ENVIRONMENTAL EXPOSURES AND SELF-RATED HEALTH PRIOR TO MULTIPLE SCLEROSIS AMONG WOMEN IN THE DANISH NATIONAL BIRTH COHORT

Multiple Sclerosis is a severe disabling disease of the central nervous system. More than 12000 Danes have MS and every year 700 new cases are diagnosed. Certain environmental factors, including EBV infection, smoking, and lack of D vitamin, in interaction with genetic susceptibility, are considered to be importance contributors to the etiology of MS. However, they cannot alone explain the occurrence of MS and definitely not the increasing incidence of MS observed within the last decades in many western countries including Denmark.

The human population has experienced a considerable change in way of living and has through time been exposed to a still growing number of environmental factors. Surprisingly, few and mostly older case-control studies, have addressed the possible association between environmental factors, such as alcohol and occupational exposures and MS. Furthermore, recent studies have suggested that immunological changes may appear several years before onset of MS, however, it is not known whether these changes are reflected by declining health and with lowered scores in self-rated health (SRH).

We aim to study the possible associations between a range of environmental exposures and MS and further, evaluate whether MS patients experience signs of declining health and lowered SRH prior to onset of MS. By linking nation-wide register data on MS with the Danish National Birth Cohort, which contains extensive interview data on life style, health, and occupational exposures for 100,000 Danish women, among whom 400 have developed MS, we will have an unique opportunity to address both these issues. We believe the present study will lead to new knowledge concerning risk factors and to a better understanding of the course and length of the premorbid phase of MS.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disorder, characterized by relapsing neurological symptoms from different parts of the central nervous system. MS typically begins in the early adulthood and despite episodes of remission the disease eventually progresses into severe disabilities\(^1\). Worldwide, approx. 2,500,000 individuals are living with MS, which makes MS an important cause of early disability, early retirement, and reduced quality of life\(^2;3\).
The etiology is still unknown but is believed to involve genetics as well as environmental factors, among which the most well-recognized are Epstein Barr Virus (EBV), smoking, and vitamin D. However, these factors cannot alone explain the occurrence of MS and certainly not the increasing incidence of MS observed within the last decades. Accordingly, other factors are hypothesized to contribute to the etiology of MS. Our way of living, including nutrition, occupational choices and environment have certainly changed within the last generations. However, our knowledge concerning life style factors and MS is very sparse. A few studies of diet found that animal fat intake increases the risk of MS whereas others found no association. Likewise, alcohol and coffee intake has been associated with MS in some studies, but not all. Drug abuse, stress, and occupational exposures particularly to organic solvents have also been associated with MS, but again results are inconclusive. This is mainly due the fact that most of the previous studies are case-control studies; a type of study design which is very vulnerable to both recall and selection bias.

Many MS patients have described retrospectively the appearance of unspecific symptoms and declining health several years prior to MS. Findings, which have been supported by smaller studies and case reports suggesting a preclinical stage of MS lasting approximately 10 years. Thus, persons destined to developed MS appear to have an increased frequency of GP consultations 5-10 years before they are diagnosed with MS, due to a variety of different unspecific symptoms, and mental changes such as anxiety, depression and dementia have likewise been described many years before more specific signs of MS.

The existence of a preclinical phase of MS has furthermore been supported by observations of radiological abnormalities in the absence of clinical symptoms of MS and immunological changes including increased titers against EBV antigens many years prior to disease onset. Immunological changes several years before disease onset has also been observed for other autoimmune diseases such as rheumatoid arthritis, type 1 diabetes, and systemic lupus erythematosus and inflammatory changes have been connected to poor self-rated health (SRH), why we hypothesize that such changes might also lead to declining health and possibly lowered SRH among persons, who later on develop MS. However, our knowledge concerning health and SRH prior to MS is very sparse and primarily based on case reports.

The Danish National Birth Cohort, which contains detailed information on life style factors, medication, alcohol, exercise, health etc. and SRH for 100,000 women, provide a unique opportunity to investigate the association between a number of important environmental exposures, health conditions, and MS. Investigations, which are not possible to carry out using register information based on hospitalizations or other administrative data solely.
Aim
The aim of the study is to investigate the possible associations between a number of environmental factors and risk of MS and further, evaluate whether MS patients experience a declining health and lowered SRH years before onset of MS.

Material and methods
The study cohort will be based on the 100,000 women enrolled in the Danish National Birth Cohort (DNBC) between 1996 and 2002, preferably in the first trimester of pregnancy\textsuperscript{31}. Besides important data concerning the pregnancy and the offspring, thorough data concerning maternal lifestyle, diet, occupational exposures, socio-demography, and health prior to pregnancy as well as during pregnancy has also been gathered through telephone-interviews twice during and twice after pregnancy (table 1). In the present/applied study only information from the first interview (16\textsuperscript{th} week of gestation) will be used since this covers environmental exposures, general health of the women including SRH. Information on SRH is collected using questions similar to one of the most widely recognized instruments in health status measurements, “the Short Form 36”\textsuperscript{32}.

Table 1: All focus areas in the DNBC first questionnaire:
- Earlier pregnancies and childbirths, IVF treatment
- Health in general and during pregnancy as well as medical pregnancy examinations
- Drug use
- Work environment
- Home environment
- Diet - vitamins - dietary supplements
- Use of alcohol and tobacco
- Sleep
- Exercise
- Oestrogen
- Socio-economic/occupational variables
- Psycho-social stress

MS cases in the DNBC will be identified in the Danish Multiple Sclerosis Registry (DMSR) and the National Patient Register (NPR). The DMSR was established in 1956, in continuation of a nationwide MS prevalence study carried out a few years earlier. The register has since collected information about MS patients from all Danish hospital departments of neurology and neuropathology, practicing neurologists, MS rehabilitation centers, death certificates, and from 1977, also from the NPR. All cases have been reclassified by neurologists at the DMSR, and the register has been estimated to be more than 90\% complete and to have a diagnostic validity of 94\%\textsuperscript{33}. The validity of the diagnosis MS (ICD-8 code:340 and ICD-10 code: G35) in the
NPR is considered slightly lower\textsuperscript{34}, however the NPR is updated to current date, in contrast to the DMSR, which is a few years behind.

**Statistics**
Women in the cohort will be followed from date of first interview until development of MS, emigration, death, or end of follow up, December 31, 2012. To estimate associations between exposure to different potential risk factors on risk of MS, we will use Cox proportional hazards regression to estimate hazard ratios (HR) with 95% confidence intervals (CI) using age as underlying time scale. All the analyses will be adjusted for age and period as well as for relevant confounders such as education and parity, using information from the DNBC and nationwide registers including the Civil Registration System and the NPR.

**Statistical power**
According to preliminarily analyses based on information from the NPR, 400 women among the 100,000 women in the DNBC have developed MS, of whom, 300 developed MS after the first interview. In the following we provide an example of a power calculation of the effect of alcohol and self-rated health on the risk of MS. Approximately 80% of the women in the DNBC have reported drinking more than 1 unit per week prior to pregnancy and 50% have rated their health prior to pregnancy as fair or poor\textsuperscript{35}. Thus, for the effect of alcohol and self-rated health, respectively, we expect to be able to identify an HR of 1.50 and 1.40 for MS, with 80% power at a level of 5% significance. The power of our study will off course vary according to the specific exposure under study.

**Ethics**
The present study is register-based, and participants will not be contacted, hence no ethical approval is needed for study. We will apply the Data Protection Board and the DNBC-Steering Committee for approval of the study. Furthermore, all analyses and reporting of results will be carried out conscientiously and with anonymity for the individual participant.

**Participants**
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**Location and time schedule**
The study will be carried out at the Department of Epidemiology Research in close cooperation with the Danish MS Registry, the Danish MS Research Center, Rigshospitalet. The Department of Epidemiology Research has a very long and high-impact expertise in register-based epidemiological research and furthermore possesses the computational resources needed to perform the above-mentioned data management and statistical analysis.

**Perspectives**
In the proposed project we aim to utilize the unique Danish National Birth Cohort and the nation-wide Danish health registers to address the possible associations between several previously suggested risk factors and potential new risk factors for MS and to examine the premorbid health among women who later on develop MS. Only through the prospectively collected data in DNBC is it possible to examine and explore whether several different exposures should be associated with later development of MS, without recall and selection bias.

We hope that the present study will lead to a better understanding of the etiology of MS through verifying or denying earlier suggested risk factors or by identifying new possible risk factors. New and more detailed knowledge on possible exposures associated with an increased risk of MS, will be of high value in the future prevention and treatment strategy for MS. A better understanding of the premorbid phase of MS will not only provide us with information concerning health prior to MS but may also give us a clue about the length of the sub- or preclinical stage of MS. Taking into consideration the importance of early treatment of MS, knowledge about a preclinical stage of MS could lead to earlier treatment and thereby a better prognosis.

**Reference List**


(18) McDonnell GV, Cabrera-Gomez J, Calne DB, Li DK, Oger J. Clinical presentation of primary progressive multiple sclerosis 10 years after the incidental finding of typical magnetic resonance imaging brain lesions: the subclinical stage of primary progressive multiple sclerosis may last 10 years. Mult Scler 2003;9:204-209.


