately once a week 2-3 times a week Approximately every day 308	How old were you when you had your first menstruation?years
Approximately how often in the last year have you drunk alcohol that equals at least 5 small bottles of beer, a bottle of wine, or 1/4 bottle of spirits? Not in the last year	you when you stopped having menstruation?years Apart from pregnancy and after giving birth, have your menstruation ever stopped for 6 months or more?
For approximately how many years has your alcohol consumption been as you described above?years	What date did your last menstruation begin? \(\text{\cdots} \) 333 \(\text{\cdots} \) 7es \(\text{No} \) relieve period pains? \(\text{\cdots} \) 339 \(\text{\cdots} \)
- before age 20	If you have given birth, fill out for each child the year of birth and approximately how many months you breastfed the child. Child Year of birth: Number of months breastfed 1 348
	CONTRACEPTION AND OESTROGEN Do you, or have you ever, used: Contraceptive pills (incl. minipill) A hormonal intrauterine device Oestrogen (tablets or patches) Oestrogen (cream or suppositories) If you use contraceptive pills, hormonal intrauterine device, or oestrogen, what brand do you currently use? If you use, or have ever used, contraceptive pills: Age when you began taking the pill? How many years in total have you taken the pill? Journal of the very sears of the pill of
	If you have given birth, how many years did you take the pill before your first child? If you have stopped taking the pill: "

Tromsø Health Survey for the over 70s

The main aim of the Tromsø Study is to improve our knowledge about cardiovascular diseases in order to aid prevention. The survey is also intended to improve our knowledge of cancer and other general conditions, such as allergies, muscle pains and mental conditions. The ultimate aim is to gain an overview of the general health of the elderly population. We would therefore like you to answer the questions below.

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

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

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

Thank you in advance for helping us.

Faculty of Medicine

University of Tromsø

Yours sincerely,

National Health

Screening Service

If you do not wish to answer the questionnaire, tick the box below and return the form. Then you will not receive reminders. I do not wish to answer the questionnaire. **Day Month Year** Date for filling in this form:

CHILDHOOD/YOUTH

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

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

How was your family's financial situation while you were Growing up?

Very good29 🖵 1 Good Difficult Very difficult

ow ola w	ere your parents when they died?	
Mother	30	Year
Father	32	Year

HOME		10-16
Who do you live with? Tick once for each item and give the number. Yes	No	Number
Spouse/partner		
Other persons over 18 years		
Persons under 18 years		
What type of home do you live in?	_	
Villa/ detached house41 🖵 1		
Farm 2		
Flat/apartment		
Terraced /semi-detached house 4 Other 5		
How long have you lived in your present home?	42	Year
Yes	No	1001
Is your home adapted to your needs?4 If "No", do you have problems with:	_	
Space	_	
too cold/too warm46 🖵		
Stairs47 📮		
Toilet48 🖵		
	_	
Bath/shower49 🖵		
Bath/shower		
Bath/shower49	00 0	
Bath/shower 49 Maintenance 50 Mainte	0	
Bath/shower 49 Maintenance 50 Mintenance 51 Mintenance 51 Mintenance 551 Mintenan	ION	lid
Bath/shower Maintenance Other (please specify) Would you like to move into a retirement home? PREVIOUS WORK AND FINANCIAL SITUAT Which statement best describes the type of work y for the last 5-10 years before you retired? I was mainly seated while working 50 10	ION you c	
Bath/shower Maintenance Other (please specify) Would you like to move into a retirement home? PREVIOUS WORK AND FINANCIAL SITUAT Which statement best describes the type of work y for the last 5-10 years before you retired? I was mainly seated while working (e.g., desk/assembly work)	ION you c	
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Bath/shower Maintenance Other (please specify) Would you like to move into a retirement home? PREVIOUS WORK AND FINANCIAL SITUAT Which statement best describes the type of work y for the last 5-10 years before you retired? I was mainly seated while working (e.g., desk/assembly work) My work required a lot of walking (e.g., shop assistant, housewife, teaching) My work required a lot of walking and lifting (e.g., postman, nurse, construction work) I did heavy physical work (e.g., forestry, heavy agricultural work, heavy construction work) Did you do any of the following jobs (full- or part-time)? Tick one box only for each item. Driver	TION you c	2
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Bath/shower Maintenance Other (please specify) Would you like to move into a retirement home? PREVIOUS WORK AND FINANCIAL SITUAT Which statement best describes the type of work y for the last 5-10 years before you retired? I was mainly seated while working (e.g., desk/assembly work) My work required a lot of walking (e.g., shop assistant, housewife, teaching) My work required a lot of walking and lifting (e.g., postman, nurse, construction work) I did heavy physical work (e.g., forestry, heavy agricultural work, heavy construction work) Did you do any of the following jobs (full- or part-time)? Tick one box only for each item. Driver Farmer Fisherman How old were you when you retired? What kind of pension do you have? Basic state pension 50 51 52 53 55 56 The provided state pension The provided state pension state pension state pension The provided state pension state pension state pension state pension The provided state pension stat	No	3
Bath/shower Maintenance Other (please specify) Would you like to move into a retirement home? PREVIOUS WORK AND FINANCIAL SITUAT Which statement best describes the type of work y for the last 5-10 years before you retired? I was mainly seated while working (e.g., desk/assembly work) My work required a lot of walking (e.g., shop assistant, housewife, teaching) My work required a lot of walking and lifting (e.g., postman, nurse, construction work) I did heavy physical work (e.g., forestry, heavy agricultural work, heavy construction work) Did you do any of the following jobs (full- or part-time)? Tick one box only for each item. Driver Farmer Fisherman How old were you when you retired? What kind of pension do you have? Basic state pension Additional pensions	No	Year

Very difficult

ILLNESS IN THE FAMILY HEALTH AND ILLNESS Has your state of health changed in the last year? Put a mark for relatives who have, or have ever had, any of the following conditions: Tick "None" for conditions which none of your relatives have had. No, unchanged 2 Mother Father Brother Sister Child None Stroke or brain haemorrhage 114 🔲 🔲 How do you feel your health is now compared to Myocardial infarction before age 60_{20} \square others of your age? Cancer 126 🔲 🖸 Much worse 63 1 Hypertension ... Asthma 138 🔲 🔲 About the same Osteoporosis144 🗖 🗖 A little better Arthrosis (osteoarthritis).....150 🔲 🗓 Much better Dementia162 🔲 🔲 YOUR OWN ILLNESSES Diabetes mellitus168 🖵 🗖 Have you ever had: - age when they got Tick one box only for each item. Give your age at the time. diabetes _____174 __ ___ If you have had the condition several times, how old were you last time? No Age **SYMPTOMS** Hip fracture64 Yes No Wrist /forearm fracture Do you cough daily for periods of the year?184 Whiplash70 🖵 If "Yes": Is your cough productive?185 Gastric ulcer76 🖵 Have you had this kind of cough for as long Duodenal ulcer79 as 3 months in each of the last two years? 186 Gastric/duodenal ulcer surgery82 Throat/neck surgery _______85 📮 Have you had periods of wheezing in your chest? If "Yes", has this occurred: Have you ever had, or do you still have: Tick one box only for each item. Yes No Tick one box only for each item. At night 188 Cancer88 🖵 In connection with respiratory infections Epilepsy 🖵 In connection with physical exertion Migraine In connection with very cold weather191 Parkinsons disease Chronic bronchitis Have you noticed sudden changes in your pulse or heart rhythm in the last year? Psoriasis 93 🖵 Osteoporosis Have you lost weight in the last year?193 Fibromyalgia/fibrositis/chronic pain syndrome If "Yes". Psychological problems for which you have sought help How many kilograms?194 ___ Thyroid disease How often do you suffer from sleeplessness? Liver disease98 Recurrent urinary incontinence 1-2 times a month 2 Glaucoma Cataract More than once a week 4 Arthrosis (osteoarthritis) Rheumatoid arthritis If you suffer from periods of sleeplessness, what times of Kidney stones the year does it affect you most? Appendectomy Allergy and hypersensitivity Especially during the midnight sun period 🖵 3 Atopic eczema (e.g., childhood eczema) 🖵 Especially in spring and autumn 🖵 4 Hand eczema Hey fever108 🖵 No Food allergy Do you usually take a nap during the day? Other hypersensitivity (not allergy) Do you feel that you usually get enough sleep? How many times have you had a cold, influenza (flue), diarrhoea little lot /vomiting, or similar in the last six months? 111 ____ Times Do you suffer from: Dizziness ă No Have you had any of these in the last Poor memory 🖵 Lack of energy 🖵 two weeks?

Constipation 203

Does the thought of getting a serious illness worry you? Not at all Only a little Some Very much	2	04 🔲		services your manicipality supplies: 165 140	ee Don't know
BODILY FUNCTIONS Can you manage the following everyday activities on your own without help from others? Walking indoors on one level	🗖	With some hel	No p	Do you feel confident that you can receive the health care home assistance you require if you need it? Confident Not confident Very unsure Don't know	and
Walking approx. 500 metres Going to the toilet Washing yourself Taking a bath/shower Dressing and undressing Getting in and out of bed Eating meals		1000000	0000000	MEDICATION AND DIETARY SUPPLEMENTS Have you for any length of time in the past year used any the following medicines every day or almost daily? Indicate how many months you used them for. Write <u>0</u> for items you have <u>not</u> used. Medication:	of
Cooking Doing light housework (e.g., washing up) Doing heavier housework (e.g., cleaning floc Going shopping Taking the bus	15 or)	00000	00000	Painkillers	mths
Can you hear normal speech (if necessary with a hearing aid)?	20 🔲	With difficulty	No	Asthma drugs Heart medicine (not blood pressure) Insulin Diabetes tablets Thyroxin tablets (for metabolic disorder)	mths mths mths
Walking stick	Yes	No		Remedies for constipation Dietary supplements: Iron tablets Vitamin D supplement	mths mths mths mths mths
Safety alarm device 22 USE OF HEALTH SERVICE	S			Calcium tablets or bonemeal289	mths mths
How many visits have you made during the pyear due to your own health or illness: Put 0 if you have not had such contact To a general practitioner (GP)/emergency Psychologist or psychiatrist r Other medical specialist (not at a hospital Hospital out-patient clinic Hospital admission Physiotherapist Chiropractor Acupuncturist Dentist	GP	234	rear	can tark confidentially with and who give you help	Good riends
Alternative medical practitioner (homoeopath, foot zone Healer, Faith healer, clairvoyant Do you have domestic help?	therap	ist, etc.) ———	_	Do you feel that you belong to a community or group of p who can depend on each other and who feel committed to other (e.g., a political party, religious group, relatives, neignork place, or organisation)?	to each
Do you have domestic help? Private25 Municipal Do you receive services from the district nurse?	2 🔲			Strong sense of belonging 300 1 Some sense of belonging 2 Not sure 3 Little or no sense of belonging 4	

How often do you normally take part in organised gatherings, e.g., sewing circles, sports clubs, political meetings, religious or other associations?	WELL BEING
Never, or just a few times a year301	How content do you concrelly fool with growing old?
1-2 times a month	How content do you generally feel with growing old? Good
Approximately once a week 3	Quite good
More than once a week	Up and down
55 558	Bad
Middle could be at he DIET MAKE astronogramme)	D44
	What is your view of the future?
Number	Bright1
How many meals a day do you normally eat	Not too bad 2
(dinner and bread meals)?302	Quite worried
	Dark 🖵 4
How many times a week do you eat a hot dinner?304	
Mile at I dead of here and the control on heaven mendals decrease	TO BE ANSWERED BY WOMEN ONLY
What kind of bread (bought or home-made) do you usually eat?	TO BE ANSWERED BY WOMEN ONLY
Tick one or two boxes! White textured Ordinary Coarse Crisp	Management and the second seco
Dread . brown broad	MENSTRUATION
The bread I eat is most similar to	How old were you when you had your first menstruation? Years
What kind of fat is normally used in <u>cooking</u>	Inclistration:
(not on the bread) in your home? Butter	How old were you when you stopped having menstruations? Years
Hard margarine 🖵 Soft margarine	PREGNANCY
Butter/margarine blend	How many children have you given birth to?340Children
How <u>much</u> (in <u>number</u> of glasses, cups, potatoes or slices) do you usually eat or drink <u>daily</u> of the following foodstuffs? Tick one box for <u>each</u> foodstuff. 0 Less 1-2 3 or than 1 more	If you have given birth, fill out for each child the year of birth and approximately how many months you breastfed the child. If you have given birth to more than 6 children, note their birth year and number of months you breastfed at the space provided below for comments.
Milk of all types (glasses)	Child Year of birth: Number of months
Orange juice (glasses)	breastfed:
Potatoes	1 342
Slices of bread in total (Incl. crispbread)	2 346
Slices of bread with	3
- fish (e.g., mackerel in tomato sauce) 🔲 🔲 🔲	4
- cheese (e.g., Norwegia)	5 358
- smoked cod caviar322	6
How <u>many times per week</u> do you normally eat the following foodstuffs? Tick a box for all foodstuffs listed.	During pregnancy, have you had high blood pressure and/or Yes No proteinuria?
Less 2 or	
Never than 1 1 more	If "Yes", during which pregnancy? Pregnancy First Later
Yoghurt323 🔲 🔲 🛄	High blood pressure
Boiled or fried egg 🔲 🔲 🛄	Proteinuria
Breakfast cereal/oat meal, etc 🔲 🔲 🖳	1 Totaliuliu
For dinner	OESTROGEN
- meat	OLSTROGER
- fat fish (e.g., salmon/red-fish)	Do you use, or have you ever used oestrogen:
- lean fish (e.g., cod)328 🔲 🔲 🔲	Now Used to Never
- vegetables (raw or cooked)	Tablets or patches371 🔲 🔲
Carrots (raw or cooked)	Cream or suppositories
Cauliflower/cabbage/broccoli	
Apples/pears	If you use oestrogen, what brand do you currently use?
Oranges, mandarins, etc333	Calant pile. Michil Zerovi Stract. 2011 - 459, in 172 central consideration for the Language Calant Consideration of Calant Consideration.
1 2 3 4	
Your comments:	



The form will be read electronically. Please use a blue or black pen

	You can not use comas, use upper-case letters.	
	2007 - 2008 Confidential	
1	HEALTH AND DISEASES How do you in general consider your own health to be?	Below you find a list of different situations. Have you experienced some of them in the last week (including today)? (Tick once for each complaint) No Little Pretty Very complaint complaint much much
	 Very good Good Neither good nor bad Bad Very bad 	Sudden fear without reason
2	How is your health compared to others in your age? $\hfill \Box \hfill \hf$	upset
	☐ A little better☐ About the same☐ A little worse	Pepressed, sad
3	☐ Much worse Age first Do you have, or have you had? Yes No time Heart attack	Feeling of hopelessness with regard to the future
	Angina pectoris	Have you during the past year visited: If YES; how many times? Yes No No. of times
	High blood pressure	Psychiatrist/psychologist
	Chronic bronchitis/Emphysyma/COPD	Physiotherapist
4	Migraine	Have you during the last 12 months been to a hospital? Yes No No. of times Admitted to a hospital
5	 Yes □ No How often have you suffered from sleeplessness during the last 12 months? □ Never, or just a few times □ 1-3 times a month □ Approximately once a week □ More that once a week 	Had consultation in a hospital without admission; At psychiatric out-patient clinic At another out-patient clinic Have you undergone any surgery during the last 3 years? Yes No

FAMILY AND FRIENDS USE OF MEDICINE Who do you live with? (Tick for each question 10 Do you take, or have you taken some of the and give the number) following medications? (Tick once for each line) Yes No Number Never Spouse/cohabitant used Now Earlier Other persons older than 18 years.. \Box Drugs for high blood pressure Persons younger than 18 years Lipid lowering drugs Drugs for heart disease Tick for relatives who have or have had Parents Children Siblings Diuretics Medications for Myocardial infarction \square osteoporosis Myocardial infarction before 60 years Insulin Angina pectoris Tablets for diabetes Stroke/brain haemorrhage Drugs for metabolism Osteoporosis Thyroxine/levaxin Stomach/duodenal ulcer How often have you during the last 4 weeks used the following medications?(Tick once for each line) Asthma П Diabetes mellitus Not used Less than Every the last every week, but Dementia 4 weeks week Daily not daily Psychological problems Painkillers on prescription Drugs/substance abuse Painkillers non-Do you have enough friends who can give you prescription help when you need it? Sleeping pills \Box ☐ Yes ☐ No Tranquillizers Do you have enough friends whom you can talk confidentially with? Antidepressants .. How often do you normally take part in 12 State the names of all medications -both those organised gatherings, e.g. sports clubs, political on prescription and non-prescription drugs- you meetings, religious or other associations? have used regularly during the last 4 weeks. Do not include vitamins, minerals, herbs, natural Never, or just a few times a year remedies, other nutritional supplements, etc. 1-2 times a month Approximately once a week More than once a week WORK, SOCIAL SECURITY AND INCOME What is the highest level of education you have completed? (Tick one) ☐ Primary, 1-2 years secondary school Vocational school ☐ High secondary school (A-level) ☐ College/university less than 4 years ☐ College/university 4 years or more If the space is not enough for all medications, use an additional paper of your own. 19 What is your main occupation/activity? (Tick one) When attending the survey centre you will be asked whether you have used antibiotics or ☐ Full time work Housekeeping painkillers the last 24 hours. If you have, you ☐ Part time work Retired/benefit recipient will be asked to provide the name of the drug, strength, dose and time of use.

Unemployed

Student/military service

Do you receive any of the following benefits Old-age, early retirement or survivor pens Sickness benefit (are in a sick leave) Rehabilitation benefit Full disability pension Partial disability pension Unemployment benefits Transition benefit for single parents Social welfare benefits	
What was the households total taxable incoryear? Include income from work, social beneand similar □ Less than 125 000 NOK □ 401 000-550 000 □ 125 000-200 000 NOK □ 551 000-700 000 □ 201 000-300 000 NOK □ 701 000 -850 000 □ 301 000-400 000 NOK □ More than 850	How often do you drink alcohol? Never No Nok Monthly or more infrequently 2-4 times a month Non Nok 2-3 times a week 4 or more times a week
 Do you work outdoors at least 25% of the tir in cold buildings (e.g. storehouse/industry buildings)? Yes No 	How many units of alcohol (a beer, a glass of wine or a drink) do you usually drink when you drink alcohol? 1-2
PHYSICAL ACTIVITY 23 If you have paid or unpaid work, which state describes your work best? Mostly sedentary work (e.g. office work, mounting) Work that requires a lot of walking (e.g. shop assistant, light industrial work, teaching) Work that requires a lot of walking and lif (e.g. postman, nursing, construction) Heavy manual labour	Never Less frequently than monthly Monthly Weekly Daily or almost daily Do you smoke sometimes, but not daily?
 Describe your exercise and physical exertion leisure time. If you activity varies much, for example between summer and winter, then an average. The question refers only to the year. (Tick the one that fits best) Reading, watching TV, or other sedentary activity. Walking, cycling, or other forms of exercise at least 4 hours a week (here including walking cycling to place of work, Sunday-walking, etc.) Participation in recreational sports, heavy getc. (note:duration of activity at least 4 hours a week Participation in hard training or sports competitions, regularly several times a week 	Do you/did you smoke daily? I give last Yes, Yes, Never previously If you previously smoked daily, how long is it since you stopped? Number of years If you currently smoke, or have smoked before: How many cigarettes do you or did you usually smoke per day? Number of cigarettes Number of cigarettes
How often do you exercise? (With exercise we for example walking, skiing, swimming or training/sports) Never Less than once a week Once a week 2-3 times a week Approximately every day	Number of years How many years in all have you smoked daily? Number of years Do you use or have you used snuff or chewing tobacco? No, never Yes, sometimes Yes, previously Yes, daily

	DIET		QUESTONS FOR WOMEN		
38	Do you usually eat breakfast every day?		Are you currently pregnant?		
	☐ Yes ☐ No		☐ Yes ☐ No ☐ Uncertain		
	How many units of fruits or vegetables do you eat		How many children have you given birth to?		
39	on average per day? (units means for example	'	Number		
	a fruit, a cup of juice, potatoes, vegetables)	48	If you have given birth, fill in for each child:		
	Number of units		birth year, birth weight and months of breastfeeding (Fill in the best you can)		
40	How many times per week do you eat hot dinner?		Child Birth year Birth weight in grams breastfeeding		
	Number		1		
41	How often do you usually eat these products?		2		
	(Tick once for each line) 0-1 2-3 1-3 4-6 1-2	<u>!</u>	3		
	times/ times/ times/ times/ time mth mth week week day		4		
	Potatoes		5		
	Pasta/rice		6		
	Meat (not processed)	49	During pregnancy, have you had high blood		
	$(sausages/meatloaf/meatballs) \ \square \ \square \ \square \ \square$		pressure?		
	Fruits, vegetables, berries		☐ Yes ☐ No		
	Lean fish	50	If yes, which pregnancy?		
	(e.g. salmon, trout, mackerel, herring, halibut, redfish)		☐ The first ☐ Second or later		
42	How much do you normally drink the following? (Tick once for each line) Rarely/ glasses / day Milk, curdled milk, yoghurt	52	During pregnancy, have you had proteinuria? Yes No If yes, which pregnancy? The first Second or later Were any of your children delivered prematurely (a month or more before the due date) because of preeclampsia? Yes No		
43	How many cups of coffee and tea do you drink				
	daily? (Put 0 for the types you do not drink daily)	54	If yes, which child? 1st child 2nd child 3rd child 4th child 5th child 6th child		
	Number of cups Filtered coffee				
	Boiled coffee (coarsely ground coffee for brewing)	55	How old were you when you started		
	Other types of coffee		menstruating?		
	Tea		Age +		
44	How often do you usually eat cod liver and roe? (i.e. "mølje") Rarely/never		Do you currently use any prescribed drug influencing the menstruation?		
			Oral contraceptives, hormonal IUD or similar Yes No		
	\square 7-12 times/year \square More than 12 times/year	Hormone treatment for menopausal problems			
45	Do you use the following supplements?		menopausat problems 163 - 100		
+	Daily Sometimes No Cod liver oil or fish oil capsules		When attending the survey centre you will get a questionnaire about menstruation and possible use of hormones. Write down on a paper the names of all the hormones you have used and bring the paper with you. You will also be asked whether your menstruation have ceased and possibly when and why.		



