

Faculty of Health Sciences Department of Clinical Medicine

Ischemic stroke in a general population: Time trends in incidence, case fatality and the impact of risk factors.

The Tromsø Study

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A dissertation for the degree of Philosophiae Doctor – October 2017



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"When we try to pick out anything by itself, we find it hitched to everything else in the universe".

John Muir (1838–1914)

Scottish-American glaciologist and environmental philosopher, and an early advocate for the preservation of wilderness in the United States.

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# **Summary**

Cerebral stroke is a clinical syndrome caused by lack of blood supply to the brain. About 80-85% of the strokes are ischemic, due to a reduction or complete blockage of blood flow to the brain, while approximately 15% are a result of hemorrhage. The impact of stroke as a global health problem will most likely increase in coming years due to ongoing demographic changes, including aging population and health transitions in developing countries.

Lack of national data regarding time trends in incidence and case fatality of ischemic stroke (IS) in Norway represented a main motivation for this study. Data from the population-based Tromsø Study, following >40,000 attendees from six surveys through 2012, provided an excellent opportunity to reveal time trends of IS and assess the potential mechanisms behind these trends.

We found that the overall age- and sex adjusted incidence of IS in persons aged ≥30 years declined with 27% from 1995–2012. The time trends differed by age, with increasing IS incidence in women aged 30–49 years, a non-significant rising trend among the youngest men, and declining incidence in women aged 50–74 years and men aged 65–74 years. In men aged 50–64 years, the IS incidence in 2012 did not differ from the incidence two decades earlier. The IS incidence also remained stable in persons aged 75 years and older. The age-adjusted 30-days case fatality decreased in men aged 30–84 years while no significant decline was found in women aged 30-84 years or in attendees ≥85 years.

Overall, the combined changes in seven cardiovascular risk factors, the systolic blood pressure (SBP), total cholesterol, HDL- cholesterol, daily smoking, physical activity, diabetes and body mass index accounted for 57% (95% CI 28–100) of the decrease in IS incidence from 1995 through 2012, with decreasing blood pressure and decline in smoking prevalence as the most important contributors. The increasing diabetes prevalence contributed negatively, as did the change in body mass index, although not significant.

We found that a feasible joint hypothetical intervention on six metabolic and lifestyle risk factors (SBP, total cholesterol, weight, physical activity, smoking and alcohol intake) would reduce the 18-year stroke risk in our population by 19% (1995–2012). A combination of more intensive interventions would reduce the estimated 18-years stroke risk by 55%. Blood pressure reduction and quitting smoking significantly reduced the risk when applied separately.

# Sammendrag

Hjerneslag er et klinisk syndrom forårsaket av manglende blodtilførsel til hjernen. Omlag 80-85% av hjerneslagene er ischemiske, dvs. forårsaket av en redusert eller blokkert blodtilførsel til hjernen, mens ca. 15% er forårsaket av blødning. På grunn av demografiske endringer, som en aldrende befolkning og endringer i helsetilstand i utviklingsland, vil konsekvensene av hjerneslag som et globalt helseproblem sannsynligvis øke i årene som kommer.

Mangelen på nasjonale data vedrørende tidstrender i insidens og letalitet av ischemiske slag (IS) i Norge var en hovedmotivasjon for denne studien. Data fra den populasjonsbaserte Tromsøundersøkelsen, der >40,000 deltakere fra seks tverrsnitts-undersøkelser ble fulgt opp med registering av førstegangs IS til og med 2012, ga oss en unik mulighet til å avdekke tidstrender i insidens av IS, og mulige mekanismer som kunne forklare disse tidstrendene.

Vi fant at insidensen av IS blant personer ≥30 år falt med 27% fra 1995–2012. I de yngste aldersgruppene (30-49 år) fant vi en økende insidens av IS blant kvinner og en ikke signifikant økende trend blant menn. I samme periode var det en signifikant nedgang i insidens hos kvinner i alderen 50-74 og hos menn i alderen 65-74 år. Blant menn 50-64 år var insidensen i 2012 ikke forskjellig fra tyve år tidligere. Blant personer 75 år og eldre holdt IS insidensen seg også uendret. Aldersjustert 30-dagers letalitet av IS fra 1995–2012 falt blant menn i alderen 30-84 år, mens det ikke var signifikant endring over tid hos kvinner eller blant personer ≥85 år.

Endinger i syv kardiovaskulære risikofaktorer, systolisk blodtrykk, total kolesterol, HDL kolesterol, daglig røyking, fysisk aktivitet, diabetes og kroppsmasseindeks, forklarte samlet sett 57% (95% CI 28–100) av reduksjonen i IS insidens fra 1995 til og med 2012, med fallende blodtrykk og redusert prevalens av daglig røyking som de viktigste bidragsytere. Den økende prevalensen av diabetes bidro negativt, dvs. motvirket fallet i insidens av IS. Det samme gjorde økningen i kroppsmasseindeks, men ikke signifikant.

Vi fant at en hypotetisk, men gjennomførbar kombinert endring av seks kardiovaskulære risikofaktorer (systolisk blodtrykk, total kolesterol, vekt, fysisk aktivitet, daglig røyking og alkoholinntak) kunne ha redusert risikoen for hjerneslag i vår populasjon med 19% i perioden 1995–2012. En mer intensiv kombinert endring av de samme risikofaktorene kunne ha endret den estimerte 18-årige risikoen for hjerneslag med 55%. Reduksjon av blodtrykk og røykestopp ville hver for seg ha ført til signifikant reduksjon i forekomsten av IS.

# **List of papers**

This thesis is based on the following papers:

- Vangen-Lønne AM, Wilsgaard T, Johnsen SH, Carlsson M, Mathiesen EB.
   Time trends in incidence and case fatality of ischemic stroke:
   The Tromsø study 1977–2010. Stroke. 2015;46: 1173–1179.
- II. Vangen-Lønne AM, Wilsgaard T, Johnsen SH, Løchen ML, Njølstad I, Mathiesen EB. Declining incidence of ischemic stroke: What is the impact of changing risk factors? The Tromsø study 1995–2010. Stroke. 2017;48: 544–550.
- III. Vangen-Lønne AM, Ueda P, Gulayin P, Wilsgaard T, Mathiesen EB, Danaei G. Hypothetical interventions to prevent stroke: An application of the parametric g-formula to a healthy middle-aged population. (Submitted)

# **Abbreviations**

AF: Atrial fibrillation

BMI: Body mass index

BP: Blood pressure

CVD: Cardiovascular disease

DBP: Diastolic blood pressure

GBD study: Global Burden of Disease Study

HDL: High density lipoprotein

HT: Hypertension

ICH: Intracerebral hemorrhage

IRR: Incidence rate ratio

IS: Ischemic stroke

LDL: Low density lipoprotein

PA: Physical activity

PAR: Population attributable risk

RCT: Randomized clinical trial

SAH: Subarachnoid hemorrhage

SBP: Systolic blood pressure

# 1. Introduction

### 1.1 What is stroke?

More than 2400 years ago, the physician Hippocrates of Cos (460–370 BC) presented the Greek term "apoplexy" (from "apoplessein": "to strike down and incapacitate") to describe an acute, non-traumatic brain injury associated with a sudden paralysis or impaired speech. The Swiss pathologist Johan Jacob Wepfer (1620–1695) discovered in the mid-1600s that patients who died with apoplexy could have a bleeding in the brain as well as an obstruction in one of the brain's blood vessels (1). However, the term "stroke" was probably first introduced into medicine in 1689 by William Cole (1635–1716) in his book "A Physio-Medical Essay concerning the Late Frequencies of Apoplexies".

Cerebral stroke is a clinical syndrome, defined by the World Health Organization (WHO) as "rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin" (2). Generally, a stroke is caused by lack of blood supply to the brain. This depletion of sufficient blood supply can, as discovered in the mid-1600s, be caused by different mechanisms, which all lead to an injured brain tissue and where the neurological deficits reflect the cerebral area involved. Ischemic strokes are caused by a reduction or complete blockage of blood flow to the brain, and account for about 80–85% of all stroke cases globally. Approximately 15% of the strokes are hemorrhagic, either as intracerebral hemorrhage (ICH, approximately 10–12%) or subarachnoid hemorrhage (SAH, approximately 3%). Although ischemic stroke (IS) is the dominating pathological type of stroke worldwide, the proportional frequency of ICH vs. IS tend to be noticeably greater in low-and middle income countries than in high-income countries (3).

### 1.2 Ischemic stroke

The arterial occlusion preceding an IS can be caused by several mechanisms: by atherothrombosis (extra or intracranial); by embolism (cardiogenic or artery to artery embolism); by small vessel disease; by non-atherosclerotic abnormalities (dissection, artery diseases, vasculitis, coagulopathy, metabolic diseases with arteriopathy) or by decreased perfusion due to systemic hypotension (Figure 1).

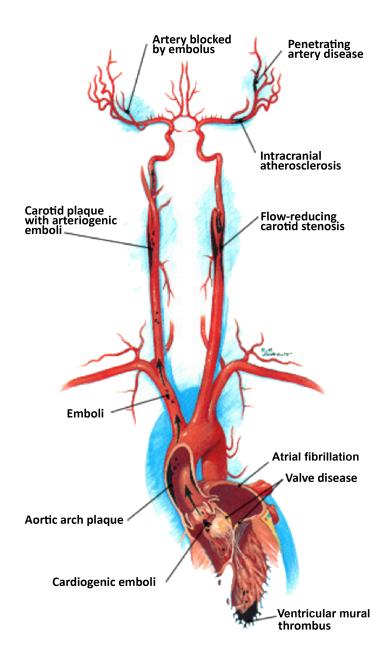


Figure 1 Patophysiological mechanisms for ischemic stroke

From Hart RG, Benavante O. Am Fam Physician 1999; 2475–82.

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Several classification systems for subtyping of IS exist, based on etiology, clinical manifestations, localization or combinations of these. Which one to use depends on the purpose of subclassification (e.g. clinical decision-making or description of patient characteristics in an epidemiological study). The frequently used TOAST classification (Trial of ORG 10172 in Acute Stroke Treatment) denotes five subtypes of ischemic stroke: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology (4). Other classification systems are the Causative Classifications System (5) and the Oxfordshire Community Stroke Project (OCSP) Subtype Classification (6).

## 1.3 Epidemiology

#### 1.3.1 The burden of stroke in numbers

Stroke is the second leading cause of death worldwide and a frequent cause of adult disability in most regions. Worldwide, during the last decades, the age-standardized stroke mortality rates have declined, as a result of declining stroke incidence as well as reduced case fatality (7). Despite this global decrease in age-standardized stroke mortality, the absolute numbers of people who experience a stroke every year, live with the consequences of stroke or die from their stroke, is increasing. In 2013, there were globally 10.3 million new strokes (67% were IS), 6.5 million deaths from stroke (51% from IS) and nearly 25.7 million who had survived a stroke (71% with IS) (8). The incidence rate of stroke increases markedly with age (9). Worryingly, the impact of stroke as a global health problem is likely to further increase in coming years due to ongoing demographic changes, including aging of the population and health transitions observed in developing countries (8). In the absence of effective clinical or public health interventions, it is estimated that in 2030, 23 million people will have a first ever stroke, including 7.8 million fatal strokes (10).

### 1.3.2 Geographical variation in stroke burden

The largest stroke burden is carried by countries with low and middle income (developing countries). In 2010, more than 71% of the global stroke deaths and 69% of all incident strokes took place in developing countries (11). There are considerable geographical variations with regard to stroke incidence, prevalence and mortality rates due to differences in prevalence of risk factors and access to appropriate health care (including primary prevention, acute treatment of strokes and secondary prevention given). Moreover, comparison of estimates from different studies are often complicated by heterogeneity in study designs and types of population. A major challenge in stroke epidemiology is also the lack of good-quality epidemiological studies from low-income countries (12).

Changes in stroke burden over the last decades differ substantially by country income level.

A 42% reduction in age-adjusted stroke incidence rate (1.1% annual reduction) was found in high-income countries (1970-2008) while there was a 100% increase in countries with low and middle income (3). The percentage decline in age-standardized mortality rate was nearly twice as large in developed compared to developing countries from 1990 to 2010 (11), (Figure 2 shows mortality decline from 1990 to 2013).

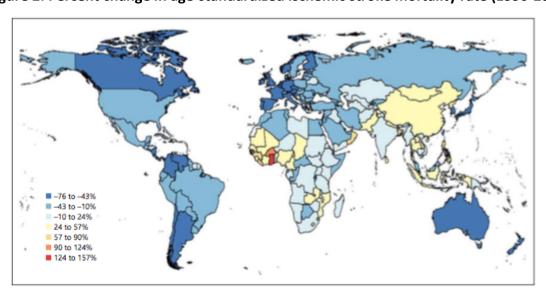


Figure 2. Percent change in age-standardized ischemic stroke mortality rate (1990-2013)

From Feigin V, Mensah GA, Norrving B et al. Neuroepidemiology. 2015;45:230–236. Reproduced with permission from the publisher

#### 1.3.3 Incidence

Incidence is defined as the number of new cases of a disease that occur over a specified period of time. In 2010, the worldwide incidence rate for stroke (age-adjusted) was 258 per 100,000 person-years; 217 per 100,000 person-years in high-income countries (11). In a population-based European register study, the risk of stroke (age standardized) varied more than 2-fold between the European populations, with higher incidence rates observed in eastern, and lower rates in southern European countries (13).

With the exception of estimations from the Innherred study, covering the years 1994-96 (14), complete national data on stroke incidence in Norway or estimates based on data from well-defined Norwegian cohorts were lacking until 2012-2013. At this time, the Norwegian Patient registry became person-specific, and the Norwegian Cardiovascular Disease Registry was established as a national register. Furthermore, there are no studies of how the stroke incidence and case fatality *have changed over time* in Norway. The lack of national data regarding time trends in incidence and case fatality of ischemic stroke represents a main motivation for this study.

#### 1.3.4 Time trends in incidence

The Global Burden of Disease (GBD) Study revealed a 13% significant reduction of IS incidence (age-standardized) in high-income countries from 1990–2010, driven by a significant IS incidence decline among those <75 years (15). No significant change in the overall incidence if IS was found in persons aged ≥75 years. Time trends of stroke incidence differ in direction and steepness also among high-income populations, as well as across the different age groups. However, possible diverging trends across age may not be acknowledged in age-unstratified analyses.

While a downward trend in age-adjusted stroke incidence is shown for middle aged and slightly older in several high-income populations (16–18), other studies found no decline in incidence

with time (19). From studies which include younger age groups, worrying reports have risen about an increasing incidence of stroke at younger age (17, 20, 21), while stable incidence rates among the youngest ones are reported in other studies (19). Many studies of stroke incidence have not included the eldest ones; but among the limited number of studies, both a stable time trend (22) and a decreasing trend (17, 20, 23) is reported.

A decrease in stroke incidence in both sexes has been demonstrated in many high-income populations the last decades (16, 18). Some studies have revealed relatively stable male/female ratios of incidence decline over time, suggesting that primary preventive measures have been equally effective in men and women (24). Other studies from developed countries reported an overall significant IS incidence decline in men only (25), or a steeper incidence decline in men for IS (26). Contrary, the worldwide data from the GBD study revealed a significant decrease of IS in women from 1990 to 2013, while no significant change in IS incidence was detected in men (27).

#### 1.3.5 Case fatality

Early case fatality is defined as the proportion of cases with an event (here: IS) followed by death within 30 days (28 days to 1 month), irrespective of the reason of death. A systematic review based on population-based studies (published 1970–2008) from high-, middle- and low-income countries found that early (21 days to 1 month) stroke case fatality differed substantially among countries and study periods (3), as was previously reported in the MONICA study (28). In 2000–2008, case fatality for IS ranged from 13–23% in high income countries (3). A Norwegian population-based study reported 11% case fatality (30 days) for IS in 1994–96 (14).

The case fatality increases steeply with advancing age (29), and comparison of populations with different age profiles may be challenging. A systematic review of studies on stroke in the very old reported a three time odds for death within 30 days after stroke in persons aged ≥80 years

compared to those < 80 years (29). Moreover, the case fatality depends on the severity of the events, comorbidity and treatment given (19). In terms of sex differences in case fatality, conflicting results are reported; of increased risk in women (24, 30) as well as no difference between men and women (31, 32).

#### 1.3.6 Time trends in case fatality

In a Swedish cohort in the MONICA study, 28-days case fatality after stroke declined significantly from 20% in 1985 to 12% in 1998 (both for men and women, first-ever and recurrent stroke), without concurrent change in the distribution of stroke subtypes during this period (for IS; 18%–12%) (33). In Oxford Vascular study, the 30-day incident stroke case fatality was not significantly different in 2002–2004 compared to 1981–1984 (17% vs. 18%) (34), while a national-wide Finnish register study found a significant 28-days case fatality reduction of incident stroke from 1999 to 2007 ( for IS: 13% to 10%) (35). A nationwide registry-based study from Scotland, looking at all first hospitalizations for stroke, showed decreasing case fatality for all age groups (men and women separately) from 1986 to 2005 (<55, 55–64, 65–74, 75–84, 85+, adjusted for comorbidity and admission year), but a steeper decline in men than in women, resulting in an increasing difference in case fatality across sex with time (24). This is in contrast to studies reporting similar decline in case fatality across sex (i.e. no interaction between sex and year) during comparable study periods (26).

#### 1.4 Risk factors for ischemic stroke

The risk factors for stroke are traditionally classified as non-modifiable and modifiable risk factors, and overlap with the risk factors for cardiovascular disease (CVD). Several studies have estimated population-attributable risks (PARs) for the associations of IS with cardiovascular risk factors (36-38). With approximately 75% of strokes being first-ever events (39), primary prevention directed towards modifiable risk factors is particularly important to reduce the burden of stroke. Although most risk factors perform an independent effect, significant interactions between individual risk factors exist, which must be considered when predicting the overall risk. While a risk factor traditionally is defined as a factor associated with a pathological medical condition (40), the levels of evidence supporting a causal relationship between these risk factors and subsequent stroke risk vary substantially between the risk factors. IS and ICH share several of their most important risk factors, despite diverse underlying pathogenesis, but the relative impact of a common risk factor on risk of IS vs. ICH differ (41). Correspondingly, the associations between well known risk factors for IS and the different subtypes of IS vary, and are still debated (42).

Table 1. Non-modifiable and modifiable risk factors for ischemic stroke

Non-modifiable risk factors	Modifiable risk factors		
Age	High blood pressure		
Male gender	Diabetes		
Race	Smoking		
Genetics (mono- or polygenic)	Atrial fibrillation		
Low birth weight	Dyslipidemia		
Previous TIA or stroke	Obesity		
Heart disease	Physical inactivity		
	Alcohol		
	Unhealthy diet		
	Illicit drug use		

#### 1.4.1 Non-modifiable risk factors

The risk of stroke more than doubles for each successive 10 years after age 55 (9), and the effect of **ageing** seems to carry the same risk in women as in men (43).

Male sex generally carries about 1.3 times the stroke risk compared to females at the same age, but this risk difference tends to decrease with age (44). However, slightly higher stroke risk in women aged 35−44 compared to equally aged men has been reported, with oral contraceptive use and pregnancy as possible contributors (9). Among the eldest (≥85 years), some studies found higher stroke incidence in women compared to men (45), but male and female rates in the eldest age category are not directly comparable when the age band is open ended (44). Women are on average 4 years older than men when they get their first stroke, but longer life expectancy in women results in a higher lifetime risk for stroke (31,44).

Stroke incidences differ by **ethnicity**; e.g. African American show a nearly twice times higher risk for stroke than European Americans (46). However, some of this difference may be related to disparities in management of modifiable risk factors.

Twin studies have revealed nearly a five times higher stroke prevalence in monozygotic as compared to dizygotic twins, which strongly support **genetic factors** related to stroke risk (47). Several established stroke risk factors (as hypertension and diabetes) provide both genetic and behavioral components (48). Moreover, various genetic diseases show association with stroke (49).

**Low birth weight** is found to be associated with increased risk of stroke in adult life, and higher risk of vascular disease in adulthood seems to remain even after adjustment for socioeconomical factors in childhood (50).

Although being non-modifiable, these factors identify those at highest risk of stroke who may benefit most from rigorous prevention or treatment of the modifiable risk factors.

#### 1.4.2 Modifiable risk factors

Hypertension (HT) is regarded as the single most important treatable risk factor for IS (42,51) and stroke in general (36, 38). The relationship between blood pressure (BP) and cardio-vascular risk is "continuous, consistent, and independent of other risk factors"(51). Hence, there is no "threshold" for BP; a significant proportion of all strokes happen in persons with normal BP or "mild" hypertension. Both systolic (SBP) (52) and diastolic blood pressure (DBP) (53) is of importance for stroke risk; but prospective studies have shown SBP to be a better predictor for CVD risk, especially in middle-aged and older adults in whom most cardio-vascular disease occur (52). In INTERSTROKE, being hypertensive (defined as self-reported HT or BP ≥140/90 mmHg) gave an odds ratio (OR) of 2.21 for IS (age- and sex matched) in sub-analyses on data from Western Europe, USA and Australia (41). From BP level of 115/75 mmHg, the risk of death from stroke doubles for each increment of 20/10 mmHg (52).

Having **diabetes** more than doubles the risk for stroke; the estimated risk for IS in diabetic persons is 1.8 to 5-fold compared to non-diabetics (48). Individuals without diabetes, but with an elevated fasting blood glucose, do also carry an excess risk for stroke (54). Diabetes is found to increase the risk for IS for all age groups, but age-specific risk for IS in diabetics vs. non-diabetics is most prominent in those aged <65 years compared to elder ones (55). While some studies have suggested a higher proportion of lacunar strokes in diabetic IS patients (56), this in not confirmed by others (57). The effect of diabetes may in part be mediated through other risk factors such as HT and lipid alterations (55, 58). Potentiating effects of diabetes with other risk factors on stroke risk is also suggested (55, 58).

Cigarette smoking is an independent risk factor for stroke, especially IS; and is associated with approximately a doubling of risk (59,60). Smoking likely contributes to higher stroke risk through both acute effects (aggregation of blood platelets / thrombus generation) and long-term effects (increased burden of atherosclerosis) (61). Moreover, a strong dose-response relationship has been shown between number of cigarettes and risk of IS (59, 61). Cigarette

smoking may also potentiate the effect of other risk factors for stroke (61, 62). In a pooled analysis of prospective data (3.9 million individuals; >42,000 strokes from 81 cohorts worldwide), the excess stroke risk by smoking was similar by sex, while in Western cohorts, smoking was a stronger risk factor for stroke in women than in men (60). Smoking cessation have been shown to reduce the stroke risk by 50% by the first year after cessation, reaching the stroke risk of never-smokers within 2–5 years (63, 64).

**Atrial fibrillation** (AF) alone is associated with an overall 4 to 5-times excess risk of IS (65), by embolism of thrombi developed in the left atrial appendage. However, among persons with AF, the absolute stroke risk differs 20-fold, depending on age and associated cardiovascular risk factors (66). IS associated with AF tend to be larger and more disabling than other IS, with a higher case fatality (67). The incidence of AF increases with age, and is higher in men than in women in all age groups (68). Diabetes, hypertension, smoking and obesity are modifiable risk factors that contribute to the development of AF (68). A recent review reported the prevalence of AF in adult population (>20 years) to be between 2.5% and 3.5%; ranging from 0.1% in adults <55years to 10% or more in persons aged 80 years and older (68). In The Tromsø population, the point prevalence of AF at the end of 2007 was 2.2% in women and 3.3% in men (mean age 57 years) (69). About 25% of IS among those ≥80 years are due to AF (65) (66). In the Framingham Heart Study, both prevalence and incidence of AF (age-adjusted and sex stratified) showed a roughly four times increase from 1958–2007. However, the incidence of AF in the Framingham Heart Study electrocardiograms (ECGs) did not change significantly across time, leading to the conclusion that enhanced detection may be part of the explanation behind increasing trends in AF prevalence and incidence (70).

The associations between **dyslipidemia** and stroke incidence are complex. Several large, observational studies have found high **total cholesterol** to be a significant risk factor for IS (71,72) while other studies have shown only a weak (73), or no association (74). This relationship also seems to differ by subtype of IS, with strongest associations for

atherosclerotic subtypes (especially large artery atherosclerosis) (75). Conversely, an inverse relationship between cholesterol level and ICH risk is found (76). Some studies have shown associations between increased **low-density lipoprotein cholesterol (LDL)**, and higher risk of IS (71), while no significant association was found in others (73). Despite relatively sparse epidemiological findings regarding novel levels of LDL and risk of IS, primary stroke prevention trials have demonstrated risk reduction of incident stroke ranging from 11%−40% in high-risk populations when receiving statin treatment (75). In a meta-analysis, an estimated 21% risk reduction of stroke was found with each 1 mmol/L reduction in LDL (77). Regarding **high-density lipoprotein cholesterol (HDL)**, a systematic review reported a reduced risk of IS ranging from 11−15% for each 10mg/dL (≈0.26 mmol/L) increase in HDL (78). Studies evaluating **triglycerides** vs. IS risk have shown mixed results (73, 75).

High **body-mass index (BMI)** is an important risk factor for stroke, and increased BP, cholesterol and glucose partly mediates its effects. In a meta-analysis of 97 prospective cohorts (1.8 million individuals; >31,000 strokes), about three quarters of the effect BMI exerted on stroke risk was mediated by these three metabolic risk factors, with BP as the most important mediator, accounting for two thirds of excess risk (79). In this study, each 5 kg/m2 increase of BMI was associated with a 4% higher risk of stroke, while persons with obesity (BMI  $\geq$ 30 kg/m²) showed a 14% excess risk of stroke compared to normal-weighted (BMI  $\geq$ 20 to <25 kg/m²) (79).

Several studies have reported a beneficial effect of regular **physical activity (PA)** on stroke risk, but studies comparing the effects of vigorous and lower levels of PA are limited (48). Even if the types and frequency of exercise necessary to prevent stroke are not fully established, meta-analyses conclude that regular PA reduces stroke risk by 25–30% when compared to least active persons (48,80). In INTERSTROKE, PA (defined as regularly moderate or strenuous leisure-time PA ≥4 hours per week) was associated with 27% reduced risk for stroke in Western populations (41). The protective effect of PA on stroke risk is partly mediated through declining BP, and by controlling other cardiovascular risk factors as diabetes and high BMI (81).

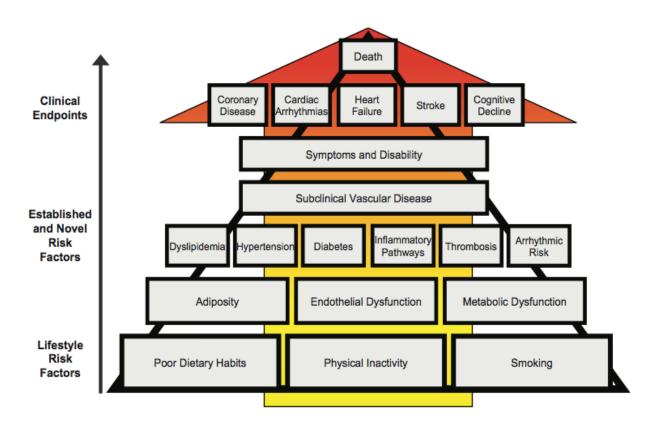
The impact of **diet** patterns on the risk of stroke have been assessed in recent years, as opposed to earlier research which focused on the impact of individual nutrients or food groups. High adhesion to a Mediterranean diet (high intake of olive oil, fruit, nuts, vegetables and cereals; moderate intake of fish and poultry; low intake of dairy products, red meat, processed meats and sweets; and wine in moderation) was related to a 39% reduction of incident strokes in the PREDIMED trial (Prevencion con Dieta Mediterranea) (82). The Dietary Approach to Stop Hypertension (DASH) diet (a diet rich in fruits, vegetables and low-fat diary products; low in saturated and total fat) significantly reduced blood pressure among persons with hypertension (SBP ≥140 mmHg and/ or DBP ≥90 mmHg) as well as among non-hyper- tensive (83). The beneficial effects of these dietary patterns on stroke risk have later been confirmed in meta-analyses for a Mediterranean (84) as well as for a DASH type of diet (85).

Several studies report a protective effect of light to moderate **alcohol consumption** on the risk of IS (86, 87), while others (88) claim that this finding could be due to e.g. residual confounding or contamination of the teetotaler group by ex-drinkers. A high consumption of alcohol (87) as well as binge drinking (89) have been associated with higher risk of stroke. The Scandinavian pattern of drinking is commonly characterized by low rates of abstinence and fairly high rates of binge drinking (90); 23% of male drinkers and 12% of female drinkers reported binge drinking (≥6 units of alcohol in one occasion) at least once a month in a national survey in 2012 (91).

**Drug abuse** (cocaine, amphetamines, heroin) may cause stroke through several pathogenetic mechanisms, e.g. by embolization after i.v. drug injection (infectious, air, talkum); by hypersensitivity reactions; by vasculitic-like changes; by induced vasospasm (especially cocaine), or by altered cerebral autoregulation / hypertensive crisis (66).

### 1.4.3 Modifiable risk factors include both metabolic and lifestyle risk factors

Metabolic risk factors as hypertension, diabetes and dyslipidemia, being traditional major foci for practice guidelines and clinical research, are strongly influenced by lifestyle factors, and act as intermediate factors between lifestyle factors (e.g. diet, physical inactivity, adiposity, smoking) and ischemic stroke. Generally, risk factors can be characterized as proximal or more distal causal factors in relation to an outcome (here: IS). As illustrated in figure 3, lifestyle factors also influence IS risk through other novel risk factors, as altered endothelial function, inflammation/oxidative stress, thrombosis/coagulation, arrhythmia and other pathways (92).



**Figure 3.** The relations of lifestyle, established metabolic risk factors and novel risk factors on cardiovascular disease. Lifestyle factors influence disease risk through established cardiovascular risk factors (e.g. hypertension, diabetes) as well as through their effect on other novel risk factors (e.g. endothelial dysfunction, inflammatory pathways).

From Mozaffarian D, Wilson PWF, Kannel WB. Circulation. 2008;117:3031–3038.

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#### 1.4.4 Observed time trends in risk factors vs. time trends in stroke incidence

Changes in stroke incidence mirror the changes in risk factors over time, and the implementation of primary prevention (7, 93). The American Heart Association/American Stroke Association proposed that 20–40% of the decrease in first-ever stroke incidence is attributed to the improvement of risk factor control (7). Nevertheless, at population level, a combined risk score of trends in systolic BP, daily cigarette smoking, serum cholesterol and body mass index explained only a small proportion of stroke incidence decrease between 1982 and 1995 (94). Most studies on the relationship between changes in risk factors over time and alterations of stroke incidence have based their estimates on ecological data or mathematical modeling of aggregated data (19, 94, 95) Fewer studies used individual person data from repeated surveys to assess how the changing trends in IS incidence are associated with changes in modifiable cardiovascular risk factors (16, 18, 34); some of these studies were limited to subgroups of age (16) or did not study out-of-hospital strokes (18).

#### 1.4.5 "What if...?" Estimating the effect of risk factor change on future stroke risk

In a public health perspective, an important question is: What would be the impact of a *change* in risk factor exposition in a population, on the subsequent population risk of first-ever stroke?

Randomized clinical trials (RCTs) have shown that treatment of hypertension reduces the risk of first-ever stroke by 35–40% (51, 96), and that usage of statin in low-risk, healthy individuals reduces stroke incidence by 24% (97). In contrast, only a few RCTs have evaluated the effect of lifestyle improvement on first-ever stroke risk (82, 98). However, clinical trials often have short follow-up time and limited generalizability. Therefore, evidence for long-term effect of interventions on stroke prevention may best be derived from prospective observational studies.

Several *prospective observational studies* have assessed the long-term associations between lifestyle risk factors and stroke risk in healthy populations (37, 99, 100) and found that 35–55%

of events were attributable to unhealthy lifestyle (i.e. smoking, heavy or irregular drinking, unhealthy diet and physical inactivity). Similarly, meta-analyses of observational studies have reported lower risk of stroke with lower levels of BP and serum cholesterol (52, 101, 102).

However, these observational studies cited above either used only baseline values of risk factors or used updated values of risk factors during follow-up (37) without appropriately adjusting for time-varying confounding. Furthermore, these observational studies estimated the lifelong impact of risk factors, (i.e. what would the stroke risk be if these risk factors were erased); whereas of more interest (and closer to real-life scenario) is the potential impact of a change in risk factor in midlife or later as an intervention.

Therefore, there is a need for reliable estimates of the potential impact of interventions on risk factors initiated in midlife or later (as in the clinical trials) over a long period of time in healthy populations (as in the observational studies).

A particular methodological challenge is to estimate the unbiased effect of a time-varying exposure in the presence of time-varying confounders if those confounders are affected by prior exposure (103). For example, if the effect of long-term weight loss is of interest, prior physical activity should be adjusted as a time-varying confounder but future physical activity can be affected by weight loss. In such cases, conventional regression models fail to adjust for confounding and may indeed introduce bias. G-methods, including the parametric g-formula, have been developed to handle such situations.

## 2. Aims of the thesis

The aims of the thesis were:

- To investigate age- and sex-specific trends in incidence and case fatality of first-ever ischemic stroke in a general Norwegian population
- To estimate the impact of changing risk factor levels across time on the concurrent change in ischemic stroke incidence
- To assess the effects of risk factor interventions (separate and combined) on the subsequent population risk of stroke and ischemic stroke

# 3. Study population and methods

## 3.1 The Tromsø Study cohort

The Tromsø Study is a single-center population-based health study, conducted in the municipality of Tromsø, Norway. Tromsø is located at 69° N and is a center of education, research, administration and fishing related activities. The Tromsø population is dominated by Caucasians of mainly Norwegian origin (including a Sami minority), and may be considered representative of a Northern European, white, urban population (104). From 1974 to 2012 the number of inhabitants increased from 42,200 to 68,000. Seven cross-sectional screening surveys (Tromsø 1–7) have been carried out so far; the first one in 1974, followed by repeated surveys with 6–7 years interval (1979–80, 1986–87, 1994–95, 2001, 2007–08 and 2015–16). Total birth cohorts and additional random samples of inhabitants in Tromsø were invited to surveys by written invitations sent by mail, and the attendance rate ranged from 65% to 77% (Table 2). The initial main focus in 1974 was cardiovascular diseases, but the study has expanded throughout the years to include other research areas and health aspects. In this study, data from Tromsø 1 (1974) to Tromsø 6 (2007–08) is used.

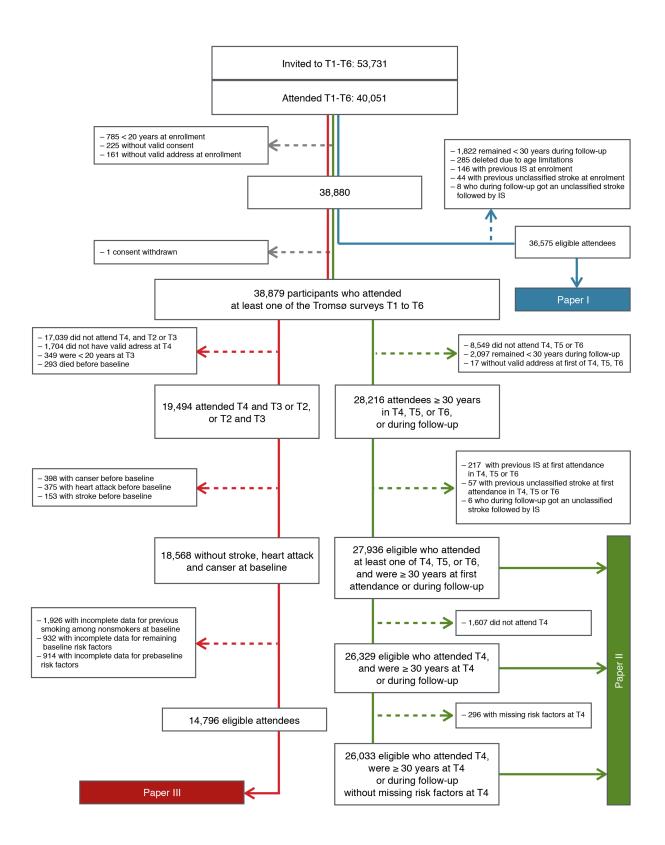
Table 2. Year of screening, age, number and attendance rate of eligible participants. The Tromsø Study.

Year of screening	Age group	Participants	Attendance	Participants	Attendance
		men, n	rate, %	women, n	rate, %
1974	20–49	6 595	74.4	_	-
1979–80	20-54*	8 477	73.8	8 144	81.8
1986–87	20-61†	10 413	71.7	10 189	79.1
1994–95	25–97	12 865	69.6	14 293	74.9
2001	30–89	3 511	75.7	4 619	80.8
2007–08	30–87	6 054	62.9	6 930	68.4

<sup>\*20–49</sup> years in women

<sup>†20–56</sup> years in women

Figure 4. Flowchart of the study population



### 3.1.1 Paper I study population

In Paper I we investigated the age- and sex-specific time trends in incidence and case fatality of IS. Of the 38,880 men and women who attended at least one of the studies Tromsø 1–6 and were aged ≥20 years, registered as inhabitants in Tromsø at the date of enrollment and had valid informed consent to medical research; we excluded 1,822 participants who remained <30 years during the entire follow-up period. (Participants who were enrolled at an age younger then 30, but became 30 years during follow-up, were followed from age 30 and onwards). Moreover, we excluded 146 with previous IS and 44 with previous unclassified stroke at time of inclusion; and 8 who after enrollment got an unclassified stroke followed by an IS. The analyses were stratified by gender and age (30–49, 50–64, 65–74 75–84 and 85 years and older). Because the oldest birth cohorts were included in the study at a later point of time than the younger ones, the time periods for the trend analyses and incidence rates were different for each age group (see Table 1 and detailed description in Paper I). Thus for men, age-specific trends for the age groups 30–49, 50–64, 65–74, 75–84 and ≥85 years could be estimated for the time periods 1974–2010, 1989–2010, 1995–2010, 1995–2010 and 1995–2010, respectively. As lack of access to computed tomography (CT) before 1977 made it more difficult to rule out hemorrhage, onset of follow-up for men aged 30-49 years was set to January 1st, 1977. For women, analyses for the corresponding age groups were done for the time periods 1980–2010, 1994–2010, 1995–2010, 1995–2010 and 1995–2010. Due to age limitations, we had to exclude another 285 subjects from the trend analyses. Hence the total number of persons included in the analyses on incident ischemic stroke was 36,575; 18,367 women and 18,208 men.

### 3.1.2 Paper II Study population

In Paper II we estimated the impact of changing risk factor levels across time on the concurrent change in ischemic stroke incidence. In the time between writing Paper I and Paper II, one participant withdraw the consent to research, leaving 38,879 participants aged ≥20 years who

had attended at least one of the studies Tromsø 1–6 with valid consent and valid address in Tromsø at enrolment. Of these, we excluded 10,663 who did not attend any of the surveys Tromsø 4, Tromsø 5 or Tromsø 6 or who remained <30 years during the entire follow—up period, leaving 28,216 persons who attended at least one of the surveys Tromsø 4–6 and were aged ≥30 years at survey date or during follow—up. (Participants who were enrolled at an age younger then 30, but became 30 years during follow—up, were followed from age 30 and onwards). Further, we excluded 217 with previous IS at baseline (the first survey the person participated in out of Tromsø 4-6); 57 with previous unclassified stroke at time of inclusion; and 6 who after enrollment got an unclassified stroke followed by an IS, leaving 27,936 persons (14,697 women and 13,239 men) eligible for the background analyses in Paper II (see Figure 4 and detailed description in Paper II). Included in the main analysis in Paper II, however, were those out of the 27,936 who had attended Tromsø without missing risk factors; who were 30 years or older at Tromsø 4 or became 30 years during follow—up Hence, we excluded 1,607 who did not attend Tromsø 4, and 296 with missing risk factors for at least one of the variables at Tromsø 4, leaving 26,033 persons who were included in the main analysis in Paper II.

#### 3.1.3 Paper III Study population

In paper III we assessed the effect of risk factor intervention on the subsequent population risk of stroke and IS. We chose Tromsø 4 (1994–95) as baseline in order to have complete prebaseline data on the selected covariates. From the 38,879 participants aged ≥20 years who had attended at least one of the studies Tromsø 1–6 with valid consent and valid address in Tromsø at enrolment, we excluded 17,039 who did not attend baseline and at least one of the prior surveys Tromsø 2 or Tromsø 3; 1,997 without valid address at baseline and 349 who were <20 years in Tromsø 3. Participants who were 25 years or older at Tromsø 4 and had attended at least one prior cycle were eligible for our study (n=19,494). We excluded 4,698 participants who at baseline had experienced cancer, heart attack or stroke or had incomplete pre-baseline or baseline covariate data after carrying data one cycle forward (see Figure 4 and detailed

description in Paper III). After exclusions, our cohort included 14,796 persons (7,547 women and 7,249 men.)

#### **3.1.4 Ethics**

The Tromsø Study was approved by the Norwegian Data Inspectorate and recommended by the Regional Committee of Research Ethics. In Tromsø 4, 5, and 6, each participant signed a written informed consent.

#### 3.2 Physical measurements, blood samples and questionnaires

Each Tromsø survey applied a standardized protocol with physical measurements, blood samples and self-administered questionnaires. Blood pressure (BP) was measured by trained personnel with an automatic device ("Dinamap") from 1986 and onwards (Tromsø 3), and by stethoscope and mercury sphygmomanometer ("ERKAmeter") in the two earliest surveys. Validation studies have shown systematic slightly lower blood pressure values when measured with Dinamap as compared to ERKA-meter (Details in supplement, Paper III). Hence, in paper III, because some participants contributed with pre-baseline data from Tromsø 2; Dinamap measurements were transformed to ERKA-meter values in accordance with previously validated methods (105). Hypertension was defined as systolic BP (SBP)  $\geq$ 140 mmHg and/or diastolic BP (DBP)  $\geq$ 90 mmHg and/or use of BP-lowering medication. Body Mass Index (BMI) was calculated as weight divided by the square of height (kg/m²). Overweight was defined as BMI  $\geq$ 25 to <30 kg/m² and obesity as BMI  $\geq$ 30 kg/m².

Non-fasting blood samples were analyzed for serum total cholesterol and high-density lipoprotein cholesterol by standard methods at the University Hospital of Northern Norway. Hyperlipidemia was defined as total cholesterol/HDL ratio >5.

In all Tromsø Surveys, a questionnaire was enclosed in the invitation. In Tromsø 2–6, the participants were given a second questionnaire and asked to return it by mail in a pre-

addressed stamped envelope; approximately 90% did so. The questionnaires include questions regarding a wide range of diseases and symptoms, socio-economic status, lifestyle aspects and use of medication. In our study, we used this self-reported information regarding prevalent cancer and CVD, cardiovascular symptoms, family history of coronary heart disease, race, education and employment. Moreover, diabetes was self-reported by questionnaire, as were smoking, alcohol consumption and leisure-time physical activity (PA). In paper II attendees were defined as physically active if they reported performance of strenuous physical activity (i.e. became breathless and sweaty) at least one hour/week. In paper III, where we wanted to assess one feasible and one intensive PA intervention, participants were categorized according to PA as: 'sedentary'; 'intermediate physically active' (some light PA and /or vigorous PA less than 3–4 hours per week) and 'highly physically active' (vigorous PA several times or ≥3–4 hours per week) (Details in supplement, Paper III).

### 3.3 Ascertainment of endpoints

First-ever ischemic stroke was the primary endpoint in Paper I and II. In Paper III, first-ever stroke was the primary endpoint, but separate analyses were performed for first-ever ischemic stroke. Stroke was defined according to the WHO definition ("rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting ≥24 hours or leading to death, with no apparent cause other than vascular origin") (2). Hence, silent infarcts discovered only by radiological imaging were not included. A stroke was classified as an ischemic stroke when computed tomography (CT), magnetic resonance imaging (MRI) and/or autopsy had ruled out intracerebral and subarachnoid hemorrhage. If imaging or autopsy had not been conducted in the acute stage, the stroke was categorized as unclassified. The unique national identification number was used to link each participant to the discharge diagnosis registry at University Hospital of North Norway (the only hospital serving Tromsø) and to the National Causes of Death Registry and the Population Registry of Norway. An independent endpoint committee adjudicated all possible hospitalized and out of hospital events using medical

records, autopsy reports and death certificates. Information from additional sources (records from nursing homes, general practitioners, and ambulance services) was used for validation. Participants were followed until the first-ever IS event (Paper I, II, III) or first-ever stroke (Paper III), emigration from Tromsø, death, or administrative end of follow-up, whichever happened first. End of follow-up was 31.12.2010 in Paper I, and 31.12.2012 in Paper II and III. The endpoint registry was updated through 2012 after the publication of Paper I. Hence, we repeated the main analyses in paper I with end of follow-up 31.12.2012, these additional analyses are referred separately.

#### 3.4 Statistical analyses

The analyses in paper I were performed using STATA, version 12 and 13 (Stata Corp LP Texas, USA), while STATA 13 and SAS 9.4 (SAS Institute, Cary, NC) were used for the analyses in paper II and III. Additionally, in paper III we applied the parametric g-formula (<a href="http://www.hsph">http://www.hsph</a>.harvard.edu/causal/software) to estimate the 18-years cumulative risk of stroke under different hypothetical interventions.

#### 3.4.1 Paper I

Sex-specific crude incidence rates (per 1,000 person-years) were calculated for the age groups 30–49, 50–64, 65–74, 75–84 and 85 years and older by dividing the number of all events in the period of time by the corresponding person-years at risk. Time trends in incidence rates were estimated by taking into account the possibility of non-linearity. In each sex and age strata, calendar year was fitted by second-degree fractional polynomials and regressed on the incidence of stroke in Poisson regression models. The stratified analyses were age-adjusted by including age as a continuous variable in the models. Of the forty-four models fitted and compared for each stratum, the best fractional polynomial model of degree 2 was compared with the best model of degree 1, and the model with the best likelihood ratio test statistic for the fractional polynomial term was selected. The p-value of the selected model represents the

p-value for the time trend.

Incidence rate ratio (IRR) was defined as the incidence rate in the last year of follow-up divided by the incidence rate in the first year. For all age groups, except women aged 30–49 years, IRR was calculated from start of follow-up (see 3.1.1) through Dec.31 2010. In women aged 30–49 years, IRR was calculated from 1989, when the first stroke occurred in this stratum. Additional analyses were done with a combined endpoint of ischemic and unclassified stroke.

Crude case fatality rates were calculated for the time periods 1995-2000, 2001-2005 and 2006-2010. Logistic regression was used to estimate age-adjusted odds ratios (OR) for case fatality in the period 2001-2005 and 2006-2010, using 1995-2000 as the reference. Possible non-linear time trends of case fatality from 1995 to 2010 were assessed in separate sex-specific logistic regression models by including fractional polynomials of calendar year, with age included as a covariate. Age-adjusted ORs for case fatality were estimated for the years 2003 and 2010, using 1995 as the reference. Trends across age and sex were compared by including two-way interaction terms between time and age and time and sex. A probability value of <0.2 was considered statistically significant for tests of interaction, while a two-sided level of significance of P < 0.05 was used for all other analyses.

#### **3.4.2 Paper II**

Descriptive baseline characteristics were presented as means (95% CI) or frequencies (%) for the study participants with or without incident IS during follow-up; *P*-values for baseline differences were estimated by linear and logistic regression for continuous and categorical variables, respectively. Age- and sex-adjusted means or prevalences of risk factors *over time* were estimated by generalized estimating equations (GEE), accounting for dependencies between repeated observations.

Hazard ratios (HR) of IS were estimated for the different cardiovascular risk factors with Cox proportional hazards regression. For attendees who participated in more than one survey and

who were still free of IS, cardiovascular risk factors were updated at the date of subsequent examinations (106). HRs were adjusted for age and sex in model 1 and additionally adjusted for systolic BP, cholesterol, HDL, daily smoking, BMI, diabetes and physical activity in model 2. The proportional hazard assumption was verified by visual inspection of Schoenfeld residuals and log minus log survival plots.

Incidence analyses were based on the participants of Tromsø 4 in 1994–95 (n=26,329). Time trends in incidence were standardized by age and sex using the Tromsø population in 2007 as the standard population. Linear time trends were estimated by Poisson regression.

The proportion of the IS incidence decline explained by the change in each risk factor over time (SBP, daily smoking, diabetes, BMI, total cholesterol, HDL cholesterol, physical activity) could be estimated among those who attended Tromsø 4 in 1994–95 without missing values of risk factors (n=26,033), by the expression ( $\beta$ 0 –  $\beta$ 1)/ $\beta$ 0. The  $\beta$ s are time trend coefficients from Poisson regression models, where  $\beta$ 0 is adjusted for age and sex and the  $\beta$ 1 additionally adjusted for risk factors added to the model as time-dependent covariates. End of follow-up was defined to 2001 for those who did not attend the 2001 survey and to 2007 for those who did not attend the 2007–08 survey. Individuals who had an IS event were censored from the analyses at the time of their event. One thousand bootstrapped samples were selected to estimate 95% confidence interval for the explained decline. We performed supplemental Poisson regression analyses stratified by sex and by age group (baseline age <60 years and  $\geq$ 60 years, this cut-off was chosen to get sufficient power in both groups). A two-sided level of P <0.05 was considered statistically significant.

## 3.4.3 Paper III

We applied the parametric g-formula to estimate the 18-years cumulative risk of stroke under different hypothetical interventions (107). The parametric g-formula represents a generalization of standardization for time-varying exposures and confounders, and the analytical steps of this method are described in paper III.

This method can be described as constructing a hypothetical RCT based on data from a prospective cohort study, where the control group and the treatment group consists of the same individuals. Our cohort under the "natural scenario" represents the "control group" (with the risk factor distribution and concurrent stroke incidence we observed in "real life", i.e. no intervention), and each hypothetical intervention (separate or combined) applied on this cohort defines a new "treatment group".

The models included the following potential baseline confounders: age (continuous and quadratic), sex, marital status, education, work-time physical activity, night- or shiftwork, former smoking and family history of coronary heart disease in parents or siblings, as well as pre-baseline HDL cholesterol and diabetes mellitus, and the pre-baseline values of six selected intervention variables: smoking, physical activity, alcohol use, BMI, systolic BP and total cholesterol.

We evaluated six feasible and six intensive hypothetical interventions, and their combination. The feasible interventions were: 13% of smokers quit smoking (108); all participants were somewhat physically active (some light PA and /or vigorous PA <3–4 hours per week); 20% of alcohol drinkers quit drinking (109); all overweight or obese participants lost weight by 10% every 6 years; all participants maintained systolic blood pressure (SBP) <140 mmHg (51); and all maintained total cholesterol <6.22 mmol/L (110). The intensive interventions were: all smokers quit smoking; all participants performed vigorous PA  $\geq$ 3–4 hours per week; all drinkers quitted alcohol; all participants had normal body mass index (i.e.<25 kg/m²); all maintained SBP <120

mmHg (111) and total serum cholesterol <5.18 mmol/L (110).

We compared the estimated stroke risks under different hypothetical interventions with the 18-years stroke risk under no intervention to calculate the population risk ratios and the population risk differences. Subgroup analyses were done for men and women, for participants aged <55 vs. ≥55 years at baseline, and for participants with highest attained baseline education level ≤10 and >10 years. We conducted sensitivity analyses in which we varied the ordering of the time-varying covariates in our model, and excluded attendees with diabetes at baseline. Separate analyses were done with ischemic stroke as endpoint. We used nonparametric bootstrapping with 500 samples to estimate the 95% confidence intervals. The proportion of participants who were hypothetically intervened on in any period were also computed, as well as the average proportion of attendees intervened on, in each 6-years period.

# 4. Main results

4.1 Time trends in incidence and case fatality of first-ever ischemic stroke.

The Tromsø Study 1977–2010 (paper I)

Among 36,575 attendees aged ≥30 years there were 1,214 first-ever ischemic strokes within a total follow-up time of 611,176 person-years. The overall age- and sex-adjusted incidence declined by 24% from 1995 through 2010 (IRR 0.76, 95% CI 0.62–0.92; p for trend <0.001). In women aged 30 to 49 years, the incidence increased significantly from 1980 to 2010 (IRR: 2.69, 95% CI 1.04–6.99; p for trend 0.003). In men aged 30–49 years, there was a non-significant, rising trend from 1977 to 2010. Men aged 50–64 years had similar incidence in 2010 compared to 1989. From the mid-1990s to 2010, the incidence declined significantly in women aged 50–74 years and in men aged 65–74 years, but remained stable in those aged ≥75 years. Despite this indication of interaction of age by different shapes of the curves, we did not reveal any statistical significant interaction by age (P=0.87). This may be due to that our test for interaction lack power. There was no significant interaction by sex. Mean age at IS onset was approximately 4 years higher in women aged 30–84 years compared to men. In the combined endpoint analyses where 77 unclassifiable strokes were included, time trends remained fundamentally unchanged, but the IRRs were no longer significant in women aged 30–49 and men aged 50–64 years.

Between 1995 and 2010, the mean crude case fatality for IS in persons aged 30–84 years was 7%, and 20% in participants ≥85 years. The age-adjusted case fatality decreased significantly in men aged 30 to 84 years from 1995 to 2010, whereas there was no significant change in women (p for interaction =0.007). Age-adjusted case fatality of IS was higher for women than men through the whole period.

# 4.2 Declining incidence of ischemic stroke: What is the impact of changing risk factors? The Tromsø Study 1995–2012 (paper II)

There were 1,226 first-ever IS (45% in women) during 367,636 person-years of follow-up among 27,936 attendees ≥30 years followed through 2012. Mean observation time was 12.8 years (SD 6.0). Several cardiovascular risk factors changed favorably across the three surveys Tromsø 4–6. Systolic and diastolic BP, total cholesterol, proportions of hypertension, hyperlipidemia, and daily smoking declined, and the proportion of participants who reported ≥1 hour strenuous physical activity per week enlarged. However, the prevalence of obesity and diabetes mellitus increased substantially from Tromsø 4 (1994–95) to Tromsø 6 (2007–08). While the diabetes prevalence increased with 100% among attendees aged ≥30 in this period, the prevalence of overweight and obesity combined increased from 51% to 61%.

In Cox proportional hazard regression, hypertension was the strongest risk factor for IS, with 92% increased hazard (multi-adjusted) in hypertensive participants. Diabetes was associated with 80%, and daily smoking with71% higher IS risk. Obese attendees had 28% higher hazard for IS compared to those normal weighted. The risk of IS was 28% increased in attendees with hyperlipidemia, while HDL was protective for IS, with 22% reduced HR per 1 mmol/l increase in mean HDL. Associations that were significant in the age- and sex-adjusted model remained significant in the multivariate model, except for overweight and physical activity.

Overall, the combined change in seven cardiovascular risk factors (systolic blood pressure, daily smoking, diabetes, BMI, total cholesterol, HDL, physical activity) accounted for 57% (95% CI 28–100%) of the decrease in IS incidence from 1995 through 2012 in those who attended Tromsø 4 without missing risk factors (n=26,033). The most important contributors were decreasing mean systolic blood pressure and smoking prevalence, accounting for 26% (95% CI 15–56) and 17% (95% CI 8–41) of the observed decline, respectively. Changing levels of HDL contributed with 2% (95% CI 0.3–7), while reduction of total cholesterol and increase in physical activity were associated with 12% and 5% of the declining IS incidence (not significant). In contrast, the

increasing diabetes prevalence contributed negatively with 4% increase in risk, (95% CI −10 to −1), as did the change in BMI over time, which was associated with 5% increasing risk, though not significant. The sex-stratified analyses revealed that the reduction in SBP and decreasing prevalence of daily smoking contributed most to the declining IS incidence in both women and men. Age-stratified analyses (baseline age <60 years and ≥60 years) showed no differences in risk factor contribution to the IS incidence reduction (p=0.58), and hence no significant interaction by age in the fully adjusted model.

# 4.3 Hypothetical interventions to prevent stroke: An application of the parametric g-formula to a healthy middle-aged population (paper III)

Among the 14,796 eligible participants (mean age at baseline 46.1 years, 51% women) there were 871 deaths and 524 cases of stroke during 18-years follow-up (399 IS, 61 ICH, 33 SAH and 31 unspecified strokes). Of the 6,917 participants who were not eligible through all 18 years of follow-up, 68% (n=4,718) were not invited to a later survey due to logistics; 21% (n=1,425) moved out of Tromsø, and 11% (n=774) had missing data on two subsequent surveys. The simulated 18-years risk of stroke under no intervention was 5.50% (95% CI 5.03– 5.99) and similar to the observed risk at 5.89%.

Even *feasible reductions* substantially reduced the stroke risk. Specifically, reducing SBP to <140 mmHg was estimated to lower the 18-years population risk of stroke by 15% (95% CI 10–20), compared to "no intervention". Smoking cessation in 13% of smokers would reduce the risk by 2% (95% CI 0–4), and quitting drinking in 20% of drinkers would reduce risk by 8% (95% CI –1 to 14); whereas increasing physical activity, reducing body-mass index or lowering total cholesterol to <6.22 mmol/l did not substantially alter the population stroke risk. The 18-years risk of stroke would be reduced by 19% (95% CI 8–30) when all six feasible interventions were applied. Maintaining adherence to the strategy of feasible reduction of SBP in this particular population would require changing the SBP of an average of 31% of participants in each period,

while adherence to a strategy with joint feasible interventions would require risk factor changes of an average of 80% of the attendees in each period.

Under *more intensive interventions*, lowering SBP to <120 mmHg would reduce this populations 18-year stroke risk by 32% (95% CI 22–40), quitting drinking by 25% (95% CI –2 to 45) and quitting smoking by 9% (95% CI 1–17). The other intensive interventions did not change the stroke risk substantially when applied separately. Combining all the intensive interventions would reduce the estimated 18-years risk of stroke by 55% (95% CI 32–72).

In sub-group analyses, the estimated impact of an intensive combined intervention on all six risk factors did not differ significantly by the selected subgroups in multiplicative or additive scale. The estimates of relative risks and risk differences did not change materially in any of the sensitivity analyses conducted.

For IS, the observed 18-years risk was 4.55% and the simulated risk under no intervention was 4.23% (95% CI 3.80–4.67). Separate intensive interventions on SBP and alcohol drinking reduced the risk of ischemic stroke. If all drinkers had quit alcohol, the 18-years IS risk would be reduced by 32% (95% CI 3–54), nearly as much as lowering SBP to <120 mmHg (35% (95% CI 25–44)). The 18-year risk of ischemic stroke would be reduced by 64% (95% CI 39–79) under the intensive joint intervention on all risk factors, while a more feasible combined intervention would give an estimated 24% (95% CI 9–35) IS incidence decline. Separate feasible interventions on SBP reduced the risk of IS with 18% (95% CI 12–23). The risk reduction by quitting alcohol in 20% of drinkers was 10% (95% CI 1–17), while smoking cessation in 13% of smokers would reduce the IS risk by 2% (95% CI 0–4).

# 5. Discussion

# **5.1 Methodological considerations**

The renown epidemiologist Kenneth Rothman has written that "The objective of an epidemiological study is to obtain a valid and precise estimate of the frequency of a disease or of the effect of an exposure on the occurrence of a disease in the source population of the study" (112). Essential to epidemiological studies is accuracy in measurements. Accuracy is defined as the degree to which a measurement, or estimate based on measurements represent the true value of the attribute being measured (113). Threats against accuracy in estimations are random errors (lack of precision) and systematic errors (bias). If not recognized, errors will generate false knowledge. Precision, as a measure of random error, refers to the magnitude of differences between repeated measurements (reliability, reproducibility). Precision is expressed through the confidence interval and depends of the study size and the study efficiency. Systematic errors in estimates (systematic deviations from the truth) are commonly referred to as bias. Bias can occur at every step of the research process, with weakening of a true association or production of a false association as consequence. The opposite of bias is validity, so that an estimate with little systematic error may be described as valid (112). Moreover, validity refers to how the study results apply to the target population. Validity can be separated into two components: Internal and external validity, where the former is a prerequisite for the latter.

#### **5.1.1** Internal validity

Internal validity (or lack of systematic error) refers to the inference drawn from the sample to the source population, i.e. whether the results of a study are representative, true or valid for the population under study (112). Three types of errors may threaten the internal validity of an epidemiological study: selection bias, information bias (= measurement bias) and confounding. Any observed association might also occur by chance alone.

#### **Selection bias**

Selection bias is defined as "a systematic error that results from procedures used to select study subjects, and from factors that influence study participation" (112). Hence, this type of bias can also occur if many attendees are lost to follow-up. The common consequence of selection bias is that the association between exposure and outcome is different for those who participate and for all those who should have been theoretically eligible for study, including those who did not participate (112). In a population survey, selection bias can be a problem especially if the participation rate is low.

The design of the Tromsø Study, with invitation of total birth cohorts and random samples ensures a representative study population. Despite a lower attendance rate in the sixth survey, the participation rates to the Tromsø Study surveys have generally been high (Table 1). In the Tromsø Study, a higher proportion of non-attendees belonged to the youngest age group or was ≥80 years; a higher proportion was single and the proportion of men was higher compared with attendees. Legal restrictions have precluded analyses of mortality and morbidity among non-attendees. However, healthy persons may generally be more prone to attend population studies than the less healthy ones (known as healthy participant bias or non-response bias)(114). We cannot exclude that a healthy participant bias may have affected our estimates in paper I, II and III, diluting the true associations between risk factors and outcome, even if a high participation rate minimize its impact on the risk estimates.

The loss to follow-up in the Tromsø Study is negligible due to usage of the unique personal identity number to search official health registries. Selective survival, especially among the eldest ones, may also be a source of selection bias, with higher representation during follow-up of attendees with a more favorable risk factor profile compared to deceased persons from the same birth cohort. Lower mortality was previously demonstrated among subjects who were consistent attendees in the three surveys Tromsø 2, 3 and 4, compared to those who were invited to all three surveys, but only attended Tromsø 4 (104). In the main analysis in paper II,

the associations between trends in IS incidence and trends in risk factors were based on participants with updated risk factors. In paper III, the eligible participants were those with complete baseline and pre-baseline data. The criteria of subsequent attendance in paper III and the use of data only from the years with updated risk factors (in the main analysis paper II, and in paper III) could also introduce healthy participant bias as well as survival bias (due to higher contribution from consistent attendees).

#### Information bias and misclassification

An important source of error in cohort studies is information bias (measurement bias); defined as "an error that arises from systematic differences in the way that information on exposure or disease is obtained from the study groups" (115). Information bias may distort an effect estimate when exposure status or disease status is incorrectly measured or classified (113).

Thorough validation of measurement methods and questionnaires are crucial to minimize measurement error in the exposure variables. For discrete variables, measurement error is usually named misclassification (112). Classification error (of exposure or outcome variables) that depends on the actual value of other variables is called differential misclassification, while non-differential misclassification is classification error not dependent on the values of other variables. Non-differential misclassification will most often weaken a true association, (although with more than two levels in the exposure or the disease variable, the direction of the bias may be more difficult to interpret) (112). Differential misclassification is more serious, and can alter the estimates in any direction.

In a prospective cohort study, the level of exposure is registered prior to the registration of outcome status, and the classification errors of exposure tend to be non-differential.

The physical measurements (blood pressure, height, weight) were performed by standard protocol in the Tromsø surveys to minimize measurement error (see 3.2). Non-fasting blood lipids were registered. The effect of non-fasting condition on total and HDL cholesterol is

negligible, while triglyceride levels vary substantially throughout the day (116). The questionnaire instrument is subjective and imprecise and some misclassification may exist. This will probably be most pronounced in the self-reported lifestyle variables. HbA1C was introduced as an additional diagnostic test for diabetes during the study period, and the proportion with unrecognized diabetes may have been higher in the earliest phase of our study (117). Nevertheless, self report on well defined medical conditions often have a high positive predictive value (118). The validity of the physical activity questions is discussed in paper II and III (supplements). A meta-analysis revealed that the validity of self-reported smoking were generally high (119). However, for smoking (120) and alcohol consumption (121), an underreport must be expected, while over-reporting is more liable with regard to physical activity (122). As a result of some non-differential misclassification of these exposure variables, the effect estimates in paper II and III could be diluted or underestimated.

Several steps were taken to ensure an accurate classification of the outcome variables IS and stroke (Details in 3.3). However, despite a thorough case ascertainment, we cannot exclude that some IS (or in paper III: strokes) remained unidentified, due to sparse symptomatology leading to non-detection, non-referral (or both).

The amount of misclassification of IS over time, due to non-detection, is difficult to assume. The definition of IS in our study is based on the clinical stroke definition by WHO (2) and exclusion of hemorrhage. The considerable improvements in radiological imaging the last decades include gradual implementation of CT and MRI modalities with increasing sensitivity for small ischemic lesions (123). Despite that the IS endpoint classification in our study is based on a clinical stroke definition (i.e. silent cerebral infarcts are not included in the IS endpoint), the enhanced options to verify a small ischemic lesion by imaging could still lead to information bias by changing the proportions of misclassified IS with time. Under the assumption that radiological confirmation of ischemia (in the clinical setting) may lead to a higher awareness of clinical signs/ more thorough clinical examination), fewer of the IS cases with only minimal

clinical signs would (wrongly) be classified as "not IS" in the latest period, compared to the earliest years of our study. This represents a source for potential differential misclassification of those IS with only sparse clinical signs. Furthermore, improved treatment options for stroke may have lowered the threshold for referral of stroke patients to hospital, leading to increased detection rate in the latter part of the follow-up period.

#### Confounding

When an association between an exposure and an outcome is distorted due to the effect of a covariate related to both the exposure and the outcome, this is called confounding (114). Most simply, confounding can be defined as a "mixing" of effects. Hence, a confounder is a factor which is associated both with the exposure (causally or non-causally) and the outcome variable (causally), and which accounts for some of the relationship observed between the exposure and the outcome. To be a confounder, this factor must not be an intermediate factor between these two.

Confounding can also be considered in terms of the counterfactual ideal (114). Counterfactual means "contrary to the fact", a logic expressing of what has not happened but could, would or might have happened under differing conditions (124). In a cohort study, the ideal comparison group should consist of exactly the same persons as in the exposure group, *had they not been exposed* to the risk factor of interest. Because it is not possible in real life for the same individual to be exposed and unexposed simultaneously, the obvious comparison group (reference group) in a cohort study will consist of *other persons*, namely those not exposed to the risk factor of interest. Confounding can be viewed as a failure of the comparison group to reflect the counterfactual experience of the exposed group (115).

Confounding may under- or overestimate the association under study, it may change the direction of an effect, or it may obscure a true causal relationship (114). If sufficient information about possible confounders is available, confounding can (partly) be accounted for

in the statistical analyses. Strategies that can be used to minimize bias due to confounding are stratification and multivariate adjusted models with inclusion of potential confounders.

In paper I, we performed age-and sex stratified analyses of time trends in incidence and case fatality of IS. Moreover, the stratified analyses were age-adjusted by including age as a continuous variable in the regression models.

In paper II (main analysis), the association between changes over time in levels or prevalence of each risk factor (updated values) vs. time trends in incidence of the outcome (IS) ("explained decline of IS incidence") was assessed in an age-and sex adjusted Poisson regression model for each risk factor separately. Moreover, a multi-adjusted Poisson model estimated the joint effect of the observed risk factor change on the concurrent 18-years risk of IS. Separate sex stratified analyses were done, as well as analyses stratified on baseline age <60 and >60 years. Due to relatively few number of IS in the youngest age group (30–49 years), and additionally the prerequisite of using updated risk factor values in the main analysis, we did not have sufficient power to run separate analyses for explained decline for the youngest age group.

In the background analysis in paper II, the associations between the different risk factors (updated values) and the outcome (IS) were assessed in a multivariate adjusted Cox regression model, but also shown in an age-and sex adjusted model.

In paper III, in a framework of counterfactual consideration of confounding, we applied (by parametric g-formula) hypothetical interventions on the sample of eligible attendees, using the identical sample under no intervention (i.e. the "natural scenario") as the comparison group. Thus, the analyses in paper III are performed in a (hypothetical) setting where the exposure group and the comparison (reference) group consist of the same individuals (see 3.4.3). In addition to reduce the possibilities for confounding by ensuring an identical exposure and comparison group, the parametric g-formula is found to appropriately adjust for time dependent confounding. For example, if the effect of long-term weight loss is of interest, prior

physical activity should be adjusted as a time-varying confounder, but future physical activity can be affected by weight loss. Hence, a particular methodological challenge is to estimate the unbiased effect of a time-varying exposure in the presence of time-varying confounders if those confounders are affected by prior exposure (103). In such cases, conventional regression models fail to adjust for confounding and may indeed introduce bias. G-methods, including the parametric g-formula, have been developed to handle such situations (107).

## 5.1.2 External validity

The external validity of a study refers to whether the study findings are valid for people outside the study population, i.e. the generalizability of the results. The age and sex distribution of the Tromsø Study mirror the Tromsø population in general. The Tromsø population is not substantially different from other Western populations with regard to risk factor levels and incidence of cardiovascular diseases. Our results are therefore likely applicable to other Western populations, however, generalizability may be restricted to ethnicity, as the Tromsø population consists of mainly Caucasians (104, 125).

## 5.2 Discussion of main results

### 5.2.1 Time trends in incidence and case fatality of first-ever ischemic stroke

The overall age-and sex adjusted incidence of IS declined with 24% from 1995–2010; this decline was driven by the changing incidences across time among the middle-aged and elderly, in whom the vast majority of ischemic strokes occur. The age-stratified analyses, however, revealed different time trends across the predefined age groups.

The increasing incidence of IS among women aged 30–49 years in our cohort is worrying. Although these findings must be interpreted with caution due to the low number of endpoints in this age group, they are in line with other studies reporting an increase in incidence for the youngest age groups (17,20,21). In a prospective, population-based study from Dijon the incidence of first-time IS among men and women <55 years increased significantly from 1994–2002 to 2003–2011 (21). A significant increasing IS incidence in persons aged 20–44 years was also reported in the retrospective, population-based Greater Cincinnati/Northern Kentucky Stroke Study between 1993 and 2005 (20), while a continuous rising incidence of IS in people aged 18–44 years was found in a nationwide Swedish study from 1987 to 2010 (17).

Similarly, increasing incidence was revealed in a register based study among Dutch men and women aged 35–64 years from 1997 to 2005 (22). A rise in hospitalization rate for acute IS in people <45 years of age from 1995 to 2008 was also discovered in a study based on administrative data from USA (126). Even if some of these referred trends were rather weak and even if stable IS time trends in younger age groups are reported in other studies (19), a recent editorial in Journal of the American Heart Association proclaimed the large amount of evidence regarding increasing incidence of IS in young adults, but stated that the reasons for this trend are probably multiple (127) (see 5.2.2).

The declining IS incidence from the mid-1990s among women aged 50 to 74 and men aged 65–74 years are in line with findings from other high-income populations (16–18). The decrease is explained by the combined effect of reduction in risk factor levels and improved primary prevention (16, 34, 93).

The rising trend among men aged 50–64 years from 1989 to early 2000, followed by a decline until 2010, is difficult to interpret. Rosengren et al. found an increase in the IS incidence in people aged 45 to 64 years, from the late 1980s, to the late 1990s, followed by a decline to 2010 (17). In the ARIC cohort, no decline in stroke incidence was found from 1987 to 2011 in the age group 45–64 years in contrast to decreasing incidence in those >65 years (18).

We found no significant change in incidence over time among participants aged 75–84 and ≥85 years, which was also reported in the Global Burden of Disease Study (1990–2010) (15), and in the Netherlands from 1997 to 2005 (22). In contrast, studies from Sweden showed a significant declining trend of IS in subjects aged 75–84 from the mid-1990s to 2010, and a reduced stroke incidence in women ≥85 years old (17, 23).

Paper I was written when the endpoint registry was updated through 2010. When updated through 2012, 164 IS were added, and the main analyses in paper I were repeated with end of follow-up set to 31.12.2012 (Table 3). The overall age- and sex-adjusted incidence decline from 1995 through 2012 was 27% (95% CI 13%–39%) and similar in men and women. The increasing trend in IS incidence among the youngest women (30–49 years) persisted through 2012 and the corresponding P-value for this rising time trend was strengthened (IRR 2012 vs. 1980: 3.29, 95% CI 1.19–9.09; p for trend 0.0007), as compared to the original analyses with end of follow-up 31.12.2010 (IRR 2.69, 95% CI 1.04–6.99; p for trend 0.0033). In men aged 30–49 years, a non-significant, rising trend was found from 1977 to 2012; in men aged 50–64 years, the IS incidence in 2012 was not significantly different from that in 1989. The incidence decline was significant through 2012 also in women aged 50–64 and men aged 65–74 years. Women 65–74

years showed a significant declining time trend (non-linear). Among attendees aged 75–84 and ≥85 years, the incidence remained stable also after the end-point registry was updated through 2012.

Table 3. Age-adjusted incidence rate ratio (IRR) of ischemic stroke by age group and sex. The Tromsø Study

Age group (y)	Period	No. of ischemic strokes	IRR* (95% CI)	p value time trend <sup>†</sup>
Men				
30–49	1977 – 2012	63	4.18 (0.43-40.31)	0.152
50–64	1989 – 2012	225	1.55 (0.90–2.68)	< 0.0001
65–74	1995 – 2012	219	0.56 (0.37–0.85)	0.0082
75–84	1995 – 2012	211	0.86 (0.54-1.38)	0.173
≥ 85	1995 – 2012	72	0.92 (0.44–1.95)	0.832
≥ 30 <sup>‡</sup>	1995 – 2012	744	0.73 (0.58–0.93)	0.0089
Women				
30–49	1980 – 2012	31	3.29 (1.19 –9.09)	0.0007
50–64	1994 – 2012	86	0.42 (0.21–0.85)	0.019
65–74	1995 – 2012	116	0.55 (0.31–1.01)	0.049
75–84	1995 – 2012	228	0.83 (0.54–1.28)	0.397
≥ 85	1995 – 2012	127	1.34 (0.64–2.81)	0.432
≥ 30 <sup>‡</sup>	1995 – 2012	575	0.72 (0.55–0.95)	0.018
AII ≥ 30 <sup>‡</sup>	1995 – 2012	1319	0.73 (0.61–0.87)	0.0004

CI: Confidence Interval; IRR: Incidence Rate ratio

<sup>\*</sup> Incidence rate ratio (IRR) is calculated from start of follow up (year) until 2012 except for women aged 30–49 years, where IRR is calculated from 1989 to 2012.

<sup>†</sup> P-values are for time trends using fractional polynomials.

<sup>‡</sup> Estimated from 1995 to ensure that the whole age span was represented.

Table 4. Odds ratios for 30-days case fatality (CF) of ischemic stroke according to calendar year by sex and age group\*. The Tromsø Study 1995–2012

	1995-2000	2001-2006	2007-2012	1995-2012	p-value time trend†
Men					
30-84 years					
Ischemic strokes, n	201	248	223	672	
30-days CF, n (%)	18 (8.9)	10 (4.0)	10 (4.5)	38 (5.7)	
Odds Ratio (95%CI)‡	1.00	0.40 (0.18-0.89)	0.44 (0.20-0.99)		
Odds Ratio (95%CI)§	1.00	0.45 (0.22-0.93)	0.31 (0.11-0.90)		0.035
≥ 85 years					
Ischemic strokes, n	14	28	30	72	
30-days CF, n (%)	3 (21.4)	7 (25.0)	2 (6.6)	12 (16.7)	
Odds Ratio (95%CI)‡	1.00	1.24 (0.26-5.82)	0.28 (0.04-1.96)		
Odds Ratio (95%CI)§	1.00	n.a. <sup>  </sup>	n.a. <sup>  </sup>		0.027
Women					
30-84 years					
Ischemic strokes, n	144	155	149	448	
30-days CF, n (%)	13 (9.0)	9 (5.8)	18 (12.1)	40 (8.9)	
Odds Ratio (95%CI)‡	1.00	0.59 (0.24-1.43)	1.32 (0.62-2.82)		
Odds Ratio (95%CI)§	1.00	1.17 (0.88-1.66)	1.60 (0.56-4.56)		0.384
≥ 85 years					
Ischemic strokes, n	16	57	54	127	
30-days CF, n (%)	2 (12.5)	12 (21.0)	16 (29.6)	30 (23.6)	
Odds Ratio (95%CI)‡	1.00	1.69 (0.33-8.56)	2.31 (0.46-11.74)		
Odds Ratio (95%CI)§	1.00	1.46 (0.87-2.47)	3.11 (0.66-14.66)		0.149

CI: Confidence Interval

<sup>\*</sup> Adjusted for age using logistic regression models.

<sup>†</sup> P-values for time trends using fractional polynomials.

<sup>‡</sup> Age-adjusted odds ratios comparing the periods 2001-2006 and 2007-2012 with 1995-2000.

<sup>§</sup> Age-adjusted odds ratios comparing 2003 (middle year in period 2001-2006) and 2012 with 1995.

<sup>11</sup> n.a.: Not applicable due to low number of ischemic strokes.

Between 1995 and 2010, the age-adjusted case fatality declined in men aged 30–84 years while no significant time trend was found in women aged 30–84 or in attendees aged ≥85 years. Due to relatively few endpoints, we did not have the power to stratify in smaller age groups. When the endpoint registry was updated through 2012, the results were essentially unchanged (Table 4). In high-income countries, trends in IS case fatality have either declined (3, 22) or remained stable (128) during the last decades. Declining case fatality has been viewed as a measure of treatment effect for hospitalized strokes (19, 23). It may also reflect a real decrease in stroke severity with time, as well as increased detection of less severe strokes due to improved imaging of ischemic lesions by CT or MRI (19, 129). Some studies showed an equal decline in case fatality for men and women with time (26, 130), while different time trends with a steeper decrease in men than women were revealed by others (24). Compared to men, the lack of reduction in case fatality among women in our study is noteworthy. Whether the reasons are due to sex-differences in stroke severity, comorbidity or treatment effects over time still remains an open question.

## 5.2.2 The impact of risk factor change on ischemic stroke incidence

In paper II, we sought to answer the following question: "To which degree could changes in risk factors across time explain the changing incidence of ischemic stroke?"

We found that changes in cardiovascular risk factors accounted for 57% of the decrease in incidence of IS from 1995 to 2012. The concept of explained decline used in our analysis reflects both the proportion of the decline in risk for IS that can be attributed to specific risk factors (the population-attributable risk: PAR) and the change of each particular risk factor in this cohort during the time-period of interest. We were not able to find other studies estimating the impact of risk factor contribution to changing stroke incidence by similar methodology as in our study. Several studies have estimated population-attributable risks for the association of IS with established as well as potential risk factors (36-38). However, with PAR as effect estimate, the dimension of time is not included. A large case-control study from 22 countries found that hypertension, current smoking, abdominal obesity, diet and physical activity accounted for 82% of the global risk of IS (PAR 82%; 95% CI 73-87) (36). In contrast to these high values of combined PAR, the population-based Rotterdam Study reported a total PAR of 55% (95% CI 41–68) for the combined risk factors hypertension, smoking, diabetes, atrial fibrillation, coronary disease, overweight/obesity and total cholesterol/HDL (38). The differences in the combined PAR estimates may partly be explained by differences in selection of risk factors, in the populations under study and in study design.

We did not have the statistical power to run separate Poisson analyses for those aged 30 to 49 years. Hence, we cannot causally assess to which degree changing risk factors in the youngest age group can explain the increasing IS incidence in the youngest women, and the lack of decline among the youngest men. However, the background analyses revealed some risk factor patterns, by which hypotheses regarding possible causes for increasing IS in the youngest age group can be generated. This will be briefly discussed in the latest paragraph in this chapter.

Decline in systolic blood pressure contributed most to the decreasing stroke incidence in our study. Hypertension is the single most important treatable risk factor for IS, with estimated PAR between 26% and 33% (36,38,131). However, there is no "threshold" for BP and a significant proportion of all strokes happen in persons with normal BP or "mild" hypertension. Globally, BP levels have decreased the last decades, with the most pronounced decline in Western countries and in high-income groups (132). A recent study from the Tromsø Study cohort demonstrated a secular decrease in the entire range of BP distribution, indicating a mass-population effect rather than a treatment effect of individuals with hypertension (133).

We found that decreasing prevalence of daily smoking contributed second most to the observed IS risk reduction. The estimated multi-adjusted PARs of daily smoking for IS vary from 12% to 21% (36, 131), and the prevalence of daily smoking in attendees ≥30 years decreased by 34% in our study from Tromsø 4 (1994–1995) to Tromsø 6 (2007–2008).

The concurrent 100% increase in diabetes prevalence contributed negatively to the decline in IS incidence. The prevalence of diabetes has increased steadily the last decades, both in developed countries and globally (134). However, (as discussed in 5.1.1) this increase might have been influenced by changing criteria for diabetes in the time period (117).

The estimated contribution of the change in BMI on the declining incidence of IS was negative, reflecting the increasing BMI in our cohort, however statistically non-significant. While both elevated blood pressure, cholesterol and glucose mediate the effects of elevated BMI, the effect of the BMI increase on IS incidence during the study period mirrors the divergent time trends in these mediators in our cohort. Additionally, an elevated BMI seem to mediate its effect on atherosclerosis through an inflammatory pathway (135).

Although baseline cholesterol levels were associated with increased risk of IS in our cohort, changes in total cholesterol level did not contribute significantly to the decline in incidence of

IS, despite decreasing total cholesterol during the observation period. In most, but not all observational studies, there is an association between higher total cholesterol levels (and higher LDL cholesterol) and IS, but the associations seem to differ with the subtype of IS, and different cohorts may have different IS subtype distribution (75). In our study, we had regretfully no information regarding the distribution of IS subtypes.

Our results are in line with other studies from high-income countries. In a cohort of 9,152 persons aged ≥55 years from the Framingham study, the age-adjusted incidence of first-ever stroke declined significantly between 1950 and 2004, concurrent with an overall reduction in prevalence of risk factors (16). Similar diverging trends as in our study were observed, with a decline in systolic BP, total cholesterol, prevalence of hypertension and daily smoking, while mean BMI and diabetes prevalence (in women) increased significantly over time.

In the OXVASC study the age-standardized incidence of first-ever IS fell by 27% (p=0.0002) from 1981 to 2004, simultaneously with significant reductions in the premorbid levels of systolic BP, cholesterol and the proportions of smokers (34).

The Atherosclerosis Risk in Communities Study found a significant decrease in stroke incidence from 1987–2011 with an age-adjusted decrease in stroke risk by 24% (95%CI 13–34%) per 10 years. However, the results were not consistent for participants aged <65 years. Concomitantly the age-adjusted rates of diabetes increased, as did the rate of hypertension, while the prevalence of current smoking declined, resulting in a relatively small effect on the IS risk estimates when adjusting for time-varying risk factors and demographic variables (18).

The main analysis in paper II was performed on the entire age-span, i.e. on eligible attendees aged 30 years and older. However, eligible were those who had attended Tromsø 4 without missing risk factors (n=26,033) (see 3.1.2); moreover, only updated risk factors contributed in the analysis (see 3.4.2). As a consequence, data from consistent attendees with complete risk

factor registration contributed to a larger degree in the main analysis in paper II than was the case in a background analysis (Poisson analysis applied on the sample of 26,329 attendees in paper II), in which there was no additional criteria with regard to risk factors (5.1.1, Figure 2).

Table 5 shows the percentage decline in IS incidence across different subsamples. The non-significant difference in IS risk decline from 1995 through 2012 (37% (95% CI 19–52) vs. 26% (95% CI 11–39) is probably a result of healthy participant bias as well as survival bias, affecting our analysis when only updated risk factor values contributed as in the main analysis in paper II.

Table 5. Percentage decline in incidence<sup>\*</sup> of ischemic stroke from 1995–2012, by sample and Poisson regression model characteristics

	Poisson regression model (power)	Number of eligible attendees	Incidence rate ratio (95% CI) 2012/1995	% decline IS incidence (95% CI) 1995-2012	P-value time trend
Paper I updated analyses <sup>†</sup>	fractional polynomial (3)	32,327	0.727 (0.608-0.869)	27% (13-39%)	0.0004
Paper II (cohort in Figure 1)	fractional polynomial (3)	26,329	0.737 (0.611-0.889)	26% (11-39%)	0.0014
Paper II  (cohort in Figure 1)	linear	26,329	0.747 (0.619-0.903)	25% (10–38%)	0.0025
Paper II (cohort in Table 4)	linear	26,033	0.628 (0.484-0.813)	37% (19–52%)	<0.001

CI: Confidence Interval. \*Age- and sex-adjusted <sup>†</sup>Total number of eligible attendees in the updated analyses was 36,574 (after one person withdrew concent) whereas 32,327 attendees could be followed from 1995 (all age groups included).

Generally, the search for possible explanations behind the increasing incidence of IS in young adults is complicated by the fact that the underlying cause of "young stroke" despite thorough investigations remains undetermined in about one third of the cases (127). A higher proportion of IS in young adults is thought to be caused by more "rare" etiologies compared to those associated with the traditional cardiovascular risk factors seen in older stroke patients, which may explain why IS incidence in this age group is less influenced by changes in CVD risk factor levels. However, results from other previous studies indicate that the role of traditional vascular risk factors in the young may have been underestimated (136).

A study from Greater Cincinnati/Northern Kentucky Stroke Study suggested that diabetes may particularly increase the risk of IS in the young (55). The 15 Cities Young Stroke Study, which included 3944 European patients with first ever IS aged 15–45 years, revealed high frequencies of well documented vascular risk factors; as 49% were current smokers, 46% had dyslipidemia and 36% were hypertensive (136).

Among 4,467 prospectively recruited European TIA or IS patients (Stroke in Young Fabry Patients Study, median age 47 years), the most frequent well-documented modifiable risk factor was smoking (56%), followed by physical inactivity (48%), hypertension (47%), dyslipidemia (35%) and obesity (22%) (137).

In our study, systolic and diastolic blood pressure changed favorably across time both in the youngest age group and among those aged ≥50 years, as did the prevalence of smoking. The use of BP lowering drugs increased similarly in both groups (with 150% and 131% from Tromsø 4 to Tromsø 6, respectively). However, while the prevalence of overweight and obesity increased generally, there was an augmented ascent in obesity prevalence among those aged 30–49 compared to those aged ≥50 years (118% increase vs. 42% increase of obesity prevalence, respectively). Concomitantly, the diabetes prevalence rose with 171% in the age group 30–49 years, and with 76% in those aged ≥50 years.

## 5.2.3 Hypothetical interventions to prevent stroke

In paper III, we wanted to assess the effects of particular interventions on the subsequent risk of stroke and IS. Hence, we sought to answer research questions as: "What would be the 18-years population risk of stroke (compared to what happened in "real life") if everyone with a systolic blood pressure of ≥140 mm Hg were "placed" at a systolic blood pressure <140?" Or: "What would be the effect on the 18-years population risk of stroke, compared to the 18-years stroke risk observed in our cohort, if everyone who smoke daily, quitted smoking?" Or "What if all feasible interventions were applied jointly?" This approach contrasts the main analysis in paper II, where we estimated the impact of concurrent risk factor trends on the already observed decline in ischemic stroke risk.

We found that a combination of feasible modification of lifestyle and metabolic risk factors (smoking, alcohol use, physical activity, BMI, SBP and total cholesterol) could prevent 19% of all strokes observed during 18 years of follow-up. Solely reducing SBP to <140 mmHg in all attendees with SBP ≥140 mmHg would reduce the 18-year population risk of stroke by 15%. A more intensive combined intervention resulted in a 55% reduction in stroke risk, whereas reducing SBP to <120 mmHg alone would reduce the risk by almost a third.

The results from our hypothetical interventions on SBP are in line with the strong, graded and independent relationship between SBP and stroke risk. A recent meta-analysis of randomized trials found that 10 mmHg reduction in SBP reduced the risk of stroke by 27% (138). There was no evidence that the proportional effects were weaker in trials that included persons with lower SBP (<130 mmHg) at baseline, or in trials including high-risk populations. In comparison, the estimated 32% reduced stroke risk in our study, under the intensive intervention on SBP was due to a 21 mmHg average reduction in SBP by the end of follow-up. The smaller effect size in our study may be due to residual confounding, model misspecification or to differences between the study populations.

We did not observe a significant effect of reducing serum total cholesterol on the 18-years population risk of stroke. While some studies found total cholesterol to be a risk factor for IS (71), this was not supported by others (73, 74) (see 1.4.2). Moreover, the relationship between cholesterol level and risk of hemorrhagic stroke seem to be inverse (76).

The significant risk reduction for stroke by smoking cessation in our study is consistent with the prior evidence linking smoking to stroke (60, 61). Smoking cessation was also associated with a considerable decline in stroke risk among 117,000 participants in the Nurse Health Study, with the excess risk among former smokers disappearing 2–4 years after quitting (63).

We did not find a significant effect for physical activity or weight loss. The questionnaires on physical activity were not consistent across surveys in our study and therefore we had to define rather broad categories, which limited our ability to define appropriate interventions (e.g. separating moderate from vigorous activity). Previous analyses of prospective studies using parametric g-formula that investigated effect of weight loss did not find an impact on CHD (139) and death (140), which may be due to either residual confounding by undiagnosed diseases at baseline or irreversibly increased risk due to weight gain.

The estimated benefits of abstinence in our study combines both the accepted positive effect of alcohol cessation in those with heavy or binge drinking and the presumed negative effects of quitting drinking among light to moderate drinkers. Information on amount of alcohol and drinking pattern were not consistently reported across the surveys, limiting the analyses to use vs. no use. Hence, we were not able to estimate the effect of regular low to moderate drinking, which is a limitation. Neither did we have access to consistent data on diet, and detailed data on use of BP-lowering drugs, statins and aspirin were insufficient in the earliest rounds of the study.

In this study, we applied the parametric g-formula to adjust for time-varying confounding by major risk factors for stroke and to simulate long-term interventions on lifestyle and metabolic

risk factors. Importantly, as for other observational studies, the validity of our results relies on the assumptions of no residual confounding, no measurement error and no model misspecification. We included all presumed important fixed and time-varying confounders that were available to us, but despite adjustment for a large number of potential confounders, the possibility of residual confounding cannot be logically excluded. Some measurement error is expected, especially for self-reported lifestyle variables, and may have contributed to bias. We were able to reproduce the observed risk factor patterns and stroke risk with the parametric g-formula, which indicates that under no intervention, the models were not grossly misspecified.

# 6. Conclusions and implications for further research

We found that the overall age-and sex adjusted incidence of ischemic stroke declined with 27% from 1995–2012 in this large, general Norwegian cohort of men and women aged ≥30 years. This decline was driven by the changing incidences across time among the middle-aged and elderly, which is line with that reported from several other high-income countries the last decades. The age-stratified analyses revealed different time trends across the predefined strata, with increasing incidence in women aged 30–49 years, a non-significant rising trend among the youngest men (30–49 years), and declining incidence in women aged 50–74 and men aged 65–74. In men aged 50 to 64 years, the ischemic stroke incidence in 2012 was not significantly different from the incidence two decades earlier. The incidence also remained stable in persons aged 75 years and older. The increasing trend in ischemic stroke incidence among the youngest women adds to the worrying reports about an increasing incidence of stroke at younger age.

Mean crude case fatality for ischemic stroke in persons aged 30–84 years (1995–2012) was 7%, and 21% in participants ≥85 years. Age-adjusted case fatality was higher for women than men through the whole period. Between 1995 and 2012, the age-adjusted case fatality decreased in men aged 30–84 years while no significant decline was found in women aged 30–84 or in attendees ≥85 years.

Our results showed that changes in seven cardiovascular risk factors (systolic blood pressure, total cholesterol, HDL, daily smoking, physical activity, diabetes and BMI) accounted for 57% (95% CI 28–100) of the decrease in ischemic stroke incidence from 1995 through 2012, with decreasing mean systolic blood pressure and decline in smoking prevalence as the most important contributors. The increasing diabetes prevalence contributed negatively, as did the change in BMI, although not significant.

We found that a feasible joint hypothetical intervention on six metabolic and lifestyle risk factors (systolic blood pressure, total cholesterol, weight, physical activity, smoking and alcohol intake) would reduce the 18-year stroke risk in our population by 19%. A combination of more intensive interventions would reduce the estimated 18-years stroke risk by 55%. Blood pressure reduction and quitting smoking significantly reduced the risk when applied separately.

While an ischemic stroke could be caused by several pathological mechanisms, there is a need for future studies that include subclassification of ischemic strokes. Ideally, separate time trends should be presented for each subtype of ischemic stroke across age, to assess potential differences in time trends for the different pathological subtypes by age groups. This calls for studies with a high number of endpoints. Moreover, there is an urgent need for further research to explore the impact of risk factor change on the disquieting change in incidence of ischemic stroke among the youngest ones. To explore the possible reasons behind the divergent time trends of case fatality in men and women, future studies should, in addition to sub-classification of ischemic strokes, include information regarding severity of the stroke events, the patients comorbidity and the treatment given.

The Tromsø Study represents a valuable source for exploring the impact of lifestyle and more distal variables (ecological variables) on the long-term risk of stroke. The newly completed Tromsø 7 survey includes extended data on diet, physical activity and socioeconomic status, with possibilities for an even more comprehensive approach in future projects.

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#### Appendix 1a

Questionnaire 1, the 2<sup>nd</sup> Tromsø Study 1979–80

Do you have, or have you had:	Do you smoke daily at present?
A heart attack?	If the answer was "Yes" in the previous question,
Angina pectoris (heart cramp)?	then:
Any other heart disease?	Do you smoke cigarettes daily? 53
Hardened arteries in the legs?	(hand-rolled or factory made)
A cerebral stroke?	If you do not smoke cigarettes at present, then:
Diabetes?	Have you previously smoked cigarettes daily?
	If "Yes", how long is it since you stopped:
Are you being treated for: High blood pressure?	1 Less than 3 months?
	2 3 months to 1 year?
Do you use:	3 1 to 5 years?
Nitroglycerine?	More than 5 years?
B Yes N	
Do you have get or discomfort in the chest when:	
Walking up hills or stairs, or walking fast on level ground? 41 Walking at normal pace at level ground? 42	How many years altogether have you smoked daily?
If you get pain or discomfort in the chest when	How many cigarettes do you smoke, or did you. No. of cigarette
walking, do you usually:	smoke daily? Give number of cigarettes per day # (hand-rolled or factory made)
1 Stop?	Do you smoke tobacco products other than
2 Slow down?	cigarettes daily? Cigars or cigarillos?
3 Carry on at the same pace?	A pipe? 65
If you stop or slow down, does the pain	If you smoke a pipe, how many packs of tobacco
disappear:	(50 grams) do you smoke per week?
Within 10 minutes?	Give the average number of packs per week.
<sup>2</sup> After more than 10 minutes?	E Yes No
Do you get pain in the calf while:	Do you usually work shifts or at nights?
Walking?	Can you usually come home from work:
Resting?	Every day?
If you get pain in the calf, then:	Every weekend?
Does the pain increase when you walk faster or uphill?	Are there periods during which your working days are longer than usual?
Does the pain disappear when you stop?*	(e.g. fishing season, harvest)
Do you usually have:	During the last year, have you had:
Cough in the morning?	Tick "Yes" beside description that fits best
Phlegm chest in the morning?	1 Mostly sedentary work?
Exercise and physical exertion in leisure time.	Work that requires a lot of walking
If your activity varies much, for example	Work that requires a lot of walking and lifting?
between summer and winter, then give an average.	(e.g. postman, heavy industrial work, construction)
The question refers only to the last twelve months:	4 Heavy manual labour?
	(e.g. forestry, heavy farm-work, heavy construction)
Tick "Yes" beside the description that fits best:  1 Reading, watching TV, or other sedentary	During the last 12 months, have you had
Activity?	to move for work reasons?
<sup>2</sup> Walking, cycling, or other forms of	Is housekeeping your main occupation?
exercise at least 4 hours a week?	Have you within the last 12 months received unemployment benefit?
Sunday walk/stroll, etc.)  3 Participation in recreational sports,	Are you at present on sick leave, or receiving
heavy gardening, etc.?	renabilitation allowance?
(note: duration of activity at least 4 hours a week)	Do you receive a complete or partial disability pension?
4 Participation in hard training or sports	Have one or more of your parents on sistens
competitions, regularly several times a week?	Have one or more of your parents or sisters or brothers had a heart attack (heart wound), or angina pectoris (heart cramp)?
	Are two or more of your grandparents of Finnish origin?
	Are two or more of your grandparents of Sami origin?

#### Appendix 1b

Questionnaire 2, the 2<sup>nd</sup> Tromsø Study 1979–80

LABEL

TR-11

# ADDITIONAL QUESTIONS FOR PERSONS ATTENDING THE MASS X-RAY EXAMINATION IN TROMSØ

Together with the invitation to attend you received a questionnaire from the National Mass Radiography Service. You delivered this questionnaire at the examination.

Cardiovascular diseases are, however, a complex group of diseases. The causes are still partly unknown. In Tromsø we are therefore trying to obtain a more complete description of factors which may be of importance for the course of these diseases, such as diet, psychological pressure ("stress"), social conditions, and occurrence of disease in relatives. We hope you will take the trouble to complete this questionnaire as well, an return it to the Tromsø Board of Health in the enclosed envelope.

All information in connection with the mass x-ray examination will be treated as strictly confidential.

confidential.			
I YOUR OWN DIET  I What type of bread do you usually Tick the most appropriate box.  White bread (e.g. French bread)  Ordinary bread (light texture)  Whole meal (brown) bread  Home-made (brown) bread	2	. 2-6 slices 7-12 slices	
2. What type of butter of margarine de you usually eat? Tick the most appropriate box.  Butter  Ordinary margarine  Plant margarine spread  Soft margarine spread		Tick the most appi Do not drink m Full cream milk Skimmed milk:	c do you usually drink? ropriate box.  pilk
5. The drawings below show cubes of Tick the box above the cube which If in doubt, try buttering a slice.  Do not use butter or margarine.	best resemble		on a slice of bread. 4

b. How many glasses/cups of milk do you usually drink daily? Tick the most appropriate box.  Do not drink milk, or drink less than 1 glass/cup	9. Approximately how often during the last 12 months have you drunk so much wine, beer or spirits that you got drunk?  Tick the most appropriate box.  Have never been drunk, or have not been drunk during the last year
7. How many cups of coffee do you usually drink daily?	3 or more times a weeks
Tick the most appropriate box.  Do not drink coffee, or drink less than 1 cup	VES  No. How often does your main meal consist of fish or fish dishes?  Tick the most appropriate box.  Less than once a week
8. Are you a teetotaller?	5-6 times a week
If "No",	
— How often do you usually drink beer? Tick the most appropriate box.  Never or just a few times a year Once or twice a month About once a week	M. How often do you eat fruit or vegetables? Tick the most appropriate box.  Never eat fruit or vegetables.  A few time a year.  Once or twice a month.  About once a week.  2-3 times a week.
Tick the most appropriate box.  Never or just a few times a year  Once or twice a month	More or less daily  YES  12. How many times a month do you eat  holled or fried cause described less
More or less daily	boiled or fried sausages, meat balls, other processed meat, etc.?  Tick the most appropriate box.  Never or less than once a month

Have you made any changes in your diduring the last 5 years as regards the fol food items?  Tick each item in the appropriate	The DO VOG Have, Of have had you the	1
box.  Ordinary margarine or butter  Skimmed milk	19. Have you had allergy-induced eczer your hands during the last 12 month	
Lean meat  Full cream milk  Soya margarine (soft)  Fatty meat	20. Have you been on sick leave, or been on you to work due to allergic eczema on you hands at any time during the past 3 years.	ar Man
Iown illnesses past and present	21. Have you ever had arthritis? (chro rheumatoid arthritis)	1 1
4. Have you ever had?  Sudden paralysis or numbness on one side of your face or body, in your hand or foot	22. Have you suffered from back pain during the past 12 months lasting more than 4 weeks?	f
Sudden loss of eye sight, complete or partial, or sudden onset of double vision  15. Have you had a peptic ulcer?	23. Have you suffered from morning stiffness in your back lasting more than 30 minutes?	
Do you often have a gnawing pain in the upper part of your stomach?	24. Have you suffered from pains lasti more than 3 months, in the joints listed below during the last 3 years Knees Elbows Innermost finger joints Other joints If yes, did you suffer from stiff join in the mornings lasting more than 30 minutes?	nts
16. Have you had kidney stones or stones in the urinary tract?	YES No  25. Have you had any infectious disease during the past 14 days? (influenza, common cold, vomiting, diarrhoea, YES No	
17. Have you ever had cancer?	26. Have you taken iron tablets durin the past 14 days?	

27. How often do you take painkillers such as Globoid, Novid, Dispril, Albyl, etc.? Tick the most appropriate box.  1-3 times a week  1-3 times a month  Seldom or never  Have you used such painkillers during the last 14 days?	28. Have you changed the amount of physical exercise you take in leisure time during the last five years? Tick the most appropriate box.  As before  More than before  Less than before
ILLNESS IN PARENTS AND SIBLINGS  29. Have any of these relatives had:  Cerebral stroke or brain haemorrhage Diabetes Arthritis (chronic rheumatoid arthritis) Cancer Kidney stones or stone in urinary tract Psoriasis Peptic ulcer None of the above mentioned illnesses	
SOCIAL CONDITIONS AND PSYCHOLOGICAL PRESSURE ("STRESS")  30. How many years of education have you had? (including primary and secondary schools)  31. How was your family's financial situation when you were growing up?	33. Have you had difficulty sleeping in the past couple of weeks? Tick the most appropriate box.  Not at all  No more than usual  Rather more than usual  Much more than usual
Tick the most appropriate box.  Very good  Good  Poor  Very poor  YES No  32. Do you suffer from sleeplessness?  If yes, at what time of the year do you  suffer from sleeplessness?	34. Have you felt unhappy and depressed during the last couple of weeks? Tick the most appropriate box.  Not at all  No more than usual  Rather more than usual  Much more than usual
suffer from sleeplessness? Tick the most appropriate box. No particular time	35. Have you felt unable to cope with your difficulties during the last couple of weeks? Tick the most appropriate box.  Not at all  No more than usual  Rather more than usual  Much more than usual

#### Appendix 2a

Questionnaire 1, the 3<sup>rd</sup> Tromsø Study 1986–87

# THE TROMSØ HEALTH SURVEY (Applies only to the person to whom the letter is addressed.) The health so You find the You will find enclosed broadlessed.

The health survey is coming now to your district.

You find the time and place for attendance below.

You will find an orientation on the survey in the enclosed brochure.

We would like you to fill in the form on the back and take it with you to the survey.

We ask those possibly not attending to report their absence in the attached absence report.

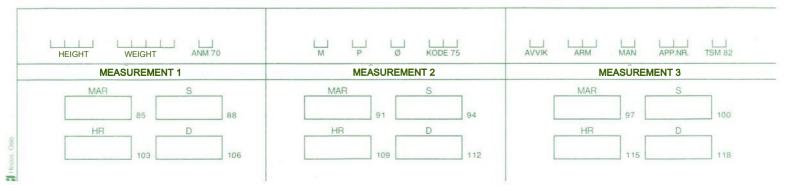
Yours sincerely

MUNICIPAL HEALTH AUTHORITY OF TROMSØ
COUNTY DOCTOR OF TROMS UNIVERSITY OF TROMSØ
NATIONAL HEALTH SCREENING SERVICE

Birth date Personal number Municipality Circuit number

First
letter of

Meeting place Gender last name Day and date Time



FAMILY	4 7 4 9 7	F SMOKING	Yes
Have one or more of your parents or siblings	Yes No Don't	Do you smoke daily at present?30	
had a heart attack (heart wound) or angina	know	If the answer is "YES", then:	FE.
pectoris (heart cramp)?		Do you smoke cigarettes daily?31	
OWN ILLNESSES	-5 10 2 2 8	(hand-rolled or factory made)	
OWN ILLNESSES		If you do not smoke cigarettes at present,	
Do you have or have you had:	Yes No	then:	
Do you have, or have you had:		Have you previously smoked cigarettes daily?32	
A heart attack?		If you answered "Yes", how long is it since	
Angina pectoris (heart cramp)?		you stopped:  Less than 3 months?	
Diabetes? 16		3 months to 1 year?	
Are you being treated for:		1 -5 years?	
Are you being treated for:		More than 5 years?	
High blood pressure?		To be answered by those who smoke or	
Do you use:		who have smoked previously:	
Nitroglycerine?		How many years altogether have you smoked daily?	
Nitrogrycerine:		How many cigarettes do you smoke or	Y
SYMPTOMS	and the same	did you smoke daily?	
		Give number of cigarettes per day	
Do you get pain or discomfort in the chest when	Yes No	(hand-rolled + factory made)	Ciga
Walking up hills or stairs, or walking fast on level ground?19		Do you smoke anything else other than cigarettes daily?	
Walking at normal pace at level ground?20		Cigars or cigarillos/cheroots?40	_
The state of the s		A pipe?41	
If you get pain or discomfort in the chest when walking, do you usually:		If you smoke a pipe, how many packs of	
Stop?21	1	tobacco (50 grams) do you smoke	
Slow down?	2	per week?	
Carry on at the same pace?	3	Give the average number of packs per week42	
If you stop or slow down, does the pain			Tob
disappear:	1	G COFFEE	
After less than 10 minutes?	2	How many cups of coffee do you usually	
Do you usually have:	Yes No	drink daily?	
Cough in the morning?23		Tick the most appropriate box.	= 1
Phlegm chest in the morning?		Do not drink coffee, or less than one cup45	
EXERCISE	6146 m	1 -4 cups	
		5 -8 cups	
Exercise and physical exertion in leisure time. If your activity varies much, for example between		9 or more cups	
summer and winter, then give an average.		What type of coffee do you usually drink daily?	
The question refers only to the last year:		Coarsely ground coffee for brewing (boiled)46 Finely ground filter coffee47	11
Tick the most appropriate box.		Instant coffee	
Reading, watching TV, or other sedentary	1	Caffeine free coffee	
activity?25		Do not drink coffee	
Walking, cycling or other forms of exercise at least 4 hours a week?	2	H EMPLOYMENT	Yes
(include walking or cycling to		Have you within the last 12 months received	
work, Sunday walk/stroll, etc.)		unemployment benefit? 51	
Participation in recreational sports, heavy gardening, etc.?	3	Are you at present on sick leave, or	= 4
(note: duration of activity at least		receiving rehabilitation benefit? 52	
4 hours a week)		32	
Participation in hard training or sports		Do you receive a complete or partial disability pension? 53	
competitions, regularly several times a week?	N-1-10	Do you usually work shifts or at	
SALT/ FAT		night?54	
How often do you use salted meat		TOURS AND ADDRESS OF THE PROPERTY OF THE PROPERTY AND ADDRESS OF THE PROPERTY	
		During the last year, have you had:	
or salted fish for dinner?		<b>During the last year, have you had:</b> Tick the most appropriate box.	
or salted fish for dinner? Tick the most appropriate box.		Tick the most appropriate box.  Mostly sedentary work?55	
or salted fish for dinner?  Tick the most appropriate box.		Tick the most appropriate box.  Mostly sedentary work?	
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month	1 2	Tick the most appropriate box.  Mostly sedentary work?55	
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month		Tick the most appropriate box.  Mostly sedentary work?	
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month	2	Tick the most appropriate box.  Mostly sedentary work?	
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month	2 3	Tick the most appropriate box.  Mostly sedentary work?	
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month	2 3	Tick the most appropriate box.  Mostly sedentary work?	
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month	3 4	Tick the most appropriate box.  Mostly sedentary work?	Yes
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month	2 3 4	Tick the most appropriate box.  Mostly sedentary work?	Yes
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month	2 3 4	Tick the most appropriate box.  Mostly sedentary work?	Yes
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month Once a week or less Twice a week or less More than twice a week.  How often do you add extra salt to your dinner?  Tick the most appropriate box.  Rarely or never	2 3 4	Tick the most appropriate box.  Mostly sedentary work?	Yes
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month Once a week or less Twice a week or less More than twice a week.  How often do you add extra salt to your dinner?  Tick the most appropriate box. Rarely or never	2 3 4	Tick the most appropriate box.  Mostly sedentary work?	Yes
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month	2 3 4	Tick the most appropriate box.  Mostly sedentary work?	Yes
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month	2 3 4	Tick the most appropriate box.  Mostly sedentary work?	Yes
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month	2 3 4	Tick the most appropriate box.  Mostly sedentary work?	Yes
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month	2 3 4	Tick the most appropriate box.  Mostly sedentary work?	Yes
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month	2 3 4	Tick the most appropriate box.  Mostly sedentary work?	Yes
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month	2 3 4	Tick the most appropriate box.  Mostly sedentary work?	Yes
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month	2 3 4	Tick the most appropriate box.  Mostly sedentary work?	
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month Once a week or less Twice a week or less More than twice a week.  How often do you add extra salt to your dinner?  Tick the most appropriate box. Rarely or never	2 3 4	Tick the most appropriate box.  Mostly sedentary work?	
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month Once a week or less Twice a week or less More than twice a week.  How often do you add extra salt to your dinner?  Tick the most appropriate box. Rarely or never	2 3 4 1 2 3 3 4 5	Tick the most appropriate box.  Mostly sedentary work?	
or salted fish for dinner?  Tick the most appropriate box.  Never or less than once a month Once a week or less Twice a week or less More than twice a week.  How often do you add extra salt to your dinner?  Tick the most appropriate box. Rarely or never	2 3 4 1 2 3 3 4 5	Tick the most appropriate box.  Mostly sedentary work?	Yes

### Appendix 2b

Questionnaire 2, the 3<sup>rd</sup> Tromsø Study 1986–87

# ADDITIONAL QUESTIONS TO THE TROMSØ HEALTH SURVEY 1986-87.

Cardiovascular heart and circulatory diseases, on which the surveys of the 1974 and 1979-80 focused, are a very varied category of diseases whose causes are still partly unknown. In Tromsø we are therefore trying to obtain a more complete description of factors which may be important for the course of these diseases, such as diet, psychological pressure, "stress", social conditions and the occurrence of disease in relatives. Such a description is also important in the search of factors that contribute to cancer, a group of diseases which also we try to combat in the coming years.

When you were called in, you received a questionnaire which you handed in at the survey. The present questionnaire asks for further information about your health and includes questions on various diseases and physical and psychological complaints. We have included questions on pregnancy, birth and menstruation.

In addition, we are interested in obtaining information on the public use of medical health services in order to find out how to improve the health service.

We hope that you will take the trouble to fill in yet another questionnaire and return it to "Tromsø Board of Health" in the enclosed envelope. All information will be treated with strict confidentiality If you have any comments regarding the survey, you may write them down in the space provided on the last page of the questionnaire.

#### Yours sincerely

Tromsø Board of Health

Department of medicine University of Tromsø

GENERAL STATE OF HEALTH  How is your health? Tick the box where "Yes" is appropriate.  Very bad	Yes
ILLNESSES	
Do you have, or have you had: Tick "Yes" or "No" for each question. The skin disease psoriasis 13 Asthma 14 Allergic eczema 15 Hay fever 16 Chronic bronchitis 17 Gastric ulcer 18 Duodenal ulcer 19 Your appendix removed 20 An operation for a stomach ulcer 21 Chronic rheumatoid arthritis 22 Cancer 23 Epilepsy 24 Migraine 25	Yes No
INFECTIONS	
How many times in the last 6 months have you had infections like a cold, influenza (flu) diarrhoea/vomiting, or similar illnesses? 26	Number Yes No
Have you had one of these infections in the past 14 days?27	les ivo

ILLNESSES IN PARENTS OR SIBLINGS		l contra
Tick for the relatives who have or have ever had any of the following illnesses:  Cerebral stroke or brain haemorrhage Diabetes	28 32 36	mother father brother Sists
Tick if none of the relatives have or have had any of those illnesses	56	Yes No
MEDICINIES		
MEDICINES		
Have you during the last year used tablets/sprays or had injections for asthma or allergies?	.60	Yes No

CONTACT DUE TO OWN HEALTH OR ILLNESS		DINNER	
How many visits have you made during the past year due to your own health or illness?  To a GP (general practitioner) 71 To a specialist (not hospital) 72 Emergency GP 85 Medical officer at work 87 Physiotherapist 89 Chiropractor 81 Alternative practitioner	Number of visits	How often do you eat meat for dinner? Tick the box where "Yes" is appropriate. Less than once a week	Yes
(homoeopath, foot zone therapist, etc.) 83 Hospital outpatient department		dinner? Tick the box where "Yes" is appropriate.  Less than once a week	Yes
How many slices of bread do you usually eat daily?  Tick the box where "Yes" is appropriate.	Yes	Do you usually eat vegetables with your dinner?	Yes No
Less than 2 slices	1 2 3 4 5 5 Yes 1 2	FRUIT  How often do you usually eat fruit? Tick the box where "Yes" is appropriate.  Less than once a week	Yes
Semi-skimmed milk	□ 3 □ 4	ALCOHOL  Are you a teetotaller?	Yes No
drink daily?  Less than 1 glass/cup	Yes	If not, - How often do you usually drink beer? Tick the box where "Yes" is appropriate. Never or just a few times a year	Yes
lean fish for dinner or in a sandwich? Tick the box where "Yes" is appropriate. Less than once a week	Yes	How often do you usually drink wine? Tick the box where "Yes" is appropriate.  Never or just a few times a year	Yes
dinner or in a sandwich? Tick the box where "Yes" is appropriate.  Less than once a week	Yes	- How often do you usually drink spirits? Tick the box where "Yes" is appropriate.  Never or just a few times a year	Yes
Tick the box where "Yes" is appropriate.  No	Yes 1 2 3	Approximately how often have you during the last year consumed alcohol corresponding to at least 5 small bottles of beer, a bottle of wine, or 1/4 bottle of spirits?  Tick the box where "Yes" is appropriate.  Not at all the past year	Yes

PHYSICAL ACTIVITY	l	BACK AND JOINTS CONDITIONS		
How often do you take part in physical activity lasting at least 20 minutes, which makes you		During this last year have you suffered from back pain that has lasted longer than 4 weeks? 123	Yes	No
perspire or become breathless? Tick the box where "Yes" is appropriate. Rarely or never	Yes 1	If yes, does the pain improve when you move around?124		
Weekly	□ 2 □ 3 □ 4	Have you suffered from morning stiffness in your back lasting more than 30 minutes?		
If you usually take part in this type of activity at least weekly, how much time do you spend exercising?  Tick the box where "Yes" is appropriate.  Less than 30 minutes a week	Yes	from pain in any of the following joints lasting more than 30 minutes?  Knees	Yes	No
CHANGE IN DIETARY HABITS AND OTHER HABITS		NECK, HEAD AND SHOULDER COMPLAINTS		
Have you changed any of the following habits during the last 5 years: (Tick once for each question)  Dietary fat	Now use  As more before Less	How often do you suffer from headache? Tick the box where "Yes" is appropriate. Rarely of never	Yes	
Physical activity 111  MARRIAGE / PARTNER		shoulder? Tick the box where "Yes" is appropriate. Rarely of never	Yes 1	
Are you married or partner	Yes No	Once or more a month Once or more a week Daily	☐ 2 ☐ 3 ☐ 4	
Moved in with a partner? 113	years	Do the pains in your head, neck or shoulder reduce your ability to work?	\\\	
HOUSEHOLD		Tick the box where "Yes" is appropriate.  Little or no effect	Yes 1	
How many people live in your household? 115	Number	To some degree To a large degree Cannot do ordinary work	☐ 2 ☐ 3 ☐ 4	
Is anyone in your household 10 years or younger?	Yes No	Have your back, shoulder, and/or neck ever been x-rayed?	Yes	No
Does anyone in your household need special care/assistance – other than the children?118	Yes No	SLEEPLESSNESS/ LOSS OF CONSCIOUSNESS		
SCHOOLING		SLEEP LESSINESS/ EGGS OF GOINSCHOOSINESS	Yes	No
How many years education have you had? (including primary and secondary schools) 119	years	Have you ever suffered from sleeplessness? 135 If yes, what time of the year does it affect you most? Tick the box where "Yes" is appropriate.	Yes	
EMPLOYMENT	1	No particular time	□ 1	
Have you had paid work the entire past year? Tick the box where "Yes" is appropriate.  Full-time work	Yes	Especially during the polar night	2 3 4 Yes	No
yourself? Tick the box where "Yes" is appropriate. All or almost all	□ 1 □ 2	Have you suffered from sudden loss of consciousness in the past year?138	Yes	No
More than quarterLess than quarter	□ 3 □ 4	Have you noticed sudden changes in your pulse rate of heartbeat in the past year?139	Yes	No

REACTION TO PROBLEMS			1
If you have major personal problems, do you expect to get help and support from your spouse or family?	Yes No Yes No Yes	During the past 2 weeks have you felt unhappy or depressed? Tick the box where "Yes" is appropriate. Seldom or never	Yes
Seldom or never	1 2 3 4	Sometimes Rarely or never	☐ 2 ☐ 3
MENSTRUATION		Do the complaints disappear when you get	Yes No
How old were you when you started menstruating? 145	years	your period?	Yes No
When did your last period start? 147	day month year	11 11 0	
How many days usually pass from the first day of one period to the first day of your		PREGNANY	number
next period (the time lapsed between the start of two periods)	days	How many children have given birth to? 163	Turriber
Do/ did you menstruate regularly? 155	Yes No	How old were you when you got pregnant for the first time?	years
Do you usually take painkillers during menstruation? 156	Yes No	CONTRACEPTION	
PRE-MENSTRUAL TENSION		Do you use or have you ever used oral contraceptive pills or an intrauterine device?166 If yes, for how many years altogether have	Yes No
Do you have any of the following complaints before your period:  - Are you depressed or irritable?	Vac	you used: The pill?	years years
Tick the box where "Yes" is appropriate.  Hardly at all	Yes 1 2 3	How old were you when you started using: The pill?	years years
- Are your breasts painful? Tick the box where "Yes" is appropriate.	Yes	If you have stopped taking the pill, did 6 months or more pass without menstruating without you being pregnant? 175	Yes No
Hardly at all	☐ 2 ☐ 3	Did you have to stop taking the pill due to high blood pressure?176	Yes No
- Do you have swollen hands/feet, put on weight, or feel bloated?		CERVICAL SMEAR TEST  How many times have you had a cervical	Number of tests
Tick the box where "Yes" is appropriate.  Hardly at all	Yes	smear test in the last 3 years?177	Number of tests
Noticeably	2 3	How many years is it since you had your last cervical smear test? 178	years
Your comments:			

#### Appendix 3a

Questionnaire 1, the 4<sup>rd</sup> Tromsø Study 1994–95

# **HEALTH SURVEY**Invitation



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 measured recently.

Yours sincerely, **Municipal Health Authorities** 

Faculty of Medicine - University of Tromsø National Health Screening Service



TOOK OWN REALIN	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 good 2	Time spent going to work counts as leisure time.
Good 3	Hours per week
Very good 4	Light activity (not None Less than 1 1-2 3 or more
Do you have, or have you had:  Yes No Age first time	sweating/out of breath) 56
bo you have, or have you had.	Hard activity (sweating/
A heart affack	out of breath)57
Angina pectoris (heart cramp) 16	1 2 3 4
A cerebral stroke/ brain haemorrhage 19 years	COFFEE
Asthma years	How many cups of coffee do you drink daily?
Diabetes years	Put 0 if you do not drink coffee daily.
The state of the s	Coarsely ground coffee for brewing 58
Do you use blood pressure lowering drugs?	Other coffee 60 Cups
Currently 28 1	
Previously, but not now 2	ALCOHOL
Never used 3	Are you a teetotaller? 62 Yes No
	How many times a month do you normally drink
Have you during the last year suffered from pains	alcohol? Do not count low-alcohol beer.
and/or stiffness in muscles and joints that have lasted continuously for at least 3 months?	Put 0 if less than once a month 63
lasted continuously for at least 3 months?	
	How many glasses of beer, wine or spirits do you normally drink in a fortnight? 65 Beer Wine Spirits
Have you in the last two weeks felt:	Do not count low-alcohol beer. Glasses Glasses Glasses
Very	Put 0 if less than once a month.
No A little A lot much	
Nervous or worried?, 30	FAT What type of margarine or butter do you usually use on
Anxious?31	bread? Tick one box only.
Confident and calm? 32	Don't use butter/margarine 71 1
Irritable?33	Butter
Happy and optimistic? 34	Hard margarine 3
Down/depressed?35	Soft margarine
Lonely? 36	Butter/margarine mixtures
1 2 3 4	Light margarine
SMOKING	EDUCATION/WORK
Did any of the adults at home smoke while Yes No	What is the highest level of education you have completed?
you were growing up?	7-10 years primary/secondary school,
	modern secondary school <sup>72</sup>
Do you currently, or did you previously, live together Yes No	Technical school, middle school, vocational
with daily smokers after your 20 <sup>th</sup> birthday? 38	school, 1-2 years senior high school
If "YES", for how many years in all?	High school diploma (3-4 years)
iii 125 , for now many yours in air:	(3-4 years)3  College/university, less than 4 years
How many hours a day do you normally spend	College/university, 4 or more years
in smoke-filled rooms? 41 Hours	
Put 0 if you do not spend time in smoke-filled rooms.	What is your current work situation?
Do you yourself smoke:	Paid work
Cigarettes daily?	Education, military service
	Unemployed, on leave without payment 76
Cigars/ cigarillos daily? 44 A pipe daily? 45	How many hours of paid work do you have per No. of
	week? 77 hours
If you previously smoked daily, how long	Do you receive any of the following benefits?
is it since you quit?	Sickness benefit (sick leave)
If you currently smoke, or have smoked	Rehabilitation benefit 80
previously:	Disability pension 81
How many cigarettes do you or did you	Old-age pension 82 Social welfare benefit 83
usually smoke per day? 48	Unemployment benefit 83 Unemployment benefit 84 Unemployment benefit 84 Unemployment benefit 85 Unempl
How old were you when you began	
daily smoking?	ILLNESS IN THE FAMILY
How many years in all have you smoked  Years	Have one or more of your parents or siblings, had a heart attack or had
daily? 54	siblings had a heart attack or had angina (heart cramp)?
ddily:	

#### Appendix 3b

Questionnaire 2 (<70 years), the 4<sup>th</sup> Tromsø Study 1994–95

#### The 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 a 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.

Yours sincerely.

**Faculty of Medicine** University of Tromsø

**National Health Screening Service** 

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

I do not wish to answer the questionnaire ......

Day Month Year Date for filling in this form:

CUII	ΙПП	20	חו	MO	UTH
СΠІ	LИП	UU	וטי	TU	υіп

In which Norwegian municipality did you live at the age of 1 year?

......24 - 28 If you did not live in Norway, give country of residence instead of municipality.

How was your family's financial situation during your childhood?

Good ..... Difficult ..... Very difficult ......

How many 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

How many of the first 15 years of your life

- did you live in a town/city? .....vears
- did your family have a cat or dog in the home? ......<sup>34</sup> \_\_\_\_\_vears

HOME	White shall like
prominent in the second	
Who do you live with?  Tick once for each item and give the number.  Spouse/partner	Numbe
How many of the children attend day care/kindergarten?	13
What type of house do you live in?  Villa/detached house	
How big is your house?46 _	m
Approximately what year was your house built?49 _	
Yes Has your house been insulated after 1970?53	No
Do you live on the lower ground floor/basement?54 If "Yes", is the floor laid on concrete?55	00
What is the main source of heat in your home?  Electric heating	No
Do you have fitted carpets in the living room?	
WORK	Ben Hyv
If you have paid or unpaid work, how would you describe your work?  Mostly sedentary work?	
(e.g. office work, mounting)  Work that requires a lot of walking?	
Work that requires a lot of walking and lifting?	
Can you decide yourself how your work should be organised?  No, not at all	

Yes, I decide myself ...... 4

Farmer .....

Fisherman ......

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

Yes No

No

TOOK OWN ILLNESSES	STWPTOWS
Have you ever had:	Yes No
Tick one box only for each item. Give your age at the time. If you have had the condition several times, how old were you <b>last</b> time?	Do you cough about daily for some periods of the year?177
Yes No Age	Is your cough productive ?
	Have you had this kind of cough for as long as
Hip fracture	3 months in each of the last two years?
Whiplash75 🔲 🔲	
Injury requiring hospital admission	Have you had episodes of wheezing in your chest? <sub>180</sub>
Gastric ulcer81 🔲 🔲	Tick one box only for each item.
Duodenal ulcer84 🔲 🔲	At night
Gastric/duodenal ulcer surgery87	In connection with respiratory infections
Neck surgery90 🗖 🔲	In connection with physical exertion
Have you you ever had, or do you still have:	to the second superior and the second
Tick one box only for each item.  Yes No	Have you noticed sudden changes in your pulse
Cancer93 🔲	or heart rhythm in the last year?185
Epilepsy	How often do you suffer from sleeplessness?
Migraine	Never, or just a few times a year186
Chronic bronchitis	1-2 times a month
Psoriasis	Approximately once a week
Osteoporosis	More than once a week 4
Fibromyalgia/fibrositis/chronic pain syndrome	If you suffer from sleeplessness, what time
Psychological problems for which you have sought help	of the year does it affect you most?
Thyroid disease	No particular time of year
Liver disease	Especially during the polar night
Kidney disease	Especially during the midnight sun season
Appendectomy	
Allergy and hypersensitivity:	Have you in the last year suffered from sleeplessness Yes No to the extent that it has affected your ability to work?188
Atopic eczema (e.g. childhood eczema)	to the oxione that it has allocted your ability to work
Hand eczema	How often do you suffer from headaches?
Hay fever	Rarely or never
Food allergy	Once or more a month
Other hypersensitivity (not allergy)	Once or more a week
and the same of the same of the same	2.00.00
How many times have you had a cold, influenza (flu), vomiting/diarrhoea, or similar in the last six months?times	Does the thought of getting a serious illness ever worry you?
vorniting/diamnoea, or similar in the last six months?times	Not at all
Yes No	Only a little
Have you had this in the last 14 days?	Some
THE PARTY OF THE P	Very much 4
ILLNESS IN THE FAMILY	
Tick for the relatives who have or have ever had any of the following diseases:	USE OF HEALTH SERVICES
Tick "None" if none of your relatives have had the disease.	How many visits have you made during the past year
	due to your own health or illness: Number of time
Mother Father Brother Sister Child None	Tick <b>0</b> if you have <b>not</b> had such contact the past yea
Cerebral stroke or brain haemorrhage 113	T (OD)/F OD
Heart attack before age 60 119	To a general practitioner (GP)/Emergency GP
Cancer	To a psychologist or psychiatrist  To an other medical specialist (not at a hospital)
Asthma	To a hospital out-patient clinic
Gastric/duodenal ulcer	Admitted to a hospital
Osteoporosis	Admitted to a hospital
Psychological problems149	To a physiotherapist
Allergy155 Q Q Q Q	To a chiropractor
Diabetes	To an acupuncturist
age when they got	To a definist
diabetes167	To a healer, faith healer, clairvoyant

#### **MEDICATION AND DIETARY SUPPLEMENTS**

Have you for any length of time in the past year used any of the following medicines or dietary supplements daily or almost daily? Indicate how many months you have used them. Put **0** for items you have **not** used. Medicines Painkillers \_\_\_\_\_months Sleeping pills ......months Tranquillizers .....\_\_\_months Alleray drugs ......months Asthma drugs ......months Dietary supplements Iron tablets 227 months Calcium tablets or bonemeal ......months Vitamin D supplements ...... months Cod liver oil or fish oil capsules ......months Have you in the last 14 days used the following medicines or dietary supplements? Tick one box only for each item. Medicines Painkillers ......237 Antipyretic drugs (to reduce fever) ...... Migraine drugs ..... Eczema cream/ointment ..... Heart medicines (not blood pressure) ...... Cholesterol lowering drugs ..... Sleeping pills ...... Tranquillizers ...... Antidepressants ...... Gastric ulcer drugs Insulin Diabetes tablets ...... Drugs for hypothyroidism (Thyroxine) ...... Cortisone tablets ......252 Other medicine(s) Dietary supplements Iron tablets ..... Calcium tablets or bonemeal ...... Vitamin D supplements ..... Cod liver oil or fish oil capsules ...... **FRIENDS** good How many good friends do you have whom you can talk confidentially with and who give you help when you need it? 259 \_ friends Do not count people you live with, but do include other relatives! How many of these good friends do you have contact with at least once a month? ......261 Yes No Do you feel you have enough good friends? ............263 How often do you normally take part in organised gatherings, e.g. sewing circles, sports clubs, political meetings, religious or other associations? 1-2 times a month ...... Approximately once a week ....... 

#### **FOOD HABITS**

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

			•			
A catering portion is enough for about			265		slices	
What kind of fat is normally used in coc (not on the bread) in your home?  Butter  Hard margarine  Soft margarine  Butter/margarine blend  Oils						
What kind of bread (bought or home-matrick one or two boxes! White bread to the bread I eat is most similar to:			ary Co	oarse	Crisp bread	
How much (in <b>number</b> of glasses, cups usually eat or drink <b>daily</b> of the followin	s, pota	toes	or slic	es) d	o you	
Tick one box for <b>each</b> foodstuff.  O Full milk (ordinary or curdled) (glasses) 276 Semi-skimmed milk	Less	1-2		5-6	More than 6	
(ordinary or curdled) (glasses) Skimmed milk (ordinary or curdled) (glasses) Tea (cups)	0000	0000	0000	0000	0000	
Slices of bread in total (incl. crisp-bread)						
(e.g. mackerel in tomato sauce) 🖵						
- lean meat (e.g. ham) □				ū		
- fat meat (e.g. salami)		000003	00000	00000	00000	
How many <b>times per week</b> do you norr	mally e	-	e follo	wing	foodst	uffs?
Tick a box for <b>all</b> foodstuffs listed.  Never  Yoghurt	Less than 1	1000	2-3	4-5	almost daily	
- unprocessed meat	000000000000000	000000000000000	000000000000000	000000000000000	0000000000000000	

ALCOHOL	TO BE ANSWERED BY WOMEN ONLY
How often do you usually drink beer? wine? spirits?  Never, or just a few times a year	MENSTRUATION
About once a week	How old were you when you started menstruating?year  If you no longer menstruate, how old were
Approximately how often during the last year have you consumed alcohol corresponding to at least 5 small bottles of beer, a bottle	you when you stopped menstruating?years  Apart from pregnancy and after giving birth, have
of wine, or 1/4 bottle of spirits?  Not at all the last year	you ever stopped having menstruation for Yes No 6 months or more?
1-2 times a month  1-2 times a week 4  3 or more times a week 5  5	If you still menstruate or are pregnant: day/month/year
For approximately how many years has your alcohol consumption been as you described above?years	What date did your last menstruation period begin?.333//
WEIGHT REDUCTION	Do you usually use painkillers to Yes No relieve period pains?
About how many times have you deliberately tried to	PREGNANCY
lose weight? Write 0 if you never have before age 20	How many children have you given birth to?340 children Yes No Don't know
- later times	Are you pregnant at the moment?
If you have lost weight deliberately, about how many kilos have you ever lost at the most?  - before age 20	Have you during pregnancy had high blood pressure and/or proteinuria?
- later kg	If "Yes", during which pregnancy?  Pregnancy First Later
What weight would you be satisfied with (your "ideal weight")?kg	High blood pressure 344 Proteinuria 346 Proteinuria 346 346 346 346 346 346 346 346 346 346
URINARY INCONTINENCE	If you have given birth, fill in for each child the year of birth and approximately how many months you breastfed the child.
How often do you suffer from urinary incontinence?  Never	Child Year of birth: Number of months
Not more than once a month 2 Two or more times a month 3 Once a week or more 4	breastfed:  1 348 2
Your comments:	3 356
	5 364
	CONTRACEPTION AND ESTROGEN
	Do you use, or have you ever used: Now Before Nevel Oral contraceptive pills (incl. minipill) <sub>372</sub>
	Hormonal intrauterine device 🖵 📮
	Estrogen (tablets or patches)
	If you use oral contraceptive pills, hormonal intrauterine device, or estrogen, what brand do you currently use?
	If you use or have ever used oral contraceptive pills:  Age when you started to take the pill?yea
	How many years in total have you taken the pill?yea
	If you have given birth, how many years did you take the pill before your first delivery?yea
	If you have stopped taking the pill:  Age when you stopped?yea

# Appendix 3c

Questionnaire 2 (≥70 years), the 4<sup>th</sup> Tromsø Study 1994–95

# 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. Finally, the survey should give knowledge about the older part of the population. We would therefore like you to answer the questions below.

This form is a 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.

#### Yours sincerely,

Faculty of Medicine University of Tromsø	National Health Screening Service
If you do not wish to answer the quant return the form. Then you will no	estionnaire, tick the box below ot receive reminders.
I do not wish to answer the question	naire17 🗖
	Day Month Year
Date for filling in this form:	18//

#### CHILDHOOD/YOUTH

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

In which Norwegian municipality did you live at the age of 1 year?

How was your family's financial situation during your childhood?

Very good29	1
Good	2
Difficult	3
Very difficult	
• • • • • • • • • • • • • • • • • • • •	

How old were your parents when they died?

<b>Mother</b>		Years
Father	32	Years

HOME	1	10 15
Who do you live with? Tick once for each item and give the number. Yes	No	Number
Spouse/partner34		
Other people over 18 years35	$\bar{\Box}$	
the stranger control of the second se	_	
People under 18 years	J	
What type of house do you live in? Villa/ detached house		
Farm		
Flat/apartment		
Terraced /semi-detached house 4 Other		
How long have you lived in your present home?	42	years
Yes Is your home adapted to your needs?44	No	
If "No", do you have problems with:		
Living space45 🗖		
Variable temperature,		
too cold/too warm		
Stairs 47 🗖 Toilet 48 🗖	7	
Bath/shower 49 4	10	
Maintenance 50	6	
Other (please specify)	ō	
Would you like to move into a retirement home?52		
Trodic you like to move into a real circle in finite.		
PREVIOUS WORK AND FINANCIAL SITUAT	ION	manual Pari
How will you describe the type of work you had for the years before you retired?	e las	t 5-10
Mostly sedentary work?53 (e.g. office work, mounting)		Í
Work that requires a lot of walking?(e.g. shop assistant, housewife, teaching)		2
Work that requires a lot of walking and lifting? (e.g. postman, nurse, construction)		3
Heavy manual work		1
(e.g. forestry, heavy farm-work, heavy construction)		
Did you do any of the following jobs (full-time or part-time)?		
Tick one box only for each item.	No	
Driver54 📮		
Farmer	5	
How old were you when you retired?	57	Years
What kind of pension do you have?		
Basic state pension59		
An additional pension60		
How is your current financial situation?		
Very good61		í
Good		

Very difficult ...... 4

HEALTH AND ILLNESS	Tames 1	ILLNESS IN THE FAMILY	
Has your state of health changed in the last year?		Tick for the relatives who have or have ever had	
Yes, it has got worse62 🖵 1		any of the following diseases:	
No, unchanged	2	Tick "None" if none of your relatives have had the disease.	
Yes, it has got better 🔲	3		
How do you feel your health is now compared to		Mother Father Brother Sister C Cerebral stroke or brain haemorrhage 114	
others of your age?			
Much worse		Hypertension	
About the same		Hypertension	5 5
A little better		Osteoporosis 144 🔲 🔲 🔲	
Much better		Arthrosis (osteoarthritis)150	
YOUR OWN ILLNESSES	zhiota L	Dementia162	
Have you ever had:		Diabetes	
Tick one box only for each item. Give your age at the time. If you have had the condition several times, how old were you <u>last</u> time?		diabetes174	-
Yes No	Age	SYMPTOMS	
		Van	M-
		Do you cough about daily for some periods of the year?	No
		of the year?	_
Injury requiring hospital admission		Is your cough productive?185	
			-
		Have you had this kind of cough for as long	
		as 3 months in each of the last two years?186	_
Neck surgery85 🗖		Have you had episodes with wheezing in your chest? <sub>187</sub> If "Yes", has this occurred:	
Have you ever had, or do you have:		Tick one box only for each item.	
Tick one box only for each item.	No	At night188	
Cancer		In connection with respiratory infections 🖳	
Epilepsy		In connection with physical exertion	
Migraine	ä	In connection with very cold weather	_
Parkinson's disease	ä	Have you noticed sudden changes in your pulse	
Chronic bronchitis	ä	or heart rhythm in the last year?	
Psoriasis	ä	1 650 1000 T	
Fibromyalgia/fibrositis/chronic pain syndrome	ö	Have you lost weight in the last year?193	
Psychological problems for which you have sought help	<u>-</u>	If "Yes":	
Thyroid disease	ā	How many kilograms?194	K
Liver disease	<u>-</u>	How often do you suffer from sleeplessness?	
Recurrent urinary incontinence	ā	Never, or just a few times a year196	1
Glaucoma	ā	1-2 times a month	2
Cataract		Approximately once a week	
Arthrosis (osteoarthritis)		More than once a week	4
Rheumatoid arthritis103		If you suffer from sleeplessness, what time of	
Kidney stones		the year does it affect you most?	
Appendectomy		No particular time of year	1
Allergy and hypersensitivity		Especially during the polar night 🛄	2
Atopic eczema (e.g. childhood eczema)		Especially during the midnight sun season 💾	
Hand eczema		Especially in spring and autumn	4
Hey fever108 🖵		Yes No	
Food allergy 🖵		Do you usually take a nap during the day?198	
Other hypersensitivity (not allergy)		Do you feel that you usually get enough sleep?	
How many times have you had a common cold, influenza (	flu),	No "A	A lot
diarrhoea/vomiting or similar in the last 6 months? 1111		Do you suffer from:	A IUL
•		Dizziness200 🔲 🛄	
Yes No		Poor memory	
Have you had this in the last 14 days?113		Lack of energy	
		Constipation	-

Does the thought of getting a serious illness ever			Are you pleased with the health care and home		D II
worry you?			assistance services in the municipality?	No	Don't know
Not at all2			Assigned family GP255 🖵		CIIOW
Some			Home nursing care	ŏ	ă
Very much			Home assistance services		
BODILY FUNCTIONS	szter pilu	87	Do you feel confident that you will receive health		
Can you manage the following everyday		-	care and home assistance services if you need it?		
activities on your own without help from Yes	With some help	No	Confident25		
others? Walking indoors on one level205	Some neip		Very unsure		
Walking up/down stairs	ă	ă	Don't know		
Walking outdoors	ā	ō			
Walking approx. 500 metres					
Going to the toilet			MEDICATION AND DIETARY SUPPLEM	ENTS	
Washing yourself210			Here you for any length of time in the last year your		the
Taking a bath/shower			Have you for any length of time in the last year used a following medicines or dietary supplements daily or a	illy of ilmos	t dailv?
Dressing and undressing			Indicate how many months you have used them.		·
Getting in and out of bed			Put <u>0</u> for items you have <u>not</u> used.		
Eating			Medicines:		
Cooking 215 Q	<u> </u>		Painkillers259		
Doing light housework (e.g. washing up)	<u> </u>	7	Sleeping pills		
Doing heavier housework (e.g. cleaning floor)	<u> </u>	ŏ	Tranquillizers		
Take the bus	<u> </u>	ā	Antidepressants265		
		_	Allergy drugs		_months
Yes	With difficulty	No	Asthma drugs		_months
Can you near normal speech	2000 1	_	Heart medicines (not blood pressure)271		
(if necessary with hearing aid)?			Insulin		_months
Can you read (if necessary with glasses)?221	_	_	Diabetes tablets		_months
Are you dependent on any of the following aids??			Drugs for hypothyroidism (Thyroxine)277		
Yes	No		Cortisone tablets		
Walking stick222 📮	7		Remedies for constipation		_months
Crutches			Dietary supplements:		
Walking frame/zimmer frame	ă		Iron tablets283		
Hearing aid			Vitamin D supplements		
Safety alarm device227			Other vitamin supplements		_months
			Calcium tablets or bone meal289		
USE OF HEALTH SERVICES	A TOP		Cod liver oil or fish oil capsules		months
How many visits have you made during the past year			FAMILY AND FRIENDS	Sm T	inagin
	lumber of till the past ye		Do you have close relatives who can give Yes	No	
To a general practitioner (GP)/emergency GP	200000000		you help and support when you need it?293		
To a psychologist or psychiatrist			If "Yes", who can give you help?		
			Spouse/partner294	H	
To an other medical specialist (not at a hospital) .			Children		
To a hospital out-patient clinic			Others		
Admitted to a hospital			How many good friends do you have whom you can talk confidentially with and who give you		good
To a physiotherapist			help when you need it?29	7	friends
To a chiropractor	.240		Do not count people you live with, but do include		
To a acupuncturist			other relatives!	NI.	
To a dentist			according to the second	No	
To a chiropodist	.246		Do you feel you have enough good friends?299		
To an alternative practitioner (homoeopath, foot zone therapist			Do you feel that you belong to a community (group or	f peor	ole)
To a healer, faith healer, clairvoyant			who can depend on each other and who feel committ other (e.g. a political party, religious group, relatives,	ed to	each
Do you have home aid? Yes	-		work place, or organisation)?		
Private	5		Strong sense of belonging	2	
Do you receive home nursing care?			Not sureLittle or no sense of belonging	<b>3</b> 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 generally feel with growing old?
1-2 times a month	Good334 🔲 1
Approximately once a week 3	Quite good
More than once a week 🖵 4	Up and down
FOOD HARITO	Bad 🖵 4
FOOD HABITS	What is your view of the future?
Num	
How many meals a day do you normally eat	Not too bad 2
(dinner and bread meals)?302	
How many times a week do you eat warm dinner?304	Dark
What kind of bread (bought or home-made) do you usually eat?	TO BE ANSWERED BY WOMEN ONLY
Tick one or two boxes. White Light Ordinary Coarse Cris	
Bread textured brown brown bre The bread type is most similar to:	au .
306 310	How old were you when you started
What kind of fat is normally used in <i>cooking</i>	menstruating?years
(not on the bread) in your home?	How old were you when you stopped menstruating?338years
Butter311	Journal of the four months of the four months and and four months and and four months and and four months are months
Hard margarine Soft margarine	PREGNANCY
Butter/margarine blend	
Oils315 🛄	How many children have you given birth to?340 Children
Milk of all types (glasses)	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.  Child Year of birth: Number of months breastfed:  1 342
Dinner with	
	ESTROGEN
	Do you use, or have you ever used estrogen:
- lean fish (e.g. cod)328 □ □ □	Now Previously Never
	Tablets or patches
	Cream or suppositories
	If you use estrogen, what brand do you currently use?
	5
J	4
Your comments:	

# Appendix 4a

Questionnaire 1 (<70 years), the 5<sup>th</sup> Tromsø Study 2001–02

Γ



# **Personal Invitation**

Don't write here	5.3 (Municipality)	(County)	(Country)			
9.3 (Business)		9.4 (Occupation)		14.7 (Mark)		

1. \	OUR OWN HEALTH	3.	OTHER COMPLAINTS				
1.1	What is your current state of health? (Tick one only)  Poor Not so good Good Very good  1 2 3 4	3.1	Below is a list of various problems. Have you experienced any of this during the last week (including today)?  (Tick once for each complaint)  No Little Pretty Very				
			complaint complaint much much				
1.2	Do you have, or have you had?:  Age first						
	Yes No	Т	Felt afraid or anxious				
	Asthma						
	Hay fever		Felt tense or upset				
	nay level		Tend to blame yourself				
	Chronic bronchitis/emphysema		Depressed, sad				
			Feeling of being useless, worthless				
	Diabetes		Feeling that everything is a struggle				
	Osteoporosis		Feeling of hopelessness with regard to the future 1 2 3 4				
	Fibromyalgia/chronic pain syndrome	4.	USE OF HEALTH SERVICES				
	Psychological problems for which you have sought help	4.1	How many times in the last 12 months have you been to/used: (Tick once for each line)  None 1-3 4 or times more				
	A heart attack		General practitioner (GP)				
			Medical officer at work				
	Angina pectoris (heart cramp)		Psychologist or psychiatrist				
	Cerebral stroke/brain haemorrhage		Other specialist (private or out-patient clinic)				
			Emergency GP (private or public)				
1.3	Have you noticed attacks of sudden changes in Yes No		Hospital admission				
	your pulse or heart rhythm in the last year? Yes No	Т	Home nursing care				
1.4	Do you get pain or discomfort in the chest when:  Walking up hills, stairs or walking fast on level ground?	'	Physiotherapist				
1.5	If you get such pain, do you usually:		Chiropractor				
	Stop? Slow down? Carry on at the same pace?		Dentist				
	1		Alternative practitioner				
1.6	If you stop, does the pain disappear within  10 minutes?	5.	CHILDHOOD/YOUTH AND AFFILIATION				
	Yes No	5.1	How long altogether have you lived in the county?				
1.7	Can such pain occur even if you are at rest?	011	(Put 0 if less than half a year)				
2. I	MUSCULAR AND SKELETAL COMPLAINTS	5.2	How long altogether have you lived in the municipality?				
2.1	Have you suffered from pain and/or stiffness in muscles and joints during the <u>last 4 weeks</u> ?  (Give duration only if you have had problems)  Duration		(Put 0 if less than half a year)  Where did you live most of the time before the age of 16?				
	(Give duration only if you have had problems)  No Some Severe Complaint comp	0.0	(Tick one option and specify)				
	Neck/shoulders		Same municipality └─1				
	Arms, hands		Another municipality in the county 2 Which one:				
	Upper part of your back		Another county in Norway 3 Which one:				
	Lumbar region		Outside Norway 4 Country::				
	Hips, legs, feet	5.4	Have you moved within the last five years?				
	Other places		No Yes, one time Yes, more than once				
	ı 2 3 ı 2 Age last time						
2.2	Have you ever had:  Yes No						
	Fracture in the wrist/forearm	6.	BODY WEIGHT				
	Hip fracture?	6.1	Estimate your body weight when you were 25 years old:				

7. F	FOOD AND BEVERAGES	8. 8	SMOKING
7.1	How often do you usually eat these foods?  (Tick once per line) Rarely 1-3 times 1-3 times 4-6 times 1-2 times 3 times or /never /month /week /week /day more /day	8.1	How many hours a day do you normally spend in smoke-filled rooms? Number of total hours
	Fruit, berries	8.2	Did any of the adults smoke at home while you were growing up?
	Cheese (all types)	8.3	Do you currently, or did you previously live together with a daily smoker after your 20th birthday?
	Boiled vegetables	8.4	Yes, now Yes, previously Neve Do you/did you smoke daily?
	Fresh vegetables/salad	8.5	If you smoke daily <u>now</u> , do you smoke: Yes No
7.2	trout, mackerel, herring) 1 2 3 4 5 6  What type of fat do you usually use? (Tick once per line)		Cigarettes?
	Don't Hard Soft/light use Butter margarine margarine Oils Other		Cigars/cigarillos?
	For cooking	0.0	A pipe?
7.3	1 2 3 4 5 6  Do you use the following dietary		If you previously smoked daily, how long is it since you quit?  Number of years
	supplements:  Cod liver oil, fish oil capsules	8.7	If you currently smoke, or have smoked previously:
	Vitamins and/or mineral supplements?		How many cigarettes do you or did you normally smoke per day?  Number of cigarettes
7.4	How much of the following do you usually drink? (Tick once per line)  Rarely 1-6 1 glass 2-3 4 glasses / day glasses or more		How old were you when you began daily smoking?  Age in years
	Full milk, full-fat curdled milk, /week /day /day yoghurt		How many years in all have you smoked daily?  Number of years
	curdled milk,low-fat yoghurt	9. E	EDUCATION AND WORK
	Extra semi-skimmed milk	9.1	How many years of education have you completed?  Number of years
	Juice		(Include all the years you have attended school or studied)
	Water U U U U U Mineral water (e.g. Farris,		Do you currently have paid work?  'es, full-time 1 Yes, part-time 2 No 3
	Ramløsa etc)  Cola-containing soft drink		Describe the activity at the workplace where
	Other soda/soft drink	3.3	you had paid work for the longest period in the last 12 months. (e.g. Accountancy firm, school, paediatric department, carpentry workshop, garage, bank, grocery store, etc.)
	Do you usually drink soft drink: with sugar ☐ 1 without sugar ☐ 2		Business:
7.6	(Put 0 for the types you don't drink daily)		If retired, enter the former business and occupation. Also applies to 9.4
	Filtered coffee	9.4	Which occupation/title have or had you at this workplace? (e.g. Secretary, teacher, industrial worker, nurse, carpenter, manager, salesman, driver, etc.)
	Boiled coffee/coarsely ground coffee for brewing		Occupation:
	Other type of coffee	9.5	In your main occupation, do you work as self-employed, as an employee or family member without regular salary?  Self-employed Employee Family member
		0.6	Do you believe that you are in danger of losing Yes No
7.7	Approximately how often have you during the last year consumed alcohol? (Do not count low-alcohol and alcohol-free beer)  Never Have not consumed A few times About 1 time consumed alcohol alcohol last year last year a month	9.0	your current work or income within the next two years?
	$\square_1$ $\square_2$ $\square_3$ $\square_4$	9.7	Do you receive any of the following benefits? Yes No
	2-3 times About1 time 2-3 times 4-7 times per month a week a week a week		Sickness benefit (are on sick leave)
	To those who have consumed the last year:		Old age pension, early retirement (AFP) or survivor pension
	When you drink alcohol, how many glasses or drinks do you normally drink?	T	Rehabilitation/reintegration benefit
7.9	Approximately how many times during the last year have you consumed alcohol equivalent to 5 glasses or drinks within 24 hours? Number of times		Disability pension (full or partial)
7.10	When you drink, do you normally drink: (Tick one or more)		Unemployment benefits during unemployment
	Beer Wine Spirits		Transition benefit for single parents

not applicable

Beyer Hecos

# Appendix 4b

Questionnaire 1 (≥70 years), the 5<sup>th</sup> Tromsø Study 2001–02



Health

# **Personal invitation**

Do not write here:				
E13 (Municipality)	(County)	(Country)	E15 (Mark)	

E1. YOUR OWN HEALIH	E3. COMPLAINTS
What is your current state of health? (Tick only once)  Poor Not so good Good Very good  1 2 3 4	Below is a list of various problems.  Have you experienced any of this during the last week (including today)?  (Tick once for each line)  No Little Pretty Complaint complaint much much
Do you have, or have you had?:  Age first time	Sudden fear without reason
Yes No	Felt afraid or anxious
Asthma	Faintness or dizziness
Chronic bronchitis/emphysema	Felt tense or upset
	Tend to blame yourself
Diabetes	Sleeping problems
Osteoporosis	Depressed, sad
Fibramy (alaia /abrania nain ayadrama	Feeling that everything is a struggle
Fibromyalgia/chronic pain syndrome	Feeling of hopelessness with regard
Psychological problems for which you have sought help	to the future.
A heart attack	E4. TEETH, MUSCLE AND SKELETON
Angina pectoris (heart cramp)	How many teeth have you lost/extracted? Number of teeth (disregard milk-teeth and wisdom teeth)
Cerebral stroke/brain haemorrhage	Have you been bothered by pain and/or stiffness in
Cerebral stroke/brain nacmonnage	muscles and joints during the <u>last 4 weeks?</u> No Little Severe
Do you get pain or discomfort in the chest when: Yes No	complaint complaint
Walking up hills, stairs, or walking fast on level ground?	Neck / shoulders
3 3 4 3, 2 3 3 3 3 3 3 3 3	Upper part of the back
If you get such pain, do you usually:	Lumbar regions
Stop? Slow down? Carry on at the same pace?	Hips, legs, feet
	Other places
If you stop, does the pain disappear within 10 minutes?	Utiler places
Can such pain occur even if you are at rest?	Have you ever had:
	Fracture in wrist/forearm?
E2. ILLNESS IN THE FAMILY	
Have one or more of your parents or siblings had: $ op$	Hip fracture?
A heart attack (heart wounds) or Yes No know angina pectoris (heart cramp)	Have you fallen down during the last year? (Tick once only)  No Yes, 1-2 times Yes, more than 2 times
Tick for the relatives who have or have had any of the illnesses: (Tick for each line)	E5. EXERCISE AND PHYSICAL ACTIVITY
Cerebral stroke or Mother Father Brother Sister Child of these	
brain haemorrhage U U U U U U U Heart attack	How has your physical activity been during this last year?  Think of a weekly average for the year.  Answer both questions.
before age of 60 years U U U U U	Hours per week
Asthma	None Less than 1 1-2 3 or more Light activity
Cancer	(not sweating/out of breath)
Diabetes	Hard physical activity (sweating/out of breath)
If any relatives have diabetes, at what age did they get diabetes (if for e.g. many siblings, consider the one who	1 2 3 4
got it earliest in life)  Brother's Sister's	E6. BODY WEIGHT
Don't know, Mother's age Father's age age Child's age not applicable	Estimate your body weight when you were 25 years old:

E7. EDUCATION	E9. SMOKING
How many years of education have you completed?  (include all the years you have attended school or studied)	How many hours a day do you normally spend in smoke-filled rooms?  Number of total hours  Yes No
E8. FOOD AND BEVERAGES	Did any of the adults smoke at home while you were growing up?
How often do you usually eat these foods? (Tick once for each line)  Rarely 1-3 times 1-3 times 4-6 times 1-2 times 3 times o /never /month /week /week /day more /day	,
Fruit, berries	Do you/did you smoke daily? Yes, now previously Never
Potatoes	If you have <u>NEVER</u> smoked daily; Go to question E11 (BODILY FUNCTIONS AND SAFETY)
Fresh vegetables/salad	If you smoke daily <u>now</u> , do you smoke:  Yes No
Fat fish (e.g. salmon, trout, mackerel, herring) 1 2 3 4 5 6	Cigarettes?
Do you use dietary supplements: Yes, daily Sometimes No	Cigars/cigarillos?
Cod liver oil, fish oil capsules U	If you previously smoked daily, how
How much of the following do you usually drink?	long is it since you quit?  Number of years
(Tick once for each line)  Rarely 1-6 1 glass 2-3 4 glasses glasses /day glasses or more	If you currently smoke, or have smoked previously:
milk, yoghurt	How many cigarettes do you or did you normally smoke per day? Number of cigarettes
curdled milk, low-fat yoghurt	How old were you when you began daily smoking?  Age in years
Extra semi-skimmed milk	
Juice	How many years in all have you smoked daily?  Number of years
Water U U U U U Soft drink, mineral water U U U U U U U U U U U U U U U U	E10. BODILY FUNCTIONS AND SAFETY
1 2 3 4 5	Would you feel safe by walking alone in the evening
How many cups of coffee and tea do you drink daily?  (Put 0 for the types you do not drink daily)  Number of cups	in the area where you live?  Yes A little unsafe Very unsafe
Filtered coffee	
Boiled coffee/coarsely ground coffee for brewing	When it comes to mobility, sight and hearing, can you: (Tick once for each line)  Without With some With great No
Other type of coffee	Take a 5 minute walk in fairly high pace? problems problems problems
Tea	Read ordinary text in newspaper, if necessary with glasses?
Approximately, how often have you during the last year consumed alcohol? (Do not count low-alcohol and alcohol-free beer)	Hear what is said in a normal conversation?
Never consumed alcohol alcohol alcohol last year last year About 1 time a month  2 -3 times About 1 time 2 -3 times 4-7 times	Do you because of chronic health problems have difficulties with: (Tick once for each line) No Some Great
per month a week a week a week	difficulties difficulties difficulties  Move around in your home?
	Get out of your home by yourself?
To those who have consumed the last year:  When you drink alcohol, how many glasses or drinks do you normally drink?  Number	Participate in organization or other leisure time activities?
Approximately how many times during the last year have you consumed alcohol equivalent to	Use public transport?
5 glasses or drinks within 24 hours? Number of times	Perform necessary daily shopping?

#### **USE OF HEALTH SERVICES** E14. **USE OF MEDICINES** With medicines, we mean drugs purchased at pharmacies. How many times in the last 12 months have you been to/used: Supplements and vitamins are not considered here 1-3 4 or (Tick once for each line) times more Do you use? previously. Never but not now used (Tick once for each line) A general practitioner (GP) ..... Т Blood pressure lowering drugs ..... Specialist (private or out-patient clinic) Cholesterol-lowering drugs ..... Emergency GP (private or public)..... Drugs for osteoporosis ..... Hospital admission ..... Insulin..... Home nursing care ..... Tablets for diabetes ..... Physiotherapist ..... How often have you during the last 4 weeks used the Chiropractor ..... following medicines? Not used Less Every week Municipal home care ..... (Tick once for each line) in the last than every but not Daily 4 weeks week daily Painkillers non-prescription...... Alternative practitioner ..... Painkillers on prescription ....... Sleeping pills..... Are you confident that you YES NO Don't know will receive health care and Tranquillizers ..... home assistance if you need it? Antidepressants ..... Other prescription medicines .... E12. **FAMILY AND FRIENDS** State the name of the medicines you are using now and the At home? $\square_1$ In an institution/shared apartment? $\square_2$ reason you are taking the medicines (disease or symptom): Do you live with: YES NO How long have you used the medicine (Tick for each duration you have used the medicine) Spouse/ partner?..... One year or more Name of the medicine: Reason for use of 1 year (one name per line): the medicine: Other people? ..... How many good friends do you have? Number of Count the ones you can talk confidentially with friends and who can give you help when you need it. Do not count people you live with, but do include your children and other relatives..... How much interest do people show for what you do? (Tick only once) Great Some Little Nο Uncertain interest interest interest interest ۵ لـــ 」₂ How many associations, sport clubs, If there is not enough space here, you may continue on a separate sheet that you attach. groups, religious communities, Number or similar do you take part in? E15. THE REST OF THE FORM IS TO (write 0 if none) **BE ANSWERED BY WOMEN ONLY** CHILDHOOD/YOUTH AND AFFILIATION How old were you when you Age in years started menstruating? 02.01 How long altogether have you lived in the county? vears How old were you when you Age in years stopped menstruating? Beyer-Hecos How long altogether have you lived in the municipality? vears How many children have you Number of given birth to? children Where did you live most of the time before the age of 16? (Tick one option and specify) Total number 050000-1043-1 - 9.000 Same municipality...... 1 Do you use, or have you ever used estrogen? of vears Never Previously Another municipality Tablets or patches ..... in the county...... \( \subseteq 2 \) Which one: Another county in Norway 3 Which one: Cream or suppositories ..... Outside Norway .......... 4 Country: If you use estrogen, which brand you use now? Have you moved during the last five years? Т No Yes, once Yes, more than once Yes No

Have you ever used contraceptives pills? .....

# Appendix 4c

Questionnaire 2, the 5<sup>th</sup> Tromsø Study 2001–02

#### Additional questions to the health survey in Troms and Finnmark 2001-2002

The main aim of the Tromsø Study is to improve our knowledge about cardiovascular diseases in order to aid prevention. The study is also intended to improve our knowledge of cancer and other general conditions, such as allergies, muscle pains and mental conditions. We

wou fact and which Insp	and therefore like you to answer some questions about tors that may be relevant for your risk of getting these I other illnesses. This form is part of the Health Survey, ch has been approved by the Norwegian Data pectorate and the Regional Board of Research Ethics. It is answers will only be used for research purposes and be treated strictly confidential.
T1.	NEIGHBORHOOD AND HOME
1.1	In which municipality did you live at the age of 1 year? (If you have not lived in Norway, state country of residence instead of the municipality)
1.2	What type of house do you live in? (Tick only once)
	Detached house/villa
1.3	How big is your house? $m^2$ (gross)
1.4	Are you bothered by: (Tick once for each line)  No Little Severe complaint complain complain
	Moisture, drought or coldness in your home  Other forms of bad indoor climate
1.5	What home language did your grandparents have? (Tick for one or more alternatives)
	Norwegian Sami Kven/ Other language  Mother's mother

All pollution from wood/oil fleating, factory etc.					
What home language d (Tick for one or more alto		dparents l	nave?		
Norwegia	an Sami	Kven/ Finnish	Other language		
Mother's mother					
Mother's father					
Father's mother					
Father's father					

The information you give us may later be linked with information from other public health registers in accordance with the rules laid down by the Data Inspectorate and the Regional Board of Research Ethics.

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

The completed form should be sent to us in the enclosed prepaid envelope. Thank you in advance for helping us.

	Yours sincerely	
	partment of Community Medicine versity of Tromsø	National Health Screening Service
	ou do not wish to answer the questionr ow and return the form. Then you will r	
l do	not wish to answer the questionnair	е 🗌
Date	of completion:	
Da		Т
T1.	NEIGHBORHOOD AND HOME	E (cont.)
1.6	What do you consider yourself as? (Tick for one or more alternatives)  Norwegian Sami Kven/Finnish	Other
1.7	Do you feel that you have enough good friends?	Yes No
1.8	How often do you normally take part gatherings, e.g. sewing circles, spor political meetings or other association ( <i>Tick only once</i> )	ts clubs,
	Never, or just a few times a year	
T2.	PAID AND UNPAID WORK	
2.1	If you have paid or unpaid work, how describe your work? (Tick only once) Mostly sedentary work?	v would you
	(e.g. office work, mounting)	1
	Work that requires a lot of walking? (e.g. shop assistant, light industrial work	, teaching) $\square$ 2
	Work that requires a lot of walking and (e.g. Postman, nursing, construction)	lifting?
	Heavy manual labour? (e.g. forestry, heavy farm-work, heavy construction)	4
2.2	Can you decide <u>yourself</u> how your w or unpaid) should be organised? (Ti	ork (paid ck only once)
	No, not at all	
	To a small extent	2
	Yes, to a large extent	
	Yes, I decide myself	4
2.3	Are you on call, do you work shifts or nights?	Yes No

T3.	TOBACCO	T7. ILLNESSES AND INJURIES
3.1	Yes, daily Yes, sometimes No, never	7.1 Have you ever had:  Tick once for each question. Also give the age at the time. If you have had the condition several times how old were you the last time.  Age last
	If "Yes, sometimes" What do you smoke?	Several times, how old were you the last time  Severe injury requiring  hospital admission
	☐ Cigarettes ☐ Pipe ☐ Cigar/cigarillos	
3.2	Have you used or do you use snuff daily?	Ankle fractureyea
	Yes, now Yes, previously Never	Peptic ulceryea
	If YES: How many years altogether have you	Peptic ulcer surgery yea
T4.	used snuff? years  ALCOHOL	Neck surgery gyea
	Are you a teetotaller?	Prostate surgery gea
		7.2 Do you have, or have you ever had:
4.2	normally drink alcohol?	(Tick once for each question)  Cancer
	Put 0 if less than once a month)	Psoriasis
4.3	How many glasses of beer, wine or spirits do you normally drink in a fortnight?	Thyroid disease
	Beer Wine Spirits	Glaucoma
	(Do not count low-alcohol beer. Put 0 if you do not drink alcohol)	Cataract
4.4	For approximately how many years	Osteoarthritis (arthrosis)
	has your alcohol consumption been at the same level you described above?	Bent fingers
	•	Skin contractions in your palms
4.5	Have you, in one or more periods in the last 5 years consumed so much alcohol that it has	Kidney stone
	inhibited your work or social life?  Yes, Yes, both No,	Hernia surgery
	at work socially at work and never social life	Surgery/treatment for urine incontinence
		Epilepsy
T5.	FOOD AND DIETARY SUPPLEMENTS	Poliomyelitis (polio)
5.1	Pes No Do you usually eat breakfast every day?	Parkinson's disease
5.2	How many times a week do you	Migraine
0.2	eat a warm dinner? times	Leg ulcer
5.3	How important is it for you to have a healthy diet?	Allergy and hypersensitivity: Yes No
	Very Somewhat Little Not	Atopic eczema (e.g. childhood eczema)
5.4	Do you use the following dietary supplements?	Hand eczema
	Yes, daily sometimes No	_ Food allergy U
	Iron tablets	Other hypersensitivity (not allergy)
	Vitamin D supplements	7.3 Have you had common cold, influenza, gastroenteritis, etc. during the last 14 days?
T6.		7.4 Have you during the last 3 weeks had common cold, influenza, bronchitis, pneumonia, sinusitis, or other respiratory
6.1		infection?
0.1	body weight?  Yes, I try to No  Sain weight  Yes, I try to lose weight	7.5 Have you ever had bronchitis or pneumonia?
	1 2 3	7.6 Have you during the last 2 years had bronchitis or pneumonia? (Tick only once)
6.2	What weight would you be satisfied with (your "ideal weight")?kg	No 1-2 times More than 2 times $\square_1$

T8.	SYMPTOMS		T8. SYMPTOMS (continue)
8.1	Have you in the last two weeks felt: (Tick once for each question)  No A Little A lo	Ver ot mud	8.8 How often do you suffer from sleeplessness? (Tick only once)
	Nervous or worried		Never, or just a few times a year
	Bothered by anxiety		1-3 times a month
	Confident and calm		Approximately once a week
			More than once a week4
	Irritable		8.9 If you suffer from sleeplessness monthly or more
	Happy and optimistic		frequently, what time of the year does it affect you most?
	Down/depressed		No particular time of the year
	Lonely 1 2 3	4	Especially during the polar night 2
			$\top$ Especially during the midnight sun season $\square$ 3
8.2	Do you cough about daily for periods of the year?	Yes No	Especially in spring and autumn 4
	If YES:		8.10 Have you in the last year suffered from sleeplessness to the extend that it has
	Is your cough productive?		affected your ability to work?
	Have you had this kind of cough for as long		8.11 Do you usually sleep during the day?
	as 3 months in each of the last two years?		8.12 How often do you suffer from urinary incontinence?
8.3	Have you had episodes with wheezing in the chest?		Never 1
	If YES:		Not more than once a month 2
	,	Yes No	
	At night		Once a week or more 4
	In connection with respiratory infections		
	In connection with physical exertion		8.13 Are you able to walk down 10 steps without
	In connection with very cold weather		holding on to something (e.g. a handrail)
	,	Yes No	8.14 Do you use glasses?
8.4	Do you get pain in the calf while walking		8.15 Do you use a hearing aid?
	If YES:		8.16 How is your memory?
	How long can you go before you notice the pain?	meter	(Tick once for each question)  Do you forget what you just have  Yes No
8.5	Do you get short-winded in the following situation	ons?	Do you forget what you just have Yes No heard or read?
	(Tick once for each question)		Do you forget where you have placed things?
	While walking fast on level ground or slight up hills	Yes No	is it more difficult to refriettiber flow that realiters
	While walking calmly on		Do you more often write memos now than earlier?
	level ground		If "YES" on one of these questions;
	While washing or dressing yourself		Is this a problem in your daily life? $\square$
	While resting		
8.6	Do you have to stop because of short-windedness	Yes No	T9. MEDICINES
	while walking in your own pace on level ground?		9.1 Do you use, or have you used any of
8.7	Have you during the last year suffered from		the following medicines:  Age when Previously, used 1st time Never
	pain and/or stiffness in muscles and joints that have lasted continuously for	Yes No	Now but not now used
	at least 3 months?		osteoporosis years
	If YES: Has the complaint reduced your leisure	Yes No	Tablets for diabetes
	time activity?		
	For how long has the complaint endured in total	?	Drugs for hypothyroidism (thyroxine) years
			(tilyroxino)yearo =
	approx. years and months		9.2 Do you use any medicines which you take Yes No
	Has the complaint reduced your ability to work during	9	9.2 Do you use any medicines which you take as injections?
	the last year? (Also applies to domestic workers and pensioners (Tick once)		If YES:
	. ,	s4 le∞ =:	Give the name of the medicines (for injection):  (one name per line)
	No/insignificantly To some extend Significantly reduced Do no	ot know 4	(
		Do	not
	Have you been on sick leave due to these Yes complaints during the last year?	10 W	ork 

T12.THE REST IS TO BE ANSWERED BY WOMEN ONLY

T10. ILLNESS IN THE FAMILY

6th child

(If more children, use additional sheet)

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# Appendix 5a

Questionnaire 1, the 6<sup>th</sup> Tromsø Study 2007–08



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 wee (including today)? (Tick once for each complaint)  No Little Pretty Very
	☐ Very good	complaint complaint much
	Good	Sudden fear without reason $\square$ $\square$ $\square$
	☐ Neither good nor bad	You felt afraid or
	☐ Bad	worried
	□ Very bad +	Faintness or dizziness
	•	upset
7	How is your health compared to others in your age?	Easily blamed yourself
	☐ Much better	Sleeping problems
	☐ A little better	Depressed, sad
	☐ About the same	You felt useless,
	☐ A little worse	worthless
	☐ Much worse	Feeling that life is a struggle $\square$ $\square$ $\square$
2	Age first  Do you have, or have you had?  Yes No time	Feeling of hopelessness with regard to the future
J	Heart attack	_
	Angina pectoris	USE OF HEALTH SERVICES
	Stroke/brain hemorrhage	Have you during the past year visited:
	Atrial fibrillation	If YES; how many times?  Yes No No. of times
	High blood pressure	General practitioner (GP)
	Osteoporosis	Psychiatrist/psychologist
	Asthma	Medical specialist outside hospital
	Chronic bronchitis/Emphysyma/COPD	(other than general practitioner/psychiatrist)
	Diabetes mellitus	Physiotherapist
	Psychological problems (for which you	Chiropractor
	have sought help )	(homeopath, acupuncturist, foot zone therapist,
		herbal medical practitioner, laying on hands  practitioner, healer, clairvoyant, etc.)
	Kidney disease, not including urinary tract infection (UTI)	Dentist/dental service
	Migraine	Have you during the last 12 months been to
4	Do you have persistent or constantly recurring pain that has lasted for 3 months or more?	a hospital? Yes No No. of times
	Yes No	Admitted to a hospital
_		Had consultation in a hospital without admission;
5	How often have you suffered from sleeplessness during the last 12 months?	At psychiatric out-patient clinic 🗌 🔲 💹
	$\square$ Never, or just a few times	At another out-patient clinic $\Box$ $\Box$ $\Box$ $\Box$
	1-3 times a month	Have you undergone any surgery during the last 3 years?
	Approximately once a week	☐ Yes ☐ No
	☐ More that once a week	+

#### **FAMILY AND FRIENDS USE OF MEDICINE** Do you take, or have you taken some of the Who do you live with? (Tick for each question and give the number) following medications? (Tick once for each line) ¥ Yes No Number Age Never first Spouse/cohabitant ...... used Now Earlier time Other persons older than 18 years.. $\square$ 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 ...... П Angina pectoris ...... 🗀 Tablets for diabetes ...... Stroke/brain haemorrhage ........ П 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 ...... Diabetes mellitus ..... Not used Less than Every the last every week, but Dementia ...... 4 weeks week Daily not daily Psychological problems ...... $\square$ 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 ...... Yes Tranquillizers ..... Do you have enough friends whom you can talk confidentially with? Antidepressants .. □ ☐ Yes How often do you normally take part in 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 Full time work Housekeeping asked whether you have used antibiotics or 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

20	<ul> <li>Old-age, early retirement or survivor pension</li> <li>Sickness benefit (are in a sick leave)</li> <li>Rehabilitation benefit</li> <li>Full disability pension</li> </ul>		How hard do you exercise on average?  Easy- do not become short-winded or sweaty  You become short-winded and sweaty  Hard- you become exhausted  For how long time do you exercise every time on average?  Less than 15 minutes
21	What was the households total taxable income last		
	year? Include income from work, social benefits and similar  ☐ Less than 125 000 NOK ☐ 401 000-550 000 NOK ☐ 125 000-200 000 NOK ☐ 551 000-700 000 NOK ☐ 201 000-300 000 NOK ☐ 701 000 -850 000 NOK ☐ 301 000-400 000 NOK ☐ More than 850 000 NOK	28	How often do you drink alcohol?  Never  Monthly or more infrequently  2-4 times a month  2-3 times a week  4 or more times a week
22	Do you work outdoors at least 25% of the time, or in cold buildings (e.g. storehouse/industry	29	( , , 3
	buildings)?		a drink) do you usually drink when you drink alcohol?  1-2  5-6  10 or more
	☐ Yes ☐ No		□ 3-4 □ 7-9
23	PHYSICAL ACTIVITY  If you have paid or unpaid work, which statement describes your work best?	30	How often do you drink 6 units of alcohol or more in one occasion?
	☐ Mostly sedentary work		Less frequently than monthly
	(e.g. office work, mounting)		☐ Monthly
	☐ Work that requires a lot of walking		☐ Weekly
	<ul><li>(e.g. shop assistant, light industrial work, teaching)</li><li>Work that requires a lot of walking and lifting</li></ul>		☐ Daily or almost daily
	(e.g. postman, nursing, construction)	31	Do you smoke sometimes, but not daily?
	☐ Heavy manual labour		☐ Yes ☐ No
24	example between summer and winter, then give an average. The question refers only to the last vear. (Tick the one that fits best)		Do you/did you smoke daily?  Yes, Yes, Never previously  If you previously smoked daily, how long is it
	☐ Reading, watching TV, or other sedentary activity.		since you stopped?  Number of
	☐ Walking, cycling, or other forms of exercise		years
	at least 4 hours a Week (here including walking or cycling to place of work, Sunday-walking, etc.)	34	If you currently smoke, or have smoked before: How many cigarettes do you or did you usually
	☐ Participation in recreational sports, heavy gardening,		smoke per day?
	etc. (note:duration of activity at least 4 hours a week)  Participation in hard training or sports		Number of cigarettes
	competitions regularly several times a week	35	How old were you when you began smoking daily?
25	How often do you exercise? (With exercise we mean for example walking, skiing, swimming or		Number of years
		36	How many years in all have you smoked daily?
	Never		Number of
	Less than once a week	27	years  Do you use or have you used snuff or chewing tobacco?
	Once a week	3/	
	2-3 times a week		□ No, never □ Yes, sometimes □ Yes, previously □ Yes daily
	Approximately every day		$\square$ Yes, previously $\square$ Yes, daily $+$

	DIET		QUESTONS FOR WOMEN
38	Do you usually eat breakfast every day?	46	Are you currently pregnant?
	☐ Yes ☐ No		☐ Yes ☐ No ☐ Uncertain
		47	How many children have you given birth to?
39	How many units of fruits or vegetables do you eat on average per day? (units means for example a fruit, a cup of juice, potatoes, vegetables)	7/	Number
	Number of units	48	If you have given birth, fill in for each child: 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?		Months of 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		3
	times/ times/ times/ times/ times mth mth week week day	/	4
	Potatoes		5
	Pasta/rice		6
	Processed meat	49	
	(sausages/meatloaf/meatballs)		pressure?
	Fruits, vegetables, berries		☐ Yes ☐ No
	Fat 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?	51	During pregnancy, have you had proteinuria?
	(Tick once for each line)		☐ Yes ☐ No
	1-6 1 2-3 4 or more Rarely/ glasses glass glasses glasses		
	never /week /day /day /day	52	If yes, which pregnancy?
	Milk, curdled milk, yoghurt		☐ The first ☐ Second or later
	Juice	53	Were any of your children delivered prematurely
	Soft drinks with sugar		(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?
		5-7	1st child 2nd child 3rd child 4th child 5th child 6th child
	Number of cups		
	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")	56	Do you currently use any prescribed drug influencing the menstruation?
	$\square$ Rarely/never $\square$ 1-3 times/year $\square$ 4-6 times/y	ear	Oral contraceptives, hormonal IUD or similar Yes No
	$\square$ 7-12 times/year $\square$ More than 12 times/year		Hormone treatment for menopausal problems $\square$ Yes $\square$ No
45	Do you use the following supplements?		
+	Daily Sometimes N	0	When attending the survey centre you will get a questionnaire about menstruation and possible use
I	Cod liver oil or fish oil capsules		of hormones. Write down on a paper the names of all the hormones you have used and bring the paper
	Omega 3 capsules (fish oil, seal oil)		with you. You will also be asked whether your menstruation have ceased and possibly when and
	Vitamins and/or mineral supplements $\square$		why.

# Appendix 5b

Questionnaire 2, the 6<sup>th</sup> Tromsø Study 2007–08

### 1. DESCRIPTION OF YOUR HEALTH STATUS

Mark the statement that best fits your state of health today by ticking once in one of the boxes under each of the five groups below:

To allow you to show us how good or bad your state of health is we have made a scale (almost like a thermometer) where the best state of health you can imagine is marked 100 and the worst 0. We ask you to show your state of health by drawing a line from the box below to the point on the scale that best fits your state of health.

Mobility		Best imaginable
I have no problems in walking		health state $\pm$ 100
about		± 100
I have little problems in walking about		‡
I am confined to bed		± 90
		#
I.02 Self-care		‡
☐ I have no problems with self-care		<b>‡</b> 80
☐ I have some problems washing or		<u> </u>
dressing myself		‡
I am unable to wash or dress myself		<del>+</del> 70
		<u> </u>
		‡
Usual activities (e.g. work, study, housework,		<del>+</del> 60
family or leisure activities)		‡
$\square$ I have no problems with performing my	Your own health	<b>‡</b>
usual activities	state today	<del>+</del> 50
I have some problems with performing my usual activities		<del>-</del>
I am unable to perform my usual		‡
activities		± 40
		‡
LO4 Pain and discomfort		₹ 30
I have no pain or discomfort		± 30
I have moderate pain or discomfort		‡
I have extreme pain or discomfort		± 20
Thave extreme pain of disconnoic		‡
		Ŧ
Anxiety and depression		<del>‡</del> 10
I am not anxious or depressed		<u> </u>
I am moderately anxious or depressed		‡
I am extremely anxious or depressed		<sup></sup> 0
		Best imaginable health state
		ilcattii state

3

## 2. CHILDHOOD/YOUTH AND AFFILIATION

☐ In Finnmark ☐ In Nordland ☐ Kven/F	thnicity	,	
•	y siblings a /have you		n do
situation during your childhood?			
<ul><li>✓ Very good</li><li>✓ Good</li><li>Number of</li></ul>	f children		
☐ Difficult ☐ Very difficult ☐ Yes	other alive		
If NO: her 2.03 What is the importance of religion	age when	she died	
☐ Very important ☐ Yes	ther alive?		
Somewhat important  Not important  If NO: his a	age when h	ne died	
2.07 What was/is the highest completed education for your pare (Tick once for each column)	ents and yo Mother	our spouse/o	Spouse/
Primary 7-10 years, 1-2 years secondary school Vocational school			cohabitant
High secondary school (A level)			
College or university (4 years or more)			

## 3. WELL BEING AND LIVING CONDITIONS

st	atements about	tatements about views on your o nents by ticking	wn health.	Show I	how	you	agr	ee o	r di	sagre	ee w	rith
	ick once for each	, .	Co	mpletel Iisagree	y	2	3	4	5	6		Completely agree
In	most ways my lif	e is close to my	ideal									
Му	life conditions a	re excellent										
l a	m satisfied with	my life										
I h	ave a positive vi	ew of my future	health									
Ву	living healthy, I	can prevent seri	ous disease	S								
		atements concer last job you had			-				or i	f you	ı are	e not
				mpletely isagree	, 1	2	2	4	5	4	_	Completely agree
Mv	work is tiring, pl	nysically or ment		•			3	4	5	6	7	agree
I ha	ave sufficient inf	luence on when a	and how									
l ar	n being bullied o	r harassed at wo airly at work	rk									
(i	-			_						ety		
	•	ong period expe	rienced an	y of the	e fol		_	(Ticl			mor	
fo	r each line)			N	lo		es, a chi	ld		es, adult	la	Yes, st year
Bee	n beaten, kicked a	threatened with	er types of vi	olence					[			
	•	ose family have u that it has cause										
lf y	ou have experie	nced anything of	the above,	how mu	uch	are y	you a	affec	ted	by t	hat ı	now?
	Not affected	Affected	to some ext	ent _	Af	fecte	ed to	a la	arge	exte	ent	

### 4. ILLNESS AND WORRIES

4.01 Have you during the <u>last month</u>	If you suffer from sleeplessness monthly or
experienced any illness or injury?	more often, what time of the year does it
☐ Yes ☐ No	affect you most? (Put one or more ticks)  No special time
If YES: have you during the same period?	•
(Tick once for each line)	☐ Polar night time
Yes No	Midnight sun time
Been to a general practitioner	Spring and autumn
Been to a medical specialist	4.06 Have you had difficulty sleeping during
Been to emergency department	the past couple of weeks?
Been admitted to a hospital	Not at all
Been to an alternative practitioner	No more than usual
(chiropractor, homeopath or similar) 🔲 📙	Rather more than usual
4.02 Have you noticed sudden changes in your	igsqcup Much more than usual
pulse or heart rythm in the <u>last year?</u>	4.07 Have you during the last two weeks felt
☐ Yes ☐ No	unhappy and depressed?
4.03 Do you become breathless in the following	☐ Not at all
situations? (tick once for each question)	No more than usual
V N-	Rather more than usual
When you walk rapidly on level res No ground or up a moderate slope	☐ Much more than usual
When you walk calmly on level	
ground	4.08 Have you during the last two weeks felt
While you are washing or dressing	unable to cope with your difficulties?  Not at all
At rest	No more than usual     □     Restricted the state of the stat
4.04 Do you cough about daily for some	Rather more than usual
periods of the year?	Much more than usual
☐ Yes ☐ No	(III Polow place answer a few questions
If YES: Is the cough usually productive?	4.09 Below, please answer a few questions about your memory: (tick once for each
☐ Yes ☐ No	question) Yes No
	Do you think that your memory has declined?
Have you had this kind of cough for as long	
as 3 months in each of the last two years?	Do you often forget where you
☐ Yes ☐ No	have placed your things?
	Do you have difficulties finding common words in a conversation?
4.05 How often do you suffer from sleeplessness?	Have you problems performing
(tick once)	daily tasks you used to master?
Never, or just a few times a year	
1-3 times a month	Have you been examined for memory problems?
Approximately once a week	• •
More than once a week	If YES to at least one of the first four questions
<del>_</del>	above: Is this a problem in your daily life?
	☐ Yes ☐ No
- 4	<del></del>

4.11 Have you during the last last year suffered	4.16 To which degree have you had the following
from pain and/or stiffness in muscles or	complaints during the last 12 months?
joints in your neck/shoulders lasting for	Never Little Much
at least 3 consecutive months?	Nausea
(tick once for each line)	Heartburn/regurgitation
No A little A lot	Diarrhoea
Neck, shoulder	Constipation
Arms, hands	Alternating diarrhoea
Upper part of the back	and constipation
The lumbar region	Bloated stomach
Hips, leg, feet	Abdominal pain
Other places	Fa
·	4.17 If you have had abdominal pain or
4.11 Have you suffered from pain and/or	discomfort during the last year: Yes No
stiffness in muscles or joints during	
the last 4 weeks	Was it located in your upper stomach?. U
No A little A lot	Were you bothered as often as once a
Neck, shoulder	week or more during the last 3 months?
Arms, hands	Became better after bowel movement?
Upper part of the back	Are the symptoms related to more frequent or rare bowel movements
The lumbar region	than normally?
	Are the symptoms related to more
Hips, leg, feet	loose or hard stool than normally?
Other places	Do the symptoms appear after a meal? $\square$
4.12 Have you ever had: Age	Ago
Yes No last time Fracture in the	4.18 <b>Have you ever had:</b> Age Yes No last time
wrist/underarm?	
	Stomach ulcer 🗀 🗀
Hip fracture?	Duodenal ulcer
4.13 Have you been diagnosed with arthrosis	
by a doctor?	Ulcer surgery 🗀 🗀 🗀
Yes No	4.19 For women: Have you ever had a
4.14 Do you have or have you ever had some	miscarriage?
of the following:	☐ Yes ☐ No ☐ Do not know
Never Little Much	If Yes: number of times
Nickel allergy	400
Pollen allergy	4.20 For men: Have your partner ever had
Other allergies $\Box$	a miscarriage?
4.15 Have you ever experienced infertility	Yes No Do not know
for more than 1 year?	If Yes: number of times
Yes No	
	4.21 Is your diet gluten-free?
If Yes: was it due to:  Do not	Yes No Do not know
Yes No know A condition concerning you?	4.22 Have you been diagnosed with
A condition concerning your	Dermatitis Herpetiformis (DH)?
partner?	Yes No Do not know
+	

Have you been diagnosed with spelies	<del>-</del>						
4.23 Have you been diagnosed with coeliac disease, based on a biopsy from your	4.30 What is the intensity of your headache?						
intestine taken in an endoscopy	Mild (do not hinder normal activity)						
examination?	Moderate (decrease normal activity)						
Yes No Do not know	Strong (block normal activity)						
4.24 <b>Do you have your natural teeth?</b> Yes No	What is the duration of the headache usually?  Less than 4 hours						
4.25 How many amalgam tooth fillings do	4 hours - 1 day						
you have/have you had?	1-3 days						
0 1-5 6-10 10+	☐ More than 3 days						
4.26 Have you been suffering from headache the last year?  Yes No	4.32 If you suffer from headache, when during the year does it affect you most? (tick one or more)  No special time						
If No: go to section 5, food habits	Polar night time						
What kind of headache are you suffering from?	<ul><li>Midnight sun time</li><li>Spring and/or Autumn</li></ul>						
☐ Migraine ☐ Other headache	4.33 Before or during the headache, do you						
4.28 How many days <u>per month</u> do you	have a transient: Yes No						
suffer from headache?	Visual disturbances? (flickering.						
Less than one day	blurred vision, flashes of light)						
1-6 days	Unilateral numbness in your face or hand?						
7-14 days	Deterioration by moderate physical						
More than 14 days	Activity?						
	Nausea and/or vomiting?						
4.29 <b>Is the headache usually:</b> (tick one for each line)	4.34 Describe how many days you have been						
Yes No	away from work or school during the						
Pounding/pulsatory pain	last month due to headache?  Number of days						
Pressing/tightening pain	Humber of days						

### 5. FOOD HABITS

5.01 How often do you usually eat	t the foll	lowing? (ti	ck once for	each line	1	
			0-1 times per month			More than 3 times per week
Fresh water fish (not farmed)			·			
Salt water fish (not farmed)						
Farmed fish (salmon, trout, char)						
Tuna fish (fresh or canned)						
Fish bread spread						
Mussels, shells						
The brown content in crabs						
Whale or seal meat						
Pluck (liver/kidney/heart) from						
Pluck (liver/kidney/heart) from	ptarmiga	ın/grouse				
$^{5.02}$ How many time during the y	ear do/c	lid you us	ually eat th	ne followin	g? (number	of times)
				In ad	ulthood In	childhood
Mølje (cod or pollack meat, li		•				
Gulls egg (Number of eggs per yea	r)					
Reindeer meat (Number of times	per year)					
Local mushroom and wild berrie	es (blueber		rries/cloudberi of times per y			
5.03 How many times per month canned (tinned) foods (from Number	metal b		Do you ta suppleme Yes, da	nts?	s and/or m	
5.05 How often do you eat?	Never	1-3 times per month		4-6 times 1	-2 times 3 per day	times per day or more
Davis also a late						
Dark chocolate						
Light chocolate/milk chocolate						
Chocolate cake						
Other sweets						
5.06 <b>If you eat chocolate, how m</b> Compared with the size of a lead of the much do you eat in relation to	Kvikk-Lur	-				describe how ore than 2
5.07 How often do you drink	Nover	1-3 times		4-6 times	1-2 times	3 times per
cocoa/hot chocolate?	Never	per month	per week	per week	per day	day or more

## 6. ALCOHOL

6.01 How often have you in the last year: Nev	Less than er monthly	Monthly	Weekly	almost daily				
Not been able to stop drinking alcohol when you have started?								
Failed to do what was normally expected of you because of drinking?								
yourself going after a heavy drinking session?								
Had feeling of guilt or remorse after drinking?								
Not been unable to remember what happened the night before because of your drinking?								
		\ Never	es, but not in the last year	_				
6.02 Have you or someone else been injured be Drinking?								
Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?								
7. WEI	GHT							
7. Have you involuntary lost weight during the last 6 months?	7.03 Are you sa weight?	atisfied w $\square$ N		ent body				
If Yes: how many kilograms?	7.04 What weig			fied with				
7.02 Estimate your body weight when you were 25 years old: Number of kilograms								
8. SOLV	ENTS							
How many hours per week, do you do the following leisure- or professional activities:  Automobile repair/paint, ceramic work, painting/solvents, hair dressing, glazier, electrician. (Put 0 if you do not engage in such leisure or professional activities)  Number of hours per week on average	1es							

## 9. USE OF HEALTH SERVICES

<ul> <li>Have you ever experienced that disease has been inadequately examined or treated, and that this had serious consequences?</li> <li>Yes, this has happened to me</li> <li>Yes, this has happened to a close relative (child, parents, spouse)</li> <li>No</li> </ul>	At the last visit to the general practitioner, did the doctor(s) speak to you in a way so you understand them? Answers to a scale from 0 to 10, where 0 = they were difficult to understand and 10 = they were always easy to understand  0 1 2 3 4 5 6 7 8 9 10
If Yes, where do you think the reason of the problem is? (tick once or more):  With a general practitioner  With an emergency medical doctor	How would you characterize the treatment or counselling, you got the last time you were with a doctor? Answer on a scale from 0 to 10, where 0 = very bad treatment, and 10 = very good treatment  0 1 2 3 4 5 6 7 8 9 10
With an alternative practitioner	Do you have during the last 12 months experienced that it has been difficult to be referred to special investigations (like X-ray or similar) or to specialized health service (private practising specialist or at hospital)?
9.02 Have you ever felt persuaded to accept an examination or treatment that you do not want?  Yes No	<ul><li>□ Not applicable</li><li>□ No problem</li><li>□ Some problems</li><li>□ Great problems</li></ul>
If Yes, do you think this has had unfortunate health-related consequences?  Yes No	Have you during the last 12 months experienced that it is difficult to be referred to physiotherapist, chiropractor or similar?
<ul> <li>Have you ever complained about a treatment you have got?</li> <li>Have never a reason for complaining</li> <li>Have considered complaining, but</li> </ul>	<ul><li>Not applicable</li><li>No problem</li><li>Some problems</li><li>Great problems</li></ul>
did not do that	All in all, have you experienced that it is difficult or simply to be referred to specialized health services?
<ul> <li>How long have you had your current general practitioner/other physician?</li> <li>Less than 6 months</li> <li>6 to 12 months</li> <li>12 to 24 months</li> <li>More than 2 years</li> </ul>	Not applicable Very difficult Somehow difficult Reasonably easy Very easy

### 10. USE OF ANTIBIOTICS

form of tablets, syrups or injections)	months? (all penicillin-like medicine in the
☐ Yes ☐ No ☐ Do not remember	er
If YES: What did you get the treatment for? Have you taken many antibiotic treatments, Tr tick for each treatment.	reatment Treatment Treatment Treatment Treatment 1 2 3 4 5 6
<ul> <li>Urinary tract infection (bladder infection, cystitis)</li> </ul>	s)
<ul> <li>Respiratory tract infection (ear, sinus, throat or lung infection, bronchitis)</li> <li>Other</li> </ul>	
Treatment duration: number of days	
How did you acquire the antibiotics for treatme Have you acquired many treatments, tick for ea	
Yes No  If YES:is this after an agreement with your doctor for treatment of chronic or frequently recurring disease?  Yes No  If No: how did you acquire this antibiotic? (Multiple ticks are possible)	Would you consider using antibiotics without consulting your doctor?  Yes No  If YES: which conditions would you treat in such situation? (multiple ticks are possible) Common cold
Purchased from a pharmacy abroad  Purchased over the internet	Sinusitis

#### 11. YOUR CIRCADIAN RHYTHM

We will ask you some questions about your sleeping habits Have you worked in a shift work schedule during the last 3 months? Yes No Number of days per week which you cannot freely choose when you sleep (e.g. work days)? Then I go to bed at ..... I get ready to fall asleep at ..... Number of minutes I need to fall asleep I wake up at With help of: Alarm clock External stimulus (noise, family members etc.) By myself Number of minutes I need to get up Number of days per week which you can freely choose when you sleep (e.g. free days or holidays) Then I go to bed at ..... I get ready to fall asleep at ..... Number of minutes I need to fall asleep I wake up at ..... With help of: Alarm clock External stimulus (noise, family members etc.) By myself

Number of minutes I need to get up .....

### 12. SKIN AND DERMATOLOGY

IZ.II How often do you usually take a shower or a bath? (tick once)	12.05 Have you often or always any of the following complaints? (tick once for each line
2 or more times daily	Swelling in the ankles or legs, Yes No
$\square$ 1 time daily	particularly in the evenings
4-6 times per week	Varicose veins
2-3 times per week	Eczema (red, itchy rash) on
Once a week	your legs
Less than once a week	Leg pain when you walk, but is relieved when you stand still
12.02 How often do you during a day usually	19 29 Have a series had the Calley Con d'annuar
wash your hands with soap? (tick once)	Have you ever had the following diagnoses by a physician? (tick once for each line)
0 times	Yes No
1-5 times	Psoriasis
6-10 times	Atopic eczema
11-20 times	Rosacea
☐ More than 20 times	12.07 Have you recurring large acne/abscesses
Have you ever taken any antibiotics (penicillin and similar medicines) because of a skin disease, for example infected eczema, acne, non-healing leg	that are tender/painful and often form scars in the following places? (tick once for each line)  Yes No
ulcers, recurrent abscess?	Armpits
☐ Yes ☐ No	Under the breasts
If Van Haw many times in average and account	Stomach groove/the navel
If Yes: How many times in average per year you take antibiotics during the period you w	A 1.1
most affected (tick once)	Around the anus
☐ 1-2 ☐ 3-4 ☐ More than 4 times	The groin
Have you or have you ever had the follow skin disorders? (tick once for each line)  Yes No	because of abscesses?
Atopic eczema (children's eczema)	If Yes, did you get any of the following
Recurrent hand eczema	treatments? (tick once for each line)
Recurrent pimples/spots for	Yes No
several months	Antibiotic ointment
Leg or foot ulcer that did not heal	Antibiotic tablets
for 3-4 weeks L	Surgical drainage
If Yes for the question on leg and/or foot ulcer, do you have the ulcer today?	A larger surgical intervention including skin removal
Yes No	Surgical laser treatment