Is high socioeconomic status a risk factor for multiple sclerosis?

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Abstract

Multiple sclerosis (MS) is a chronic disease of the central nervous system characterised by inflammation and neurodegeneration. An increased risk of the disease among those of high socioeconomic status (SES) was first observed over 50 years ago. This is in contrast to a more common pattern whereby adverse health outcomes are generally associated with *low* SES. Most MS risk factors, such as smoking, obesity, and a late age of EBV infection, vary in their prevalence by SES, and thus all provide pathways through which SES could affect disease risk. Alternatively, stress-related immune changes linked to SES could influence disease susceptibility. To establish the strength and nature of the association between SES and MS, two studies were performed as part of this manuscript-based thesis.

The first manuscript is a systematic review of published cohort and case-control studies that examined the association between SES and MS risk. 21 articles were included. 5 studies, all from countries with higher levels of income inequality, reported an association between high SES and increased MS risk. 13 studies reported insufficient evidence of an association, and 2 studies reported an association with low SES; these largely came from more egalitarian nations. Few studies adequately controlled for all important mediators and confounders, precluding clear conclusions about the nature of the SES-MS association.

The second manuscript is an original analysis of the association between SES and MS, using data from the multinational Environmental Risk Factors in MS (EnvIMS) case-control study. The study population comprised 2,144 cases and 3,859 controls, from Norway, Canada, and Italy. Multiple logistic regression was used to evaluate the association between SES and MS, with SES measured by parental education level. Analyses were adjusted for age, sex, sunlight exposure, history of infectious mononucleosis, smoking, obesity, and family size. In

Canada, the OR (95% CI) for MS among individuals with university-educated parents relative to those whose parents had primary school education or below was 1.47 (1.03-2.09), with a statistically significant dose-response relationship across education levels (p for trend = 0.029). In Norway, this association was only present for those who grew up during a period of rising inequality (p for trend = 0.031). No evidence for an association was found in Italy.

These two studies provide only partial support for an association between high SES and increased MS risk. Differing ages of EBV infection by social class, or stress-related immune changes linked to SES, are both possible explanations for the findings.

Résumé

La sclérose en plaques (SP) est une maladie chronique qui se caractérise par l'inflammation et la neurodégénérescence du système nerveux central. Les chercheurs ont identifié il y a plus de 50 ans que les personnes ayant un statut socioéconomique (SSE) élevé présentaient un risque accru de développer la SP. Ces observations se démarquent de la tendance plus répandue voulant que les problèmes de santé soient associés à un faible SSE. La prévalence de la plupart des facteurs de risque de la SP, comme le tabagisme, l'obésité et l'exposition au virus Epstein-Barr à un âge avancé, varie selon le SSE. Ceci fournit ainsi des trajectoires par lesquelles le SSE peut influencer le risque de développer la maladie. Autrement, la susceptibilité à la maladie pourrait être influencée par les changements immunitaires liés au stress associé au SSE. Deux études ont été menées dans le cadre de cette thèse par articles afin de définir la force et la nature de l'association entre le SSE et la SP.

Le premier article présente une revue systématique d'études par cohorte et cas-témoins ayant examiné le lien entre le SSE et le risque de développer la SP. Au total, 21 articles ont

été conservés. De ceux-ci, cinq études, chacune issue de pays ayant une inégalité du revenu prononcée, ont rapporté un lien entre un SSE élevé et un risque accru de développer la SP. Treize études ont, quant à elles, indiqué avoir trop peu d'éléments pour conclure à une association et deux études ont rapporté une association avec un SSE faible; à noter que ces études provenaient principalement de pays plus égalitaires. Peu d'études ont réussi à contrôler adéquatement pour tous les médiateurs et les variables de confusion importants, ce qui empêche d'obtenir des conclusions claires sur la nature du lien entre le SSE et la SP.

Le deuxième article est une analyse originale de l'association entre le SSE et le développement de la SP à l'aide de données tirées de l'étude cas-témoin multinationale sur les facteurs de risque environnementaux de la SP (EnviMS). La population étudiée était composée de 2 144 cas et de 3 859 témoins vivant en Norvège, au Canada et en Italie. Une analyse de régression logistique multiple a été faite pour évaluer le lien entre le SSE et la SP, où le SSE était mesuré par le niveau de scolarité des parents. Les analyses ont été ajustées pour l'âge, le sexe, l'exposition au soleil, les antécédents de mononucléose infectieuse, le tabagisme, l'obésité et la taille de la famille. Au Canada, le rapport de cotes (IC de 95 %) pour la SP chez les personnes dont les parents ont été à l'université en comparaison avec ceux dont les parents ont une éducation primaire ou moins était de 1,47 (1,03-2,09), avec une relation dose-réponse statistiquement significative pour tous les niveaux de scolarité (p de tendance = 0,029). En Norvège, cette association a été observée uniquement chez les gens qui ont grandi pendant une période où les inégalités augmentaient (p de tendance = 0,031). Aucun indice d'association n'a été observé en Italie.

Ces deux études soutiennent seulement en partie l'association entre un SSE élevé et un risque accru de développer la SP. Ces observations pourraient être expliquées par les âges

différents d'exposition au virus Epstein-Barr selon la classe sociale ou les changements immunitaires liés au stress associés au SSE.

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Preface and contributions of authors

Manuscript 1. Is high socioeconomic status a risk factor for multiple sclerosis? A systematic review

- Robert Goulden: study design, screening of articles, data extraction, quality assessment, drafting and revision of the manuscript.
- Tamara Ibrahim: study design, screening of articles, data extraction.
- Christina Wolfson: study design, quality assessment, revision of the manuscript

Manuscript 2. Does low socioeconomic status in early life protect against multiple sclerosis? A multi-national, case-control study

- Robert Goulden: study design, statistical analysis, drafting and revision of the manuscript.
- Trond Riise: study design, revision of the manuscript.
- Kjell-Morten Myhr: study design, revision of the manuscript.
- Maura Pugliatti: study design, revision of the manuscript.
- Christina Wolfson: study design, revision of the manuscript

1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system driven by inflammation and neurodegeneration. In Western countries, its prevalence ranges between 100 and 300 per 100,000, with most affected individuals developing the disease in early adulthood (1,2). While typically beginning as an episodic illness with a relatively minor impact on functional status, in most patients it eventually develops into a disease of progressive and substantial disability. Its relatively early onset and high prevalence means that it presents a considerable, long-term health burden to its sufferers and to wider society. A large number of risk factors and casual pathways have been investigated in the search for MS's etiology, but only a few have been consistently linked to the disease. These include Epstein Barr virus (EBV), vitamin D or sunlight deficiency, cigarette smoke exposure, and obesity. In addition to these environmental factors, female sex confers a more than two-fold higher risk of disease, and a number of genetic risk loci have been identified. Much of what determines a given individual's risk of disease, however, remains unexplained, and the search for additional risk factors and causal mechanisms is the subject of considerable research efforts.

One such factor may be socioeconomic status (SES). While many diseases are commoner in those of low SES, MS is one of a smaller group of conditions which have been linked to *high* SES (3–11). This observation was first made over 50 years ago (3), but its continued validity and relevance is uncertain, and the extent to which it can be explained by known risk factors remains to be clarified. The aim of this thesis is to address this uncertainty. In particular, it aims to (a) systematically review existing research on the association between MS and SES, and (b) carry out an original analysis of the question using data from a large, multinational

case-control study, *Environmental Risk Factors in Multiple Sclerosis* (EnvIMS). If a link between high SES and MS is found after taking known risk factors into account, this would imply one of two things. Either high SES itself – or more specifically its psychologically-mediated physiological correlates – is a risk factor for MS. Or alternatively, high SES is a marker of some, as yet, unmeasured risk factor. Although this research does not seek to identify a plausible target for a public health intervention, it seeks to enhance our understanding of MS's etiology and thereby support the ultimate goal of disease prevention.

Following this introduction, Chapter 2 provides an overview of the pathological, clinical, and epidemiological features of MS, including a discussion of the potential role of SES in its etiology. Chapter 3 contains the first manuscript, "Is high socioeconomic status a risk factor for multiple sclerosis? A systematic review". Chapter 4 describes the EnvIMS case-control study. Chapter 5 contains the second manuscript, "Does low socioeconomic status in early life protects against multiple sclerosis? A multinational, case-control study". Finally, Chapter 6 contains a summary of the findings, along with a discussion of their implications and concluding comments.

2. Multiple sclerosis: pathophysiology, clinical features, and epidemiology

Pathophysiology

The initial phase of MS is characterised by focal damage to the myelin sheaths surrounding axons in the central nervous system (CNS), with a subsequent loss in the efficiency of signal transmission and impairment of neurological function. In addition to demyelination, inflammation and axonal injury are key features of MS lesions or 'plaques' (12). The process is primarily driven by autoreactive CD4 T-cells – particularly Th1 and Th17 cells – which have crossed the blood-brain barrier. There is also evidence of B cell involvement, as well as a number of other immune cells and inflammatory mediators (13,14). While MS is widely thought to be an autoimmune condition, conclusive evidence of specific autoantibodies to self-antigens has not yet been demonstrated (12). Similarly, it is unclear whether the initial trigger for the disease involves cross-reaction with an external agent, such as a virus, or some endogenous process of spontaneous immune dysregulation. During this earlier inflammatory stage, damage is focal and often followed by some degree of remyelination (15). Following this, however, the progressive phase of the disease is characterised by a widespread neurodegenerative process of axonal loss and cerebral atrophy, whose mechanisms are not well understood (12).

Clinical features

The age of MS onset is usually between the ages of 20 and 40. For most patients (around 85%), it begins as a relapsing-remitting disease (RRMS), with discrete episodes of focal neurological deficit ('relapses') interspersed with periods of remission. A wide range of signs

and symptoms are seen in MS. Common presentations include weakness or numbness in one or more limbs, optic neuritis, and symptoms of brainstem or cerebellar lesions such as diplopia, vertigo, or ataxia (14). Relapses typically peak in their severity within days to weeks, then resolve, to a variable extent, over subsequent weeks. They occur with a frequency of around 0.5-1.5 per year (12,16). There may be a gradual accumulation of disability due to residual deficits after each attack, along with non-focal symptoms such as fatigue and generalized weakness. Most patients eventually enter a secondary progressive phase of the disease ('secondary progressive MS'), in which episodic disease is replaced by steadily increasing disability. Advancing weakness leads most to require a cane for walking, while many become wheelchair-bound (17). Other common symptoms during this stage include sensory deficits and pain, visual problems, cognitive impairment, and bowel and bladder dysfunction. Life expectancy in MS is typically reduced by around 7-14 years, with respiratory failure or infection a common cause of death (18).

Approximately 10% of individuals with MS have progressive disease from the outset ('primary progressive MS', PPMS), while around 15% of those with RRMS never progress from the relapsing-remitting phase ('benign MS') (12). Some individuals (around 5%) are identified as having 'progressive relapsing MS', characterized by both progressive disease and distinct relapses from the outset.

First developed in 2001, the McDonald criteria for MS brought a more evidence-based approach to diagnosis, and clarified the role of MRI in determining the presence of disease (1). According to the most recent revision in 2010, diagnosis of RRMS requires evidence of 2 or more lesions, based upon clinical or MRI findings, disseminated in space and time (19). That is, they most occur at different areas in the CNS, and take place at least 30 days apart.

Diagnosis of PPMS requires 1 year of disease progression, plus evidence of disease on MRI or the presence of oligoclonal bands in cerebrospinal fluid.

Starting with β-interferon in the mid-1990s, recent years have seen a range of immune-modulating medical therapies become available for the treatment of RRMS. Most drugs are injected, and reduce relapse rates by between 30% (β-interferon) and 68% (natalizumab) (7). During acute attacks, methylprednisolone can be given to reduce symptom severity and duration. However, there are no therapies which have been proven to prevent or treat progressive MS (14).

Epidemiology and risk factors

Descriptive epidemiology and demographic features

There are marked disparities in the occurrence of MS across the world. Its prevalence in Western Europe and North America is around 5 to 10 times higher than in Asia, Africa, and South America (1). While some of this disparity may be explained by differences in diagnosis and ascertainment, it is likely to reflect a genuine difference in disease frequency. In the Western countries where MS is commonest, prevalence is typically between 100 and 300 per 100,000, and annual incidence is around 5 per 100,000 (1). One UK study reported a lifetime risk of over 1 in 200 for women and 1 in 500 for men (2). The geographical distribution of MS was traditionally thought to reflect a latitude effect, with reduced sunlight exposure believed to increase disease risk among those living further from the equator. This was supported by the fact that *within* Europe and North America, the disease was commoner at higher latitudes. Recent evidence suggest this latitude effect is declining, however, and may never have been as substantial as originally thought (1,20–22). The fact that disease prevalence correlates much more closely with gross domestic product (GDP)

than latitude suggest that developmental differences between countries could be a more plausible explanation for its worldwide distribution (23). In addition, genetic differences between populations may play a role (1).

MS is commoner among women, with a female to male ratio of around 2.5:1. This ratio has increased markedly since the 1950s, when there was no apparent sex difference. The increasing incidence in women is thought to explain most of the overall rise in incidence since the mid-20th century (1). Although female sex is now one of the best-established risk factors for the disease, the mechanism of its effect is poorly understood, although hormonally-driven changes in immune function are one possible explanation (24,25). Recent decades have also seen shifts in the racial distribution of MS. While initially thought of as being commoner in whites, recent research among US army veterans has reported a slightly higher incidence in blacks (26). Other ethnic groups were found to have lower incidence rates than both blacks and whites.

The median age of MS onset is 23.5, and the mean age is 30 (12), with onset rare in children (3-5% of patients) and in those over the age of 60 (14). The relatively young age of onset points to the importance of exposures in early life. This is supported by evidence from migration studies, which have found that those who migrate before age 15 acquire the risk profile of their destination country, while those who migrate at older ages carry the risk profile or their origin country (27). This would suggest that exposures after this age are less important, though other migration studies do not find evidence for this threshold (28), and many studies have found subsequent exposures to also affect disease risk (27).

Epstein Barr Virus

The varied geographical distribution of MS, and reports of case clusters or epidemics (29), suggest a possible role for a microorganism in the disease's etiology, either as the cause of a chronic infection or as a trigger for an autoimmune process. While various bacteria and viruses have been considered, Epstein Barr Virus (EBV) is the agent which has most convincingly and consistently been linked to the disease. By measuring serum antibodies to EBV, around 90% of individuals in the general population show evidence of infection at some point in their life, but this rate approaches 100% for MS patients (30). In a review of studies which used two independent methods of antibody detection to maximize sensitivity, not a single adult with MS without evidence of prior EBV infection was identified (31). This pattern suggests that EBV is a necessary but not sufficient cause of the disease (27). One explanation for the varying effect of EBV on MS risk is the age of primary infection. Infection with EBV in childhood is usually asymptomatic, while infections in adolescence and adulthood can result in infectious mononucleosis (IM). There is a well-established association between a history of IM and MS – a meta-analysis reported a relative risk (95% CI) of 2.17 (1.97-2.39) – lending support to the idea that a late age of EBV infection increases disease risk (32). This is consistent with the geographical distribution of the disease, as in developing countries where incidence is low, EBV is usually acquired in early childhood. It has therefore been suggested that high levels of hygiene in childhood, characteristic of developed countries, delays the primary age of EBV infection with a resulting increase in MS risk (33). The hygiene hypothesis was in fact implicated in MS etiology before EBV was well-established as a risk factor, in an early Israeli study which found MS incidence was lower in areas of poor sanitation (34). Further evidence that EBV is implicated in MS pathogenesis comes from analysis of serum samples collected from individuals who later went on to

develop the disease, which showed that MS onset is often preceded by a sharp rise in EBV antibody levels (35). Regardless of the age of MS onset, this increase in antibody titres occurred between the late teens and mid-20s. This implicates late adolescence and early adulthood as a key time for MS acquisition, in which some additional factor may affect the immune response to EBV in such a way as to increase MS risk.

Vitamin D and sunlight exposure

The possibility that low sunlight exposure might increase the risk of MS – likely mediated through low vitamin D levels – was first suggested by the apparent latitude gradient in its frequency (36). While evidence for this gradient is now weaker (1,20–22), a number of other studies have implicated low sunlight exposure and low vitamin D levels in MS risk. In studies where participants reported past sunlight exposure, higher exposure was associated with reduced risk of MS (37–39). Children born in April and May in the northern hemisphere are reported to be at higher risk of MS, perhaps due to lower sunlight exposure during early pregnancy (40). However, this finding may be confounded by geographical and temporal variability in birth rates (41). Support for the role of low vitamin D comes from an inverse association between MS and both high serum concentrations of vitamin D (42) and fatty fish consumption (43), an important dietary source of the micronutrient. One purported mechanism of vitamin D's protective effect is its promotion of regulatory T-cell function, although it is also known to have other immunomodulatory effects (44).

Genetics

A genetic aspect to MS pathogenesis is suggested by the roughly 10 fold higher risk of disease in first-degree relatives of MS patients compared to the general population (15,28). The concordance rate for monozygotic twins is around 15%, compared to 3% for dizygotic

twins (45,46). A number of risk alleles have been identified which may account for some of this familial aggregation. Linkage studies had long suggested a role for genes in the human leukocyte antigen (HLA) region of chromosome 6, a finding confirmed by later genome-wide association studies (GWAS) (47). In the largest GWAS of MS, a large number of susceptibility loci outside the HLA region were also identified (48). These findings point to the role of several immune processes in MS pathogenesis, including antigen recognition, T cell differentiation, and responses to cytokines such as IL-2 and IL-7. However, even the strongest genetic risk alleles have modest effect sizes, suggesting that other genetic, epistatic, epigenetic, and shared environmental factors are required to fully explain MS's heritability (47).

Other factors

A number of other risk factors have been consistently linked to MS, including smoking (49,50), passive smoke exposure (51,52), and obesity (53,54). The higher risk in females has led to a search for the role of hormonal factors, with early menarche (55) and nulliparity (56) linked to increased incidence. The latter association, however, may be due to reverse causality (57).

Socioeconomic status

An association between high socioeconomic status (SES) and MS was first noted in descriptive studies from the UK, in which individuals in higher occupational classes were found to be over-represented among MS patients relative to the general population (3,4). Although this finding has been replicated in ecological (6–11) and case-control studies (5,58), some research has found no association (59), or even a link with low SES (60,61).

There exists, therefore, a need to clarify the existence and nature of any association between SES and MS.

In considering this association, it is important to think about possible mechanisms linking SES to MS risk. An extensive field of research had explored the relationship between SES and health outcomes (62–64). Much of this is devoted to explaining the association between *low* SES and increased morbidity and mortality from a number of conditions. One possible explanation is differences in health behaviours, with smoking, obesity, poor diet, and lack of exercise all commoner in those of low SES (65). However, analyses which adjust for these factors still find an association between SES and poor health. While such behaviours are found to explain most of the association in some cohorts, in others less than 20% is explained, with a statistically and clinically significant association between low SES and all-cause mortality even in fully adjusted models (66). Additionally, socioeconomic differences in health outcomes are seen in countries both with and without a universal healthcare system, suggesting that differential access to healthcare does not fully explain the relationship (67). Other causal mechanisms have therefore been posited to explain the link, including differential exposure to environmental toxins, dangerous neighbourhoods or living conditions, and the physiological effects of negative emotional states such as stress (68,69).

This suggests that any account of the causal pathways linking SES to MS risk may be complex and multi-faceted. Indeed, almost all risk factors for the disease are also associated with SES. Delayed EBV infection (70–73) and nulliparity (74) have been linked to high SES, while smoking (75), obesity (76), early menarche (77), and a family history of MS (78,79) are linked to low SES. Given the clear tendency of so many exposures to vary by social class, it is also

possible that some as yet unidentified risk factor for MS might explain any observed association.

In addition to such indirect pathways, it is possible that the psychological correlates of SES itself might affect MS risk. Individuals of low SES experience higher levels of psychological distress, in both childhood and adult life (63,80–82). This leads to measureable differences in physiological markers of stress, such as elevations in the stress hormone cortisol (83,84). Cortisol and other stress-related hormones such as catecholamines are known to have significant effects on the immune system. One such effect is that cortisol causes a shift in the T helper cell population away from Th1 cells, important in cell-mediated immunity, and towards Th2 cells, drivers of humoral immunity (85–88). Low SES children with asthma, a Th2-driven disease, have higher levels of circulating Th2 cytokines, an effect which is mediated through negative emotional states, and which may contribute towards more severe disease activity (89). Evidence for psychologically-mediated Th1 suppression comes from studies in which chronically stressed subjects who are experimentally inoculated with the common cold virus are more likely to become infected than less stressed individuals, suggesting impaired cell-mediated immunity (90). The same effect is seen for childhood SES, whereby adults whose parents had rented as opposed to owned their homes were more likely to become infected (91). This is consistent with observational studies showing an increased risk of viral infections in stressed individuals (92).

While stress-related immune changes are often posited as explanations of the *harmful* effects of low SES on health, the opposite may be true in MS. Given that Th1 cells play a role in MS pathogenesis (86–88), stress-induced suppression of Th1 activity is one possible pathway through which low SES might reduce the risk of disease. A number of other Th1-

associated diseases are also less common in those of low SES, including type 1 diabetes (93,94), coeliac disease (95,96), and Crohn's disease (97). In the most popular animal model of MS, experimental autoimmune encephalomyelitis (EAE), 10 out of 12 studies that looked at the effects of chronic stress applied prior to disease induction found that stress reduced the incidence and/or severity of EAE (98). Acute stress applied after EAE induction, however, was found to exacerbate the disease. This is consistent with the notion that while chronic stress is immunosuppressive, acute stress is immunoenhancing and thus potentially exacerbates immune-mediated disease (88,99). An association between acute stressors and increased MS relapse rate has been reported in two meta-analyses (100,101). However, a protective effect of chronic stress in humans has not previously been considered. Two studies have looked at the relationship between stressful events in childhood and MS risk, hypothesizing that they would be harmful (102,103). There was insufficient evidence of an effect for most events, with some having wide confidence intervals ranging from a 3-fold reduced risk to a 2-fold higher risk. Only parental divorce was linked to a statistically significant increase in risk, with a modest effect size (RR 1.11, 95% CI 1.03-1.20). Additionally, the focus on stressful *events* is somewhat different from the lower-level ongoing stress of low SES.

In summary, a number of indirect and direct pathways might link SES to MS. This highlights the importance of adjusting for known risk factors when evaluating the relationship, to assess the direct effect of SES on disease risk.

3. Manuscript 1.

The first manuscript of this thesis is a systematic review of the association between MS and SES. It summarizes the results of 21 cohort and case-control studies, published between 1967 and 2014. Although the results were inconsistent and there was considerable heterogeneity in the study settings, there was some evidence that high SES increased the risk of MS in countries and time periods with higher levels of economic inequality. The text below is the second version of the manuscript submitted to the *European Journal of Neurology*, having been revised in response to comments on the first version from two anonymous reviewers.

Is high socioeconomic status a risk factor for multiple sclerosis? A systematic review

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Abstract

Background

High socioeconomic status (SES) is generally associated with better health outcomes, but some research has linked it with an increased risk of multiple sclerosis (MS). The evidence for this association is inconsistent, and has not previously been systematically reviewed.

Methods

We conducted a systematic review of cohort and case-control studies in any language looking at the association between MS and SES. Medline and Embase were searched for articles in all languages published up until 23 August 2013.

Results

21 studies from 13 countries were included in the review. Heterogeneity of study settings precluded carrying out a meta-analysis, and a qualitative synthesis was performed instead. 5 studies, all from more unequal countries, reported an association between high SES and MS. 13 studies reported no evidence of an association, and 3 studies reported an association with low SES. These 16 studies largely came from more egalitarian countries.

Conclusions

The evidence for an association between high SES and increased MS risk is inconsistent, but with some indication of a stronger effect in countries and time periods with higher inequality. Firm conclusions are hampered by the failure of most studies to control for other important risk factors for MS.

Background

Multiple sclerosis (MS) is a chronic disease of the central nervous system driven by inflammation and neurodegeneration. While its precise etiology remains unknown, several risk factors have been reported, including female sex, low sunlight exposure, low vitamin D levels, Epstein-Barr virus infection, and smoking (28). Though less widely researched, numerous studies have posited a link between socioeconomic status (SES) and MS. While many diseases are associated with low SES, MS is one of a smaller set of conditions linked to *high* social class (3,4,6,7). The relationship, however, is unclear and poorly characterised. Internationally, MS occurs with greater frequency in high income nations (23). Within countries, however, some studies find MS occurs more frequently among high SES groups, while other studies find no social gradient, or even the opposite (59,60). Much recent and ongoing research includes SES as a potential confounding factor without a clear understanding of the relationship. The aim of this systematic review is to determine whether SES is related to the risk of developing MS.

Methods

Search strategy and study selection

A search was performed in Medline and Embase, both via Ovid, for articles in any language published up until 23 August 2013. Subject headings and titles/abstracts were searched for a combination of MS and SES-related terms, outlined in Table 1.

Table 1. Search terms used.

Search field	MS-related terms	SES-related terms
Medline MeSH headings	exp multiple sclerosis	exp socioeconomic factors
Embase Emtree headings	exp multiple sclerosis	exp social status or exp socioeconomics
Title and abstract (used in both)	"multiple sclerosis" or "disseminated sclerosis"	socioeconomic* or "socio-economic*" or SES or "social status" or "social class" or income or occupation* or employment or unemploy* or education* or wealth or affluen* or poverty or depriv* or residence or neighborhood

exp: 'Exploded' search, with all lower branches of the term searched. *: Wildcard character.

Studies were included if they were cohort or case-control studies, with MS occurrence as the outcome and SES as the exposure. Descriptive and ecological studies were excluded as we were interested in establishing the causal nature, if any, of the relationship between SES and MS, and this would not be possible in such uncontrolled studies. Measures of SES had to apply to a time before disease onset. They could relate to income, education level, occupation, or neighbourhood characteristics, either of the subject or their parents.

Two reviewers (RG, TI) first screened the title and abstract of all articles retrieved by the search. The full text of selected studies was further assessed for eligibility and final inclusion in the study. The reference lists of these studies, and review articles, were manually searched to identify further relevant articles.

Data extraction

The following data were extracted from each study: location, study design, case and control population, SES measure used, potential confounders examined, and the measure of association with MS. Estimated odds ratios (ORs) or relative risks (RRs), and their confidence intervals, were extracted if they were reported, otherwise they were calculated if there

were sufficient data available. Data were extracted by one author (RG) and reviewed by another (TI).

Quality assessment

Quality assessment criteria that were specific to the features of our question were developed using an iterative process. Two authors (RG, CW) independently assessed a sample of five articles using the Newcastle Ottawa Scale (104) and discussed any discrepancies in scoring. This process was used as a basis to outline the features of an "ideal" study to which each article would be compared. Studies were assessed against this standard by one author (RG), with a second author (CW) reviewing this process; disagreements were resolved through consensus. Studies were evaluated on their susceptibility to the three main categories of bias – selection, information, and confounding – and the appropriateness of their analytic methods. An overall summary score was not assigned, as we feel that study quality is a multi-dimensional and qualitative concept. Rather, each specific criteria was evaluated with both a score (A to C, with A being the highest) and a descriptive explanation for this rating.

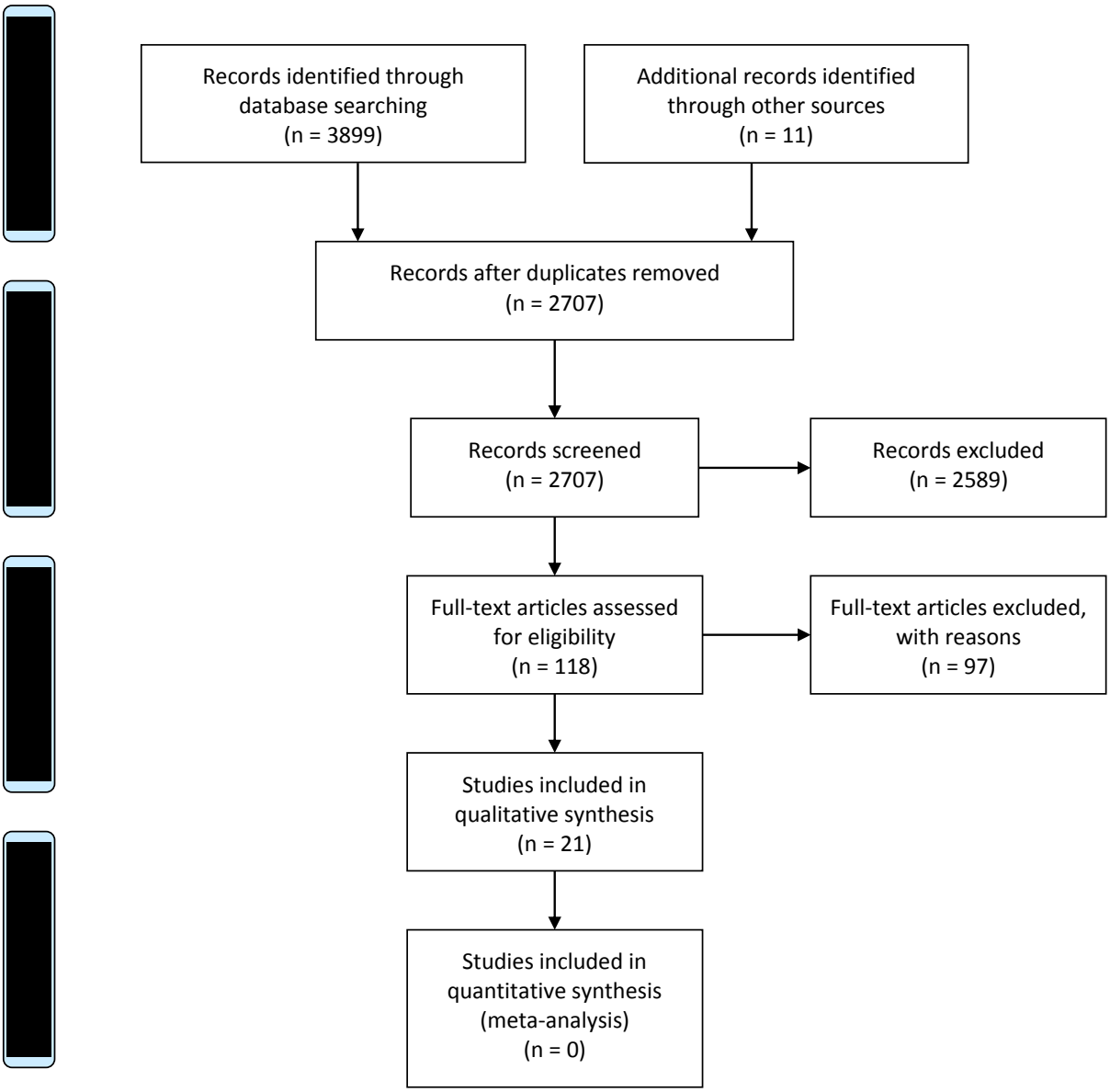
Results

Literature search

The search strategy retrieved 1517 articles from Medline and 2382 from Embase (Figure 1). 107 of these articles were selected for full text review, of which 17 met the inclusion criteria. 10 articles identified from reference lists had their full text reviewed, of which three were included. One study that was only available as a conference abstract during the initial search was subsequently published as a full article, and was also included (61). This gave a total of 21 articles, of which 18 were in English, and three in Spanish. The main reasons for

excluding articles whose full text was reviewed were: SES was included only as a confounder (*n* = 32), the study was a case series or ecological study (*n* = 25), they were review articles or commentaries (*n* = 20), or their measure of SES referred to a time point after disease onset (*n* = 10).

Figure 1. PRISMA flow diagram of search strategy (105)**.**



The 21 included studies are summarized in Table 2. The studies came from 13 different

countries, published across 47 years (1967-2014), and ranging in size from study of 16 cases and 56 controls, to a cohort study of over 1.5 million individuals. Due to the geographical and temporal diversity of the included studies, and the wide range of SES measures used, a qualitative synthesis was performed.

Table 2. Summary of studies.

Reference	Design	Country	Cases		Controls		Premorbid SES measure		Measure of association (95% CI) for high SES
			n	Source	*n*	Source			
Studies finding an association between high SES and MS									
Casetta et al. 1994 (58)	Case-control	Italy	104	Prevalent cases living in Ferrara province.	150	Random sample of hospital and community controls, matched for age, sex, and residential area.	Education (high school vs. primary/middle school)		OR: 2.3 (1.2-4.5)
							Education (high school/university vs. primary)		OR: 2.19 (1.15-4.16)
							Parental education		No association[2]
							Parental occupation		No association[2]
Hopkins et al. 1991 (106)	Case-control	US	16	Prevalent cases in Polk Township, Ohio, identified via patient group, clinics, and media in 1987.	56	Random sample of local population, matched for age, race, and sex.	Education (high school graduate vs. non-graduate)		OR undefined as all cases exposed
							Education (college graduate vs. non-graduate)		aOR: 13.1 (2.8-62.0)
							Father's occupation		No association[2]
Kurtzke and Page 1997 (5)	Case-control (nested)	US	1489	Incident cases among US army veterans of WW2 and Korean War, during or within 7 years of military service.	1624	Random sample of US army veterans of WW2 and Korean War, matched for age, time of army enrolment, race, and sex.	Education (≥9 years vs. <9 years)	White males (WW2)	aOR: 1.95[3]
								White males (KW)	aOR: 2.33[3]
								Black males	aOR: 2.17[3]
								White females	No association[2]
							Socioeconomic score by occupation at army enrolment	White males (WW2)	No association[2]
								White males (KW)	aOR: 4.97[3]
								Black males	No association[2]
								White females	No association[2]
Tarrats et al. 2002 (107)	Case-control	Mexico	94	Consecutive patients treated in national referral centre.	210	110 hospital controls from consecutive series of non-MS patients, 100 hospital workers.	Education (total years)		Higher SES in cases[4]
Zilber and Kahana 1996 (108)	Case-control	Israel	93	Prevalent cases in 1975, who were Jewish and Israeli-born, identified from national MS registry.	94	Random sample of national population from government population data, matched for age, sex, ethnic group, and country of birth.	20-item SES scale at age 10 (high vs. low SES)		No difference[4]
							20-item SES scale at age 10 (high vs. very low SES)		Higher SES in cases[4]
							4-item SES scale at onset		No difference[4]
							3-item SES scale at onset		Higher SES in cases[4]
Studies not finding an association between SES and MS									
Alter and Speer 1968 (109)	Case-control	US	36	Consecutive patients treated in one hospital network, Minnesota.	72	Non-MS patients from same hospital network, matched for age and sex.	Social class at onset		OR: 1.76 (0.39-7.55)[1]
	Case-control	Israel	241		917		Occupation of respondent at age of onset		OR: 1.00 (0.65-1.50)[1]
							Occupation of head of household at onset		OR: 0.93 (0.67-1.29)[1]

Antonovsky et al. 1967 (110)				Prevalent cases from national survey of hospitals and clinics in 1960.		Random sample from 3 major cities using census data, matched for age, sex, and country of birth.	Occupation of head of household at age 10	OR: 0.99 (0.74-1.34)[1]
							Education level at age of onset	OR: 1.23 (0.92-1.65)[1]
							Education level of household head at onset	OR: 0.93 (0.68-1.27)[1]
							Self-estimate of SES at age 10	OR: 1.33 (0.98-1.82)[1]
Berr et al. 1989 (111)	Case-control	France	63	Prevalent cases in the Hautes-Pyrénées region identified via their doctors.	63	Unrelated control, matched for age, sex, and parish of residence.	Father's occupation	No difference[4]
							Education (total years)	No difference[4]
							Academic level	No difference[4]
Breland and Currier 1967 (112)	Case-control	US	54	Prevalent cases from survey of hospitals and clinics in Jackson, Mississippi in 1965.	344	Random sample of patients from same group of hospitals and clinics, matched for race and sex.	Occupation (non-manual vs. manual)	OR: 1.64 (0.84-3.29)[1]
Frutos-Alegría et al. 2002 (113)	Case-control	Spain	37	Prevalent cases from single hospital in Alcoi	148	Controls from emergency department of same hospital, matched for age, sex, and textile industry employment	Education	No association[2]
Frutos-Alegría et al. 2002 (114)	Case-control	Spain	47	Prevalent cases from hospitals in Alicante and Villajoyosa	188	Controls from emergency departments of same hospitals, matched for age, sex, and residential area	Education (high school and above vs. no high school)	OR: 0.98 (0.47-1.99)[1]
Koch-Henriksen 1989 (115)	Case-control	Denmark	324	Prevalent cases in Funen region in 1981-1984, identified via national MS registry or hospital records.	324	Random sample of local population on national population registry, matched for age and sex.	Occupation at time of maximal social ability before affected by disease	OR: 1.23 (0.86-1.77)[1]
							Occupation of economically leading parent	OR: 1.00 (0.72-1.38)[1]
							Education (≥10 years vs. <10 years)	OR: 0.88 (0.59-1.30)[1]
Kotzamani et al. 2012 (116)	Case-control	Greece	657	Incidence cases on Crete in 1980-2008, identified via regional MS registry.	593	Random sample of local population matched for age, gender, and rural/urban residence.	Education (university vs. non-university)	OR: 0.94 (0.72-1.25)[1]
							Occupation at onset	OR: 0.50 (0.36-0.70)[1]
							Maternal occupation (female subjects only)	OR: 1.92 (1.05-3.57)[1]
							Paternal occupation (male subjects only)	OR: 1.16 (0.79-1.71)[1]
Kurtzke et al. 1997 (117)	Case-control	Denmark	23	Prevalent cases in the Faroe Islands, 1978-1979.	127	Family, neighbours, and sample of age and sex matched residents of separate towns.	Completed years of education	No difference[4]
							Occupation aged 16-20	OR: 0.92 (0.24-2.93)[1]
							Occupation aged 21-30	OR: 0.63 (0.14-2.29)[1]
Martínez-Sobrepera et al. 2001 (118)	Case-control	Cuba	50	Prevalent cases in Cienfuegos, Santa Clara, and Sancti Spíritus, identified via hospitals.	50	Family members of cases.	Education (post-secondary vs. secondary and below)	OR: 2.23 (0.94-5.43)[1]
Nielsen et al. 2013 (59)	Cohort	Denmark	2205	Incident cases in national MS registry in 1981-2007.	1.57 million	Cohort from national population registry born in 1966-1992	Childhood household income quintile (highest vs. lowest)	aRR: 0.93 (0.80-1.08)
							Maternal education (higher vs. basic)	aRR: 0.86 (0.76-0.97)
							Paternal education (higher vs. basic)	aRR: 0.93 (0.82-1.06)

Panelius 1970 (119)	Case-control	Finland	146	Prevalent cases in Turku area in 1967, identified via national pensions registry, hospital records, and doctors.	141	Random sample of local population on national health insurance registry, matched for age and residence.	Education (high school vs. elementary)	OR: 1.19 (0.70-2.01)[1]
Poskanzer et al. 1980 (120)	Case-control	UK	82	Prevalent cases in Orkney and Shetland in 1974-1977, identified through doctors, hospital records, and MS societies.	153	Two age and sex matched controls per case, one from the same parish and the other from a non-adjacent parish.	Father's occupation	No difference[4]
							Occupation at onset	OR: 1.40 (0.82-2.44)[1]
							Subjective opinion of SES during childhood	No difference[4]
Studies finding an association between low SES and MS								
Briggs et al. 2014 (61)	Case-control	US	1023	Prevalent cases in the Kaiser Permanente Medical Care Plan, Northern California, in 2010.	620	Random sample of individuals from the same care plan, matched for age, sex, race, and ZIP code.	Education level (college vs. below)	aOR: 0.77 (0.59-1.00)
							Parental education level (college vs. below)	aOR: 0.78 (0.61-0.99)
							Parental home ownership (own vs. rent)	aOR: 0.68 (0.50-0.92)
							Cumulative SES exposure	aOR: 0.67 (0.49-0.92)
							Social mobility path (high to high vs. low to low)	aOR: 0.57 (0.42-0.79)
Ghadirian et al. 2001 (121)	Case-control	Canada	200	Incident cases in Montreal in 1991-1994, identified via MS group, clinics, and media.	202	Random sample of local population from telephone directory, matched for age, sex, and phone number area.	Education (≥18 years vs. <18 years)	aOR: 0.4 (0.3-0.8)
Riise et al. 2011 (60)	Cohort	Norway	648	Incident cases in 1981-2007, identified via national MS registry and hospital records.	428346	Cohort from national employment registry comprising petroleum workers and referents matched on age, gender, area of residence, and age of starting work.	Education (graduate vs. elementary)	aRR: 0.43 (0.27-0.66)

CI: confidence interval; OR: odds ratio; aOR: adjusted odds ratio; aRR: adjusted rate ratio; WW2: World War 2; KW: Korean War.

1. No OR reported, but crude OR calculated for the present review using the reported data.

2. No OR reported and insufficient data to allow calculation. In-text description of result included instead, according to statistical significance.

3. CI not reported and insufficient data to allow calculation, but effect reported as statistically significant.

4. Cases and controls compared using a t-test or χ^2 test.

Studies reporting an association with high SES

Four case-control studies (58,106–108) and one nested case-control study (5) reported a statistically significant association between high SES and increased MS risk. The largest of these studies, and the only one using prospectively collected data, was nested in a cohort of US army veterans of the Korean and Second World Wars (5). As conscription was in use during these conflicts, the study population was likely representative of the US male population, but less so of women, who comprised less than 10% of the cohort and were not conscripted. The point estimates for the ORs in most of these studies ranged between 1.5 and 2.5. Two studies did not report a measure of association, but reported a higher SES in cases as compared to controls that was statistically significant according to a t-test (107,108).

Studies not reporting an association with SES

Twelve case-control studies (109–120) and one cohort study (59) did not find an association between SES and MS risk. The cohort study included all incident cases in Denmark over a 26 year period, and benefited from contemporaneous collection of data on childhood SES. It is the largest and what we judged to be the highest quality study in this review. Seven of the 12 case-control studies in this group reported wide 95% CIs that included substantial effect sizes – RR or OR of ≤0.5 or ≥2.0 – along with the null value (109,112,114,117–120). Two further studies did not report a measure of association, instead simply noting that the difference in SES between cases and controls was not statistically significant (111,113).

Studies reporting an association with low SES

Three studies – two case-control (61,121) and one cohort (60) – reported an association between low SES and increased MS risk. The larger of the two case-control studies, set

among members of a private health care plan in California, was notable for being the only study in this review which adjusted for all potential confounders and mediators of the SES-MS association (61). The cohort study, meanwhile, used data from the Norwegian national MS registry. SES was initially included as a confounder in an analysis of petroleum industry exposure, but was part of a more detailed post-hoc analysis after a strong association was noted. The point estimates of the RRs and ORs for high SES in these studies ranged between 0.4 and 0.8.

Study quality

The quality assessment for each study is summarized in Table 3. It should be noted that many of the older studies included in this review could not have been reasonably expected to meet all of the quality criteria. In particular, several risk factors have only been identified in recent years. The quality rating is therefore not a comment on the competence of the investigators given their constraints, but an evaluation of the utility of their results from the perspective of current knowledge.

Table 3. Quality assessment.

For each category, does the study have the properties of the ideal study? A = Yes, B = Partially, C = No						
Reference	**Selection**		**Measurement**		**Comparability of cases and controls**	**Analysis**
	Cases	**Controls**	**Exposure**	**Outcome**		
Ideal study	*Large,[1] representative sample of incident cases in the general population.*	*Representative sample from the same source population as cases.*	*Contemporaneously measured record of pre-morbid SES. Same method in cases and controls.*	*Neurologist diagnosis of MS using recognised diagnostic criteria.*	*Results adjusted for age, gender, EBV infection (including infectious mononucleosis), sunlight exposure or vitamin D, smoking, body weight, and family history of MS.*	*Statistical analysis appropriate to the data collected and study design.*
Studies finding an association between high SES and MS						
Casetta et al. 1994 (58)	C. Small sample of prevalent cases.	A	B. Based on recall. Interviewers not blinded to case status.	A	C. No adjustment.	B. Testing of ≥3 measures of SES without specifying primary.
Hopkins et al. 1991 (106)	C. Small sample of prevalent cases from one small population.	A	B. Based on recall. Interviewers not blinded to case status.	A	B. Adjusted for age, sex, and race. No association found between MS and infectious mononucleosis in their data.	B. Testing of 3≥ measures of SES without specifying primary.
Kurtzke and Page 1997 (5)	B. Cases drawn from a national cohort of conscripted soldiers, which is highly representative of the male general population but contains few women.	A	A	A	B. Adjusted for latitude, urban or rural residence, education, socioeconomic class by occupation, visual acuity, ethnicity by surname and state. Stratified by race, gender, and war cohort.	B. Included two measures of SES in multivariable model.
Tarrats et al. 2002 (107)	C. Small sample of consecutive cases at one centre.	B. Hospital controls.	B. Based on recall. Interviewers not blinded to case status.	A	C. No adjustment.	A
Zilber and Kahana 1996 (108)	C. Small sample of prevalent cases.	A	B. Based on recall. Interviewers not blinded to case status.	A	C. No adjustment.	B. Testing of 3≥ measures of SES without specifying primary.
Studies not finding an association between SES and MS						
Alter and Speer 1968 (109)	C. Small sample of consecutive cases at one centre, described as unrepresentative with regards to SES.	B. Hospital controls.	B. Based on recall. Interviewers not blinded to case status.	B. Neurologist diagnosis, but no information on diagnostic criteria.	C. No adjustment.	A

Antonovsky et al. 1967 (110)	B. Prevalent cases.	A	B. Based on recall. Interviewers not blinded to case status.	B. Neurologist diagnosis, but using non-standard criteria.	C. No adjustment.	C. Testing of 3≥ measures of SES without specifying primary. No statistical analysis performed.
Berr et al. 1989 (111)	C. Small sample of consecutive cases.	C. All matched on parish of residence, a possible measure of SES. No details on recruitment procedure.	B. Based on recall. Interviewers not blinded to case status.	A	B. Adjusted for age, sex, and parish of residence.	B. Testing of 3≥ different measures of SES without specifying primary.
Breland and Currier 1967 (112)	C. Small sample of prevalent cases.	B. Hospital controls.	A	B. Neurologist diagnosis, but using non-standard criteria.	C. No adjustment.	C. Testing of ≥3 measures of SES without specifying primary. No statistical analysis performed.
Frutos-Alegría et al. 2002 (113)	C. Small sample of prevalent cases.	C. Hospital controls, matched on industry of employment, a possible marker of SES.	B. Based on recall. Interviewers not blinded to case status.	A	C. No adjustment.	A
Frutos-Alegría et al. 2002 (114)	C. Small sample of prevalent cases.	C. Hospital controls, matched on area of residence, a possible marker of SES.	B. Based on recall. Interviewers not blinded to case status.	A	C. No adjustment.	A
Koch-Henriksen 1989 (115)	B. Prevalent cases.	A	B. Based on recall. Interviewers not blinded to case status.	A	B. Adjusted for age and sex.	B. Testing of 3≥ different measures of SES without specifying primary.
Kotzamani et al. 2012 (116)	A	B. Limited details on recruitment procedure.	B. Based on recall. Interviewers not blinded to case status.	A	B. Analysis stratified by gender.	A
Kurtzke et al. 1997 (117)	C. Small sample of prevalent cases from one small population.	A	B. Based on recall. Interviewers not blinded to case status.	C. No information on how cases were recruited or assessed.	C. No adjustment.	B. Testing of 3≥ different measures of SES without specifying primary.
Martínez-Sobrepera et al. 2001 (118)	C. Small sample of prevalent cases.	C. Family controls, likely to be very closely matched on SES.	B. Based on recall. Interviewers not blinded to case status.	A	C. No adjustment	A
Nielsen et al. 2013 (59)	A	A	A	A	B. Adjusted for sex, age, calendar period, household category, number of children in household	B. Testing of 3≥ different measures of SES without specifying primary.

Panelius 1970 (119)	B. Prevalent cases	B. All matched on residence, a possible measure of SES.	C. Based on recall. Interviewers not blinded to case status. Different method for cases and controls.	A	C. No adjustment.	A
Poskanzer et al. 1980 (120)	C. Small sample of prevalent cases from one small population.	A	B. Based on recall. Interviewers not blinded to case status.	A	C. No adjustment.	B. Testing of 3≥ different measures of SES without specifying primary.
Studies finding an association between low SES and MS						
Briggs et al. 2014 (61)	B. Prevalent cases.	A	B. Based on recall. Interviewers not blinded to case status.	A	A	A. Multiple testing, but justified in the context of a research question looking at lifetime SES exposure.
Ghadirian et al. 2001 (121)	A	B. All matched on phone number area, a possible measure of SES.	B. Based on recall. Interviewers not blinded to case status.	C. No information on how media-recruited cases were assessed.	B. Adjusted for age, sex, smoking. Adjustment for energy intake found not to modify results.	A
Riise et al. 2011 (60)	B. Cases selected from a cohort with over-representation of workers from the petroleum industry, as this was the original focus of the study.	A	A	A	B. Adjusted for gender, age, year of first exposure to petroleum industry, and area of residence.	B. SES was looked at as part of a secondary analysis, having originally been considered a confounder.

1. A study with 110 cases and 220 controls is the smallest size that can detect an OR of 2.00 with 80% power and α of 0.05, assuming a prevalence of the exposure in controls of 50%.

Selection bias is always a concern in case-control studies, but most studies included here appeared to have minimized this risk. Only two studies reported response rates of under 75% (61,121), while in many instances the response rates were over 90%. Despite this strength, many of the case-control studies suffered from small sample sizes, resulting in wide confidence intervals which included large effect sizes along with the null value (109,112,114,117–120). Additionally, many studies used prevalent rather than incident cases (58,61,106,108,110–115,117–120). This increases the risk of bias as recall of events or exposures in the pre-morbid state might be distorted by the length of time since diagnosis and the effect of disease (122). Poor recall due to the passage of time might lead to non-differential misclassification of the exposure, biasing the result towards the null, while the effects of disease are harder to predict. As MS might lead to lower SES through disability and unemployment, as well as impacting memory due to its cognitive effects, recall of early life SES might be more distorted in cases than controls.

There was incomplete reporting of the data in many of the studies, with several of them neither reporting measures of association nor providing sufficient data to calculate them (58,107,108,111,113,117,120). Another common weakness was the assessment of the role of multiple measures of SES without specifying a primary measure (58,59,106,108,110–113,115,117,120), increasing the probability of a type 1 error.

The main threat to the validity of the overall body of evidence was the failure to adequately adjust for other reported risk factors for MS. Nine studies performed no statistical adjustment at all (58,107–110,112,117–120), while only one adjusted for all important risk factors (61). Given that almost all reported risk factors of MS could plausibly serve as

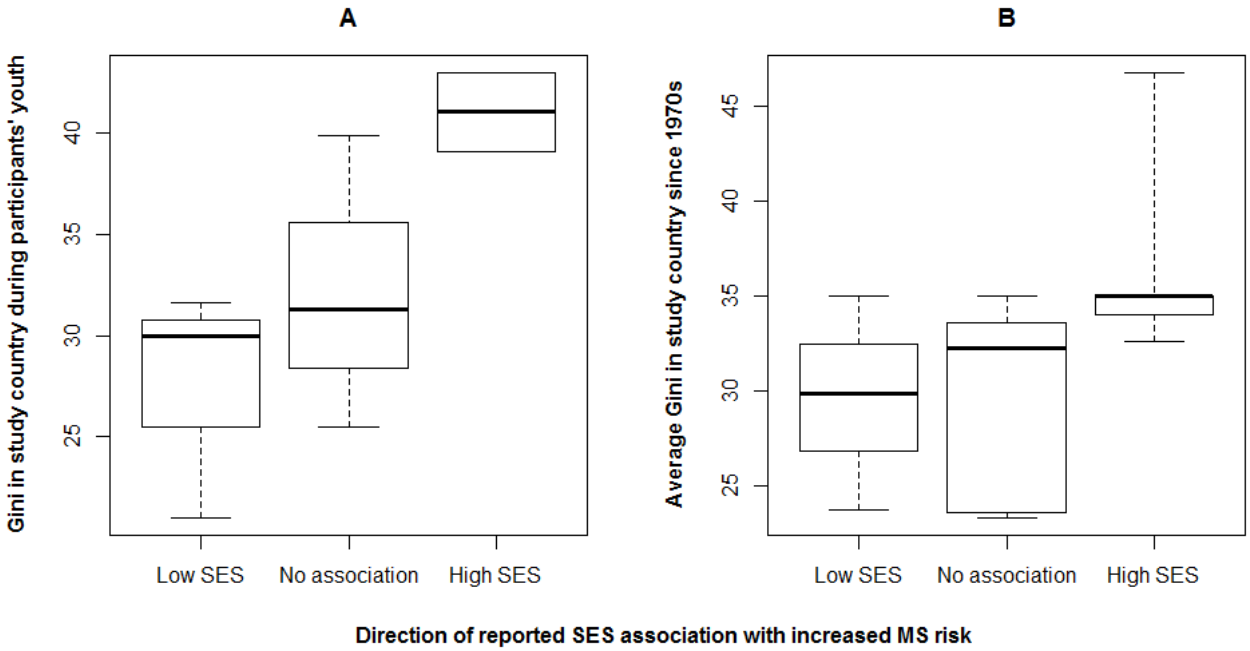
mediators or confounders of the association with SES, this is a major limitation of this body of research.

Synthesis

On most criteria, there were no differences between studies reporting a positive, negative, or no association between SES and MS risk. The three groups of studies did not vary systematically by date, SES criteria used, study design, or study quality. This makes synthesising such disparate results problematic.

There is, however, one distinctive feature of the studies that reported an association with high SES: they were all conducted in countries with high levels of inequality, such as the US, Italy, and Israel. Many of the studies reporting no association, meanwhile, came from egalitarian Scandinavian countries. Although one study from the US did not fit this pattern (61), its participants experienced adolescence and early adulthood – likely to be a key period for MS acquisition (27) – at a time when US inequality was at historically record lows (123). If there is indeed an association between SES and MS, one would expect to find a stronger effect where inequality, and hence exposure variance, is greatest. For other health outcomes, this has been shown for changes in inequality over time (124), and, albeit inconsistently, for differences between countries (125). Grouping the studies by their results, Figure 2A plots the Gini index of income inequality for the study country when the participants' mean age was 20. The relevant inequality data for this measure was only available for 9 studies, however (123). Figure 2B plots the average Gini inequality index in the study country from the 1970s until the present (126), a period for which standardized, cross-national data is available for almost all studies (n=20), but without necessarily covering the most relevant exposure period for participants.

Figure 2. Association between Gini index score in study country and direction of reported SES association with MS (123,126)**.**



Discussion

The possibility that high SES might be associated with increased MS risk, first suggested in 1960 (3), found support in only a minority of studies and often with moderate effect sizes. Most research found insufficient evidence of an association, and three studies even found an association with low SES. Two factors, however, suggest we cannot yet rule out the possibility of an association between high SES and MS. Firstly, the positive findings were not randomly distributed among studies, but rather concentrated in research from countries and time periods in which we would expect social status to have a greater impact. That so many studies did not find an association may in part reflect the preponderance of research from egalitarian Scandinavian countries. Several studies from the more unequal US, UK, and Australia – which were not included as they were case series or ecological studies – found an association between high SES and MS (3,4,6–8,127). Secondly, most studies did not

sufficiently adjust for potential mediators and confounders of the association. Only one study adequately adjusted for all risk factors, although interestingly it found an association with *low* SES (61). However, this study had the lowest response rate among controls of all included studies. Comparison with population data suggests that those who *did* respond were of disproportionately high SES (128), a potential source of selection bias which could create an association between MS and low SES. In addition, adjustment tended to weaken the association between low SES and MS – albeit only slightly – suggesting studies which did not adjust for these factors might be biased towards an association with lower SES.

The most commonly cited mechanism linking MS and SES was the hygiene hypothesis, whereby lower exposure to pathogens in early life leaves high SES individuals vulnerable to an aberrant immune response to infections at a later age (5,59,108). However, if an association between MS and SES exists, a number of pathways might explain the link. Delayed EBV infection – as per the hygiene hypothesis – and nulliparity might create an association with high SES, while smoking, obesity, and a family history of MS may create an association with low SES. It is also possible that a more direct pathway exists between SES, or its psychological effects, and MS risk. Low SES in early life is linked to a number of stressors (81), as well as elevated levels of stress hormones such as cortisol (83). Chronic stress and its physiological correlates suppress Th1 cytokine expression (129), which may be one reason why chronically stressed (92) and low SES (130) individuals are at higher risk of viral infections. The corollary of such observations is that chronic stress and low SES might *lower* the risk of diseases in which Th1 activity plays a role, such as MS. High SES also appears to increase the risk of other Th1-associated diseases (94,95). In animal models of MS, chronic stress applied prior to disease induction reduces disease incidence and severity

(98). Existing research on early life stress and subsequent MS risk in humans is, however, inconclusive (102).

Conclusion

The overall body of current research on this question provides only limited support for an association between high SES and MS. Studies in countries and time periods where socioeconomic gradients are steeper often find a positive relationship, but most research comes from egalitarian societies where no association is observed. As greater exposure variance increases study power, more research from unequal societies would help clarify the association. Reliable inferences are additionally complicated by the fact that almost all purported risk factors for MS are associated with SES. To advance knowledge in this area, future studies should account for these potential confounders and mediators.

4. EnvIMS: a multi-national case control study of MS

Environmental Risk Factors in MS (EnvIMS) is a multi-national case-control study which collected information from individuals with MS (cases) and controls in Norway, Canada, Italy, Sweden, and Serbia. The study has a number of advantages over previous case-control studies of MS. Firstly, the use of standardized data collection in several countries allows the exploration of effect heterogeneity for MS risk factors across varied social and geographical settings. Secondly, where appropriate, data can be pooled between countries to create larger sample sizes than could be attained from single country studies. Finally, the study was informed by several decades of epidemiological investigations of MS, allowing questions to be targeted at gathering richer details on those exposures which have been consistently identified as risk factors, while exploring areas where the literature suggests a need for further clarification.

Data were collected using a self-administered postal questionnaire, EnvIMS-Q (131). The questionnaire was initially drafted in English, through a collaborative process between investigators from all study sites which built on earlier efforts at developing guidelines for the epidemiological study of MS (132). It was then translated into local languages, and found to have cross-cultural feasibility, acceptability, and test-retest reliability in pilot studies in all study sites. Questions covered several domains, collecting information on exposure at various points in childhood and early adulthood. The areas covered were: demographics, sun exposure, diet, participant and family medical history, smoking habits and lifestyle factors, and, for female participants, hormonal factors. In addition to core questions common to all countries, a small number of country-specific questions were

asked, largely relating to dietary factors which might affect vitamin D levels. The English language version of the questionnaire is included in the appendix.

After validation of the questionnaire, recruitment took place between 2008 and 2013. To maximize study recruitment while minimizing the potential biases of a prevalence study, only cases diagnosed in the previous 10 years were included into the study. Further details of the country-specific recruitment procedures are outlined in Chapter 5.

A number of analyses have already been conducted using EnvIMS data from Norway and Italy, which were the first sites to complete data collection. In an analysis of the effect of sunlight levels, higher exposure in early life was linked to reduced MS risk (39). Although the effect of sun exposure was only statistically significant at certain ages, the point estimates suggested a protective effect throughout childhood and early adulthood. Another analysis found that season of infection, age of infection, and latitude did not modify the effect of infectious mononucleosis on MS risk (133). Finally, the relationship between active and passive smoking and MS was explored using EnvIMS data (134). The previously reported association with active smoking was replicated, while the effects of passive smoke were not statistically significant, albeit similar in magnitude to prior findings.

For the analysis reported in Chapter 5, data from Norway, Italy, and Canada were used, as finalized data were not yet available from Sweden and Serbia. The EnvIMS data are ideally suited to exploring the effects of SES on MS risk. SES was measured by asking participants about the highest level of education attained by themselves, their father, and their mother. Relative to measures of income or wealth, educational attainment is a useful measure of SES in studies relying on self-report, as it can be easily recalled and may be less prone to reporting bias (135). Additionally, educational attainment is likely to influence both health-

related behaviours (136) and lifelong income trajectories (137). A particular advantage of the data was that it was possible to estimate the direct effect of SES on MS risk, by adjusting for all the various potential mediators and confounders of the association. As suggested by the systematic review (Chapter 3), the effects of SES may be greatest in countries and time periods of higher inequality. The difference in study sites, as well as the wide age range of study participants, allowed us to examine the effects of SES in varying economic contexts. Additionally, all three study countries have universal healthcare systems, reducing the risk that differences in health outcomes by SES are determined by differential healthcare access. The details and results of this analysis, the first to use EnvIMS data from three study sites, are reported in Chapter 5.

5. Manuscript 2.

The second manuscript in this thesis is an original analysis of the association between MS and SES, using data from Norwegian, Canadian, and Italian participants in the EnvIMS case-control study. While there was evidence of increased MS risk in those of high SES in Canada, the effect in Norway was limited to participants who grew up in a period of rising inequality. No effect was found in Italy. These inconsistent results mean that the null hypothesis of no effect cannot be confidently rejected. This manuscript will be submitted to the *Multiple Sclerosis Journal*.

Does low socioeconomic status in early life protect against multiple sclerosis? A multi-national, case-control study

Authors

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Abstract

Background

The findings from existing research on the association between socioeconomic status (SES) and multiple sclerosis (MS) are inconsistent. While some studies report an increased risk of MS among those of high SES, others find an association with low SES, while many find no evidence of a link. Most of the studies are limited to one country and do not adequately adjust for other risk factors for the disease.

Methods

The association between SES and MS was analysed using data from the multinational Environmental Risk Factors in MS (EnvIMS) case-control study. The study population comprised a total of 2,144 cases and 3,859 controls from Norway, Canada, and Italy. Multiple logistic regression was used to estimate the odds ratios (OR) and 95% confidence intervals (95% CIs) for the association between early life SES, measured by parental educational level, and MS. Analyses were adjusted for age, sex, sunlight exposure, history of infectious mononucleosis, smoking, obesity, and family size. We hypothesized that, in the fully adjusted model, low SES in early life would be protective against MS.

Results

In Canada, the OR (95% CI) for MS among individuals with university-educated parents relative to those whose parents had primary school education or below was 1.47 (1.03-2.09), with a statistically significant dose-response relationship across education levels (p for trend = 0.029). In Norway, this association was only present for those who grew up during a period of rising inequality (p for trend = 0.031). No evidence for an association was found in Italy (p for trend = 0.227).

Conclusions

There was insufficient evidence to reject the null hypothesis, with a protective effect of low SES in early life on MS risk limited to certain countries and time periods.

Background

Socioeconomic status (SES) is associated with several health outcomes. In particular, mortality and morbidity from a wide range of diseases are more common among those of low SES (65). The observed association remains even after adjusting for a number of potential mediating factors, such as smoking, diet, and body mass index (BMI) (66). It has been suggested that the chronic stress of low SES itself affects health, through various endocrine and immune pathways (69,138).

Multiple sclerosis (MS) is one of a few conditions which have been linked to *high* SES (3–8,11). However, a recent systematic review found that the results were inconsistent, with an association between high SES and MS being observed only in countries and time periods with higher levels of inequality (Manuscript 1, Chapter 3). The evidence from this body of research was also hampered by the failure of many investigators to adjust for important confounders and mediators. This means that the mechanism for any association between SES and MS risk has not been fully elucidated. Most reported risk factors for MS have been linked to SES, including age of EBV infection (73), smoking (75), obesity (76), and a family history of the disease (78). These all present routes through which SES could affect disease risk.

In addition to these indirect pathways, we hypothesize that SES and its psychological correlates may directly affect MS risk: specifically, that low SES is protective against MS. In the animal model of MS, experimental autoimmune encephalomyelitis (EAE), moderate

chronic stress applied prior to disease induction has been consistently found to reduce its incidence and severity (98). In contrast, acute stress applied after EAE onset tends to exacerbate the course of the disease. This latter effect has been noted in humans, with acute stress found to trigger MS relapses (100,101). A protective effect of chronic early life stress has not previously been considered. Existing cohort studies of early life stress and MS risk have focused on severe and acute stressors, with inconclusive findings (102,103). A potential protective mechanism is that stress supresses Th1 cell activity (86–88), which plays a role in MS pathophysiology (139,140). A number of other Th1-associated diseases are also reported to be less common in those of low SES, including type 1 diabetes (93,94), coeliac disease (95,96), and Crohn's disease (97).

On this background, we explored the association between MS and early life SES using data from a large, multi-national case control study. We hypothesized that, after controlling for potential confounders and mediators, the odds of disease would be reduced in those of low SES. In addition, we expected the effect to be strongest among participants who experienced early life during times of higher and rising economic inequality.

Methods

Study population and design

We used data collected in Norway, Canada, and Italy as part of the the Environmental Risk Factors in Multiple Sclerosis (EnvIMS) case-control study. Cases were aged 18 years or older at the time of recruitment – 2009-2011 in Norway and Italy, and 2012-2013 in Canada – and had disease onset in the previous 10 years. Diagnosis was according to the McDonald criteria (141). Controls were frequency-matched on age and sex, and each was assigned an index age based on the distribution of onset age among cases, with all exposures assessed

relative to this age. Two important confounders in our analysis – body size and outdoor activity – were measured for age 20, so cases with disease onset before 20 (*n*=107) and their corresponding controls (*n*=169) were excluded. The study sample for this analysis therefore comprised 2,144 cases and 3,859 controls. A detailed description of the EnvIMS questionnaire has been reported elsewhere (131).

In Norway, cases were recruited from the Norwegian MS registry and Biobank (142), and controls from a general population registry. In Canada, cases were recruited from MS clinics in the cities of Montreal, Winnipeg, and Toronto, and controls were recruited via random digit dialling (RDD) in the same areas. In Italy, cases were recruited from patient registries in the regions of Sardinia, insular Italy, and Ferrara, northern Italy, and controls were recruited from local population registries. Response rates for cases and controls were as follows: 70% and 36% in Norway, 80% and 7% in Canada, and 43% and 21% in Italy. The low rate among controls in Canada reflects the low yield of RDD (i.e. 'cold calls') relative to the targeted letters sent out in Norway and Italy. Among telephone respondents who agreed to be sent the questionnaire in Canada, the response rate was 54%. It should also be noted that nonresponse rates are only a weak predictor of nonresponse bias (143). However, to assess the extent of this potential source of bias, we compared the education level of controls to general population data in each country (144).

Demographic information on the participants is provided in Table 1.

Table 1. Demographic characteristics of participants.

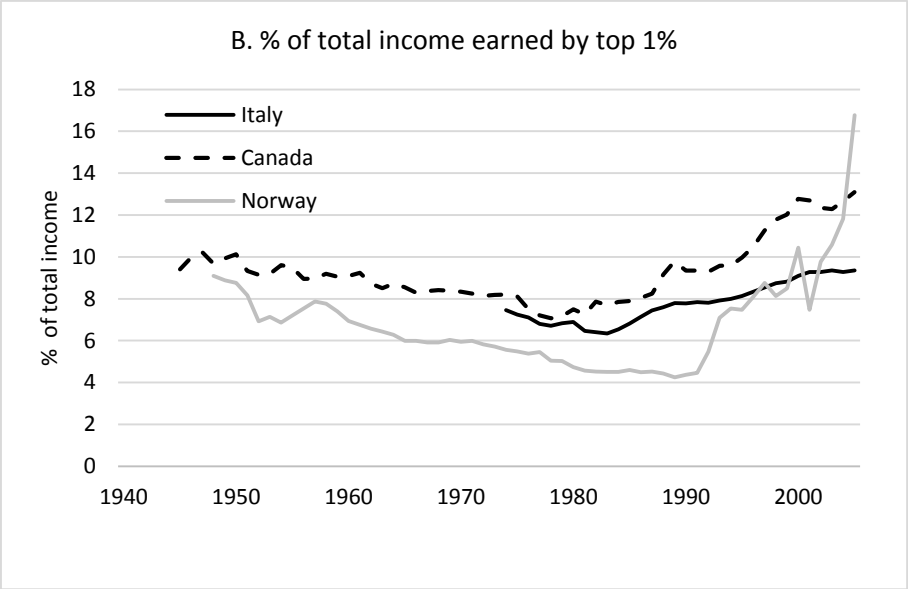
	Norway (n=2,605)		Canada (n=1,505)		Italy (n= 1,893)	
	Cases (n=932)	**Controls (n=1,673)**	**Cases (n=557)**	**Controls (n=948)**	**Cases (n=655)**	**Controls (n=1,238)**
Birth year, mean (range)	1962 (1923-1987)	1964 (1929-1987)	1963 (1943-1991)	1970 (1944-1990)	1968 (1930-1989)	1969 (1943-1987)
Age, mean (SD)	45.4 (10.1)	46.6 (10.3)	41.9 (9.8)	49.3 (10.7)	40.0 (9.4)	40.6 (9.9)
Age at MS onset, mean (SD)	38.2 (9.7)		35.5 (9.8)		34.5 (9.3)	
Female sex, %	69.7%	73.0%	73.8%	68.1%	64.9%	69.1%

Exposure

Most environmental risk factors for MS relate to exposures in adolescence and young adulthood, and migration studies suggest that the risk of disease is acquired in early life (27,33,145). Low SES in early life is also known to shape long term health (62), with elevated levels of stress hormones such as cortisol posited as one potential mechanism (83,84). In this analysis, we therefore used early life SES as our primary exposure, measured by the highest level of education – primary or below, secondary, or university – achieved by either parent of the participant.

Long-term trends in income inequality in Norway, Canada and Italy are shown in Figure 1. For between-country variation, we hypothesized that the effect of SES would be weakest in Norway, the most equal country of the three. For within-country variation, we looked at the level of inequality in the study country during the first 20 years of each participants' life. For Italy, the only measure of inequality with sufficiently long-term data for this analysis was the Gini index of income inequality (Figure 1A). For Norway and Canada, it was the share of total income earned by the top 1% (Figure 1B). The two measures are highly correlated (146) and both are widely used indicators of economic inequality (123).

Figure 1. Measures of income inequality, by country, 1945-2005 (123)**. A: Gini index of income inequality. B: % of total income earned by top 1% of earners.**



We calculated the mean level of inequality in the study country of each participant during the first 20 years of their life. The median of these means was used to divide the study population in each country into evenly-sized low and high inequality groups. In Norway, the low inequality group were those born between 1963 and 1978, in Canada it was those born between 1958 and 1975, and in Italy it was all those born before 1971. To examine the effect of trends in inequality, participants were grouped by whether inequality rose or

declined during the first 20 years of their lives. This was determined by deducting inequality at birth from inequality at age 20. In Norway, those born up until 1972 experienced declining inequality, in Canada it was those born up until 1967, and in Italy it was those born up until 1978. Those born subsequently grew up in times of rising inequality.

Statistical analysis

Logistic regression was used to estimate the odds ratios (OR) and 95% confidence intervals (95% CIs) for the association between early life SES and MS. Since our analysis took place in a dynamic population, with controls recruited at the same time as cases, the OR approximates the rate ratio (147). Given that the rare disease assumption holds, the OR also approximates the risk ratio.

As we were interested in the direct effect of SES on MS risk, we adjusted for a number of potential mediators and confounders of the association. These included nearly all reported risk factors for MS: age, sex, number of siblings, history of infectious mononucleosis (binary), smoking history, history of MS among first-degree relatives (binary), body size, and sun exposure as measured by frequency of outdoor activities. Age, sex, and family history of MS were considered potential confounders of the relationship, affecting both SES and MS risk, while the remaining factors were all potential mediators, as they can be affected by SES while in turn affecting MS risk. Smoking was measured as the number of years of smoking before MS onset (or index age), and categorised as follows: never smoker, 0-4 years smoking, 5-9 years smoking, 10-14 years smoking, ≥15 years smoking. Body size at age 10, 15, and 20 was reported using a figure rating scale ranging from 1 (thinnest) to 9 (largest) (148). Due to the small number of responses for the higher categories, figures 6 to 9 were collapsed into one category of ‘large’ body size. Frequency of outdoor activities in summer

were rated on a 4 point scale: not that often (1), reasonably often (2), quite often (3), and virtually all the time (4). We created a summary measure which was the mean response for ages 0 to 5, 6 to 10, 11 to 15, and 16 to 20 (0 to 6, 7 to 12, 13 to 15 and 16 to 18 for Norway). In Italy and Canada, where data were collected in distinct regions (2 in Italy, 3 in Canada), the region was also adjusted for. Other, less established risk factors for MS were considered for inclusion in our model, but found not to be associated with the exposure and/or the outcome. They were: passive smoke exposure, fish consumption, ethnicity, and among female participants, age of menarche and reproductive history.

SES in adulthood, as measured by participant educational attainment (primary or below, secondary, or university), was also included in our model. This allowed us to adjust for the selection bias that would result from higher SES participants being over-represented in our study population, particularly among controls.

We hypothesized that MS in a parent or sibling could be a confounder, through its negative financial impact on the family (78), and increased risk of disease in the participant. It was considered highly improbable that this exposure would not be recalled if present, therefore missing data ('don't know' or blank) were treated as negative responses. For all other variables, missing data were assumed to be missing at random and estimated by multiple imputation using chained equations (149). Details of the imputation procedure are provided in the Appendix, along with information about missing data (Table e-1).

All statistical analyses were performed using Stata 13.1 (StataCorp, Texas, USA), and were carried out for each country separately. A p-value of <0.05 was considered statistically significant. In addition to reporting the effect estimates for each parental education level, tests for trend were performed by treating the measure as a continuous variable. When

comparing effect sizes between countries and inequality levels, parental education level was converted into a binary measure (primary or below vs. secondary or above) to facilitate analysis, with heterogeneity assessed using the Wald test (150). In a post-hoc subgroup analysis, separate effect sizes were estimated and compared for the two study regions in Italy.

Participant consent and ethics approval

EnvIMS is an anonymous postal questionnaire. Participants were sent the questionnaire with a cover letter explaining the study's aims, and informed consent was assumed when a completed questionnaire was returned. The study received ethical approval in each collaborating institution. In Canada it was approved by the McGill University IRB (A08-M78-11B), in Italy by the Sassari, Olbia-Tempio, Nuoro, Cagliari and Province of Ferrara Ethical Committees, and in Norway by the regional Ethical Committee for Medical and Health Research for Western Norway (2008/11259-ANØL). The secondary analysis reported here received approval from the McGill University IRB (A02-B09-14B).

Results

Complete descriptive statistics for all the variables are provided in Table e-1 (Appendix).

The effects of SES on MS risk by country are reported in Table 2. Overall, there was only evidence of an effect in Canada. Relative to those whose parents had primary school education or below, the OR (95% CI) for MS among individuals with university-educated parents was 1.47 (1.03-2.09) in Canada, with a statistically significant dose-response relationship (p=0.029). In Norway and Italy, there was no statistically significant effect of SES on MS risk. When parental SES was treated as a binary measure, the overall difference in effects between countries was not statistically significant (p=0.059).

The effects of adding each exposure variable to an age and sex adjusted model is reported in Table e-2 (Appendix). The biggest change in the effect size of the main exposure variable was caused by adding participants' own education level. Most potential mediators had only a small impact, with adjustment for smoking the most significant, tending to increase the effect size.

Table 2. OR (95% CI) for association between early life SES and MS, by country

Highest parental education level	Norway		Canada		Italy	
	Basic model[a]	Full model[b]	Basic model[a]	Full model[b]	Basic model[a]	Full model[b]
≤Primary	1.00	1.00	1.00	1.00	1.00	1.00
Secondary	1.11 (0.90-1.36)	1.23 (0.99-1.55)	1.06 (0.82-1.39)	1.27 (0.94-1.70)	0.92 (0.73-1.15)	0.94 (0.73-1.20)
University	0.90 (0.73-1.12)	1.07 (0.84-1.37)	1.15 (0.85-1.55)	1.47 (1.03-2.09)	0.62 (0.39-0.98)	0.69 (0.42-1.14)
Test for trend	p=0.444	p=0.453	p=0.378	p=0.029	p=0.077	p=0.227

a. Adjusted for age and sex.

b. Adjusted for age, sex, region, participant education level, history of infectious mononucleosis, smoking history, family history of MS, number of siblings, frequency of summer outdoor activities age 0-20, and body size at age 10, 15, and 20.

Table 3 shows the effect of SES on MS risk by the level of inequality experienced by study subjects in the first 20 years of their lives. There were no statistically significant differences in effects between those who grew up during periods of high or low inequality.

Table 3. OR (95% CI) for association between early life SES and MS, by country and inequality level

Mean inequality age 0-20	Parental education level	Norway		Canada		Italy	
		Basic model[a]	Full model[b]	Basic model[a]	Full model[b]	Basic model[a]	Full model[b]
Low	≤Primary	1.00	1.00	1.00	1.00	1.00	1.00
	Secondary	1.13 (0.85-1.51)	1.24 (0.90-1.72)	1.09 (0.78-1.53)	1.27 (0.87-1.86)	1.00 (0.72-1.39)	1.01 (0.70-1.47)
	University	1.03 (0.77-1.37)	1.20 (0.85-1.69)	1.21 (0.81-1.81)	1.54 (0.98-2.48)	0.65 (0.36-1.17)	0.70 (0.36-1.36)
	Trend	p=0.846	p=0.287	p=0.351	p=0.068	p=0.310	p=0.491
High	≤Primary	1.00	1.00	1.00	1.00	1.00	1.00
	Secondary	1.13 (0.84-1.52)	1.27 (0.92-1.77)	1.05 (0.69-1.61)	1.31 (0.80-2.16)	0.84 (0.61-1.15)	0.83 (0.58-1.20)
	University	0.77 (0.84-1.52)	0.93 (0.64-1.35)	1.09 (0.69-1.73)	1.46 (0.84-2.54)	0.63 (0.30-1.31)	0.68 (0.30-1.58)
	Trend	p=0.205	p=0.970	p=0.720	p=0.180	p=0.128	p=0.228
Test for heterogeneity[c]			p=0.701		p=0.924		p=0.460

a. Adjusted for age and sex.

b. Adjusted for age, sex, region, participant education level, history of infectious mononucleosis, smoking history, family history of MS, number of siblings, frequency of summer outdoor activities age 0-20, and body size at age 10, 15, and 20.

c. Parental education was treated as a binary variable (≤Primary vs. ≥Secondary) for this analysis.

Table 4 shows the effect of SES on MS risk by the trends in inequality experienced by study subjects in the first 20 years of their lives. For those who grew up in times of rising inequality, high SES was associated with increased MS risk in Norway (p for trend = 0.047) and Canada (p for trend = 0.028). The difference in effect between the declining and rising inequality periods was statistically significant in Norway (p=0.031) but not in Canada (p=0.380). There were no statistically significant effects in Italy.

Table 4. OR (95% CI) for association between early life SES and MS, by country and inequality trend

Inequality trend age 0-20	Parental education level	Norway		Canada		Italy	
		Basic model[a]	Full model[b]	Basic model[a]	Full model[b]	Basic model[a]	Full model[b]
Declining	≤Primary	1.00	1.00	1.00	1.00	1.00	1.00
	Secondary	1.04 (0.83-1.30)	1.14 (0.89-1.46)	1.00 (0.70-1.45)	1.24 (0.82-1.89)	0.97 (0.76-1.23)	0.98 (0.75-1.28)
	University	0.81 (0.63-1.03)	0.91 (0.69-1.21)	0.99 (0.63-1.55)	1.37 (0.81-2.32)	0.64 (0.38-1.09)	0.74 (0.41-1.33)
	Trend	p=0.127	p=0.700	p=0.973	p=0.198	p=0.231	p=0.490
Rising	≤Primary	1.00	1.00	1.00	1.00	1.00	1.00
	Secondary	1.72 (1.02-2.91)	2.08 (1.12-3.88)	1.22 (0.82-1.80)	1.47 (0.93-2.31)	0.57 (0.27-1.21)	0.51 (0.21-1.26)
	University	1.48 (0.89-2.45)	2.05 (1.09-3.86)	1.36 (0.89-2.08)	1.78 (1.07-2.97)	0.40 (0.14-1.14)	0.29 (0.08-1.07)
	Trend	p=0.234	p=0.047	p=0.153	p=0.028	p=0.081	p=0.058
Test for heterogeneity[c]			p=0.031		p=0.380		p=0.112

a. Adjusted for age and sex.
b. Adjusted for age, sex, region, participant education level, history of infectious mononucleosis, smoking history, family history of MS, number of siblings, frequency of summer outdoor activities age 0-20, and body size at age 10, 15, and 20.
c. Parental education was treated as a binary variable (≤Primary vs. ≥Secondary) for this analysis.

The results of the subgroup analysis of the two Italian regions are reported in Table e-3 (Appendix). Although the point estimates of the fully adjusted models suggested a harmful effect of high SES in Ferrara (OR: 1.39; 95% CI: 0.30-6.39) and a protective effect in Sardinia (OR: 0.65; 95% CI: 0.38-1.12), neither effect was statistically significant and there was no statistical evidence of heterogeneity (p=0.316).

Discussion

We found no consistent evidence for a protective effect of low parental SES on MS risk. While the predicted effect was found in Canada, an association was only seen in Norway during times of rising inequality. There was evidence of a dose-response effect in Canada, but there appeared to be a threshold effect for the period-specific effect in Norway, with a similarly increased risk for children of secondary and university-educated parents. Contrary to our expectation that the effect of SES would be weakest in Norway, Italy was the only country in which no statistically significant effect was seen. Although the between-country heterogeneity was not statistically significant according to a significance threshold of 0.05 (p=0.059), it has been suggested that higher thresholds may be more appropriate for heterogeneity tests given their much lower power (151).

A number of potential factors might explain the lack of any effect in Italy. It had the highest rates of missing data of the three countries, such that information biases may have been greater there, despite the use of multiple imputation (Table e-1). Most study participants (88%) in Italy came from Sardinia, which is known to have one of the highest rates of MS in the world (152). In particular, it contains several possible clusters (153,154), implying that there may be distinct local factors – such as genetics or environmental exposures specific to sub-regions – which distort the effects of SES. Although the region-specific effect estimates were not statistically significant, they are consistent with previous research which found a harmful effect of low SES in Sardinia (155) and a protective effect in Ferrara (58). Despite these considerations, the results for Italy are strong evidence in favour of the null hypothesis.

We hypothesized that the chronic stress of low SES in early life may be protective against MS through its immunological effects. Another mechanism linking SES and MS may be a later age of EBV infection in those of high SES (70,73), a well-established MS risk factor. In our study population, infectious mononucleosis (IM) – a sign of late EBV infection – was more common in those of high SES in all three countries, though this difference was not statistically significant in Canada (Table e-4, Appendix). The fact that adjustment for IM did not significantly alter the SES-MS relationship may be due to the fact that most cases of late EBV infection do not result in a clinical diagnosis of IM (70,156,157), suggesting that there may be residual confounding from this unmeasured variable. This is not necessarily an *alternative* explanation for any link between high SES and MS. The mechanisms which determine the timing of EBV infection are poorly understood (158), and stress-induced immunological changes could be one factor affecting age of infection.

Risk of bias

Our control population was over-representative of individuals who had attained high SES in adulthood. Assuming the sampling frames for controls were representative of the general population, university educated individuals invited to participate were around two times more likely to accept than non-university educated individuals (Table e-5, Appendix). The extent of this disparity was not related to response rates. As we were interested in early life SES, however, controlling for participants' own education level should have reduced the risk of selection bias. This adjustment was found to considerably strengthen the association between high parental SES and MS risk in Norway and Canda (Table e-2).

There was a risk of information bias in the study due to the dependence on participant recall. This is particularly true for those born earlier, who in all three countries were those

born in the period of declining inequality. We assume that any misclassification of early life SES would be non-differential with respect to the outcome, biasing the result towards the null. This may in part explain the lack of any significant effect for this group. A number of mediators of the effect of SES on MS risk, including smoking, infrequent outdoor activities, and large body size, may be affected by response bias. In so far as these factors are under-reported, there would be residual confounding. Given that these are more prevalent among those of low SES (65), the protective effect of low SES may be underestimated.

Comparison with other research

Our finding of an association between high SES and increased MS risk in Canada is consistent with a recent ecological study in Winnipeg, which reported a higher incidence of MS in neighbourhoods with low unemployment rates (11). Our results for Norway are consistent with evidence that the traditionally social democratic Scandinavian countries have only seen socioeconomic disparities in health appear during the recent era of rising inequality (125).

However, two recent, high quality case-control studies of the association between childhood SES and MS risk reported clear evidence against an increased risk in those of high SES. The first included all incident cases of MS in Denmark between 1981 and 2007, and found no effect of childhood SES on MS risk (59). It benefitted from being nested in a population-wide cohort with contemporaneously collected exposure information, but there was no adjustment for mediators such as infectious mononucleosis, smoking, and obesity. However, our study suggested that, with the possible exception of smoking, these factors did not substantially alter the main effect estimate (Table e-2). The second was a case-control study carried out among members of a private healthcare plan in California, which

reported that *low* childhood SES was associated with increased MS risk (61). This was only true when parental education was coded as a binary variable, however, while a trend test for a continuous measure was not statistically significant. The study population was also older than ours, with a mean birth year of 1957 (SD 8.2). This suggests that the vast majority were born in a period of declining inequality, a group for whom we found no effect of SES.

Conclusion

We were not able to reject the null hypothesis, finding only inconsistent evidence in favour of a protective effect of low parental SES on MS risk. Future research on this question should ideally be set in large, socioeconomically representative cohorts, which include information on smoking history.

Appendix to manuscript 2

Multiple imputation

Multiple imputation using chained equations was carried out with the *mi impute chained* command in Stata 13.1. In addition to all the variables in the analysis model, the imputation model included current BMI, body size, and frequency of outdoor activity, and parental smoking history. Ordinal logistic regression was used to estimate parental education level, participant education level, number of siblings, and frequency of outdoor activities in adolescence. Logistic regression was used to estimate infectious mononucleosis and parental smoking history. Predictive mean matching was used to estimate body size at age 10, 15, and 20; the regression failed to converge when these were modelled using ordinal logistic regression. Linear regression was used to estimate current BMI.

Separate imputations were carried out for each country and inequality trend group – as the complete case analysis suggested heterogeneity across these groups – using the *by()* option. 40 imputations were performed.

An additional multiple imputation was run with early life SES as a binary variable, estimated using logistic regression. This was used for the assessment of heterogeneity and the subgroup analysis in Italy.

Supplementary tables

Table e-1. Descriptive statistics. N (%) or mean (SD).

	Norway (n=2,605)		**Canada (n=1,505)**		**Italy (n=1,893)**	
	Cases (n=932)	**Controls (n=1,673)**	**Cases (n=557)**	**Controls (n=948)**	**Cases (n=655)**	**Controls (n=1,238)**
Female sex	650 (69.7%)	1,221 (73.0%)	411 (73.8%)	646 (68.1%)	425 (64.9%)	855 (69.1%)
Age, mean (SD)	45.4 (10.1)	46.6 (10.3)	41.9 (9.8)	49.3 (10.7)	40.0 (9.4)	40.6 (9.9)
Age at disease onset, mean (SD)	38.2 (9.7)		35.5 (9.8)		34.5 (9.3)	
Parental education[a]						
≤Primary	382 (41.0%)	736 (44.0%)	177 (31.8%)	401 (42.3%)	301 (46.0%)	546 (44.1%)
Secondary	252 (27.0%)	399 (23.9%)	201 (36.1%)	316 (33.3%)	279 (42.6%)	511 (41.3%)
University	225 (24.1%)	429 (25.6%)	146 (26.2%)	184 (19.4%)	29 (4.4%)	80 (6.5%)
Missing	73 (7.8%)	109 (6.5%)	33 (5.9%)	47 (5.0%)	46 (7.0%)	101 (8.2%)
Participant education						
≤Primary	149 (16.0%)	201 (12.0%)	83 (14.9%)	107 (11.3%)	27 (4.1%)	45 (3.6%)
Secondary	375 (40.2%)	576 (34.4%)	231 (41.5%)	399 (42.1%)	506 (77.3%)	889 (71.8%)
University	392 (42.1%)	872 (52.1%)	237 (42.6%)	421 (44.4%)	106 (16.2%)	263 (21.2%)
Missing	16 (1.7%)	24 (1.4%)	6 (1.1%)	21 (2.2%)	16 (2.4%)	41 (3.3%)
Infectious mononucleosis (ever)						
Yes	148 (15.9%)	138 (8.2%)	122 (21.9%)	111 (11.7%)	48 (7.3%)	50 (4.0%)
No	716 (76.8%)	1461 (87.3%)	404 (72.5%)	795 (83.9%)	501 (76.5%)	995 (80.4%)
Missing	68 (7.3%)	74 (4.4%)	41 (5.6%)	42 (4.4%)	106 (16.2%)	193 (15.6%)
History of MS in parent or sibling						

Yes	83 (8.9%)	37 (2.2%)	48 (8.6%)	29 (3.1%)	44 (6.7%)	20 (1.6%)
No	737 (79.1%)	1500 (89.7%)	459 (82.4%)	846 (89.2%)	510 (77.9%)	1043 (84.2%)
Missing	112 (12.0%)	136 (8.1%)	50 (9.0%)	73 (7.7%)	101 (15.4%)	175 (14.1%)
Years of smoking						
Never smoker	278 (29.8%)	788 (47.1%)	258 (46.3%)	489 (51.6%)	279 (42.6%)	682 (55.1%)
0-4 years	23 (2.5%)	85 (5.1%)	22 (3.9%)	36 (3.8%)	42 (6.4%)	49 (4.0%)
5-9 years	77 (8.2%)	129 (7.7%)	68 (12.2%)	75 (7.9%)	68 (10.4%)	100 (8.1%)
10-14 years	85 (9.1%)	155 (9.3%)	70 (12.6%)	84 (8.9%)	77 (11.8%)	117 (9.5%)
≥15 years	353 (37.9%)	473 (28.3%)	134 (24.1%)	244 (25.7%)	156 (23.8%)	223 (18.0%)
Missing	116 (12.4%)	43 (2.6%)	5 (0.9%)	20 (2.1%)	33 (5.0%)	67 (5.4%)
Number of siblings						
0	45 (4.8%)	68 (4.1%)	47 (8.4%)	47 (5.0%)	43 (6.6%)	71 (5.7%)
1	268 (28.8%)	462 (27.6%)	187 (33.6%)	233 (24.6%)	175 (26.7%)	356 (28.8%)
2	304 (32.6%)	542 (32.4%)	138 (24.8%)	219 (23.1%)	179 (27.3%)	313 (25.3%)
3	178 (19.1%)	309 (18.5%)	69 (12.4%)	153 (16.1%)	91 (13.4%)	187 (15.1%)
≥4	123 (13.2%)	278 (16.6%)	89 (15.6%)	242 (25.5%)	149 (22.7%)	298 (24.1%)
Missing	14 (1.5%)	14 (0.8%)	27 (4.8%)	54 (5.7%)	18 (2.7%)	13 (1.1%)
Body size at age 10						
1 (slimmest)	218 (23.4%)	499 (29.8%)	146 (26.2%)	304 (32.1%)	191 (29.2%)	401 (32.4%)
2	273 (29.3%)	482 (28.8%)	140 (25.1%)	263 (27.7%)	151 (23.1%)	302 (24.4%)
3	157 (16.8%)	255 (15.2%)	104 (18.7%)	166 (17.5%)	100 (15.3%)	135 (10.9%)
4	132 (14.2%)	204 (12.2%)	71 (12.7%)	97 (10.2%)	68 (10.4%)	116 (9.4%)
5	66 (7.1%)	105 (6.3%)	49 (8.8%)	62 (6.5%)	31 (4.7%)	68 (5.5%)
6 (largest)	36 (3.9%)	70 (4.2%)	38 (6.8%)	33 (3.5%)	21 (3.2%)	45 (3.6%)
Missing	50 (5.4%)	58 (3.5%)	9 (1.6%)	23 (2.4%)	93 (14.2%)	171 (13.8%)
Body size at age 15						

1 (slimmest)	133 (14.3%)	339 (20.3%)	84 (15.1%)	213 (22.5%)	120 (18.3%)	235 (19.0%)
2	253 (27.1%)	478 (28.6%)	140 (25.1%)	240 (25.3%)	149 (22.7%)	346 (27.9%)
3	222 (23.8%)	359 (21.5%)	131 (23.5%)	218 (23.0%)	152 (23.2%)	222 (17.9%)
4	164 (17.6%)	271 (16.2%)	95 (17.1%)	144 (15.2%)	84 (12.8%)	148 (12.0%)
5	77 (8.3%)	119 (7.1%)	58 (10.4%)	67 (7.1%)	44 (6.7%)	89 (7.2%)
6 (largest)	39 (4.2%)	50 (3.0%)	42 (7.5%)	47 (5.0%)	21 (3.2%)	40 (3.2%)
Missing	44 (4.7%)	57 (3.4%)	7 (1.3%)	19 (2.0%)	85 (13.0%)	158 (12.8%)
Body size at age 20						
1 (slimmest)	81 (8.7%)	205 (12.3%)	50 (9.0%)	132 (13.9%)	66 (10.1%)	149 (12.0%)
2	208 (22.3%)	434 (25.9%)	122 (21.9%)	223 (23.5%)	159 (24.0%)	326 (26.3%)
3	257 (27.6%)	436 (26.1%)	139 (25.0%)	277 (29.2%)	166 (25.3%)	279 (22.5%)
4	183 (19.6%)	335 (20.0%)	126 (22.6%)	182 (19.2%)	122 (18.6%)	219 (17.7%)
5	111 (11.9%)	139 (8.3%)	63 (11.3%)	75 (7.9%)	39 (6.0%)	73 (5.9%)
6 (largest)	49 (5.3%)	68 (4.1%)	49 (8.8%)	44 (4.6%)	24 (3.7%)	36 (2.9%)
Missing	43 (4.6%)	56 (3.3%)	8 (1.4%)	15 (1.6%)	81 (12.4%)	156 (12.6%)
Frequency of outdoor activities ages 0-20						
Never	39 (4.2%)	47 (2.8%)	29 (5.2%)	31 (3.3%)	30 (4.6%)	57 (4.6%)
Reasonably often	421 (45.2%)	697 (41.7%)	171 (30.7%)	216 (22.8%)	210 (32.1%)	353 (28.5%)
Quite often	412 (44.2%)	820 (49.0%)	288 (51.7%)	544 (57.4%)	325 (49.6%)	628 (50.7%)
Virtually all the time	45 (4.8%)	92 (5.5%)	60 (10.8%)	138 (14.6%)	78 (11.9%)	182 (14.7%)
Missing	15 (1.6%)	17 (1.0%)	9 (1.6%)	19 (2.0%)	12 (1.8%)	18 (1.5%)
Complete cases[b]	635 (68.1%)	1356 (81.1%)	418 (75.0%)	717 (75.6%)	378 (57.7%)	736 (59.5%)

a. Highest educational attainment of either parent.

b. Participants with information for all variables.

Table e-2. Effect of adjustment for other exposure variables on OR (95% CI) for association between early life SES and MS

Parental education level	Age and sex	Participant education level	Family history of MS	Infectious mononucleosis	Number of siblings	Outdoor activities	Smoking history	Body size at age 10, 15, and 20	Full model[b]
Norway									
≤Primary	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Secondary	1.11 (0.90-1.36)	1.24 (1.01-1.54)	1.12 (0.91-1.38)	1.10 (0.89-1.35)	1.09 (0.89-1.34)	1.11 (0.90-1.37)	1.15 (0.93-1.43)	1.10 (0.89-1.36)	1.23 (0.99-1.55)
University	0.90 (0.73-1.12)	1.15 (0.91-1.44)	0.90 (0.73-1.12)	0.86 (0.70-1.07)	0.89 (072-1.10)	0.91 (0.73-1.12)	0.97 (0.78-1.21)	0.89 (0.72-1.11)	1.07 (0.84-1.37)
Canada									
≤Primary	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Secondary	1.13 (0.87-1.48)	1.33 (1.00-1.76)	1.10 (0.84-1.45)	1.11 (0.85-1.46)	1.11 (0.85-1.46)	1.15 (0.88-1.51)	1.20 (0.92-1.58)	1.12 (0.85-1.47)	1.27 (0.94-1.70)
University	1.21 (0.89-1.65)	1.55 (1.11-2.16)	1.17 (0.86-1.60)	1.20 (0.88-1.64)	1.18 (0.86-1.61)	1.24 (0.91-1.69)	1.28 (0.93-1.74)	1.20 (0.88-1.65)	1.47 (1.03-2.09)
Italy									
≤Primary	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Secondary	0.94 (0.75-1.18)	0.99 (0.78-1.24)	0.95 (0.76-1.20)	0.91 (0.73-1.15)	0.91 (0.72-1.15)	0.94 (0.75-1.18)	0.95 (0.76-1.20)	0.94 (0.75-1.18)	0.94 (0.73-1.20)
University	0.64 (0.40-1.01)	0.75 (0.46-1.21)	0.65 (0.41-1.03)	0.62 (0.39-0.98)	0.60 (0.38-0.96)	0.64 (0.41-1.02)	0.64 (0.40-1.01)	0.65 (0.41-1.03)	0.69 (0.42-1.14)

a. Each model adjusts for age, sex, the listed variable, and – in Canada and Italy – the study region.

b. Adjusted for age, sex, region, participant education level, history of infectious mononucleosis, smoking history, family history of MS, number of siblings, frequency of summer outdoor activities age 0-20, and body size at age 10, 15, and 20.

Table e-3. OR (95% CI) for association between early life SES and MS, by Italian region.

Parental education level	Sardinia (n=1,657)		Ferrara (n=236)	
	Basic model[a]	Full model[b]	Basic model[a]	Full model[b]
≤Primary	1.00	1.00	1.00	1.00
Secondary	0.92 (0.72-1.17)	0.91 (0.70-1.18)	1.16 (0.57-2.37)	1.37 (0.57-3.28)
University	0.58 (0.35-0.95)	0.65 (0.38-1.12)	1.07 (0.31-3.72)	1.39 (0.30-6.39)
Trend	0.069	0.162	0.782	0.520

a. Adjusted for age and sex.

b. Adjusted for age, sex, participant education level, history of infectious mononucleosis, smoking history, history of MS in a parent or sibling, number of siblings, frequency of summer outdoor activities age 0-20, and body size at age 10, 15, and 20.

Table e-4. Rate of infectious mononucleosis by SES

Parental education level	History of infectious mononucleosis (ever)		
	Norway	Canada	Italy
≤Primary	8.1%	14.9%	3.5%
≥Secondary	14.9%	17.3%	8.6%
P-value (χ^2-test)	<0.001	0.229	<0.001

Table e-5. RR (95% CI) for study participation among invited controls by education level[a]

Education level	Norway	Canada	Italy
Non-university educated	1.00	1.00	1.00
University-educated	1.91 (1.77-2.06)	2.37 (2.11-2.66)	1.60 (1.42-1.79)

a. Assuming the sample frames are representative of the general population in terms of education level (144).

6. Discussion and conclusions

While several risk factors for MS have been identified, much remains unknown about what causes the disease and who will be affected. The goal of this thesis was to examine whether high SES, intermittently linked to the disease for over 50 years, could be firmly established as a risk factor for MS.

The first step in exploring the association between SES and MS was to conduct a systematic review of the relationship, reported in Chapter 3. 21 cohort and case-control studies were identified, spanning a 47 year period. An association was reported in only 5 of these studies. However, much of the research was hampered by small sample sizes and inadequate adjustment for other risk factors. While such inconsistent findings do not lend themselves to a straightforward interpretation, it was found that the effect of SES was greatest in countries and time periods of higher inequality. This is consistent with the effect of an exposure being more easily observed when there is greater exposure variance.

Following this systematic review, an original analysis was carried out using data from a large, multinational case-control study. This manuscript was presented in Chapter 5. The analysis benefited from the ability to adjust for potential confounders and mediators of the MS-SES relationship, and the possible insights that might be gained from looking at the association in multiple countries. Much as with the systematic review, however, the findings provided only mixed support for an association between high SES and increased MS risk. There was clear evidence for an association in Canada, including a statistically significant dose-response relationship. In Norway, the link was limited to participants who grew up in a

time of rising inequality. No association was seen in Italy, despite the expectation that such a relatively unequal country would show a stronger association than Norway.

The inconsistency of the findings call into question the plausibility of a link. At the very least, high SES does not appear to be a strong and consistent predictor of increased MS risk. Rather its effects, if any, are dependent on the prevalent level of economic inequality. In addition, the possibility of residual confounding from unmeasured age of EBV infection means that even adjustment for all known risk factors does not necessarily provide an estimate of the direct effect of SES. The mechanism of any MS-SES association, therefore, remains unresolved. Conversely, however, what factors affect the age of EBV infection – likely a key determinant of MS risk – are themselves poorly understood and merit further investigation (158). An SES gradient in both MS risk and age of EBV infection may provide important clues in such research.

Given the potential for selection bias in case-control studies of the effects of SES, future research on its relationship with MS should ideally take place within socioeconomically representative, population-based cohorts. Only one study has done this, finding no evidence of an association between SES and MS (59). In this study, however, the authors lacked the necessary information to adjust for other important risk factors for the disease. While the analysis presented in the manuscript in Chapter 5 suggested that only smoking might significantly alter the relationship, it is possible that recall and reporting bias led to an underestimate of the effects of this and other factors. Additionally, the study was carried out in Denmark, the most economically equal country in the world, and thus not an ideal setting for exploring the effects of socioeconomic disparities (126). It is regrettable that no large-scale cohort study has looked at the effect of SES on MS risk in the UK, where the

association was first noted in two case series (3,4). A number of recent ecological studies in the UK have also noted an association (8–10). A potential data source for such an analysis would be the Clinical Practice Research Datalink, a nationally representative primary care database which includes several thousand MS patients (159).

Until such further research is conducted, the question of whether high SES is a risk factor for MS does not have a clear answer.

References

1. Koch-Henriksen N, Sørensen PS. The changing demographic pattern of multiple sclerosis epidemiology. The Lancet Neurology. 2010 May;9(5):520–32.

2. Alonso A, Jick SS, Olek MJ, Hernán MA. Incidence of multiple sclerosis in the United Kingdom : findings from a population-based cohort. J Neurol. 2007 Dec;254(12):1736–41.

3. Miller H, Ridley A, Schapira K. Multiple sclerosis: a note on social incidence. Br Med J. 1960 Jul 30;2(5195):343–5.

4. Russell WR. MULTIPLE SCLEROSIS: OCCUPATION AND SOCIAL GROUP AT ONSET. The Lancet. 1971 Oct 16;298(7729):832–4.

5. Kurtzke JF, Page WF. Epidemiology of multiple sclerosis in US veterans: VII. Risk factors for MS. Neurology. 1997 Jan;48(1):204–13.

6. Lauer K. The risk of multiple sclerosis in the U.S.A. in relation to sociogeographic features: a factor-analytic study. J Clin Epidemiol. 1994 Jan;47(1):43–8.

7. Hammond SR, McLeod JG, Macaskill P, English DR. Multiple sclerosis in Australia: socioeconomic factors. J Neurol Neurosurg Psychiatry. 1996 Sep 1;61(3):311–3.

8. Murray S, Bashir K, Penrice G, Womersley SJ. Epidemiology of multiple sclerosis in Glasgow. Scott Med J. 2004 Aug;49(3):100–4.

9. Visser EM, Wilde K, Wilson JF, Yong KK, Counsell CE. A new prevalence study of multiple sclerosis in Orkney, Shetland and Aberdeen city. J Neurol Neurosurg Psychiatry. 2012 Jul 1;83(7):719–24.

10. Phil Perry Moore KH. Neighbourhood socioeconomic status and multiple sclerosis: the impact of area level deprivation on multiple sclerosis risk frequency and disease progression. Multiple Sclerosis. 2013;19(S1):98.

11. Green C, Yu BN, Marrie RA. Exploring the Implications of Small-Area Variation in the Incidence of Multiple Sclerosis. Am J Epidemiol. 2013 Oct 1;178(7):1059–66.

12. Olek MJ, Gonzalez-Scarano F, Dashe JF. Epidemiology and clinical features of multiple sclerosis in adults [Internet]. UpToDate. 2014 [cited 2014 Jul 4]. Available from: http://www.uptodate.com/contents/epidemiology-and-clinical-features-of-multiple-sclerosis-in-adults

13. Weiner HL. Multiple sclerosis is an inflammatory t-cell–mediated autoimmune disease. Arch Neurol. 2004 Oct 1;61(10):1613–5.

14. Wakerley B, Nicholas R, Malik O. Multiple sclerosis. Medicine. 2012 Oct;40(10):523–8.

15. Compston A, Coles A. Multiple sclerosis. The Lancet. 2008 Oct 31;372(9648):1502–17.

16. Olek MJ. Treatment of relapsing-remitting multiple sclerosis in adults [Internet]. UpToDate. 2010 [cited 2014 Jul 4]. Available from: http://www.uptodate.com/contents/treatment-of-relapsing-remitting-multiple-sclerosis-in-adults

17. Tremlett H, Paty D, Devonshire V. Disability progression in multiple sclerosis is slower than previously reported. Neurology. 2006 Jan 24;66(2):172–7.

18. Scalfari A, Knappertz V, Cutter G, Goodin DS, Ashton R, Ebers GC. Mortality in patients with multiple sclerosis. Neurology July 9, 2013. 2013;81(2):184–92.

19. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. Ann Neurol. 2011 Feb 1;69(2):292–302.

20. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: the role of infection. Ann Neurol. 2007 Apr;61(4):288–99.

21. Koutsouraki E, Costa V, Baloyannis S. Epidemiology of multiple sclerosis in Europe: A Review. Int Rev Psychiatry. 2010 Jan 1;22(1):2–13.

22. Berg-Hansen P, Moen S, Harbo H, Celius E. High prevalence and no latitude gradient of multiple sclerosis in Norway. Mult Scler. 2014 Mar 6;

23. Buchter B, Dunkel M, Li J. Multiple sclerosis: a disease of affluence? Neuroepidemiology. 2012;39(1):51–6.

24. Whitacre CC. Sex differences in autoimmune disease. Nat Immunol. 2001 Sep;2(9):777–80.

25. Schwendimann RN, Alekseeva N. Gender Issues in Multiple Sclerosis. In: Alireza Minagar, editor. International Review of Neurobiology [Internet]. Academic Press; 2007 [cited 2014 Jul 4]. p. 377–92. Available from: http://www.sciencedirect.com/science/article/pii/S0074774207790177

26. Wallin MT, Culpepper WJ, Coffman P, Pulaski S, Maloni H, Mahan CM, et al. The Gulf War era multiple sclerosis cohort: age and incidence rates by race, sex and service. Brain. 2012 Jun 1;135(6):1778–85.

27. Goodin DS. The Causal Cascade to Multiple Sclerosis: A Model for MS Pathogenesis. PLoS ONE. 2009 Feb 26;4(2):e4565.

28. Ramagopalan SV, Dobson R, Meier UC, Giovannoni G. Multiple sclerosis: risk factors, prodromes, and potential causal pathways. The Lancet Neurology. 2010 Jul;9(7):727–39.

29. Kurtzke JF. Epidemiologic evidence for multiple sclerosis as an infection. Clin Microbiol Rev. 1993 Oct;6(4):382–427.

30. Handel AE, Giovannoni G, Ebers GC, Ramagopalan SV. Environmental factors and their timing in adult-onset multiple sclerosis. Nat Rev Neurol. 2010 Mar;6(3):156–66.

31. Pakpoor J, Disanto G, Gerber JE, Dobson R, Meier UC, Giovannoni G, et al. The risk of developing multiple sclerosis in individuals seronegative for Epstein-Barr virus: a meta-analysis. Mult Scler. 2013 Feb 1;19(2):162–6.

32. Handel AE, Williamson AJ, Disanto G, Handunnetthi L, Giovannoni G, Ramagopalan SV. An Updated Meta-Analysis of Risk of Multiple Sclerosis following Infectious Mononucleosis. PLoS ONE. 2010 Sep 1;5(9):e12496.

33. Ascherio A, Munger KL. Epstein-barr virus infection and multiple sclerosis: a review. J Neuroimmune Pharmacol. 2010 Sep;5(3):271–7.

34. Leibowitz U, Antonovsky A, Medalie JM, Smith HA, Halpern L, Alter M. Epidemiological study of multiple sclerosis in Israel. II. Multiple sclerosis and level of sanitation. J Neurol Neurosurg Psychiatr. 1966 Feb;29(1):60–8.

35. Levin L, Munger KL, Rubertone, MV. Temporal relationship between elevation of epstein-barr virus antibody titers and initial onset of neurological symptoms in multiple sclerosis. JAMA. 2005 May 25;293(20):2496–500.

36. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. Ann Neurol. 2007 Jun;61(6):504–13.

37. Van der Mei I a. F, Ponsonby A-L, Dwyer T, Blizzard L, Simmons R, Taylor BV, et al. Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. BMJ. 2003 Aug 9;327(7410):316.

38. Kampman MT, Wilsgaard T, Mellgren SI. Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle. J Neurol. 2007 Apr 1;254(4):471–7.

39. Bjørnevik K, Riise T, Casetta I, Drulovic J, Granieri E, Holmøy T, et al. Sun exposure and multiple sclerosis risk in Norway and Italy: The EnvIMS study. Mult Scler. 2014 Jul 1;20(8):1042–9.

40. Dobson R, Giovannoni G, Ramagopalan S. The month of birth effect in multiple sclerosis: systematic review, meta-analysis and effect of latitude. J Neurol Neurosurg Psychiatry. 2013 Apr 1;84(4):427–32.

41. Fiddes B, Wason J, Kemppinen A, Ban M, Compston A, Sawcer S. Confounding Underlies the Apparent Month of Birth Effect in Multiple Sclerosis. Ann Neurol. 2013 Jun;73(6):714–20.

42. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA. 2006 Dec 20;296(23):2832–8.

43. Bäärnhielm M, Olsson T, Alfredsson L. Fatty fish intake is associated with decreased occurrence of multiple sclerosis. Mult Scler. 2014 May;20(6):726–32.

44. Ascherio A, Munger KL, Simon KC. Vitamin D and multiple sclerosis. The Lancet Neurology. 2010 Jun;9(6):599–612.

45. Westerlind H, Ramanujam R, Uvehag D, Kuja-Halkola R, Boman M, Bottai M, et al. Modest familial risks for multiple sclerosis: a registry-based study of the population of Sweden. Brain. 2014 Mar 1;137(3):770–8.

46. Fagnani C, Ricigliano VAG, Buscarinu MC, Nisticò L, Salvetti M, Stazi MA, et al. Shared environmental effects on multiple sclerosis susceptibility: conflicting evidence from twin studies. Brain. 2014 Jul 1;137(7):e287–e287.

47. Gourraud P-A, Harbo HF, Hauser SL, Baranzini SE. The genetics of multiple sclerosis: an up-to-date review. Immunological Reviews. 2012 Jul 1;248(1):87–103.

48. 2 TIMSGC& TWTCCC. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature. 2011 Aug 11;476(7359):214–9.

49. Riise T, Nortvedt MW, Ascherio A. Smoking is a risk factor for multiple sclerosis. Neurology October 28, 2003. 2003;61(8):1122–4.

50. Salzer J, Hallmans G, Nystrom M, Stenlund H, Wadell G, Sundstrom P. Smoking as a risk factor for multiple sclerosis. Multiple sclerosis. 2013 Jul;19(8):1022–7.

51. Mikaeloff Y, Caridade G, Tardieu M, Suissa S. Parental smoking at home and the risk of childhood-onset multiple sclerosis in children. Brain. 2007 Oct 1;130(10):2589–95.

52. Hedström AK, Bäärnhielm M, Olsson T, Alfredsson L. Exposure to environmental tobacco smoke is associated with increased risk for multiple sclerosis. Mult Scler. 2011 Jul;17(7):788–93.

53. Munger KL, Chitnis T, Ascherio A. Body size and risk of MS in two cohorts of US women. Neurology. 2009 Nov 10;73(19):1543–50.

54. Munger KL, Bentzen J, Laursen B, Stenager E, Koch-Henriksen N, Sorensen TI, et al. Childhood body mass index and multiple sclerosis risk: a long-term cohort study. Multiple sclerosis. 2013 Sep;19(10):1323–9.

55. Ramagopalan SV, Valdar W, Criscuoli M, DeLuca GC, Dyment DA, Orton S-M, et al. Age of puberty and the risk of multiple sclerosis: a population based study. Eur J Neurol. 2009 Mar;16(3):342–7.

56. Runmarker B, Andersen O. Pregnancy is associated with a lower risk of onset and a better prognosis in multiple sclerosis. Brain : a journal of neurology. 1995 Feb;118 (Pt 1):253–61.

57. Hedström AK, Hillert J, Olsson T, Alfredsson L. Reverse causality behind the association between reproductive history and MS. Mult Scler. 2014 Apr 1;20(4):406–11.

58. Casetta I, Granieri E, Malagù S, Tola MR, Paolino E, Caniatti LM, et al. Environmental risk factors and multiple sclerosis: a community-based, case-control study in the province of Ferrara, Italy. Neuroepidemiology. 1994;13(3):120–8.

59. Nielsen NM, Jørgensen KT, Bager P, Stenager E, Pedersen BV, Hjalgrim H, et al. Socioeconomic Factors in Childhood and the Risk of Multiple Sclerosis. Am J Epidemiol. 2013 Jun 1;177(11):1289–95.

60. Riise T, Kirkeleit J, Aarseth JH, Farbu E, Midgard R, Mygland Å, et al. Risk of MS is not associated with exposure to crude oil, but increases with low level of education. Mult Scler. 2011 Jul 1;17(7):780–7.

61. Briggs FBS, Acuña BS, Shen L, Bellesis KH, Ramsay PP, Quach H, et al. Adverse socioeconomic position during the life course is associated with multiple sclerosis. J Epidemiol Community Health. 2014 Feb 27;jech–2013–203184.

62. Cohen S, Janicki-Deverts D, Chen E, Matthews KA. Childhood socioeconomic status and adult health. Annals of the New York Academy of Sciences. 2010 Feb 1;1186(1):37–55.

63. Marmot M. Status Syndrome: How Your Social Standing Directly Affects Your Health. Bloomsbury Publishing; 2012. 322 p.

64. Chen E, Miller GE. Socioeconomic Status and Health: Mediating and Moderating Factors. Annual Review of Clinical Psychology. 2013;9(1):723–49.

65. Adler NE, Ostrove JM. Socioeconomic Status and Health: What We Know and What We Don't. Annals of the New York Academy of Sciences. 1999 Dec 1;896(1):3–15.

66. Stringhini S, Dugravot A, Shipley M, Goldberg M, Zins M, Kivimäki M, et al. Health Behaviours, Socioeconomic Status, and Mortality: Further Analyses of the British Whitehall II and the French GAZEL Prospective Cohorts. PLoS Med. 2011 Feb 22;8(2):e1000419.

67. Eikemo TA, Bambra C, Joyce K, Dahl E. Welfare state regimes and income-related health inequalities: a comparison of 23 European countries. Eur J Public Health. 2008 Dec 1;18(6):593–9.

68. Evans GW, Kantrowitz E. SOCIOECONOMIC STATUS AND HEALTH: The Potential Role of Environmental Risk Exposure. Annual Review of Public Health. 2002;23(1):303–31.

69. McEwen BS, Gianaros PJ. Central role of the brain in stress and adaptation: Links to socioeconomic status, health, and disease. Annals of the New York Academy of Sciences. 2010 Feb 1;1186(1):190–222.

70. Hallee TJ, Evans AS, Niederman JC, Brooks CM, Voegtly JH. Infectious Mononucleosis at the United States Military Academy. A Prospective Study of a Single Class Over Four Years. Yale J Biol Med. 1974 Sep;47(3):182–95.

71. Crowcroft NS, Vyse A, Brown DW, Strachan DP. Epidemiology of Epstein-Barr virus infection in pre-adolescent children: application of a new salivary method in Edinburgh, Scotland. J Epidemiol Community Health. 1998 Feb 1;52(2):101–4.

72. Haahr S, Plesner AM, Vestergaard BF, Hollsberg P. A role of late Epstein-Barr virus infection in multiple sclerosis. Acta neurologica Scandinavica. 2004 Apr;109(4):270–5.

73. Balfour HH, Sifakis F, Sliman JA, Knight JA, Schmeling DO, Thomas W. Age-Specific Prevalence of Epstein–Barr Virus Infection Among Individuals Aged 6–19 Years in the United States and Factors Affecting Its Acquisition. J Infect Dis. 2013 Oct 15;208(8):1286–93.

74. Borg MO. The income--fertility relationship: effect of the net price of a child. Demography. 1989 May;26(2):301–10.

75. Hiscock R, Bauld L, Amos A, Fidler JA, Munafo M. Socioeconomic status and smoking: a review. Annals of the New York Academy of Sciences. 2012 Feb;1248:107–23.

76. McLaren L. Socioeconomic status and obesity. Epidemiologic reviews. 2007;29:29–48.

77. James-Todd T, Tehranifar P, Rich-Edwards J, Titievsky L, Terry MB. The impact of socioeconomic status across early life on age at menarche among a racially diverse population of girls. Annals of epidemiology. 2010 Nov;20(11):836–42.

78. Amato MP, Battaglia MA, Caputo D, Fattore G, Gerzeli S, Pitaro M, et al. The costs of multiple sclerosis: A cross-sectional, multicenter cost-of-illness study in Italy. Journal of Neurology. 2002;249(2):152–63.

79. Jennum P, Wanscher B, Frederiksen J, Kjellberg J. The socioeconomic consequences of multiple sclerosis: A controlled national study. European Neuropsychopharmacology. 2012 Jan;22(1):36–43.

80. Bradley RH, Corwyn RF. Socioeconomic Status and Child Development. Annual Review of Psychology. 2002;53(1):371–99.

81. Evans GW. The Environment of Childhood Poverty. American Psychologist. 2004;59(2):77–92.

82. Hackman DA, Farah MJ, Meaney MJ. Socioeconomic status and the brain: mechanistic insights from human and animal research. Nat Rev Neurosci. 2010 Sep;11(9):651–9.

83. Lupien SJ, King S, Meaney MJ, McEwen BS. Child's stress hormone levels correlate with mother's socioeconomic status and depressive state. Biological Psychiatry. 2000 Nov 15;48(10):976–80.

84. Chen E, Cohen S, Miller GE. How Low Socioeconomic Status Affects 2-Year Hormonal Trajectories in Children. Psychological Science. 2010 Jan 1;21(1):31–7.

85. Elenkov IJ, Chrousos GP. Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. Ann N Y Acad Sci. 2002 Jun;966:290–303.

86. Plotnikoff NP. Cytokines : stress and immunity. 2nd ed. Boca Raton, FL: CRC/Taylor & Francis; 2007. 405 p. p.

87. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nature reviews Immunology. 2005 Mar;5(3):243–51.

88. Dhabhar FS. Enhancing versus Suppressive Effects of Stress on Immune Function: Implications for Immunoprotection versus Immunopathology. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2008 Mar 15;4(1):2–11.

89. Chen E, Hanson MD, Paterson LQ, Griffin MJ, Walker HA, Miller GE. Socioeconomic status and inflammatory processes in childhood asthma: The role of psychological stress. Journal of Allergy and Clinical Immunology. 2006 May;117(5):1014–20.

90. Cohen S, Frank E, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM. Types of stressors that increase susceptibility to the common cold in healthy adults. Health Psychol. 1998;17(3):214–23.

91. Cohen S, Doyle WJ, Turner RB, Alper CM, Skoner DP. Childhood socioeconomic status and host resistance to infectious illness in adulthood. Psychosomatic medicine. 2004 Jul;66(4):553–8.

92. Chida Y, Mao X. Does psychosocial stress predict symptomatic herpes simplex virus recurrence? A meta-analytic investigation on prospective studies. Brain, behavior, and immunity. 2009 Oct;23(7):917–25.

93. D'Angeli MA, Merzon E, Valbuena LF, Tirschwell D, Paris CA, Mueller BA. Environmental factors associated with childhood-onset type 1 diabetes mellitus: an exploration of the hygiene and overload hypotheses. Archives of pediatrics & adolescent medicine. 2010 Aug;164(8):732–8.

94. Haynes A, Bulsara MK, Bower C, Codde JP, Jones TW, Davis EA. Independent effects of socioeconomic status and place of residence on the incidence of childhood type 1 diabetes in Western Australia. Pediatric diabetes. 2006 Apr;7(2):94–100.

95. Olen O, Bihagen E, Rasmussen F, Ludvigsson JF. Socioeconomic position and education in patients with coeliac disease. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2012 Jun;44(6):471–6.

96. Whyte L, Kotecha S, Watkins W, Jenkins H. Coeliac disease is more common in children with high socio-economic status. Acta paediatrica [Internet]. 2013 Nov 4; Available from: http://www.ncbi.nlm.nih.gov/pubmed/24188384

97. Green C, Elliott L, Beaudoin C, Bernstein CN. A population-based ecologic study of inflammatory bowel disease: searching for etiologic clues. American journal of epidemiology. 2006 Oct 1;164(7):615–23; discussion 624–8.

98. Heesen C, Gold SM, Huitinga I, Reul JMHM. Stress and hypothalamic-pituitary-adrenal axis function in experimental autoimmune encephalomyelitis and multiple sclerosis - a review. Psychoneuroendocrinology. 2007;32(6):604–18.

99. Elenkov null, Chrousos null. Stress Hormones, Th1/Th2 patterns, Pro/Anti-inflammatory Cytokines and Susceptibility to Disease. Trends Endocrinol Metab. 1999 Nov;10(9):359–68.

100. Mohr DC, Hart SL, Julian L, Cox D, Pelletier D. Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis. Bmj. 2004 Mar 27;328(7442):731.

101. Artemiadis AK, Anagnostouli MC, Alexopoulos EC. Stress as a risk factor for multiple sclerosis onset or relapse: a systematic review. Neuroepidemiology. 2011;36(2):109–20.

102. Riise T, Mohr DC, Munger KL, Rich-Edwards JW, Kawachi I, Ascherio A. Stress and the risk of multiple sclerosis. Neurology. 2011 May 31;76(22):1866–71.

103. Nielsen NM, Pedersen BV, Stenager E, Koch-Henriksen N, Frisch M. Stressful life-events in childhood and risk of multiple sclerosis: a Danish nationwide cohort study. Mult Scler. 2014 Mar 31;1352458514528761.

104. Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. [cited 2014 Jul 4]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

105. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097.

106. Hopkins RS, Indian RW, Pinnow E, Conomy J. Multiple sclerosis in Galion, Ohio: prevalence and results of a case-control study. Neuroepidemiology. 1991;10(4):192–9.

107. Tarrats R, Ordonez G, Rios C, Sotelo J. Varicella, ephemeral breastfeeding and eczema as risk factors for multiple sclerosis in Mexicans. Acta Neurol Scand. 2002 Feb;105(2):88–94.

108. Zilber N, Kahana E. Risk factors for multiple sclerosis: a case-control study in Israel. Acta Neurol Scand. 1996 Dec;94(6):395–403.

109. Alter M, Speer J. Clinical evaluation of possible etiologic factors in multiple sclerosis. Neurology. 1968 Feb 1;18(2):109–16.

110. Antonovsky A. Epidemiological study of multiple sclerosis in israel. iii. multiple sclerosis and socio-economic status. Journal of Neurology, Neurosurgery and Psychiatry. 1967;30(1):1–6.

111. Berr C, Puel J, Clanet M, Ruidavets JB, Mas JL, Alperovitch A. Risk factors in multiple sclerosis: a population-based case-control study in Hautes-Pyrénées, France. Acta Neurol Scand. 1989 Jul;80(1):46–50.

112. Breland AE Jr, Currier RD. Multiple sclerosis and amyotrophic lateral sclerosis in Mississippi. Neurology. 1967 Oct;17(10):1011–6.

113. Frutos Alegria MT, Beltran-Blasco I, Quilez-Iborra C, Molto-Jorda J, Diaz-Marin C, Matias-Guiu J. Epidemiologia de la esclerosis multiple en Alcoi. Datos analiticos. Revista de neurologia. 2002 May;34(9):813–6.

114. Frutos-Alegria MT, Beltran-Blasco I, Quilez-Iborra C, Molto-Jorda J, Diaz-Marin C, Matias-Guiu J. Estudio de casos y controles sobre la esclerosis multiple en las areas de Alicante y Villajoyosa. Rev Neurol. 2002 Jun 1;34(11):1013–6.

115. Koch-Henriksen N. An epidemiological study of multiple sclerosis. Familial aggregation social determinants, and exogenic factors. Acta Neurol Scand, Suppl.c. 1989;124:1–123.

116. Kotzamani D, Panou T, Mastorodemos V, Tzagournissakis M, Nikolakaki H, Spanaki C, et al. Rising incidence of multiple sclerosis in females associated with urbanization. Neurology. 2012 May 29;78(22):1728–35.

117. Kurtzke JF, Hyllested K, Arbuckle JD, Bronnum-Hansen H, Wallin MT, Heltberg A, et al. Multiple sclerosis in the Faroe Islands. 7. Results of a case control questionnaire with multiple controls. Acta Neurol Scand. 1997 Sep;96(3):149–57.

118. Martinez Sobrepera HJ, Cabrera Gomez JA, Tuero Iglesias A. Factores exogenos en la etiologia de la esclerosis multiple en Cuba. Rev Neurol. 2001 Nov 16;33(10):931–7.

119. Panelius M. Studies on epidemiological, clinical and etiological aspects of multiple sclerosis. Acta neurologica Scandinavica. 1969;Suppl 39:1–82.

120. Poskanzer DC, Sheridan JL, Prenney LB, Walker AM. Multiple sclerosis in the Orkney and Shetland Islands. II: The search for an exogenous aetiology. J Epidemiol Community Health. 1980 Dec 1;34(4):240–52.

121. Ghadirian P, Dadgostar B, Azani R, Maisonneuve P. A case-control study of the association between socio-demographic, lifestyle and medical history factors and multiple sclerosis. Can J Public Health. 2001 Aug;92(4):281–5.

122. Begg CB, Gray RJ. Methodology for case-control studies with prevalent cases. Biometrika. 1987;74(1):191–5.

123. Atkinson AB, Morelli S. Chartbook of economic inequality [Internet]. 2014. Available from: http://www.chartbookofeconomicinequality.com/

124. Zheng H, George LK. Rising U.S. income inequality and the changing gradient of socioeconomic status on physical functioning and activity limitations, 1984–2007. Social Science & Medicine. 2012 Dec;75(12):2170–82.

125. Bambra C. In defence of (social) democracy: on health inequalities and the welfare state. J Epidemiol Community Health. 2013 Sep 1;67(9):713–4.

126. LIS. LIS Inequality and Poverty Key Figures [Internet]. [cited 2014 Jul 4]. Available from: http://www.lisdatacenter.org

127. Phadke JG, Downie AW. Epidemiology of multiple sclerosis in the north-east (Grampian region) of Scotland--an update. J Epidemiol Community Health. 1987 Mar;41(1):5–13.

128. US Census Bureau DIS. Current Population Survey (CPS), CPS Table Creator [Internet]. [cited 2014 May 5]. Available from: http://www.census.gov/cps/data/cpstablecreator.html

129. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol. 2005 Mar;5(3):243–51.

130. Cohen S, Doyle WJ, Turner RB, Alper CM, Skoner DP. Childhood socioeconomic status and host resistance to infectious illness in adulthood. Psychosom Med. 2004 Aug;66(4):553–8.

131. Pugliatti M, Casetta I, Drulovic J, Granieri E, Holmøy T, Kampman MT, et al. A questionnaire for multinational case-control studies of environmental risk factors in multiple sclerosis (EnvIMS-Q). Acta Neurol Scand, Suppl.c. 2012;(195):43–50.

132. Wolfson C, Riise T. The epidemiologic study of exogenous factors in the etiology of multiple sclerosis. Neurology. 1997;49(Suppl 2).

133. Lossius A, Riise T, Pugliatti M, Bjørnevik K, Casetta I, Drulovic J, et al. Season of infectious mononucleosis and risk of multiple sclerosis at different latitudes; the EnvIMS Study. Mult Scler. 2014 May 1;20(6):669–74.

134. Styles A. Environmental Risk Factors in Multiple Sclerosis: The Role of Active and Passive Cigarette Smoke Exposure. [Montreal]: McGill University; 2011.

135. Marquis KH, Marquis MS, Polich JM. Response Bias and Reliability in Sensitive Topic Surveys. Journal of the American Statistical Association. 1986 Jun 1;81(394):381–9.

136. Pill R, Peters TJ, Robling MR. Social class and preventive health behaviour: a British example. J Epidemiol Community Health. 1995 Feb;49(1):28–32.

137. Psacharopoulos G, Patrinos HA. Returns to investment in education: a further update. Education Economics. 2004;12(2):111–34.

138. Miller G, Chen E, Cole SW. Health Psychology: Developing Biologically Plausible Models Linking the Social World and Physical Health. Annual Review of Psychology. 2009;60(1):501–24.

139. Lassmann H, Ransohoff RM. The CD4–Th1 model for multiple sclerosis: a crucial re-appraisal. Trends in Immunology. 2004 Mar;25(3):132–7.

140. Lovett-Racke AE, Yang Y, Racke MK. Th1 versus Th17: Are T cell cytokines relevant in multiple sclerosis? Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2011 Feb;1812(2):246–51.

141. Polman CH, Reingold SC, Edan G, Filippi M, Hartung H-P, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria."Ann Neurol. 2005 Dec 1;58(6):840–6.

142. Myhr K-M, Grytten N, Aarseth JH. The Norwegian Multiple Sclerosis Registry and Biobank. Acta Neurol Scand. 2012 Dec 1;126:20–3.

143. Groves RM. Nonresponse Rates and Nonresponse Bias in Household Surveys. Public Opin Q. 2006 Jan 1;70(5):646–75.

144. OECD. Education at a Glance 2012 [Internet]. Paris: Organisation for Economic Co-operation and Development; 2012 [cited 2014 May 3]. Available from: http://www.oecd-ilibrary.org/content/book/eag-2012-en

145. Hedström AK, Olsson T, Alfredsson L. High body mass index before age 20 is associated with increased risk for multiple sclerosis in both men and women. Mult Scler. 2012 Sep 1;18(9):1334–6.

146. Leigh A. How Closely Do Top Income Shares Track Other Measures of Inequality?*. The Economic Journal. 2007 Nov 1;117(524):F619–F633.

147. Vandenbroucke JP, Pearce N. Case–control studies: basic concepts. Int J Epidemiol. 2012 Oct 1;41(5):1480–9.

148. Stunkard AJ, Sørensen T, Schulsinger F. Use of the Danish Adoption Register for the study of obesity and thinness. Research publications-Association for Research in Nervous and Mental Disease. 1983;60:115.

149. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Statist Med. 2011 Feb 20;30(4):377–99.

150. Greenland S, Rothman KJ. Introduction to stratified analysis. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2008.

151. Selvin S. The Analysis of Contingency Table Data: Logistic Model I. Statistical Analysis of Epidemiologic Data. Oxford University Press; 2004.

152. Granieri E, Casetta I, Govoni V, Tola MR, Marchi D, Murgia SB, et al. The increasing incidence and prevalence of MS in a Sardinian province. Neurology. 2000 Sep 26;55(6):842–8.

153. Pugliatti M, Solinas G, Sotgiu S, Castiglia P, Rosati G. Multiple sclerosis distribution in northern Sardinia Spatial cluster analysis of prevalence. Neurology. 2002 Jan 22;58(2):277–82.

154. Cocco E, Sardu C, Massa R, Mamusa E, Musu L, Ferrigno P, et al. Epidemiology of multiple sclerosis in south-western Sardinia. Mult Scler. 2011 Nov 1;17(11):1282–9.

155. Rosati G, Pinna L, Granieri E, Aiello I, De Bastiani P, Tola R, et al. The distribution of multiple sclerosis in Sardinia. Riv Patol Nerv Ment. 1977 Feb;98(1):46–64.

156. Infectious Mononucleosis and its Relationship to EB Virus Antibody: A JOINT INVESTIGATION BY UNIVERSITY HEALTH PHYSICIANS AND P.H.L.S. LABORATORIES. British Medical Journal. 1971 Dec 11;4(5788):643–6.

157. Crawford DH, Macsween KF, Higgins CD, Thomas R, McAulay K, Williams H, et al. A Cohort Study among University Students: Identification of Risk Factors for Epstein-Barr Virus Seroconversion and Infectious Mononucleosis. Clin Infect Dis. 2006 Aug 1;43(3):276–82.

158. Balfour HH. Editorial Commentary: Genetics and Infectious Mononucleosis. Clin Infect Dis. 2014 Jun 15;58(12):1690–1.

159. Bazelier MT, van Staa T, Uitdehaag BMJ, Cooper C, Leufkens HGM, Vestergaard P, et al. The risk of fracture in patients with multiple sclerosis: the UK general practice research database. J Bone Miner Res. 2011 Sep;26(9):2271–9.