THE CORRELATION BETWEEN SMOKING, SNUFF AND MS

A CASE – CONTROL STUDY

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Summary

MS is an immune mediated, demyelinating disease of the central nervous system. The disease is multifactorial, and it is believed that both genetic and environmental factors matter in the development of the disease. Our assignment is part of an ongoing study of MS and environmental risk factors done at Oslo University Hospital, based on a questionnaire where the participants among other issues were asked about smoking habits, exposure to passive smoking and snuffing habits throughout their current lifespan.

The data in the patient group was adjusted to correspond to the time of disease onset. A total of 1374 persons were included in the study; 455 patients from Oslo MS Registry and 919 controls from The Norwegian Bone Marrow Donation Registry. We investigated tobacco as a risk factor for developing MS by comparing active and passive smoking and snuffing habits among the MS patients compared to the controls. Hedström et al. did a similar study in Sweden in 2009, and we have compared our results with their data.

We found no significantly elevated risk for developing MS for those who had been exposed to tobacco through snuffing or passive smoking nor for ex-smokers, but an elevated risk for current smokers. While the risk seemed to be elevated with the first 1-5 pack years of smoking, we found no significantly elevated risk for higher amounts of pack years. Sources of error such as selection bias, recall bias and errors due to adjusting of data in the patient group to match that at the onset of the disease may have influenced the results.

Contents

Preface

This medical student thesis was carried out in 2011-2012 as a mandatory part of the medical studies at the Faculty of Medicine, University of Oslo. As we find neurology interesting and wished to learn more about how a clinical study is conducted, we chose to join this study which is part of a bigger project at Oslo University Hospital. We wish to thank our supervisors Hanne F. Harbo, Elisabeth G. Celius and Marte W. Gustavsen for good support and guidance while working with the assignment.

Introduction

Multiple sclerosis is an immune mediated, demyelinating disease of the central nervous system (CNS). Norway is a country with a relatively high prevalence of the disease, with approximately 150 cases per 100 000 citizens. (1) About twice as many women as men are affected. (2) Age at onset of the disease is usually in the early 30s. (3)

The disease is multifactorial, and it is believed that both genetic and environmental factors matter in the development of the disease. (4;5) MS has been studied for more than a hundred years, and one is still unsure about the cause of the disease.

Pathogenesis

The pathogenesis of MS is still only partly known. It is believed to be an autoimmune disease (6), and response to immune modulatory drugs is seen when treating MS patients. One of many theories suggests that the disease begins with an increased migration of autoreactive lymphocytes across the blood-brain-barrier (BBB). (7)

MS may have two forms of presentation, and symptoms are caused both due to inflammation and degeneration in the CNS tissue. The inflammation is local but can be disseminated in all parts of the CNS, develops in subacute attacks and is often recurrent (relapsing remitting). Degeneration of the CNS tissue is diffuse and can appear early and lead to chronic and progressive symptoms.

The inflammation affects the myelin surrounding most of the neurons in the CNS. After several relapses of inflammation, the myelin is no longer capable of regeneration and there is a chronic damage and axonal loss in that specific area. Relapses of the inflammatory component are the main causes of the irreversible damages seen in MS. (8)

Clinical aspects

The clinical symptoms of MS can appear from any parts of the CNS. Examples are numbness or other sensory symptoms, spasticity, double vision, paresis, ataxia and bladder control problems. (3)

MS is usually divided into two groups: Primary progressive MS (PP-MS) and relapsing remitting MS (RR-MS). The majority of the persons with RR-MS will eventually develop secondary progressive MS (SP-MS). RR-MS is characterized by several episodic relapses with symptoms and neurological deficits from different parts of the CNS. It occurs during a short period of time and may resolve over days to weeks (9), in contrast to the patients with PP-MS and SP-MS in which the symptoms gradually progress. A Norwegian cohort study initiated in 2006 showed this distribution: RR-MS was seen in 73.6% and PP-MS in 24.1%. (The initial disease could not be defined in 0.02% of the patients.) (9)

Diagnostic tools

Diagnosis is made clinically, after the patient has experienced symptoms and neurological deficits at two or more independent occasions from different parts of the body. In addition a thorough medical history, a complete neurological examination, an investigation of the cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) of the brain are done. The MRI pictures usually show plaques consistent with demyelination and gliosis. The characteristic picture is loss of myelin, gliosis, a variable degree of axonal damage correlating to neurological dysfunction. (10)

The CSF usually displays a moderate pleocytosis and increased intrathecal immunoglobulin G. Approximately 95% of MS-patients have increased CSF serum IgG ratio and/or oligoclonal bonds. (11)

Treatment and prognosis

An MS relapse is treated with corticosteroids in the acute phase. If a patient has an active relapsing remitting disease, immunomodulatory treatment is recommended. Apart from this most of the treatment is symptomatic. (11)

MS is not generally a fatal disease, and most people live normal or near-normal lives. The causes of death are mainly the same as in the general population (mainly heart disease and cancer). However, having the condition can be tough, and the suicide rates among MS patients are higher than average. About 20% of patients remain asymptomatic or only experience one or two light episodes with mild symptoms. Another 20% will develop a rapidly progressive MS. The remaining 60% will have some disease progression. (12)

The following factors have by multivariate regression analysis been found to be associated with longer survival in patients with MS: Age under 30 years when developing the primary symptoms, initial symptoms affecting brainstem/cerebellar functions in comparison with motor skills, and being diagnosed with RR-MS rather than PP-MS. (9)

Genetics

There is no increased prevalence of MS in partners of patients with MS, but the risk of developing the disease is higher in offspring of two parents with MS than if only one of the parents has the disease. (13-15)

The risk of developing MS increases from approximately 0.015 in the general Norwegian population to around 2-3% if someone closely related (e.g. siblings, parents, children) has MS. (7)

The risk of developing the disease in half-siblings of MS patients is approximately half the risk of the one seen in siblings, independent of whether they are raised together or separately. (16) There is no increased risk in step siblings, who are not genetically related.

These data suggest that living together with someone who has MS or will develop MS in the future has little or no influence unless one is genetically related to them, and then the risk will increase according to the family relation with the patient. (17)

The risk is reduced from approximately 3% in first-degree relatives (siblings 5%, parents and children 2%) to 1% in second-/third-degree relatives. (7) A study done in the UK and Canada among twins where one of them had MS showed a higher concordance among monozygotic compared to dizygotic twins (concordance 25% vs. 5%). (18;19)

The association between MS and MHC-alleles was identified in the early 70s. (20) The HLA-DRB1 locus has been found to be the major genetic risk factor for developing MS, but recently more than 50 other MS risk loci have also been identified. (21;22)

Distribution

Some studies have found an increasing prevalence of MS with increasing distance north and south from equator. Migration studies supporting this finding have found migration from high- to low-risk regions during childhood to be associated with decreased risk of developing MS and in reverse, thus supporting a theory of exposure to certain environmental factors during childhood contributing to the risk of developing MS. (23) Other studies do not find such an association between age at migration and MS. (24;25)

Vulnerable age hypothesis

An interesting but controversial theory published in 1995 by Kurtzke et al claims that the cause of MS is an asymptomatic primary infection only affecting a few of those exposed. It was based on data gathered on the Faroe Islands, which showed that the incidence of MS among the inhabitants after 1943 was increasing from values close to zero after an increasing contact with foreigners on the islands due to World War 2, but only in the inhabitants aged 11-45 at the time of exposure. (26)

Environmental factors

Many different environmental factors have been suggested as risk factors for developing MS. There are indications that among other factors, smoking, low levels of vitamin D and infection with Epstein Barr virus may contribute to the risk of developing MS.

Vitamin D

Vitamin D has several functions in the body, the most well known being its regulatory effects on phosphate and calcium concentrations in blood and extracellular fluid. Therefore, vitamin D deficiency traditionally has been linked to affection of the skeleton, mainly rickets in children and osteomalacia in adults. (27;28) Over the last years, however, there has been found evidence of other health issues influenced by vitamin D deficiency, among these

development of cardiovascular disease, diabetes mellitus, cancer, allergy, asthma, depression and multiple sclerosis. (28)

The consumption of vitamin D in humans takes place through diet, dietary supplements and production in the skin. Production of vitamin D in the skin through exposure to sunlight is, for most people, the most important source of vitamin D. (29) It has long been known that dark-skinned are at a higher risk of developing low levels of vitamin D than fair-skinned (30;31), which can be explained in different ways. Several studies have found that they need higher doses of ultraviolet radiation to produce the same amount of vitamin D as fair-skinned (32), while others do not find this connection between skin pigmentation and vitamin D production. (33) There are few groceries that naturally contain vitamin D, and the ones that do have a very variable vitamin D-content. (34) The most important source of vitamin D in the Norwegian diet is fatty fish and vitamin-enriched margarine, in addition to one vitamin D-enriched milk type and an oil. (27)

There has for a long time been speculated on the impact of vitamin D on the risk of developing MS. Several facts indicate a connection, among others the following: The prevalence of MS is lowest around equator, increasing with latitude on both the northern and southern hemisphere. (35-37) Some studies have found the prevalence of MS in migrants to lie in between that of their birthplace and that of their place of residence, and when migration takes place in childhood, the MS prevalence is closer to that of their place of residence than when migration takes place later in life. (38) These findings can be explained by decreasing amounts of UVB with increasing distance from equator, leading to a lower production of vitamin D in the population.

There is a high prevalence of osteoporosis among MS patients, and a Norwegian study comparing bone mineral density between MS patients and controls found it to be reduced already early in the course of MS. This could be explained by a common etiology between the two conditions, supporting the theory of low vitamin D levels influencing the risk of developing MS. (39)

Epstein - Barr virus

Epstein-Barr virus (EBV), also known as human herpes virus 4, consists of a double stranded, linear DNA surrounded by a protein capsule. (40) EBV can be found in more than 90% of the world's population, which makes it one of the most common viruses in human beings. The primary infection with EBV in children is usually asymptomatic, while infection later in life more often gives symptoms, for over 50% as infectious mononucleosis. The acute illness usually passes in a matter of weeks, but EBV remains in an inactive form in memory B-cells for the rest of the patient´s life. Later on, the virus can get periodically reactivated. (41)

Multiple studies have shown a relation between infection with EBV and development of MS.

Among other things, there has been found elevated titres of EBV-antibodies in MS patients compared with healthy controls. (42;43) One study found seropositivity of EBV in 99.9% of MS-patients, compared to 94.2% in the control group. (44) Similar results have been found in other studies. EBNA1 (Epstein-Barr nuclear antigen 1)-specific CD4+ memory T-cells that are an important part of the body´s defence mechanism towards EBV, have been found to be present in larger quantities in MS-patients compared to healthy carriers of the virus. (41) There has also been observed increased numbers of CD8+ T-cells against EBV among patients in early stadiums of MS. (45) If these results are caused by an elevated risk of developing MS after an infection with EBV or if they are due to an increased tendency of viral reactivation in patients with MS is being discussed. MS and infectious mononucleosis show the same distribution globally, with prevalence increasing with distance from equator. (41) A meta-analysis of earlier publications of cohort and case–control studies on infectious mononucleosis and MS found a combined relative risk of 2.3 for developing MS after exposure to mononucleosis. (46) The same discovery was found in a Danish study, where the risk of developing MS was shown to remain elevated for 30 years after the infection. (44)

Isolation of EBV or other microbes from the MS brain has so far been unsuccessful, and thereby it is supposed that MS is not caused by infection of nerve cells. (47) There has been found a cross-activation between EBV-specific antigens and myelin proteins in the CNS (molecular mimicry), which can point in the direction of an autoimmune mechanism in the development of MS. (48;49)

Smoking

In the Norwegian population, 17% smoke on a daily basis, and there are many more that smoke occasionally. (50) Differences in Norwegian smoking habits related to sex and age are demonstrated by the Central Bureau of Statistics in Norway (SSB). Results from 2011 show that the percentage of smokers (daily and occasional) in the Norwegian male population varies between 27-34% in the age group of 16-64 years. The prevalence is reduced to 18% after 65 years of age. In the female population, the prevalence of people smoking varies between 19 and 35%, being lowest in the group above 65 years and highest in the group between 45 and 54 years of age.

Smoking affects our health in many different ways, and increases the risk of developing heart or lung disease, infections and cancer. (51) Smoking is also associated with increased risk of developing autoimmune diseases like MS, rheumatoid factor positive rheumatoid arthritis, systemic lupus erythematosus, autoimmune disease of the thyroid, and optic neuropathy. (52-54) Several studies have seen a connection between smoking and MS. (55;56)

Smoking also increases the frequency and the duration of several airway infections. This may be relevant in MS because infections are an important factor in the etiology of MS, even though specific causes have not yet been identified. (53)

A study from 2005 (57) concludes that smoking probably is associated with a deterioration of the disease. This study showed that the risk of developing SP-MS among RR-MS patients was three times higher for smoking patients than for non-smoking patients. Kock et al (2007), on the other hand, concluded that there was no correlation between smoking and deterioration of the disease. (58)

Nicotine and other substances in cigarette smoke affect the blood-brain-barrier (BBB), blood circulation in the brain and signaling pathways of the CNS. One of the hypothesis concerning the etiology is the crossing of lymphocytes over the BBB. One theory suggests that the nicotine, and possibly other substances, influence the BBB in a way making it easier for substances to cross over to the brain and the CSF and cause damage. (59)

Passive smoking

There have not yet been done many studies concerning the relation between passive smoking and MS. In general it is believed that passive smoking, like active smoking, increases the risk of lung diseases and other diseases related to cigarette smoke. (60) A Swedish study by Hedström et al from 2011 found an increased risk of developing MS when previously exposed to passive smoke, and suggested that the irritation of the lungs could be a possible cause of the disease. (55)

Snuff

Snuff is a type of smokeless tobacco that is made from pulverized tobacco leaves. In the Norwegian population 8% snuff on a daily basis and even more snuff occasionally. The numbers are increasing in both sexes, mainly in the age group of 16-24 years. (50) The number of snuffers, both daily and occasional snuffers, in the male population varies between 3 and 41%, the prevalence being highest in the group between 16-24 years and then decreasing to 3% in the age group of 65 to 74 years. In the female population, the same pattern of age distribution is seen, the prevalence being highest in those aged 16 – 24 and then decreasing to 1% with higher age. (61)

Snuff contains more than 2500 chemical substances, among them nicotine. The amount of nicotine ingested depends on the type of snuff and the duration of which the snuff stays in one's mouth. (62)

Many people switch from smoking to snuffing because they believe that there is a lesser risk of developing nicotine-related diseases when snuffing compared to smoking. Use of snuff leads to exposure to similar or higher doses of nicotine than when smoking tobacco, but the exposure of nicotine to the airways is diminished. There has been seen an association

between tobacco smoking and the risk of inflammatory diseases like MS in many studies done previously, but impacts of smokeless tobacco have not yet been fully investigated. A study done in Sweden in 2009, however, showed an increased risk of developing MS among smokers, and a decreased risk of developing MS among snuffers. (56)

Methods

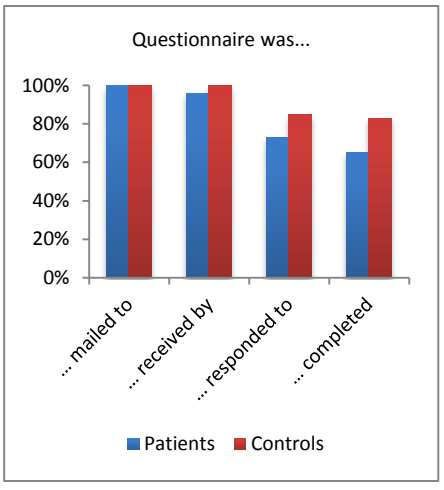
Our study is part of an ongoing study of MS and environmental risk factors, done at Oslo University Hospital. Our work, which is a case-control study, studies tobacco as a risk factor for developing MS by comparing active and passive smoking and snuff habits in MS patients with those of the controls. Hedström et al. did similar studies in Sweden in 2009 and 2011 (55;56), and we have compared our results with their study from 2009 when analyzing our own data. To be able to compare the results, we used their study as a model when choosing definitions and subdivisions of our data.

Figure 1: Collection and processing of data

Choosing a patient and a control group.
↓
Collecting/validating questions invented and gathered from other studies. Making the Questionnaire (Q).
↓
Test-retest of 50 hospital employees.
↓
Approval by the Norwegian Ethical Committee.
↓
Sending out the Q by mail.
↓
Sending out a reminder.
↓
Scanning and selection of relevant data.
↓
Revising improbable data. Collecting missing data.
↓
Calculating OR and 95% CI.
↓
Comparing with Swedish study. Writing the assignment.

The present study is part of a larger standardized questionnaire with questions collected from other validated studies, among these the HUNT (Nord-Trøndelag Health Study) and the GEMS study (Genes and Environment in Multiple Sclerosis). The questions used in this study are validated. The questionnaire was sent by mail to patients and controls after we had done a local validation by a test-retest including 50 hospital employees. Some of the questions were changed after this in order to increase their reliability. The questionnaire was approved by The Norwegian Ethical Committee, and all the patients included in the study, gave written informed consent.

Figure 2: Collection of data



The MS group consists of patients registered in The Oslo MS Registry. It includes people living mainly in Oslo. The healthy control group was chosen from The Norwegian Bone Marrow Donation Registry. These controls have available DNA-samples and HLA-data, which will be used in extensions of this study.

The questionnaire was sent to 720 MS patients. 30 of these were returned unopened by the postal services, thus 690 patients received the questionnaire. 526 patients responded, 60 of

these checked for not wishing to answer the questions. That leaves us with a response rate of 76.2%, and 67.5% completed the questionnaire. The questionnaire was sent to 1100 controls, of which three were returned unopened by the postal services. Of the 1097 who received the questionnaire, 931 responded and 19 of these checked for not wishing to answer the questions. The response rate among the controls was therefore 84.9%, and 83.1% completed the questionnaire.

Three of the controls reported to have MS. They were excluded from the study. In cases where the questionnaire was not filled in correctly, but the meaning of the answer was clear (e.g. in cases where the participant had not checked for if they smoked or not, but filled in the years and amount of smoking in the next question), the missing part was corrected. Missing information on sex and age, in addition to all information on year of MS debut and type of MS, were gathered from a database based upon the patients' journals. The rest of the answers with insufficient response were marked as invalid data. These were not included in the statistical analysis. In cases where parts of the questionnaire have been filled in correctly, only the answers considered as invalid data was removed from the analysis.

The questionnaire covered a number of diseases and risk factors. Of these, we looked at the questions covering age, sex, highest level of education completed, MS status and age at onset of MS in addition to information concerning smoking habits, passive smoking and snuff use. The questionnaire separated cigars, cigarillos and pipes from cigarettes. To simplify the analyses, we chose to gather all these into one single group of tobacco use. In the question about education, the participants were asked to indicate which of the five listed levels of education that was the highest they had completed. In our work, we gathered these into two categories; those who had completed high school or less, and those who had a degree from college/university.

The questionnaire investigated smoking and snuff use up to the current date. Since our main focus was the exposure before onset of disease in the patients, these data have been adjusted to correspond to the time of onset of MS. This was done by comparing the years of onset and quitting of smoking/snuffing with their debut year of MS. When not specifically indicated otherwise, the adjusted information was used when analyzing the patient data.

In order to be able to compare the cumulative consumption of smoking and snuff use with the risk of developing MS, we used the collected data to calculate pack years. One pack year of smoking is defined as 20 cigarettes smoked per day for 1 year, while one pack year of snuff use is defined as consuming 1 packet of snuff daily for 1 year.

The pack years for smoking and snuffing were divided into groups of 0, 1-5, 6-10, 11-15 and 16 or more years, and the years of exposure to passive smoking was divided into the same pattern. The group of 0 pack years includes both the ones who never have been exposed, and the ones who have been exposed in too small values to reach one pack year. The results

were also divided into one group of those who never had been exposed, and another group of those who had been exposed at least once in their lives (including all the subdivisions of pack years/years of exposure). The smokers were also divided into current smokers and ex-smokers, and the ex-smokers were subdivided into those who had stopped smoking 1-4 years ago and those who had stopped smoking 5 years ago or more. Odds ratio (OR) and 95% confidence interval (95% CI) were then calculated based upon these groups, comparing the risk of developing MS among tobacco exposed patients with that of the tobacco exposed controls (Tables 3-5).

Results

General characteristics

Of the 1374 individuals included in our study, 455 were MS patients and 919 were controls. The patient group consisted of 117 (25.7%) men and 338 (74.3%) women. Of the controls, 383 (41.7%) were men and 536 (58.3%) women. The mean age at the time of filling in the questionnaire was 52.7 for the patients and 43.9 for the controls. The mean age at onset of MS for the patients was 32.2. Of the patients, 279 (61.3%) had a degree from college or university. The corresponding number for the controls was 568 (61.8%). (Table 1)

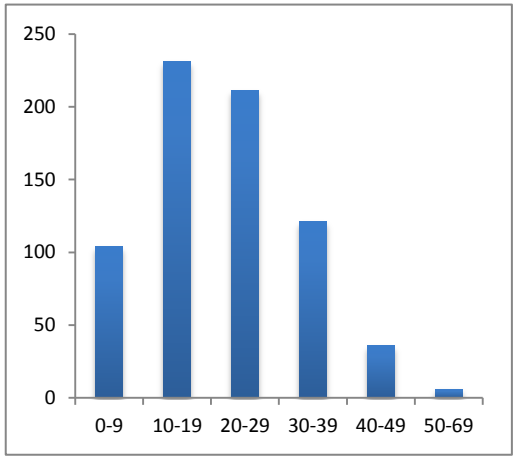
Table 1: Distribution of gender, age and education

	Patients		Controls	
	n=	%	n=	%
Gender				
Men	117	25.7%	383	41.7%
Women	338	74.3%	536	58.3%
Age				
20-39 years	68	14.9%	268	29.2%
40-49 years	122	26.8%	433	47.1%
50-59 years	130	28.6%	213	23.2%
≥ 60 years	135	29.7%	5	0.5%
Education				
High school or less	173	38.3%	338	37.3%
College or more	279	61.7%	568	62.7%

The ones diagnosed with relapsing remitting or secondary progressive MS made up 398 (88.2%) of the patients, of which 92 (23.1%) were men and 306 (76.9%) women. Of the remaining patients, 53 (11.8%) had the diagnosis primary progressive MS, including 25 (47.2%) men and 28 (52.8%) women. (Table 2)

Table 2: MS					
		RR/SP n=	%	PP n=	%
Type of MS					
	Men	92	23.1%	25	47.2%
	Women	306	76.9%	28	52.8%
	Total	398		53	
Age at MS onset					
	0-29 years	195	49.0%	13	24.5%
	30-39 years	130	32.7%	14	26.4%
	40-49 years	63	15.8%	14	26.4%
	≥50 years	10	2.5%	12	22.6%

Figure 3: Years since onset of MS in the patient group



Smoking

Compared to never-smokers, ever-smokers had a risk of 2.8 (1.2-2.0) for developing MS. The result for the current smokers was 5.7 (1.6-2.8), while it was 0.8 (0.6-1.3) for ex-smokers. When dividing the ex-smokers into groups of those who had stopped smoking 1-4 years ago and those who had stopped smoking 5 years ago or more, there seemed to be a slightly increased correlation to the development of MS in the first group, but those data were nonsignificant. The risk of developing MS rised to 3.3 (1.2-2.3) with the first 1-5 pack years of smoking, while the data for higher number of pack years did not show any significant differences compared to zero pack years. (Table 3)

Table 3: Smoking						
	Patients		Controls		OR	95% CI
	n=	%	n=	%		
Smoking habits						
Never-smokers	103	23.0%	414	45.6%	1.0	-
Ever-smokers	345	77.0%	493	54.4%	2.8	1.2-2.0
Ever-smokers						
Ex-smokers	60	17.4%	292	59.2%	0.8	0.6-1.3
Current smokers	285	82.6%	201	40.8%	5.7	1.6-2.8
Years since smoking cessation						
1-4 years	25	47.2%	65	22.7%	1.5	0.7-2.0
5 years or more	28	52.8%	221	77.3%	0.5	0.5-1.2
Pack years smoking						
0 years	154	37.3%	474	53.8%	1.0	-
1-5 years	99	24.0%	93	10.6%	3.3	1.2-2.3
6-10 years	66	16.0%	83	9.4%	2.4	1.0-2.1
11-15 years	52	12.6%	76	8.6%	2.1	0.9-2.1
≥16 years	42	10.2%	155	17.6%	0.8	0.6-1.4

Passive smoking

The risk of developing MS for those who had been exposed to passive smoking at home was 1.1 (0.8-1.4), which was not significantly different from those who never had been exposed to passive smoking. (Table 4)

Table 4: Passive smoking						
	Patients		Controls		OR	95% CI
	n=	%	n=	%		
Exposure to passive smoking						
No	115	25.3%	253	28.0%	1.0	-
Yes	339	74.7%	652	72.0%	1.1	0.8-1.4
Years of exposure						
0 years	152	33.9%	257	28.5%	1.0	-
1-5 years	38	8.5%	46	5.1%	1.4	0.7-1.9
6-10 years	32	7.1%	63	7.0%	0.9	0.6-1.5
11-15 years	38	8.5%	65	7.2%	1.0	0.6-1.6
≥16 years	188	42.0%	471	52.2%	0.7	0.6-1.1

Snuff

The group of ever-snuffers was made up of 39 (8.6%) patients and 141 (15.3%) controls, and the ever-smokers of 345 (75.8%) of the patients and 493 (53.6%) of the controls. Among the passive smokers, 339 (74.5%) of the patients and 652 (70.9%) of the controls had been exposed to passive smoking at home. (Tables 3-5)

We found an OR of 0.5 (95% CI: 0.5-1.1) for ever-snuffers compared to those who never had used snuff (Table 5), and therefore no correlation between the use of snuff and development of MS.

Table 5: Snuff

	Patients		Controls		OR	95% CI
	n=	%	n=	%		
Snuff use						
Never-snuffers	412	91.4%	766	84.5%	1.0	-
Ever-snuffers	39	8.6%	141	15.5%	0.5	0.5-1.1
Pack years snuff						
0 years	429	98.8%	800	93.8%	1.0	-
1-5 years	5	1.2%	39	4.6%	0.2	0.2-1.4
≥ 6 years	0	0.0%	14	1.6%	0.0	-

Comparison with Swedish study

Hedström et al (56) found an elevated risk of developing MS among current smokers (OR 1.4, 95% CI 1.1-1.8) and ever-smokers (OR 1.5, 95% CI 1.3-1.8). Among ex-smokers they found the risk to be increased for the first 5 years after smoking cessation (OR 1.5, 95% CI 1.1-1.2). They also found snuff to be a possible protective factor for the development of MS, both when comparing pack years of snuff with zero pack years among never-smokers (1-5 pack years; OR 0.4, 95% CI 0.01-13, over 5 pack years; OR 0.4, 95% CI 0.01-18) and among ever-smokers (1-5 pack years; OR 0.5, 95% CI 0.2-1.3, over 5 pack years; OR 0.3, 95% CI 0.1-0.9). In accordance with their data we found an elevated risk of developing MS among current smokers, but we found no increased incidence of MS in ex-smokers nor any correlation between MS and snuffing.

Discussion

According to our observations there was an increased risk of developing MS in smokers, but we found no significantly elevated risk in those who had stopped smoking. Our study did not find any correlation between neither passive smoking, nor the use of snuff, and MS.

As mentioned earlier, our finding of an increased risk of developing MS in current smokers is consistent with the results of Hedström et al. (56) They also found an increased risk of developing MS for the first 5 years after smoking cessation (OR 1.4, 95% CI 1.0-1.6), while we did not find this risk to be elevated in any of the ex-smokers. In accordance with their results, we also found an increased risk of developing MS for the first 1-5 pack years of smoking, but for higher values of pack years our data were inconclusive. Hedström et al found the risk to increase slightly with number of pack years. While Hedström et al found snuff to be a possible protecting factor for developing MS, we found no connection between the two. Our data may differ from theirs due to different factors, for instance our comparatively lower number of patients and controls or one or more of the sources of error discussed below.

Since data in the patient group was adjusted to correspond to the time of onset of MS, lifestyle information gathered through the questionnaire may reflect habits the patients had up to several decades ago. (Figure 3) While the number of daily smokers in the Norwegian population has been reduced by almost 50% over the last 15 years, the incidence of snuffers is increasing. This change in tobacco intake over time could contribute to the apparent differences in smoking and snuffing habits between the patients and the controls in our work. The time lag between the two groups could also explain the three times higher prevalence of ex-smokers among the controls than among the patients, and the number of people who quit smoking less than 5 years ago being highest among the patients. (Table 3) Although the patient group is somewhat older than the control group at the time of filling in the questionnaire (Table 1), the patients in general were younger than the controls are now when they were diagnosed with MS (Table 2). The overrepresentation of males in the control group compared to the patient group could also contribute to the discussed differences. The age difference and the overrepresentation of males in the control compared to the patient group could also contribute to the discussed differences. Snuff use is increasing more among younger than older individuals, and more males than females snuff in the general population. (50)

Although the education level seemed to be the same in the two groups, a significantly smaller number of controls than patients stated to be ever-smokers, while the rate of snuffing was highest among the controls. The controls were chosen from a bone marrow registry, and it therefore is likely that they in general are healthy individuals, and may be more concerned with lifestyle factors than the rest of the population. In addition, we got feedback from caregivers of some of the MS patients with the message that due to cognitive impairment caused by the disease, those patients were not able to answer the questionnaire. This is reflected by a somewhat lower response rate, and a lower number of completed questionnaires among the responders in the patient group.

Since most of the questions were answered in retrospect, we cannot exclude the risk of a recall bias. Being asked about everyday habits decades ago, naturally gives some degree of uncertainty in the answers, probably in both our trial groups. The mean age difference of almost nine years between the patients and the controls when filling in the questionnaire, in addition to a possible reduced cognitive function in the patients due to the disease, could lead to a higher degree of uncertainty in the answers of the patients than those of the controls. On the other hand, people diagnosed with a chronic disease naturally focus more on possible risk factors, which may lead to more thought through answers among the patients.

By using validated questions, we tried to ensure a best possible quality of the questionnaire. However, when going through the answers, it was clear that some of the questions had been badly interpreted. By checking all unlikely values, and excluding the ones clearly misunderstood, we tried to diminish this source of error. As the questionnaire included fourteen pages, while the questions used in our study only made up four of these, it is understandable that only a limited amount of time has been used answering each question, this being a possible source of error.

Conclusion

Smoking seems to increase the risk of developing MS. Our results showed a marked increased risk of developing MS within the first 5 pack years, but thereafter no significantly elevated risk with higher quantities of smoking. This differs from results in other studies, among them the Swedish study discussed earlier, which found an elevated risk of developing MS also for higher numbers of pack years. For those who had ceased smoking, we found the same risk of developing MS as in the general population. We found snuff and passive smoking neither to increase nor decrease the risk of developing MS, and we believe that further and more detailed studies will have to be conducted in order to investigate their possible influence on the risk of developing MS. Our results must be considered in the light of the discussed time lag between the patient and the control group due to adjustments of patient data done to match the timing of onset of the disease.

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Attachments

Questionnaire (original Norwegian version)

9446436354

Oslo universitetssykehus

Kode | | | | | | |

Spørreskjema om miljøfaktorer

Kjære deltaker.

Dette spørreskjemaet inneholder spørsmål om din familiebakgrunn, utdannelse og arbeid, kosthold og andre livsstilsforhold, og sykdommer du har eller har hatt. Se vedlagt informasjonsbrev for utfyllende informasjon.

Om å fylle ut skjemaet:
Skjemaet skal leses optisk. Vennligst bruk blå eller sort kulepenn. Hvis du skriver feil, stryk tydelig over med en rett linje og kryss av i riktig boks. Vi ber deg krysse av i midten av rutene og skrive med STORE bokstaver i rutefeltene som vist under. Dersom noe skrives utenfor de markerte feltene, vil ikke dette bli registrert. Hvis du har kommentarer eller tilbakemeldinger, ber vi deg skrive dette i kommentarfeltet på siste side.

Slik: X | O | S | L | O | |

Ikke slik: X | O | S | L | O |

På forhånd tusen takk for ditt verdifulle bidrag!

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss i rutene under og og returner skjemaet i vedlagt svarkonvolutt. Da slipper du purring!

☐ Jeg ønsker ikke å besvare skjemaet

☐ Kvinne ☐ Mann Alder: | |

Bakgrunn

1. Kjønn: ☐ Kvinne ☐ Mann

2. Fødselsmåned:
(01 for jan, 02 for feb osv.) ☐☐ **Fødselsår:** ☐☐☐☐

3. Høyde og vekt

Hva er din høyde? ☐☐☐ cm

Hva er din vekt? ☐☐☐ kg

Omtrent hva var din høyde da du var 18 år? ☐☐☐ cm ☐ Husker ikke

Omtrent hva var din vekt da du var 18 år? ☐☐☐ kg ☐ Husker ikke

4. Ditt fødeland: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Hvis du ikke er født i Norge, hvilket år flyttet du hit? ☐☐☐☐

5. Fødeland til dine biologiske foreldre og besteforeldre:

Mormor: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Mor: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Morfar: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Farmor: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Far: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Farfar: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Sykdommer eller kirurgisk behandling

6. Har du, eller har du noen gang hatt, noen av disse sykdommene/plagene:
(Sett ett kryss pr. linje)

	Ja	Nei	**Hvis ja,** hvor gammel var du første gang?
Hjerteinfarkt	☐	☐	☐☐ År gammel
Angina pectoris (hjertekrampe)	☐	☐	☐☐ År gammel
Hjertesvikt	☐	☐	☐☐ År gammel
Annen hjertesykdom	☐	☐	☐☐ År gammel
Hjerneslag/hjerneblødning	☐	☐	☐☐ År gammel
Nyresykdom	☐	☐	☐☐ År gammel
Astma	☐	☐	☐☐ År gammel
Kronisk bronkitt, emfysem, KOLS	☐	☐	☐☐ År gammel
Diabetes (sukkersyke) type 1	☐	☐	☐☐ År gammel
Diabetes (sukkersyke) type 2	☐	☐	☐☐ År gammel
Psoriasis	☐	☐	☐☐ År gammel
Leddgikt (reumatoid artritt)	☐	☐	☐☐ År gammel
Bechterews sykdom	☐	☐	☐☐ År gammel
Sarkoidose	☐	☐	☐☐ År gammel
Benskjørhet (osteoporose)	☐	☐	☐☐ År gammel
Slitasjegikt (artrose)	☐	☐	☐☐ År gammel
Myasthenia Gravis	☐	☐	☐☐ År gammel
MS (multippel sklerose)	☐	☐	☐☐ År gammel
PSC (primær skleroserende kolangitt)	☐	☐	☐☐ År gammel

Fortsettelse spørsmål 6:

	Ja	Nei	**Hvis ja**, hvor gammel var du <u>første</u> gang?
Cøliaki	☐	☐	☐☐ År gammel
Inflammatorisk tarmsykdom (ulcerøs kolitt eller Crohns sykdom)	☐	☐	☐☐ År gammel
SLE (systemisk lupus erytematosus)	☐	☐	☐☐ År gammel
Sjøgrens sykdom	☐	☐	☐☐ År gammel
Lavt stoffskifte (hypotyreose)	☐	☐	☐☐ År gammel
Høyt stoffskifte (hypertyreose)	☐	☐	☐☐ År gammel
Fjernet mandler (tonsillektomi)	☐	☐	☐☐ År gammel
Fjernet blindtarmen (appendektomi)	☐	☐	☐☐ År gammel
Migrene	☐	☐	☐☐ År gammel

Infeksjonssykdommer

7. Har du hatt kyssesyke (mononukleose)? ☐ Ja ☐ Nei ☐ Vet ikke

Hvis ja, hvor gammel var du da du hadde sykdommen? ☐☐ År gammel

8. Har du hatt annen infeksjonssykdom før fylte 18 år som krevde sykehusinnleggelse? ☐ Ja ☐ Nei ☐ Vet ikke

Hvis ja, hva slags infeksjon hadde du?

☐ Lungebetennelse

☐ Nyre/urinveisinfeksjon

☐ Mage/tarminfeksjon

☐ Infeksjon i hjerne/hjernehinne

☐ Annen infeksjon

Tannhelse

9. Har du noensinne hatt infeksjoner i tenner (rotinfeksjon)? ☐ Ja ☐ Nei

Hvis ja, i hvilket/hvilke år?

10. Har du noensinne hatt infeksjoner i tannkjøtt (tannløsningssykdom/periodontitt) ☐ Ja ☐ Nei

Hvis ja, i hvilket/hvilke år?

Vaksiner

11. Fulgte du vanlig vaksinasjonsprogram som barn?

☐ Ja ☐ Nei ☐ Delvis/avbrutt ☐ Vet ikke

Kjæledyr/husdyr under oppvekst

12. Hadde du kjæledyr eller husdyr under oppveksten? ☐ Ja ☐ Nei

Hvis ja, hva slags dyr hadde du?

☐ Katt ☐ Hund ☐ Hest ☐ Annet dyr:

Neglelakk

13. Hvor mange ganger har du brukt neglelakk <u>det siste året?</u>

☐ Aldri ☐ 1-10 ☐ 11-20 ☐ 21-30 ☐ 31-40 ☐ 41-50 ☐ Mer enn 50 ganger

Tobakk

14. Røyker du selv?

☐ Ja, sigaretter av og til (fest/ferie, ikke daglig)

☐ Ja, sigaretter daglig

☐ Ja, sigarer/sigarillos/pipe av og til

☐ Ja, sigarer/sigarillos/pipe daglig

☐ Nei, jeg har sluttet å røyke

☐ Nei, jeg har aldri røykt

Hvis du aldri har røykt, hopp til spørsmål 17.

15. Svar på dette hvis du nå røyker *daglig* eller tidligere har røykt *daglig*:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig?	☐☐ Sigaretter pr. dag
Hvor gammel var du da du begynte å røyke daglig?	☐☐ År gammel
Hvis du tidligere har røykt daglig, hvor gammel var du da du sluttet?	☐☐ År gammel

16. Svar på dette hvis du røyker eller har røykt *av og til,* men ikke daglig:

Hvor mange sigaretter røyker eller røykte du vanligvis i måneden?	☐☐☐ Sigaretter pr. mnd
Hvor gammel var du da du begynte å røyke av og til?	☐☐ År gammel
Hvis du tidligere har røykt av og til, hvor gammel var du da du sluttet?	☐☐ År gammel

17. Har du noen gang bodd sammen med én eller flere personer som daglig har røykt i hjemmet?

☐ Ja ☐ Nei

Hvis ja, angi tidsperiode(r) nedenfor:
(f.eks. fra og med år 1980 til og med år 1985)

Fra og med år: ☐☐☐☐ — Til og med år: ☐☐☐☐

Fra og med år: ☐☐☐☐ — Til og med år: ☐☐☐☐

Fra og med år: ☐☐☐☐ — Til og med år: ☐☐☐☐

Fra og med år: ☐☐☐☐ — Til og med år: ☐☐☐☐

18. Bruker du, eller har du brukt, snus?

☐ Nei, aldri

☐ Jeg har brukt snus tidligere, men jeg har sluttet

☐ Ja, av og til

☐ Ja, daglig

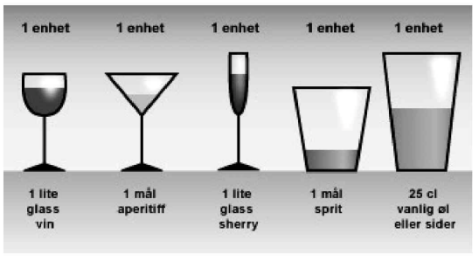
Hvis du aldri har brukt snus, hopp til spørsmål 20.

19. Hvis du bruker/har brukt snus:

Hvor gammel var du da du begynte med snus? ☐☐ År gammel

Hvor mange esker snus bruker/brukte du pr.måned? ☐☐ Antall esker

Alkohol



Figuren viser hva som tilsvarer én alkoholenhet for de ulike drikkene

20. Hvor mange enheter alkohol drikker du pr. dag? *Tenk forbruk over 4 uker og del på antall dager*

☐ Drikker ikke alkohol

☐ 0-1 enheter

☐ 1-3 enheter

☐ Mer enn 3 enheter

21. Hvor mange enheter alkohol drakk du pr. dag da du var 18 år? *Tenk forbruk over 4 uker og del på antall dager*

☐ Drakk ikke alkohol

☐ 0-1 enheter

☐ 1-3 enheter

☐ Mer enn 3 enheter

Kaffe/te

22. Hvor mange kopper kaffe/te drikker du pr. døgn?
(Sett 0 dersom du ikke drikker kaffe/te)

Kaffe: ☐☐ Te: ☐☐

23. Hvor mange kopper kaffe/te drakk du pr. døgn da du var ca 18 år?
(Sett 0 dersom du ikke drakk kaffe/te)

Kaffe: ☐☐ Te: ☐☐

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Matvaner/kosttilskudd

24. Hvor ofte spiser du vanligvis disse matvarene nå?

	0-3 ganger pr. mnd.	1-3 ganger pr. uke	4-6 ganger pr. uke	1 gang pr. dag	2 ganger eller mer pr. dag
Frukt/bær	☐	☐	☐	☐	☐
Grønnsaker	☐	☐	☐	☐	☐
Rødt kjøtt *(storfe, får, svin)*	☐	☐	☐	☐	☐
Fet fisk *(laks, ørret, sild, makrell, uer)*	☐	☐	☐	☐	☐
Mager fisk *(torsk, sei, kolje, vitting)*	☐	☐	☐	☐	☐

25. Hvor ofte spiste du vanligvis disse matvarene i barndom/ungdom inntil du var ca 18 år?

	0-3 ganger pr. mnd.	1-3 ganger pr.uke	4-6 ganger pr. uke	1 gang pr. dag	2 ganger eller mer pr. dag
Frukt/bær	☐	☐	☐	☐	☐
Grønnsaker	☐	☐	☐	☐	☐
Rødt kjøtt *(storfe, får, svin)*	☐	☐	☐	☐	☐
Fet fisk *(laks, ørret, sild, makrell, uer)*	☐	☐	☐	☐	☐
Mager fisk *(torsk, sei, kolje, vitting)*	☐	☐	☐	☐	☐

26. Bruker du følgende kosttilskudd?

	Ja, daglig	Av og til	Nei
Tran	☐	☐	☐
Omega-3-kapsler	☐	☐	☐
Vitamin- og/eller mineraltilskudd	☐	☐	☐

27. Brukte du følgende kosttilskudd da du var 18 år?

	Ja, daglig	Av og til	Nei
Tran	☐	☐	☐
Omega-3-kapsler	☐	☐	☐
Vitamin- og/eller mineraltilskudd	☐	☐	☐

Solvaner

28. Hvor mange uker pr. år har du solt deg/drevet aktivitet i solen i områder med svært sterk sol (f.eks. Afrika eller "syden")? *(Sett ett kryss pr. linje)*

	Aldri	1-2 uker	3-5 uker	6 uker eller mer
I løpet av de siste 12 mnd.	☐	☐	☐	☐
Før 10 års alder	☐	☐	☐	☐
Ved 10-19 års alder	☐	☐	☐	☐
20 år eller eldre	☐	☐	☐	☐

29. Hvor ofte har du solt deg/drevet aktivitet i solen i Norden vår/sommer/høst? *(Sett ett kryss pr. linje)*

	Aldri	Noen timer pr. måned	Noen timer pr. uke	Noen timer pr. dag
I løpet av de siste 12 mnd.	☐	☐	☐	☐
Før 10 års alder	☐	☐	☐	☐
Ved 10-19 års alder	☐	☐	☐	☐
20 år eller eldre	☐	☐	☐	☐

30. Hvor ofte har du solt deg i solarium? *(Sett ett kryss pr. linje)*

	Aldri	Noen ganger pr. år	Noen ganger pr. måned	Flere ganger pr. måned
I løpet av de siste 12 mnd.	☐	☐	☐	☐
Før 10 års alder	☐	☐	☐	☐
Ved 10-19 års alder	☐	☐	☐	☐
20 år eller eldre	☐	☐	☐	☐

Utdannelse og arbeidssituasjon

31. Hvilken utdannelse er den høyeste du har fullført? *(Sett ett kryss)*

☐ Mindre enn 7 år grunnskole

☐ Grunnskole 7-10 år, framhaldskole, folkeskole

☐ Videregående skole, realskole, yrkesskole (10-13 år)

☐ Høgskole/universitet mindre enn 4 år

☐ Høgskole/universitet 4 år eller mer

32. Hva slags arbeidssituasjon har du nå? *(Sett ett eller flere kryss)*

☐ Ansatt med lønnet arbeid

☐ Selvstendig næringsdrivende

☐ Heltids husarbeid

☐ Utdanning, militærtjeneste

☐ Trygdet

☐ Pensjonist

33. Hva er ditt nåværende eller tidligere arbeid? *(Sett ett eller flere kryss. Besvares også om du er trygdet eller pensjonert)*

☐ Administrativ leder, politiker eller direktør

☐ Akademisk yrke (sivilingeniør, lege, jurist, økonom, lektor)

☐ Yrke med kortere høyskole-/universitetsutdanning og teknikere (sykepleier, ingeniør, politi, fysio, optiker)

☐ Kontor og kundeserviceyrke (sekretær, økonomimedarbeider, resepsjonist)

☐ Salgs- , service- og omsorgsyrke (kundebehandler, hjelpepleier, frisør)

☐ Yrke innen jordbruk, skogbruk og fiske

☐ Håndtverker (mekaniker, elektriker, snekker, maler, baker, slakter)

☐ Prosess- og maskinoperatør, transportarbeider ol.

☐ Militært yrke (menig, befal)

☐ Annet yrke:

34. Har du på din nåværende eller tidligere arbeidsplass vært betydelig eksponert over tid for noe av det følgende?

	Ja	Nei	**Hvis ja**, hvor gammel var du da eksponeringen startet?	**Hvis ja**, hvor mange år har du vært eksponert?
Motorolje	☐	☐	☐☐ År gammel	☐☐ År med eksponering
Skjæreolje	☐	☐	☐☐ År gammel	☐☐ År med eksponering
Formolje	☐	☐	☐☐ År gammel	☐☐ År med eksponering
Hydraulikkolje	☐	☐	☐☐ År gammel	☐☐ År med eksponering
Turbinolje	☐	☐	☐☐ År gammel	☐☐ År med eksponering
Asfalt	☐	☐	☐☐ År gammel	☐☐ År med eksponering
Råolje	☐	☐	☐☐ År gammel	☐☐ År med eksponering
Narkosegasser	☐	☐	☐☐ År gammel	☐☐ År med eksponering
Organiske løsemidler*	☐	☐	☐☐ År gammel	☐☐ År med eksponering

**Med organiske løsemidler menes f.eks. avfettingsmidler, trikloroetylen, white spirit, tynnere, toluen, styren, xylen e.l.*

9121436354

Til deg som er kvinne

35. Hvor gammel var du da du fikk menstruasjon for første gang? ☐☐ År gammel

36. Har du sluttet å menstruere? ☐ Ja ☐ Nei

Hvis ja, ved hvilken alder? ☐☐ År gammel

37. Har du brukt p-piller (ikke minipille), p-ring eller p-plaster? ☐ Ja ☐ Nei

Hvis ja, ca hvor lenge? *(antall år)* ☐☐ År

38. Har du noen gang brukt en annen form for hormonelt prevensjonsmiddel. F.eks. minipille, p-sprøyte eller hormonspiral (ikke kopperspiral)? ☐ Ja ☐ Nei

Hvis ja, ca hvor lenge? *(antall år)* ☐☐ År

39. Har du hatt en graviditet som har endt med spontanabort eller abort? ☐ Ja ☐ Nei

Hvis ja, hvor mange? ☐☐

40. Har du gjennomgått hormonell behandling for barnløshet? ☐ Ja ☐ Nei

41. Har du noen gang vært gravid? ☐ Ja ☐ Nei

☐ Jeg er gravid nå

Hvis ja, fyll ut for hvert barn du har født følgende opplysninger om fødselsår og antall måneder du ammet *(fylles også ut for dødfødte eller for barn som døde senere i livet)*

Barn	Fødselsår	Antall måneder med amming	Barn	Fødselsår	Antall måneder med amming
1	☐☐☐☐	☐☐	5	☐☐☐☐	☐☐
2	☐☐☐☐	☐☐	6	☐☐☐☐	☐☐
3	☐☐☐☐	☐☐	7	☐☐☐☐	☐☐
4	☐☐☐☐	☐☐	8	☐☐☐☐	☐☐

13

Takk for din deltakelse!

Eventuelle kommentarer og tilbakemeldinger:

Questionnaire (English translation)

9446436354

Oslo universitetssykehus

Code | | | | | | |

Questionnaire of environmental factors

Dear participant.

This questionnaire contains questions about your family history, education and work, diet and other lifestyle factors, and diseases you have or have had. See attached information letter for supplementary information.

About filling in the questionnaire:
The questionnaire is to be read optically. Please use blue or black ballpoint pen. If you mistype, cross it out with a straigth line and check off the correct box. We ask you to check off in the middle of the squares and write with CAPITAL letters in the squares like shown below. If anything is written outside the marked fields, it will not be registered. If you have comments or feedbacks, we ask you to use the commentary area on the last page.

Like this: ☒ | O | S | L | O | |

Not like this: ☒ | O S L | | | O |

Thanks in advance for your valuable contribution!

If you do not wish to answer the questionnaire, check off in the squares below and return the questionnaire in the attached response envelope. Then you´ll avoid receiving duns!

☐ I don´t wish to answer the questionnaire

☐ Woman ☐ Man Age: | | |

Background

1. Sex: ☐ Woman ☐ Man

2. Month of birth:
(01 for jan, 02 for feb etc.) ☐☐ Year of birth: ☐☐☐☐

3. Height and weight:

How tall are you? ☐☐☐ cm

How much do you weigh? ☐☐☐ kg

Approximately how tall were you when you were 18? ☐☐☐ cm ☐ Don´t remember

Approximately how much did you weigh when you were 18? ☐☐☐ kg ☐ Don´t remember

4. Your country of birth: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

If you were not born in Norway, in what year did you move here? ☐☐☐☐

5. Country of birth of your biological parents and grandparents:

Mother: ☐☐☐☐☐☐☐☐☐☐☐☐

Father: ☐☐☐☐☐☐☐☐☐☐☐☐

Maternal grandmother: ☐☐☐☐☐☐☐☐☐☐☐☐

Maternal grandfather: ☐☐☐☐☐☐☐☐☐☐☐☐

Paternal grandmother: ☐☐☐☐☐☐☐☐☐☐☐☐

Paternal grandfather: ☐☐☐☐☐☐☐☐☐☐☐☐

Diseases or surgical treatment

6. Have you, or have you ever had, any of these diseases/illnesses:
(Check once per line)

	Yes	No	If yes, how old were you the first time?	
Heart attack	☐	☐	☐☐	Years
Angina pectoris	☐	☐	☐☐	Years
Heart failure	☐	☐	☐☐	Years
Other heart disease	☐	☐	☐☐	Years
Cerebral infarction/intracranial hemorrhage	☐	☐	☐☐	Years
Kidney disease	☐	☐	☐☐	Years
Asthma	☐	☐	☐☐	Years
Chronic bronchitis, emphysema, COPD	☐	☐	☐☐	Years
Diabetes type 1	☐	☐	☐☐	Years
Diabetes type 2	☐	☐	☐☐	Years
Psoriasis	☐	☐	☐☐	Years
Rheumatoid arthritis	☐	☐	☐☐	Years
Bechterews disease	☐	☐	☐☐	Years
Sarcoidosis	☐	☐	☐☐	Years
Osteoporosis	☐	☐	☐☐	Years
Osteoarthritis	☐	☐	☐☐	Years
Myasthenia Gravis	☐	☐	☐☐	Years
MS (multiple sclerosis)	☐	☐	☐☐	Years
PSC (primary sclerosing cholangitis)	☐	☐	☐☐	Years

Continuation question 6:

	Yes	No	If yes, how old were you the first time?
Coeliac disease	☐	☐	☐☐ Years
Inflammatory bowel disease (Ulcerative colitis, Crohns disease)	☐	☐	☐☐ Years
SLE (systemic lupus erythematosus)	☐	☐	☐☐ Years
Sjøgren´s disease	☐	☐	☐☐ Years
Hypothyreosis	☐	☐	☐☐ Years
Hyperthyreosis	☐	☐	☐☐ Years
Tonsillectomy	☐	☐	☐☐ Years
Appendectomy	☐	☐	☐☐ Years
Migraine	☐	☐	☐☐ Years

Infectious diseases

7. Have you ever had mononucleosis? ☐ Yes ☐ No ☐ Don´t know

If yes, how old were you when you had the disease? ☐☐ Years

8. Have you had any other infectious disease(s) before the age of 18 that demanded hospitalization? ☐ Yes ☐ No ☐ Don´t know

If yes, what kind of infection did you have?

☐ Pneumonia

☐ Kidney/urinary tract infection

☐ Stomach/bowel infection

☐ Infection of the brain/meningitis

☐ Other infection

Dental health

9. Have you ever had infections of the teeth (root infection)? ☐ Yes ☐ No

If yes, in what year(s)? ☐☐☐☐ ☐☐☐☐

10. Have you ever had infecions of the gums (periodontitis)? ☐ Yes ☐ No

If yes, in what year(s)? ☐☐☐☐ ☐☐☐☐

Vaccinations

11. Did you follow the normal vaccination program as a child?

☐ Yes ☐ No ☐ Partly/interrupted ☐ Don´t know

Pets during childhood

12. Did you have pets during your childhood? ☐ Yes ☐ No

If yes, what kind(s) of animal(s) did you have?

☐ Cat ☐ Dog ☐ Horse ☐ Other: ☐☐☐☐☐☐☐☐☐☐ ☐☐☐☐☐☐☐☐☐☐ ☐☐☐☐☐☐☐☐☐☐

Nail polish

13. How many times have you been using nail polish the last year?_____

☐ Never ☐ 1--10 ☐ 11--20 ☐ 21--30 ☐ 31--40 ☐ 41--50 ☐ More than 50 times

Tobacco

14. Do you smoke?

☐ Yes, cigarettes sometimes (parties/holidays, not daily)

☐ Yes, cigarettes daily

☐ Yes, cigars/cigarillos/pipe sometimes

☐ Yes, cigars/cigarillos/pipe daily

☐ No, I have stopped smoking

☐ No, I have never smoked

If you´ve never smoked, go directly to question 17.

15. Answer this question if you now smoke daily, or earlier have smoked daily:

How many cigarettes do or did you normally smoke daily? _____ ☐☐ Cigarettes pr. day

How old were you when you started smoking daily? ☐☐ Years

If you have smoked daily earlier, how old were you when you quitted? ☐☐ Years

16. Answer this question if you smoke or have smoked sometimes, but not daily:

How many cigarettes do or did you normally smoke per month? ☐☐☐ Cigarettes pr. month

How old were you when you started smoking sometimes? ☐☐ Years

If you have smoked sometimes earlier, how old were you when you quitted? ☐☐ Years

17. Have you ever lived with one person or more who smoked daily in your surrondings? (Inside the house etc)

☐ Yes ☐ No

If yes, in what time period? (f.ex. from 1980 through 1985)

From: ☐☐☐☐ — Through: ☐☐☐☐

From: ☐☐☐☐ — Through: ☐☐☐☐

From: ☐☐☐☐ — Through: ☐☐☐☐

From ☐☐☐☐ — Through: ☐☐☐☐

18. Do you use, or have you ever used, snuff?

☐ No, never

☐ I have used snuff in the past, but I have stopped using snuff.

☐ Yes, sometimes

☐ Yes, daily

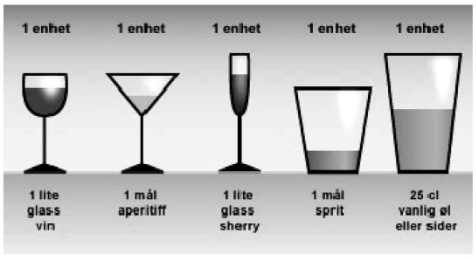
If you have never used snuff, go directly to question 20.

19. If you use/have ever used snuff:

How old were you when you started using snuff? ☐☐ Years

How many boxes of snuff do/did you use per month? ☐☐ Number of boxes

Alcohol



This figure demonstrate what one unit of alcohol signifies.

20. How many units of alcohol do you drink per day? (Think about how much you drink during 4 weeks, and divide this amount in number of days)

- ☐ I don't drink alcohol
- ☐ 0--1 units
- ☐ 1--3 units
- ☐ More than 3 units

21. How many units of alcohol did you drink per ~~day when~~ you were 18 Years? (Think consumption over 4 weeks and divide with number of days)

- ☐ Didn't drink alcohol
- ☐ 0--1 units
- ☐ 1--3 units
- ☐ More than 3 units

Coffee/tea

22. How many cups of coffee/tea do you drink per day?
(Answer 0 if you don't drink coffee/tea)

Coffee: ☐☐ Tea:: ☐☐

23. How many cups of coffee/tea did you drink per day when you were 18 Years?
(Answer 0 if you didn't drink coffee/tea)

Coffee: ☐☐ Tea: ☐☐

Eating habits/supplements

24. How often do you eat the following types of food nowadays?

	0--3 times per month	1--3 times per week	4--6 times per week	1 time per day	2 times or more per day
Fruit/berries	☐	☐	☐	☐	☐
Vegetables	☐	☐	☐	☐	☐
Red meat (cattle/sheep/pig)	☐	☐	☐	☐	☐
Fat fisk (salmon,trout,herring, mackerel, redfish)	☐	☐	☐	☐	☐
Lean fish (cod,pollock,haddock,vitting)	☐	☐	☐	☐	☐

25. How often did you normally eat the following types of food in your childhood up to the age of 18?

	0--3 times per month	1--3 times per week	4--6 times per week	1 time per day	2 times or more per day
Fruit/berries	☐	☐	☐	☐	☐
Vegetables	☐	☐	☐	☐	☐
Red meat (storfe, får, svin)	☐	☐	☐	☐	☐
Fat fish (salmon,trout,herring, mackerel, redfish)	☐	☐	☐	☐	☐
Lean fish (cod,pollock,haddock,vitting)	☐	☐	☐	☐	☐

26. Do you use the following supplements?

	Yes, daily	Sometimes	No
Cod oil	☐	☐	☐
Omega 3 capsules	☐	☐	☐
Vitamine or mineral supplements	☐	☐	☐

27. Did you use the following supplements when you were 18 Years?

	Yes, daily	Sometimes	No
Cod oil	☐	☐	☐
Omega 3 capsules	☐	☐	☐
Vitamine or mineral supplements	☐	☐	☐

Sun bathing habits

28. How many weeks per year have you been taking sunbaths/ doing activities in the sun in areas with very strong sun radiation (such as in Africa or in the Southern parts of Europe)? (Check once per line.)

	Never	1--2 weeks	3--5 weeks	6 weeks or more
During the last 12 months	☐	☐	☐	☐
Before the age of 10	☐	☐	☐	☐
Between the ages of 10 and 19	☐	☐	☐	☐
20 years or older	☐	☐	☐	☐

29. How often have you been sunbathing or doing activity in the sun in Scandinavia during spring/summer/fall? (Check once per line)

	Never	A few hours per month	A few hours per week	A few hours per day
During the last 12 months	☐	☐	☐	☐
Before the age of 10	☐	☐	☐	☐
Between the ages of 10 and 19	☐	☐	☐	☐
20 years or older	☐	☐	☐	☐

30. How often have you sunbathing in a solarium? (Check once per line)

	Never	A few times per year	A few times per month	Several times per month
During the last 12 months	☐	☐	☐	☐
Before the age of 10	☐	☐	☐	☐
Between the ages of 10 and 19	☐	☐	☐	☐
20 years or older	☐	☐	☐	☐

Education and working situation

31. What is the highest education you have completed? (Check one)

- ☐ Less than 7 years of primary school
- ☐ Primary 7-10 years, the continuation school, elementary school
- ☐ High school, lower secondary school, vocational school (10-13 years)
- ☐ College / university 4 years or less
- ☐ College / university 4 years or more

32. What kind of work/job do you have now? (Check one or more boxes)

- ☐ Employed in paid work
- ☐ Selfemployed
- ☐ Fulltime housework
- ☐ Education, military service
- ☐ Unemployed
- ☐ Retired

33. What is your current or most recent job? (Check one or more boxes. Also respond if you are unemployed or retired)

- ☐ Administrative director, politician, director
- ☐ Academic profession (engineer, doctor, lawyer, economist, lecturer)
- ☐ Occupation with shorter college / university education and technicians (nursing, engineering, police, physiotherapi, optometrist)
- ☐ Office and customer service (secretary, finance staff, receptionist)
- ☐ Sales, service and care work (customer service representative, "helping nurse", hairdresser)
- ☐ Occupation in the agriculture, forestry and fishing
- ☐ Home Entertainment Systems/Artisan? (mechanic, electrician, carpenter, painter, baker, butcher)
- ☐ Process and machine operators, transport workers, etc..
- ☐ Military occupation (private, officer)
- ☐ Other occupation/job:

34. Have you, on your current or previous occupation, been significantly exposed over time for any of the following?

	Yes	No	If yes, how old were you when the exposure started	If yes, how many years have you been exposed?
Motor oil	☐	☐	☐☐ Years	☐☐ Years of exposure
Cutting oil/ Skjæreolje	☐	☐	☐☐ Years	☐☐ Years of exposure
Oil/ Formolje	☐	☐	☐☐ Years	☐☐ Years of exposure
Hydraulic oil	☐	☐	☐☐ Years	☐☐ Years of exposure
Turbine oil	☐	☐	☐☐ Years	☐☐ Years of exposure
Asfalpht (asfalt)	☐	☐	☐☐ Years	☐☐ Years of exposure
Oil/ Råolje	☐	☐	☐☐ Years	☐☐ Years of exposure
Anesthetic gases	☐	☐	☐☐ Years	☐☐ Years of exposure
Organic solvents*	☐	☐	☐☐ Years	☐☐ Years of exposure

*Organic solvents such as degreasers, trichlorethylene, white spirit, thinner, toluene, styrene, xylene etc. (Med organiske løsemidler menes f.eks. avfettingsmidler, trikloroetylen, white spirit, tynnere, toluen, styren, xylen e.l.)

Women

35. How old were you when you had your period for the first time? ☐☐ Years

36. Has your menstruation ceased? ☐ Yes ☐ No

If yes, at what age? ☐☐ Years

37. Have you used birth control pills (not mini pills) , vaginal ring or patch? ☐ Yes ☐ No

If yes, approximately for how long? (Years) ☐☐ Years

38. Have you ever used another form of hormonal contraceptive? For instance mini pill, birth control shot or IUS (not copper IUD) ☐ Yes ☐ No

If yes, approximately for how long? (Years) ☐☐ Years

39. Have you had a pregnancy that ended in a miscarriage or an abortion? ☐ Yes ☐ No

If yes, how many? ☐☐

40. Have you had hormonal therapy for infertility? ☐ Yes ☐ No

41. Have you ever been pregnant? ☐ Yes ☐ No

☐ I'm currently pregnant

If yes, fill in, for each child you have born, the following information about birth year and how many months you breast-fed. (Also to be filled in for stillborn or children who died later in life).

Child	Year of birth	Number of months with breastfeeding	Child	Year of birth	Number of months with breastfeeding
1	☐☐☐☐	☐☐	5	☐☐☐☐	☐☐
2	☐☐☐☐	☐☐	6	☐☐☐☐	☐☐
3	☐☐☐☐	☐☐	7	☐☐☐☐	☐☐
4	☐☐☐☐	☐☐	8	☐☐☐☐	☐☐

Thank you for your participation

Comments and feedback: