Age-related macular degeneration: Prevalence and risk factors – a cross-sectional study

The Tromsø Study 2007/2008

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Prevalence and risk factors - a cross-sectional study
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Tromsø, October 2012
Maja Gran Erke
LIST OF PAPERS

This thesis is based on the work described in following papers:


ABBREVIATIONS

AMD  Age-related macular degeneration
BMI  Body mass index
CI   Confidence interval
CVD  Cardiovascular disease
CZM  Carl Zeiss Meditec
GA   Geographic atrophy
HbA$_{1c}$ Glycosylated haemoglobin A$_{1c}$
HDL  High density lipoprotein
LDL  Low density lipoprotein
nvAMD Neovascular AMD
OHT  Oral hormone treatment
OR   Odds ratio
SD   Standard deviation
VEGF Vascular endothelial growth factor
SUMMARY

Age-related macular degeneration (AMD) is an important cause of visual impairment and blindness worldwide. The number of people affected by the disease is expected to rise due to increasing longevity. Development of adequate eye care for these patients should be based on knowledge about the prevalence of AMD. Further, preventive measures are the best strategy for any disease. The aims of this thesis were to estimate the prevalence of AMD and examine risk factors associated with AMD.

We described prevalence rates of AMD among Caucasian elderly participants from the Tromsø Eye Study, a population-based study in Norway. The overall prevalence of late AMD was 3.5 % among the participants aged 65-87 years old. Neovascular AMD outnumbered geographic atrophy. Symmetry between eyes was relatively low. Prevalence increased strongly with age. No significant sex differences in prevalence rates of AMD were observed. Refractive error was lower in eyes with late AMD than in eyes without late AMD.

We then analysed relationships between traditional cardiovascular risk factors and AMD. Daily smoking was a strong predictor for the presence of late AMD. We found a significant interaction between age and sex for late AMD, suggesting that age may be a stronger risk factor for late AMD in women than in men. Higher systolic blood pressure, higher pulse pressure, infrequent physical exercise and overweight or obesity were in adjusted analyses associated with late AMD in females, but this was not observed in men.

Based on our observation of sex and AMD, we studied associations between female hormone related factors and AMD. We found a significant inverse relationship between duration of lactation and late
AMD. No significant relationships were found between late AMD and exogenous oestrogen exposure in the form of contraceptives or hormone therapy. Nor did we find an association between late AMD and onset, end or length of fertile years, bilateral oophorectomy or parity as surrogate measures.
1. INTRODUCTION

1.1 Background

Age-related macular degeneration (AMD) can lead to severe visual impairment and blindness. As the name implies, the disease affects elderly. Macula, the central retina in the back of the eye, is responsible for our sharp-sightedness. The macula undergoes destructive and irreversible changes throughout the course of the disease that endangers visual acuity. Early AMD consist of retinal or subretinal drusen (yellow-white spots) and/or retinal pigment abnormalities. Early AMD has been shown to increase the risk of developing late AMD. Late or end-stage AMD is divided into neovascular AMD (nvAMD), also called wet or exudative AMD, and geographic atrophy (GA). Confusingly, both early AMD and GA are called dry AMD even though the clinical difference is considerable. Examples of drusen and late AMD are presented below on photographs taken from Tromsø Eye Study (Figure 1-3).

Figure 1. Fundus photograph; numerous drusen of different sizes.
Patients with early AMD do not necessarily experience visual loss. When GA develops there is no visual function in the affected area due to permanent loss of photoreceptors and retinal pigment epithelium. Wet AMD is a result of neovascularisation within or beneath the retina with leakage of fluid and/or blood in the macula. Without treatment, the eye will rapidly deteriorate due to retinal destruction and eventually scarring.
Preventive measures have been to advise cessation of smoking and anti-oxidant supplementation for those at high risk of developing late stage disease. Currently, treatment is only available for wet AMD. It consists mainly of inhibitors of vascular endothelial growth factor (VEGF) injected into the eye at intervals of usually 1-3 months. Although not curative, it has since its debut in the mid-2000 revolutionised the treatment of wet AMD. This has also imposed a considerable economic and logistic burden on the health care system due to high numbers of patients needing repeated intravitreal injections. According to numbers reported by the Norwegian Ophthalmological Association more than 30 000 injections were given in Norway in 2010 [1].

1.2 Epidemiology of AMD

AMD has been identified as the leading cause of blindness in the developed part of the world and ranks as the third leading cause globally [2]. Previous population-based surveys on AMD which have used standardised classification protocols based on fundus photography have reported varying prevalence. The Beaver Dam Eye Study [3-5] from USA found late AMD in 7.7 % in their cohort aged 75-86 years old. The Blue Mountains Eye Study [6-8] found a lower prevalence of 5.7 %. In Europe results from two larger surveys have been published. The Rotterdam Study [9-11] reported a prevalence of 3.7 % in people aged 75-84 years old. The European Eye Study [12] is a multicentre survey including participants 65 years and older from 7 European countries. A few other surveys have been conducted in North Europe and in the Arctic population (Copenhagen [13, 14], Reykjavik [15-17], Greenland [18, 19]. High prevalence of late AMD was reported among Inuit on Greenland aged ≥60 years of 9.5 % [18]. The prevalence of AMD has previously been described in Norway
only in a small study from Oslo [20] and as part of the multinational European Eye Study [12].

Table 1. Prevalence of AMD among elderly, selected population-based studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence by age groups</th>
<th>Prevalence, overall</th>
<th>Differing age groups:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>65-74 years</td>
<td>75-86 years</td>
<td>Late AMD</td>
</tr>
<tr>
<td>Tromsø [21]</td>
<td>1.4</td>
<td>7.7</td>
<td>3.50</td>
</tr>
<tr>
<td>Beaver Dam [3]</td>
<td>1.4</td>
<td>7.1</td>
<td>-</td>
</tr>
<tr>
<td>Blue Mountains [6]</td>
<td>0.7</td>
<td>5.7</td>
<td>-</td>
</tr>
<tr>
<td>Rotterdam [11]</td>
<td>0.8</td>
<td>3.7</td>
<td>-</td>
</tr>
<tr>
<td>European Eye Study* [12]</td>
<td>-</td>
<td>-</td>
<td>≥65 years</td>
</tr>
<tr>
<td>Oslo [20]</td>
<td>-</td>
<td>-</td>
<td>61-90 years</td>
</tr>
<tr>
<td>Reykjavik/ AGES [16]</td>
<td>-</td>
<td>-</td>
<td>≥66 years</td>
</tr>
<tr>
<td>Greenland [18]</td>
<td>-</td>
<td>-</td>
<td>≥60 years</td>
</tr>
</tbody>
</table>

AMD: age-related macular degeneration
Numbers are percentages if not otherwise labelled.
*Only participants from the Norwegian sub-study included

1.3 Risk factors for AMD

Evidence so far suggests that AMD is a multi-factorial disease but the full aetiopathogenesis of AMD has not yet been unveiled. High age and smoking are consistently reported as strong risk factors for late AMD [22-27]. Further have family history, genetics and early AMD shown to be strong risk factors for developing late AMD [5, 9, 28-31]. Due to the similarities between drusen deposition and the development of atherosclerosis [32, 33], traditional cardiovascular risk factors have been suggested as risk factors also for AMD. Persons
with AMD are reported to have increased risk of stroke and coronary heart disease in some studies [34-36], but previous epidemiologic studies evaluating risk factors for cardiovascular disease and AMD have not yielded consistent relationships or strong associations [24]. The exception is the strong evidence for increasing age and smoking as factors common for both diseases [22, 24, 25]. There are some evidence for high blood pressure [37-39] and obesity [40, 41] as risk factors for AMD. Sex, dyslipidaemia, and diabetes have also been associated with AMD in some, but not all studies [22-25, 36, 38, 42-45]. Physical activity has shown a protective effect in a few studies [46, 47].

Some publications suggest sex differences in the epidemiology of AMD. A recent large meta-analysis found that women might have a slightly higher risk for neovascular AMD compared to men [22]. Reports have suggested female hormones may play a role in the epidemiology of AMD [24, 48]. Various surrogates have been used for exogenous and endogenous oestrogen exposure in both cross-sectional and longitudinal studies and the association with AMD has been inconsistent [24, 49, 50]. To our knowledge, studies have not addressed the effect of lactation on maternal AMD.

Lately, an increasing body of evidence has shown that genetic susceptibility seems to play a significant role in the development of AMD [24, 51]. Twin studies have estimated the genetic contribution on the genesis of AMD range between 46-71 % [52]. In other words, there is a considerable opportunity altering the prevalence of AMD through identification and management of modifiable risk factors.
2. OBJECTIVES

The aims of this thesis were:

- To describe the sex- and age-specific prevalence of AMD in elderly Caucasians, the symmetry of disease, vision and refraction in eyes with AMD.
- To examine associations between traditional cardiovascular risk factors and AMD.
- To examine associations between female hormone related factors and AMD in women.
3. MATERIAL AND METHODS

3.1 Tromsø, the Tromsø Study and the Tromsø Eye Study

Tromsø is a municipality in Troms County and the largest city of North Norway. It is situated at sea level at 69 degrees north with a Caucasian urban population of 70 000 inhabitants in the municipality (2011 Statistics Norway). Although located above the Arctic Circle, it has a sub-arctic climate due to the Gulf Stream, with middle temperature of 10-12 degrees Celsius in July and about zero in January. Tromsø has an extreme seasonal variation in daylight sun exposure. The polar night lasts for 2 months in the winter with no sun over the horizon, and the duration of the midnight sun period is 2 months in the summer.

The Tromsø Study is an investigator initiated population-based prospective study. The design includes repeated health surveys conducted between 1974 and 2008. The 6th survey consisted of two separate consecutive visits, an initial 1st visit where basic information was collected and a 2nd visit a few weeks later where special investigations were performed. Eye examination was one of the special investigations included in the 6th survey and laid the foundation for the Tromsø Eye Study, a sub-study of the 6th Tromsø Study. The present thesis is based on data from the Tromsø Eye Study conducted in 2007/2008. The methodology is described in paper I.

3.2 Study population

The eligible population for the Tromsø Study consisted of residents in the municipality of Tromsø based on the official population registry. Both whole birth cohorts and random samples from the population have been invited to participate in the Tromsø Study. Different sampling methods have been used and are described elsewhere in
In the 6th survey all residents aged 40-42 years and 60-87 years (n=12578), were invited to the 1st visit. An additional 10% random sample of individuals aged 30-39 years (n=1056), a 40% random sample of individuals aged 43-59 years (n= 5787), and subjects who had attended the 2nd visit of the 4th survey, if not already included in the three groups above (n=341) were invited. The participation rate in the 1st visit was 66%, with a total of 12984 subjects participating.

The eligible subjects for the 2nd visit were pre-selected and participation in the 1st visit was a prerequisite. The groups invited were; all subjects aged 50-62 years or aged 75-84 years (n=7657), a 20% random sample aged 63-74 years (n=942) and subjects, if not already included in the two groups above, who had attended the 2nd visit of the 4th survey (n=2885). The participation rate in the 2nd visit was 92%, with a total of 7307 subjects participating.

The participants in the 2nd visit were mainly Caucasians with 91% reporting Norwegian ethnicity and 1.5% reporting Sami ethnicity.

The study population which this thesis was based on included 3025 participants aged ≥65 years from the 2nd visit of the 6th Tromsø Study. In paper IV, only female participants were included (n=1743). A participation flowchart is presented in Figure 4.
3.3 Ethics

The 6th survey of the Tromsø Study and cross-sectional studies originating from it were approved by the Regional Committee for Medical and Health Research Ethics and the Data Inspectorate. The study followed the tenets of the Helsinki Declaration. All participants have given written informed consent.
3.4 Data acquisition

3.4.1 1st visit: General part

*Questionnaires*

The invitation to participation included a questionnaire (Appendix A) addressing life style habits and extent of smoking and alcohol use, socioeconomic status, physical activity, health and diseases, and use of medication. Women were also asked questions relevant to female hormones, pregnancy and childbirth. A more extensive questionnaire (Appendix B) was given participants at the 1st visit.

*General examination and measurements*

All participants underwent a standardised medical examination comprising measuring height, weight, waist and hip circumference, heart rate and blood pressure. A non-fasting blood sample was collected.

*Cardiovascular risk factors*

Based on the self-reported questionnaires and physical examinations, we classified variables as follow: Persons living with their spouse or other persons >18 years were classified as cohabiting. Education was defined as highest completed level equivalent to primary school only or to higher education. Alcohol use was categorized after frequency of intake to 1) never 2) monthly or 3) weekly. A binary variable was in addition constructed for an approximate intake of more or less than one unit of alcohol daily (consumption 2-3 times a week and usually 3 units or more each time). To be physically active was defined as at least one hour weekly exercise and becoming sweaty or short-winded, or two days weekly with at least 1 hour each without becoming sweaty and short-winded. Four other binary variables were also constructed; 1) minimum activity 30 minutes when exercising versus less 2) the exercise makes the person sweaty/short-winded versus not 3)
exercises minimum weekly versus less and 4) practice hard training/sports competitions versus not. The use of lipid-lowering drugs was dichotomized as never used versus uses/has used. Waist-to-hip ratio was calculated as the waist circumference divided by the hip circumference. Blood pressure was recorded with a fully automatic device (Dinamap Vital Signs Monitor, Tampa, FL, USA). The average of the last two of three recordings was used for analysis. Pulse pressure was calculated as systolic minus diastolic blood pressure.

Blood samples were analyzed for glycosylated hemoglobin A1c (HbA1c) and serum lipids (total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides) by standard enzymatic methods at the Department of Clinical Chemistry, University Hospital of North Norway. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. BMI was handled as both continuous and categorized as underweight <20 kg/m², normal 20-24.9 kg/m², overweight 25.0-29.9 kg/m², and obese ≥30 kg/m². Diabetes was defined as non-fasting serum glucose ≥11.1 mmol/L or HbA1c >6.5 % or current use of insulin or anti-diabetic tablets. We defined cardiovascular disease as heart attack or stroke. The Tromsø Study runs a continuously updated and validated endpoint registry of cardiovascular events [54]. All first time cardiovascular events are recorded and confirmed by hospital records or the Cause of Death Registry of Norway. Data from this registry were linked to the study sample for identification and verification of subjects with cardiovascular disease. All other variables were used as they were recorded and stored in the Tromsø Study database (available at: http://tromsoundersokelsen.uit.no/tromso/).
Female hormone related factors

Data on number of children given birth to, age at first childbirth, duration of breastfeeding for each child, age at menarche, age at menopause, number of fertile years, reason for menopause, use of contraceptives and/or oral hormone therapy (OHT) were obtained from questionnaires. The variable “number of children” was handled with ≥6 children as maximum. Length of breastfeeding was defined as months of breastfeeding in total divided by number of children, and additional 4 dichotomized variables were constructed; 1) ever breastfed versus never breastfed, 2) breastfed all children minimum 3 months versus not, 3) breastfed all children minimum 4 months versus not and 4) breastfed all children minimum 6 months versus not. The reason for menopause was dichotomized as 1) natural (stopped by itself) versus not (hysterectomy, both ovaries removed, other reasons) and 2) had both ovaries removed versus not (stopped by itself, hysterectomy and other reasons). The use of hormones was dichotomized to 1) ever used contraceptives versus never used 2) ever used OHT versus never used and 3) ever used contraceptives and/or OHT versus never used. The remaining risk factors were used as continuous variables.

3.4.2 2nd visit: Special investigations

Interview

Subjects participating in the Tromsø Eye Study were interviewed in Norwegian whether they had or ever have had AMD, diabetic retinopathy, cataract, glaucoma or any other eye disease or eye surgery. The Norwegian common terms were also used.

Eye examinations

Detailed information on the eye examinations is described in paper I. Visual acuity was measured by Nidek AR 660A auto refractor (Nidek
Mydriasis was obtained by application of one drop Tropicamide 0.5 % (Chauvin Pharmaceuticals Ltd. Kingston upon Thames, Surrey, England) in both eyes after visual acuity measurements. Retinal photography was performed in both eyes with a Visucam PRONM (Carl Zeiss Meditec (CZM)) digital retinal camera 10-45 minutes after application of Tropicamide. Five field’s 45 degree colour retinal photographs with resolution 2196x1958 pixels were taken using the camera pre-set internal fixation. A sixth image, 30 degree (resolution 1620x1444 pixels) was taken centred on the macula. Images were stored using Visupac 4.4.1/4.4.3 (CZM). Grading of retinal images was performed using high quality 24” LCD-monitors (Eizo ColorEdge CG241W/CG242W). The same monitor was used throughout the grading process in a room with subdued light.

3.5 Grading of photographs and definitions

The retinal photographs were graded by a single grader (MG Erke) trained at Moorfields Eye Hospital Reading Centre, London, UK. The grader was masked for all other variables. Both eyes were graded consecutively. The grading protocol for retinal photographs was based on The International Classification and Grading System for AMD [55, 56] with modifications. All photos on every participant were used in the grading in order to achieve the best possible grading. A Visupac Analysis Grid (CZM v. 4.4) was centred over foveola in the macular field image and used for determining lesion size and fields (Figure 4). The diameter of the outer circle corresponded to 6000 μm. Standard circles of 63 μm, 125 μm and 175 μm were used to estimate size of lesion, and only features within the grid as a whole were graded.
Image quality was classified in five categories: “good”, “fair”, “poor but gradable”, “ungradable because of poor quality” and “good quality but not properly centred on fovea”. All photographs were classified by predominant phenotype. Retinal pigment abnormalities were not graded. In case of uncertainty about the predominant phenotype, the image was adjudicated by the Reading Centre. All photos with end-stage AMD were reassessed by two retinal specialists (AK Sjølie and T Peto) and the final predominant phenotype was then created in a hierarchical manner for those with multiple grades. Intra and intergrader reliability was evaluated by regrading five percent of the images by MG Erke and the Reading Centre independently. Images were randomly selected from all categories by the Reading Centre. In addition, a set of photos provided by the Reading Centre was graded by MG Erke at the start and at the end of the grading period to assess temporal drift.
3.6 Data management and statistical methods

Common for all papers

Custom-made databases (Microsoft Access 2002) were developed for handling AMD grading. Stata/SE 10.0-12.0 (StataCorp LP, Texas, USA) was used for all statistical analysis. Independent t-test or Wilcoxon rank sum test, as appropriate, was used for comparison of means; Pearson chi square test or Fisher’s exact test, as appropriate, was used for comparing proportions. P-values <0.05 were considered significant. We used multivariable logistic regression to describe associations and calculate odds ratios (ORs) with 95 % confidence intervals (CIs). Interactions were assessed by including the cross-product term in the multivariable model. Significant interaction terms were evaluated multiplicatively by -2 log likelihood test. The assumptions of logistic regression were tested.

Paper I- II

In paper I/II we evaluated the inter- and intra-grader variability by exact agreement and kappa (κ) statistics between original grading, second grading and external grading. Intra-grader variability was evaluated similarly for temporal drift in grading. Symmetry in phenotype between eyes was calculated by unweighted and linear weighted κ statistics. Prevalence of drusen and AMD was stratified by sex and age groups (5 or 7 year) and presented with 95 % CIs. Visual acuity was presented by eye in categories adjusted to the World Health Organization’s and International Statistical Classification of Diseases and Related Health Problems 10th Revision’s recommendations for low vision (Snellen < 6/18 or 0.3 and ≥ to 3/60 or 0.05) and blindness (Snellen < 3/60 or 0.05).

The overall intra-grader exact agreement was 75 % and κ 0.66. Inter-grader exact agreement was 63 % and κ 0.48. Exact agreement and κ for temporal drift was 68 % and 0.54 respectively. κ results were considered moderate to substantial according to Landis and Koch [57].
Figures for inter-grader agreement and κ in paper I and II are unequal. In paper I we compared with the second grading by the Reading Centre which was performed in Tromsø with the same screen as used throughout the original grading. In paper II and above, we used the first grading which was performed at the Reading Centre in London.

**Paper III**

In paper III we examined the associations between traditional cardiovascular risk factors and AMD using multivariable logistic regression. Late AMD cases were excluded from analyses of associations with drusen >125 μm. We performed a stepwise backward selection procedure in a multivariable logistic regression model including sex and all variables with p-values <0.25 from univariable analyses. The variable with highest p-value was removed for each step, except for sex. Next, variables were singly added to the reduced model and the model assessed by Hosmer-Lemeshow chi-square tests and -2 log likelihood tests. Interactions were assessed between smoking and pulse pressure; and between smoking and BMI, smoking and sex and between smoking and age; further between sex and age; sex and pulse pressure; and between sex and variables of physical activity.

**Paper IV**

In paper IV we examined the associations between female hormone related factors and AMD using multivariable logistic regression. Late AMD cases were excluded from analyses of associations with drusen >125 μm. Women with extreme values for duration of breastfeeding were excluded from analysis (n=2 for total months of breastfeeding>80 and n=4 for months of breastfeeding per child>22). Interactions were assessed between breastfeeding and smoking; breastfeeding and systolic blood pressure; and breastfeeding and BMI.
4. SUMMARY OF RESULTS

General for papers II-III

Among the 3025 participants, 372 subjects had no photos and 22 subjects had ungradable photos from both eyes. The remaining 2631 participants had photographs gradable for AMD. Participants not providing photos were older (73.8 vs. 72.3 years, p<0.0001) than participants with gradable photographs.

Paper II

Participants without photographs had lower visual acuity (Snellen ≤0.32, 6.4 % vs. 2.2 %, p<0.01), and had higher frequency of self-reported glaucoma (13.2 % vs. 5.2 %, p<0.001) and cataract (39.9 % vs. 21.3 %, p<0.001) than participants with gradable photographs. No difference with respect to sex, self-reported AMD, diabetic retinopathy, and diabetes mellitus was observed.

The crude prevalence of late AMD was 3.5 % (n = 92), for subjects 75 years and older it was 7.1 % and for those 80 years or older it was 10.9 %. The prevalence of both drusen >125 µm and late AMD increased significantly with age. For drusen >125 µm OR per 5-year increase was 1.44 (95 % CI, 1.33–1.57), no significant sex difference was observed. For late AMD OR per 5-year increase was 2.32; 95 % CI, 1.92–2.82 and no sex difference was observed.

Sixty-five percent of participants had the same predominant phenotype in both eyes (κ 0.44). When subjects with bilateral normal phenotype, defined as no drusen or only hard drusen (n = 920), were excluded, overall agreement with respect to symmetry was 44 % (κ 0.16). Percentages of symmetry were 44 % for soft drusen >125 µm, 36 % for geographic atrophy, and 29 % for neovascular AMD. Among persons with unilateral late AMD, 78 % had drusen >125 µm in the
other eye. The proportion of late AMD cases with bilateral involvement increased from 14 % in participants aged 65 to 69 years to 67 % in participants aged 80 to 87 years. There was no significant sex difference in overall symmetry.

Visual acuity ≤0.32 was present in 42.5 % of eyes with late AMD. Refractive error differed between eyes with and without late AMD: spherical equivalent +0.078 (SD 1.82) versus +0.99 (SD 2.03) diopters, respectively (P<0.0001). This remained highly significant when adjusted for age, sex and self-reported cataract (OR 0.83; 95 % CI, 0.76–0.90).

**Paper III**

Subjects without photos gradable for AMD had higher frequency of diabetes (13.8 % vs. 9.6 %, p=0.008) and cardiovascular disease (18.5 % vs. 13.4 %, p=0.006), and were less physically active (24.0 % vs. 34.5 %, p<0.001) than participants with gradable photographs. No difference between these two groups was observed with respect to education, blood pressure, BMI, daily smoking and serum lipids. Among those with gradable photos, men and women differed with respect to age, smoking habits, blood pressure, physical activity, serum cholesterol, and cardiovascular disease (all p-values <0.01).

Both late AMD and drusen >125μm were significantly associated with cohabiting, physical activity and pulse pressure in unadjusted analysis. Further, late AMD was associated with current smoking, longer duration of smoking, systolic blood pressure and underweight, whilst the presence of drusen >125μm was associated with education at primary school level only, lower alcohol consumption and lower triglyceride level.
Underweight, current daily smoking, longer duration of smoking, systolic blood pressure and pulse pressure remained significant risk factors for late AMD after controlling for age and sex. Exercising more than 30 minutes related to less, showed a significant relationship with drusen >125 μm. This relationship remained significant with additional adjustments for daily smoking, BMI and systolic blood pressure (OR=0.75, 95% CI 0.58-0.97).

No significant relationships were observed between late AMD and waist circumference, waist-to-hip ratio, cohabiting, education, alcohol consumption, diabetes mellitus or cardiovascular disease. Neither were HbA1c nor serum lipids significantly associated with late AMD.

In the model with late AMD as the outcome and including daily smoking, pulse pressure, age and sex, we observed a significant interaction between sex and age (p=0.029). Inclusion of the interaction term altered the log likelihood (p=0.028). In sex-specific analysis, we found that age was a stronger risk factor for women than for men. Current daily smoking was a strong risk factor for both women and men, but the association for former smokers was not significant. We found a dose-response relationship with the number of years smoked. Physical inactivity, higher pulse pressure, higher systolic blood pressure and overweight were associated with late AMD among women only. The effect estimates for exercise frequency were acting in opposite directions, protective for women but associated with higher odds, although not significant, for late AMD in men. The association between late AMD in women and weekly exercise was attenuated to a non-significant level when controlled further for visual impairment in addition to age and daily smoking (OR 0.61, 95% CI 0.28-1.30).
In sex-specific analysis, no associations were observed between any of the risk factors and the presence of drusen >125 μm except for the association with age.

**Paper IV**

Included in paper IV were 1512 women with gradable photos from at least one eye. Of these, 1426 had data on past use of female hormones, 1411 on age of menarche, 1213 on menopause, 1470 subjects had data on childbirth, of which 1168 women given birth had data on breastfeeding. Women without gradable photos were older (73.8 years vs. 72.2 years, \( p<0.0001 \)), had higher frequency of diabetes (14.0 % vs. 8.9 %, \( p=0.014 \)) and self reported cardiovascular disease (24.6 % vs. 15.3 %, \( p=0.001 \)), and were less physically active (20.4 % vs. 30.6 %, \( p=0.003 \)). The groups did not differ with respect to smoking, serum cholesterol, blood pressure, BMI, education, age of menarche or menopause, age at first birth, number of children given birth to, extent of breastfeeding, past use of contraceptives or OHT. A total of 48 (3.2 %) participants had late AMD and of the remaining, 378 (25 %) participants had at least one large drusen > 125 μm. Of the participants without missing data, 732 (58 %) had never used any kind of female hormones, and of 1261 with data on childbearing and breastfeeding; 139 (11 %) had never breastfed of whom 93 (7.4 %) had never given birth.

No associations were observed between late AMD and past use of contraceptives, past use of OHT, parity, age at first childbirth, age of menarche, age of menopause, number of menstruating years or the reason for menopause, all controlled for age.

Women that had breastfed all their children for at least 6 months had significantly lower odds for late AMD in multivariable analysis adjusted for age, smoking, systolic blood pressure, BMI, total cholesterol, number of children given birth to and physical activity (OR 0.12, 95 % CI 0.027-0.53). Comparable, estimates for
breastfeeding all children minimum 4 or 3 months were also
significant with OR 0.27, 95 % CI 0.11-0.68 and OR 0.41, 95 % 0.19-
0.90 respectively. We observed the same relationship for duration of
breastfeeding per child as a continuous variable (OR 0.86 per month,
95 % CI 0.76-0.97). These associations were strengthened when
women who never had given birth were excluded from analyses.
Additional adjustments for alcohol consumption and education did not
alter the relationships. No interactions between breastfeeding and
smoking status, systolic blood pressure or BMI were significant.
The presence of large drusen >125 μm was not significantly
associated with any of the female hormone related factors.
5. DISCUSSION

The main findings of this thesis are:

- The overall prevalence of late AMD was 3.5%, and among those aged $\geq 80$ years it was almost 11%. Neovascular disease outnumbered geographic atrophy. Symmetry between eyes was relatively low. Refractive error was lower in eyes with late AMD than in eyes without late AMD.

- Age and smoking were strong predictors for the presence of AMD. We found a significant effect modification on age by sex with respect to late AMD in adjusted analysis. Sex-specific multivariable analysis showed that higher systolic blood pressure, higher pulse pressure, infrequent exercise and overweight or obesity were associated with late AMD in females, but this was not observed in men. Only age was associated with the presence of large drusen.

- Longer duration of lactation was associated with lower frequency of maternal late AMD controlled for confounders. Other reproductive or female hormone related factors were not significantly associated with AMD.

5.1 Methodological considerations

Internal validity

Inference from epidemiological research depends on the study’s internal validity. Bias occurs as results of systematic errors in planning, conduct or interpretation of measurements. Main types of bias that can threaten the study’s internal validity are selection bias, information bias and confounding. Selection bias is the event when “systematic error in the ascertainment of study subjects (…) results in a tendency toward distorting the measure expressing the association
between exposure and outcome” [58]. The same mechanism applies to survival bias. Information bias in epidemiologic studies is defined as “results from either imperfect definitions of study variables or flawed data collection procedures” [58]. This includes among other misclassification and recall bias. Another threat to the internal validity is confounding. A confounding variable is a variable associated with both the exposure and the outcome under study. This third variable can lead to inducing, weakening, strengthening or elimination of the association between the putative risk factor and the outcome [58]. Medical epidemiological research is challenging because of the complexity of the disease, with possibility for co-dependent factors and that influence of factors can be evident decades after exposure.

External validity
Inference from population-based studies upon the background population or other populations depends on the studies external validity, its generalizability. This study included a homogenous Caucasian population and results can be extrapolated to similar populations of Western European ancestry. However, it might not be appropriate to assume these results apply to populations of other ethnicities. The epidemiology of AMD has been shown to differ across racial/ethnic groups [59].

Strengths and limitations
Strengths of the present research include a population-based design, a large study sample and high participation rate. Further, the use of standardized protocols and co-operation with a professional reading centre in the grading of photographs facilitated valid results comparable with previous reports on the epidemiology of AMD.

Limitations include possible selection bias due to lower number of participants with gradable photographs in the oldest age group.
Further, it is possible that visual impaired people might be less likely to attend the study. The response rate for participants 80 years and older was 40% for the first visit of the study. The prevalence rates may therefore be underestimated. The definition of early AMD differs between studies and this might limit direct comparison of prevalence of early AMD stages. Misclassification might have been introduced during the grading process in those who were undergoing VEGF inhibitor therapy for neovascular AMD. Further, we had no access to fluorescein angiography or stereo photography. Spectral domain optic coherence tomography was available. We graded samples of scans and decided the topic beyond the scope of this thesis and results will be presented later. Data on visual acuity were not available for 9% of subjects with late AMD. This may have impacted our finding of lower refractive error among late AMD cases.

In paper III the linkage to an endpoint registry validated the data on cardiovascular disease in the study population. Limitations were the cross-sectional design which precludes causal inference, classification bias, selection bias and survival bias. Further limitations were insufficient power and hence no sub-groups analysis due to few late AMD cases and the lack of fasting blood samples and genetic profiling.

Limitations in paper IV include residual confounding, recall bias, lack of power and selection bias. The cross-sectional design precludes causal inference. As we examined several variables, it is possible that the relationship between lactation and late AMD in the present study is due to chance. However, the stronger relationship with longer duration of breastfeeding suggests that the relationship is relevant.
5.2 Prevalence of AMD

Our findings are consistent with results from previous cross-sectional studies examining the prevalence of late AMD, such as the Age, Gene/Environment Susceptibility Study [16] from Reykjavik, Iceland, the Beaver Dam Eye Study [3], USA and the Norwegian participants in the European Eye Study [12]. Greenland, on the other hand, reported a very high prevalence of late AMD of 9.5 % in 642 participants 60 years or older [18]. Lower rates of late AMD were observed in the Blue Mountains Eye Study [6] (65 to 74 years; 0.7 % and 74 to 86 years; 5.7 %) and the Rotterdam Study [11] (65 to 74 years; 0.8 % and 75 to 84 years; 3.7 %). Recently, the Beaver Dam Offspring Study presented prevalence estimates for AMD where no cases of late AMD was found in their cohort of 174 persons 65 years or older [60].

Different grading procedures, study equipment, and age distribution limit comparison of AMD between studies. The International classification [55] defined early AMD as hyper- or hypopigmentation of the retinal pigment epithelium associated with drusen, or soft drusen alone. The studies from Oslo, Greenland and Reykjavik included pigment abnormalities ≥ 63 μm present alone in the definition, but the Blue Mountain Eye, Beaver Dam or Rotterdam studies did not. A study from Norway found prevalence of drusen ≥63μm to be 43 % in persons aged ≥51 years [20]. Similarly, the Rotterdam Study [11] found a prevalence of 49 % (persons aged ≥55 years); and for drusen ≥125μm the prevalence was 8.8 %. The Beaver Dam Offspring Study [60] reported a prevalence of 9.2 % for drusen ≥125μm in persons aged ≥65 years while the Age, Gene/Environment Susceptibility study from Reykjavik reported 30.7 % [16]. The Inuit study from Greenland with participants from the high north showed high prevalence of drusen, as 45 % had intermediate drusen (63-125 μm) and 15 % had large drusen ≥125μm [18]. In our work, we found
high frequencies of both intermediate (35 %) and large drusen (24 %). As we see, the combined prevalence of drusen >63 μm was similar in the latter two studies.

No overall sex differences in the prevalence of large drusen >125μm or late AMD were observed. This is consistent with studies from Western populations [6, 11, 12] and contradicts the findings from Asian populations where higher prevalence of drusen and late AMD was found in men than in women [61, 62]. Our findings of an increasing prevalence of large drusen and late AMD with age were similar to previously published studies.

Published data on symmetry of phenotype between eyes are limited. An Australian study [63] of 230 participants aged ≥49 years found symmetrical phenotype in 57 % of cases with late AMD (for geographic atrophy 56 % and for neovascular AMD 40 %). However, they included only lesions involving the foveal centre. They found the proportion of bilateral drusen >125μm was 76 %. A hospital-based study [64] of 1114 patients from the UK found symmetry of late AMD in 55 %, geographic atrophy in 40 % and neovascular AMD in 37.5 %. The symmetry rates in our study were consistently lower. Bilaterality of late AMD was 34 %, for geographic atrophy 36 % and for neovascular AMD 29 %. Symmetry was highest for soft drusen >125μm (44 %). On the basis of different study samples and methods, comparison of rates is restricted. Nevertheless, the order of bilaterality is similar across studies with highest rates for large drusen followed by geographic atrophy and thereafter neovascular disease.

5.3 Risk factors for AMD

We observed a lower refractive error among late AMD cases. The Rotterdam Study [65] and the Beijing Eye Study [66] have reported
hyperopia as risk factor for AMD. In contrast we observed a 17 % reduction in odds for every dioptre increase in spherical equivalent.

It has been hypothesized that sun exposure is a risk factor for AMD [67-69]. The Arctic Circle marks the southern extremity of the polar night (24 hour sunless night) and polar day (24-hour sunlit day). Our findings of prevalence rates of late AMD similar to that in studies south of the Arctic Circle suggest that variation in daylight exposure might not be a crucial factor that contributes to the pathogenesis of AMD. The study conducted among the Inuit in Greenland [18] included a subset of participants from Sisimiut (66 degrees north). Although they found high frequency of late AMD we think other differences, for example diet, are more likely to explain the higher prevalence than varying sunlight exposure [70].

The strength and consistency of associations between cardiovascular risk factors and AMD vary in the literature. Besides age, smoking is a well-established risk factor for late AMD in both cross-sectional [71-73] and longitudinal studies [67]. In the current study we observed a strong association between current daily smoking and prevalent late AMD (OR 3.43 compared to never smokers controlled for sex and age) and for men 12 % higher odds of late AMD per 5 years of daily smoking. To date, smoking is the single most important modifiable risk factor for late AMD, and cessation of smoking should be emphasised also on the basis of preventing visual loss and blindness.

High systolic blood pressure has been shown to be associated with lower choroidal blood flow in patients with AMD and through this ischemic mechanism suggested as one of the etiologic factors for developing AMD [74, 75]. However, there is still lack of convincing evidence for a relationship with AMD [37, 40, 45, 67]. Results from
the current work support an association between AMD and systemic blood pressure and/or pulse pressure.

Mares et al found a protective effect of physical activity in their study [47]. Further, results from the Beaver Dam Eye Study [76] reported an inverse association between substantial exercise and the incidence of late AMD. Another report from the same study population stated a reduced incidence of neovascular AMD in people with an active lifestyle [46]. Physical activity is associated with decreased cardiovascular risk and mortality [77]. Several beneficial effects on the cardiovascular system have been discussed, such as decreased oxidative stress, inflammation and vascular tone [78], hence a healthy vascular status should be an advantage also in the eye. In our study, we found that women who exercised weekly compared to less have significant lower odds of late AMD. It should be noted that the relationship between AMD and physical activity did not reach statistical significance for duration, intensity or type of physical activity.

BMI outside the normal limit has been associated with AMD in a growing number of studies [41, 42, 79, 80]. Seddon et al. [41] showed an increased risk of progression to a more advanced stage of AMD with higher levels of BMI. Smith et al. [79] reported only significant findings with early AMD, whilst the pooled Rotterdam, Beaver Dam and Blue Mountain Studies [67, 72] failed to confirm a relationship. In our study, we found the association with higher BMI only to be significant for women, and overweight showed a stronger relationship than did obesity, although this could be due to selective mortality. We also observed higher odds of late AMD in lean subjects, but within this category were only few cases and hence these results should be interpreted with caution. A recent meta-analysis suggested that women may have an increased risk of neovascular AMD compared to
men [22]. Our findings may contribute to the understanding of a small female preponderance in AMD. Apart from a possible sex-dependent causal relationship between obesity and AMD, other factors may confound this relationship. However, factors associated with increased BMI such as diabetes, HbA1c, and serum lipids were not associated with AMD in our study.

We found a significant interaction between age and sex for late AMD, indicating that the effect of age on late AMD is sex-dependent. In their recent review, Parker, Kalasky and Proctor postulated that the sex-specific plasticity of the aging cardiovascular system may contribute to the observed interactions between sex, aging, physical activity and disease risk [81]. For example, muscle sympathetic nerve activity has been shown to increase more in aging women than in men. This could in turn explain the increased risk of hypertension and cardiovascular disease progression in older women. The differences in development of atherosclerotic plaques have been described in several studies [82]. Adiposity measures seem to exert similar effect in both sexes [82]. The Framingham study reported higher hazard ratio for cardiovascular events associated with blood pressure in the higher normal range (<140/90 mmHg) in females than in males compared with subjects with optimal blood pressure (<120/80 mmHg) [83]. Diabetes is a more important risk factors for cardiovascular disease and death for women than in men [84]. Moreover, physical activity may have a more pronounced effect in women compared to men [85]. Differences in sex hormones might explain part of the sex disparity in the epidemiology of cardiovascular disease due to their influence on vascular processes [86]. Nevertheless, for AMD, results from epidemiological studies are inconsistent on whether or not a true sex difference exists [22, 72].
Previous cross-sectional studies have shown both protective effect of oestrogen exposure and no association at all [24]. Results from incidence data are also conflicting; the pooled incidence data from three continents showed no association between female reproductive factors or hormone use, and AMD [24, 67]. We did not find an association between late AMD and exogenous oestrogen exposure in the form of contraceptives or OHT. Nor did we find an association between late AMD and onset, end or length of fertile years, bilateral oophorectomy or parity as surrogate measures.

To our knowledge, no prior study has examined the association between breastfeeding and maternal AMD. Our results are in line with studies showing that breastfeeding confers protection against maternal diseases later in life, such as breast cancer and cardiovascular diseases [87, 88]. Although the pathophysiological explanation for the maternal benefits of lactation is not clear, we hypothesize that breastfeeding reduce the cardiovascular risk profile which in turn results in protection against AMD [89].

The importance of our new finding is that it shows that late AMD may be influenced by risk factor exposure during early adulthood. Further, the findings add to a growing body of literature showing maternal benefits of breastfeeding. From a public health point of view, promotion of longer lactation could have a significant impact on eye health in elderly women. However, this is a novel finding that needs confirmation in other studies.

5.4 Implications and further research

Increasing numbers of patients with AMD is anticipated due to ageing populations. Estimates of AMD prevalence are hence important for adequate community planning of eye health services and rehabilitation. Standardisation of definitions and grading procedures is
advocated to facilitate comparison between studies and provide accurate and precise rates.

Detection of modifiable risk factors is most likely a cost-effective goal as the cost associated with this disease is high. This thesis confirms age and smoking as important risk factors. Cessation of smoking should be emphasised as a preventive measure for visual loss. The sex disparity in the cardiovascular risk factors and lactation as a protective factor for late AMD implicates that further research should also include sex-specific analysis. This should preferably be carried out in larger or pooled studies due to the low prevalence of late AMD with sub-analysis on GA and nvAMD.

Risk factors for AMD in populations living in the high north are scarcely described in the literature. Further studies on this cohort will provide valuable data on AMD in a unique population and such data can provide additional aspects to the epidemiology of AMD and its interaction with environmental factors.
6. CONCLUSIONS

I. The Tromsø Eye Study utilised methodology with standardised protocols, large sample size, high attendance rates and it provides a valuable collection of data.

II. The prevalence of AMD among elderly in this study was similar to results from other Caucasian populations. Late AMD was present in 10.9% of subjects aged 80 years and older. No sex differences in prevalence of large drusen or late AMD were observed. Age was a strong risk factor for large drusen and late AMD. The symmetry between eyes was highest for large drusen followed by geographic atrophy and thereafter neovascular disease. Lower refractive error was observed in eyes with late AMD than in eyes without late AMD.

III. Smoking was a strong risk factor for late AMD in both sexes as consistently reported worldwide. Late AMD significantly associated with higher BMI, higher pulse pressure and infrequent physical exercise in women but not in men. No significant association between serum lipids, education, alcohol consumption, diabetes, cardiovascular disease and late AMD was observed.

IV. Longer duration of breastfeeding was associated with lower risk of maternal late AMD. We did not find an association between use of contraceptives or OHT and late AMD. Nor did we find an association between late AMD and onset, end or length of fertile years, bilateral oophorectomy or parity.
7. REFERENCES


41. Seddon JM, Cote J, Davis N, Rosner B: Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist-hip ratio. *Archives of ophthalmology* 2003, 121(6):785-792.


Paper I
Paper II
Paper IV
# Health and Diseases

1. How do you in general consider your own health to be?
   - □ Very good
   - □ Good
   - □ Neither good nor bad
   - □ Bad
   - □ Very bad

2. How is your health compared to others in your age?
   - □ Much better
   - □ A little better
   - □ About the same
   - □ A little worse
   - □ Much worse

3. Do you have, or have you had?
   - Yes  No  Age first time
   - A heart attack ..........................................
   - Angina pectoris (heart cramp) ............
   - Cerebral stroke/brain hemorrhage..
   - Atrial fibrillation ..................................
   - High blood pressure ............................
   - Osteoporosis ..........................................
   - Asthma ...............................................
   - Chronic bronchitis/Emphysema/COPD ....
   - Diabetes ............................................
   - Psychological problems (for which you have sought help)
   - Hypothyroidism ..................................
   - Kidney disease, not including urinary tract infection (UTI)
   - Migraine .............................................

4. Do you have persistent or constantly recurring pain that has lasted for 3 months or more?
   - Yes  □  No

5. How often have you suffered from sleeplessness during the last 12 months?
   - □ Never, or just a few times
   - □ 1-3 times a month
   - □ Approximately once a week
   - □ More that once a week

6. Below you find a list of various problems. Have you experienced any of this during the last week (including today)? (Tick once for each complaint)
   - □ Sudden fear without reason
   - □ Felt afraid or anxious
   - □ Faintness or dizziness
   - □ Felt tense or upset
   - □ Tend to blame yourself
   - □ Sleeping problems
   - □ Depressed, sad
   - □ Feeling of being useless, worthless
   - □ Feeling that everything is a struggle
   - □ Feeling of hopelessness with regard to the future

# Use of Health Services

7. Have you during the last 12 months visited:
   - Yes  No  No. of times
   - General practitioner (GP)
   - Psychiatrist/psychologist
   - Medical specialist outside hospital (other than general practitioner/psychiatrist)
   - Physiotherapist
   - Chiropractor
   - Alternative practitioner (homeopath, acupuncturist, foot zone therapist, herbal medicine practitioner, laying on hands practitioner, healer, clairvoyant, etc.)
   - Dentist/dental service

8. Have you during the last 12 months been to a hospital?
   - Yes  No  No. of times
   - Admitted to a hospital
   - Had consultation in a hospital without admission;
     - At psychiatric out-patient clinic
     - At another out-patient clinic

9. Have you undergone any surgery during the last 3 years?
   - Yes  □  No
**USE OF MEDICINES**

10. Do you currently use, or have you used some of the following medicines? (Tick once for each line)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Never used</th>
<th>Now</th>
<th>Earlier</th>
<th>Age first time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure lowering drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol lowering drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs for heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs for osteoporosis</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tablets for diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The drugs for hypothyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroxine/levaxin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11. How often have you during the last 4 weeks used the following medicines? (Tick once for each line)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Not used in the last 4 weeks</th>
<th>Less than every week</th>
<th>Every week, but not daily</th>
<th>Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painkillers on prescription</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painkillers non-prescription</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeping pills</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranquillizers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FAMILY AND FRIENDS**

13. Who do you live with? (Tick for each question and give the number)

<table>
<thead>
<tr>
<th>Relation</th>
<th>Yes</th>
<th>No</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spouse/partner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other people older than 18 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>People younger than 18 years</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

14. Tick for the relatives who have or have had

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>A heart attack</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A heart attack before age of 60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris (heart cramp)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral stroke/brain haemorrhage</td>
<td></td>
<td></td>
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<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gastric/duodenal ulcers</td>
<td></td>
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<td></td>
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<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance abuse</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

15. Do you have enough friends who can give you help when you need it?

<table>
<thead>
<tr>
<th>Answer</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

16. Do you have enough friends whom you can talk confidentially with?

<table>
<thead>
<tr>
<th>Answer</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

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

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

**WORK, SOCIAL SECURITY AND INCOME**

18. What is the highest level of education you have completed? (Tick once)

<table>
<thead>
<tr>
<th>Level</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary/secondary school, modern secondary school</td>
<td></td>
</tr>
<tr>
<td>Technical school, vocational school, 1-2 years senior high school</td>
<td></td>
</tr>
<tr>
<td>High school diploma</td>
<td></td>
</tr>
<tr>
<td>College/university less than 4 years</td>
<td></td>
</tr>
<tr>
<td>College/university 4 years or more</td>
<td></td>
</tr>
</tbody>
</table>

19. What is your main activity? (Tick once)

<table>
<thead>
<tr>
<th>Activity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Full time work</td>
<td></td>
</tr>
<tr>
<td>Housekeeping</td>
<td></td>
</tr>
<tr>
<td>Part time work</td>
<td></td>
</tr>
<tr>
<td>Retired/benefit recipient</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td></td>
</tr>
<tr>
<td>Student/military service</td>
<td></td>
</tr>
</tbody>
</table>

If there is not enough space for all medicines, continue on a separate sheet.

**When attending** you will be asked whether you have used antibiotics or painkillers the last 24 hours. If you have, you will be asked to provide the name of the drug, strength, dose and time of use.
How often do you exercise?
- With exercise we mean for example walking, skiing, swimming or training/sports

Never
Less than once a week
Once a week
2-3 times a week
Approximately every day

How many years in all have you smoked daily?

How old were you when you began daily smoking?

Do you work outdoor at least 25% of the time, or in cold buildings (e.g. storehouse/industry buildings)?
- Yes
- No

If you have paid or unpaid work, which statement describes your work best?
- Mostly sedentary work (e.g. office work, mounting)
- Work that requires a lot of walking (e.g. shop assistant, light industrial work, teaching)
- Work that requires a lot of walking and lifting (e.g. postman, nursing, construction)
- Heavy manual labour

Describe your exercise and physical exertion in leisure time. If your activity varies much, e.g. between summer and winter, then give an average. The question refers only to the last year. (Tick the most appropriate box)
- Reading, watching TV, or other sedentary activity.
- Walking, cycling, or other forms of exercise at least 4 hours a week (include walking or cycling to work, Sunday-walk/stroll, etc.)
- Participation in recreational sports, heavy gardening, etc. (note:duration of activity at least 4 hours a week)
- Participation in hard training or sports competitions, regularly several times a week.

How often do you exercise?

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
- 15-29 minutes
- 30-60 minutes
- More than 1 hour

How many units of alcohol (a beer, a glass of wine or a drink) do you usually drink when you drink alcohol?

How often do you drink alcohol?
- Never
- Monthly or less frequently
- 2-4 times a month
- 2-3 times a week
- 4 or more times a week

How many units of alcohol do you usually drink in one occasion?

How often do you drink 6 units of alcohol or more in one occasion?
- Never
- Less frequently than monthly
- Monthly
- Weekly
- Daily or almost daily

Do you smoke sometimes, but not daily?
- Yes
- No

Do you receive any of the following benefits?
- Old-age, early retirement or survivor pension
- Sickness benefit (on sick leave)
- Rehabilitation benefit
- Full disability pension
- Partial disability pension
- Unemployment benefits
- Transition benefit for single parents
- Social welfare benefits

What was the household’s total taxable income last year? Include income from work, pensions, benefits and similar
- Less than 125 000 NOK
- 125 000-200 000 NOK
- 201 000-300 000 NOK
- 301 000-400 000 NOK
- More than 400 000 NOK

Do you currently smoke, or have smoked previously:
- How many cigarettes do you or did you usually smoke per day?
- How many years have you smoked daily?
- How many years have you smoked daily?

How many years have you smoked daily?

Do you use or have you used snuff or chewing tobacco?
- No, never
- Yes, sometimes
- Yes, previously
- Yes, daily
### QUESTIONS FOR WOMEN

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you pregnant at the moment?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How many children have you given birth to?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If you have given birth, fill in for each child: birth year, birth weight and months of breastfeeding (Fill in the best you can)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How much do you usually drink the following? (Tick once for each line)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often do you usually eat these foods? (Tick once for each line)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How many cups of coffee and tea do you drink daily? (Put 0 for the types you do not drink daily)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often do you usually eat cod liver and roe? (i.e. “mølje”)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you use the following nutritional supplements?</td>
<td>Daily</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>Do you currently use any prescribed drug influencing the menstruation?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

### DIET

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you usually eat breakfast every day?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How many units of fruit or vegetables do you eat on average per day?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How many times a week do you eat warm dinner?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often do you usually eat these foods?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How much do you usually drink the following?</td>
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<td>Do you use the following nutritional supplements?</td>
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<td>Sometimes</td>
<td>No</td>
</tr>
</tbody>
</table>

---

**When attending you will get supplementary questions about menstruation and any use of hormones. Write down on a sheet of paper the names of all the hormones you have used and bring it with you. You will also be asked whether your menstruation have ceased and possibly when and why.**
1. How do you in general consider your own health to be?
   - Very good
   - Good
   - Neither good nor bad
   - Bad
   - Very bad

2. How is your health compared to others in your age?
   - Much better
   - A little better
   - About the same
   - A little worse
   - Much worse

3. Do you have, or have you had?
   Yes  No
   - A heart attack
   - Angina pectoris (heart cramp)
   - Cerebral stroke/brain hemorrhage.
   - Atrial fibrillation
   - High blood pressure
   - Osteoporosis
   - Asthma
   - Chronic bronchitis/Emphysema/COPD
   - Diabetes
   - Psychological problems (for which you have sought help)
   - Hypothyroidism
   - Kidney disease, not including urinary tract infection (UTI)
   - Migraine

4. Do you have persistent or constantly recurring pain that has lasted for 3 months or more?
   - Yes  No

5. How often have you suffered from sleeplessness during the last 12 months?
   - Never, or just a few times
   - 1-3 times a month
   - Approximately once a week
   - More than once a week

6. Below you find a list of various problems. Have you experienced any of this during the last week (including today)? (Tick once for each complaint)

   - Sudden fear without reason
   - Felt afraid or anxious
   - Faintness or dizziness
   - Felt tense or upset
   - Tend to blame yourself
   - Sleeping problems
   - Depressed, sad
   - Feeling of being useless, worthless
   - Feeling that everything is a struggle
   - Feeling of hopelessness with regard to the future

7. Have you during the last 12 months visited:
   If YES; how many times?
   Yes   No   No. of times
   - General practitioner (GP)
   - Psychiatrist/psychologist
   - Medical specialist outside hospital (other than general practitioner/psychiatrist)
   - Physiotherapist
   - Chiropractor
   - Alternative practitioner (homeopath, acupuncturist, foot zone therapist, herbal medicine practitioner, laying on hands practitioner, healer, clairvoyant, etc.)
   - Dentist/dental service

8. Have you during the last 12 months been to a hospital?
   Yes  No  No. of times
   - Admitted to a hospital
   - Had consultation in a hospital without admission;
     - At psychiatric out-patient clinic
     - At another out-patient clinic

9. Have you undergone any surgery during the last 3 years?
   - Yes  No
**USE OF MEDICINES**

10. Do you currently use, or have you used some of the following medicines? (Tick once for each line)

- Blood pressure lowering drugs
- Cholesterol lowering drugs
- Drugs for heart disease
- Diuretics
- Drugs for osteoporosis
- Insulin
- Tablets for diabetes
- The drugs for hypothyroidism
- Thyroxine/levaxin

11. How often have you during the last 4 weeks used the following medicines? (Tick once for each line)

- Painkillers on prescription
- Painkillers non-prescription
- Sleeping pills
- Tranquillizers
- Antidepressants

12. State the name of all medicines -both those on prescription and non-prescription drugs- you have used regularly during the last 4 weeks. Do not include vitamins, minerals, herbs, natural remedies, other nutritional supplements, etc.

13. Who do you live with? (Tick for each question and give the number)

- Spouse/partner
- Other people older than 18 years
- People younger than 18 years

14. Tick for the relatives who have or have had

- A heart attack
- A heart attack before age of 60
- Angina pectoris
- Cerebral stroke/brain haemorrhage
- Osteoporosis
- Gastric/duodenal ulcers
- Asthma
- Diabetes
- Dementia
- Psychological problems
- Substance abuse

15. Do you have enough friends who can give you help when you need it?

- Yes
- No

16. Do you have enough friends whom you can talk confidentially with?

- Yes
- No

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

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

18. What is the highest level of education you have completed? (Tick once)

- Primary/secondary school, modern secondary school
- Technical school, vocational school, 1-2 years senior high school
- High school diploma
- College/university less than 4 years
- College/university 4 years or more

19. What is your main activity? (Tick once)

- Full time work
- Part time work
- Retired/benefit recipient
- Unemployed
- Student/military service

---

If there is not enough space for all medicines, continue on a separate sheet.

When attending you will be asked whether you have used antibiotics or painkillers the last 24 hours. If you have, you will be asked to provide the name of the drug, strength, dose and time of use.
20 Do you receive any of the following benefits?
- Old-age, early retirement or survivor pension
- Sickness benefit (on sick leave)
- Rehabilitation benefit
- Full disability pension
- Partial disability pension
- Unemployment benefits
- Transition benefit for single parents
- Social welfare benefits

21 What was the household's total taxable income last year? Include income from work, pensions, benefits and similar
- Less than 125 000 NOK
- 125 000-200 000 NOK
- 201 000-300 000 NOK
- 301 000-400 000 NOK
- More than 400 000 NOK

22 Do you work outdoor at least 25% of the time, or in cold buildings (e.g. storehouse/industry buildings)?
- Yes
- No

23 If you have paid or unpaid work, which statement describes your work best?
- Mostly sedentary work
  (e.g. office work, mounting)
- Work that requires a lot of walking
  (e.g. shop assistant, light industrial work, teaching)
- Work that requires a lot of walking and lifting
  (e.g. postman, nursing, construction)
- Heavy manual labour

24 Describe your exercise and physical exertion in leisure time. If your activity varies much, e.g. between summer and winter, then give an average. The question refers only to the last year. (Tick the most appropriate box)
- Reading, watching TV, or other sedentary activity.
- Walking, cycling, or other forms of exercise at least 4 hours a week (include walking or cycling to work, Sunday-walk/stroll, etc.)
- Participation in recreational sports, heavy gardening, etc. (note:duration of activity at least 4 hours a week)
- Participation in hard training or sports competitions, regularly several times a week.

25 How often do you exercise? (With exercise we mean for example walking, skiing, swimming or training/sports)
- Never
- Less than once a week
- Once a week
- 2-3 times a week
- Approximately every day

26 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

27 For how long do you exercise every time on average?
- Less than 15 minutes
- 15-29 minutes
- 30-60 minutes
- More than 1 hour

28 How often do you drink alcohol?
- Never
- Monthly or less frequently
- 2-4 times a month
- 2-3 times a week
- 4 or more times a week

29 How many units of alcohol (a beer, a glass of wine or a drink) do you usually drink when you drink alcohol?
- 1-2
- 3-4
- 5-6
- 7-9
- 10 or more

30 How often do you drink 6 units of alcohol or more in one occasion?
- Never
- Monthly or less frequently
- 2-4 times a month
- 2-3 times a week
- 4 or more times a week

31 How many years in all have you smoked daily?
- Number of years

32 How old were you when you began daily smoking?
- Age in years

33 How many cigarettes do you or did you usually smoke per day?
- Number of cigarettes

34 If you previously smoked daily, how long is it since you quit?
- Number of years

35 If you currently smoke, or have smoked previously: How many cigarettes do you or did you usually smoke per day?
- Number of cigarettes

36 How old were you when you began daily smoking?
- Age in years

37 How many years in all have you smoked daily?
- Number of years

38 Do you use or have you used snuff or chewing tobacco?
- No, never
- Yes, sometimes
- Yes, previously
- Yes, daily
### QUESTIONS FOR WOMEN

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you pregnant at the moment?</td>
<td>Yes, No, Uncertain</td>
</tr>
<tr>
<td>How many children have you given birth to?</td>
<td>Number</td>
</tr>
<tr>
<td>If you have given birth, fill in for each child: birth year, birth weight and months of breastfeeding (Fill in the best you can)</td>
<td>Child</td>
</tr>
<tr>
<td>Have you during pregnancy had high blood pressure?</td>
<td>Yes, No</td>
</tr>
<tr>
<td>If yes, during which pregnancy?</td>
<td>The first, Second or later</td>
</tr>
<tr>
<td>Have you during pregnancy had proteinuria?</td>
<td>Yes, No</td>
</tr>
<tr>
<td>If yes, during which pregnancy?</td>
<td>The first, Second or later</td>
</tr>
<tr>
<td>Were any of your children delivered prematurely (a month or more before the due date) because of preeclampsia?</td>
<td>Yes, No</td>
</tr>
<tr>
<td>If yes, which child?</td>
<td>1st child, 2nd child, 3rd child, 4th child, 5th child, 6th child</td>
</tr>
<tr>
<td>How old were you when you started menstruating?</td>
<td>Age</td>
</tr>
<tr>
<td>Do you currently use any prescribed drug influencing the menstruation?</td>
<td>Yes, No</td>
</tr>
<tr>
<td>Hormone treatment for menopausal problems</td>
<td>Yes, No</td>
</tr>
</tbody>
</table>

### DIET

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
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<tr>
<td>Do you usually eat breakfast every day?</td>
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</tr>
<tr>
<td>How many units of fruit or vegetables do you eat on average per day?</td>
<td>Number</td>
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<tr>
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</tr>
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<td>How often do you usually eat cod liver and roe? (i.e. “mølje”)</td>
<td></td>
</tr>
<tr>
<td>Do you use the following nutritional supplements?</td>
<td>Daily, Sometimes, No</td>
</tr>
</tbody>
</table>

When attending you will get supplementary questions about menstruation and any use of hormones. Write down on a sheet of paper the names of all the hormones you have used and bring it with you. You will also be asked whether your menstruation have ceased and possibly when and why.
Appendix B
FILL OUT THE FORM IN THIS WAY:

The form would be read by machine, it is therefore important that you tick appropriately:

- □ Correct
- ✔️ Wrong
- ✗ Wrong

If you tick the wrong box, correct by filling the box like this:

Write the numbers clearly 1 2 3 4 5 6 7 8 9 0

```
7 4  ✔️ Correct
7 6  ✗ Wrong
```

Use only black or blue pen, do not use pencil or felt tip pen.
1. DESCRIPTION OF YOUR HEALTH STATUS

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today:

1.01 Mobility
   □ I have no problems in walking about
   □ I have some problems in walking about
   □ I am confined to bed

1.02 Self-care
   □ I have no problems with self-care
   □ I have some problems washing or dressing myself
   □ I am unable to wash or dress myself

1.03 Usual activities (e.g. work, study, housework, family or leisure activities)
   □ I have no problems with performing my usual activities
   □ I have some problems with performing my usual activities
   □ I am unable to perform my usual activities

1.04 Pain and discomfort
   □ I have no pain or discomfort
   □ I have moderate pain or discomfort
   □ I have extreme pain or discomfort

1.05 Anxiety and depression
   □ I am not anxious or depressed
   □ I am moderately anxious or depressed
   □ I am extremely anxious or depressed

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.
2. CHILDHOOD/YOUTH AND AFFILIATION

2.01 Where did you live at the age of 1 year?
- In Tromsø (with present municipal borders)
- In Toms, but not Tromsø
- In Finnmark
- In Nordland
- Another place in Norway
- Abroad

2.02 How was your family’s financial situation during your childhood?
- Very good
- Good
- Difficult
- Very difficult

2.03 What is the importance of religion in your life?
- Very important
- Somewhat important
- Not important

2.04 What do you consider yourself as? (Tick for one or more alternatives)
- Norwegian
- Sami
- Kven/Finnish
- Another

2.05 How many siblings and children do you have/have you had?
Number of siblings: □ □
Number of children: □ □

2.06 Is your mother alive?
- Yes □
- No □
If NO: her age when she died: □ □

2.07 Is your father alive?
- Yes □
- No □
If NO: his age when he died: □ □

2.07 What was/is the highest completed education for your parents and your spouse/partner? (Tick once for each column)

<table>
<thead>
<tr>
<th>Education</th>
<th>Mother</th>
<th>Father</th>
<th>Spouse/partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-10 years primary/secondary school, modern secondary school</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technical school, vocational school, 1-2 years senior high school</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school diploma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>College or university (less than 4 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>College or university (4 years or more)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. WELL BEING AND LIVING CONDITIONS

3.01 Below are three statements about satisfaction with life as a whole. Then there are two statements about views on your own health. Show how you agree or disagree with each of the statements by ticking in the box for the number you think fits best for you. (tick once for each statement)

<table>
<thead>
<tr>
<th>Complete</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. In most ways my life is close to my ideal ..................</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2. My life conditions are excellent ................................</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>3. I am satisfied with my life .......................................</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>4. I have a positive view of my future health ...............</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>5. By living healthy, I can prevent serious diseases</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

3.02 Below are four statements concerning your current job conditions, or if you are not working now, the last job you had. (Tick once for each statement)

<table>
<thead>
<tr>
<th>Complete</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. My work is tiring, physically or mentally ................</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>7. I have sufficient influence on when and how my work should be done ........................................</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>8. I am being bullied or harassed at work ....................</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>9. I am being treated fairly at work ............................</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

3.03 I consider my occupation to have the following social status in the society
(if you are not currently employed, think about your latest occupation)

☐ Very high status
☐ Fairly high status
☐ Medium status
☐ Fairly low status
☐ Very low status

3.04 Have you over a long period experienced any of the following? (Tick one or more for each line)

<table>
<thead>
<tr>
<th></th>
<th>Yes, as a child</th>
<th>Yes, as adult</th>
<th>Yes, last year</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Been tormented, or threatened with violence ............</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>11. Been beaten, kicked at or victim of other types of violence</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>12. Someone in your close family have used alcohol or drugs in such a way that it has caused you worry ..........</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

If you have experienced anything of the above, how much are you affected by that now?

☐ Not affected  ☐ Affected to some extent  ☐ Affected to a large extent
4. ILLNESS AND WORRIES

4.01 Have you during the last month experienced any illness or injury?
☐ Yes    ☐ No

If YES: have you during the same period?
(Tick once for each line)    Yes  No

Been to a general practitioner       ☐ ☐
Been to a medical specialist         ☐ ☐
Been to emergency department         ☐ ☐
Been admitted to a hospital           ☐ ☐
Been to an alternative practitioner  (chiropractor, homeopath or similar) ☐ ☐

4.02 Have you noticed sudden changes in your pulse or heart rhythm in the last year?
☐ Yes    ☐ No

4.03 Do you become breathless in the following situations? (tick once for each question)

When you walk rapidly on level ground or up a moderate slope       ☐ ☐
When you walk calmly on level ground                               ☐ ☐
While you are washing or dressing                                  ☐ ☐
At rest                                                            ☐ ☐

4.04 Do you cough about daily for some periods of the year?
☐ Yes    ☐ No

If YES: Is the cough usually productive?
☐ Yes    ☐ No

Have you had this kind of cough for as long as 3 months in each of the last two years?
☐ Yes    ☐ No

4.05 How often do you suffer from sleeplessness? (tick once)
☐ Never, or just a few times a year
☐ 1-3 times a month
☐ Approximately once a week
☐ More than once a week

If you suffer from sleeplessness monthly or more often, what time of the year does it affect you most? (Put one or more ticks)
☐ No particular time
☐ Polar night time
☐ Midnight sun time
☐ Spring and autumn

4.06 Have you had difficulty sleeping during the past couple of weeks?
☐ Not at all
☐ No more than usual
☐ Rather more than usual
☐ Much more than usual

4.07 Have you during the last two weeks felt unhappy and depressed?
☐ Not at all
☐ No more than usual
☐ Rather more than usual
☐ Much more than usual

4.08 Have you during the last two weeks felt unable to cope with your difficulties?
☐ Not at all
☐ No more than usual
☐ Rather more than usual
☐ Much more than usual

4.09 Below, please answer a few questions about your memory: (tick once for each question)

Do you think that your memory has declined?                        ☐ ☐
Do you often forget where you have placed your things?             ☐ ☐
Do you have difficulties finding common words in a conversation?   ☐ ☐
Have you problems performing daily tasks you used to master?       ☐ ☐
Have you been examined for memory problems?                        ☐ ☐

If YES to at least one of the first four questions above: Is this a problem in your daily life?
☐ Yes    ☐ No
4.10 Have you during the last last year suffered from pain and/or stiffness in muscles or joints in your neck/shoulders lasting for at least 3 consecutive months? (tick once for each line)

<table>
<thead>
<tr>
<th>No complaint</th>
<th>Little complaint</th>
<th>Severe complaint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck, shoulders</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Arms, hands</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Upper part of the back</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>The lumbar region</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Hips, leg, feet</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Other places</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

4.11 Have you suffered from pain and/or stiffness in muscles or joints during the last 4 weeks? (tick once for each line)

<table>
<thead>
<tr>
<th>No complaint</th>
<th>Little complaint</th>
<th>Severe complaint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck, shoulders</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Arms, hands</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Upper part of the back</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>The lumbar region</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Hips, leg, feet</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Other places</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

4.12 Have you ever had:

<table>
<thead>
<tr>
<th>Fracture in the wrist/forearm?</th>
<th>Yes</th>
<th>No</th>
<th>Age last time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture?</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
</tbody>
</table>

4.13 Have you been diagnosed with arthrosis by a physician?

□ Yes  □ No

4.14 Do you have or have you ever had some of the following:

<table>
<thead>
<tr>
<th>Nickel allergy</th>
<th>Never</th>
<th>Some</th>
<th>Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollen allergy</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Other allergies</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

4.15 Have you ever experienced infertility for more than 1 year?

□ Yes  □ No

If Yes: was it due to:

<table>
<thead>
<tr>
<th>A condition concerning you?</th>
<th>Yes</th>
<th>No</th>
<th>Do not know</th>
</tr>
</thead>
<tbody>
<tr>
<td>A condition concerning your partner?</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
</tbody>
</table>

4.16 To which degree have you had the following complaints during the last 12 months?

<table>
<thead>
<tr>
<th>Nausea</th>
<th>Heartburn/regurgitation</th>
<th>Diarrhoea</th>
<th>Constipation</th>
<th>Alternating diarrhoea and constipation</th>
<th>Bloating stomach</th>
<th>Abdominal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

4.17 If you have had abdominal pain or discomfort during the last year:

<table>
<thead>
<tr>
<th>Was it located in your upper stomach?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were you bothered as often as once a week or more during the last 3 months?</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Do you feel symptoms relief after bowel movement?</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Are the symptoms related to more frequent or rare bowel movements than normally?</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Are the symptoms related to more loose or hard stool than normally?</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Do the symptoms appear after a meal?</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

4.18 Have you ever had:

<table>
<thead>
<tr>
<th>Gastric ulcer</th>
<th>Duodenal ulcer</th>
<th>Ulcer surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

4.19 For women: Have you ever had a miscarriage?

□ Yes  □ No  □ Do not know

If Yes: number of times

4.20 For men: Have your partner ever had a miscarriage?

□ Yes  □ No  □ Do not know

If Yes: number of times

4.21 Is your diet gluten-free?

□ Yes  □ No  □ Do not know

4.22 Have you been diagnosed with Dermatitis Herpetiformis (DH)?

□ Yes  □ No  □ Do not know
4.23 Have you been diagnosed with coeliac disease, based on a biopsy from your intestine taken in a gastroscopy examination?
☐ Yes ☐ No ☐ Do not know

4.24 Do you have your natural teeth?
☐ Yes ☐ No

4.25 How many amalgam tooth fillings do you have/have you had?
☐ 0 ☐ 1-5 ☐ 6-10 ☐ 10+

4.26 Have you been suffering from headache the last year?
☐ Yes ☐ No

If No: go to section 5, food habits

4.27 What kind of headache are you suffering from?
☐ Migraine ☐ Other headache

4.28 How many days per month do you suffer from headache?
☐ Less than one day
☐ 1-6 days
☐ 7-14 days
☐ More than 14 days

4.29 Is the headache attacks usually:
(tick once for each line)
☐ Yes ☐ No
Pounding/pulsatory pain........... ☐ ☐
Pressing/tightening pain........... ☐ ☐
Unilateral pain (right or left)........... ☐ ☐

4.30 What is the normal intensity of your headache attacks?
☐ Mild (do not hinder normal activity)
☐ Moderate (decrease normal activity)
☐ Strong (block normal activity)

4.31 What is the normal duration of the headache attacks?
☐ Less than 4 hours
☐ 4 hours - 1 day
☐ 1-3 days
☐ More than 3 days

4.32 If you suffer from headache, when during the year does it affect you most? (tick one or more)
☐ No particular time
☐ Polar night time
☐ Midnight sun time
☐ Spring and/or Autumn

4.33 Before or during the headache, do you have a temporary:

☐ Yes ☐ No
Visual disturbances? (flickering, blurred vision, flashes of light).................. ☐ ☐
Unilateral numbness in your face or hand? ........................................... ☐ ☐
Aggravated pain by moderate physical activity? ....................................... ☐ ☐
Nausea and/or vomiting? ................................................................. ☐ ☐

4.34 Describe how many days you have been away from work or school during the last month due to headache?
Number of days............................................. ☐


**5. FOOD HABITS**

5.01 How often do you usually eat the following? (tick once for each line)

<table>
<thead>
<tr>
<th>Food Item</th>
<th>0-1 times per month</th>
<th>2-3 times per month</th>
<th>1-3 times per week</th>
<th>More than 3 times per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh water fish <em>(not farmed)</em></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Salt water fish <em>(not farmed)</em></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Farmed fish <em>(salmon, trout, char)</em></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Tuna fish <em>(fresh or canned)</em></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Fish bread spread</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Mussels, shells</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>The brown content in crabs</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Whale or seal meat</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Pluck <em>(liver/kidney/heart)</em> from reindeer or elk/moose</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Pluck <em>(liver/kidney/heart)</em> from ptarmigan/grouse</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

5.02 How many times during the year do/did you usually eat the following? (number of times)

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Number of times per year</th>
<th>In adulthood</th>
<th>In childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malje <em>(cod or pollack meat, liver, and roe)</em></td>
<td></td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Sea gull’s egg <em>(Number of eggs per year)</em></td>
<td></td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Reindeer meat <em>(Number of times per year)</em></td>
<td></td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Local mushroom and wild berries <em>(blueberries/lingonberries/cloudberries)</em></td>
<td></td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

5.03 How many times per month do you eat canned (tinned) foods (from metal boxes)?

| Number                     | ☐ |

5.05 How often do you eat?

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Never</th>
<th>1-3 times per month</th>
<th>1-3 times per week</th>
<th>4-6 times per week</th>
<th>1-2 times per day</th>
<th>3 times per day or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dark chocolate</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Light chocolate/milk chocolate</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Chocolate cake</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other sweets</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

5.06 If you eat chocolate, how much do you usually eat each time?

Compared with the size of a Kvikk-Lunsj sjokolade *(a chocolate brand in the market)* and describe how much do you eat in relation to it.

<table>
<thead>
<tr>
<th>Amount</th>
<th>☐</th>
<th>☐</th>
<th>☐</th>
<th>☐</th>
<th>☐</th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>¼</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>½</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>1</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>1 ½</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>More than 2</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

5.07 How often do you drink cocoa/hot chocolate?

<table>
<thead>
<tr>
<th>Number</th>
<th>Never</th>
<th>1-3 times per month</th>
<th>1-3 times per week</th>
<th>4-6 times per week</th>
<th>1-2 times per day</th>
<th>3 times per day or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dark chocolate/milk chocolate</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Chocolate cake</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other sweets</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
### 6. ALCOHOL

**6.01 How often have you in the last year:**

<table>
<thead>
<tr>
<th>Never</th>
<th>Less than monthly</th>
<th>Monthly</th>
<th>Weekly</th>
<th>Daily or almost daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

- Not been able to stop drinking alcohol when you have started? ☐
- Failed to do what was normally expected of you because of drinking? ☐
- Needed a drink in the morning to get 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? ☐

**6.02 Have you or someone else been injured because of your drinking?**

<table>
<thead>
<tr>
<th>Never</th>
<th>Yes, but not in the last year</th>
<th>Yes, during the last year</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

- Has a relative, friend, physician, or other health care workers been concerned about your drinking or suggested you to cut down? ☐

### 7. WEIGHT

**7.01 Have you involuntary lost weight during the last 6 months?**

- ☐ Yes  ☐ No

If Yes: how many kilograms? ☐

**7.02 Estimate your body weight when you were 25 years old:**

<table>
<thead>
<tr>
<th>Number of kilograms</th>
<th>☐ ☐</th>
</tr>
</thead>
</table>

**7.03 Are you satisfied with your present body weight?**

- ☐ Yes  ☐ No

**7.04 What weight would you be satisfied with (your “ideal” weight)?**

<table>
<thead>
<tr>
<th>Number of kilograms</th>
<th>☐ ☐</th>
</tr>
</thead>
</table>

### 8. SOLVENTS

**8.01 How many hours per week, do you do the following leisure- or professional activities:**

- Automobile repair/paint, ceramic work, painting/varnishing/solvents, hair dressing, glazier, electrician. (Put 0 if you do not engage in such leisure or professional activities)

<table>
<thead>
<tr>
<th>Number of hours per week on average</th>
<th>☐ ☐</th>
</tr>
</thead>
</table>

**8.02 Do you use hair color preparations**

- ☐ Yes  ☐ No

If Yes: How many times per year? ☐
9. USE OF HEALTH SERVICES

9.01 Have you ever experienced that diseases have been insufficiently examined or treated, and this has had a serious consequence? 
☐ Yes, this has happened to me
☐ Yes, this has happened to a close relative (child, parents, spouse)
☐ No

If Yes, was it caused by? (tick once or more):
☐ general practitioner
☐ emergency medical doctor
☐ private practising specialist
☐ hospital doctor
☐ other health personnel
☐ alternative practitioner
☐ more than one person due to deficient routines and interaction

9.02 Have you ever felt persuaded to accept an examination or treatment that you did not want? 
☐ Yes ☐ No

If Yes, do you think this has had unfortunate consequences for your health? 
☐ Yes ☐ No

9.03 Have you ever complained about a treatment you have received? 
☐ Have never had a reason for complaining
☐ Have considered complaining, but did not do
☐ Have complained verbally
☐ Have complained in writing

9.04 How long have you had your current general practitioner/other physician? 
☐ Less than 6 months
☐ 6 to 12 months
☐ 12 to 24 months
☐ More than 2 years

9.05 At the last visit to your GP, did you have a hard time to understand what the doctor(s) told you? Answer on 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

9.06 How would you rate the treatment or counselling, you got at your last visit to your GP? Answer on a scale from 0 to 10, where 0 = worst treatment or counselling, and 10 = best treatment or counselling

0 1 2 3 4 5 6 7 8 9 10

9.07 During the last 12 months, how much of a problem, if any, was it to get a referral to special examinations (as x-ray, etc.) or to a specialist health care (private practising specialist or at hospital)?

☐ Not relevant
☐ No problem
☐ Some problem
☐ Major problem

9.08 During the last 12 months, how much of a problem, if any, was it to get a referral to physiotherapist, chiropractor, etc.?

☐ Not relevant
☐ No problem
☐ Some problem
☐ Major problem

9.09 Altogether, how much of a problem, if any, was it to get a referral to specialist health care?

☐ Not relevant
☐ Very difficult
☐ Some difficulties
☐ Easy
☐ Very easy
9.10 During the last 12 months, have you been examined or treated by the specialist health care?
☐ Yes     ☐ No

If Yes, did you have a difficult time to understand what the doctor(s) told you? Answer on 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
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

9.11 How would you rate the treatment or counselling you got at your last visit to a specialist? Answer on a scale from 0 to 10, where 0 = worst treatment or counselling, and 10 = best treatment or counselling
0 1 2 3 4 5 6 7 8 9 10
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

9.12 Have you ever, previous to the year 2002, had an operation at a hospital or a specialist clinic?
☐ Yes     ☐ No

9.13 Have you, during the last 12 months, used herbal or natural medicine?
☐ Yes     ☐ No

9.14 Have you, during the last 12 months, used meditation, yoga, qi gong or thai chi as self-treatment?
☐ Yes     ☐ No
10. USE OF ANTIBIOTICS

Have you used antibiotics during the last 12 months? (all penicillin-like medicine in the form of tablets, syrups or injections)

☐ Yes  ☐ No  ☐ Do not remember

If YES: What did you get the treatment for?

Have you taken many antibiotic treatments, tick for each treatment.

• Urinary tract infection (bladder infection, cystitis) ....
• Respiratory tract infection (ear, sinus, throat or lung infection, bronchitis) ...................................
• Other ..............................................................................................................................

Treatment duration: number of days ............... 

How did you acquire the antibiotics for treatment?

Have you acquired many treatments, tick for each one.

With prescription from a physician/dentist .......... 

Without contacting a physician/without prescription:

• Purchase from a pharmacy abroad ..............
• Purchase over the internet ............................
• Remnants from earlier treatment at home .......
• From family/friends .....................................
• Other ways ................................................

Do you presently have antibiotics at home?  

☐ Yes  ☐ No

If YES: is this after an agreement with your physician for treatment of chronic or frequently recurring disease?

☐ Yes  ☐ No

If No: how did you acquire this antibiotic?

(Multiple ticks are possible)

Purchased from a pharmacy abroad ....
Purchased over the internet ..............
Remnants from earlier treatment .......
From family/friends ...........................
Other ways ........................................

Would you consider using antibiotics without consulting your physician?

☐ Yes  ☐ No

If YES: which conditions would you treat in such situation? (multiple ticks are possible)

Common cold ........................................
Cough ..................................................
Bronchitis .........................................
Sore throat ......................................
Sinusitis .......................................... 
Fever ................................................
Influenza ...........................................
Ear infection .....................................
Diarrhoea ........................................
Urinary tract infection ........................
Other infections ...............................
11. YOUR CIRCADIAN RHYTHM

We will ask you some questions about your sleeping habits

II.1 Have you worked in a shift work schedule during the last 3 months?
☐ Yes ☐ No

II.2 Number of days per week which you cannot freely choose when you sleep (e.g. work days)?

<p>| | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

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 ..................................

II.3 Number of days per week which you can freely choose when you sleep (e.g. free days or holidays)

<p>| | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

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

12.0 How often do you usually take a shower or a bath? (tick once)

☐ 2 or more times daily
☐ 1 time daily
☐ 4-6 times per week
☐ 2-3 times per week
☐ Once a week
☐ Less than once a week

12.1 How often do you usually wash your hands with soap daily? (tick once)

☐ 0 times
☐ 1-5 times
☐ 6-10 times
☐ 11-20 times
☐ More than 20 times

12.2 Have you ever taken any antibiotics (penicillin and penicillin-like medicines) because of a skin disease, for example infected eczema, acne, non-healing leg ulcers, recurrent abscess?

☐ Yes ☐ No

If Yes: How many times in average per year did you take antibiotics during the period you were most affected (tick once)

☐ 1-2 ☐ 3-4 ☐ More than 4 times

12.3 Have you or have you ever had the following skin disorders? (tick once for each line)

Psoriasis ☐ Yes ☐ No
Atopic eczema (children’s eczema) ☐ Yes ☐ No
Recurrent hand eczema ☐ Yes ☐ No
Recurrent pimples/spots for several months ☐ Yes ☐ No
Leg or foot ulcer that did not heal for 3-4 weeks ☐ Yes ☐ No

If YES on the question concerning leg and/or foot ulcer, do you have any leg ulcer today?

☐ Yes ☐ No

12.4 Have you often or always any of the following complaints? (tick once for each line)

Swelling in the ankles or legs, particularly in the evenings ☐ Yes ☐ No
Varicose veins ☐ Yes ☐ No
Eczema (red, itchy rash) on your legs ☐ Yes ☐ No
Leg pain that is getting worse when you are walking and is relieved when you are standing still ☐ Yes ☐ No

12.5 Have you ever had the following diagnoses by a physician? (tick once for each line)

Psoriasis ☐ Yes ☐ No
Atopic eczema ☐ Yes ☐ No
Rosacea ☐ Yes ☐ No

12.6 Have you recurring large acne/abscesses that are tender/painful and often form scars in the following places? (tick once for each line)

Armpits ☐ Yes ☐ No
Under the breasts ☐ Yes ☐ No
Stomach groove/the navel ☐ Yes ☐ No
Around the genitalia ☐ Yes ☐ No
Around the anus ☐ Yes ☐ No
The groin ☐ Yes ☐ No

If Yes: Have you ever visited a physician because of abscesses?

☐ Yes ☐ No

If Yes, did you get any of the following treatments? (tick once for each line)

Antibiotic ointment ☐ Yes ☐ No
Antibiotic tablets ☐ Yes ☐ No
Surgical drainage ☐ Yes ☐ No
A larger surgical intervention including skin removal ☐ Yes ☐ No
Surgical laser treatment ☐ Yes ☐ No
Follow-up questions
The following pages with questions should not be answered by everybody. If you have answered yes to one or more of questions below, we ask you to move on to the follow-up questions on the topic or topics you have answered yes to. The first four topics are from the first questionnaire and the last question is from this form.

We have for the sake of simplicity highlighted topics with different colours so that you will find the questions that applies to you.

If you answered YES to that you have: long-term or recurrent pain that has lasted for 3 months or more, please answer the questions on page 19 and 20. The margin is marked with green.

If you answered YES to that you have undergone any surgery during the last 3 years, please answer the questions on page 21 and 22. The margin is marked with purple.

If you answered YES to that you’re working outdoors at least 25% of the time, or in facilities with low temperature, such as warehouse/industrial halls, please answer the questions on page 23. The margin is marked with red.

If you answered YES to that you have used non-prescription pain relievers, please answer questions on page 24. The margin is marked with orange.

If you answered YES to that you have or have ever had skin problems (such as psoriasis, atopic eczema, non-healing leg or foot ulcers, recurrent hand eczema, acne or abscesses), please answer the questions on page 25. The margin is marked with yellow.

If you have answered NO to these five questions, you are finished with your answers. The questionnaire is to be returned in the reply envelope you were given at the survey site. The postage is already paid.

Should you wish to give us written feedback on either the questionnaire or The Tromsø Study in general, you are welcome to that on page 26.

Do you have any questions, please contact us by phone or by e-mail. You can find the contact information on the back of the form. THANK YOU for taking the time to the survey and to answer our questions.
13. FOLLOW-UP QUESTIONS ON PAIN

You answered in the first questionnaire that you have protracted or constantly recurrent pain that has lasted for 3 months or more. Here, we ask you to describe the pain a little closer.

How long have you had this pain?
Number of years □ □ months □ □

How often do you have this pain?
□ Every day
□ Once a week or more
□ Once a month or more
□ Less than once a month

Where does it hurt? (Tick for all locations where you have protracted or constantly recurrent pain)
□ Head/face
□ Jaw/temporo-mandibular joint
□ Neck
□ Back
□ Shoulder
□ Arm/elbow
□ Hand
□ Hip
□ Thigh/knee/leg
□ Ankle/foot
□ Chest/breast
□ Stomach
□ Genitalia /reproductive organs
□ Skin
□ Other location

What do you believe is the cause of the pain? (Tick for all known causes)
□ Accident /acute injury
□ Long-term stress
□ Surgical intervention/operation
□ Herniated disk (prolapse) /lumbago
□ Whiplash
□ Migraine/headache
□ Osteoarthritis
□ Rheumatoid arthritis
□ Bechterews syndrome
□ Fibromyalgia
□ Angina pectoris
□ Poor blood circulation
□ Cancer
□ Nerve damage/neuropathy
□ Infection
□ Herpes zoster
□ Another cause (describe below)
□ Don’t know

Describe the other cause:

Which kind of treatment have you received for the pain? (Tick for all types of pain treatments you have received)
□ No treatment
□ Analgesic medications/painkillers
□ Physiotherapy/chiropractic treatment
□ Treatment at a pain clinic
□ Surgery
□ Psycho-educative/relaxation training/psychotherapy
□ Acupuncture
□ Complimentary and alternative medicine (homeopathy, healing, aromatherapy, etc.)
□ Other treatment
On a scale of 0 to 10, where 0 corresponds to no pain and 10 corresponds to the worst possible pain you can imagine:

<table>
<thead>
<tr>
<th>Question</th>
<th>No pain</th>
<th>Worst imaginable pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>How strong would you say that the pain usually is?</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>How strong is the pain when it is in its strongest intensity?</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>To what degree does the pain interfere with your sleep?</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>To what degree does the pain interfere with performing common activities at home and at work?</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>
14. FOLLOW-UP QUESTIONS ON SURGERY

In the first questionnaire you answered that you have undergone an operation during the last 3 years.

14.01 How many times have you undergone surgery during the last 3 years?
Number ________________________________________________  

Below, please describe the operation. If you have undergone several operations during the last 3 years, these questions concern the last surgery you underwent.

14.02 Where in your body did you have surgery?  
(If you were operated simultaneously in several places in the body, tick more than once)
Surgery in the head/neck/back
   • Head/face ____________________________  
   • Neck/throat ________________________  
   • Back ________________________________  
Surgery in the chest
   • Heart _______________________________  
   • Lungs _______________________________  
   • Breasts _____________________________  
   • Another surgery in the chest region ______  
Surgery in the stomach/pelvis
   • Stomach/intestines ____________  
   • Inguinal hernia ________________  
   • Urinary tract/reproductive organs ______  
   • Gall bladder/biliary tract ......  
   • Another surgery in the stomach/pelvis ____________  
Surgery in the hip/legs
   • Hip/thigh ___________________________  
   • Knee/leg ___________________________  
   • Ankle/foot __________________________  
   • Amputation ________________________  
Surgery in the shoulder and arm
   • Shoulder/overarm _________________  
   • Elbow/underarm ____________________  
   • Hand _______________________________  
   • Amputation ________________________  

14.03 Reason for the surgery:
   Acute illness/trauma ________________  
   Planned non-cosmetic operation _______  
   Planned cosmetic operation ____________  

14.04 Where did you have the surgery?
   The hospital in Tromsø _____________  
   The hospital in Harstad ______________  
   Other public hospital ________________  
   Private clinic ________________________  

14.05 How long time is it since you had surgery?
Number of years ________  Months ________  

14.06 Do you have reduced sensitivity in an area near the surgical scar?
   Yes ________  No ________________________  

14.07 Are you hypersensitive to touch, heat or cold in an area near the surgical scar?
   Yes ________  No ________________________  

14.08 Does slight touch from clothes, showering or similar cause discomfort/pain?
   Yes ________  No ________________________  

14.09 If you had pain at the site of surgery before you had surgery, do you have the same type of pain now?
   Yes ________  No ________________________  

The pain at the site of surgery: Answer on a scale from 0 to 10, where 0=no pain and 10=worst pain you can imagine

How strong pain did you have at the site of surgery before you had surgery

No pain

Worst imaginable pain

How strong pain do you normally have at the site of surgery now ...........

No pain

Worst imaginable pain

How strong pain do you normally have at the site of surgery when it is most intense ..................................
# 15. FOLLOW-UP QUESTIONS ABOUT WORK IN COLD ENVIRONMENT

In the first questionnaire you answered yes to that you work in cold environments. Here are some follow-up questions that we hope you will answer.

## 15.01 Do you feel cold at work?
- Yes, often
- Yes, sometimes
- No, never

## 15.02 For how long have you been exposed to cold air below 0°C during the last winter?
- Leisure/hobbies (hours/week)
- Work (hours/week)
- Outdoors, with suitable clothing (hours/week)
- Outdoors, without suitable clothing (hours/week)
- Indoors, with no heating (hours/week)
- In cold, with wet clothing (hours/week)
- Contact with cold objects/tools (hours/week)

## 15.03 What ambient temperature prevents you from:
- Working outdoors
- Training outdoors
- Performing other activities outdoors

## 15.04 Have you during the last 12 months had a frostbite with blisters, sores or skin injury?
- Yes
- No

## 15.05 Have you had itching and/or rash in relation to cold exposure?
- Yes
- No

## 15.06 Have you during the last 12 months had an accident where cold has been involved, and which required medical treatment?
- Yes
- No

## 15.07 Do you experience any of the following symptoms while you are in a cold environment? If so, at what temperature do the symptoms occur?
- Breathing problems
- Wheezy breathing
- Mucus secretion from lungs
- Chest pain
- Disturbance in heart rhythm
- Impaired blood circulation in hands/feet
- Visual disturbance (short term/transient)
- Migraine (short term/transient)
- Fingers turning white (short term/transient)
- Fingers turning blue-red (short term/transient)

## 15.08 How does cold environments and cold-related symptoms influence your performance?

<table>
<thead>
<tr>
<th></th>
<th>Decrease</th>
<th>No effect</th>
<th>Improve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finger sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finger dexterity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control of movement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy physical work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-lasting physical work</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
16. USE OF NON-PRESCRIPTION PAINKILLERS

In the first questionnaire you answered that you had used non-prescription painkillers (analgesics) in the last 4 weeks. Here are some follow-up questions we hope you will answer.

16.01 What types of non-prescription painkillers have you used?

Paracetamol: (Pamol, Panodil, Paracet, Paracetamol, Pinex)
- Not used
- Less than every week
- Every week, but not daily
- Daily
How much do you usually take daily when you use these medicines?
(number of tablets, suppositories) ...........................................

Acetylsalicylates: (Aspirin, Dispril, Globoïd)
- Not used
- Less than every week
- Every week, but not daily
- Daily
How much do you usually take daily when you use these medicines?
(number of tablets) ...........................................................

Ibuprofen: (Ibumetin, Ibuprofen, Ibuproxy, Ibux)
- Not used
- Less than every week
- Every week, but not daily
- Daily
How much do you usually take daily when you use these medicines?
(number of tablets, suppositories) ...........................................

Naproxen: (Ledox, Naproxen)
- Not used
- Less than every week
- Every week, but not daily
- Daily
How much do you usually take daily when you use these medicines?
(number of tablets) ...........................................................

Phenazone with caffeine: (Antineuralgica, Fanalgin, Fenazon-koffein, Fenazon-koffein sterke)
- Not used
- Less than every week
- Every week, but not daily
- Daily
How much do you usually take daily when you use these medicines?
(number of tablets) ...........................................................

16.02 For which complaints do you use non-prescription painkillers? (multiple ticks are possible)
- Headache
- Menstrual discomfort
- Migraine
- Back pain
- Muscle/joint pain
- Tooth pain
- Other

16.03 Do you think you have experienced side effects of some of the medicines? (tick once for each line)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylsalicylates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenazone with caffeine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

16.04 Where do you usually purchase painkillers?
- Pharmacy
- Grocery
- Petrol stations
- Abroad
- Internet

16.05 Do you combine the treatment with the use of painkillers on prescription?
- Yes
- No
17. FOLLOW-UP QUESTIONS ABOUT SKIN DISEASES

On page 15 in this questionnaire you answered that you have or have had a skin disease. Here are some follow-up questions we hope you will answer.

Answer on a scale from 0 to 10, where 0 corresponds to no symptoms and 10 correspond to worst imaginable complaints. If you answered YES to that you have or have had:

<table>
<thead>
<tr>
<th>17.01 Psoriasis</th>
<th>No complaint</th>
<th>Worst imaginable complaints</th>
</tr>
</thead>
<tbody>
<tr>
<td>How much are you affected by your psoriasis today?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>How much are you affected by your psoriasis when it is most severe?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 17.02 Atopic eczema | | |
|---------------------|----|
| How much are you affected by your atopic eczema today? | | |
| How much are you affected by your atopic eczema when it is most severe? | | |

| 17.03 Hand eczema | | |
|------------------|----|
| How much are you affected by your hand eczema today? | | |
| How much are you affected by your hand eczema when it is most severe? | | |

| 17.04 Acne | | |
|------------|----|
| How much are you affected by your acne today? | | |
| How much are you affected by your acne when it is most severe? | | |

| 17.05 Abscesses | | |
|----------------|----|
| How much are you affected by your abscesses today? | | |
| How much are you affected by your abscesses when it is most severe? | | |

<table>
<thead>
<tr>
<th>17.06 Here is a list of factors that might trigger or exacerbate abscesses, tick for what you think apply to you:</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress/psychological strain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narrow/tight clothing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual periods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 17.07 How many episodes of abscesses do you usually have per year? (tick once) | | |
|-----------------------------|----|
| 0-1 | | |
| 2-3 | | |
| 4-6 | | |
| More than 6 | | |

| 17.08 How old were you when you got abscesses for the first time? | | |
|-----------------|---|
| 0-12 years | 26-35 years |
| 13-19 years | 36-50 years |
| 20-25 years | Older than 50 years |

| 17.09 If you no longer have abscesses, how old were you when it disappeared? | | |
|-----------------|---|
| 0-12 years | 26-35 years |
| 13-19 years | 36-50 years |
| 20-25 years | Older than 50 years |
Should you wish to give us a written feedback on either the questionnaire or The Tromsø Study in general, you are welcome to do it here:
Thank you for your help
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