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Shift work at young age is associated with increased risk of multiple sclerosis in a Danish population

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ABSTRACT

Background: Epidemiological studies suggest an important role for environmental factors in developing multiple sclerosis (MS). Furthermore several studies have indicated that the effect of environmental factors may be especially pronounced in adolescents. Recently only one study investigated and found that shift work at young age is associated with an increased risk of developing MS. In this study we focused on the effect of shift work in the vulnerable period between 15–19 years.
Objective: The aim of this study was to investigate the association between shift work at young age and the risk of developing MS.
Methods: We performed a large case-control study including 1723 patients diagnosed with MS and 4067 controls. MS patients were recruited from the Danish Multiple Sclerosis Biobank and controls from The Danish Blood Donor Study. Information on working patterns and lifestyle factors was obtained using a comprehensive lifestyle-environmental factor questionnaire with participants enrolled between 2009 and 2014. Logistic regression models were used to investigate the association between shift work at age 15–19 years and the subsequent risk of MS and were controlled for effects due to established MS risk factors.
Results: We found a statistically significant association when total numbers of night shifts were compared with non-shift workers. For every additional 100 night shifts the odds ratio (OR) for MS was 1.20 (95% confidence interval (CI), 1.08–1.34, $p=0.001$). Increasing intensity of shift work also increased MS risk. For every additional night per month the OR was 1.04 (95% CI, 1.01–1.06, $p=0.002$). Duration of shift work in years was not associated with risk of MS.
Conclusion: This study supports a statistically significant association between shift work at age 15–19 years and MS risk.

1. Introduction

Multiple sclerosis (MS) is an immune-mediated disease that affects the CNS. Disease mechanisms involve autoimmune inflammatory responses which damage myelin, axons and neurons and thus contribute to the formation of multiple demyelinated plaques in the brain and spinal cord.

The etiology of MS is complex. Susceptibility to develop MS is determined by both genetic and environmental factors. Several environmental risk factors, including tobacco smoking (Jafari and Hintzen, 2011), passive smoking (Hedstrom et al., 2011a), vitamin D deficiency (Ascherio et al., 2010), obesity (Gianfrancesco et al., 2014; Hedstrom et al., 2012), Epstein-Barr virus infection and lack of exposure to sunlight (Islam et al., 2007), are shown to be associated with a risk of developing MS. Inconsistent results have been found regarding the risk of MS and alcohol consumption (Hedstrom et al., 2014; Pakpoor et al., 2014). Furthermore, several studies have indicated that the effect of environmental factors may be especially pronounced in adolescents (Ascherio et al., 2010; Gianfrancesco et al., 2014; Hedstrom et al., 2012; Islam et al., 2007; Dean and Kurtzke, 1971). Therefore prepuberty and puberty may be a vulnerable period for triggering MS onset.

Another possible environmental risk factor is shift work. Shift work has been associated with an increased risk of cardiovascular events (Vyas et al., 2012), type 2 diabetes (Pan et al., 2011), cancer (Grundy et al., 2013; Parent et al., 2012) and recently also

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autoimmune diseases such as rheumatoid arthritis (Puttonen et al., 2010), psoriasis (Li et al., 2013) and thyroid disorders (Magrini et al., 2006). Shift workers are more likely to report poor health and specific health risk factors including smoking and overweight. Studies investigating the association between shift work and alcohol consumption or physical activity have shown inconsistent results (KivimÄki et al., 2001).

To our best knowledge, only one Swedish cohort study has suggested the importance of shift work at young age in the development of MS (Hedstrom et al., 2011b). The causal factors underlying these associations are not clear, although working outside regular day shifts may lead to disruption of the circadian rhythm and sleep restriction. This may lead to changes in melatonin level and biomarkers of systemic inflammation such as leukocyte count and T cell regulation (Vogel et al., 2012; Born et al., 1997; Lange et al., 2010). Furthermore shift workers may be prone to deficits in vitamin D status (Ward et al., 2011) which is proved to be associated with an increased risk of developing MS. In this large Danish case-control study we aimed to investigate the association between shift work at young age and risk of developing MS.

2. Materials and methods

2.1. Study population

The dataset consisted of 2048 MS patients and 4547 healthy Danish blood donor controls. Patients were recruited from The Danish Multiple Sclerosis Biobank (DMSB) at Rigshospitalet in Copenhagen. All patients fulfilled the McDonald criteria 2005 or 2010 for definite multiple sclerosis (Polman et al., 2011, 2005) and were recruited by neurologists from MS centers from all of Denmark, although the majority of patients were recruited from the Copenhagen area. By December 2014 the Biobank contained DNA from 2775 MS patients, who were all asked to fill out a comprehensive questionnaire about lifestyle and environmental factors from October 2009 to December 2014. At the time of this study 2048 (74%) MS patients had filled out the questionnaire. The questionnaire was originally developed in Sweden and translated into Danish with the permission from Karolinska Institute in Stockholm (Hedstrom et al., 2011b). The control group consisted of healthy white Danish blood donors residing in the Copenhagen area. The donors fulfilled the exact same questionnaire as the MS patients and were recruited as an independent sub-study as part of the Danish Blood Donor Study from five major donor locations. Only two places were able to calculate the response rate which was 75% and 90%, respectively. We assume that the response rate has been comparable at the other donor locations. Blood samples and the lifestyle-environmental factor questionnaires were collected on the same day for each participant in the period from October 2012 to December 2014.

To minimize the risk of including participants where outcome had occurred before exposure all patients with age at onset of MS before the age of 20 years (147 cases) were excluded. Since no controls were born before 1945 and only few MS patients were born after 1989 we excluded 25 cases and 173 controls born before 1945 and after 1989 respectively to optimize age matching. Participants born in other countries than Denmark constituted 6.6% (123/1866) of the cases and 3.0% (127/4301) of the controls. Among those, 44 cases and 31 controls were born in Nordic countries (Norway, Sweden, Iceland and Faroe Islands) and were also included because of genetic consistency, cultural similarity and climate comparability among these countries. To minimize the possibility of genetic variation, only participants of Scandinavian origin were included. Thereby 62 cases and 127 controls were excluded because their parents had immigrated to Denmark, Norway, Sweden, Iceland or Faroe Islands. Missing or invalid information on date of birth, country of birth, MS diagnosis and shift work excluded 12 cases and 84 controls.

2.2. Definition of shift work

There is no consensus on the definition of shift work. In this study shift work refers to working hours before 6 a.m. and after 11 p.m., both permanent and alternating, and in the following referred as night shift.

2.3. Data management

In the questionnaire participants were asked 'Have you ever during work or education worked nights?', if yes, which periods (years) and how many nights per month. *Shift work* was first classified in two major categories; ever or never exposed. Because of the questionnaire design the definition of ever exposed are participants who have worked at least one night shift per month for at least a year.

Second, shift work was classified in total number of night shifts divided by 100 at age 15–19 years. Furthermore the participants were categorized into subgroups based on duration (years) and intensity (night shifts per month).

In our analyses *smoking habits* were dichotomized into ever or never smokers, and furthermore adjusted for pack-years for smokers at age 15–19 years. Exposure to ultraviolet radiation (UVR) was based on one question describing a subject's *outdoor activity* in the summer period – June to September – dichotomized into time spent outdoors at least two hours daily or less at age 10–19 years. *Body mass index (BMI)* was calculated by self-reported height and weight at 20 years of age and divided into two categories, overweight (BMI $>$ 25) or not (BMI $<$ 25).

Because of the Danish drinking culture with relative large *alcohol consumption* at young age, alcohol consumption at age 15–19 years was included in the analysis. Danish Health and Medicine Authority recommend drinking less than 14 units for women per week and 21 units for men (Danish Health and Medicine Authority, 2015). Alcohol consumption was dichotomized into within recommended level or above recommendation.

Level of education was characterized in three major groups (elementary/primary school or lower; technical college or high school; bachelor, master or Ph.D. degree or other longer education).

Age of MS onset was defined as the first neurological event interpreted as an MS relapse by a neurologist and data were collected from the Danish MS Treatment Registry (Koch-Henriksen et al., 2015).

Other confounding factors considered were *heredity* (first-degree relative with MS or not), *intake* of *vitamin D supplements* (yes/no) and *physical activity* (inactive/sedentary; moderate physical activity in spare time; moderate, regular exercise in spare time; regular exercise and work out).

2.4. Statistical analysis

Logistic regression analyses (SPSS version 20 for Windows) were used to calculate odds ratios (OR)s for MS outcome versus no MS for the different levels of shift work. Different models were defined.

In the first model the exposure was never or ever exposed to shift work; in the second model the exposure was defined as the number of night shifts divided by 100 (continuous variable); in the third model the exposure was the duration of shift work expressed in years; in the fourth model the exposure consisted in the intensity of shift work defined as the number of night shifts per month; and in the fifth model both the duration and intensity of