

The socioeconomic impact of living with multiple sclerosis in New Zealand

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Abstract

Multiple sclerosis (MS) is a disease where the majority of people are diagnosed in early adulthood however they experience a long sequela, with chronic progressive deterioration in most cases and a median survival time of 35-42 years. The increasing levels of disability reduce the individual's potential to work fully and in time their ability to perform their activities of daily living. As these patients are affected in their most productive years the resulting impact on their health, employment and social status means that there is likely to be a large socioeconomic cost to the individual, their families, and those countries with a high prevalence of multiple sclerosis.

In 2006 the New Zealand National MS Prevalence Study (NZNMSPS) was undertaken to ascertain the prevalence, distribution and profile of MS in New Zealand (NZ). In conjunction with the prevalence study, demographic features, disease characteristics and socioeconomic markers of people living with MS were investigated by this study to characterise the effects of the disease process on the socioeconomic status (SES) of the working age (25-64 years) MS population. The overriding objective was to identify the predictors of change in work, income and socioeconomic status for people with MS, thereby enabling targeting of disease modifying therapies, and allied health support to increase and prolong workforce participation.

Capture-recapture methods estimated that over 96% of the clinically definite MS population in NZ had been identified. Data was collected through a postal survey sent to all people with MS, with a response rate of 71.1% (2073 individuals). The NZNMSPS confirmed the high prevalence of MS in NZ, and the presence of a latitudinal gradient below 37° South. A novel finding was that the latitudinal gradient was mostly driven by females with the relapsing remitting MS (RRMS) phenotype indicating that genetic and/or environmental factors do not affect all MS cases equally.

This study found MS had a profound impact on work status, income and socioeconomic status which occurred early in the disease course and at low levels of disability. Both males and females were affected however the effect was significantly

greater for females. On prevalence day 54.6% of the working age MS population were not working. People with MS who were not working were more likely to report an income below both the NZ and MS median annual personal incomes. Income loss occurred early with increased effect in the older age groups. Results highlight the significant difference in median annual personal income for people with MS when compared with their age stratified NZ peers.

The New Zealand Socioeconomic Index (NZSEI) was used to evaluate the impact of MS on the SES of people living with the disease. Change in SES occurred early in the disease course with an apparent cumulative effect over the working age time-span, with the oldest age group most affected by loss of SES. Notably, people who remained in the workforce, whether full time or part time, were most likely to retain their SES.

The major original contributions of this work are the descriptive epidemiology of the work, income, and socioeconomic status of people living with MS in NZ. Recommendations include review of government policy on timely access to disease modifying therapy to prevent disability accumulation and delay disease progression enabling people with MS to continue working and contributing to society. Furthermore improved planning, with both workplace and social support services, will maximise opportunities for people with MS to remain employed and living in the community.

Preface

Scope of research

When I commenced this research I was employed as the study coordinator for the New Zealand Multiple Sclerosis Research group with my role being to run the National Prevalence Study of MS in New Zealand. My personal goal was to investigate the socioeconomic impact of living with a chronic progressive disease of early adult onset.

For the NZNMSPS we aimed to recruit every person living with MS in New Zealand. This would enable us to compare the whole MS population with that of the New Zealand population giving large numbers to analyse and greater power to the results. Seventy five percent (75%) of those who responded to the study agreed to be on a national register for people with MS. If we are able to establish this register it will serve as a basis for ongoing research, a gene study has already been conducted.

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List of Abbreviations

ACC	Accident Compensation Corporation
AI	Ambulatory Index
AIC	Akaike information criterion
ANZGene	Australia and New Zealand Genetics Consortium
ASP	Age standardised prevalence
BDI	Beck depression inventory
CAT	Computerised axial tomography
CDMS	Clinically definite multiple sclerosis
CI	Confidence interval
CIS	Clinically isolated syndrome
CNS	Central nervous system
CSF	Cerebrospinal fluid
DHB	District health boards
DMD	Disease modifying drugs
DSS	Disability status scale
EBV	Epstein Barr virus
EDMUS	European database in multiple sclerosis
EDSS	Expanded disability status scale
EGS	EDMUS grading scale
FSS	Fatigue severity scale
GWAS	Genome-wide association study
HHV6	Human herpes virus 6
HLA	Human leucocyte antigen
HRC	Health Research Council
HRQOL	Health related quality of life
IgG	Immunoglobulin G
MOH	Ministry of Health
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple sclerosis functional composite

MSQLI	Multiple sclerosis quality of life inventory
MSQOL	Multiple sclerosis quality of life
MSS	Multiple sclerosis society
MSSS	Multiple sclerosis severity score
MST	PHARMAC list
NARCOMS	North American Research Committee on Multiple Sclerosis
NHC	National Health Committee
NHS	Nurses health study
NZ	New Zealand
NZDEP	New Zealand index of deprivation
NZHIS	New Zealand health information service
NZNMSPS	New Zealand National Multiple Sclerosis Prevalence Study
NZSCO	New Zealand standard classification of occupations
NZSEI	New Zealand Socioeconomic Index
OR	Odds ratio
PASAT	Paced auditory serial addition test
PHARMAC	Pharmaceutical management agency of New Zealand
PPMS	Primary progressive multiple sclerosis
PWC	Population weighted latitude and longitude centroid
RR	Relative risk
RRMS	Relapsing remitting multiple sclerosis
SCRIPPS NRS	Scripps neurological rating scale
SES	Socioeconomic status
SF 36	Short form -36
SNP	Single nucleotide polymorphisms
SPMS	Secondary progressive multiple sclerosis
UIN	Unique identification number
UK	United Kingdom
US	United States
USA	United States of America
UVR	Ultraviolet radiation
VEP	Visual evoked potential
25 (OH)D	25-hydroxyvitamin-D

Chapter One

Multiple Sclerosis

1.1

Introduction

This chapter presents an overview of the disease multiple sclerosis (MS) including its history, clinical presentation, and the current views on its aetiology and treatment. A comprehensive narrative review of the published literature pertaining to socioeconomic status for people with MS is presented, providing information relevant to the understanding of the thesis.

Narrative reviews are valuable for surveying the state of knowledge on a topic, integrating information from a range of studies with different methodologies and identifying areas which would benefit from further research. The main limitation of using a narrative review approach is that it lacks reproducibility. Less explicit methods are used in the selection, appraisal and synthesis of the literature, and whilst they provide a broad overview of the subject, they do not generally address a specific hypothesis as in the case of systematic literature reviews.

The literature search of socioeconomic studies relating to MS included the databases; MEDLINE, EMBASE, Cochrane library, CINAHL, and ISI Web of Knowledge for articles containing the keywords ‘multiple sclerosis, MS, socioeconomic status (also spelt socio-economic), employment, work, job, income, labour force’, from 1965 to present, in English. In addition, article reference lists were reviewed to identify additional studies. No studies specifically investigating socioeconomic status and MS were identified however there are a number which describe employment status, burden of illness and quality of life for people with MS contributing pertinent knowledge to the study.

1.2

Multiple sclerosis

The name multiple sclerosis (MS) is derived from the gross appearance of the lesions or plaques found scattered throughout the central nervous system (CNS) of patients with this chronic demyelinating disease. The CNS consists of the brain and spinal cord. These

characteristic focal areas are the result of damage to the myelin sheath, the protective cover, which surrounds axons and permits rapid conduction of nerve impulses in the brain and spinal cord. MS is the most common neurological disease of young adult Caucasians of Northern European ancestry¹. Onset occurs in the majority of patients before the sixth decade². The disease is more common in females than in males, with a ratio of approximately three to one^{3,4,5,6}. The low mortality rate from MS and the chronic progressive nature of the disability associated with the disease results in a large burden of morbidity.

1.3

Historical background

The diary of Augustus d'Este, an illegitimate grandson of King George III, dated from December 1822 to his death in 1848 is considered to be the first detailed written description of someone experiencing a relapsing remitting illness of a demyelinating nature⁷. The central nervous system plaques of multiple sclerosis were first depicted in 1838 by Carswell, a Scottish physician, following his examination of human cadavers^{8,9}. The first systematic study of human demyelinating disease commenced in the mid-19th century and focussed on both the clinical presentation and pathological features within the brain. It was during this period that many of the features currently recognised as components of the disease were described. Jean-Martin Charcot, a French professor of neurology in Paris, wrote a comprehensive scientific description of the disease and the changes in the brain that accompany it^{10,11}. He was able to correlate clinical symptoms, such as amblyopia, nystagmus, dysarthria and ataxia with the anatomical locations in the cerebrum, cerebellum, and brainstem. Based on his observations he recognised that the key feature of the disease was the scattering of symptoms over different time periods and clinical locations. One of Charcot's pupils, Pierre Marie (1853-1940), also recorded dysfunction of the bowel, bladder and sexual function^{2,12}. He recognised the variable symptoms at onset between patients with MS, and differences in the clinical course of the disease process, writing an accurate, detailed account of primary progressive MS.

Pathological study of the brain during autopsy revealed plaques, areas with abnormal firmness or consistency, located in irregularly defined parts of the white matter, but rarely in the grey matter of the brain. Rindfleisch (1863) noted that these plaques were found around blood vessels which he argued was evidence of a chronic inflammatory process¹³.

Technological development enabled microscopic study of brain tissue from deceased patients with MS, and in 1916 James Dawson, a Scottish doctor, described the inflammation and demyelination with associated scarring occurring in these specimens¹⁴. Marburg, further advancing knowledge of the disease process, noted that these observations were not limited to the brain and spinal cord, observing that in some cases similar changes occurred in the peripheral nervous system¹⁵. The causal agent at this time was thought to be a virus or toxin however no evidence was discovered to support this theory. By 1950 cerebral spinal fluid (CSF) testing was introduced as a diagnostic tool as research had shown that unusual protein by-products, known as oligoclonal bands, could be found in the CSF of patients with MS¹⁶.

It was not until early in the 20th century that the first epidemiological studies of multiple sclerosis were conducted in England, Europe and the USA. These studies were largely aimed at describing variations in the presentation of the condition and giving an indication of the frequency of the illness rather than an accurate enumeration of cases. As early as the 1920's, Davenport recognised differences in the expected prevalence rates between different racial groups with higher rates recorded in people of Finnish and Scandinavian descent, and lower than expected rates in Italians. He also noted that rates of disease were low in native Africans and Japanese¹⁷. A latitudinal gradient was observed to be present in the United States and Europe. He also surmised that MS was not an inherited or familial illness^{17,18}. Further development in the epidemiology of MS was limited until the 1950s when Dean studied the effect of migration to South Africa on the frequency of MS¹⁹. He observed that South Africa had a low number of cases of MS, all of which were Caucasian, and that MS occurred mainly in European immigrants and was less common in native born Afrikaners. The Association for Research in Nervous and Mental Diseases (1950) presented figures which showed that mortality rates were higher in temperate zones than in the tropics or sub-tropics²⁰. It also demonstrated that the figures for people with MS were higher in northern parts of the United States and Italy than in southern regions²⁰. Goldberg and Kurland (1962) surveyed 33 countries showing similar latitudinal variations in the disease²¹. Aetiological hypotheses including environmental factors were investigated as part of the epidemiological studies in an attempt to identify potential causal factors.

Throughout this period multiple sclerosis was known by various names including sclerose en plaques, disseminated sclerosis and diffuse sclerosis. The formation of lay support organisations in the 1950's brought about the need for a consistent term for the

disease. The publication of the book, “Multiple Sclerosis”, established multiple sclerosis as the universal name for the disease².

Since the 1950’s John Kurtzke has worked extensively with the data pertaining to the international epidemiology of MS. He suggested that the prevalence of MS fitted into three bands; high risk ($\geq 30/100,000$), medium risk (5-29/100,000) and low risk ($\leq 5/100,000$), which were associated with latitudinal location, with those residing closer to the equator having the lower risk of developing MS²². He was interested in the methodology used by researchers including how diagnosis was confirmed and how to quantify the progression of the disease and disability levels of patients. This interest led him to derive the Kurtzke Expanded Disability Status Scale (EDSS), an ordinal measure of disability for patients with MS. Although there are some recognised limitations, this scale continues to be used as a standard measure of disability in people with MS by researchers and clinicians.

In the 1960’s a panel of medical experts led by Dr George Schumacher developed standard guidelines for the diagnosis of MS¹⁰. These were designed to assist doctors in making earlier, more accurate diagnoses. Further refinement of these diagnostic criteria was made by the Poser committee in 1983. It was during this period that CAT scans, now superseded by MRI scans, were incorporated into the array of diagnostic tools used to confirm the diagnosis of MS. The advent of the MRI as a diagnostic tool brought about the modification of the diagnostic criteria by McDonald et al in 2001 and 2005 to include MRI findings^{23,24}.

From the 1960s disease modifying drugs were being developed and introduced to help manage the disease. The mechanism of the disease process was thought to be an autoimmune response and steroids were established as a means to treat acute attacks. Between 1980 and 1990 numerous clinical trials took place to test potential treatments. Currently there are around six disease modifying therapies in the market which act by either suppressing or altering the immune system in some way. The focus has also moved to incorporate allied health expertise, including physiotherapy and occupational therapy, to maximise function and rehabilitate MS patients where possible.

1.4

Pathology of multiple sclerosis

MS is primarily considered to be a chronic inflammatory and demyelinating disease of the CNS. The disease process is characterised by destruction of the myelin sheath surrounding the axons of nerves in the brain and spinal cord^{25,26}. These areas of damage are called lesions or plaques. A characteristic pathological feature of MS is the chronic persistent inflammation which affects both the areas of demyelinated plaques as well as large parts of the normal appearing white and grey matter in the CNS²⁷. In these cases, the inflammatory response ultimately results in a breakdown of the myelin sheath which protects the axons in the nerve pathways. The axons can no longer function correctly impeding the flow of electrical signals between the neurons. Axonal loss is not always contingent on demyelination in MS. It can be a completely independent process whereby progressive axonal loss due to neuronal loss occurs in the absence of inflammation. The outcome of this process is the progressive increase in disability observed in cases of primary and secondary progressive MS where there is no or minimal measurable inflammation²⁷. Although the essential features of MS pathology have been known for many years, the mechanisms which cause the process have been a more challenging area of investigation highlighting the complexity of the disease process²⁷. Different mechanisms of demyelination have been identified in different subgroups of MS patients and different patterns of pathology can be found in MS lesions^{27,28}.

1.4.1

Immunology

The immune system has been identified as having a central role in MS. The immune system comprises the mechanisms used by the body to protect against environmental agents that are foreign to the body. Immunity may be innate or adaptive (acquired)²⁹. The innate immune response is present from birth and does not require prior sensitisation to an antigen, either through infection or vaccination, to be activated. Examples of components of the innate immune system include skin integrity, chemicals in the blood, and mucous in the lungs as well as antimicrobial cells. It is a non-specific defence mechanism which activates a short time after an antigen appears in the body and uses numerous cell types including basophils, mast cells, neutrophils, dendritic cells and macrophages to eliminate invading microbes. When a pathogen invades the body, dendritic cells and macrophages

engulf and phagocytise the organism. Pieces of the phagocytised pathogen are then presented on the surface of the macrophage or antigen-presenting cells (APC's) and bound to its major histocompatibility complex (MHC)²⁹. This enables the body's immune system to recognise those cells which have foreign material present within them.

One of the outcomes of the innate immune response is to activate the adaptive immune response using the Toll-like receptors. Toll-like receptors activate the pathway which regulates cytokine expression including inflammatory cytokines IL-1, IL-6, IL-8, IL-10, TNF alpha and IL-12, IL-13. Adaptive immunity is an antigen-specific immune response. In response to a recognised antigen, T-cells and B-cells are activated within the immune system²⁹. Both T-cells and B-cells are coated with various substances with each group, composed of different chemical molecules, known as cluster differentiation (CD). Immature T-cells are stored in the thymus and have CD2, CD3, CD4, CD8, CD28 and CD45R molecules on their surface. Immature B-cells are in the bone marrow and have CD21, CD35, CD40 and CD45 molecules on their surface. Both CD4⁺ helper T-cells and CD8⁺ cytotoxic or killer T-cells are activated by the APC if the T-cells recognise the antigen presented by the macrophage. Each group of T-cells can be further classified according to the types of cytokines they produce.

CD8⁺ killer T-cells represent the cell-mediating immune response, directly attacking and destroying other cells, and carrying pieces of the target antigen on their MHC II surface proteins³⁰. The cytokines produced during this process include IL-1, as the target antigens are most commonly viral infections and tumour cells. CD4⁺ helper-T cells control the process by managing the immune response the body makes to a pathogen³¹. They are also required for B-cell activation. The CD4⁺ T-cells are further divided by the cytokines they produce into the Th1, Th2, and Th17 cells. The Th2 response activates the B-cells creating proliferation and immunoglobulin production specific to that antigen through the production of IL-4, IL-10 and IL-13. The immunoglobulin or antibodies bind to the antigen, most commonly bacteria and protozoa, and phagocyte cells engulf and phagocytise it. This process is the humoral immune response. More recently the Th17 cells have been identified as an inflammatory T-cell response following chronic immune stimuli and produce the cytokine IL-17³².

CD4⁺ T-cells are able to create memory T-cells which are programmed to recognise and respond to a pathogen once it has previously invaded and been repelled. This process, termed immunisation, enables the individual to acquire the immunity required to

withstand and resist a subsequent attack by the same offending agent. Following an active immune response, the T-regulatory or Th3 cells act to discontinue the immune response.

Under normal circumstances the immune system attacks foreign agents and ignores the host's structures³³. However if a component of the T-cell immune process becomes deregulated they may attack normal tissues causing damage and an autoimmune disease response³⁴. MS is thought to be an example of an autoimmune disease where Th1 and Th17 lymphocytes play a major role, resulting in damage to the myelin sheath due to candidate antigens eliciting autoimmune responses against the myelin of the CNS^{32,35-45}.

Early symptoms of MS are considered to be the result of axonal demyelination, whilst remission from the symptoms is attributed to the resolution of the inflammatory response and to partial remyelination, restoring function to the nerve pathway²⁶. However recurring episodes of disease activity over time are believed to eventuate in irreversible axonal injury leading to the progressive loss of neurologic function. MRI scans show that from early on the disease process remains active even though symptoms may not be clinically visible. MS is a difficult disease to characterise due to the random nature of the development and severity of these plaques. This results in wide variations in the type and severity of the symptoms and as a consequence the disease is both unpredictable and variable both in an individual patient and between patients.

1.5

Clinical presentation

Describing the course and pattern of multiple sclerosis in a standard manner is critical for clarity and understanding between clinicians and researchers working with MS patients. Clinical features include episodes characteristic of demyelination, with signs of the symptomatic lesion on clinical examination. At least 30 days must separate two clinical episodes suggestive of demyelination for the consideration of a diagnosis of multiple sclerosis^{23,46,47}.

Patients characteristically present in one of three ways.

- Individuals with relapsing-remitting episodes originating from separate sites within the CNS in whom demyelination is the most likely pathophysiological explanation for each event (Relapsing-remitting MS).

- Individuals who present with a recent, clinically isolated episode typical of demyelination, with or without a suspicious past history of demyelinating disease (Clinically isolated syndrome).
- Individuals with slowly progressive neurological symptoms which might be due to demyelination (Primary-progressive MS).

The first neurological episode is commonly referred to as a clinically isolated syndrome (CIS). To fit the criteria for CIS, the episode must involve dysfunction of the central nervous system or spinal cord; have an acute or sub-acute onset which is followed by recovery; and with consideration of paraclinical investigations exclude all other explanations than suspected MS⁴⁸⁻⁵². The development of a second neurological episode involving a new site within the CNS confirms that the person has converted to definite MS. On average 85% of initial neurological episodes will remit or partially remit⁵³. Most patients are able to recognise the distinct periods of relapse, but are less certain regarding the point at which the disease becomes progressive.

Multiple sclerosis is characterised by episodes of relapses, remissions and chronic progression. Progression can occur from onset of the disease (primary progressive MS) or following an initial period of relapses and remissions (secondary progressive MS). There is no current consensus on the frequency of relapses with estimates ranging from 0.1 – 1.5 per year⁴⁹. Onset of progression for the total MS population, including people with the primary progressive form, has a median time of 11 years. Whereas the time to progression for people with the relapsing remitting form of MS is a median of 19 years. Age at onset is the strongest predictor of conversion to secondary progression, that being the older the age at onset, the shorter the time to progression⁵⁴⁻⁵⁶. Evidence indicates that MS of primary progressive onset is more commonly a disorder of motor deficits occurring in older males, whereas relapsing remitting MS has a female preponderance. As gender, age, clinical features and course at onset of disease are all interdependent there is potential for confounding of contributing factors. Although the grouped data from numerous studies show reasonable consistency as to the prognosis for progression of disability in MS, there is extensive individual variation in the course of the disease⁴⁹.

1.6

Phenotypes of multiple sclerosis

In 1996 an attempt was made to standardise the terminology used to describe the pattern and course of multiple sclerosis. An international survey of physicians was conducted and the consensus classified the disease course into four categories⁵⁷.

- **Relapsing Remitting MS (RRMS)**
Most MS patients (80-85%) are diagnosed with this form of the disease. It is characterised by distinct relapses with full recovery or minor residual deficit upon recovery, alternating with periods between relapses characterised by lack of disease progression.
- **Secondary Progressive MS (SPMS)**
After a number of years the majority of patients diagnosed with relapsing remitting disease will proceed to develop this progressive form of the disease which may or may not include occasional relapses, minor remissions and plateaus.
- **Primary progressive MS (PPMS)**
A small proportion of MS patients (15-20%) experience a slow progression of the disease from onset. These patients may experience occasional relapses, plateaus and temporary minor improvements however the disease course overall remains progressive.
- **Progressive relapsing MS**
This form of MS is rare and is described as a progressive disease from onset, during which the patient has acute relapses, without full recovery, and the phase between relapses is characterised by constant progression.

Due to ongoing debate between physicians over these classifications, the fourth category is no longer used and MS patients are largely assigned to one of the first three descriptions for MS.

1.7

Diagnosis

No single clinical feature or diagnostic test is sufficient to confirm a diagnosis of MS. Other than histological examination of tissue from multiple sites within the central nervous system, a highly invasive and inappropriate approach, there are currently no specific laboratory tests which confer a definitive diagnosis of MS. The diagnosis is therefore made through a combination of patient history, clinical features and various diagnostic tests. The purpose of diagnostic tests is to confirm features of MS are present, provide evidence of dissemination in time and space, and to exclude all other possible conditions which mimic demyelination.

1.7.1

Radiological examination

Magnetic resonance imaging (MRI) scans give detailed high resolution images of cross sections of the brain and spinal cord. MRI scans were shown to be able to identify MS lesions which corresponded with demyelinating plaques at autopsy⁵⁸. Since 1981, MRI of the brain has become the most sensitive diagnostic tools for use in suspected cases of MS. T2-weighted and T2 variant (FLAIR) MRI scans show MS lesions as pale areas enabling neurologists to confirm the location of probable demyelinating plaques and in some cases correlate these with the patient's signs and symptoms.

Abnormalities on MRI scans are observed in approximately 95% of patients with clinically definite MS⁵⁹. MRI abnormalities may be found in a number of other diseases and in some healthy volunteers, requiring the development of criteria which enable the evidence on MRI scans to be classified as suggestive of MS^{48,59}. Lesions are considered typical of MS if they are of high intensity on T2-weighted images, measure greater than 3 mm in diameter, and are located predominantly in the white matter. The purpose of MRI is to document definite tissue abnormality of a demyelinating nature, and to confirm features of dissemination over time and space. Use of MRI scans has reduced the time from onset of first symptoms to diagnosis for patients.

1.7.2

Visual function tests

Delayed visual evoked potential response (VEP) tests the conduction of the optic nerves. Patients are visually stimulated with reversing black and white squares in a checkerboard pattern and defined wave patterns (VEPs) are recorded with scalp electrodes. As demyelination occurs, conduction along the optic nerve slows^{60,61}. The presence of delayed evoked potentials can contribute to determining whether there is a pathological process of demyelination present.

1.7.3

Laboratory tests

Historically CSF from lumbar punctures was used to aid diagnosis of MS, however with increased access to MRI scans it is less frequently used and mainly in more complex cases. The purpose of CSF examination is to confirm the presence of intrathecal inflammation through evidence of intrathecal immunoglobulin G (IgG) synthesis. This is indicated by the presence of two or more oligoclonal bands in the CSF combined with the absence of oligoclonal bands in the paired blood serum, that is, CSF and blood samples which are collected at the same time⁶²⁻⁶⁵. Though indicative of an illness caused by an immunological response, these findings are not specific for MS.

1.7.4

Diagnosis conclusion

Despite the advances in technology and increased access to testing facilities, none of these tests are specific for MS and their purpose is essentially to confirm that there is an abnormality indicative of MS whilst eliminating other diseases which resemble multiple sclerosis.

1.8

Diagnostic criteria

With increasing numbers of epidemiological studies since the 1950s, the need for standardised diagnostic criteria became critical. The first diagnostic criteria were based purely on clinical features, but as technology has advanced the diagnostic criteria have evolved to incorporate findings from para-clinical sources.

Allison (1931) classified cases as typical; early, in which disseminated sclerosis was the most likely diagnosis; impossible to assess, due to lack of adequate documentation; and doubtful as the signs and symptoms were inconclusive⁶⁶.

Allison and Millar (1954) developed diagnostic criteria to describe cases as early, with few physical signs but a recent history of remitting symptoms; probable, as there is little doubt regarding the diagnosis; possible, where findings suggest a diagnosis of MS however the history is insufficient for evidence of scattered lesions (dissemination in space) and no other cause could be found; and discarded^{10,67}.

Schumacher led a panel of medical experts in the 1960's to develop standard guidelines for the diagnosis of MS⁶⁸. Based on the principles developed by Kurtzke in classifying US army veterans with MS, new diagnostic criteria were formalised by this group. These criteria were designed to assist doctors in making earlier, more accurate diagnoses. The Schumacher criteria define definite MS as showing objective evidence for disease affecting 2 or more white matter parts of the CNS, which occur in episodes generally lasting more than 24 hours, each separated by at least one month or with progression over six months. The person should be between 10-50 years of age at onset and there should be no better explanation for the illness. Most research surveys continued to use the Allison and Millar criteria with the addition of this modification.

Rose et al. (1976) added two more classifications to the Schumacher criteria: probable, with two episodes of demyelinating illness but with signs at only a single site (dissemination in time but not space), or a single episode but with signs of widespread disease (dissemination in space but not time); and possible, with a history of two episodes of illness with few or no signs⁶⁹.

Further modifications were introduced by McDonald and Halliday (1977) who added proven MS, evidence from autopsy or biopsy; early probable, two episodes and a single affected site or a single episode and two affected sites; progressive probable, progressive

history with multiple sites affected; and suspected probable, one episode at a single site unless the optic nerves are affected⁶¹.

In 1983 the Poser committee introduced criteria that were widely accepted as the gold standard for about 20 years. Their criteria incorporated information available from laboratory investigations into the categories of clinically definite and probable MS but did not deal with suspected cases¹⁰. The Poser criteria are:

Table 1.1 Poser diagnostic criteria for MS

Diagnosis	Criteria
Clinically definite MS	2 attacks and 2 areas of clinical evidence Or 2 attacks, one episode of clinical evidence and one of paraclinical evidence.
Laboratory supported definite MS	Two attacks, one area of clinical evidence or one of paraclinical evidence and CSF positive for oligoclonal bands/Immunoglobulin G. Or one attack and two areas of clinical evidence and CSF positive for oligoclonal bands/Immunoglobulin G. Or one attack, one area of clinical evidence, and one area of paraclinical evidence and CSF positive for oligoclonal/bands Immunoglobulin G.
Clinically probable MS	Two attacks and one area of clinical evidence Or one attack and two areas of clinical evidence Or one attack, one area of clinical evidence and one area of paraclinical evidence
Laboratory supported probable MS	Two attacks and CSF positive for oligoclonal bands/Immunoglobulin G.

McDonald et al in 2001 and 2005 modified the diagnostic criteria to allow for the inclusion of radiological findings. It is recommended that these criteria are best applied to people between 10 and 59 years of age with the diagnostic categories being MS when the criteria are met, Possible MS – for those at risk of MS but for whom the diagnosis is not definite, and not MS^{10,23,24}. For a positive diagnosis of MS according to the McDonald Criteria the patient must fill one of the following criteria:

Table 1.2 McDonald diagnostic criteria for MS

Clinical presentation	Additional data needed for a diagnosis of MS
Two or more attacks, objective clinical evidence of two or more lesions	
Two or more attacks, objective clinical evidence of one lesion	And dissemination in space demonstrated by MRI Or up to two MRI detected lesions consistent with MS plus positive CSF Or await further clinical attack implicating a different site
One attack, objective clinical evidence of two or more lesions	And dissemination in time demonstrated by MRI Or second clinical attack
One attack, objective clinical evidence of one lesion (monosymptomatic presentation; CIS)	And dissemination in space as demonstrated by MRI Or up to two MRI detected lesions consistent with MS plus positive CSF and dissemination in time as demonstrated by MRI Or a second clinical attack
Insidious neurological progression suggestive of MS	Positive CSF and dissemination in space demonstrated by: a.) nine or more T2 lesions in the brain; b) two or more lesions in the spinal cord; c) four to eight brain lesions and one spinal cord lesion. OR Abnormal visual evoked potential associated with four to eight brain lesions, or with fewer than four brain lesions plus one spinal cord lesion demonstrated by MRI. OR continued progression for one year.

The McDonald criteria have largely been the basis for case selection for this thesis, however as a few of the older patients were diagnosed prior to MRI imaging, confirmation of their diagnosis was made using the Poser Criteria.

1.9

Presenting symptoms

The symptoms of MS are extremely variable in their presentation, duration and severity. The spectrum of MS severity ranges from a benign form with little or no accumulation of disability throughout the disease course, to a rapidly fatal form with substantial cerebral demyelination⁷⁰. Clinical signs and symptoms vary reflecting the location and severity of the demyelinating areas. The optic nerves, periventricular areas, corpus callosum, brain stem and cervical spinal cord are commonly affected areas. Common presentations include motor symptoms with weakness in one or more limbs, visual problems such as diplopia and loss of vision, sensory symptoms, coordination and balance problems, bowel and/or bladder symptoms, cognitive difficulties and fatigue^{49,53,71-73}.

The prevalence of presenting symptoms reported in different studies varies greatly. Factors which affect the collected data include the study sample selection, for example, community dwelling, or hospital cases; the diagnostic criteria used in each study, and the method of assessment of the symptoms, such as retrospective recall, or patient records audit. There is also great potential for confounding due to interdependence of contributing factors such as age, sex and clinical features. However symptoms at onset can be divided into four main categories. Dysfunction of the long tracts which include motor, sensory, cerebella or sphincter disturbances account for approximately 50% of initial presentations. Visual changes including optic neuritis, double vision and loss of sight represent 15% of cases. Isolated brainstem dysfunction has a 10% incidence, and 25% of initial presentations have multiple symptoms which include various combinations of these features⁷⁴.

The most common sites which produce initial symptoms in patients with relapsing remitting disease are the brainstem, cerebellum, cervical spine and the optic nerve. Patients with primary progressive disease are predominantly affected by spinal cord symptoms^{4,75-79}.

Numbness and tingling in various parts of the body is the most common presenting symptom in relapsing remitting MS. Vertigo and balance problems can also occur. Optic neuritis or lesions of the optic nerves cause visual problems which the patient may describe as blurred vision, double vision, tunnel vision, temporary episodes of blindness or severe eye pain. Another common symptom is difficulty walking due to weak muscles

or spasticity. Over time this may cause the patient to require assistance for walking in the form of a stick, crutches, a walker or in the advanced stages a wheelchair. Bladder and or bowel function may be affected.

Cognitive functions which may be affected include the memory, organisational planning, problem-solving and speech⁸⁰. Some patients may experience emotional changes including depression. Extreme fatigue which comes on suddenly and tends to get worse over the course of the day affects many patients with MS⁸¹. Less common is pain with patients suffering from both chronic and acute pain often described as burning, tingling, aching, or Lhermitte's sign; a sensation like electric shocks down the back and into the limbs.

In the early stages of relapsing remitting illness patients often experience a full recovery from symptoms during remissions; however as the disease advances patients are often left with residual deficits following an attack. There is also a tendency for old symptoms to recur during subsequent attacks. In primary progressive disease there is a gradual progression with accumulation of neurological deficits from the ongoing demyelination process.

1.10

Disability measures

Until the 1950's assessment of the level of disability in MS patients was usually based either on the person's capacity to work or on their mobility. Basing an assessment of disability on the person's ability to work is unreliable as it is dependent on the person's type of job, their other support systems, their financial need and their desire to work regardless of their health. As such the degree of mobility emerged as the basis on which disability scales were developed. The limitations of these scales is that MS does not purely affect people's mobility and as such the scales do not measure limitations in their upper limb function, vision, cognition, bladder and bowel function, fatigue or changes in affect. Another consideration when assigning disability scores is that co-morbidities and changes associated with normal ageing can also impact on the person's disability level⁸².

1.10.1

Disability Status Score (DSS)

The Disability Status Score, a reasonably simple to administer instrument, was developed by John Kurtzke in 1961 as a means to summarise all the neurological deficits found in the disease in a way that reflected all levels of disability. Patients were given a score between 0 (no disability) and 10 (death due to MS). The main disadvantage in using this system is that it is weighted towards ambulation, combines impairment and disability and has been shown to have only moderate inter-rater reliability^{11,83-85}.

1.10.2

Expanded Disability Status Score (EDSS)

Kurtzke subsequently modified the DSS, developing the Expanded Disability Status Score (EDSS) in 1983. This scoring scale is ordinal and categorical but not quantitative or continuous. It ranges in steps of 0.5 from a score of 0 - normal function, to 10 – death due to MS. Difficulties with using this instrument include its emphasis on the patient's ability to walk, and the lack of sensitivity to upper limb and cognitive changes. The design of the scale is not sensitive to the range of clinical changes MS patients' experience, resulting in patients scored on the EDSS displaying a bimodal progression with peaks at scores 1-2 and 6-7 with patients spending longer periods at different points on the scale than others. Consequently disease progression cannot be predicted or considered as equivalent, and as such this disability measure is unable to be used as a means for assessing the length of time of disease to reach a selected level of disability. However despite these criticisms the EDSS is still widely used as measure of disability in clinical settings, research and clinical trials which allows comparability of results^{10,82,86}.

1.10.3

EDMUS Grading Scale (EGS)

The EDMUS Grading Scale (EGS) is an adaptation of the DSS which has been validated against the EDSS⁸⁷. It is a quick and suitable instrument to use in a variety of research settings including epidemiology studies, and retrospective case note reviews, as well as in clinical practice. As it is based on the EDSS it has similar disadvantages in that it is weighted towards the ambulatory disability levels. However, with simplified, concise wording it is able to be implemented more uniformly⁸⁷.

1.10.4

Multiple Sclerosis Severity Score (MSSS)

The Multiple Sclerosis Severity Score was developed in response to a need for a validated instrument to assess the rate of disability accumulation in the individual patient. This method uses a simple arithmetical formula to correct EDSS for duration of disease to enable comparison of the individual's disability level with the distribution of scores of other cases with equivalent disease duration⁸⁸. This method provides a score for the severity of disease in the individual at that time however individual scores on the MSSS may alter over time and as such caution is needed in using the MSSS to predict the future severity of disease for individual patients.

1.10.5

Multiple Sclerosis Functional Composite Measure (MSFC)

The National MS Society of USA led an international initiative to develop the Multiple Sclerosis Functional Composite measure⁸⁹⁻⁹¹. It is a quantitative test of neurological function. This disability measure uses timed tests of walking, arm control with a hole peg test, and cognitive ability to produce a single score along a continuous scale. The advantages of this instrument are that as well as impaired ambulatory function, it captures impaired hand/arm function and cognitive function, all significant features of MS. For analytic purposes it produces a continuous scale and review has shown it has good inter and intra-rater reliability⁹⁰. However some studies have found significant practice effects with repeated exposure, in particular to the Paced Auditory Serial Addition Test (PASAT) component of the instrument. It has been suggested that patients be trained to use this instrument prior to baseline testing to overcome this issue, although this limits its ease of application in the clinical setting⁸⁶.

1.10.6

SCRIPPS Neurological Rating Scale (SCRIPPS NRS)

The Scripps Neurological rating scale is a simple to administer instrument used to assess neurological impairment scored from standardised neurological assessments. It assesses all aspects of neurological function including bowel and bladder. The scoring ranges from a value of 100 being normal and decreasing with increased disability load offering a greater range of scores than the EDSS⁸⁶. The negative aspect of this scale is

that its validity and reliability have not been adequately established as it lacks precise guidelines relating to its administration. It also lacks sensitivity to changes in cognitive function and mood as well as ambulation and as such it is rarely used⁸².

1.10.7

Fatigue Severity Scale (FSS)

The Fatigue Severity Scale (FSS) is an instrument for measuring fatigue in a variety of illnesses. It is designed to differentiate fatigue from clinical depression. The instrument is a subjective measure of fatigue using a nine item self-response, Likert scale questionnaire. Although the results of this measure are clinically relevant and have been shown to be reliable, they provide a subjective measure of the patient's perspective on their illness, rather than an objective clinical assessment⁹².

1.10.8

Multiple Sclerosis Quality of Life (MSQOL-54)

The Multiple Sclerosis Quality of Life – 54 is a derivative of the Short Form-36 (SF-36) with additional disease specific items included. As the SF36 is a widely used, well validated instrument it underpins the construct validity of the MSQOL due to it being a large component of the MS scale. Another advantage of it being based on the SF36 is that it enables comparison of MS with other diseases. A potential disadvantage of this tool is that it is self-administered which may mean that the more disabled person with MS will require assistance in completing the questionnaire. It must also be noted that it is a measure of quality of life rather than a measure of disability, although both are inter-related^{82,93}.

1.10.9

Disability measures conclusion

Despite the number and variety of disability assessment measures available, no single measure has been identified as the ideal measure of disability in MS patients. The variability in the course and consequence of the disease for the individual patient and between patients limits the effectiveness of many of the disability measures suggesting that it may be preferable to use a combination of assessment measures to gauge the full impact of disability due to multiple sclerosis. The EDSS (and EDMUS for phone

assessments) was selected for measuring level of disability in this study due to its extensive use in both research studies and clinical settings, and its ease of application and interpretation. Its limitations are widely recognised and acknowledged which assists the wider audience with the interpretation and applicability of the study results.

1.11

Disease progression

Prognostic prediction in an individual patient at the time of diagnosis is difficult however some clinical features at onset of the disease have been shown to influence the long term outcome for patients. A large Canadian cohort which included 1099 MS patients were followed between 1972 and 1984 with time to DSS 6 used as the primary outcome measure⁹⁴. Multivariate analysis showed that male sex, older age, and cerebellar involvement at onset or progressive onset with motor deficit as an initial symptom were significantly associated with a poorer outcome ($p < 0.005$). Further factors which correlated with a worse prognosis included a greater number of attacks in the first two years following disease onset ($p < 0.001$); shorter intervals between the first attacks ($p < 0.001$); and greater disability accumulation at two and five years following disease onset ($p < 0.001$).

Hammond et al. (2000) obtained similar results from their Australian study which compared patients with mild disability (DSS 0-3) to those with moderate disability (DSS 4-6) and those with severe disability (DSS 7-9). They identified older age at onset, cerebellar, pyramidal or multiple symptoms at onset and progressive disease as associated with a poorer prognosis⁹⁵.

The long term follow-up of natural history cohorts in Europe and Canada has provided data on the accumulation of disability in an essentially immunomodulatory untreated population of multiple sclerosis patients⁹⁶⁻⁹⁸. These studies have investigated patients' progression from the time of onset of multiple sclerosis to the assignment of disability landmarks using life table analysis techniques. In the past, the most widely used measures of progression have been the Disability Status Scale (DSS) and the Expanded Disability Status Scale (EDSS).

Disability outcome measures varied between the studies, with some studies including DSS 3 as moderate dysfunction; whilst others included DSS 4, described as relatively severe dysfunction with limited walking ability without aid or rest ≥ 500 meters but not

interfering with the patient's ability to work, for minor outcomes. DSS 6, assistance required for walking, was taken as a major outcome by all studies. For severe outcomes some studies used DSS 7, restricted to wheelchair, whilst DSS 8, restricted to bed but with effective use of arms, was used by others.

Overall the median time from onset to DSS 3 is estimated at 7.7-11 years, DSS 6 is 14-20 years, and DSS 7 29.9 years. Furthermore, at 15 years following diagnosis, about 10-15% required the use of a wheelchair, while 20-25% remained unrestricted in their ambulation (EDSS 0-2.5), demonstrating the variation of disease severity between individual patients^{53,99}.

1.12

Epidemiology

Epidemiology is the study of the distribution and determinants of disease in human populations¹⁰⁰. The distribution of many diseases is a reflection of the complex interaction of genetic and environmental factors. Morbidity studies survey populations living with the disease of interest. Investigation of the prevalence and incidence rates of the disease gathered from morbidity studies, can contribute information regarding the importance of genetic and environmental influences on the risk of developing the disease. Factors which indicate genetic influences include; a difference in morbidity rates in different ethnic groups and the extent of familial clustering. Factors which indicate environmental influences include; a change in morbidity rates over time, a difference in morbidity rates in different geographical areas, a difference in morbidity rates in groups that migrated to another location compared to the population of origin, and clustering of cases within a small geographical area. Through increased understanding of diseases and their causes it is possible to reduce the impact of disease by prevention, early detection and better treatment¹⁰¹. Epidemiology can also be used for health service evaluation to assist with planning of health services to match the needs of the community. Furthermore, findings from epidemiological studies can inform hypotheses for further research in that area¹⁰².

1.12.1

Incidence

Incidence rates refer to the number of new cases in a defined area over a set period of time. Research shows that the incidence rates of MS peak late in the third decade of life, with a range of 1-10 ten cases/100,000 people diagnosed annually in high risk areas¹⁰³. Incidence rates have mostly been derived from cross-sectional studies due to the difficulty and expense of conducting long-term follow-up of cases in prospective studies for chronic conditions such as MS. Prospective studies have the advantage of following a disease-free cohort and enumerating incident cases as they are diagnosed, giving an estimate of the incidence rate for the disease, with the main limitation being loss to follow-up of participants over time. Cross-sectional studies conducted at a specific point in time with people known to have the disease being studied, have the advantage of timeliness and cost-effectiveness. However, as they commonly rely on self-reported data there is the potential for the introduction of measurement error and recall bias regarding date of disease onset in relation to incidence.

Scandinavian countries have extensive records due to largely stable homogenous populations with high MS awareness and universal access to healthcare. Denmark has kept a disease registry for MS since 1948 enabling MS trends among the Danes to be followed over the last 60 years. Rates there and in Sweden appear to have fluctuated or remained stable during this time, however, in Norway incidence rates appear to have increased between the 1950's and the 1980's¹⁰⁴⁻¹⁰⁸.

There is further evidence that MS rates have increased during this century shown in results from the Rochester Epidemiology Project, a prospective longitudinal study of incident cases enrolled on the MS register at diagnosis conducted in Olmstead County, Minnesota. The incidence rates there in 1905-1914 were 1.2/100,000 and have increased to 6.5/100,000 in the 1975-1984 period. The accuracy of these figures is supported by evidence that 92% of cases had clinically definite MS (without use of MRI as it did not exist in the early time frame)¹⁰⁹. Other studies which have shown increased rates are considered less reliable as it is possible to attribute the change to better case ascertainment rather than a true increase in incidence rates.

A higher level of evidence in research is determined by the systematic review of the literature pertaining to a specific hypothesis. Systematic reviews use explicit methods to methodically search, synthesise and critically appraise all the research evidence in the

literature which meets the pre-determined study criteria for inclusion. In a recent systematic review of incidence studies of MS published in Medline and EMBASE between 1966 and 2007, Alonso and Hernan (2008) found the overall incidence rate for MS was 3.6 cases per 100,000 person-years (95% CI 3.0, 4.2) in women and 2.0 (95% CI 1.5, 2.4) in men; with a higher latitude associated with higher MS incidence¹¹⁰. The latitudinal gradient was however found to be attenuated after 1980 indicating an increased incidence of MS in the lower latitudes in more recent years.

1.12.2

Prevalence

Prevalence studies are descriptive cross-sectional studies which examine the prevalence of the disease and other variables of interest as they exist in a defined population at a particular point in time. Prevalence rates define the number of people with a confirmed diagnosis of a disease living in a population at risk during a set period of time. The prevalence of multiple sclerosis in populations has been widely studied throughout the world since the early 20th century with over 400 articles dealing with the prevalence of MS published since 1929¹¹¹. Comparison between these studies is limited due to the studies being carried out at different times and in different areas introducing the confounder of population variability due to differences in population size, age structure and ethnicity. As prevalence rates are influenced by incidence rates, migration and duration of disease, comparison of prevalence rates between studies must also consider differences in survival between populations. Variability in case ascertainment is affected by the availability of study resources, patient access to medical facilities, local medical expertise, number of neurologists, access to diagnostic facilities, public awareness and newer techniques and criteria for diagnosis developing over time. One further source of bias in comparing previous studies is the use of different diagnostic criteria and the application of those criteria in determining cases of definite multiple sclerosis, and those of early and benign MS^{112,113}. Despite these difficulties extensive information pertaining to the worldwide prevalence of MS has been collected and published over the past century. Of particular note is an increasing awareness of the effect of environmental factors in the development of MS; knowledge of the importance of genetic factors in the development of MS; and an observed increase in morbidity rates over time.

1.12.2.1

MS prevalence in Europe

The prevalence of MS seems to be higher in people of a northern European ancestry, with the highest prevalence in Europe found in Scotland with rates of 145-193 per 100,000. This supports the hypothesis that Scottish ancestry may reflect a greater susceptibility to multiple sclerosis^{111,112,114-116}. In the United Kingdom and the Republic of Ireland, rates are reported to range between 66-168 per 100,000¹¹⁷⁻¹²¹.

In other European countries there is wide variation in prevalence rates. The prevalence rates are calculated as:

- Denmark, 112 per 100,000¹⁰⁶
- Faroe Islands, 66 per 100,000¹⁰⁷
- Sweden, 96 per 100,000^{122,123}
- Finland, 108-202 per 100,000¹²⁴
- Norway, 75-150 per 100,000 among the Caucasian population however among northern areas populated by the native Samis, formerly known as Lapps, the rate is lower at 21-37 per 100,000^{104,105,108,125}
- Iceland (1999), 119 per 100,000⁹⁸
- Germany, 85-108 per 100,000^{111,112,126}
- Switzerland, 110 per 100,000¹²⁷
- Spain^{128,129}, France¹³⁰ and the mainland of Italy¹³¹⁻¹³⁹ have been reported to be between 50 and 100 per 100,000.

However an exception is the Italian island of Sardinia, which has reported prevalence rates of around 144 to 152 per 100,000¹⁴⁰. Pugilatti et al (2002a) suggest that this may reflect their different genetic structure compared with other Italians due to their isolation and lack of interbreeding resulting in a genetic makeup peculiar to the Sardinians¹¹². Another genetically distinct European group is the Maltese, who in contrast to their neighbours, the Sardinians, have the lowest reported prevalence in the Mediterranean areas of 4 per 100,000; however difficulties with case ascertainment cannot be excluded¹¹². Furthermore, repeated detailed cross-sectional studies of cities in Sicily, a province of Italy, indicate that although study populations were small, the increased prevalence in this location is partially due to a real increase as better diagnosis or case ascertainment was unable to fully explain the difference^{136,139}.

There is less prevalence data available for other regions of Europe, however, in Siberia, the prevalence of MS ranges from 12 to 41 per 100,000¹⁴¹, and until 1972, no MS case had been observed among native Siberian people. In Croatia the prevalence ranges from 24-142 per 100,000¹⁴², and in Belgrade, Yugoslavia in 1996 the prevalence was recorded as 41.5 per 100,000¹⁴³. The variability in MS prevalence across and within the European countries supports the argument that MS is a disease determined by both genetic and environmental factors¹⁴⁴.

1.12.2.2

MS prevalence in North and South America

In North America, the highest ever reported prevalence rate for MS was in Saskatoon, Canada at 298 per 100,000¹⁴⁵, probably reflecting an exceptionally high case ascertainment. The prevalence rates throughout the rest of Canada range from 180-240 per 100,000, with the exception of people of North American Indian and Canadian Hutterite descent who have a very low susceptibility to the disease despite living in the same environment^{112,146,147}.

Prevalence studies conducted since the 1970s in the United States show the distribution of MS ranges from 22 per 100,000 in Los Angeles in the South¹⁴⁸; to 177 per 100,000 in Olmsted County, Minnesota in the North¹⁴⁹ tending to reflect a north-south latitudinal gradient but the low level of comparability of the studies makes interpretation difficult¹¹¹.

In Latin America the data on the distribution of MS is limited; however recent studies have shown rates ranging between 5 and 30 per 100,000^{150,151}, with very low rates in people of South American Indian and African descent.

1.12.2.3

MS prevalence in Asia

In Asia MS is thought to be rare, although the number of studies conducted there are limited and there are some doubts regarding the validity of diagnosis and methodology used¹¹¹. The recorded prevalence in Bombay, India is 1 per 100,000; China 1-2 per 100,000 (1980s); and Japan 1-10 per 100,000^{111,112,152}.

1.12.2.4

MS prevalence in Africa and the Middle East

In the Middle East, MS prevalence ranges from 7-8 per 100,000 in Jordan and Saudi Arabia, to 10-24 per 100,000 in Kuwait and 29-38 per 100,000 in Israel. In South Africa, MS is more common among English speaking South Africans with 13 per 100,000, than Afrikaners with 4 per 100,000, and vary rare among black Africans^{19,111,112,153}.

1.12.2.5

MS prevalence in Australia and New Zealand

In Australia and New Zealand, a number of prevalence studies were conducted in the 1980's, reporting prevalence rates ranging from 11 per 100,000 in North Queensland, Australia to 69 per 100,000 in Otago-Southland, New Zealand¹⁵⁴⁻¹⁶². Both countries have a large latitudinal spread and these results indicated a south-north latitudinal gradient in the distribution of MS.

In Australia, McLeod et al (1994) showed a greater than six-fold increase in age-standardised MS prevalence between Brisbane, Queensland (11.8 per 100,000, latitude 19 degrees S) and Hobart, Tasmania (75.6 per 100,000, latitude 43 degrees S)¹⁵⁵. Barnett et al. (2003) in a repeat study in Newcastle, Australia, found a steady and significant rise in MS prevalence and incidence from 1961 to 1996. The authors acknowledge that there is a possibility that better case ascertainment contributed to the increase, however they concluded that the homogeneity of the studied population and the application of identical study methods on each occasion suggests a true increase in prevalence. They attributed the increase in prevalence to an increased incidence in females and increased survival rates in the MS population as a whole¹⁵⁶. More recently, Simpson et al (2011) conducted a time-trend analysis of MS epidemiology in Hobart from 1951-2009. The study revealed that MS prevalence had increased threefold and the incidence had nearly doubled. The increase in prevalence was attributed to three factors; increased survival, increased incidence and increased longevity¹⁶².

Prevalence studies were carried out in New Zealand in the early 1980s, with the inclusion criteria being only those people with confirmed MS, and excluding those with a possible or probable diagnosis. These studies showed a prevalence rate of 24 per 100,000 in the Waikato, mid North Island; 60 per 100,000 in Wellington, lower North Island; and 69 per 100,000 in Otago, lower South Island. The results from these studies also indicated

there was a latitudinal gradient; however they acknowledged that this may also be a reflection of the higher levels of Scottish ancestry of the Otago population¹⁵⁹. MS was reported to be rare among the New Zealand Maoris.

Most recently, in 2001, a prevalence study of MS was conducted in the Bay of Plenty region of the North Island of New Zealand¹⁶¹. This study included all definite cases of MS in the region finding a prevalence rate of 50 per 100,000, much higher than the 24 per 100,000 found in the Waikato, a neighbouring region, 20 years previous to this study. Possible explanations for this variation are better case ascertainment, an increase in prevalence over the twenty years, improved survival rates due to improved healthcare, and possibly better diagnostic techniques resulting in earlier diagnosis of cases. This study confirmed that MS in New Zealand Maori is very rare¹⁶¹. The prevalence data from these studies provide further evidence that both genetic and environmental differences appear to be important factors in the development of MS¹⁴⁴.

1.13.

Causative theories

The causes of MS remain unknown despite extensive research using a range of research methodologies. There is evidence implicating both environmental and genetic factors.

1.13.1

Environmental factors

Numerous studies have been conducted throughout the world to explore the relationship between environmental factors and the development of MS. Studies designed to ascertain whether a certain exposure or risk factor causes a particular outcome are analytical studies. They are undertaken to test a hypothesis, in particular whether the exposure preceded (and thereby caused) the outcome. Analytical study types include cohort studies, and case-control studies; with systematic reviews and meta-analyses of the published research on an area of interest providing a higher level of evidence.

Prospective cohort studies observe a general group of people over a period of time in order to measure the frequency of the incidence of the disease being studied. The cohort can be selected by taking a random sample from a population, selecting a geographical area, or taking a particular group of people (e.g. the US army veterans). Exposures and

other variables of interest are recorded at baseline and then at pre-determined intervals throughout the study. The subsequent risk of developing the disease according to exposure can then be measured. The prospective cohort study aims to identify associations between the suspected causal agent and the development of the disease. Some cohort studies can be conducted retrospectively, collecting information regarding events which have already occurred, however these have a greater potential to be affected by recall bias. Cohort studies can be costly, time-consuming and less effective if the exposure or disease is rare as they would require large study populations; however they are an effective way of establishing the exposure status of participants prior to any outcomes which may occur and for investigating a large number of hypotheses in one study.

Case-control studies compare the frequency of past exposure to causal agents in people who have been diagnosed with the disease of interest (cases) to those who have not (controls). Incident cases are identified and data on variables of interest is collected retrospectively for the period prior to diagnosis, controls (frequently matched by age and sex to the cases) have identical data collected for an equivalent time period to the cases. Case-control studies are suited to rare diseases as the sample is selected by having the disease (cases) or not (controls), with the statistical power of the study calculated by using the predicted number of cases, to determine the number of controls required to detect an effect of statistical significance. They are relatively timely and cost-effective, however they are limited to ascertaining the risk ratio in the exposed group rather than the absolute risk of the disease in those exposed. Equally as these studies rely on retrospective data they are subject to recall bias, a differential recall between cases and controls regarding past exposures¹⁰².

Most studies investigating causal factors related to the development of MS have been case-control studies; however a few prospective cohort studies have been conducted in the United Kingdom and the USA. More recently systematic reviews and meta-analyses of the published literature have been conducted to provide a higher level of evidence with regards potential environmental and genetic causes for MS.

1.13.1.1

Latitudinal gradient

Worldwide distribution of MS is largely based on prevalence rates from cross-sectional studies due to the scarcity of reliable incidence rate data; however data from case-control studies, cohort studies and more recently systematic reviews with meta-analyses has been published. Internationally the prevalence of MS varies considerably from a rate of around 200 per 100,000 population in the Orkney Islands of Scotland, and Saskatoon Canada to only rare cases in African blacks^{111,112}. As stated previously, Kurtzke (1993) suggested categorising the prevalence of MS into three bands based on latitude. High risk (>30 per 100,000) was found throughout northern Europe, the northern United States, Canada, southern Australia, and New Zealand; medium risk (5-30 per 100,000) was found in southern Europe, the southern United States and northern Australia; and low risk (<5 per 100,000) areas included Asia, South America, and includes the unexamined regions²².

In the USA in the 1920s it was suggested that the latitudinal gradient observed there could be attributed to the Scandinavian ancestry of the people in those regions¹⁶³⁻¹⁶⁶. The latitudinal gradient finding was supported by Kurtzke (1993) whose analysis of MS distribution in North America from an incidence series of 5305 US army veterans diagnosed with MS (cases) matched by age, military service and war survival with disease free controls ascertained that high rates of MS existed above and low rates below the 37th parallel²². Bulman and Ebers (1992) suggested this latitudinal gradient could be partly explained by the distribution of ancestral background with a high correlation ($r=0.73$, $p<0.01$) between the rank order of case-control ratios among veterans in each state and the percentage of people with a Scandinavian origin in those states¹⁶⁷.

More recently two prospective cohort studies of American women, the Nurses' Health Study (NHS and NHS II), have followed two groups of female nurses longitudinally: those born between 1920 and 1946 (NHS) and those born between 1947 and 1964 (NHS II). The NHS study incidence rate for MS showed a significant increase with latitude ($p=0.03$, trend)¹⁶⁸. The adjusted rate ratios were 3.5 (95% CI, 1.1—11.3) for the north and 2.7 (95% CI, 0.8—8.9) for the middle tiers relative to the southern tier. However, no association between latitude and MS incidence was found in the NHSII study ($p=0.89$, trend). The adjusted rate ratios were 0.8 (95% CI, 0.4—1.6) for the northern areas and 0.9 (95% CI, 0.4—1.8) for the middle areas, relative to the southern areas. Although the NHS

study confirmed the association between latitude and risk of MS in the United States, when comparing NHS to NHS II there appears to be an attenuation of the north-south gradient over time¹⁶⁸. This result may implicate genetic factors with different populations developing susceptibility to developing MS, or a change in environmental factors, such as diet and lifestyle including sun exposure, which have contributed to a change in the geographical distribution of MS.

One of the difficulties in prevalence studies is determining the extent to which a location's geographical patterns reflect genetic and environmental differences¹⁶⁹. To limit environmental confounding, the influence of genetic factors could be assessed by comparing populations with different ethnic backgrounds living within the same geographical location. However a limitation of this approach is that the lifestyle of the indigenous population may be significantly different to that of the colonising population in that locality. This would mean that not only do the two populations differ genetically, but due to their lifestyles their exposure to many environmental agents would also be different.

There has been considerable debate as to whether there is truly a latitudinal gradient associated with the distribution of MS. Review of prevalence rates in studies conducted since the 1950s shows a steady rise in the absolute number of cases identified in geographically different parts of the world. This may reflect a true increase in cases or possibly indicate improved diagnosis of MS, increased awareness of the disease, or better case ascertainment in studies¹¹².

Melcon et al (2008) studied four cities in Argentine Patagonia, an area with a latitudinal spread from 36-55 degrees South¹⁵⁰. The study used cross-sectional methods with a point prevalence day, including only cases with neurologist confirmed clinically definite MS from a wide range of community and clinical sources. It identified this region as having an estimated medium prevalence risk for MS with no evidence of a south-north latitudinal gradient.

In contrast Vukusic et al. (2007) confirmed a north-south latitudinal gradient in their recent study of French farmers. All farmers, salaried workers and their families in regional France are registered with the computerised database of the national farmer health insurance system ("Mutualité Sociale Agricole") which reimburses them partially for their general healthcare needs, but fully if they have MS (or one of 29 other listed chronic conditions)¹³⁰. All cases of MS in this study were identified from this database. The cross-sectional study found the prevalence of multiple sclerosis was significantly

higher in the north eastern regions (approximately 100 per 100,000 inhabitants) compared with the south western regions (around 50 per 100,000 inhabitants). The study sample was limited to those people living in regional areas, however the authors state that there is no evidence to indicate a different susceptibility between country and city dwellers in France.

Evidence supporting the latitudinal gradient hypothesis has also been observed in rigorous epidemiological studies utilising similar methodology in the USA, Australia and New Zealand^{156,159,164}, and more recently in two large meta-analyses of published MS prevalence and incidence studies^{144,170}. Koch-Hendriksen and Sorensen (2010), investigated incidence and prevalence rates and latitudinal gradient effect in a systematic review of 178 studies which met their criteria¹⁴⁴. Their findings indicated an increase in MS prevalence, predominantly attributable to longer survival; increased incidence of MS in many places, mostly linked to female gender; and a lack of latitudinal gradient in Europe and North America, although confirmation of its presence in Australia and New Zealand. As the data from the Australian and New Zealand studies was evaluated as having high reliability, and the ancestry of these populations being largely northern European, the only explanation for this apparent discrepancy between the southern and northern hemisphere data was that strong environmental influences were contributing to the risk of developing MS and therefore its geographical distribution.

In contrast, Simpson et al (2011) found a statistically significant association between latitude and MS globally in their meta-analysis of 321 peer-reviewed studies in 59 countries¹⁷⁰. The finding remained with adjustment for prevalence year and with age standardisation. The only areas without a latitudinal gradient were those of largely non-European descent, and Scandinavia. A possible explanation for the Scandinavian finding is the high year-round intake of vitamin D in these countries resulting in a fairly consistent distribution of MS prevalence across the Scandinavian countries, which is in contrast to other European nations whose vitamin D source is largely reliant on production through sunlight exposure (or ultraviolet radiation) to their skin, and therefore is affected by the geographical distribution of the population.

The variation in findings between the two meta-analyses can largely be attributed to differences in study design, and inclusion criteria. Although not conclusive, there is strong evidence to support a latitudinal gradient in the distribution of MS cases in both the Southern and Northern hemispheres. This finding strengthens the hypothesis that both genetic and environmental factors contribute to the development of MS.

1.13.1.2

Sunlight exposure and vitamin D

Closely linked to latitudinal location is duration and intensity of sunlight exposure. Sunlight exposure, in particular ultraviolet B radiation, which creates a series of chemical reactions in the skin resulting in the production of vitamin D, is the major source of vitamin D for most people^{171,172}. Vitamin D is necessary for bone health, parathyroid function, and modulation of the neuromuscular and immune function. In high latitude areas, vitamin D insufficiency is common, particularly by the end of the winter season.

Van der Mei et al (2001) conducted an ecological analysis in Australia, finding a strong negative correlation between ultraviolet radiation (UVR) and MS ($r=-0.91$, $p=0.01$), confirming previous findings from the USA¹⁷³. To further investigate this finding, studies have explored the relationship between the risk for MS and exposure to different levels of sunlight among people living in the same locality. Freedman et al (2000) found that after adjusting for demographic confounders, including age, sex, race and socioeconomic status, both outdoor occupation (odds ratio (OR)=0.74, 95% CI, 0.61-0.89) and living in an area of high sunlight (OR=0.53, 95% CI, 0.48-0.57) were associated with lower mortality rates for people with MS¹⁷⁴. This case-control study used data from death certificate records for three groups of people. Cases were people with a recorded mortality from MS; there were two control groups, those whose cause of mortality was recorded as non-melanoma skin cancer, and those whose mortality records excluded MS, cancer and diseases of the CNS as causes. Limitations of studies based on mortality data include the potential for death certificate information to be recorded incorrectly, and the inability to adjust for other confounders such as past environmental exposures etc; furthermore there is no means to determine if the deceased population in the study is a true reflection of those living with the disease, especially in a chronic disease such as MS which has so much variability between patients. .

More recently a Tasmanian study collected detailed information on sun exposure prior to the onset of MS in an age and sex matched case-control study. Measures of sun exposure included a questionnaire recording the average time spent in the sun on weekends and in the holidays as a child, an interview, and silicon casts of the back of the hand to assess the degree of actinic damage, a validated marker of cumulative sun exposure¹⁷⁵. All three measures of sun exposure were associated with a lower risk of MS, however for the questionnaire and interviews, differential reporting of sun exposure

between cases and controls, that is recall bias, cannot be excluded. The findings from the skin casts provide objective data, however the limitation of this technique is that reverse causality cannot be excluded, that is, to what extent the damage from sun exposure may have occurred since MS diagnosis.

Munger et al. (2006) conducted a prospective nested case-control study to determine whether serum levels of 25-hydroxyvitamin D (25(OH)D) were a predictor of MS risk¹⁷⁶. Blood serum samples of more than seven million US military personnel had been collected and stored as part of routine military protocols. Cases with a diagnosis of MS were identified from military disability databases and each was matched by age, sex, ethnicity and date of blood collection to two controls. The results determined that for every 50nmol/L increase in 25(OH)D there was 41% decrease in MS risk for white people (RR, 0.59; 95% CI, 0.36-0.97; p=0.04). However among blacks and Hispanics the associations were not significant, possibly due to the small sample size being too low to detect a difference. The results from this study suggest a protective effect of vitamin D on MS risk, however confounding from unknown factors cannot be excluded.

In a longitudinal prospective population-based cohort study Simpson et al. (2010) found that higher levels of serum 25(OH)D levels were associated with a reduced risk of relapses. The result showed a linear dose-dependent association with a 12% reduction in risk of relapse for every 10nmol/l increase in serum 25(OH)D¹⁷⁷. Participants were people who had a diagnosis of MS who were followed prospectively to examine whether relapse rates were associated with levels of serum vitamin D. The sample size of 145 participants who were followed for a mean of 2.3 years adds strength to the findings. All analyses controlled for a range of confounders collected biannually over the course of the study. A strength of this study design is the prospective data collection with repeated measures of serum vitamin D and accurate records of relapses.

Furthermore an Australian population-based case-control study found that MS cases with higher disability (EDSS>3) were more likely to have vitamin D insufficiency than age and sex matched controls, or those with low levels of disability¹⁷⁸. Although this adds support to the thesis that vitamin D levels are associated with MS, being a case-control study there is the possibility that this result may be due to unknown confounders.

Most recently, Lucas et al. (2011) examined the relationship between sun exposure, serum vitamin D levels and first demyelinating events in 4 Australian centres. The study was an incident case-control design which collected both self-reported sun exposure data and objective measures of skin actinic damage and vitamin D status over a three year

period. The results showed that higher levels of sun exposure, actinic skin damage and serum vitamin D were independently associated with a decreased risk of first demyelinating events. Furthermore the study found that when combined, differences in serum vitamin D, leisure time sun exposure and skin phenotype, contributed to latitudinal variation in the incidence of first demyelinating events¹⁷⁹. Cases were people who had a first demyelinating event, commonly a precursor to developing MS, and controls were randomly selected age, sex and region matched people from the Australian electoral roll. The strength of this study is the examination of both past sun exposure and vitamin D status prior to the onset of MS, enabling better differentiation of their etiological roles in the development of MS.

The combination of case-control studies and prospective cohort studies provide a growing body of evidence that sun exposure and serum vitamin D levels may be associated with risk of developing MS, disability accumulation and frequency of relapses. The results of these studies suggest that both increased sun exposure and supplementation with appropriate levels of vitamin D may have the potential to prevent the development of MS or slow down its progress in those already diagnosed with the disease. Future research should include a systematic review of the current evidence and formal evaluation of vitamin D supplementation in clinical trials.

1.13.1.3

Clusters

Clusters of people with MS in a particular area could also be used as evidence that an environmental factor is critical in the development of MS. Kurtzke (1993) has extensively studied the prevalence of MS in Iceland, and in the Faroes Islands, a semi-independent constituent of the Kingdom of Denmark²². He recognised that MS did not exist in native Faroes Islanders prior to 1943 after which there was an epidemic following occupation by British troops during WWII. Case ascertainment started in the 1940's and was acquired from 1900-1983 with 32 cases identified among native Faroes all presenting after 1943. Following extensive research Kurtzke speculated that these clusters were likely to be due to some infectious agent introduced to the Faroes Islands by the British troops which triggered the development of MS in genetically susceptible people, however no pathogen was able to be identified.

In Iceland, the average annual incidence rate was higher during the period 1945 to 1954 (3.2 per 100,000), compared to the period prior to and during the war (1923 to 1944, 1.6 per 100,000) or after 1954 (1955 to 1974, 1.9 per 100,000), although it has been suggested that the increases may have been due to improved recognition and diagnostic procedures rather than a true increase¹⁸⁰. The general consensus is that the study of these clusters of MS cases supports the thesis that MS is due to a combination of genetic and environmental factors.

1.13.1.4

Migrant studies

Prevalence studies have also investigated migration in relation to latitudinal location to illustrate the importance of environmental factors on disease occurrence after migration of populations¹⁶⁹. Studies have shown that migration in childhood from a high risk area to a low risk area reduces the risk of developing MS indicating an association with exposure to an environmental factor in childhood and/or early adulthood^{19,154,169,181-184}. A limitation of these descriptive migrant studies is that it is impossible to calculate whether those people would have developed MS had they stayed in the high risk area. At present there has been no conclusive evidence to show that there is a change of risk for those moving from low risk areas to a high risk area, although for subsequent generations of this group there does appear to be an increased risk similar to the levels of MS found in the general population of the high risk locality^{185,186}. The overall consensus is that migration does affect the prevalence of MS, whether people move from a high risk country to a low risk country or vice versa, once again indicating a complex interplay between environmental and genetic factors¹⁸⁷⁻¹⁸⁹.

1.13.1.5

Pathogens

Infection as a cause of multiple sclerosis was proposed in the late 19th century¹⁹⁰, and continues to be an area of interest to researchers. Suggested pathogens include measles, mumps, rubella, herpes zoster, Epstein Barr Virus (EBV), human herpes virus 6 (HHV6), canine distemper virus and many more¹⁹¹⁻¹⁹³; however, no specific organism has been directly linked to the development of MS. There have been two main schools of thought regarding infection and MS. The first is the poliomyelitis hypothesis which posits that

there is a commonly found pathogen which people in low risk areas are exposed to earlier in life than those in high risk areas. Following infection at an early age immunity is acquired, however if infection occurs in late childhood or as an adult the person's risk for developing an adverse autoimmune response related disease such as multiple sclerosis is increased, suggesting that exposure to infections at an early age might also play a protective role^{188,194}.

The second theory is the prevalence hypothesis, that is, the pathogen is commonly found in the environment of high MS risk areas and following exposure it lies dormant in the susceptible person's system presenting at a later point in time as MS^{22,188}. Recently a third hypothesis has been studied, the hygiene hypothesis. This theory is similar to the poliomyelitis hypothesis, but develops it further to include multiple pathogens with exposure in early life affording protection against MS¹⁹³. It argues that multiple sclerosis is an autoimmune response triggered in susceptible individuals in response to infections from multiple pathogens with risk increasing with older age at infection¹⁹⁶. Ascherio and Munger, (2007) suggest this hypothesis could offer a plausible explanation for many of the epidemiological characteristics of MS including the latitudinal gradient, the reduced risk of MS in those who are born in low risk areas and migrate to areas of high risk, and the increased prevalence among people of higher income and educational groups^{188,197}. They acknowledge that the limitations of this hypothesis include the unlikely possibility that multiple pathogens are equally involved in predisposing the individual to MS; and the evidence that there is an extremely low risk for MS among adults who are seronegative for Epstein-Barr virus (EBV). The hygiene hypothesis would in contrast argue that a person who has reached adulthood without exposure to the EBV is more likely to be from a higher socioeconomic group and have been raised in a more "hygienic environment" than their peers thereby avoiding childhood infection with EBV, this in turn increases their risk for infection with EBV in adulthood, and thereby their risk for developing MS¹⁸⁸.

There is however some evidence to support the hygiene theory with data showing a strong indication that EBV might be involved in the development of MS¹⁹⁸⁻²⁰⁶. Ascherio and Munch (2000), conducted a systematic review which pooled the results of eight sero-epidemiological case-control studies reporting an estimated odds ratio of 13.5 (95% CI, 6.3—31.4) for seropositivity against EBV indicating a strong association between markers of infection with EBV and the risk of developing MS¹⁹⁸. The studies in this

systematic review were eight independent studies, conducted in five different countries, reducing the risk of systematic selection bias affecting the findings.

Ascherio and Munger (2007), in a review of the published literature, analysed the relative risk for MS as a function of EBV infection in adolescence or adulthood as compared with early childhood, finding a 2-3 fold greater risk among those infected later in life despite having shared a similar childhood environment¹⁸⁸. Although this is an expansive and detailed review of the literature, details of the methodology and statistical analyses are sparse.

Although the findings presented above are based on case-control studies, the association between EBV and MS risk has been confirmed in longitudinal nested case-control studies with serum samples collected many years prior to onset of first MS symptoms^{201,204, 205}.

DeLorenze et al (2006) conducted a longitudinal nested case-control study to assess whether serum titres of anti-EBV antibodies were elevated in MS patient's blood samples collected prior to onset of first symptoms²⁰¹. Both cases (people with neurologist confirmed MS) and controls (three age and sex matched for each case) were identified from the database of a large health plan in Northern California, USA. Their blood samples had been collected and stored when they had joined the plan, and as such preceded the onset of MS. The findings indicated that elevated anti-EBV titres were significantly higher in MS cases than controls, occurred up to 20 years prior to onset of MS symptoms and remained elevated over time. The study does observe that the MS cases included in the analysis were mostly late age at MS onset (mean 46 years; range 24-69) which could introduce selection bias to the results²⁰¹. However, a longitudinal nested case-control study using similar methodology, of US Army personnel, with a much younger age of onset (mean 27 years; range 18-41) in the MS cases, attained similar findings of raised anti-EBV titres prior to the onset of MS symptoms²⁰⁴. The strength of these studies is that as the blood samples for both cases and controls had been collected years prior to the onset of MS symptoms, temporality can be established between the exposure of interest and disease onset, increasing confidence in the association found between them.

Although numerous infectious agents have been investigated for association with the development of MS, only EBV consistently presents as a strong risk factor. Despite this evidence, EBV cannot fully explain the epidemiology of MS and the role of other contributing factors must be considered.

1.13.1.6

Immunisations

Immunisations have been investigated as a possible causal factor in the development of MS. A number of large case-control studies have investigated this possibility^{188,207,208}, however only one, from the United Kingdom²⁰⁹, found any evidence to support this theory. Hernan et al. (2004) used a case-control study to specifically look at the potential link between recombinant hepatitis B vaccine and increased risk of developing multiple sclerosis. They found an increased risk OR 3.1 (95% CI, 1.5-6.3) of MS for vaccination within 3 years before the index date compared with no vaccination. There was no increased risk for developing MS with the other two vaccines they analysed; tetanus and influenza²⁰⁹. No systematic reviews or prospective studies investigating an association between immunisations and MS were identified in the literature search. At present, there is mixed evidence regarding immunisation and the risk of developing MS, as such this theory cannot be excluded.

1.13.1.7

Diet

Dietary intake in relation to MS has been explored in both ecological studies and case-control studies. Lauer (1997) reviewed descriptive cross-sectional epidemiological studies, finding a positive correlation between rates of MS and intake of total energy, total fat, animal fat, butter fat, meat fat and milk; with inverse correlations between rates of MS and intake of fish, vegetable fat, fruit and vegetables²¹⁰. Mixed results were derived from case-control studies, with most reporting no association between MS and intakes of fruit, vegetables, fat, meat and dairy products²¹¹. Higher intakes of animal fats were associated with a higher risk of developing MS in some case-controlled studies^{212,213}. However as these study designs are retrospective, they can be susceptible to confounding from unknown variables and differential recall bias, as such caution should be taken when interpreting the results²¹⁴.

The pooled results from two large prospective cohort studies (NHS and NHSII), which observed 92,422 nurses for 14 years and 95,389 nurses for four years respectively, found no evidence to suggest that higher total fat or saturated fat intake increased the risk of MS^{214,215}. Equally, this data showed no evidence that a higher intake of vegetable fat, monounsaturated fat, polyunsaturated fat, cholesterol or omega-3 fatty acids from fish,

carotenoids, vitamin C, and vitamin E decreased the risk of MS^{215,216}. Studies of the effects of dietary intake are reliant on accurate self-reporting and contain inherent difficulties as it is hard to account and control for 'hidden' ingredients in foods consumed. Studies of dietary supplements however have greater potential to indicate benefit or harm as they can be administered by specific dose and measured against a defined outcome.

Dworkin et al. (1984) performed a combined analysis of data from three randomised, double blind trials finding that linoleic acid significantly reduced the progression of disability for patients with a disability score of 0-2 at baseline and reduced the severity and duration of relapses across all baseline disability scores (measured by the EDSS)²¹⁷. Munger et al. (2004) investigated dietary vitamin D intake in relation to risk of MS in a prospective cohort study (NHS and NHS II). They found an inverse association for risk of MS for women who took > 400 IU per day when compared with women who did not take vitamin D supplements; RR 0.059 (95% CI, 0.38-0.91, p for trend 0.006), indicating a protective effect from vitamin D on risk of developing MS²¹⁸. Although these results are promising, further prospective studies including clinical trials of nutritional supplements are necessary to increase the body of evidence regarding the association between risk of developing MS, disease progression and dietary intake.

1.13.1.8

Cigarette smoking

The association between cigarette smoking and the risk of developing multiple sclerosis had been studied by several research groups with conflicting results²¹⁹⁻²²¹. More recent prospective cohort studies have found a modest increased risk of developing MS if you are a smoker, with relative risks ranging from 1.4 to 1.8 for high exposure (more than 15 cigarettes per day or more than 25 pack-years) compared to non-smokers with evidence of dose-response ($p < 0.05$, test for trend)²²¹⁻²²⁵. Although confounding cannot be excluded the consistent results across these recent studies provides a compelling argument for cigarette smoking, a modifiable risk factor, being associated with increased risk for developing MS.

1.13.1.9

Occupational and lifestyle exposures

Exposure to chemicals, radiation and trauma have been studied as risk factors for developing MS. Exposure to organic solvents, substances which have been shown to alter the immune system, change the permeability of the blood brain barrier and induce axonal swelling in the peripheral and central nervous system, may be a risk factor. Equally, organic solvents have been associated with other diseases such as peripheral neuropathy, leukaemia, Hodgkin's disease and liver damage²²⁶. Landtblom et al (1996) conducted a meta-analysis of 13 published studies identifying a relative risk point estimate range of 1.7-2.6²²⁶. The studies included in the meta-analysis were mainly case-control (9), with the remaining studies observational epidemiological studies. The limitation of the data is that it is collected retrospectively and as such may be subject to recall bias.

Riise et al. (2002) conducted a record linkage study in Norway finding a relative risk of 2.0 (0.9-4.5) for developing MS when comparing a cohort of painters (exposed to organic solvents) with construction workers and food-processing workers (unexposed cohort)²²⁷. Despite the large cohorts; painters (n=11,542), construction workers (n=36,899) and food-processing workers (n=9,314), very few people with MS who were receiving a disability pension were identified; painters (n=9), construction workers (n=12) and food-processing workers (n=6), which may limit the interpretation of the result. Equally there is the potential for selection bias as only those eligible for the disability pension were captured, which would lead to an underestimate of total MS cases.

Conversely, a similar study in Denmark showed no increased risk of MS among housepainters, carpenters/cabinet makers, and typographers/printers (exposed cohort) compared with skilled electricians, bricklayers, and butchers (unexposed cohort) standardised incidence ratio 0.9 (0.7—1.1)²²⁸. In contrast to the previous study, the cases were sourced from the Danish MS register and included all people with a definite, probable and possible diagnosis of MS regardless of level of disability. This methodology ensures a larger cohort which is likely to give more robust statistical results. The inclusion of probable and possible diagnoses could however lead to an over-estimate of the number of MS cases in this study. The results from these studies appear to indicate there may be an increased risk of multiple sclerosis for people exposed to high levels of organic solvents from an early age, however at present the evidence is inconclusive.

Exposure to ionising radiation through X-ray examination and radiological work resulting in free radical formation and oxidative damage has been investigated as a potential risk factor for MS development. Axelson et al. (2001) reviewed two case-control studies finding odds ratios of 4.4 (1.6—11.6) for radiological work and 1.8 (1.2—2.6) for X-ray examinations from the pooled results²²⁹. Once again the results indicate there may be an increased risk for developing MS with high levels of exposure to ionising radiation, however further studies, in particular with prospective cohort populations are needed to substantiate these findings.

Mercury from amalgam fillings in teeth is known to be absorbed into the body and deposited in the tissues including the central nervous system. This knowledge raised concerns regarding the potential risk for developing MS due to exposure to mercury. No association has been found between exposure to mercury from dental amalgams and risk of MS in either ecological or case-control studies^{230,231}.

Goodin et al. (1999) conducted a systematic review of the literature since 1965 pertaining to physical trauma and psychological stress acting as a trigger in the development of MS²³². They concluded that there was no evidence linking physical trauma and in particular head trauma with MS. They considered the possible link between antecedent psychological stress affecting the immune system, thereby increasing the risk for developing MS, and found that a possible association can be made but note that there are limitations on the findings due to methods used in these studies. A more recent large longitudinal study from Denmark supported an increased risk of MS following psychological stress (the death of a child); however they noted that this cohort was also at higher risk of several other illnesses including cancer²³³. These studies indicate there is possibly a link between antecedent psychological stress and the risk of developing MS, however at present the evidence is inconclusive, and additional large prospective cohort studies are warranted to explore this hypothesis further.

1.13.2

Genetics

Worldwide prevalence studies of MS have established that people of northern European decent are most at risk of developing MS^{22,144,163,197,234}. Familial clustering has been used to indicate the influence of genetic factors on the risk of MS²³⁵⁻²³⁸. Population-based twin studies show a higher concordance rate (30%) between monozygotic twins

than that of dizygotic twins whose risk is similar to that of non-twin siblings (3%)^{235,239}. Meta-analysis of recurrence risk among relatives showed that the age-adjusted risk is highest for siblings (3%), than parents (2%) and children (2%), with lower rates in second and third-degree relatives²⁴⁰. However adopted children share the same risk as the general population²⁴¹. These findings support the theory that people who develop MS have a genetic susceptibility, as second and third degree relatives are unlikely to share the same environment, whereas adopted children will, therefore the increased risk can be attributed in part to genetics rather than purely environmental exposure. Current thought is that there is a genetic predisposition to MS with more than one gene contributing to susceptibility^{241,242}.

A number of research groups are investigating whole-genome screens, searching for genetic loci associated with susceptibility to MS²⁴³⁻²⁴⁶. Currently the human leucocyte antigen (HLA) class II polymorphisms on chromosome 6p21 is the only consistently replicated genetic result in MS research^{235,246}. The region has been further refined to the DR15 subtype of DR2 and the DQ6 subtype of DQw6 which correspond to the phenotype expression of the HLA-DRB1*1501-DRB5*0101 and HLA-DQA1*0102-DQB1*0602 genotypes respectively^{235,240}. Most recently the ANZGene Consortium performed a genome-wide association study (GWAS) to identify MS susceptibility loci in a total of 3,874 cases and 5,723 controls. The results replicated several known MS associations, and identified risk-associated SNPs on chromosome 12q13-14 (rs703842, $p=5.4 \times 10^{-11}$; rs10876994, $p=2.7 \times 10^{-10}$; rs12368653, $p=1.0 \times 10^{-7}$) and upstream of CD40 on chromosome 20q13 (rs6074022, $p=1.3 \times 10^{-7}$; rs1569723, $p=2.9 \times 10^{-7}$), both of these loci have been associated with other autoimmune diseases supporting the theory that multiple sclerosis is an autoimmune disorder²⁴⁶.

1.14

Treatments

As summarised in the preceding section, multiple sclerosis is a complex disease, of which the pathogenesis is not fully understood posing difficulties in the development of treatments for the disease. Secondly, those agents that have been developed are not effective for all sub-types of the disease. Finally the definition of reliable endpoints for clinical trials has been problematic with variability between studies reducing comparability²⁴⁷. Currently a number of immunomodulating treatments which reduce

disability accumulation, slow the accumulation of new enhancing lesions, reduce relapse rates and decrease the rate of cerebral atrophy are available for patients with the relapsing remitting form of MS²⁴⁸⁻²⁵³. Jeffery (2002) reviewed a number of studies which demonstrate benefits from early initiation of treatment, suggesting that commencement as early as diagnosis of the first demyelinating event may help delay the accumulation of disability; however long-term data are not yet available²⁵⁴. These treatments target the relapsing-remitting form of MS and as yet there are no convincing studies which suggest continued disability progression in primary progressive patients can be treated²⁵⁵.

1.15

Conclusion

Evidence from epidemiological and analytical studies supports the hypothesis that multiple sclerosis is a result of both genetic make-up and exposure to environmental factors. Environmentally, there is evidence to support the hypothesis that MS is an autoimmune disorder resulting from exposure to one or more infectious agents. The strongest evidence is that age of exposure to the Epstein-Barr virus may be involved in the aetiology of MS. There is also a developing body of evidence that non-infectious agents such as cigarette smoking and exposure to UVB, diet, or exposure to chemical agents may contribute to developing MS, however the results from these studies remain inconclusive. Equally there is strong evidence that people with multiple sclerosis have a genetic predisposition to developing the disease as indicated by familial studies. These findings have led to genetic studies with several candidate genes being identified. As technology advances, complex genome wide screening of large samples will provide more information on the genetic makeup of people with MS and may indicate further environmental factors for investigation, or areas for the development of targeted disease modifying therapies.

1.16

Socioeconomic status as a predictor of health outcomes

Socioeconomic status (SES) can be described as “an individual’s relative position in the social hierarchy and can be operationalised as level of education, occupation and/or income” (Mackenbach and Kunst, 1997 pp 758). Mackenbach and Kunst (1997, pp758) have defined socioeconomic inequalities in the health-care context as being the

“differences in the occurrence of health problems between individuals of higher and lower socioeconomic status”²⁵⁶. Analysis of socioeconomic status in epidemiological studies is important due to the large social differences in morbidity and mortality between diseases and within disease type²⁵⁷. A number of international studies have found that people who are at a socioeconomic disadvantage have a greater burden of illness and higher mortality rates than their peers in higher socioeconomic groups^{256,258-263}; whereas other studies show that poor health can contribute to change in socioeconomic status, with people less likely to be employed, leading to loss of income and a decline in standard of living^{264,265}. Understanding variations in disease rates by socioeconomic status may contribute to understanding disease causation and effects, and the discovery of potential links between social status, the risk of acquiring disease, and ways of minimising the impact of the disease^{258,264}. One of the main factors that affect consistency in studies of health and socioeconomic status is choosing the best approach for measuring SES for the population and outcomes being studied^{266,267}. Socioeconomic measures have been developed throughout the world from a number of philosophical aspects. These include education, occupation, income, and access to material and social resources, and can be used as individual measures or composite tools. Selecting the most applicable socioeconomic measure is important, as after age and sex, socioeconomic factors are one of the most important determinants of health status^{268,269}.

1.16.1

Measures of socioeconomic status

Measures of socioeconomic status can be individual or composite measures. Measures at the individual level include education, income and occupation. Composite measures are developed through using various combinations of individual measures to produce an index of measurement^{266,267}.

1.16.1.1

Educational measures

Education data is usually collected through self-report of the number of years of education and/or educational milestones achieved. The advantage of using education as a measure is that it is easy, practical and convenient to measure²⁶⁷. Higher levels of education are generally predictive of better jobs, income, housing, and access to health

care²⁷⁰. Education measures are fairly stable beyond the early adult years, and are less likely to exclude members of the population, and be influenced by disease of adult onset than measures of income and occupation.

Limitations of using education as a measure of socioeconomic status include the disparities in educational exposure between cultural groups and to a lesser extent between the sexes²⁷¹. Educational achievement has also changed over time giving it different meanings across generations and between societies. One other disadvantage is that educational level is not consistently captured in administrative data and may not be routinely available for analysis^{266,272}.

1.16.1.2

Income measures

Income data is usually captured as the self-reported individual annual income. The advantage of using income as a measure of socioeconomic status is that income reflects peoples' access to goods and services that may influence their health status. These goods and services include food, housing, clothing, transport and medical care²⁶⁶. Income is also the most dynamic measure, having a cumulative effect over a lifetime, and being the one which can change most in the short term²⁷².

The limitations of using income data is that it does not measure wealth, it is age dependent, and sensitive to changes in life circumstances. In most cases income will increase throughout life until retirement, however overall it is a more unstable measure of SES than education or occupation. A further limitation of income data is that it tends to have a higher non-response rate than the other measures and it is not routinely captured in administrative data sets²⁶⁷.

1.16.1.3

Occupational measures

Occupation data offers a structural link between education and income. It is a more stable measure of socioeconomic status than income. It is also a useful measure of the environmental and working conditions, providing insight into the physical and cognitive demands of the position, and potential toxic environmental exposures²⁶⁷.

The main disadvantage of occupational data as a measure of socioeconomic status is that it can lack precision. Most occupational instruments group occupations into

occupational classes which can include a variation in education, income and prestige. The measure does not allow for racial or sex differences within the same occupation, although this issue may not be common to all societies²⁶⁶. By definition, occupational data applies to those currently in the workforce, and presents difficulties for classifying people who are retired, home carers or not in the workforce for a variety of reasons²⁷³. One further difficulty is that occupational measures were originally designed and validated on men as males were the predominant members of the workforce, now, due to the changed workforce demographics; usage of historic occupational measures is limited as extrapolation to the wider working population is no longer valid. However, as these issues with occupational measures have been identified, the measurement indices have been further refined to account for the changing occupational environment; including a wider range of occupations, female gender, and the part-time workforce²⁷⁴.

1.16.1.4

Composite measures

Composite socioeconomic measures are designed by combining data from several socioeconomic status measures, such as occupation, income, and education. These measures are designed to either measure social standing/prestige, or to measure social and material deprivation. Material deprivation is different to poverty in that poverty is the lack of financial resources to obtain goods, whereas material deprivation is not having the goods and conveniences that most people in that society would own²⁶⁶. The advantage of composite measures of socioeconomic status in research is that as the measures incorporate different aspects of socioeconomic status each aspect, a potential confounder, is adjusted for in the analysis²⁶⁷.

1.16.2

International occupational measures of socioeconomic status

Examples of non-composite indices include:

- British Registrar General's Classification²⁷⁵

This measure was developed in 1913 to assess the level of skill and standing of people in the British community. It included five social class levels; (1) Professional, (2) Intermediate, (3NM) Skilled non-manual, (3M) Skilled manual, (4) Partly skilled, (5) Unskilled. Its classification was essentially

occupational and not explicitly based on income. This measure is largely unused now as the change in occupational structure and increasing number of women in the workforce has resulted in it becoming outdated.

- Edwards-US Census Classification²⁷⁶

This occupational data measurement tool comprised thirteen levels of classification based on the distinction between manual and non-manual occupations. It is designed to reflect the occupational skill and status at each level of measurement. The main limitation of this measure is that each occupational category contains wide variation in levels of education and income.

Examples of composite indices:

- Hollingshead Index of Social Position²⁷⁷⁻²⁷⁹

This index is a prestige scale based on the combination of information on an individual's level of education and occupational rank. It is designed to produce a continuous score or alternatively can be scored categorically as social classes. Although widely used in the past, the Hollingshead Index of Social Position has not recently been updated and is now rarely used.

- Duncan Socioeconomic Index²⁸⁰⁻²⁸²

This measure produces a continuous scale based on occupational prestige rankings, classified according to income and education. The underlying philosophy was that education was a prerequisite for occupation and income was an outcome from the occupation, as such occupation acted as an indicator for both income and education²⁸². The scores range from 0-99 and are often found to have a positively skewed distribution. The main criticism of this scale is that it does not capture information beyond the individual level. Despite any shortcomings, the Duncan SEI is still in use in the USA.

As occupational rankings change over time due to new requirements and economic needs, many of the original tools are becoming out-dated, and conventional occupational class measures may underestimate the socioeconomic-health link due to their now imprecise measurement. A further limitation is that each measurement tool has been

designed for the country in which it was developed and may have limited applicability to other locations.

1.16.3

Measures of socioeconomic status in New Zealand

Socioeconomic status is frequently associated with disparities in wellbeing^{273,284}. Despite New Zealand having a publicly funded universal health system, disparities in health care accessibility and status remain. In New Zealand two main tools are used to assess socioeconomic status; the New Zealand Index of Deprivation (NZDEP)²⁸⁵ and the New Zealand Socioeconomic Index (NZSEI)^{268,274}.

1.16.3.1

NZDEP

The New Zealand Index of Deprivation (NZDEP) is an area-based classification of social deprivation. These measures have been designed to describe socioeconomic deprivation or the lack of access to material and social resources relative to the wider community or country²⁸⁶. They are useful for capturing aspects of living conditions not covered by individual measures, enabling contextual-based analyses to provide insight into how socioeconomic status influences population health²⁸⁷.

The NZDEP was originally developed from the 1996 New Zealand Census data for use in health research, resource allocation and advocacy in New Zealand²⁸⁸. It is an index of deprivation for small areas based on the aggregation of information from individuals normally resident in those small areas. The small areas are based on the smallest administrative areas used by statistics NZ (meshblocks). Very small meshblock sizes were grouped with neighbouring ones to make areas with at least 100 resident people²⁸⁵.

The NZDEP is used as a measure of small area level of need and is based on the following nine characteristics related to deprivation²⁸⁵:

- Persons aged 18-64 receiving a means tested benefit (this does not include the unemployment benefit)
- Persons aged 18-64 unemployed (this variable accounts for the unemployment benefit)
- Persons aged 18-64 without any qualifications
- Persons who are not living in their own home

- Persons aged under 65 and living in a single parent family
- Persons living in households with equivalised income (adjusted to control for household consumption) below an income threshold
- Persons having no access to a telephone
- Persons having no access to a car
- Persons living in households below equivalised bedroom-occupancy threshold

The NZDEP provides a measurement of the relative socioeconomic situation in each small meshblock area, and as such it is not synonymous with the individual's socioeconomic status²⁸⁵.

1.16.3.2

NZSEI

The New Zealand Socioeconomic Index (NZSEI) is an occupationally-based composite measure of socioeconomic status. The NZSEI was developed with the underlying premise that a person's occupation can be used to allocate them in a socioeconomic hierarchy²⁶⁸. Following that premise, it can be surmised that any differences in opportunities and lifestyles as a consequence of that position in the socioeconomic hierarchy will present in the evaluation of key health indicators. These beliefs are founded in a 'returns to human capital model' which argues that there is a fundamental relationship between cultural capital or resources (education) and access to material rewards (income) and that this occurs through the person's occupation^{268,271,283}.

The NZSEI was developed in the health research setting in New Zealand to replace the Elley-Irving scale²⁸⁹⁻²⁹¹, and was first published in 1999²⁶⁸. The NZSEI uses a combination of education and income characteristics through a mathematical algorithm to elicit a socioeconomic score for each occupational group in the scale. The data for all variables in the equation are from the NZ national census data set (originally 1991 census, more recently 1996 census).

Income is recorded in bands for the total personal annual income for the 12 months preceding the census date. For the NZSEI analysis the mid-point of each income band was used as the annual personal income for each person in that band. The top band is open-ended, as such; data from the Household Economic Survey which records exact

income values was used to determine a mid-point. As there was a skewed distribution of income scores logs were taken and these values used in the algorithm²⁶⁸.

Education was recorded in the census as highest qualification achieved. For the analysis, the qualification was converted into a numeric years of education with 10 years being no qualification, and 19 being a postgraduate qualification²⁶⁸.

The occupational groups are defined from the New Zealand Standard Classifications of Occupations (NZSCO)^{292,293}. Occupational data from the NZ national census for those currently in the workforce was coded into the NZSCO group scores which are based on the International Standard Classification of Occupations (ISCO). The NZSCO contains 10 major groups, which are then subdivided into 24 sub-major groups, 97 minor groups, 260 unit groups and 563 groups of occupations. Each of these five groups has a code with between one and five digits respectively according to the order listed above for the individual occupations included within that group. The NZSEI used the NZSCO at the 97 minor group level, which has occupations aggregated at the 3 digit coding, as the range of occupations is large enough to be useful for social research, but also has sufficient numbers within each occupational group to give stable estimates²⁶⁸.

Rather than applying subjective values of prestige to determine socioeconomic ranking, the NZSEI scale is constructed as a weighted sum of the average education and average income of defined occupational groups which is corrected for the influence of age. An algorithm which uses a series of regression equations based on this relationship and applied to census data was used to derive a socioeconomic score for the 97 standard occupational groups. These socioeconomic scores are then scaled from 10 (the lowest) to 90 (the highest) ends of socioeconomic hierarchy, this was done for consistency with the International Socioeconomic Index (ISEI)²⁶⁸. The NZSEI can be used as a continuous variable or for the development of discrete occupational classes²⁶⁸. The NZSEI was initially divided into six groups for NZSEI construct validation, and for use in research that preferred discrete classes for analysis. A combination of cluster and discriminant function analyses were used to determine the split points for the groups. Cluster analysis, through a series of mathematical iterations produced six discrete groups into which the NZSEI scores could be divided. Discriminant analysis was then used to refine the groupings to incorporate natural breaks in the NZSEI²⁷⁴. Further categorical divisions of the NZSEI calculated by the author include quintiles and quartiles for use in research depending on the available data and research project²⁹⁴.

As discussed in Section 1.16.1.3, occupational data is traditionally limited to those most commonly in fulltime work thereby presenting difficulties for classifying people who are retired, home carers or not in the workforce for a variety of reasons. In response to this dilemma, the NZSEI was revised in 1996, with this version including an extension to part-time workers, and an adjustment for underestimate of income for self-employed workers^{274,294}. This version has also developed a scale to account for those not currently employed, however it recommends that an alternative method could be to collect information on previous occupation as this data is more reliable. An imputation method is also suggested as an option, using data on respondent age and educational qualifications if they are available, however it is recommended that this method is used with caution as age and education are only approximations. Since 1996 this tool has been validated and extensively used for epidemiological research in New Zealand^{273,274,284,295,296}.

Construct validity of the NZSEI was determined by testing it against the previously used E-I scale for three key health variables known to be associated with socioeconomic status; smoking, poor self-assessed health, and general practitioner visits in the last year. The data for this analysis was collected over 12 months in the 1992-1993 Household Health Survey (HHS)²⁶⁸. The analyses confirmed the reported SES gradient, of higher levels of smoking and poor self-assessed health, from the lower SES groups to the higher SES groups, with a less obvious pattern for GP visits across the SES groups; and were comparable with the results from the E-I scale.

The NZSEI has been used to assess associations between socioeconomic status and health in several studies in NZ. Metcalf et al. (2007) found a trend towards higher cardiovascular disease risk factors in the lower socioeconomic groups as measured by income, education and NZSEI, although the strongest associations were by income and education²⁸⁴. The study was a cross-sectional health screening survey of 4108 men and 1569 women from the Auckland region, aged 40-78, years who were working. The income measure was based on self-reported combined household income. Variables collected included blood and urine samples, clinical measurements of cardiovascular status, and self-report responses to a questionnaire. A separate model, with all health variables collected, was analysed for each measure of SES and then adjusted for the effects of the other measures of SES. As this study was based on a working population, the results may not reflect the effect of SES on health of those not working or unable to work. Equally the findings are limited by the age group and region surveyed, as they may

not be representative of the general population. The study does however verify the association between lower SES and a higher level of cardiovascular risk factors²⁸⁴.

Using the same study population, the study group assessed the association between nutritional intake and measures of SES; income, education and NZSEI²⁹⁶. The findings indicated that compared with the higher socioeconomic groups, those in the lower groups had high total energy intakes, including carbohydrate, sucrose, fats and cholesterol, and lower intakes of fibre and alcohol. The findings were fairly consistent across all socioeconomic status measures. Once again the generalisability of the findings of this study was limited by the study population and locality factors described above. Secondly, the cross-sectional design provides a descriptive analysis of the data as captured in that population at that time, however causality cannot be determined as the data is captured retrospectively with no temporal sequence to exposures and outcomes. That is, it is not possible to determine if low socioeconomic status determined the health outcomes or the health status determined the socioeconomic outcomes. It is merely possible to state that there is an association between the socioeconomic status and nutrition; and socioeconomic status and cardiovascular disease risk factors for that population at that time. These studies verify that the NZSEI is a useful measure for assessing the association between SES and health outcomes in New Zealand. The NZSEI is best suited for use where the research question is investigating a direct relationship between health outcomes and personal characteristics, and to provide insight into the complexities of lifestyle health patterns rather than the impact of gross material deprivation.

1.17

Socioeconomic status and multiple sclerosis

The majority of people with multiple sclerosis are diagnosed in early adulthood however they experience a long sequela, with chronic progressive deterioration in most cases, and survival following diagnosis of a median of 35-42 years³. The disease process results in increasing levels of disability, reducing the individual's potential to work fully, and in time, their ability to perform their personal activities of daily living²⁶⁴.

Burden of illness studies have found that indirect costs, in particular lost time and productivity due to absence from work or unemployment, are the most important cost drivers for people with MS²⁹⁷⁻³⁰¹. As these patients are affected in their most productive years the resulting impact on their health, employment and social status means that there

is likely to be a large socioeconomic cost to the individual, families, and those countries with a high prevalence of multiple sclerosis³⁰²⁻³⁰⁵.

There have been few studies internationally investigating the association between socioeconomic variables and multiple sclerosis and none has been previously published from New Zealand. Previous studies report lower response rates of 48-67%^{264,306,307} and in many cases have included people with probable and possible diagnoses as well as those with definite MS^{302,308}. This study is the most comprehensive study so far reported in that case ascertainment was estimated as including over 96% of people in New Zealand, all with a confirmed diagnosis of MS, a total of 2917 individuals for whom the net survey response rate was 71%, 2073 people (refer Chapter 2).

1.17.1

Socioeconomic groups

A greater prevalence of MS in higher socioeconomic groups has been found in the United Kingdom^{264,309-312}, Canada^{313,314}, and the USA³¹⁵, however there have been variable results elsewhere^{316,317}. In Australia, Hammond et al.^{154,308} confirmed a finding of higher MS prevalence in higher socioeconomic groups, as determined by level of education; a result unlikely to be affected by selection bias as it is based on a point-prevalence survey of the whole population with a high level of case ascertainment. One reason for the contradiction in results between studies may be due to a difference in the methods used to determine socioeconomic status. Most studies have used an individual approach with one or more of the following criteria used singularly or in combination to determine socioeconomic status: occupational group, level of education, income, standard of living and self-evaluation. The limitation of this range of approaches is the lack of comparability between studies in determining the socioeconomic status of people with MS.

1.17.2

Education

Hammond et al (1996), in a cross-sectional study which covered five states in Australia, found that there was a significantly higher frequency of MS in those who left school at an older age and achieved a higher educational level for both men and women ($p < 0.001$)³⁰⁸. The study included all patients with a diagnosis of definite, probable and

possible MS aged over 20 years, and reported a high level of case ascertainment. Using educational level as a measure of SES is unlikely to be influenced by MS as most people will have completed their education prior to its onset, equally recall bias should be minimal as most people have a good recollection of when they left school or what qualification they achieved. Similarly, Visscher et al. (1981) in a population-based cross-sectional survey of two counties in the USA found people with MS had higher education levels than the general population in California³¹¹. However, Lauer (1994) found no significant association between level of education and risk of MS³¹⁵. There is a possibility that temporal factors may have influenced this finding as Lauer's data was based on socio-geographic factors taken from published sources, mainly from the 1950's. The participants in these studies were white male veterans from World War II, a period in history which could potentially have limited the opportunities available for war veterans to attain a college or post high school qualification in comparison to those who had not enlisted, thereby influencing the findings from the analysis³¹⁵. As educational expectations have changed over time in society, comparison of results from historic data with current studies should be made with caution.

1.17.3

Marital status

Hammond et al (1996) found an association between moderate to severe disability and divorce/separation³⁰⁸. Men in the severe disability group (DSS7-9) were four times more likely to be divorced or separated than men in the low disability group, and women twice as likely. In contrast, Hakim et al (2000), in a population-based survey of MS patients in one county in England, found no change in marital status rates among people with MS. This study was a self-report survey, with a good response rate of 74%, giving a study population of 304 participants³¹⁸. Green et al. (2007), in a comparative study between households with a member who had a diagnosis of MS, and households without a member with MS in the UK, found no significant difference in marital status between people with MS and the general population after controlling for socio-demographic variables³¹⁹. This study selected a random sample of people with MS from the UK MS Society and people who access the MS Society website and matched them using propensity scoring with a sample of people from the British General Household Survey. All three studies were based on self-report data collected in cross-sectional surveys,

limiting the interpretation of the results to providing descriptive data on the association between MS and marital status. The limited literature on this aspect of the disease, and the lack of case-control or prospective cohort studies provides inconclusive evidence of the association between MS and marital status.

1.18

Employment and multiple sclerosis

Previous large studies investigating employment and MS include: Hammond et al. (1996), with 2099 people with MS from five states in Australia³⁰⁸; Jacobs et al. (1999), from the New York State Multiple Sclerosis Consortium with a sample size of 3019 cases³²⁰; Julian et al. (2008) with 8867 participants from the North American Research Committee on Multiple Sclerosis (NARCOMS) MS Patient Registry³²¹; and Lauer (1994) who analysed previously reported data from the United States war veterans study which included 5305 veterans with MS³¹⁵. All other published studies had sample sizes between 14 and 987 people with MS.

Hammond et al (1996) report a high level of case ascertainment in a cross-sectional survey, however it must be noted that their sample included people with probable and possible MS as well as those with definite MS³⁰⁸. The United States war veterans study is limited to historic data from the 1950's, for white males with MS from the USA who had served in the second world war³¹⁶, and Jacobs et al's sample of people with clinically definite MS who consent to be included in the New York State Multiple Sclerosis Consortium (NYSMSC) registry, was drawn from the New York State, which may limit the profile of people with MS to the region represented in that study³²⁰. The North American Research Committee on Multiple Sclerosis (NARCOMS) registry is a patient driven database which collects self-reported data from participants twice a year by either mailed or internet based survey forms. Only patients with a confirmed diagnosis of MS are invited to join the registry. Patient driven databases may limit the scope of the population to those who are motivated and sufficiently physically and mentally able to participate in the research, introducing selection and recall bias to the study³²¹.

Studies show that most people with MS (90-98%) have employment histories³²²⁻³²⁶. However, unemployment rates among people with MS are reported as high as 70-80%^{307,308,324} with loss of employment evident from early in the disease course^{264,322,327,328}. Loss of employment due to multiple sclerosis is reported to have a

substantial impact on daily routine, social contact, sense of achievement and overall life satisfaction^{264,329,330}. Studies consistently report that the work status change experienced by people with MS was a direct consequence of the disease process^{264,307,324}. Despite the size and scope of these studies, all data is collected retrospectively in the form of cross-sectional surveys providing descriptive information regarding the association between MS and employment, however no causal inference can be made due to the lack of temporality. No case-control, prospective cohort studies or systematic reviews of the published literature were identified.

1.18.1

Employment and disease process

Studies investigating employment and disease phenotype have shown that people with relapsing remitting disease are more likely to continue employment than those with progressive forms of MS^{302,320,331}. People with relapsing remitting disease also tend to be younger and have less disability due to MS as they are earlier in their disease course. However, as most people with relapsing-remitting disease will later convert to the secondary-progressive form of MS, very few will have the benefit of a full employment career.

A cross-sectional study in the UK examining factors which affected the work status of people with MS found unemployment occurred within the first year following diagnosis for a proportion of patients. The authors noted that levels of unemployment increased steadily with disease duration, concluding that the main factors affecting employment status were disease-related³³². The study was conducted in two phases, the first to identify factors which impacted on work retention, and the second to measure the physical, psychological and social aspects of the factors affecting work retention. Information was collected via interview and a questionnaire. Limitations of this study include the small sample sizes, 62 for phase one and 100 for phase two; and the use of an entirely hospital based study population who had moderate levels of disability and disease duration over ten years, as such it is not a representative sample of the MS population and may overestimate the effect of disease duration on employment.

The Canadian Burden of Illness Study (1998), a cross-sectional survey of 198 patients with clinically definite MS recruited consecutively from neurologist clinics across eight Canadian provinces, found that despite 91% having been employed before MS onset, only

37% of MS patients with mild disability ($EDSS \leq 2.5$) worked full time compared with 85% of the age-matched Canadian population, and this rate decreased with disability and disease progression²⁹⁷. A limitation of this study is that it may not be representative of the MS population as it has only collected data from MS clinic attendees, it has a small sample size and the participants were recruited consecutively from the clinics which may introduce systematic bias.

Kornblith et al (1986) analysed data collected by interview in the US National Multiple Sclerosis Survey (1978-1979). Potential participants were notified from neurologists and hospitals throughout the USA, and a sample (n=949) interviewed for the study. A diagnosis of MS was accepted with patient confirmation rather than neurological or case note review. The study findings observed a marked change in employment from early in the disease course with 58.5% employed at the time of disease onset, dropping to 37.5% remaining in employment after 5 years³²⁴. Furthermore, 40% of those who had worked indicated that they had to leave their work due to MS. Once again this is a cross-sectional study providing descriptive data on the association between disease characteristics and employment

In a convenience sample of 50 participants, Smith and Arnett (2005) compared demographic data and disease characteristics of people with a confirmed diagnosis of definite or probable MS who worked full time, part time and who were not working. Their findings indicated that people with a higher EDSS score were more likely to be not working or work reduced hours³³¹. Although this is a small convenience sample, the assessment included a questionnaire, interview and clinical testing of cognitive, fatigue and depression measures giving a more detailed insight into factors affecting employment for people with MS.

The results of these studies provide some insight into the association between the disease characteristics of MS and employment for people living with the disease. It was noted that change in employment occurred early in the disease course, in patients with low levels of disability, and affected people with both the relapsing remitting and progressive forms of the disease. The early change in employment status for people with MS may reflect the unpredictable nature of the relapsing-remitting disease form limiting the individual's ability to maintain steady employment. Depending on the employer the periods of sick leave may reach unacceptable limits, or may become too disruptive to the work place, equally the time off work may cause the person with MS to lose their self confidence in their ability to do their job well. There is also evidence that cognitive

changes occur early in the disease course but may be subtle and not obvious at clinical visits. These cognitive changes may impact on the individual's ability to do their work to the required standard and as such affect their ability to retain their position. For people with the primary progressive form of MS, the progressive nature of the disease may lead to the rapid accumulation of disability and the curtailing of employment status earlier in the disease course.

1.18.2

Employment and disability

Outcome measures for evaluating which factors predict cessation of employment for people with MS have been based on their physical ability in some studies^{297,320,324}, whilst others have investigated cognitive factors^{328,330}. Measures which assess level of disability vary considerably across studies; however Kurtzke's DSS and EDSS appear to be most commonly selected as a measure of physical disability. A variety of tools have been used to assess cognitive function, with the Beck Depression Inventory (BDI) frequently used to assess for depression.

Historically, sensory and motor disturbances were considered the most likely reasons for a person with multiple sclerosis to be unable to work³²⁴. The prevalence of changes in cognitive function due to MS tended to be underestimated due to the difficulty of detecting it at brief clinical visits to the specialist. Cognitive change is often subtle, affecting just one domain of cognitive function, and can be quite variable between individuals⁸⁰. Cognitive impairment including impaired information processing speed, memory and sustained attention has been observed in 40-65% of people with MS³³³. These changes in cognitive function can affect the person's ability to accomplish their employment requirements and participate in family and social activities. In one study, it was noted that physical disability and demographic variables accounted for less than 14% of the variance in employment status, indicating that other factors such as cognitive function may have a substantial effect on ability to remain in employment³²³.

Beatty et al. (1995) tested a small cohort of MS patients (n=102) from the community setting in the USA with clinically definite MS, to assess the demographic, cognitive and clinical characteristics of those who continued to work. The study found cognitive deficits, in particular memory and information processing speed; physical disability; and age contributed towards early retirement (before 65 years) in MS patients³²⁸. Of the 37%

of patients in the study who continued to work, the majority had only mild to moderate disability scores using the Ambulatory Index (AI) which compares favourably with an EDSS disability score of <4, and negligible to mild cognitive impairment. As with the EDSS, the AI does not screen for upper limb difficulties, a factor which could affect employment for professionals, clerical and trades workers. The limitations of this study include the small sample size, low level of disability severity among the study population, and the exclusion criteria of all patients with poor visual acuity. The strength of the findings is the use of validated measures of cognitive and physical ability in conjunction with self-report demographic data.

Johnson et al. (2004) used qualitative interviews to explore reasons why people with MS ceased work or changed their work status³³⁰. They found fatigue, cognitive changes and physical difficulties were reasons stated by participants for change in employment status. Similarly, MS symptoms, in particular, fatigue, balance and walking difficulties, but not cognition were identified by Smith and Arnett (2005)³³¹ and O'Connor et al. (2005)³³². O'Connor et al's (2005) study also identified the employment environment including access to the workplace and flexibility of working environments as factors which impact on the ability of people with MS to retain employment³³².

Julian et al. (2008) used self-assessed performance scales collected in a cross-sectional survey to reflect disability in specific functional domains with mobility problems, hand function problems, fatigue and cognitive problems, as self-reported by the participants, significantly predictive of loss of employment³²¹.

Statistical analysis of work status in relation to validated measures of level of disability, physical or cognitive, has consistently shown an association between higher levels of disability and higher rates of unemployment for people with MS regardless of their gender^{297,308,328,332,334}. The majority of the data collected is however self-reported by the participants with the potential for the introduction of recall bias. A limitation of these studies is that they are cross-sectional, assessing the patient's disability status at the point in time of the study survey, but failing to establish the temporal relationship between disability accumulation and change in work status.

1.18.3

Employment and age

Loss of employment for people with MS has been shown to occur early in the disease course^{264,322,327,328}. As MS is most commonly diagnosed in young adults, loss of employment is occurring at a young age when most people are becoming established in their careers and entering their peak income earning period, resulting in a substantial socioeconomic burden for the individual, their family and society. Increasing age has consistently been shown to be correlated with increased unemployment in people with MS^{302,321,322,331}. This result is most likely to be related to the accumulation of disability over time associated with the disease process.

Only one study was found which investigated re-entry to the workforce for people with MS³²¹. This study found that over an 18 month period, 6% of the MS study population left the workforce, with only 3% re-entering the workforce. Those people leaving employment had worsening symptoms associated with the disease process, in particular fatigue, mobility and hand function, and had lower levels of education; whilst those re-entering the workforce had fewer disease-related symptoms, were younger and better educated³²¹. A limitation of this study is its reliance on self-reported data, including clinical information, however with over 8000 participants this is a substantial data set. The published research consistently indicates that people with MS have difficulty maintaining their position in the workforce with a range of clinical characteristics and demographic factors contributing. Equally there is some evidence to indicate that they have difficulty re-entering the workforce at a later time. A number of variables may be involved, general health, including extent of fatigue, may make a full time position too demanding, however part-time employment may be a feasible option. Reluctance of employers to support a person with a complex and unpredictable illness may limit employment opportunities. Inability physically or cognitively to continue with the type of work they have done in the past may require a change in occupation, which may incur costs to retrain or re-educate for the new position. Pragmatic research studies designed to intervene early, educating and supporting both people with MS and employers on the effects of the disease, may be a means to ensuring people with MS remain in the work place, or have a facilitated re-entry to the work place; even if it is with reduced hours or altered job descriptions.

1.18.4

Employment and gender

Compared with their peers, both men and women with MS are less likely to be in paid employment despite having higher levels of education^{264,320,321}. Differences in employment rates have been broken down by gender with mixed responses, some studies showing males are more likely to be unemployed^{302,321}, whilst others found the effect was greater for females^{323,324}. A further group of studies have found no difference between the sexes for employment rates^{308,331}. Rumrill et al. (2007) explored the employment discrimination experiences for people with MS finding both males and females had similar experiences³²⁶. They suggest that people with MS would benefit from assistance in the workplace specific to the individual's disease process or disability issues rather than focussing on the person's gender. The evidence from both small and large research studies is inconclusive about the effect of gender on employment for people with MS, however there are consistent research findings suggesting that as a population, people with MS have high levels of unemployment.

1.18.5

Employment and occupation

Occupational roles have different physical and cognitive requirements to sustain employment in that field. Occupational group has been shown to be associated with unemployment for people with multiple sclerosis. People employed in trades or heavy physical work, have been identified as being more likely to cease employment than those in professional or office positions^{302,308,327,334-336}. Verdier-Taillefer et al. (1995) conducted a case-control study analysing the relationship between occupational requirements and unemployment among people with MS. Cases were people with MS who had been out of the workforce for less than 5 years, whilst controls were people with MS who were still working. Occupations which had increased odds ratios ORs for unemployment were those which required physical strength (OR: 7.6; CI: 3.2-18.2), manual precision (OR: 3.1; CI: 1.6-6.3) or frequent moves (OR: 2.5; CI: 1.3-4.9), after adjusting for demographic factors and disease characteristics³³⁶. This study's strength is that it considered a range of occupational groups which could potentially affect the odds of becoming unemployed; however, a limitation is the small sample size of 171 participants (77 cases, 94 controls).

Several studies have found that people with MS who are better educated are able to retain their employment status for longer^{299,321,320,328}. In a small study (n=50), Smith and Arnett (2005) investigated the differences between people with MS who are not working due to MS, those who are working reduced hours due to MS, and those who have maintained full employment. Their findings showed that the not working group had higher levels of physical disability and fatigue than the other groups. The group that were working reduced hours were shown to have higher levels of education and greater responsibility in their occupations than those who were not working. They found that broad physical/neurological symptoms was the main reason offered for ceasing employment by the not working group, whereas fatigue was the main reason given for reducing hours in the group working part-time. Cognitive impairment was not found to be significant on either self-report or cognitive assessment data. They concluded that disease characteristics, in particular physical disability and fatigue; in combination with occupational standing and level of education are major determinants in work status change and employment retention for people with MS³³¹. Limitations of this study include the small sample size, the possibility of selection bias as this was a convenience sample, and recall bias due to the self-report, cross-sectional nature of the study design. Studies investigating occupational group in relation to MS consistently indicate that those occupations which require greater strength and physical ability are more likely to be associated with loss of employment for people with MS. This may be a reflection of disability accrual in people with MS; alternatively this group of people may be in lower paid labouring occupations that would experience less of a drop in income by going onto a disability pension than someone in a professional occupation. Furthermore, highly educated people with experience in their field may be harder to replace resulting in greater flexibility from the employer regarding hours worked or sick days taken to manage the effects of the disease.

1.18.6.

Employment and income

Low levels of employment are correlated with poor income levels. Low income is shown to be related to poorer housing, poorer diet, inferior working conditions and decreased access to health care and social opportunities^{328,337}. Few studies have investigated the income levels of people with MS, however burden of illness studies have

estimated that multiple sclerosis can cost an individual 40% of their lifetime earnings³³⁸⁻³⁴⁰. The Canadian Burden of Illness Study Group, (1998) found that from early in the disease course people with MS reported low income levels, and these declined further as the disease progressed²⁹⁷. Other studies have found that as the disease progresses, there are higher costs associated with access to medical care, modifications to homes and other disease related requirements^{306,341}. The consequence of loss of employment at an early age is lost earnings, cumulative over the working life-span; decreased quality of life; and increasing dependence on family and society for financial support.

1.18.7

Employment conclusion

Most studies investigating the employment status of people with MS are descriptive and consist of small sample sizes. However they have consistently shown that multiple factors combine to affect the person with MS's ability to maintain their employment status. Higher levels of physical disability were associated with higher levels of unemployment, and those who were employed in occupations requiring physical exertion were less likely to remain in employment than those who held a less physically demanding role. Cognitive function, fatigue and workplace issues were also cited as reasons for cessation of employment. The consequences of unplanned unemployment at such a young age are likely to be far reaching including reduced income, and diminished ability to establish a home and family, ultimately affecting their social status. The costs to society include loss of taxable income and an increase in financial support for the person with MS in the form of benefit payments. Limitations of these studies include the use of self-report data introducing recall bias, variable numbers in study groups, samples often drawn from one source such as hospital databases or MS society databases introducing selection bias, temporality and locality variation between studies, and the use of different tools or measures to assess level and type of disability. There are very few case-control studies, and no prospective cohort studies or systematic reviews of the literature on this topic were identified.

1.19

Chronic illness and disability in New Zealand

Globally the numbers of people living with chronic conditions is rising³⁴². In New Zealand, the Government discussion document *People with Chronic Conditions* (2005, p5) defines a chronic condition as “...people with any ongoing, long term or recurring condition that can have a significant impact on a person’s life”³⁴³. This document is largely focussed on those chronic conditions for which there are modifiable risk factors, stating “chronic conditions are largely preventable and share a common range of risk factors” (ibid, p6). As such, the document argues for early identification and diagnosis to enable early intervention. Unfortunately, MS is a disease which, although it corresponds with the definition of chronic conditions as per this document, currently has no known modifiable risk factors (although it has been suggested that Vitamin D supplements and/or vaccination against EBV may reduce the incidence of MS), is not preventable and is difficult to diagnose, especially in the early stages. This leaves extensive gaps between the findings and recommendations of the document and the reality for people with MS. Important and applicable points this document does present are that chronic conditions affect not only the individual but also their families and society as a whole³⁴³. Many chronic conditions have a tendency to increase in severity with age, and some are more likely to be associated with disabling outcomes affecting participation in society and levels of support required from family and society³⁴⁴. People with chronic conditions report finding it difficult to secure a job and family members who change their work status to care for someone with a chronic condition may be unable to earn the same income as when they were fully employed. This socioeconomic loss increases with importance as people with chronic conditions survive longer³⁴⁴. For the person with MS in NZ there is limited income if they are unable to work, even if eligible to receive a sickness or invalid’s benefit, making the financial situation difficult for themselves, their partner and families.

The document “*People with Chronic Conditions*” (2005) discusses other difficulties including limited access to support services, such as home support, lack of respite care, lack of skill among carers, and the lack of help /support for associated mental illness such as depression. Access to primary health practitioner visits, some medications and medical insurance was also limited due to their cost and the patient’s lack of income. The discussion document also highlights the disparity in New Zealand between those people

with a chronic condition as a result of an accident getting higher levels of support through Accident Compensation Corporation (ACC) entitlements than those who have a chronic medical condition³⁴³. Studies of spinal cord injured adults, a group of similar age of onset and disease duration to people with MS, indicate that the issues of most concern to them are their health, their independence and their satisfaction with lifestyle³⁴⁵. One of the key findings was that being employed was a positive predictor of functional independence and life satisfaction, highlighting the importance of being in work for the economic and social integration of people with a chronic condition.

At present planning for chronic condition care in New Zealand is focussed on preventable conditions such as diabetes, CHF, CVD and asthma and how best to modify the risk factors for these conditions to prevent, manage and control the effects of the illnesses. MS however is not a preventable condition as the risk factors are not known, and as such needs a modified approach to its management. Effective management of chronic conditions is multi-factorial including appropriate treatment, housing, income, transport, education and social services, with the severity of the patient's condition directing the level of support and services required at that time.

1.20

Ageing with disability

New Zealand like all other developed countries is experiencing a significant increase in the proportion of older adults in the total population^{344,346}. In New Zealand, the Positive Ageing Strategy (2001) aims to improve opportunities for older people to participate in the community in ways they choose. Current predictions are that future generations of older people are expected to be healthier, and remain more active in the workforce. The strategy argues that the choice to work later in life is important; “evidence suggests that those who work longer enjoy better health in their old age” (ibid, p10). Having a stable and secure income during retirement is considered essential for people to retain a healthy lifestyle as they age. The strategy aims to address the risk of social exclusion among older people which may have occurred due to a range of circumstances, one of which is health needs. It posits that older people should “age in place”, and have the ability to make choices about where to live and receive adequate support to do so³⁴⁶.

Disability and ageing are dynamic processes. The New Zealand Disability Strategy (2001, p7) states “One in five New Zealanders reports having a long term impairment”.

The strategy posits that people with young adult disability onset are much less likely to have educational qualifications and to be employed than non-disabled people, and the long-term nature of their impairments may limit their ability to fully participate in NZ society. The strategy argues that older people with disabilities may find their problems are seen as an inevitable part of ageing. The consequence of this assumption may be reduced opportunities for access to rehabilitation and support services which would assist them to remain independent. This could result in social isolation and insecurity if they become unable to remain in familiar surroundings and “age in place”³⁴⁷.

The New Zealand Disability Strategy (2001, p9) states that “as a group, disabled people are likely to have lower incomes and fewer financial and family resources than the general population.” The lack of financial support often leads to reduced housing options for people with disabilities, with those living in lower socioeconomic areas less likely to access and receive support services than those living in higher socioeconomic areas.

Hopman et al. (2007) found a positive association between higher education and income and health related quality of life (HRQOL); and a negative association between higher EDSS and use of support services and HRQOL, as measured by the MS Quality of Life Inventory (MSQLI), taken at baseline in a cohort of 300 people with MS being enrolled in a longitudinal study³⁴⁸. This is supported by a number of other studies which show socially disadvantaged groups tend to have poorer health status, increased exposure to health risks and less access to health services^{317,349,350}. This socioeconomic disadvantage is further compounded by the financial cost of having a disability. In New Zealand this has implications for Maori and Pacific Island people who are historically low users of social support, although it must be noted that MS prevalence is low in this population. The strategy notes that disabled women are more likely to have low incomes than disabled men or non-disabled women. This is particularly pertinent in MS as women have a higher prevalence of MS than men (2:1 to 3:1).

Aronson and McColl (1999) separate ageing and disability into four categories; normal ageing, such as sensory changes and changes to joints and soft tissues; pathological conditions which have increased incidence with age, such as stroke and heart disease; ageing and disability, such as progressive and/or chronic conditions like MS and arthritis; and ageing with life-long disabilities, such as congenital conditions and acquired disability from traumatic injuries³⁵¹. They note that most research in the area of ageing and disability is cross-sectional, whereas to fully understand the effects of ageing with a disability longitudinal research needs to be developed, following well-defined groups of

people over time to assess how both ageing and chronic disability affects them and to inform strategies to support them and maintain their quality of life.

The literature largely deals with disability acquired later in life; however Verbrugge and Yang (2002) discuss the concept of ageing with disability versus disability with ageing. This study uses cross-sectional survey data from the Disability Supplement 1994-1995 National Health Interview Survey (NHIS-D) to compare adaptation to disability in people with childhood or early onset disability (before 20 years of age), with those who have adult or mid to late-life disability onset (after 20 years), in the United States of America. The findings indicated that people in the 25-54 age group experienced the longest duration of disability, however the strongest indicator for decreased social and employment participation was poor general health as opposed to level of disability. They note that the greatest diversity of disability experience is in the middle ages, however they suggest the approach to developing policies and programmes for managing both groups should be similar as ageing and disability are inextricably linked³⁵².

MS primarily manifests in young adults between 20-40 years, however their lifespan remains similar to the general population. Klingbeil, Baer and Wilson (2004, pS68), in a review of management of people ageing with a childhood or early adult onset disability, state that “In addition to normal physiologic aging [sic], people with these conditions often experience secondary complications and accelerated impairments because of aging itself”. Muscle weakness, bladder and bowel dysfunction, and progressive neurological dysfunction are a few examples of normal physiologic ageing which can also be experienced by younger people with MS³⁵³. They acknowledge that MS is a challenging disease to manage due to its unpredictable and fluctuant nature. They recommend a multidisciplinary approach to managing the consequences of the disability with active interventions, as little can be done to reverse the loss of function, is the best approach as timely modifications to the support offered can be made in response to changing patient needs.

McColl et al. (1999) conducted a telephone survey of 286 people using set questionnaires to assess functional independence and life satisfaction of spinal cord patients whose injuries were acquired between 25 and 34 years of age, a similar diagnostic age-group to people with MS. Demographic and clinical data were collected from patient records at the rehabilitation hospital in which they had been a patient. Findings show that those with the highest levels of physical dependence following injury were unlikely to survive beyond 30 years post injury, whilst those who were independent

experience a slow progression to modified independence where they were still able to manage their own care but needed assistance with completing functional tasks. Life satisfaction was found to remain high for the first 30 years following injury, after which it was found to decline. Reasons for this change in life satisfaction include the suggestion that people with spinal cord injury may age earlier and more rapidly than the general population, and that concerns about their declining health, and ability to remain independent and out of institutional care may contribute to decreased life satisfaction. As life satisfaction and functional independence were both positively predicted by being employed and being married, the decreased life satisfaction after 30 years following injury may also be related to imminent retirement, and concerns over future end of life factors relating to their spouse³⁴⁵.

Kemp and Krause (1999) found life satisfaction for people ageing with post-polio disability and spinal cord injury was below that of their non-disabled counterparts. Between the disabled groups life satisfaction, in particular financial satisfaction, was lower for those with a spinal cord injury possibly due to the lower levels of employment in the latter group. Both groups reported poor satisfaction with health issues, anecdotally due to difficulties accessing adequate health care, in particular, primary health care. In contrast life satisfaction was positively correlated with measures of social support for both groups, indicating that appropriate support and intervention can improve the quality of life for people with chronic disability³⁵⁴.

Finlayson et al. (2004), in a cross-sectional study using interviews with a small convenience sample of people with MS, identified reduced freedom and increased need of assistance as major barriers for people ageing with MS. The reduced freedom limited their opportunities for social interaction as they had to plan their activities around their disabilities, including access to venues and facilities within those venues such as toilets. Financial limitations also contributed to their reduced freedom to engage in activities to the same extent as their non-disabled peers. Some participants reported that this lack of freedom ultimately resulted in losing contact with some friends as many social activities precluded participation for people with high levels of disability³⁵⁵.

A second major difference in ageing described by people with MS was the degree of assistance they required from family and friends as compared with their non-disabled peers. This assistance was in the form of shopping, housework, showering, dressing, getting in and out of bed and cooking. Finlayson et al. (2004) found that the majority of assistance came from family members, with less than 30 minutes per day of outside

support received by the majority of participants. Whilst the support was appreciated by the people with MS, they expressed concern over the increased demands it placed on their families, and observed that ageing appeared to be happening faster for them than their peers. A further observation made by participants was the difficulty in receiving appropriate services, with one participant stating that at 55 years of age she was too young for some resources and services, and was eligible but did not “fit” with others “The city has all kinds of old peoples’ apartments....But they cater to the elderly and the disabled. Well there are maybe two young disabled people and the whole building is filled with elderly people..... We’re going to be elderly someday too, but do I want to live with only elderly people?” (Finlayson et al. 2004, p250). This study has used a combination of quantitative and qualitative methods, and although the personal experience of individual participants cannot be extrapolated to all people with MS, the vignettes of life with MS give some insight into the reality experienced by someone living with the disease³⁵⁵.

The limitation of these studies is the lack of prospectively collected longitudinal data to show the effects of disease over time on people with MS. The difficulty with a study of this nature is the rarity of the disease. Even in countries of high prevalence, people with MS only make up less than 1% of the population requiring the recruitment of very large cohorts to capture sufficient incident cases to achieve robust research outcomes. Systematic reviews of the published cross-sectional data pertaining to ageing with MS would help inform and direct future avenues of research.

1.20.1

Ageing with disability conclusion

People with chronic disabling diseases are increasingly surviving to older ages. Medical complications related to the natural history of the disease process or disability combined with normal physiologic changes due to ageing can result in earlier and more rapid ageing for the disabled person. People with MS experience an early adult onset of disease with associated disability accumulation. Unlike people with spinal injuries, and post-polio syndrome, the disease course for people with MS is highly unpredictable and variable. As well as physical disabilities they acquire cognitive changes and may experience disabling chronic fatigue. As most people with MS experience a long sequela they are likely to age with increasing levels of disease related disability along with normal

ageing physiologic changes. Research has indicated that people with MS leave the workforce early with an associated loss of income. Invalids benefits or some form of early retirement pension is likely to be their main source of personal income, which may limit their ability to access the health care and support they need. Increased dependence on their family and social networks can potentially create tension and stress, or alternatively isolation if they are unwilling to ask for support. A multidisciplinary approach with adequate resourcing which addresses the health care needs of the individual and their families, including appropriate support systems, home modification, financial support, and improved access to public transport and buildings is suggested to maintain quality of life and enable people with disabilities to “age in place”.

1.21

New Zealand as a location to conduct epidemiological research on multiple sclerosis

New Zealand lies between 35 degrees S and 48 degrees S, a high north-south latitudinal spread. At the 2006 census, New Zealand had a population of 4,027,947 persons of whom 75% were located in urban centres of 1000 or more persons. The ethnic make-up of the NZ population is relatively homogenous, with 68% of New Zealanders identifying themselves as European. New Zealand has become increasingly recognised as an excellent location to conduct epidemiological and genetic research due to its isolated geographical position, its compact physical size, good medical infrastructure, relatively stable population, and the high cooperation of the New Zealand population. These features together with the relatively high prevalence of MS make New Zealand a suitable location in which to conduct research examining epidemiological factors associated with multiple sclerosis.

1.22

Chapter one - conclusion

Today there are over 2 million people worldwide diagnosed with multiple sclerosis. It is the most common disabling neurological disease in young adults in Europe and North America. Although there is an increased risk of developing the disease if an immediate family member has a diagnosis of MS, the disease is not considered to be hereditary. Women are two-three times more likely than men to develop the disease. Caucasians,

especially those of northern European descent, are at greater risk of developing MS than people of other ethnicities. There is a latitudinal gradient associated with MS with a greater prevalence of the disease in the temperate zones than in the tropical areas of the world. Current evidence including; multifaceted geographical patterns of MS prevalence within continents, countries and regions, trends over time, familial clustering and migration studies suggest a complex interplay between genetic and environmental factors, but the actual mechanism of disease development remains unknown. There is presently no cure, but immunomodulating agents are available that reduce the progression of the disease in people with RRMS.

Multiple sclerosis is most commonly diagnosed in young adults between 25 and 45 years of age. The disease process can follow an extremely variable clinical course, and although it frequently results in considerable disability for the individual, overall life expectancy is not dramatically altered for most people with MS. Accumulation of disability due to the disease process has been shown to affect the person with MS's ability to maintain their employment status, leading to reduced income and socioeconomic status. The following thesis investigates the effect of multiple sclerosis on the socioeconomic status of New Zealanders living with the disease.

Chapter Two

The New Zealand National Multiple Sclerosis Prevalence Study

2.1

Background

The New Zealand National Multiple Sclerosis Prevalence study (NZNMSPS) was conducted over a two year period commencing in 2006 to estimate the prevalence of multiple sclerosis in New Zealand. New Zealand presented a unique opportunity to study an entire country's multiple sclerosis population for several reasons. It has a Caucasian population of largely Northern European descent and a genetically distinct indigenous NZ Maori population. There is a marked North-South latitudinal spread and its locality in the temperate region of the South Pacific Ocean between 35⁰ and 48⁰ South places it in the higher risk zone for developing MS. Equally, a country with a population of just four million people, and a universal public health care system ensured the feasibility of studying how these factors impact on the prevalence of MS in New Zealand. This is the only prevalence study of MS to survey an entire country at one time in the world. It was based at the University of Otago, Christchurch, New Zealand, and was a Health Research Council (HRC) and New Zealand Multiple Sclerosis Society partnership-funded study.

2.2

Prevalence study hypothesis

The prevalence study was based on three hypotheses:

- The prevalence of multiple sclerosis in the New Zealand population is largely unknown; therefore a nationwide prevalence study would allow us to determine the size of the population living with MS, their distribution, and their level of disability. It would also allow us to phenotype the MS population in New Zealand and compare the characteristics of this population with other established cohorts to determine differences and similarities that may aid in the understanding of the pathogenesis of MS.
- It is generally thought, and supported by recent New Zealand research, that MS is less common in persons of New Zealand Maori ancestry than in other ethnic

groups especially persons of Northern European ancestry. The study would enable us to specifically measure prevalence rates in the different ethnic groups resident in New Zealand to confirm or refute this observation. If Maori ancestry was shown to be protective of MS this would open the way for more detailed studies of the genetic and environmental protective factors associated with Maori ancestry in the admixed New Zealand population.

- The previously observed latitudinal gradient of MS should be evident in New Zealand. Based on recent Australian data there should be a minimum of a two fold increase in the prevalence of MS between the North of the country and the South.

2.2.1

Prevalence study aims

The aims of the study were to:

- To estimate the national prevalence of MS in New Zealand.
- To document the extent of disability associated with MS in the above groups.
- To calculate the age-standardised prevalence (ASP) estimates of MS for New Zealand.
- To compare the ASP of MS with the ASP calculated from earlier prevalence estimates for equivalent regions in New Zealand.
- To compare the ASP of MS in Maori to ASP in non-Maori.
- To compare the ASP of MS in males with the ASP in females.
- To calculate the ASP of MS by region.
- To investigate whether there is a correlation between latitude and the ASP of MS in New Zealand.
- To investigate whether there is a correlation between latitude and disease severity.

2.3

Study coordinator

As study coordinator for the New Zealand National Multiple Sclerosis Prevalence Study I was employed to manage the study process, initially completing the ethics application procedure and final questionnaire design. In April 2006 the pilot study with 20 participants was conducted to assess the efficacy of the study design. Following minor modifications to the questionnaire, the full study was launched in May 2006. Data collection was completed over the following 24 months, along with data entry into a purpose-designed database by myself and two independent research assistants. I was responsible for overseeing the data entry and checking which were completed in September 2008 and data analyses were then commenced. All statistical analyses presented in Chapter 2 of this PhD were completed by the study biostatistician Dr John Pearson.

In addition to the data collected for the prevalence study the questionnaire included questions pertaining to the patients' socioeconomic status, including income, occupation, education, housing and marital status which are the foundation for this PhD thesis. Statistical analyses presented in Chapter 3, 4 and 5 were completed by myself with guidance from Dr John Pearson.

2.4

Ethics

The study received ethical approval from the New Zealand multi-region ethics committee with locality assessments being approved by each District Health Board in New Zealand prior to the commencement of data collection. This study was carried out with respect for the participants' autonomy; which includes respect for the individual, obtaining informed consent, and ensuring privacy and confidentiality, beneficence and non-maleficence; that is doing good and avoiding harm, and justice; participation in research without conflict of interest. Participation in the study was entirely voluntary and no rewards or incentives were used to coerce people into participating.

2.4.1

Informed consent and confirmation of diagnosis

Informed consent, including access to medical records, was sought when participants were invited into the study (Appendix 1). If the person could not be contacted or declined to participate the neurologist involved with that patient's care was asked to complete a de-identified neurological assessment that described the diagnosis of MS including all investigations, year of onset and diagnosis, MS phenotype, and current disability level. A neurological assessment form was completed for all unique notifications (Appendix 1).

If a notified case had not been seen within 12 months or they did not have confirmed MS they were directly reviewed by a study neurologist to confirm the diagnosis. All cases were confirmed as being resident in NZ on census day by questionnaire or by NZ health information statistics.

2.5

Study design

A prevalence study is an observational study, producing descriptive data which will depict the disease and disease-related phenomenon. It is a cross-sectional study; a study that examines the relationship between diseases and other variables of interest as they exist in a defined population at one particular time. The New Zealand National Multiple Sclerosis Prevalence Study explains the prevalence in relation to group characteristics, including age, gender, race, and geographic region, thereby describing the general distribution of multiple sclerosis in the New Zealand population.

The study used a technique called point prevalence which describes the group being studied at a certain point in time. The point prevalence for this study is the New Zealand national census day, March 7th 2006. The choice of this particular day was to enable the study to conduct a direct comparison between the general population of New Zealand as described in the census data and people living in New Zealand with a confirmed diagnosis of MS on that day.

Caution must be used when interpreting prevalence data as it can be influenced by a number of factors including incident (newly diagnosed) cases, migration, case ascertainment, response to treatment, and length of survival with MS. The cases of existing disease may not be representative of all cases of the disease, cases of long duration may be over-represented, and the characteristics of these may differ from the

characteristics of all cases being studied. However as this study is a complete population census of MS cases it should limit these effects.

2.5.1

Inclusion and exclusion criteria

Only 2 inclusion criteria were required:

- The person must have clinically definite multiple sclerosis (CDMS) as defined by the McDonald criteria 2005²⁴
- They must be resident in NZ on census day (prevalence day)

Exclusion criteria:

- Probable, possible or not MS diagnosis
- Clinically isolated syndromes
- Devic's disease (Neuromyelitis optica)
- Deceased before census day
- Not resident in NZ on census day
- Diagnosed post census day

2.5.2

Population sampling

In order to collect data which is relevant to the natural history of the disease the source population must be considered representative of the disease as a whole. This should include all examples from a geographically well defined area, in this way the sample would be population based and contain all variations of the disease. Hospital and clinic based samples are open to referral bias and a greater proportion of severe cases. Complete ascertainment is a challenge as benign cases do not always present in clinics, and they may not meet the study's diagnostic criteria. This can lead to an over-estimation of the disease severity. Accuracy of diagnosis is crucial especially as there is no diagnostic test for multiple sclerosis^{23,47,61}. Furthermore, the sample size needs to be large enough to detect statistical significance.

The sample for this cross-sectional study is the entire population of people in New Zealand with MS that meet the inclusion criteria (see 2.4.1). A specific sampling strategy

was not required as all people living in NZ with a confirmed diagnosis of MS were eligible.

2.5.3

Cross-sectional survey

The data for this study was collected by postal survey and was used to investigate how prevalent multiple sclerosis is in New Zealand. A standardised questionnaire was used for all participants to ensure the data collection method was consistent. The use of postal surveys is considered an efficient use of resources and can be easily reproduced and repeated using similar methods. The limitations of postal surveys include their reliance on the participant's willingness to contribute, and their ability to physically or cognitively complete the questionnaire as a result of their illness. A further limitation is the lack of a time dimension restricting the investigation of causal interactions; that is, whether disease and exposures are associated.

2.5.4

Questionnaire design

The questionnaire was designed by the research team which included two neurologists, a statistician, an epidemiologist, a health geographer and a health researcher (myself) who were all co-investigators in this study. The questionnaire was designed to gather the specific information the researchers required for the prevalence study. The questionnaire had two sections. The first section was designed to gather demographic and socioeconomic data. A number of the questions were identical to those from the 2006 census to enable a direct comparison between the MS and NZ populations to be made during analysis and interpretation of the data. The second section gathered information regarding where the participants had lived, and later worked, throughout their lives from conception until diagnosis with MS (Appendix 1).

The questions were mostly a closed tick box selection; however a few open-ended questions were included to allow for a more detailed explanation of a closed question response. The questionnaire was aimed at the average New Zealand literacy level and took approximately 45 minutes to complete. Postal questionnaire was chosen as it was logistically more feasible and cost-effective for a study of this size.

The questionnaire was approved by the New Zealand multi-regional ethics committee prior to pilot study testing on twenty MS patients from four referral sources. The purpose of the pilot test was to assess the complete study process including contacting participants, distribution of questionnaires, effectiveness of self-administered responses, follow-up of non-respondents, coding, data-entry and analysis. Written and verbal feedback was sought from both participants and referrers who offered suggestions for minor modifications to the wording of a few questions.

2.5.5

Data collection

The study was conducted throughout New Zealand. Data was collected via a postal questionnaire sent to all unique individuals with CDMS once they were enrolled in the study. Where necessary, relatives were utilised to complete the questionnaire where the person was incapacitated. Research staff also completed questionnaires over the phone and in person when requested by the study participants.

2.5.6

Data entry

All data was dual entered onto two identical data bases by the study coordinator and two independent research assistants and then cross referenced to identify discrepancies. All detected errors were directly corrected from the original paper copy.

2.5.7

Data analysis

Data analysis for the prevalence data in Chapter 2 was completed by the NZNMSPS statistician Dr John Pearson (JP). All models and analysis were completed using version 2.8.1 of the R language for statistical computing³⁵⁶. Confidence intervals for modelled parameters use the profile likelihood method³⁵⁷, confidence intervals for the 2 list analysis are by goodness of fit³⁵⁸. The information was collected on individuals however it has been assessed as group information with the results only available at group level.

2.5.8

Population denominators

All population denominators including age, gender and ethnicity denominators were obtained from the national census undertaken on the 7th of March 2006 downloaded from Statistics NZ Table Builder service on 22/01/2009. <http://www.stats.govt.nz>.

2.6

Prevalence of multiple sclerosis in New Zealand

The extent of multiple sclerosis in New Zealand has never been comprehensively ascertained, however rough estimates based on international and local regional prevalence studies have provided some indication of the spread of multiple sclerosis throughout New Zealand¹⁵⁷⁻¹⁶¹. The main reasons for the shortage of prevalence data in New Zealand were the absence of a national registry of MS in New Zealand; and secondly, the lack of a comprehensive study of MS in New Zealand. Furthermore, due to the privacy laws in New Zealand, it is not possible to trace people by a National ID as is possible in the Scandinavian countries, limiting access to study populations. As such we had to develop a method of coding people so that each would have a unique identifier which was able to be linked to data sources from different locations. This combined with a capture-recapture method of case ascertainment would enable us to estimate the total number of people in NZ with MS.

2.7

Capture-recapture methods

Capture-recapture methods originated in the field of ecology for estimating the size of wildlife populations. To estimate the population of a particular species, for example trout in a lake, a sample are caught, recorded, tagged and released³⁵⁹. After a specified time, a second sample of trout from the lake is caught. The tagged fish in the second sample are considered 'recaptured'. Using the sample sizes of the two catches, and the number of 'recaptured' fish, a simple formula based on the dilution of the tagged trout in the second sample provides an estimate of the total population size³⁵⁹. More recently, capture recapture analysis has become an established epidemiological method for assessing the size of populations³⁵⁹ that has been widely used in the estimation MS prevalence³⁶⁰⁻³⁶⁹

internationally. In New Zealand capture-recapture methods have been used in the estimation of disease incidence and prevalence in a variety of medical research studies³⁷⁰⁻³⁷².

With human populations, lists, each from a different source, of people with the disease in question (in this case MS) are collated and can be considered the initial 'capture'. If people from one of the lists appear on a second list, then they can be considered 'recaptured'³⁵⁹. Simple capture-recapture estimates are based on the basic assumption that each source is independent. The need to assume all sources are independent has traditionally been a limitation of this technique; however statistical methods like log-linear modelling can be used to adjust for dependencies among sources. Through recording the ascertainment of cases by source, and collecting data that demonstrates the number of cases by intersection of sources, estimates of missing cases and the total population affected are able to be calculated. The NZMSPS used multiple different referral sources enabling log-linear models to be fitted to explicitly adjust for dependencies among the sources. The NZNMPS is an attempted census of MS cases in New Zealand on the national census day, March 7 2006. In this context capture-recapture analysis allows an estimate of the number of cases missing and hence measures how well the census achieved the goal of a complete enumeration.

2.7.1

Accuracy of identification and matching

Gill et al. (2001) emphasise that accurate matching of patients identified from different lists is crucial and recommend the use of a unique identifier based on patient's first and last names, date of birth and national identification number³⁷³. Ismail et al. (2000) found that by adding the date of birth to the first and last name as matching criteria resulted in a 3% increase in the total number of individuals with diabetes identified in their study³⁷⁴. Bernillon et al. (2000) used a similar method for record linkage between two anonymous databases to provide an estimation of the under reporting of AIDS cases in France³⁷⁵. As both the databases were large and did not share common identifiers, they developed an algorithm based on date of birth, sex and disease characteristics in order to cross-match the databases.

In New Zealand there are no national identification numbers, and the privacy laws preclude access to the patient's first and surnames and National Health Index Number

without their consent, as such we devised a unique identification number (UIN) by combining the date of birth with the gender and first and last name initials for each person.

Dd	day
Mm	month
Yyyy	year
Gender	M or F
First name	X
Last Name	Y

For example Mary Smith, a female born on the 10th of July 1925 would have the UIN 10071925FMS.

In the NZ national prevalence study, each referral was received from the source in the form of a de-identified individual who had been coded in the format described above. The unique identifier had to be developed in such a way that every source of case ascertainment for each individual would match thereby confirming that individual. These techniques enabled us to cross-match referral sources and record the number of times an individual was referred to us from a different source. It also enabled the individual's privacy to be maintained as their personal details were only forwarded to us with their consent; however, we were able to locate many more individuals from the de-identified lists.

For any persons whose unique identification numbers were identical we planned to move one of their dates of birth by one day later and document this adjustment. However there were no duplicate UIN's found. UIN's were clerically matched within and between regions and cross referenced with original data. One incorrect UIN from date of birth was found and corrected.

Difficulties found with this process were different ways of writing the dates of birth (American mm/dd/yyyy as opposed to NZ dd/mm/yyyy). As this would affect a complete UIN referral list it was easy to identify and correct. Name changes were more difficult to identify. These were in three main forms; females who had married or divorced and changed their surname; people who were known by their middle name; and people known by 'pet' or abbreviated names, for example; Elizabeth could be Bet or Liz. Most people would let the study group know that they had been approached more than once, or the study would receive two questionnaires from the same person with different UINs by

initials clarifying the identity. Review of each participant's data in the data checking phase has confirmed that all discrepancies have been identified and corrected.

2.7.2

Referral sources

We used multiple referral sources including the multiple sclerosis society, hospital discharge codes, neurologists private practice, self-referrals, the New Zealand Health Information Service (NZHIS) and the Pharmaceutical Management Agency of New Zealand (PHARMAC) to attain as extensive coverage of the New Zealand multiple sclerosis population as possible. Hook and Regal (1999) recommend all sources are explicitly identified including their likely patterns and characteristics³⁷⁶. Data was collected from 6 sources which were amalgamated by 6 geographical regions. The method of capture from each source is described below and an example using the MS society process is depicted in the flow chart (Figure 2.1).

2.7.2.1

Multiple Sclerosis Society

Our initial approach was through the Multiple Sclerosis Society (MSS) regional branches as this group had direct access to the target population. The Multiple Sclerosis Societies are located throughout New Zealand and offer volunteer membership for people with MS. The MS societies provide information and support for members. We asked each society to assign a unique identifier to each member of their branch and forward the notification form to us. The unique IDs were then entered onto the database including information regarding the region from which the notification was received. The MS societies were then asked to contact each of their members by telephone, explain the study to them, and ask permission to forward their contact details to the study group who would send out a survey questionnaire to the participants. Two MS society groups, Auckland and Wellington requested that we send the questionnaires out through them with covering letters to invite people into the study as they felt they had too many members to telephone individually.

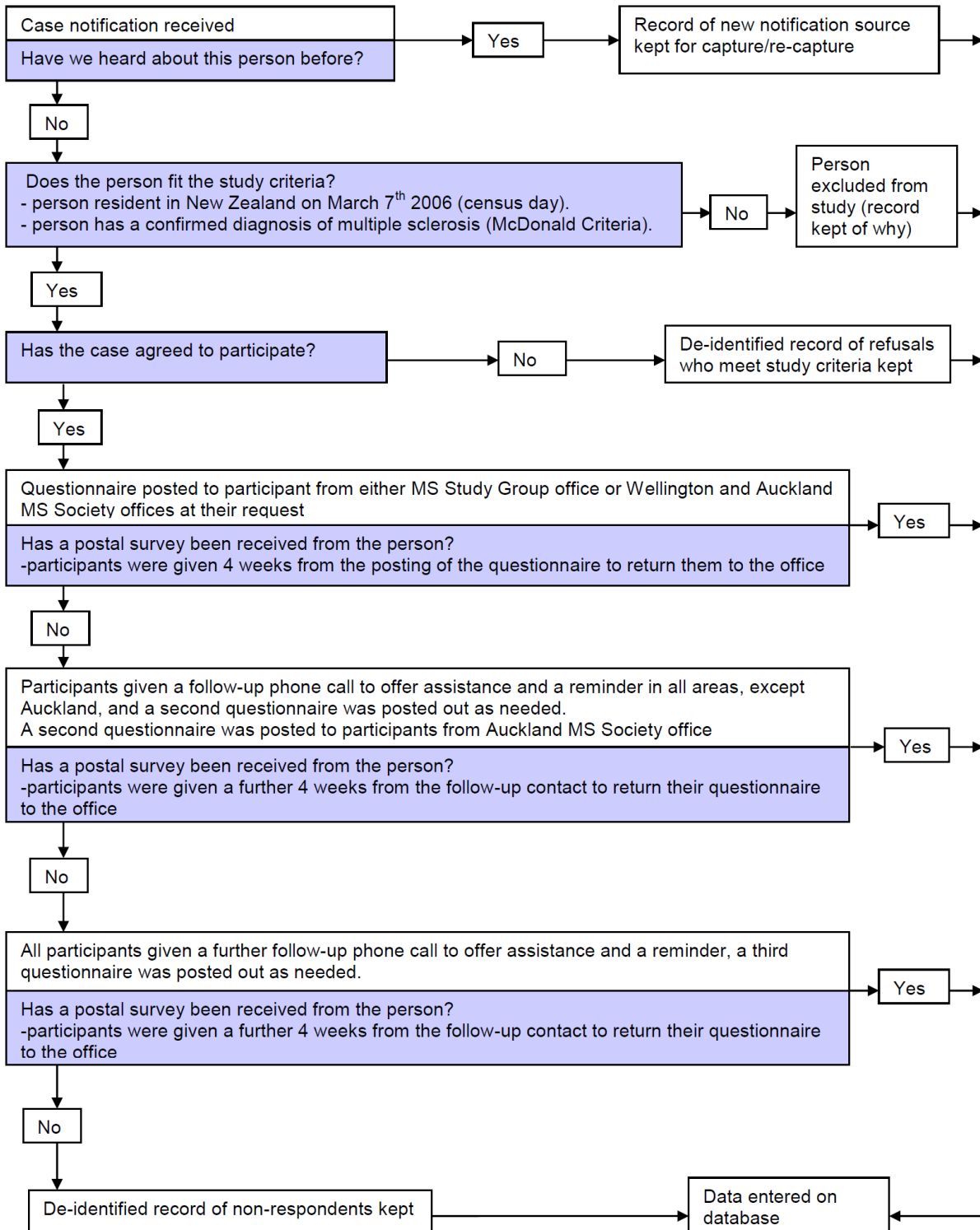


Figure 2.1 Flow chart of notification matching and data capture-recapture process

Our response rate from the initial approach was 50-60% from the groups who were telephoned and 35-45% from the postal approach. We had ethical approval to complete two follow-up contacts. The study co-ordinator then telephoned the outstanding participants from the groups for whom we had contact details and either re-sent the questionnaire or completed it over the phone with the participants. This occurred 2-4 weeks following the initial posting of the questionnaire to that society's members. The total response rate following the second approach was 60-75%. A third and final approach to any outstanding participants was made after a further 4 weeks, bringing the final response rate for these groups to 72-98%. In Auckland and Wellington we asked the MS societies to re-approach their members through telephone calls the second time. Wellington did use telephone follow-up for the 2nd and 3rd approaches. Auckland chose to do a second postal approach and the telephone contact on the 3rd and final approach. The response rate after the second approach for these groups was 50-60%, and the final response rate was 56-68%. The most complete referral source was compiled from these regional MS societies.

2.7.2.2

Regional hospitals and health professionals

Following the questionnaire mail out to the MS Society branch's members we contacted multiple sclerosis health professionals, including neurologists, hospital-based MS nurses and research nurses by region. Hospital and specialist databases used diagnostic codes to identify cases.

- Southland – There was a sole neurologist in Southland, from whom we requested a unique ID coded list from both the hospital database, and the private practice. A large number of these patients had had a diagnostic MRI in Christchurch and a unique ID list was received from the radiology group for these patients.
- Otago – There were two neurologists in Otago; we received a unique ID coded list from both the hospital database and their private practices. Dunedin Hospital also has two MS nurses who work with the neurologists and run their own clinics at the public hospital. They supplied us with unique ID coded lists for their patients.
- South Canterbury, Canterbury, West Coast, Marlborough – These regions are all covered by the Christchurch Hospital neurologists. Unique ID coded lists for the hospitals and private practice lists were supplied by all the neurologists. Being the

base of the study neurologists was an added advantage due to ease of access to the databases and patient records within ethics protocols.

- Nelson – There is one neurologist in Nelson who supplied unique ID coded lists for both the hospital and the private practice.
- Wellington – There are a number of neurologists in Wellington and a part time MS nurse at the hospital who works in conjunction with the neurologists. There are three hospitals in the Wellington region and each has a different database system. We received unique ID coded lists from the hospital databases and the neurologists' private practices; however the coverage of this region may not be as comprehensive as some other areas.
- Manawatu and Wanganui – These two regions had no resident neurologist at the time of the study commencement although one was employed in Manawatu part way through the study. The unique ID coded hospital database was sent through by a nurse who works at the hospital, but no private practice records were obtained as the previous neurologist had left and there was a significant interval prior to the current neurologist arriving in the region. MS patients in this area were also looked after by a rehabilitation physician in this region, so records for this area were somewhat disjointed.
- Hawkes Bay and Gisborne – There is a sole neurologist in the Hawkes Bay who provided us with comprehensive unique ID coded lists for both the hospitals and the private practice.
- Rotorua – MS patients in Rotorua are covered partly by Waikato Hospital neurologists and partly by the Rotorua Hospital geriatrician. The geriatrician sent us a thorough a unique ID coded list for the hospital database.
- Bay of Plenty – There is a sole neurologist at Tauranga Hospital who covers the Bay of Plenty. This neurologist had conducted a regional prevalence study for MS five years previously and was able to provide a comprehensive unique ID coded list for both the hospital and the private practice.
- Waikato – The Waikato is covered by three neurologists and has a neurology research nurse based at Waikato Hospital. The nurse provided us with a thorough unique ID coded list for the hospital database (which included Rotorua patients under their care). We received minimal private practice unique ID coded lists from the neurologists.

- Taranaki – There is no neurologist at Taranaki Base Hospital, however two of the Auckland neurologists cover this region. They provided us with comprehensive unique ID coded lists for the hospital database and their private practice records.
- Auckland – Auckland has a number of neurologists and three hospitals in the region. We received a comprehensive unique ID coded hospital database for the three Auckland hospitals. Most of the neurologists in Auckland supplied us with unique ID coded databases for their private practices, although we are uncertain as to how comprehensive these lists are.
- Northland – Northland has a sole practicing neurologist who supplied us with very thorough records. We received unique ID coded lists for both the hospital and the private practice databases.

Auckland, Christchurch, Dunedin, Bay of Plenty and Waikato Hospitals had dedicated neurology databases from which MS patients could be identified. The remaining hospitals based their database searches on discharge coding information. The notifications received from the neurologists' private practice records limits these cases to those who can afford to pay for private care. As each of these databases was received it was cross-referenced with the MS society notifications entered on the database. Any duplicate notifications were recorded and the new notifications were added to the database. The neurologists, MS nurses or research nurses were then asked to approach their patients, explain the study, obtain informed consent, and request permission for the patient's details to be released to the study group enabling us to post a questionnaire to each new patient notified to the study group. Once again we made a telephone follow-up to each non-return 2-4 weeks following the mailing of the questionnaire, and a third and final follow-up telephone call was made after a further 4 weeks.

2.7.2.3

New Zealand Health Information Service

The New Zealand Health Information Service (NZHIS) is a government organisation which keeps a national database of all discharge codes from the District Health Boards (DHB's). The study group approached the NZHIS requesting a unique ID coded list of all patients discharged from a New Zealand hospital with a coding of MS type illness in the last ten years. This list included the regions the patient had been hospitalised in and their

date of death if they were deceased. Over 4000 notifications were received from this list. The benefit of receiving this list was that it helped clarify why we had been unable to reach some patients, often they had moved to another region or were deceased but had failed to be flagged as such on the original database from which we had received their notification.

2.7.2.4

Ministry of Health

The Ministry of Health (MOH) supplied us with a unique ID coded list which was developed from a combination of hospital discharge codes, pharmacy records and other public health provider service records for MS patients in NZ. This database also included region of residence information which once again gave us an opportunity to cross-reference and clarify missing responses or duplicate referrals which had been received from different regions but were the same person.

2.7.2.5

Pharmaceutical Management Agency of New Zealand

A further independent source of referrals was PHARMAC the Pharmaceutical Management Agency of New Zealand which controls access to publicly funded disease modifying drugs (DMDs) in NZ. This is a small list as it only includes those people who have been put forward by a neurologist for approval to receive DMDs.

2.7.2.6

Other sources

A small number of cases were captured through other sources. These included General Practitioners (GP's), whose low referral rate would possibly reflect only those who have greater numbers of patients with MS or an interest in this condition or in research.

Publicity through the media and the provision of a free phone (0800) number opened up access for individuals and smaller organizations to approach us. Self-referrals from individual patients could reflect a group of people who are motivated and choose to be involved in the study. Once again this captured a small number of participants.

2.7.2.7

Referral sources summary

The median and modal number of ascertainment for those cases which were recorded is 3 (Table 2.1). There were 556 cases recorded on only 1 source, Table 2.2 shows these single referrals were less likely to be from NZHIS and PHARMAC lists (about 2% of the list totals) while making up over 12% of Specialist referrals and 13% of self referrals, a pattern not inconsistent with the nature of the sources.

Table 2.1 Ascertainment multiplicity

Number of lists recorded on	1	2	3	4	5	6
n	566	855	900	466	127	3

2.7.3

Independence

Simple capture-recapture estimates are based on the basic assumption that each source is independent. The need to assume all sources are independent has traditionally been a limitation of this technique. The NZMSPS used multiple different referral sources enabling log-linear models to be fitted to explicitly adjust for dependencies among the sources. The 6 referral lists are not all independent, in particular the NZHIS and MOH lists are mainly compiled from Hospital records. Hence we expect positive dependence between NZHIS, MOH and Hospital lists. Positive dependence between Hospital and hence NZHIS and MOH lists and the PHARMAC list is expected due to the procedure for public funding of DMDs. Negative dependence is expected between Neurologist (private health care) and public hospital lists, also between self-referrals and the other lists.

Following Hook and Regal (1999, 1984), Table 2.2 shows all lists versus others combined capture-recapture estimates of missing cases^{358,376}. These estimates do not account for variability of ascertainment probability or list dependence; nevertheless a net negative dependence will provide over estimates while positive dependence yields under estimates³⁷⁷. If, as expected, there is positive dependence between the Hospital, PHARMAC and NZHIS lists it is likely that these 2-lists underestimate the population total while the expected negative dependence between self-referrals and other lists and

between specialist and other lists would provide overestimates³⁷⁷. The 2-list estimate between MSS and other lists is close to the final estimate from the models which account for list dependence and variable ascertainment probability; this is not inconsistent with MSS being the source least dependent on the other sources which are largely derived from health care providers.

Table 2.2 Capture-recapture estimates for each list with all others combined. Confidence intervals are based on goodness of fit (Regal)

Source X	In X and others <i>a</i>	Unique to X <i>B</i>	In other sources only <i>c</i>	In X <i>a+b</i>	Estimated missing <i>d=bc/(a+1)</i>	90% confidence interval		Estimated population <i>a+b+c+d</i>
MSS	1853	236	828	2089	105.4	85.4	128.4	3022.4
NZH	1809	41	1067	1850	24.17	15.2	36.2	2941.17
Hosp	1698	130	1089	1828	83.33	65.3	104.3	3000.33
Spec	833	117	1967	950	275.95	226.9	332.9	3192.95
Pharm	551	14	2352	565	59.65	35.7	93.7	2976.65
Self	183	28	2706	211	411.78	289.8	574.8	3328.78

2.7.4

Homogeneity of ascertainment probability

Simple capture-recapture estimates assume individuals have the same chance of being recorded on a given list³⁷⁷⁻³⁷⁹. To relax this assumption covariates which account for variable ascertainment probability have been included in the models. Although those who participated in the study following ascertainment have a rich set of covariate information the only data available for complete sources is date of birth, sex and region of residence at census 2006. The final model accounts for capture probabilities dependent on region, sex and age. Figure 2.2 shows that the lists have considerable variability in ascertainment probability by region, with the Hospital and specialist lists having low capture probabilities in the central/southern North Island. The MS Societies and NZHIS show higher capture probabilities for those over 60 as expected in the literature^{264,306}. The PHARMAC and Self-referral lists have lower ascertainment probabilities for those aged over 60 years. Duration of disease (time since diagnosis) and socioeconomic status could also have an effect on probability of ascertainment however this will be partially accounted for by the old age covariate, in particular at 65 years national superannuation removes economic disparity.

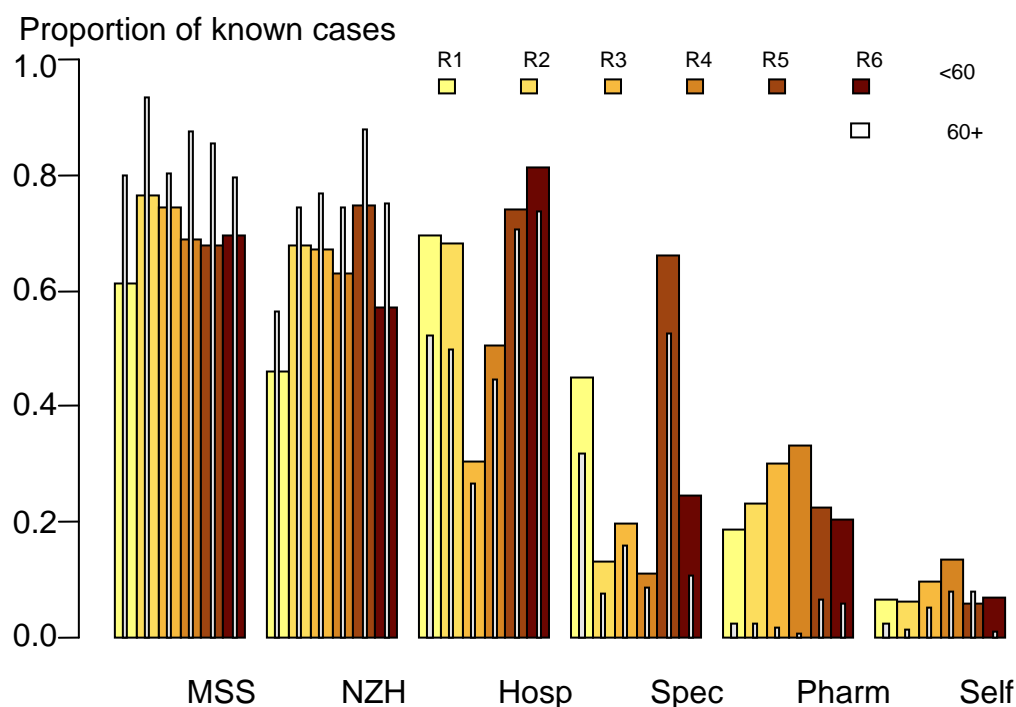


Figure 2.2 Ascertainment probability varies by region and age group

2.7.5

Population closure

Capture-recapture modelling of epidemiological surveys assumes that populations do not gain or lose members over time; that is they are closed³⁷⁸. The population closure assumption is typically violated by epidemiological studies resulting in over estimates of population size³⁷⁸, and conservative estimates of the proportion of the population they have ascertained (population coverage). The NZ population has complex migration patterns with high levels of temporary and long term migration. During 2005 there were 51,236 people (about 1.5% of the population) approved for permanent residency in New Zealand, of these 62% were through a skilled/business stream and of these the largest influx was from the UK (37%)³⁸⁰. There is also a high level of internal migration with approximately 18% of the population moving house in 2004-2006 and 15% of those moving between regions³⁸¹. Thus we expect that there is some movement to and from the NZ MS population. This movement will result in over estimates of the number of both

the population with MS and the numbers missing from the study records and an under estimate of the proportion of cases included in the study.

2.7.6

Models

Log-linear models were fitted to the national dataset and to the data stratified by region^{382,383}. To investigate the dependence between lists initial models were fitted with no interactions, all 2-way, all 3-way, all 4-way, all 5-way interactions between lists and the saturated models. For each initial model the Akaike Information Criterion (AIC) was used to select the model with the best fit as it produces less bias and more accurate estimates than competing measures of fit³⁸⁴. The AIC is a technique used to measure the goodness of fit of a statistical model. It is based on the concept of information entropy and describes the trade off between accuracy and complexity in the model construction. The AIC provides a means for model selection, which given a set of candidate models in the analysis of the data, the preferred model is the one with the minimum AIC value³⁸⁴. The estimates of the number of missing cases and population totals are based on the model including covariates for age, sex and region of residence on national census day 2006 with minimum AIC value.

All models and analysis was done using version 2.8.1 of the R language for statistical computing³⁵⁶. Confidence intervals for modelled parameters use the profile likelihood method³⁵⁷; confidence intervals for the 2 list analysis are by goodness of fit³⁵⁸. Mild over dispersion was apparent in the less well fitting models but not in the models with better fit, hence to aid comparability, no adjustment for over dispersion was made in any model. Table 2.3 shows the best fitting models for the national dataset, with and without covariates and for the regionally stratified datasets, with the statistically “best model” estimating that 91 cases (95% CI, 34 - 147) were missed bringing the MS population to 3,008 (95% CI, 2,951 - 3,064). The predicted breakdown by gender, age and region is shown in Table 2.4 indicating that the missed cases were evenly distributed by region, age group and gender.

Table 2.3 Log-linear modelling, n is the estimated number of cases missed, N is the population

Region	n	95% CI	N	AIC	Deviance	df	Zeros	list	interaction		
								terms	2way	3way	4way
National											
Saturated Model	336	(-, -)	3,253	405.9	0	0	2	15	20	15	
Best model	64	(33-117)	2,981	383.9	15.5	19	2	15	16	6	
Best model with Age Sex and Region	91	(34-147)	3,008	2669.2	857.1	1,388	1,013	14	12	4	
Regional stratification (best model)											
R1	45	(23-82)	864	273.5	49.4	38	17	12	6	0	
R2	17	(10-45)	351	192.5	52.5	48	30	8	0	0	
R3	2	(0-8)	281	204.0	3.4	23	26	15	16	2	
R4	45	(27-71)	550	235.3	31.5	43	14	10	3	2	
R5	4	(1-11)	602	231.2	21.5	37	18	14	5	2	
R6	44	(23-79)	426	203.0	24.9	39	23	12	5	6	
Total	157	(84-296)	3,074								

2.7.7

Capture-recapture results

The best fitting model estimates that 91 cases (95% CI, 34 - 147) were missed bringing the New Zealand multiple sclerosis population to 3,008 (95% CI, 2,951 - 3,064). The predicted breakdown by sex, age and region is shown in Table 2.4.

The model has all main covariates and retains the interaction between age and sex but the size of the effect is modest. The region by age and by sex interaction is dropped supporting the indication that there is minimal variation in ascertainment by sex and age across regions. There is a positive association between people of older age and ascertainment by NZHIS and MS Societies, whereas the negative interaction between old age and the other referral lists indicates that the best fitting model supports the observation that older cases are less commonly found on those lists. Males are less represented on MSS, PHARMAC and Self reports and these were the only sex by list interactions retained. The pattern of covariates and their interactions with lists in the best model was common to all the better fitting models.

Table 2.4 Missing cases by region, age and sex

Sex	Age	estimate of missing						Sum
		R1	R2	R3	R4	R5	R6	
F	(0 - 60]	16.02	5.98	3.97	12.21	4.13	11.00	53.30
M	(0 - 60]	7.00	2.61	1.73	5.33	1.80	4.80	23.28
F	(60 - 100]	3.12	1.16	0.77	2.38	0.80	2.14	10.37
M	(60 - 100]	1.14	0.42	0.28	0.87	0.29	0.78	3.78
Sum		27.27	10.17	6.75	20.78	7.02	18.72	90.72
Regional %		3.2%	3.0%	2.4%	4.0%	1.2%	4.7%	3.0%

2.7.8

Capture-recapture discussion

The distribution of missing cases in the capture-recapture analysis varied mainly by region. The model predicts the largest numbers of missing cases are for regions 1 and 4 which contain New Zealand's 2 largest urban centres, Auckland and Wellington respectively. Auckland has the highest number of cases in private care who have not accessed the public system. If these patients were omitted from their specialist's private practice referral list, there may be no alternative source from which they can be referred to the prevalence study. Equally a neurologist in Wellington recently retired and his private records were not available for the study, potentially resulting in patients solely under his care being omitted from the study. The Wellington region has 3 public hospitals each with separate databases, unlike the unified system in Auckland, this added complexity to obtaining a discharge coded list.

The predicted number of cases missing in region 6, Otago and Southland, represents 4.7% of the cases in one of the smaller regions. The greater region 6 estimate is driven by lower ascertainment by the specialists' private practice lists (Figure 2.2) which was due in part to the region being covered by only 3 neurologists. A more significant contributing factor may be that Dunedin Hospital is the only public hospital in NZ which runs nurse led MS clinics. The hospital referral list from Otago/Southland had a significantly higher case ascertainment rate, indicating that relatively more cases are dealt with in the public system in this region resulting in lower proportions of patients managed in the private sector in Otago/Southland than the national average. The lowest estimate of missing cases is in Canterbury/West Coast (Region 5) which had the most complete coverage by Neurologists (Figure 2.2), and may reflect easier access to neurologists, patients and databases as the study neurologists were based in this region.

Overall the estimates of missing cases show the study missed 3% (95% CI, 1.2% - 4.8%) of the cases of MS in New Zealand on 7th February 2006. Unaccounted for migration and any errors in assigning UIN will tend to make this an over estimate and a fuller review and analysis of migration patterns of people with MS warrants further study.

2.7.9

Limitations

The capture-recapture analysis does not fulfil the requirements of a closed population; in particular NZ has a large amount of external and internal migration, and hence is likely to produce over estimates.

Tag loss, or in this case incorrect assignment of a UIN, is a documented feature of administrative data matching^{369,370}. Matching was done clerically on double entered data with most cases examined and matched an average of 3 times. The effect of any incorrect tags is to inflate population estimate, adding to the effect of migration.

MS is not a notifiable condition in NZ and there are a small number of cases who refuse to engage with the health system or MS societies. Capture-recapture only estimates the number of cases who have a chance of ascertainment hence the estimate does not include those who refuse to take part. A further group of exclusions were patients with appropriate discharge codes or referrals by MS Society field offices where the diagnosis could not be confirmed.

2.8

Results: Prevalence data

2.8.1

Notifications and response rates

The NZNMSPS received a total of 13,803 notifications for 5,901 unique individuals from which 2917 cases of CDMS were identified as resident in NZ on prevalence day. The response rate from postal questionnaires is typically 50-80%. The NZNMSPS received 2073 completed questionnaires, producing a net response rate of 71.1%. Table 2.5 displays the notification data for all cases and response rates. Response rates were

improved through the use of follow-up telephone calls and media coverage. The population of non-respondents was compared to that of respondents to ensure there was a representative sample (Chapter 3).

Table 2.5 NZ national MS prevalence study demographics

NZ National MS Prevalence Study Demographics				
Unique Notifications	13803			
Unique Individuals	5901			
Mean notifications per individual	(mean 2.5 + range 1-9 SD 1.527)			
Confirmed CDMS cases	2917/5901 (49.4%)			
Not included reasons	2984/5901 (50.4%)			
Not Confirmed /located	547 (9.3%)			
Deceased before census	1086 (18.4%)			
Possible MS	173 (2.9%)			
CIS	393 (6.7%)			
Not in NZ on census day	62 (1.1%)			
Diagnosed post census	24 (0.4%)			
Not MS	699 (11.8%)			
Questionnaire response rates (n, %)	2073, 71.1%			
Gender ratio M : F	728:2189 1:3			
Age	Mean	Max	Min	
Overall	51.74	93	9	
Male	51.14	82	16	
Female	51.94	93	9	
MS Clinical Phenotypes & disability levels (Lublin & Rheingold)	N	Mean Age	M : F Ratio	Mean EDSS
RRMS	1541	48.6	1 ; 3.6	2.5
SPMS	918	59.6	1 ; 4.5	6.4
PPMS	458	69.7	1:1.47	6.3

2.8.2

Age standardisation

Age standardisation allows populations to be compared when the age profiles of the populations are different, whereas age-specific rates are calculated for a specific age or age range. Age standardisation enables the comparison of populations with different age distributions, by adjusting the crude rate of the population of interest to the age of the majority of the population, thereby removing confounding. Data from the NZNMSPS described people with MS in comparison with the general population of New Zealand. In the NZNMSPS the multiple sclerosis population was found to be older than the general NZ population. Age-standardisation subdivides the population according to the suspected pre-disposing factors being studied and compares the disease prevalence in each subgroup. The use of age standardisation to adjust the crude prevalence rate of the MS population to the age of the NZ population gave an accurate description of the disease for each age group, including their location, ethnicity, disease phenotype and level of disability. Statistical analysis of the data enabled the age-standardised prevalence estimates to be generated as part of the national study.

2.8.3

Analysis of latitudinal data

The New Zealand census regions were aggregated into 6 broad latitudinal regions from North to South (Figure 2.3). This process enabled each region to contain sufficient MS cases to allow for meaningful stratification by ethnicity, age, gender and MS phenotype. A population weighted latitude and longitude centroid (PWC) was calculated for each of these six regions and this centroid was taken as the latitudinal reference point for that region (Figure 2.3). The latitude gradient was estimated by calculating ASP's and their confidence intervals for each of the 6 regions and fitting this to the PWCs.

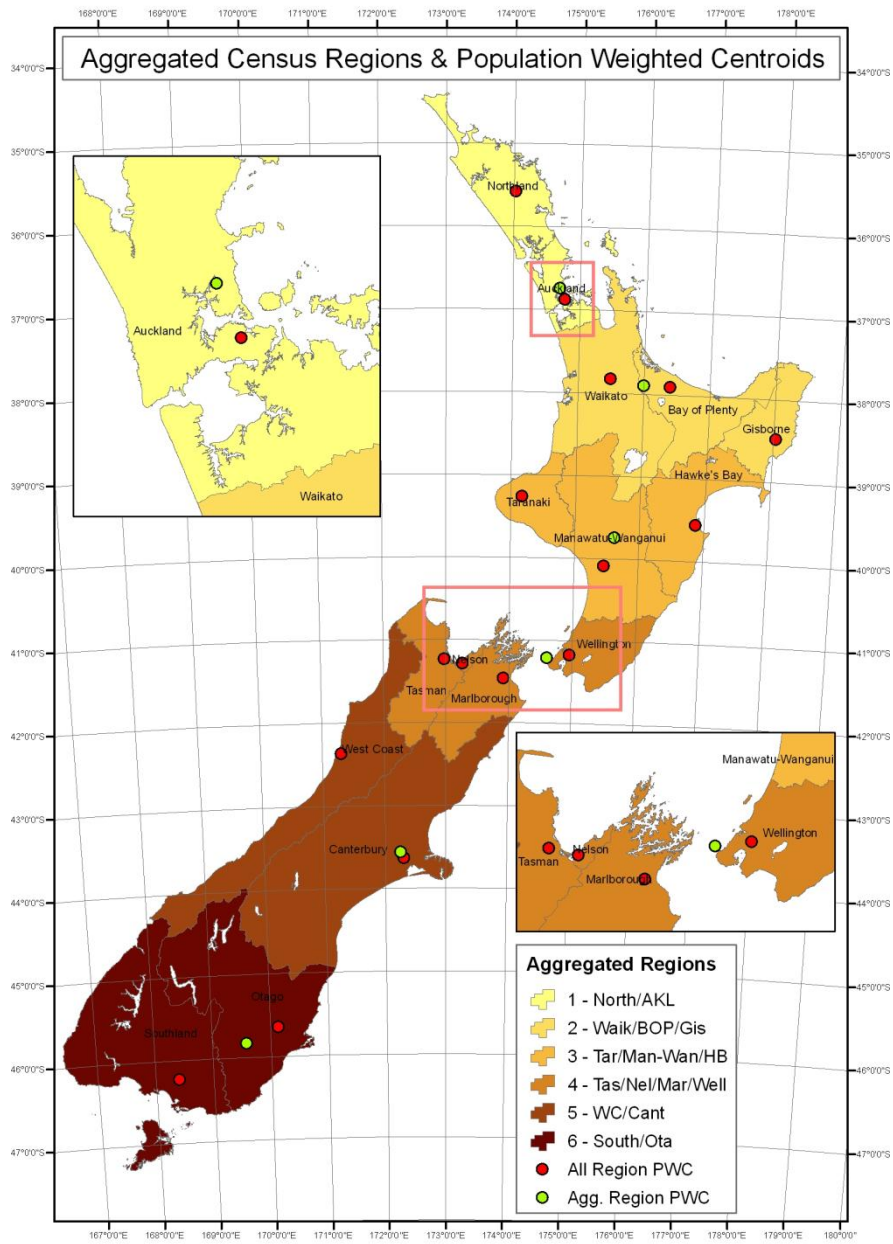


Figure 2.3 Aggregated census regions for NZ

2.8.4

Analysis of ethnicity data

The ethnicity question included in the questionnaire was identical to the self-defined ethnicity question used in the 2006 NZ population census. As well as ethnicity, the NZNMSPS study participants were asked about their ancestry. The ethnicity of all four grandparents was recorded, allowing us to define ethnicity by descent as well as self-reported ethnicity.

Prior to the 2006 census being undertaken there was a publicised national campaign in NZ to declare ethnicity as “New Zealander” under “other” ethnicity. Approximately 10% of respondents took this option making it impossible to identify their ancestry. Statistics NZ do not provide individual breakdowns by age and sex for “New Zealanders” and they were included in the others category in the census results. A further confounder was that the proportion of the population with “New Zealander” self-defined ethnicity varied throughout the country. As such we had to account for this when calculating the effect of ethnicity on latitudinal gradients. In each instance we took the worst case scenario to eliminate any bias that this ambiguous response may have generated. Ethnicity for calculation of non-Māori/Pacifica ASP’s was imputed from the questionnaire data by maintaining marginal ethnicity rates by age group, performing the analysis on non-imputed data did not produce a significantly different gradient.

2.8.5

National age and sex standardised prevalence rates

The NZNMSPS identified 2917 cases of CDMS amongst the total NZ population of 4,027,950 on census day. The crude MS prevalence rate was 72.4 per 100 000 population. The population was then age standardised to the standard European population giving a prevalence of 73.1 per 100 000 population (CI 70.5 – 75.8) (Table 2.5). The age and sex breakdown of CDMS cases in NZ when compared with the overall NZ population is presented in Figure 2.4.

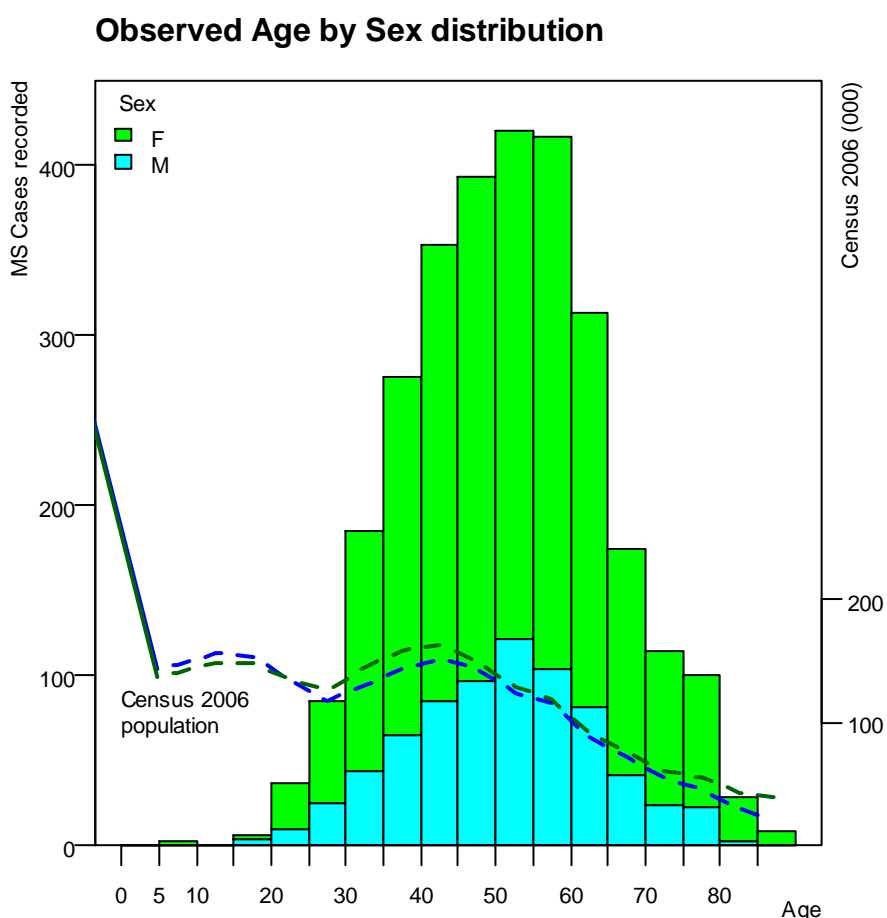


Figure 2.4 Age and sex breakdown of MS cases in NZ compared with standardised population percentages from NZ census

2.8.6

Ethnicity and MS prevalence

Although New Zealand is an ethnically diverse society, people of European origin represent the major ethnic group in all regions.

Analysis of the data is confounded by the “New Zealander” response in the national census resulting in the group classified as “others” being larger than expected. In the NZNMSPS only one respondent listed “New Zealander” as their ethnicity. A number of difficulties were encountered when trying to define the “European” population in NZ. In particular was the assumption that many of those responding “other” should be included as European. As such this study has decided that the population which best approximates European is that which is defined as Non-Māori/Pacifica. The ethnic breakdown of the

NZ population as determined by the self-reported ethnicity question in the census is presented in Table 2.6.

Table 2.6 Ethnic breakdown of the NZ population by self-report from the NZ national population census 2006

Ethnicity responses for total ethnic groups (000)(%)							
	R1	R2	R3	R4	R5	R6	NZ
European	792(54.6)	445(65.0)	332(70.0)	404(69.8)	417(75.4)	219(76.8)	2,610(64.8)
Māori	181(12.5)	164(24.0)	92(19.3)	66(11.5)	40(7.2)	23(8.0)	565(14.0)
Other	115(7.9)	76(11.1)	59(12.3)	66(11.4)	75(13.6)	40(14.1)	431(10.7)
Asian	237(16.3)	27(3.9)	14(2.9)	39(6.7)	30(5.3)	9(3.1)	355(8.8)
Pacifica	182(12.5)	20(2.9)	13(2.6)	36(6.3)	11(2.0)	5(1.6)	266(6.6)
People NEI	77(5.3)	32(4.6)	16(3.3)	19(3.3)	15(2.7)	9(3.2)	168(4.2)
MELAA	19(1.3)	3(0.5)	29(0.4)	6(1.0)	3(0.6)	1(0.5)	35(0.9)
Total Stated	1,375(94.7)	653(95.4)	458(96.7)	560(96.7)	538(97.3)	276(96.8)	3,860(95.8)
Total	1,452	685	474	579	553	285	4,028

NEI = no ethnicity listed, MELAA middle eastern Latin American African

Table 2.7 displays prevalence rates by ethnicity, divided into the 6 NZNMSPS geographical regions. These results demonstrate that the ASP of MS in NZ is significantly different between ethnic groups. Most notably, persons who ethnically define themselves as Māori have a significantly lower prevalence of MS than the European population. People of Pacific Islander origin (2 cases) and Asian origin (13 cases) have a similarly low MS prevalence. No further analysis of these two groups was undertaken due to the low numbers. Prevalence rates by ethnicity were not affected by region (data not shown).

Table 2.7 Prevalence age standardised to European standard population for major ethnic groups in New Zealand

Ethnic Group	Population	MS cases	Prevalence	ASP	ASP CIs
Total	4,027,950	2,917	72.4	73.1	70.5 -75.8
Māori	565,323	90	15.9	24.2	18.9 -29.5
non-Māori	3,462,606	2,827	81.6	78.7	75.7 – 81.6
non-Māori/PI	3,215,667	2,823	87.8	82.4	79.4 – 85.5
European	2,609,586	2,699	103.4	101.9	98 – 105.8

PI = Pacific Islander

2.8.7

MS prevalence variation by latitude and ethnicity

Multiple sclerosis prevalence in each of the six latitudinal regions of NZ (Figure 2.5) was plotted against the latitude of the population weighted centroid of each region. The outcome was an increased MS prevalence with increasing latitude below 37° South (Figure 2.5). A linear model was fitted to assess the relationship between MS prevalence and latitude; however the Northern most region was removed from this model as it appeared to go against the trend. A possible explanation for this could be that this region includes Auckland, the largest city in NZ with around one quarter of the country's total population and the highest concentration of recent migrants.

The higher number of cases in Auckland compared with Waikato/BOP, the neighbouring region, may be explained by a number of factors, including ethnic mix, internal migration, external migration, availability of services and personal support. It could be suggested that Waikato with the largest Maori population in New Zealand could be influencing the trend, however, the prevalence for non-Maori and non-Maori Pacifica groups in the Auckland and Waikato regions show this not to be the case. Equally when the Northern region is divided into the smaller groups of Northland and Auckland, Northland is shown to have a similar prevalence to the Waikato, indicating that the elevated prevalence in Auckland is due to local factors as described above.

The multiple sclerosis prevalence for the total population was shown to increase by 10.7 +/- 0.9 per 100,000 population per degree of latitude south of 37° South ($p < 0.002$). No evidence of a difference in gradient was found on comparison between the total and

non-Māori/Pacific peoples populations. The Māori population has a lower prevalence in the North Island regions than for the non-Māori/Pacific population with no evidence of a latitude gradient in the North Island. In contrast, the Maori population in the South Island displays a similar latitude gradient however it is not statistically significant due to the low numbers in this population (at 11.7 ± 1.4 increase in prevalence per degree of latitude, $p=0.07$).

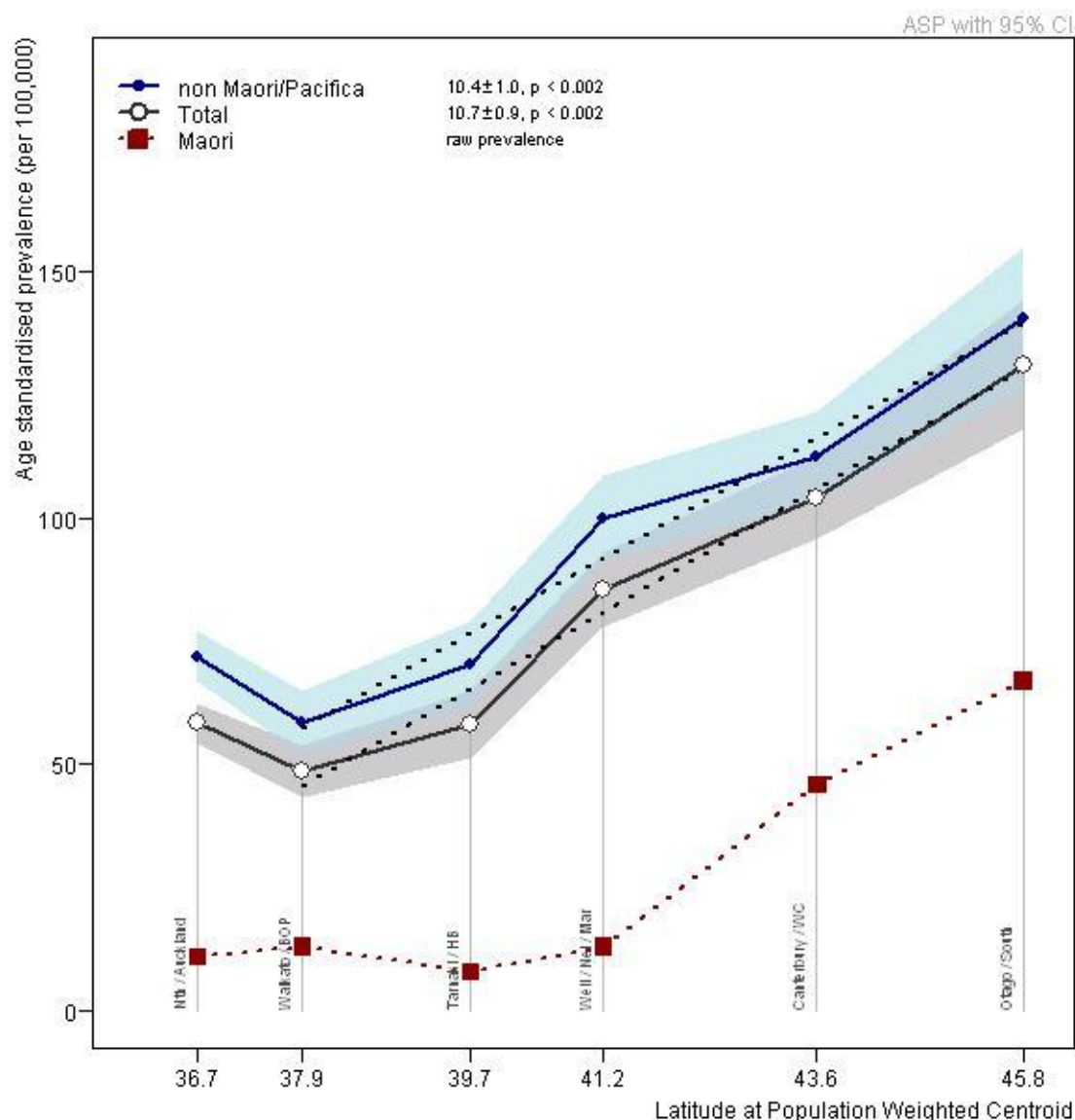


Figure 2.5 MS prevalence by latitude and major ethnic groups in NZ. MS prevalence by region age standardised to the NZ population with 95% confidence intervals is shown for the Total and Non-Māori/Pacific populations. Raw prevalence is shown for the Māori population as there are insufficient numbers of cases for a valid age standardisation

2.8.8

MS prevalence variation by latitude, sex and MS phenotype

Highly significant differences in the latitudinal gradient of MS prevalence were identified by gender (Figure 2.6a), by MS clinical course phenotype (RRMS/SPMS and PPMS), (Figure 2.6b), and when gender and clinical course phenotype were combined (Figure 2.6c).

ANOVA of a linear model of prevalence with independent slopes and intercepts for each of the four groups is shown in Figure 2.6c. RRMS/SPMS (M or F) and PPMS (M or F) show evidence for different gradients $p = 0.009$ and that this difference in gradients is driven by the female RRMS/SPMS population.

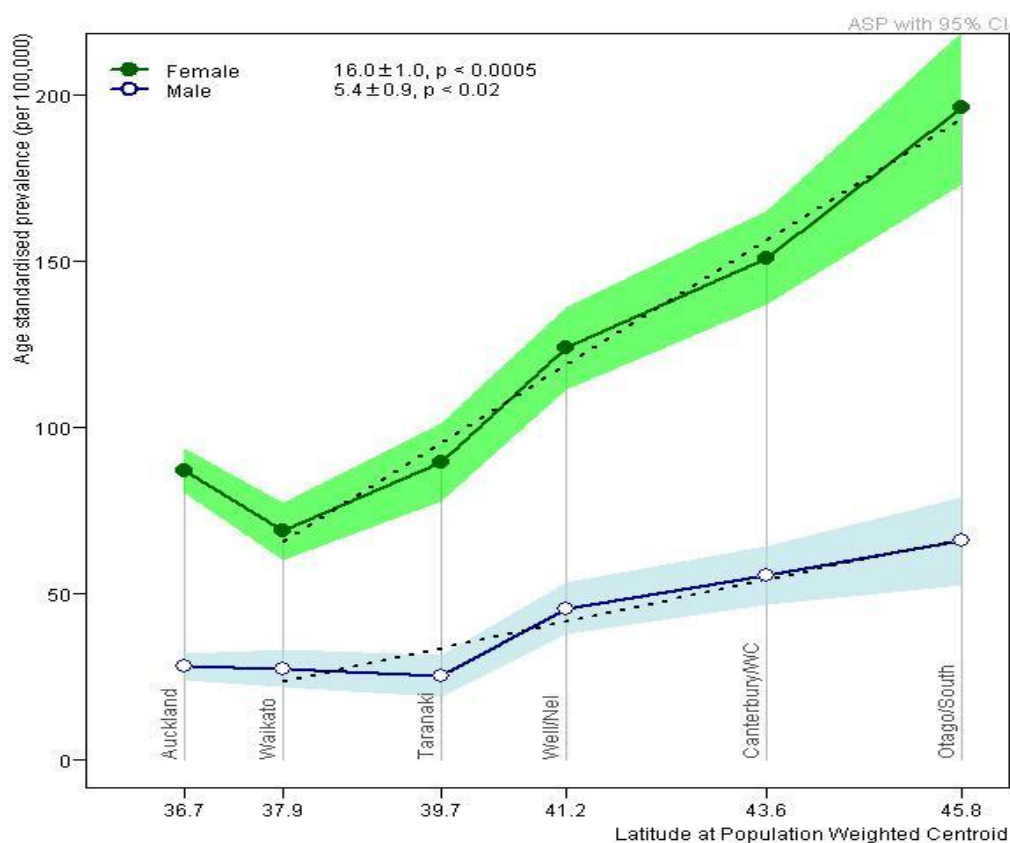


Figure 2.6a MS prevalence latitudinal gradient by gender. A linear model of prevalence on latitude and MS Type shows that the gradient for females was about 3 times that for males

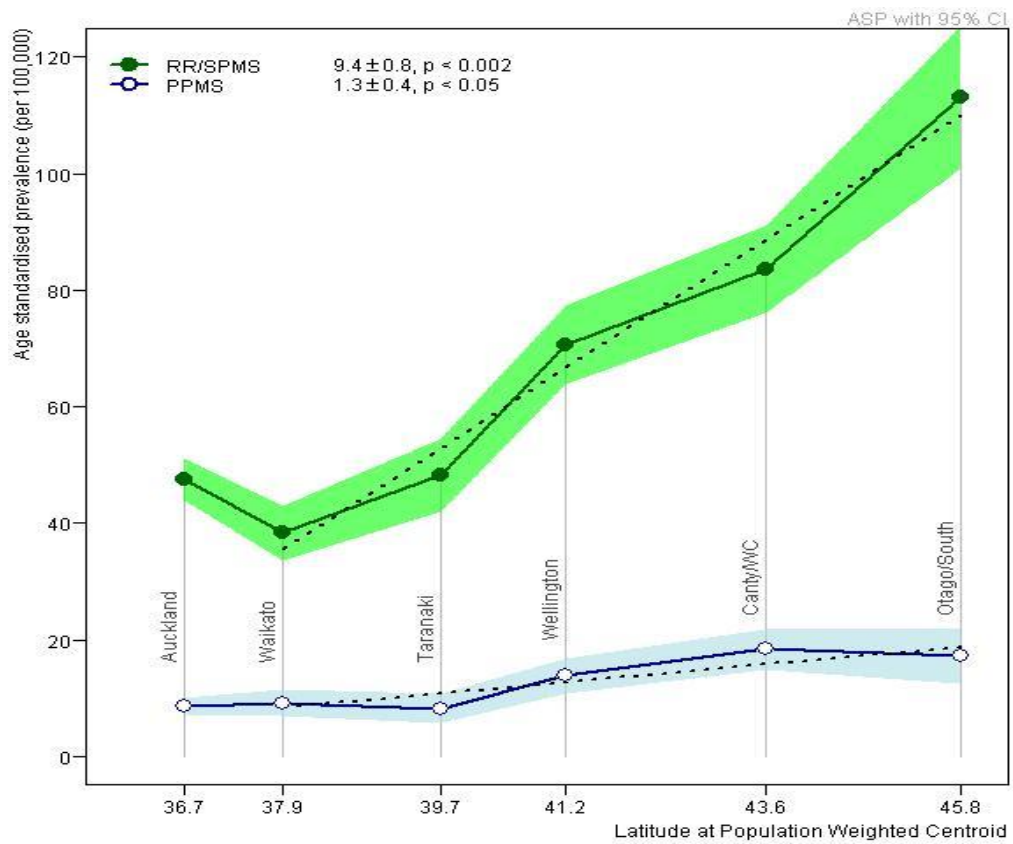


Figure 2.6b MS prevalence gradient by clinical course phenotype, a linear model of prevalence on latitude and MS Type shows that the gradient for RR/SPMS is 8+/-0.9 times higher than for PPMS, ($p < 0.0001$)

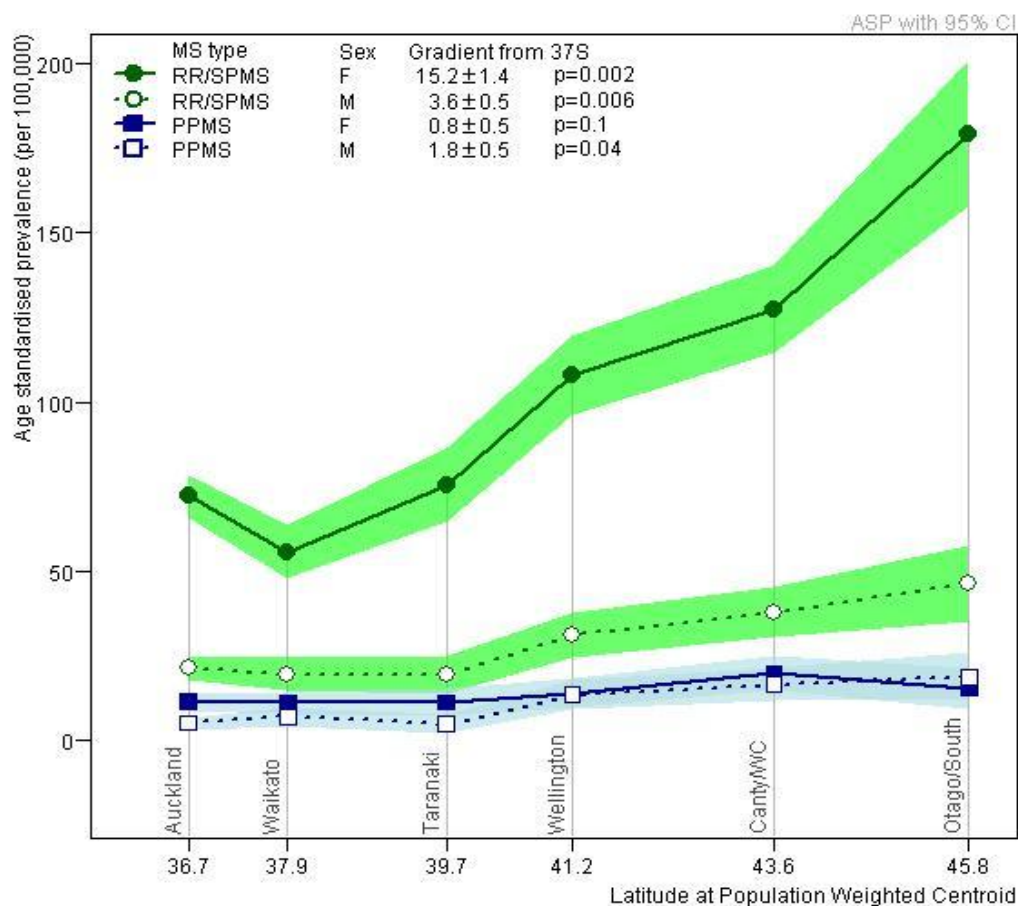


Figure 2.6c MS prevalence latitudinal gradient by gender and MS clinical course, a linear model of prevalence on latitude and MS Type shows that the gradient for females with RR/SPMS is 15.2 +/- 1.4 times higher than for females with PPMS (p=0.002)

2.8.9

Gender ratios and age at onset

The NZNMSPS found a female to male ratio of 3:1. When the sex ratios were calculated by quintennial year of birth^{385,386}, there was no evidence for an increase in gender ratios, with the female to male ratio remaining at or around 3:1 since birth year 1940. Neither gender ratios nor age at onset varied by latitude (data not shown).

2.9

Discussion

The NZNMSPS is the largest stand alone cross sectional MS prevalence survey ever undertaken. The capture-recapture analysis estimates indicate that over 96% of individuals with a confirmed diagnosis of MS living in NZ on census day, March 7th 2006, were identified and phenotyped. The completeness of this data set has enabled detailed analyses of the factors that drive the geographical variability of MS prevalence in NZ, a country ideally suited to research of this type due to its location and geographic shape.

The most significant finding from this study is the confirmation of a highly significant latitudinal gradient of MS prevalence in NZ below 37 degrees south. The prevalence increases 3 fold between the North and South of the country, and persisted following age and sex standardisation of the population. Similarly, ethnic stratification did not influence the latitudinal gradient with the gradient being strongest amongst those of European origin.

The prevalence of MS in the people of Māori descent was found to be much lower; 30% of that seen in Europeans in New Zealand. The majority of the people with self-defined Māori origin had 1 or 2 Māori grandparents, with no-one in the study having all 4 Māori grandparents. Equally MS was an uncommon disease among those with Pacific Islander origin (2 cases), and those of Asian origin (13 cases), indicating that these populations may be protected from developing MS. A latitudinal prevalence gradient was found for Māori which mirrors that seen for the European population; however, it appears to start at higher latitude indicating that the environmental factors that apply to European populations also apply to the genetically admixed Māori population.

On further analysis, the MS prevalence gradient was found to be variable, with gender and MS phenotype significantly affecting the gradient. The cases with a RRMS/SPMS phenotype had a latitudinal gradient 7.2 times greater than those with a PPMS phenotype ($p<0.001$). Females with MS were found to have a gradient 3 times greater than males with MS ($p<0.001$). Multiple regression analysis indicates that females with RRMS/SPMS are the major drivers of the latitudinal gradient ($p<0.001$). These findings indicate that the genetic and/or environmental factors which influence the development of MS do not affect all MS cases equally.

There are two possible explanations for the differential gradients. If genetic factors drive the baseline risk, and sex contributes to these factors making females more susceptible, then the baseline genetic risk should not vary with latitude. The observed gradient would suggest that at lower latitudes there is a protective factor which has a greater influence on females and on the inflammatory types of MS. Conversely, risk factors found at higher latitudes may have a greater effect on females and inflammatory forms of MS.

There are currently two biologically plausible explanations for the latitudinal gradient. The first is decreased ambient winter UVR and subsequent decreased vitamin D levels at higher latitudes. The second is latitudinal variation in susceptibility to late EBV infection¹⁹⁹. Both hypotheses were reviewed in Chapter 1 and have been discussed in detail elsewhere^{171,188,189,198}.

Finally, in contrast to recent findings in Canada^{385,386}, the NZNMSPS observed that the gender ratio did not alter with latitude in NZ, and found no evidence to suggest that the gender ratio has changed over time. The disparity may reflect the latitudinal differences between the two studies or other environmental or genetic differences between the populations.

2.10

Limitations

Prevalence studies are subject to a variety of limitations. The prevalence rate can be affected by incidence, survival, mortality, migration, access to study populations, access to health care and research methods. The use of capture-recapture methods and whole population sampling on a point prevalence day has enabled this study to identify over 96% of the MS population within NZ. The study also verified that patients were alive, living in New Zealand, and had a diagnosis of clinically definite MS on point prevalence day.

Bias is any defect in the design or conduct of the study that causes the results to deviate from the truth. It can be controlled for by study design, methods of data collection, and sources of disease information. Low response rates to postal questionnaires can limit the generalisability of the data, however, this study received a 71.1% response rate, with an even representation from throughout the regions, age groups and genders minimising the potential for selection bias.

As the questionnaires were self-report response there is the potential for the introduction of recall bias, however most questions (other than the lifetime calendar which is not included in this thesis) were in reference to current aspects of the participants' lives, and were designed to be simple tick box answers limiting the potential for error.

Confounding bias, the effect of a third variable, has been controlled for through the use of age standardisation and statistical modelling.

The following Chapters, 3, 4, and 5 form the body of the thesis and present the original aspects of the PhD study, investigating the socioeconomic impact of multiple sclerosis on people living with the disease.

Chapter Three

Employment and multiple sclerosis

3.1

Background

Over two million people worldwide are reported to have multiple sclerosis. Peak prevalence for MS is in the fourth and fifth decades, the optimum employment years for most individuals³²⁶. Evidence from multiple international studies has shown that both men and women with MS are less likely to be employed than the general population, and have a below average household income despite being in a higher social class and having higher educational levels^{264,320,321,330}. The New Zealand National Multiple Sclerosis Prevalence Study with 2,073 respondents with a confirmed diagnosis of MS is representative of the whole country allowing a comprehensive evaluation of employment status for the entire NZ multiple sclerosis population.

3.2

Study aims

MS is associated with a significant change in an individual's physical and cognitive ability affecting their opportunity to be employed. This often results in change in occupation, change in hours worked, or leaving the workforce altogether.

The aim of this chapter is to determine the employment status of people with MS throughout New Zealand on the point prevalence date of March 7th 2006 (New Zealand census day), which will then be compared with the employment rates of the general New Zealand population based on the 2006 census data. The study aimed to describe the employment status in relation to the age, sex, education, region of residence, marital status, occupation, MS phenotype, duration of disease and disability levels of the MS population thus identifying the predictors for not working within the multiple sclerosis population.

3.3

Methods

The NZNMSPS was a cross-sectional descriptive study using capture-recapture methods (see Chapter 2) which ensured participants were referred from a variety of sources enabling over 96% (by capture-recapture estimates) of the MS population in New Zealand to be located and invited into the study. The NZNMSPS achieved a moderately-high response rate of 71.1% (2073 participants) with a relatively uniform distribution from throughout New Zealand. Postal questionnaire was chosen as the method to gather demographic and socioeconomic data on people with MS as it was the most efficient and economical way to collect data on a high number of geographically dispersed people utilising the time and resources available.

3.3.1

Participants

We used two sources of data for this study. The first group included all people with MS in New Zealand. Census data for the New Zealand population from the same date was used as a base reference. Participants with MS were identified and matched from various referral sources including regional MS Societies, hospital databases, neurologists' databases and the NZHIS discharge code list (see Chapter 2 for detailed explanation).

3.3.1.1

Working age population

The working age population is defined by Statistics New Zealand (2006) as the usually resident, non-institutionalised, civilian population over 15 years of age resident in New Zealand³⁸⁷. As the purpose of this analysis was to evaluate the employment status of people with MS in NZ, the population was restricted to the working-age population, those people aged over 15 years of age. However there were too few participants with multiple sclerosis under 25 years of age (n=45) for robust statistical inference. Furthermore, as the universal superannuation (a retirement pension) is available for all people 65 years and over in New Zealand, this could confound the effect of disease on employment for this group of people. For the purpose of this study we limited the employment age group to a working age of 25-64 years inclusive.

3.3.1.2

Labour force participation rate

The labour force constitutes members of the working age population who are classified as employed or unemployed. The labour force participation rate is a measure used to calculate the extent to which the working age population is employed. Statistics New Zealand has developed definitions of the labour force population which closely conform to international standard definitions specified by the International Labour Organisation, but which apply to the New Zealand labour market³⁸⁷.

Employed refers to all persons in the working age population who worked for one or more hours in the week prior to the survey, or were on sick leave or annual leave during that week. Unemployment refers to those people in the working age population who were without paid employment but were available to work, or actively seeking employment in the four weeks prior to, or waiting to commence employment in the four weeks following the survey. The unemployment rate is the number of unemployed persons expressed as a percentage of the labour force³⁸⁷.

Those people not in the labour force included any person in the working age population who is neither employed nor unemployed:

- those who are retired
- those with personal or family responsibilities
- students
- those who are permanently unable to work due to physical or mental disabilities
- those not actively seeking work or were temporarily unavailable for work at the time of the survey

The labour force participation rate is the total labour force expressed as a percentage of the working age population, which includes all people 15 years and over in the numerator (the total labour force) and the denominator (the working age population). This definition has been developed for New Zealand as there is no compulsory retirement age and many New Zealanders remain in the workforce beyond 65 years of age³⁸⁷.

Due to the nature of the data collected, we were unable to distinguish between those people who were unemployed and those who were not in the labour force, as defined by Statistics New Zealand, for our study population. Therefore, for the analysis we calculated those people who are not working, that is those who are unemployed combined

with those not in the labour force expressed as a percentage of the total work and labour force.

3.3.2

Questionnaire

All participants with clinically definite MS who had consented to be part of the NZNMSPS were sent a questionnaire via post to self-complete, and a stamped return-addressed envelope in which to return the questionnaire (see Chapter 2). Participants were informed that the purpose of the questionnaire was to collect data which would describe the NZ MS population so that we could better understand the prevalence and profile of MS in New Zealand. The questionnaire included general demographic questions identical to those in the 2006 Statistics New Zealand Census questionnaire to enable comparison between the MS population and the general NZ population, and questions on past and current occupation, and employment and change in employment status. Variables that were recorded can be found in Table 3.1.

The questionnaire was piloted on twenty people with multiple sclerosis prior to finalising the content of the questionnaires (See Chapter 2). Questions that were taken directly from the 2006 New Zealand Census (marked * in Table 3.1) were used to compare the NZ MS population with the general NZ population. These questions had been formally validated as part of the Census Questionnaire development (personal communication, Statistics New Zealand). Participants were encouraged to answer the questionnaire as fully as possible with most responses being tick box options with some open-ended options for people to clarify “other” responses or detail some aspect, for example, what aspect of their MS had caused them to change their employment status.

Participants were told that there were no correct or incorrect answers and were asked to complete the questionnaires as fully as they were able. An 0800 free-phone number was provided and participants were informed that they could contact the research office via this number if they had queries or needed help completing the questionnaire. Participants were informed that the data from the questionnaires was confidential, being identified only by the participants unique identification number (UIN). The questionnaire is described in detail in Chapter 2 and a copy can be found in Appendix 1.

The disability data was extracted from the neurology assessment form (Appendix 1) completed by; the patient’s neurologist, a study neurologist or a trained assessor during

the NZNMSPS. Disability status was measured using the Extended Disability Status Scale (EDSS), giving a score ranging from; 0 = no disability to 9.5 = bed-bound.

Table 3.1 Data recorded from self-administered questionnaire

Demographics	Socioeconomic	Disease characteristics
Date of birth*	Current occupation	Date of initial symptoms
Sex*	Original occupation	Date of diagnosis
Country/Place of birth*	Hours of work*	Level of disability
Ethnic group*	Educational achievement*	Disease phenotype
Ancestry*	Current annual personal income*	
Marital status*	Change in work status	
Place of residence		
Place of residence 5 years ago		
Location on prevalence day		

* Questions taken directly from the 2006 Statistics NZ census

3.3.3

Data management

Data was dual entered on each of two identical custom-made Microsoft Access databases to collate the data from the questionnaires. The databases were named ‘Index’ and ‘Confirm’ Databases. The schema for the databases was exactly the same as the pages of the questionnaire with drop down menus to allow the identical data from the questionnaires to be entered on the database. This standardised data entry for those inputting the data (myself and two independent research assistants). The participant’s UIN was common between the databases. This system enabled us to directly compare the two sets of data at the conclusion of data entry and manually correct for data entry errors from the original data sources (See Chapter 2).

3.4

Statistical methods

Data was collated in the Microsoft Access database before being exported to the Statistical Package for Social Sciences (SPSS) version 17.0 for analysis³⁸⁸.

3.4.1

Statistical analysis

Descriptive analysis of the data pertaining to work status included summary statistics of the raw data. Cross-sectional analysis, of the relationship between socioeconomic factors, disease phenotype, disability and duration of disease, was performed using the chi-square test for independence, with results quoted as significant at the $p=0.05$ level, with all confidence intervals (CI) at the 95% level. The variables assessed were; demographics including age, sex, region of residence and marital status; socioeconomic factors including education, census day and original occupational group, and employment status; and disease characteristics including MS phenotype, EDSS, years since diagnosis and years since first symptoms.

To assess representation of the NZ multiple sclerosis population, frequency tables were drawn up for the whole MS population, responders and non-responders, and for the working age population responders and non-responders. The Chi-square test for independence was used to explore whether there was a significant difference between responders and non-responders for the whole MS population and for the working age MS population as most variables were categorical. Results are quoted as significant at the usual 0.05 p value, with all confidence intervals (CI) at the 95% level.

Correlation between age and disease duration was determined using the Pearson Product-Moment Coefficient as it is a continuous variable; and age and level of disability using the Spearman Rank Order Correlation as this variable is ordinal or ranked data.

Direct bivariate logistic regression was performed to determine the effect of a number of factors on the likelihood that responders would report that they were not working. Bivariate logistic regression analysis is used when the dependent variable is dichotomous in nature³⁸⁹. In this model the dependent variable was dichotomised as not working (1) and working (0). The model contained nine independent variables (age, sex, region of residence, education, marital status, original occupation, MS phenotype, level of disability and duration of disease). Regression coefficients (Exp B in SPSS) are reported as odds ratios, indicating the strength of association between an independent variable and the dependent variable. A coefficient of greater than 1.00 indicates increased odds; a coefficient of less than 1.00 indicates decreased odds; and a coefficient of 1.00 represents no change in the odds of being in the predictor category of the variable under consideration. To determine if the likelihood of the odds ratio for individual predictors

differing by greater than 1.00 was more than that which could be expected by chance, both a Wald test to assess statistical significance and confidence intervals for the effects were used³⁸⁹. Statistical significance was calculated to assess the likelihood of observing an association at least as large as the one found in the model, if in reality no association were present in the source population. It was quoted as significant with a p value <0.05 , indicating that there is a less than 5% probability that the observed result could have occurred by chance error. Confidence intervals were quoted at the 95% level indicating that there is a 95% probability that the true value lies within the confidence interval. When the confidence interval does not equal 1.00, this is similar to finding that the association is statistically significant with a p value <0.05 ^{100,101}. To investigate the dependence between independent variables, initial models were fitted with no interactions, and all 2-way interactions between lists and the saturated model. Care was taken to check for poorly populated covariate combinations, or cells, particularly due to the relatively low numbers of males and people with primary progressive disease, hence the higher order interactions were not included.

3.4.2

Statistical inference and multiple testing

Multiple comparisons or multiple testing can be of concern in very large data sets where multiple data points are compared between two or more groups simultaneously to assess whether they are different. A statistical test to adjust for multiple testing and minimise Type 1 errors, assumes that the responses are independent and provides a lower bound on likely p values. Type 1 errors are those which produce a false positive result or a result which is not actually there. In the case of multiple testing, the more terms that are put into the comparison, the greater the likelihood that one of those terms will be significantly different purely by random chance^{100,101}.

Multiple comparisons do not present a concern for the analyses in this thesis for several reasons. Firstly the study population is a census of the New Zealand MS population, not a sample of people with the disease, with an estimate of over 96% of the population being identified on capture-recapture analysis. On analysis, the population has been determined to be representative of people with MS in NZ, and there is no evidence of bias between responders and non-responders to the MS study questionnaire (See 3.5.1).

Secondly, the thesis tests three a priori hypotheses which by themselves are unique research questions. The statistical analyses are performed as there is a strong basis for expecting the result to be true; they are not used for repeated statistical testing to explore the data. The analyses test how each of the three hypotheses are modified or changed by other variables to describe the effects on the NZ working age MS population.

3.5

Results

The New Zealand National Census was held on March 7th 2006. This survey is compulsory for all people living in New Zealand and is held every five years. The results of the census provide demographic information for the New Zealand population. The NZ National MS Prevalence study was designed to coincide with the New Zealand national census to enable a direct comparison between the two populations.

The prevalence study located over 96% of people living in New Zealand with a confirmed diagnosis of MS on the point prevalence of census day 2006. The coverage was estimated by capture-recapture methods (see Chapter 2). There were 2,917 people identified as having a confirmed diagnosis of MS and all were posted a study questionnaire producing a response rate of 71.1% (2,073 individuals).

3.5.1

Representative study population

The NZNMSPS data included a complete record of age, sex and region of residence, and a near complete record of MS phenotype (97.8%), level of disability (84.4%) and duration of disease from diagnosis (98.8%) for each individual in the study. As such, we were able to assess whether the responders were representative of the MS population in New Zealand according to these variables.

3.5.1.1

Responders versus non-responders whole multiple sclerosis population

There were no significant differences ($p>0.05$) between responders and non-responders for the whole MS population by sex, level of disability or duration of disease since diagnosis (Table 3.2).

There was a significant difference by age ($p < 0.001$), with people in the 25-34 (OR 1.51, CI 1.09-2.11) and 35-44 (OR 1.57, CI 1.20-2.06) age groups one and a half times more likely to be non-responders than participants >65 years of age. The confidence intervals for all other age groups contained 1 so they were not statistically significant.

The effect for males was greater with people 25-34 years, 2.8 times (OR 2.79, CI 1.38-5.63), those 35-44 years, 2.1 times (OR 2.09, CI 1.13-3.88), and those 45-54 years, 2.4 times (OR 2.43, CI 1.35-4.35) more likely to be non-responders than those in the >65 years age group. The male 0-24 years age group CI contained 1, so it was not statistically significant.

Females who were in the 35-44 year age group were 1.5 times (OR 1.47 CI, 1.08-1.99) more likely to be non-responders than those in the >65 years age group ($p < 0.01$). All other CIs contained 1 for the female MS population making them not statistically significant. Regional variation between the 6 population weighted centroids (PWCs) was significant ($p < 0.001$) for only one area, Auckland/Northland, which had an OR 1.52 (CI 1.16-1.98) indicating that people from the Auckland/Northland region were 1.5 times more likely to be non-responders than those from the Otago/Southland region. The confidence intervals for all other regions contained 1 making them not statistically significant.

When stratified by sex, the distribution was the same for males ($p < 0.001$), with males from Auckland/Northland having an OR 2.24 (CI 1.31-3.83), indicating that they were twice as likely to be non-responders as males from the Otago/Southland region. For females, the result remained significant ($p < 0.01$), however all confidence intervals contained 1 making them not statistically significant. MS phenotype was significantly different ($p < 0.01$) with people with the relapsing remitting (RRMS) form having an OR 1.39 (CI 1.10-1.76), indicating that compared with those with primary progressive (PPMS) forms of MS they are 1.4 times more likely to be non-responders. The CI for people with secondary progressive (SPMS) included 1, so it was non-significant. When stratified by sex, the distribution for females was the same as the whole MS population (OR 1.35, CI 1.02-1.79, $p = 0.02$), however for males, even though the model reached significance ($p = 0.01$) all confidence intervals contained 1 making them not statistically significant.

Table 3.2 Demographic and disease characteristics whole MS population

		Responders (n=2073)		Non-responders (n=844)		p value
		n	%	n	%	
Age	0-24 years	30	1.4	15	1.8	p<0.001
	25-34 years	178	8.6	93	11.0	
	35-44 years	410	19.8	222	26.3	
	45-54 years	578	27.9	235	27.8	
	55-64 years	561	27.1	170	20.1	
	>65 years	316	15.2	109	12.9	
Sex	Female	1573	75.9	616	73.0	p=0.11
	Male	500	24.1	228	27.0	
Region	Northland/Auckland	525	25.3	294	34.8	p<0.001
	Waikato/BOP/Gisborne/Rot	258	12.4	76	9.0	
	Tara/Wang/Man/Hawke Bay	212	10.2	66	7.8	
	Wellington/Nelson/Marlb	361	17.4	144	17.1	
	Canterbury/WC/Sth Cant	438	21.1	161	19.1	
	Otago/Southland	279	13.5	103	12.2	
Disease Phenotype	Relapsing Remitting	1001	49.4	475	57.3	p=0.01
	Secondary Progressive	682	33.7	237	28.6	
	Primary Progressive	342	16.9	117	14.1	
Level of Disability	Mild-moderate (EDSS 0-5.5)	1030	57.9	424	62.0	p=0.07
	Moderately severe-severe (EDSS 6.0-10.0)	749	42.1	260	38.0	
Disease Duration Since Diagnosis	0-4 years	488	23.9	219	26.2	p=0.42
	5-9 years	539	26.3	213	25.4	
	>10 years	1019	49.8	405	48.4	
Disease Duration Since Diagnosis (mean years (SD))		12 (9.60)		11.42 (9.32)		p=0.13

3.5.1.2

Responders versus non-responders working age multiple sclerosis population

When the MS population is limited to the working age group (25-64 years), there were no significant differences between responders and non-responders by disease duration since diagnosis ($p>0.05$) (Table 3.3).

For the working age population there was a significant difference in response rate by sex ($p=0.03$). The results showed that compared with females, males are 1.2 times (OR 1.24, CI 1.02-1.51) more likely to be non-responders.

Age reflected the whole population results with a lower response rate from all age groups when compared with people 55-64 years of age ($p<0.001$). People 25-34 years had an OR 1.72 (CI 1.27-2.34), those aged 35-44 years had an OR 1.79 (CI 1.41-2.26), and those 45-54 had an OR 1.34 (CI 1.07-1.69) for an increased chance of not responding than those people in the 55-64 years age group.

When stratified by sex, males reflected the working age population results ($p<0.01$). Males 25-34 years were 2.5 times (OR 2.50, CI 1.39-4.51), those 35-44 years were 1.8 times (OR 1.88, CI 1.16-3.04), and those 45-54 years were twice as likely (OR 2.17, CI 1.40-3.38) to be non-responders when compared with males in the 55-64 year age group. Females aged 25-34 years were 1.5 times (OR 1.51, CI 1.06-2.15), and those aged 35-44 years were 1.8 times (OR 1.76, CI 1.34-2.31) more likely to be non responders than those aged 55-64 years. The confidence interval for the 45-54 year age group contained 1, so it was not significant.

Regionally the response rate was only significantly different ($p<0.001$) for the Auckland/Northland region which had an OR 1.56 (CI 1.17-2.08) indicating that people living in this region were one and a half times more likely to be non-responders than those living in Otago/Southland. All other region's CIs contained 1, making the results from those areas not significant.

When stratified by sex, males reflected the working age MS population with males from the Auckland/Northland region three times more likely to be non-responders than those from Otago/Southland region ($p<0.001$). All other CI's contained 1. The regional model for females reached significance, ($p=0.03$), however as the confidence intervals for all regions contained 1, the result is not statistically significant.

As with the whole MS population, people in the working age population with RRMS had a higher chance of non-response (OR 1.66, CI 1.25-2.19) when compared with people with PPMS ($p<0.001$). The CI for people with SPMS contained 1 making this result non-significant.

When stratified by sex, there remained a significantly lower response rate from both females (OR 1.69, CI 1.20-2.38, $p<0.01$) and males (OR 1.68, CI 1.03-2.75, $p=0.02$), with RRMS when compared with people with PPMS. Once again both CI for people with SPMS contained 1, making this result not statistically significant. People with mild to

moderate levels of disability had an OR 1.24 (CI 1.01-1.53) for non-response when compared with people with moderately severe to severe levels of disability ($p=0.04$). When stratified by sex however, the difference between responders and non-responders by level of disability lost significance: females ($p=0.15$) and males ($p=0.10$).

Table 3.3 Demographic and disease characteristics MS working age population (25-64 years)

		Responders (n=1727)		Non-responders (n=720)		p value
		n	%	n	%	
Age	25-34 years	178	10.3	93	12.9	$p<0.001$
	35-44 years	410	23.7	222	30.8	
	45-54 years	578	33.5	235	32.6	
	55-64 years	561	32.5	170	23.6	
Sex	Female	1308	75.7	515	71.5	$p=0.03$
	Male	419	24.3	205	28.5	
Region	Northland/Auckland	441	25.5	255	35.4	$p<0.001$
	Waikato/BOP/Gisborne/Rot	206	11.9	68	9.4	
	Taranaki/Wanganui/Manawatu/Hawke Bay	176	10.2	53	7.4	
	Wellington/Nelson/Marlborough	304	17.6	117	16.3	
	Canterbury/West Coast/Sth Cant	363	21.0	139	19.3	
	Otago/Southland	237	13.7	88	12.2	
Disease Phenotype	Relapsing Remitting	922	54.5	452	63.4	$p<0.001$
	Secondary Progressive	513	30.3	185	25.9	
	Primary Progressive	257	15.2	76	10.7	
Level of Disability	Mild-moderate (EDSS 0-5.5)	942	64.1	402	69.0	$p=0.04$
	Moderately severe-severe (EDSS 6.0-10.0)	527	35.9	181	31.0	
Disease Duration Since Diagnosis	0-4 years	445	26.1	203	28.4	$p=0.52$
	5-9 years	500	29.3	203	28.4	
	>10 years	761	44.6	310	43.3	
Disease Duration Since Diagnosis (mean years (SD))		10.48 (8.17)		10.05 (8.04)		$p=0.22$

3.5.1.3

Population representation summary

The younger population, males, those residing in the Auckland/Northland region and people with RRMS are under-represented in the responders. The patterns shown in the analysis of the responders and non-responders may reflect various aspects of multiple sclerosis. People with RRMS make up 80%-85% of the MS population at onset, are younger, and have lower levels of disability. Socioeconomically, people in the younger age groups are more likely to be striving for a career, developing social networks and trying to meet the demands of family commitments. The competing demands on their time combined with managing the effects of the disease may limit the time they have available for other activities such as completing research questionnaires. Whereas those with higher levels of disability and who are reaching retirement age may have more free time available to meet extra demands. Previous health research studies have also found lower response rates from the young adult population³⁹⁰⁻³⁹². Equally these response patterns may indicate that those with higher levels of disability have a greater personal interest in contributing to MS research, resulting in higher response rates from these groups.

A possible explanation for the lower response rate in the Northern-most region which includes Auckland, New Zealand's largest city with around one quarter of the country's total population, could be that it has the highest concentration of recent migrants, and offers a wider variety of employment opportunities; as such it attracts a greater number of people of employment age resulting in a cumulative effect of the patterns described above.

For the other variables tested, it seems that there are no significant clinical differences between responders and non-responders. The results from the population representation analysis of the working age MS population data are the same as those from the analysis of the whole MS population data indicating that the working age sample are representative of the whole MS population. Finally the results of the population representation analysis are not unexpected as age, sex and large population centres are known confounders in epidemiological studies, and overall the results show the population is well selected, and demonstrates a reasonably representative sample of people with MS in New Zealand.

3.5.2

General demographics whole multiple sclerosis population

Patient demographics reflected the reported MS populations with a female to male ratio of 3:1, and a mean age of 52 years for the whole MS population. 63.1% of all respondents were not working, with 67% reporting that their employment status had changed due to MS (Table 3.4).

Table 3.4 Demographic characteristics of the whole study population

Whole Population Demographics		Participants		New Zealand Population	
		n	%	n	%
Gender	Female	2,189	75.1	2,122,005	51.2
	Male	728	24.9	2,021,277	48.8
Mean Age	(Years)	52			
Ethnicity	European		93		63
Not Working			63.1		

3.5.3

Employment rates

Figure 3.1 illustrates the percentage of each age group in work on the point prevalence date of 7th March 2006 for both the multiple sclerosis population and the general New Zealand population. It shows both males and females with MS having an equal rate of employment to the general population in the younger age groups, but rapidly falling below the employment level of the general population from the 25-30 year age group and continuing to remain below their peer's employment level in all older age groups. The upswing in employment for males with MS in the 45-54 year age group is most likely to be explained by those people newly diagnosed with PPMS entering the multiple sclerosis population (Figure 3.1).

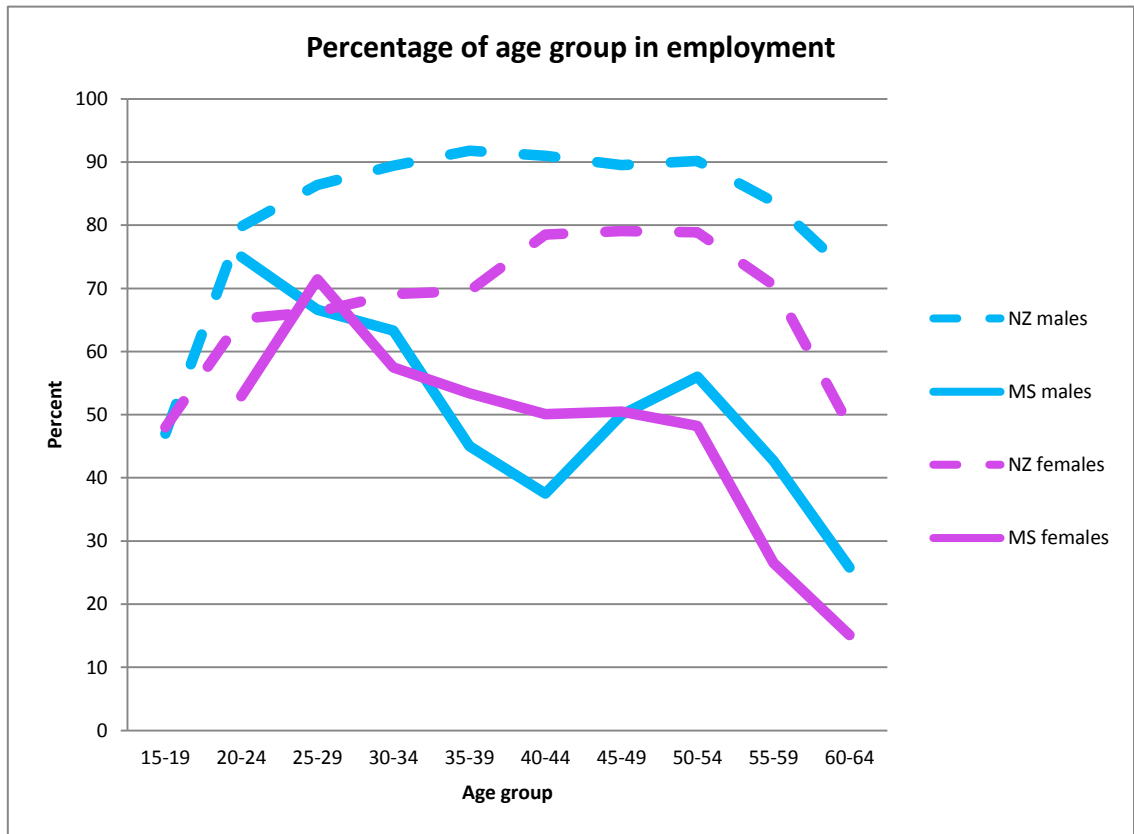


Figure 3.1 Age stratified employment rates for the NZ and MS populations

3.5.4

Responder demographics

The following analyses focus on the working age (25-64 years) population, all subsequent results and discussion will apply to this group (Table 3.5).

Table 3.5 Demographic characteristics of the working age population

Demographic Data Responders Working Age Population (25-64 years)					
		MS Participants		New Zealand Working Age Population	
		(n=1,727)		(n=2,162,892)	
		n	%	n	%
Age (mean years)	Female	48.1		43.6	
	Male	48.6		40.8	
Gender	Female	1,308	75.7	1,116,210	51.6
	Male	419	24.3	1,046,673	48.4
Marital status	Never Married/Married		77.4		83.5
	Divorced/widowed/Sep		22.6		16.5
Education	Post Secondary School		51.4		41.6
Region of residence	Northland/Auckland	441	25.5	777,318	35.9
	Waikato/Bay of Plenty	206	11.9	332,748	15.4
	Tar/Man/Hawkes Bay	176	10.2	267,021	12.3
	Wellington/Nel/MarlB	304	17.6	319,992	14.8
	Canterbury/West Coast	363	21	306,615	14.2
	Otago/Southland	237	13.7	159,198	7.4
Employment	(Full time >30hrs/week)		26.9		65.5
	(Part time =<29hr/week)		18.5		12.5
Percentage not working			54.6		22
Median Income (\$NZ)		\$20,000		\$34,750	

3.5.5

Work status by multiple sclerosis phenotype

For the working age population, 53.5% of people with RRMS, 62.2% of people with SPMS and 63.2% of those with PPMS were not working ($p < 0.01$). When compared with RRMS, people with SPMS had an OR 1.43 (CI 1.15-1.78) and PPMS an OR 1.49 (CI 1.12-1.99) for likelihood of not working (Figure 3.2). Over 80% of people diagnosed with MS have the relapsing-remitting phenotype, as over half of this population are not working this is a large proportion of people with MS requiring some form of support from families and society.

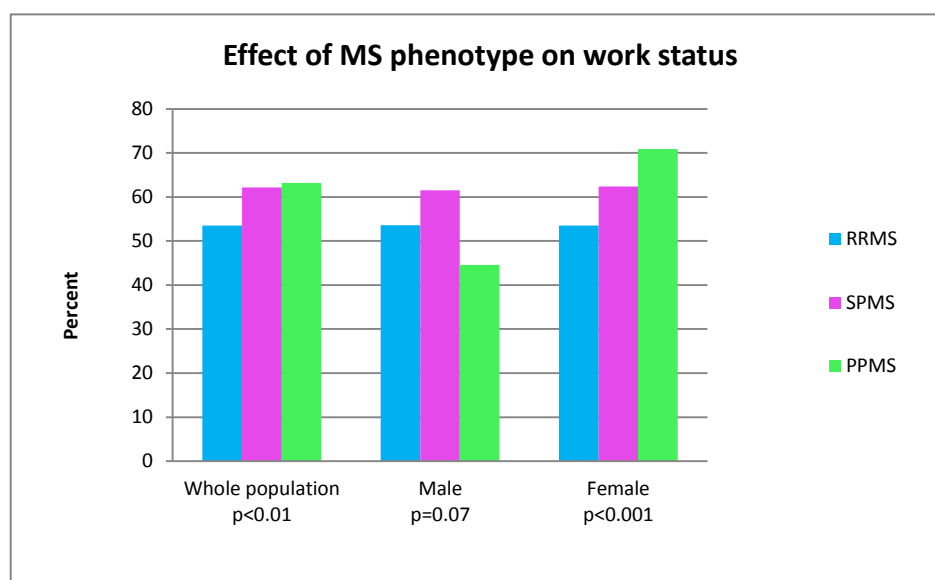


Figure 3.2 Percentage of phenotype not working by whole population and sex

When stratified by male and female respondents the proportion not working is similar for both sexes for RRMS and SPMS, however for PPMS there is a significantly higher percentage of females not working ($p < 0.001$). In females, those with RRMS, compared with SPMS had an OR 1.45 (CI 1.12-1.86) and with PPMS had an OR 2.12 (CI 1.49-3.03) for a likelihood of not working. For males, the results did not reach significance ($p = 0.07$), possibly indicating lack of power due to small sample size and reflecting that proportionally, a lower percentage of males with PPMS were not working (Figure 3.2). The lower percentage of PPMS males who are not working may reflect the later age at onset of PPMS in this cohort, when they are likely to be established in their careers and, in many cases, they may be able to continue with employment if their physical disability

does not affect their ability to do their job, and can be accommodated in the workplace^{393,394}.

3.5.6

Work status by level of disability

Level of disability as measured by the extended disability status scale (EDSS) made a small contribution to loss of work status. For the working age population, 54.5% of people with mild to moderate disability, and 62.1% of those with moderately severe to severe disability levels were not working. The results show that compared with those in the mild to moderate disability group, people with moderately severe to severe disability levels had an OR 1.37 (CI 1.10-1.70, $p=0.01$) for not working (Figure 3.3). This result indicates that although people with higher levels of disability are more likely to be not working than those with mild to moderate disability, it is a marginal increase with the mild to moderate disability group already noticeably affected with nearly 55% of that group not working.

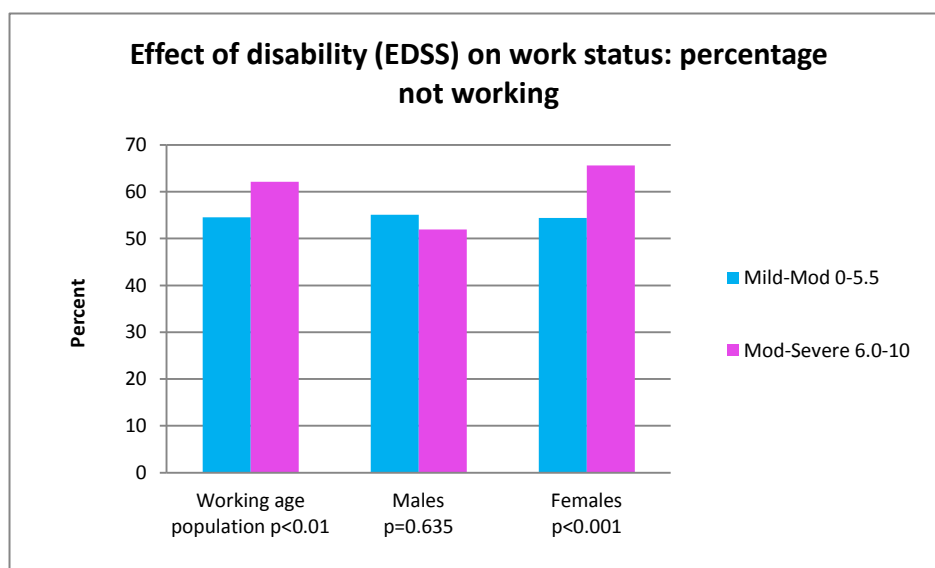


Figure 3.3 Percentage of disability group not working by whole population and sex

When stratified by sex, a higher percentage of females in the moderately severe to severe range of EDSS scores (6.0-10) are no longer working ($p<0.001$). Females with an EDSS ≥ 6.0 had an OR 1.60 (CI 1.24-2.07), indicating that females with a higher level of

disability are 1.6 times more likely to be not working than females with a lower level of disability. For males however this analysis did not reach significance ($p=0.64$).

The higher proportion of men with an EDSS score over 6.0 who are working may correspond with a phenotype of primary progressive MS. Some studies have suggested that this phenotype has a greater effect on motor function than cognition³⁹⁵, and as it develops in an older cohort, this would suggest that they may be more likely to retain their employment status if their physical disability does not limit their ability to perform their occupational requirements, or access the workplace^{394,395} (Figure 3.3).

3.5.7

Work status by duration of disease since onset

Duration of disease, either since onset of symptoms or diagnosis, was also a small contributing factor to not working. For the working age population, 51.2% of people 0-4 years since first symptoms were not working, 54.1% of people in the 5-9 year group and 60.1% of those whose disease duration since first symptoms was greater than 10 years. Those with the longest disease duration since first symptoms had an OR 1.44 (CI 1.07-1.93, $p=0.02$) for not working when compared with those 0-4 years since first symptoms (Figure 3.4a).

For females the result was similar to that of the working age population with a higher proportion of those in the longest disease duration category not working. Those with the longest disease duration had an OR 1.67 (CI 1.19-2.33, $p=0.01$) for not working when compared with those of short disease duration from first symptoms. The analysis for males did not reach significance, possibly indicating that disease duration has little effect on the work status of males with MS, or that the population size is too small to detect a difference ($p=0.70$) (Figure 3.4a).

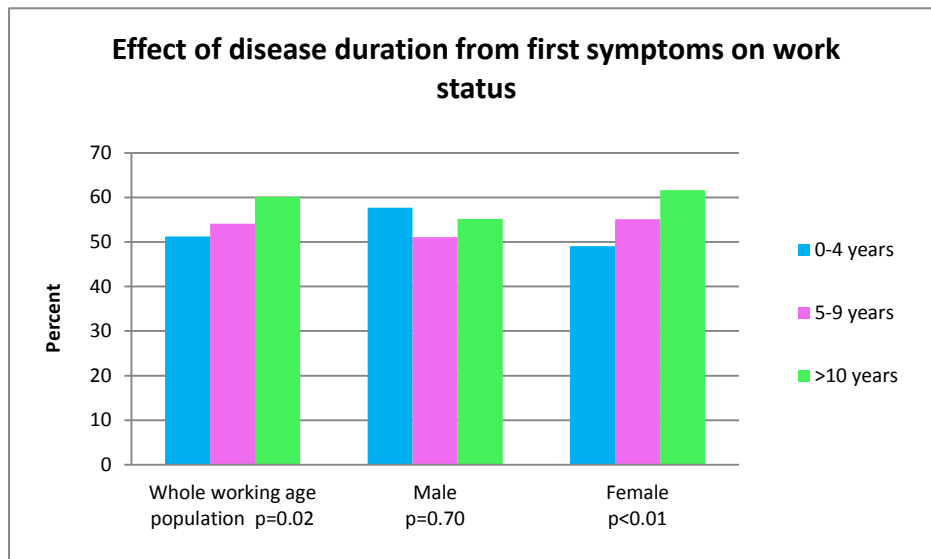


Figure 3.4a Percentage of disease duration from first symptoms group not working by whole population and sex

When plotted as a narrower interval categorical variable, similar statistical results are obtained, with loss of work status with longer disease duration more evident in the female population and the whole MS working age population. As females make up 75% of the MS population, it is evident that they are driving the effect for the whole population results (Figure 3.4b).

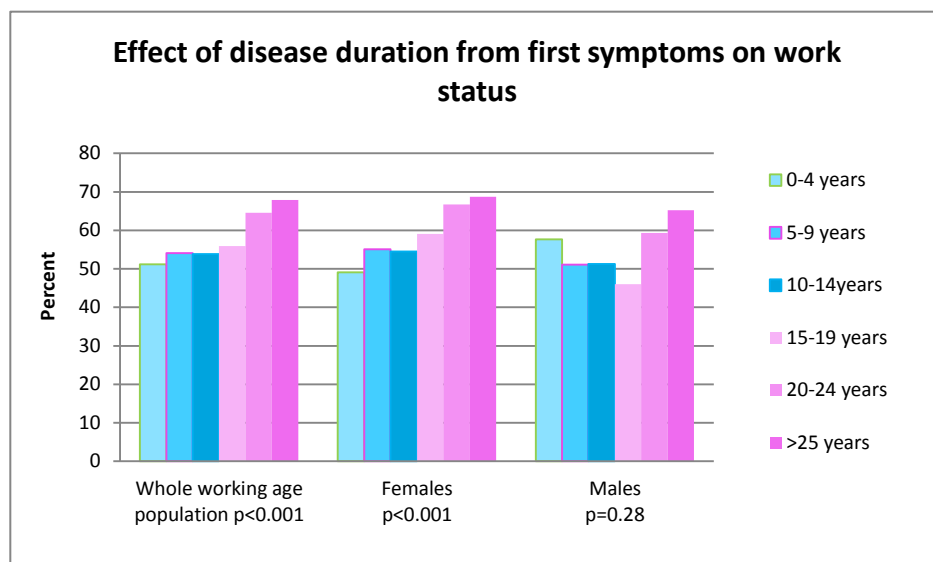


Figure 3.4b Percentage of disease duration from first symptoms group (5 year intervals) not working by whole population and sex

3.5.8

Work status by duration of disease since diagnosis

For the working age population, 55.1% of people 0-4 years since diagnosis were not working, 53.1% of people 5-9 years since diagnosis and 61.9% of those whose disease duration since diagnosis was greater than 10 years ($p < 0.01$). People with a disease duration of >10 years since diagnosis had an OR 1.32 (CI 1.04-1.68) for not working compared with those 0-4 years since diagnosis (Figure 3.5a). This indicates that although an increasing proportion of people with MS are not working as their disease duration increases; the effect is marginal compared with those who are newly diagnosed (0-4 years disease duration) as over 55% of the early disease duration group are already not working.

As with duration of disease since first symptoms, females reflected the results of the whole working age MS population with increased loss of work status with longer disease duration from diagnosis ($p = 0.01$). The results show that females with a disease duration from diagnosis of >10 years had an OR 1.41 (CI 1.07-1.86) for not working as compared with those in the 0-4 years post diagnosis group. The analysis for males did not reach significance once again indicating that either disease duration does not have a significant effect on work status for males with MS, that the sample size is too small to detect a difference, or reflecting that proportionally a higher percentage of males in the 5-9 year disease duration group are working ($p = 0.13$) (Figure 3.5a).

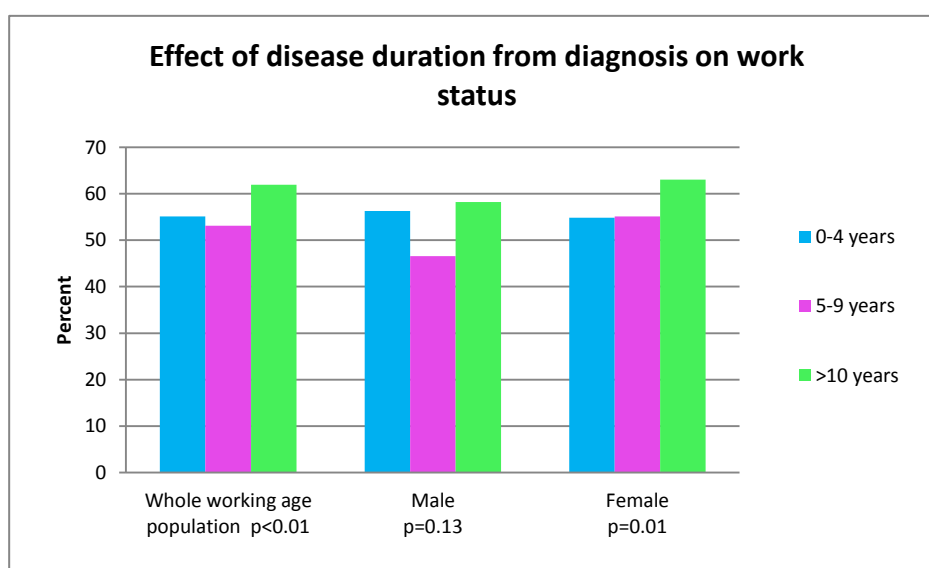


Figure 3.5a Percentage of disease duration from diagnosis group not working by whole population and sex

As with disease duration from first symptoms, when plotted in shorter categorical time periods, females with MS and the whole MS working age population have a similar pattern for loss of work status with longer disease duration (Figure 3.5b).

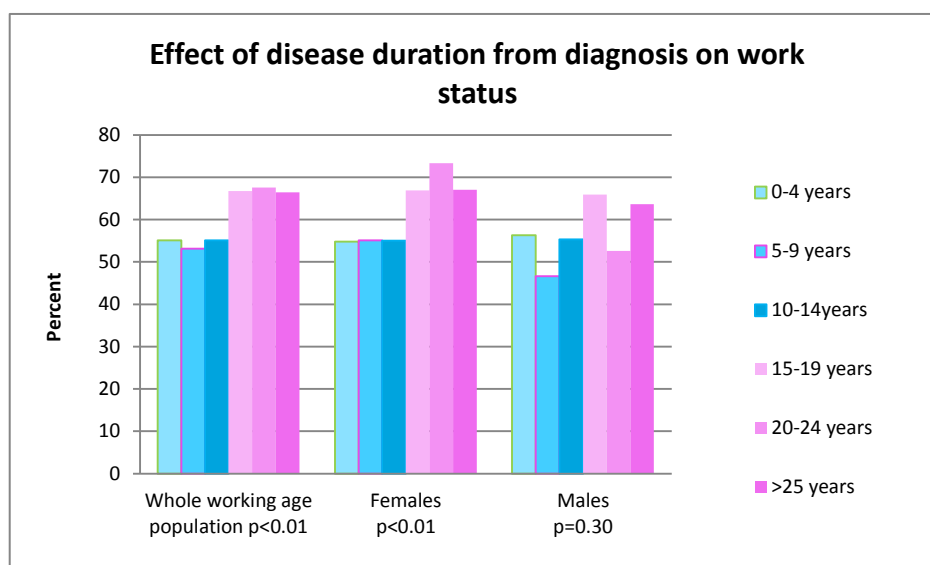


Figure 3.5b Percentage of disease duration from diagnosis group (5 year intervals) not working by whole population and sex

These results indicate that for females departure from the work force occurs very early in the disease course, with no indication of re-entry to the workforce later in life. The increase in people with MS not working at around 15-19 years post diagnosis coincides with the mean time to conversion from RRMS to SPMS of 19 years⁵⁴⁻⁵⁶, and the median time to a disability score of 6.0 (EDSS), 14-20 years. This would possibly indicate that at this time the progressive nature of the disease and the level of disability accumulated are such that those people who have managed to stay in work to this point are no longer able to continue. Males appear to have a more irregular work pattern over the duration of their disease course, with a period of increased work at around 6-9 years disease duration and again around 20 years, although the latter data point may be a reflection of smaller participant numbers in the males with over 20 years disease duration group.

3.5.9

Change in occupation

There were a number of interesting observations for occupational groups. The distribution of the working age MS populations' original occupational groups is different to that of the working age NZ population on census day. There is a higher percentage of people with MS in the clerical and administration groups and the machinery operator and labourers groups, and a lower percentage in the professional group compared with the NZ population. When stratified by sex, males with MS are underrepresented in the managers and professionals group and over represented in the machinery operator/labourer group compared with their NZ male peers. Females with MS are overrepresented in the clerical and administration group, trades and technicians group and the machinery operator/labourer group compared with their NZ female peers (Figures 3.6a-c).

The difference in occupational distribution between the MS *original* occupational groups and the NZ working age population's occupational groups may be due to temporal differences in occupation classification. Like the MS working age population's *census day* occupation, the NZ population's occupational description is based on the job that they were doing on census day 2006, not the original occupation they qualified for. The MS *original* occupation classification is based on the occupation they originally qualified for. It does not take into account career progression or change in career path over a person's working life, which will not occur if a person stops working early in their career. As this is a cross-sectional study this observation is merely speculation as temporality cannot be ascertained from the data, a prospective longitudinal study would be required to research this hypothesis.

Occupational classification at disease onset was associated with leaving the workforce ($p < 0.001$). For the whole MS population, professionals and clerical/administrative workers, occupational groups which require a significant level of cognitive input; and machinery operators/labourers, highly physical occupations have the greatest change in employment status as a consequence of MS. This indicates that both cognition, which is not routinely measured in the clinical setting, and physical disability as measured by the EDSS contribute to risk of premature departure from the work force (Figure 3.6a).

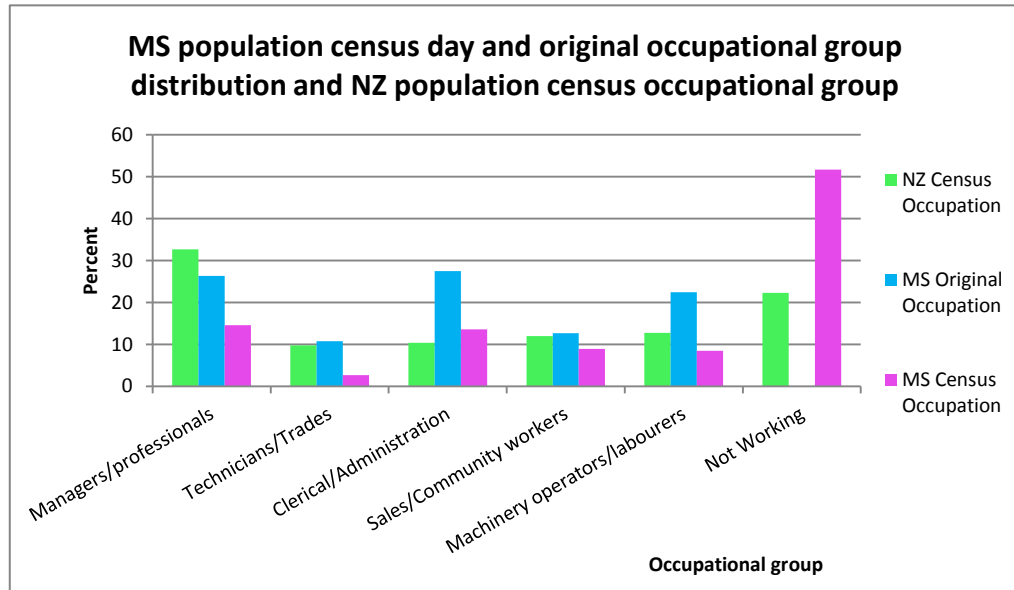


Figure 3.6a Occupational group distribution, NZ population on census day, MS population original occupation, and MS population census day occupation

Of interest, when change in occupation is stratified by male and female gender groups, the results are somewhat different. Males in professional occupations which require significant cognitive input do have a change in workforce status, but the more dramatic change is seen in those males employed in machinery operator/labouring positions, occupations which place higher demands on physical strength and ability ($p < 0.001$) (Figure 3.6b).

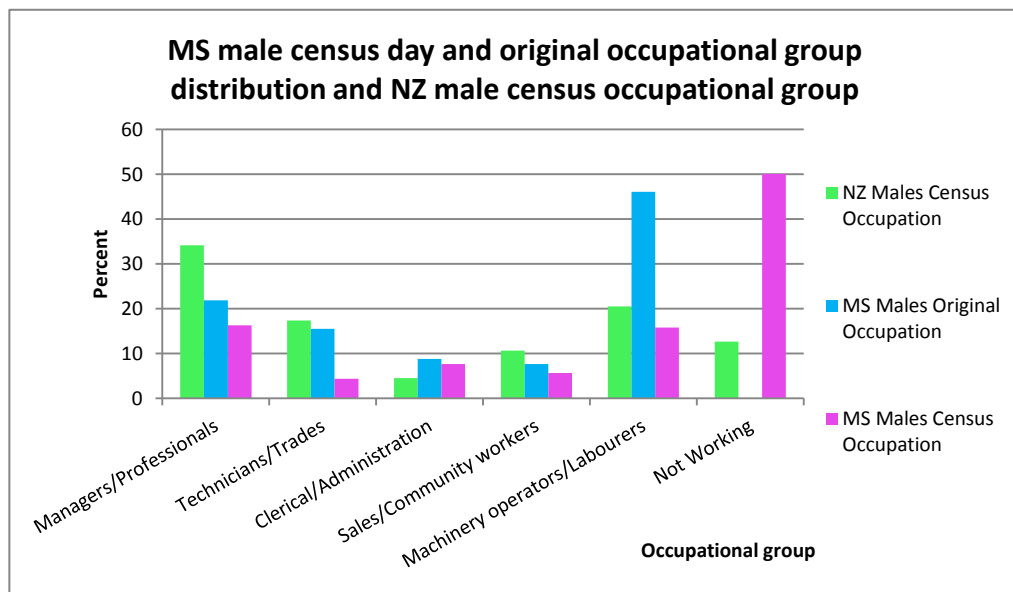


Figure 3.6b Male occupational group distribution, NZ population census day, MS population original occupation, and MS population census day occupation

Females, by contrast, experience the greatest change in workforce status when employed in professional and clerical or administrative occupations, those which require significantly more cognition ($p < 0.001$) (Figure 3.6c). This would indicate that the disease process or symptoms as a result of the disease affect males and females with MS in different ways.

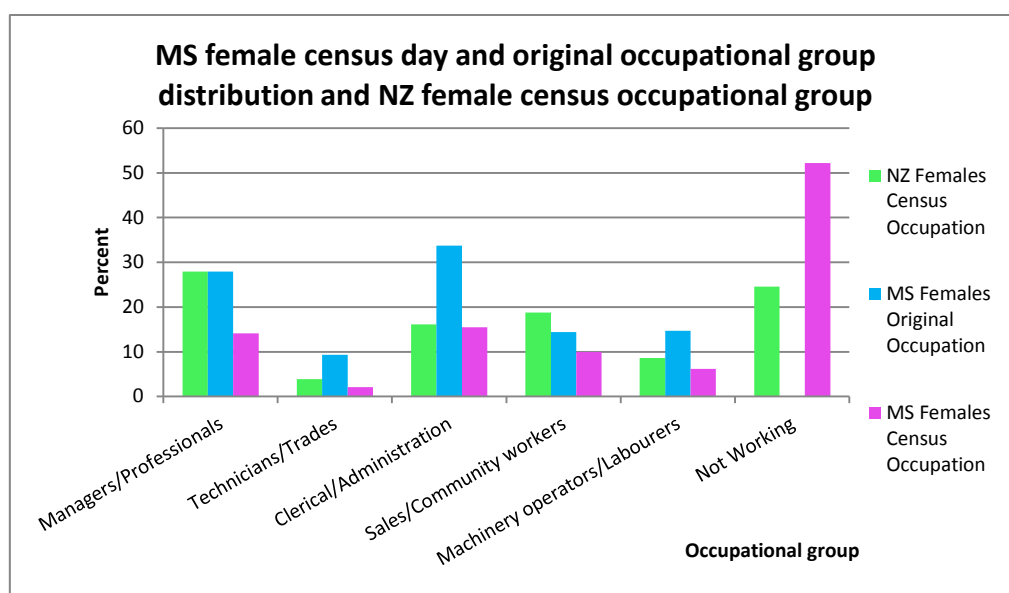


Figure 3.6c Female occupational group distribution, NZ population census day, MS population original occupation, and MS population census day occupation

3.5.10

Self-reported reasons for change in work status

This question had three sections; the first was a simple yes/no response selection asking the respondents if their employment status had changed due to MS. The second part was an open response question asking the participants to describe the factors they felt had contributed to the change in their employment status. The third part asked the participants to describe the ways in which their work status had most recently changed due to multiple sclerosis (Appendix 1). For the second and third parts to the question, participants could list as many factors as they wished, and these were recorded on the database in the order of priority as listed by the participants, as such the percentages shown in Figures 3.7a, 3.7b, 3.8a and 3.8b will add up to greater than 100%.

Sixty seven percent (67%) of our working age study participants stated that their employment status had changed in some way as a consequence of the disease process.

Self-reported reasons for change in employment status were recorded, with fatigue, lower body motor function, multiple factors and cognition most frequently reported (Figure 3.7a). The category “multiple factors” was assigned to responses such as multiple sclerosis prevented me from working, with no further details offered. Of note is that three of the four most reported reasons, fatigue, cognition and multifactorial can be linked to cognitive function and two of the four, lower body motor function and multifactorial can be linked to physical function, which are reflected in the occupations most likely to indicate loss of work (Figure 3.6a).

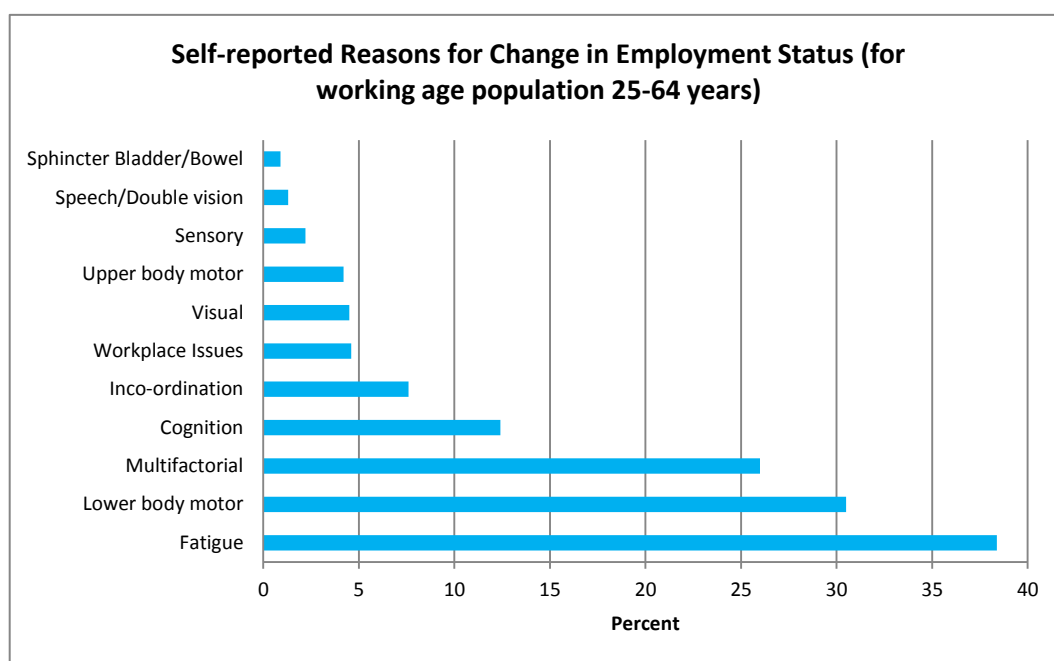


Figure 3.7a Reasons for change in work status

When the self-reported reasons for change in work status were stratified by sex, we found that females were more likely to report being affected by fatigue and change in cognitive function, whereas males more commonly reported change in lower body motor function and multifactorial reasons (Figure 3.7b). Once again this corresponds with the effect of MS on occupational status described in Figures 3.6b and 3.6c.

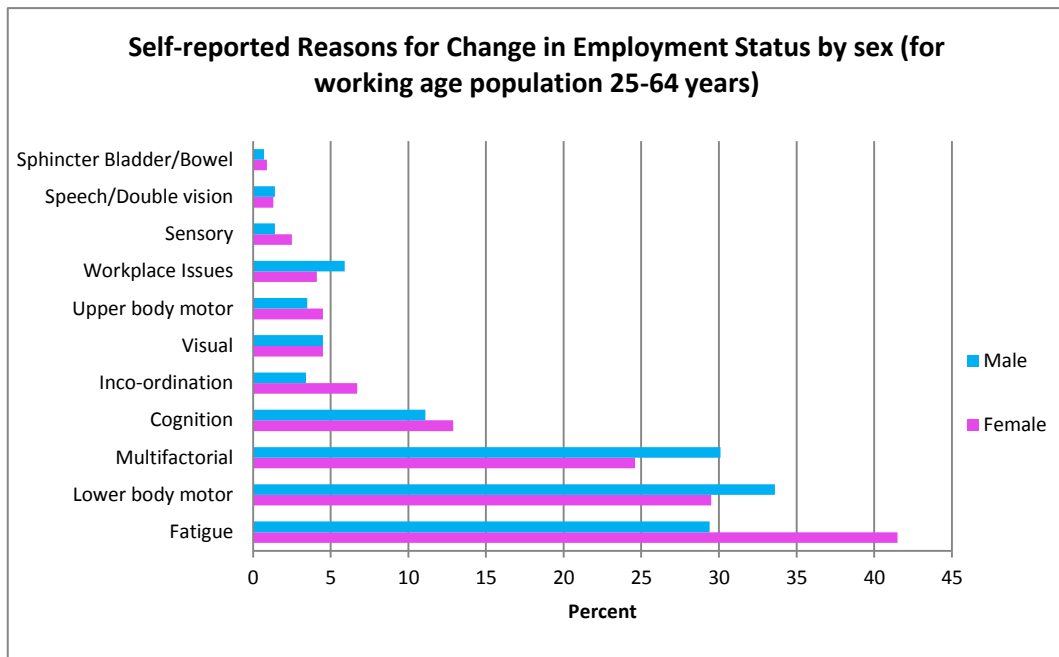


Figure 3.7b Reasons for change in work status by sex

For the MS working age population, the most common descriptions of how their work status had most recently changed due to MS were cessation of employment and reduction of working hours (Figure 3.8a).

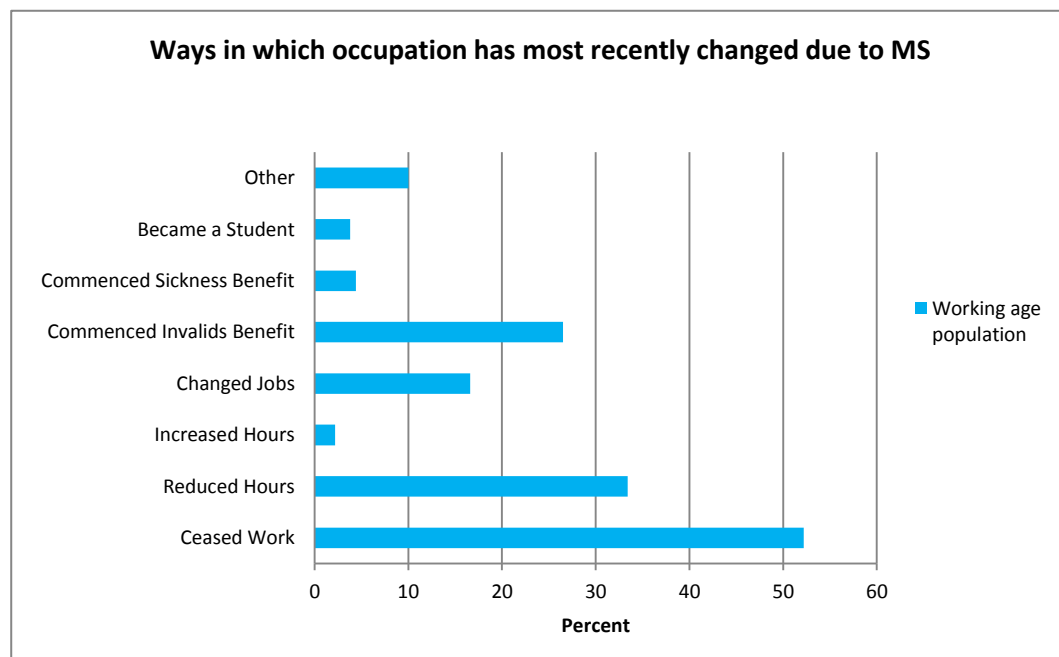


Figure 3.8a Ways in which work status had changed

When compared with females, males were 2.66 times more likely to report commencing the sickness benefit ($p < 0.01$, CI 1.53-4.61) and 1.65 times more likely to report commencing the invalids benefit ($p < 0.01$, CI 1.25-2.18), whereas females were 1.46 times more likely to report a reduction in their working hours than their male counterparts ($p = 0.01$, CI 1.10-1.94) (Figure 3.8b).

The lower proportion of females commencing a benefit may reflect the earning capacity of their partner as government benefits, other than the national superannuation, are means tested. If their partner earns above the set threshold, the person with MS will be ineligible to receive support in the form of a government benefit. Working reduced hours may also been an option more readily available to females, as in NZ society it is not uncommon for females to work part time whilst raising a family, whereas men more commonly work full time throughout their careers, therefore the option of part time work may not be offered to or considered by males with MS.

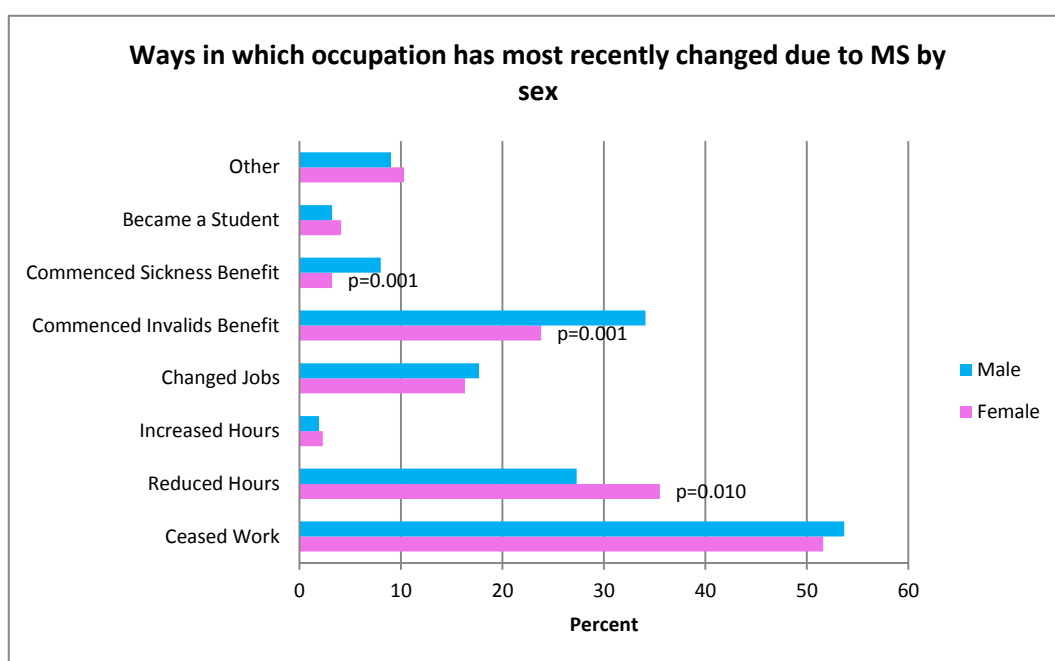


Figure 3.8b Ways in which work status had changed by sex

3.5.11

Work status by higher education

Analysis of the data showed that 51.4% of the working age MS population held a post secondary school qualification compared with 41.6% of their NZ population peers.

However 54.5% of the MS population who held a higher qualification were not working compared with 14.8% of their NZ population peers ($p < 0.001$) (Figure 3.9a).

The results indicated that for both the MS population OR 1.47 (CI 1.21-1.79); and the female population OR 1.48 (CI 1.18-1.85, $p < 0.01$) there is a 1.4 times greater chance of remaining in work if they hold a post high school qualification (Figure 3.9b). For the male MS population the results do not reach significance as the CI contains 1 (OR 1.45, CI 0.97-2.16, $p = 0.04$).

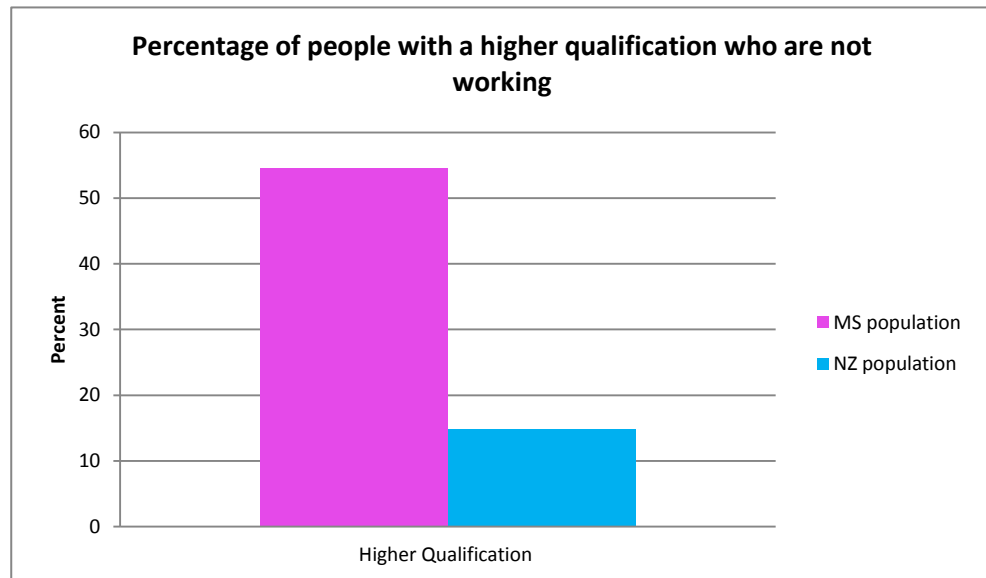


Figure 3.9a Proportion of MS and NZ working age population who hold a post high school qualification but were not working on census day

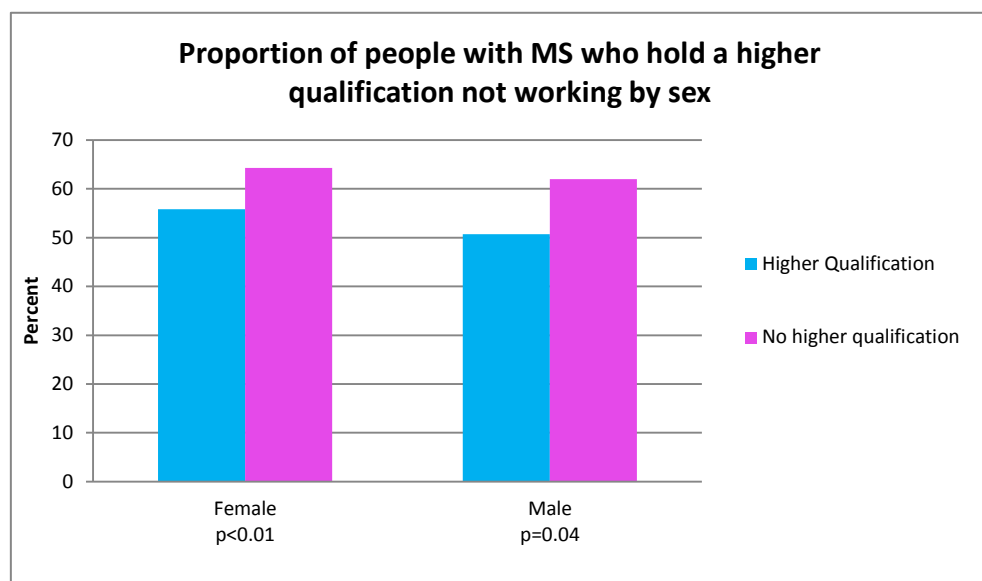


Figure 3.9b Level of qualification for MS working age population who were not working on census day by sex

People who reported their work status had changed due to MS were 1.3 times (OR 1.29, CI 1.04-1.59) more likely to hold a post high school qualification than those with no change in employment ($p=0.02$) (Figure 3.9c). When stratified by sex, females displayed the same trend with an OR 1.43 (CI 1.12-1.82) indicating that if they reported a change in work status they were 1.4 times more likely to hold a post high school qualification than those who stated they had not experienced a change in work status due to MS ($p<0.01$). For the male MS population, there was no difference in educational level between those who reported a change in work status and those who did not ($p=0.61$) (Figure 3.9c).

This may indicate that for females who hold a higher qualification there may be a greater range of work options available to them due to their knowledge being in demand. Their change in employment status may be leaving the workforce, however it may also indicate they have more flexibility for changing their hours of employment, or changing the type of work they have been doing. As the result did not reach significance for males, it may indicate that options for changing hours or type of work are less available to males with MS.

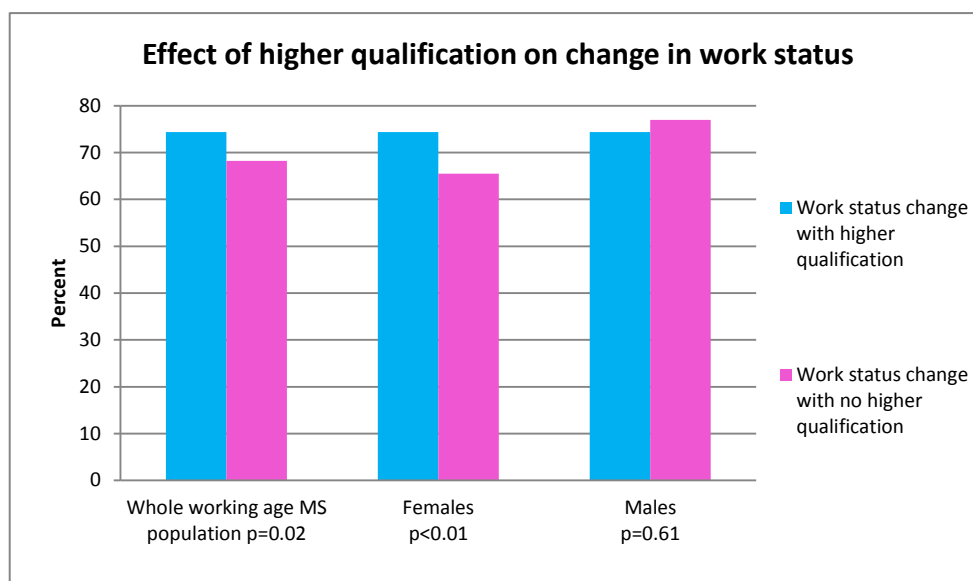


Figure 3.9c Proportion of people with and without a post high school qualification who report a change in work status

Comparison was made between the census day occupation and the original occupations people with MS had held in relation to their qualification level. Figure 3.9d shows a significant change in occupation for people with a post high school qualification.

People who were not working on census day and held a post high school qualification were 11 times more likely to have originally worked in a professional occupation (OR 11.24, CI 5.26-23.81), and three times (OR 2.84, CI 1.15-6.99) more likely to have been in the trades/technicians group when compared with those in the machinery operator/labourer group ($p < 0.001$). The CIs for the clerical/administration workers and sales/community workers groups contained 1 making the result not significant. Although the magnitude of this result is likely to be a reflection of the educational requirements of the occupations most affected, it does illustrate the effect of the disease on people with MS throughout the occupational spectrum. People with higher qualifications who are employed in professional occupations have a large amount of resources invested in their knowledge and position, as such if they are no longer in the workforce, there are no longer returns on that investment to the individual or society. .

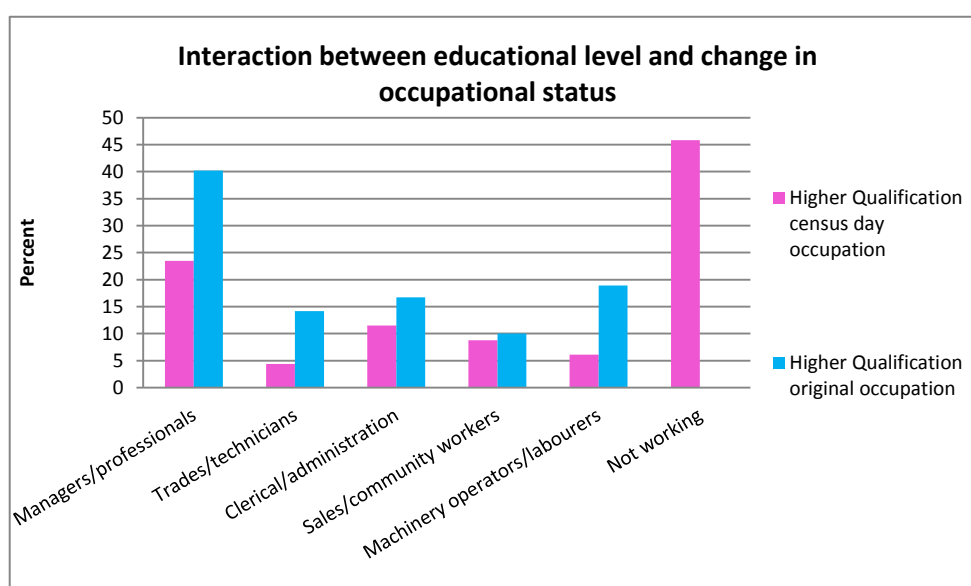


Figure 3.9d Proportion of people with MS who hold a post high school qualification by original and census day occupation group

3.5.12

Work status by marital group

Marital group was associated with work status, with those people who are divorced/separated/widowed 1.88 times less likely to be working than those who are never married/married/in a partnership ($p < 0.001$, CI 1.47-2.40) (Figure 3.10). When stratified by sex, females who are divorced/separated/widowed are 2.04 times less likely

to be working than those who are never married/married/in a partnership ($p < 0.001$, CI 1.53-2.71). Although a higher percentage of divorced/separated/widowed males are not working, the analysis does not reach significance for difference in work status by marital group for males ($p = 0.23$) (Figure 3.10).

People who are in the divorced/widowed/separated group may be less likely to be working due to less support at home resulting in them being unable to meet the demands of work, home life and cope with the disease process. However other factors which have not been assessed in this study such as the effect of disease on mood, or other support networks available to assist them, may contribute to their ability to continue in the workforce. Disease related factors, as well as other demographic factors also contribute to marital status and are discussed in Chapter 5.

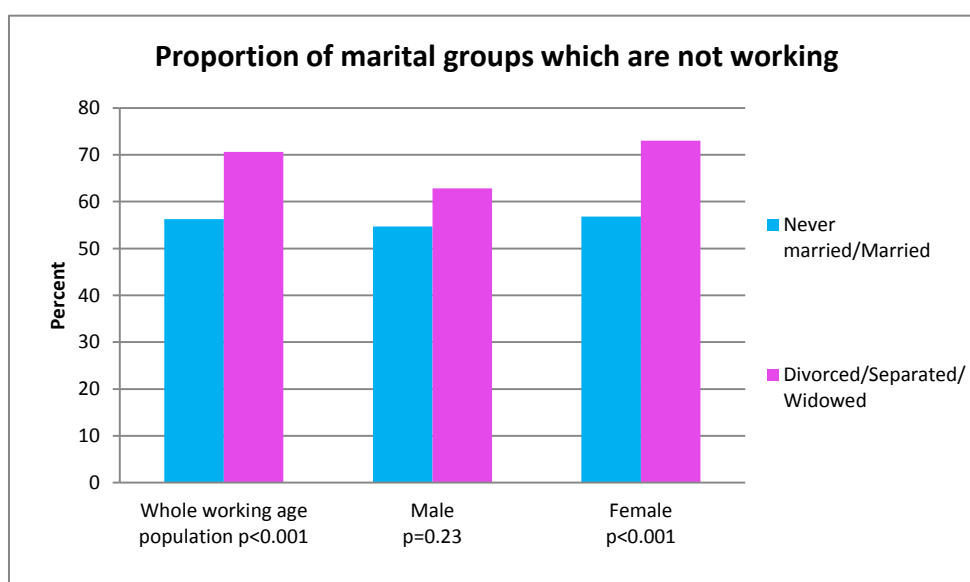


Figure 3.10 Relationship between marital group and work status for the whole working age MS population and stratified by sex

3.6

Factors predicting loss of work status

Bivariate logistic regression was used to determine which factors relating to multiple sclerosis clinical characteristics and demographic features predicted loss of work status in working age (25-64 years) people with MS. Modelling was run in steps. The first stage was regions, which included the regions in six centroids, three regional areas, Auckland and the rest of New Zealand, and no regional breakdown. When divided into six and three

regions, the confidence intervals became very wide due to the small numbers in some of the cells. When comparing the results from these models with the Auckland/rest of New Zealand model and the no region model, the factors included in the final table were very similar indicating that although there was a slight regional influence from Auckland, this was not strong enough to significantly alter the model effect.

Marital status was then put into the model as three groups; never married, married, and divorced/widowed/separated, and two groups; never married/married, and divorced/widowed/separated. We investigated what effect each marital group had on work status, and found both the never married and the married groups had a similar effect on work status, whereas the effect was different for the divorced/widowed/separated group. The two group variable was retained as it made the greatest contribution to the model effect for predicting change in work status.

Finally we divided occupational group into generic variables based on occupation title; eight occupational groupings and five occupational groupings, and also a variable based on occupational function; mainly cognitive/sedentary, light physical, and heavy physical. We found that the variable with eight occupational groupings resulted in very wide confidence intervals due to the small numbers in some of the cells. Grouping by occupational function did not increase model fit; however the variable with five occupational groups gave sufficient numbers in the cells for reliable confidence intervals and contributed to model fit.

The final model for predicting loss of work status for people with MS in New Zealand includes no regional breakdown; two marital groups; Never married/married and Divorced/widowed/separated; and five occupational groups; Managers/professionals, Trades/technicians, Clerical/administration workers, Sales/community workers, and Machinery operators/labourers can be seen in Table 3.6.

3.6.1

Model predicting loss of work status

The full model for not working containing all predictors was statistically significant, Chi-square (10, N=1246) = 107.3, $p < 0.001$, indicating that the model was able to distinguish between respondents who were working and those who were not working. The model as a whole explained between 8.3% (Cox and Snell R Square) and 11.1% (Nagelkerke R Square) of the variance in work status and correctly classified 62.4% of

cases. The remaining variance shows that the individual and their circumstances play the largest part in determining work loss.

As shown in Table 3.6, age, original occupation, sex, education and marital status were the independent variables which made unique, statistically significant, contributions to the model. The strongest predictor of not working was age, with all participants 35 years and over more likely to report that they are not working when compared with those in the 25-34 year age group. The oldest age group (55-64 years) as most affected with an odds ratio (OR) of 4.48 (CI, 2.85-7.06, $p < 0.001$). This indicates that people 55-64 years of age with MS are nearly four and a half times more likely to report they are not working than those in the 25-34 age group, after controlling for all other factors in the model.

The occupation in which people with MS had originally been employed influenced their work status ($p < 0.01$). Sales people and community workers (OR 1.57, CI 1.04-2.38); and labourers and machinery operators (OR 1.68, CI 1.16-2.42); were over 1.5 times more likely to be not working than people who were originally working in professional occupations. The result was not significant for people working in clerical and administration roles or trades and technicians positions. This would indicate that people who are in more physical roles have a greater chance of loss of work status.

Table 3.6 Bivariate logistic regression model predicting loss of work status

Variables		Odds Ratio	95% Confidence Intervals for Odds Ratio		(p value)
			Lower	Upper	
Age	25-34 years				<0.001
	35-44 years	1.53	0.97	2.41	
	45-54 years	1.74	1.12	2.70	
	55-64 years	4.48	2.85	7.06	
Original occupation	Professionals				0.01
	Trades	1.50	0.98	2.30	
	Clerical	0.96	0.68	1.36	
	Sales and community workers	1.57	1.04	2.38	
	Machinery operators and labourers	1.68	1.16	2.42	
Marital status	Married or never married				0.01
	Divorced/widowed/separated	1.48	1.10	1.98	
Sex	Female				0.02
	Male	0.71	0.53	0.96	
Post secondary qualification	Post high school qualification				0.03
	No post high school qualification	1.33	1.02	1.72	

People who were in the divorced/widowed/separated group were 1.5 times more likely to be not working than those who were in the married/never married group (OR 1.48, CI 1.10-1.98, $p=0.01$).

Males had an OR of 0.71 (CI 0.53-0.96, $p=0.02$) for not working when compared with females after controlling for all other variables in the model. This means that males were 1.4 times more likely to be working than females.

Level of education also made a significant contribution to the model ($p=0.03$). People who did not hold a post high school qualification were 1.3 times more likely to be not working than those who had a higher education (OR 1.33, CI 1.02-1.71). This means that a higher qualification is protective for work status.

Although all two way interactions were put into the analysis none were retained in the final model, indicating that the fitted interaction terms did not increase the model effect. This suggests that based on the evidence we have in this data set each variable outcome is acting independently from the others.

3.6.2

Goodness of fit – logistic regression model

The logistic regression model was assessed for best fit by changing one independent variable whilst keeping all other independent variables constant. The variables we tested were region: Auckland and the rest of NZ; Urban (Auckland, Wellington, Canterbury) and Rural (all other regions); and sex: Male and Female. These variables were selected for further analysis for the following reasons:

- Region: Auckland is New Zealand's largest city with around one quarter of the country's total population and had a lower response rate than the other regions, therefore we wanted to ensure that there was no bias introduced by this region.
- Region: Equally we wanted to ensure that the MS populations in urban and rural regions of New Zealand were not significantly different.
- Sex: As 75% of the MS population is female, and there was a lower response rate from males, it was important to investigate whether the female population was driving the model and concealing potentially different drivers of work force participation in the male MS population.

All alternate models produced similar results with age consistently being the strongest predictor of people with MS not remaining in work.

3.7

Correlations between age and disease characteristics

Age is a recognised confounder in epidemiological studies^{100,101} therefore we examined the correlation between age and the disease characteristics of MS; namely MS phenotype, level of disability, and disease duration.

Correlation analyses using the Spearman Rank Order test were used to determine the strength and direction of the linear relationship between age and level of disability and age and disease phenotype as these variables are ordinal or ranked data. The Pearson Product-Moment Coefficient was used to determine the strength and direction of the linear relationship between age and years since diagnosis as it is a continuous variable. Preliminary analyses were used to ensure there was no contravention of the assumptions of normality, linearity and homoscedasticity.

There was a moderate positive correlation between age and disease duration since diagnosis, $r = 0.428$, $n = 1727$, $p < 0.0001$, with older age associated with greater disease duration (Figure 3.11a).

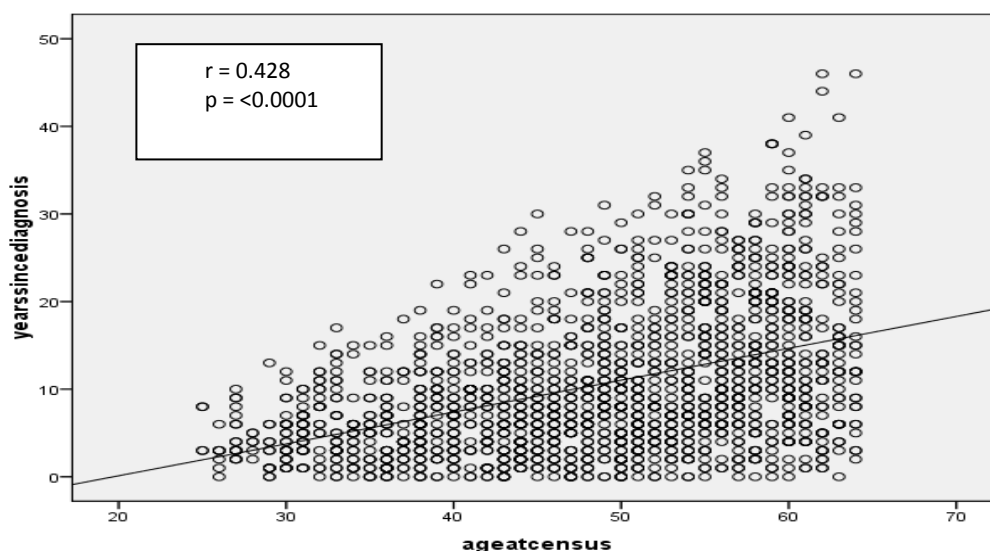


Figure 3.11a Pearson's product moment coefficient for age and disease duration

There was a moderate positive correlation between age and level of disability, $\rho = 0.361$, $n = 1727$, $p < 0.0001$, with older age associated with higher levels of disability (Figure 3.11b).

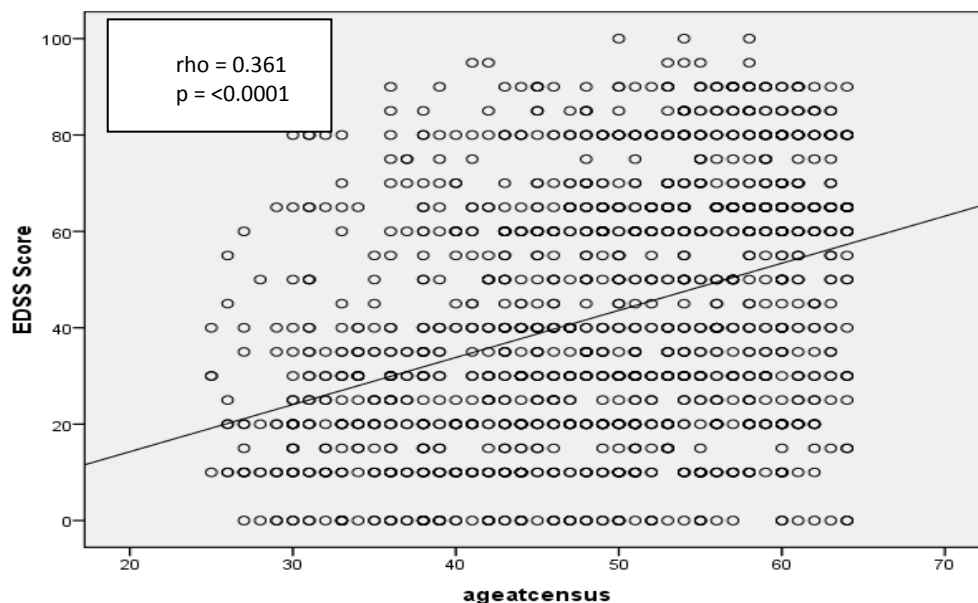


Figure 3.11b Spearman's rank order correlation for age and level of disability (EDSS coded in multiples of 10 i.e. EDSS of 2.0 = 20 on graph)

There was a moderate positive correlation between age and MS phenotype, $\rho = 0.397$, $n = 1727$, $p < 0.0001$, with older age associated with the progressive forms of the disease, in particular PPMS (Plot not shown).

The results indicate that age is positively correlated with all MS disease characteristics. This suggests that in the model predicting loss of work force status age is acting as a proxy for MS characteristics. This would indicate that a diagnosis of MS alone will predict loss of work for people with multiple sclerosis in New Zealand.

3.8

Discussion

This study was a cross-sectional design with a point prevalence day which coincided with the New Zealand national census day, March 7th 2006. The study population was sourced from both community and clinical referrals, using capture-recapture methods, which estimated over 96% of the New Zealand MS population was identified, essentially comprising a census of the MS population. The final questionnaire response rate was 71.1%, 2073 individuals. Comparison between responders and non-responders for both the full study population and the working age study cohort showed that over all the final population for the study was representative of the whole MS population.

The main demographic variables for the entire MS population are similar to those from international cohorts^{263,264,297,321}. Women represent 75% of the New Zealand MS population and 93% are Caucasian. The mean age of the whole study population was 52 years, with the mean disease duration being 12 years. 63% of all respondents were not working at the time of the study, although over 90% of the MS population over 24 years of age had a work history.

This chapter examined the factors which predicted loss of work status in those of working age (25-64years) in the MS population in New Zealand. The findings from the analysis of the employment data for the New Zealand multiple sclerosis population confirm and extend earlier international work which showed that multiple sclerosis profoundly and negatively influences work force status^{264,297,302,308}.

Loss of work at a young age with increased effect with increasing age was evident for people with MS, with those in the 55-64 year age group most affected. In contrast, in the general New Zealand population there is a fairly stable level of employment for men throughout the working age group, with 90% of males in the 50-54 years age group still working. At around 40 years of age females in the general New Zealand population increase in work participation as they re-enter the workforce, with 80% of females in the 50-54 years age group still working. At this point there is a steady decline within the general population with people in the 55-64 year age group starting to leave the workforce. However at 65 years of age 70% of NZ males and 50% of NZ females are still working as compared with 25% of males and 15% of females with MS.

The study observed that all age groups experienced a loss of work status, with the effect increasing with each older age group. Similarly previous studies have found that

people in the younger age groups were more likely to be employed, have lower levels of disability and milder disease symptoms^{321,324,331}. As this study's population were all of working age, there are implications for the individual, their families and society. A person who is unable to work is likely to have no source of income and will therefore need some sort of support to live. They will also not be paying taxes or spending their disposable income in the community. The younger they are when they leave the workforce, the greater length of time they will need to be supported by their family and society.

Age was observed to be acting as a proxy for MS disease characteristics. The study found loss of work was associated with disease phenotype, and influenced by level of disability and disease duration since diagnosis. Loss of work status manifests early in the disease course, before 5 years disease duration, and at low levels of disability as assessed by the EDSS.

People with progressive forms of the disease, higher levels of disability and longer disease duration had a higher OR for loss of work when compared with those with RRMS. However this finding appeared to be driven by a combination of female gender and disease phenotype, with males with PPMS, and higher levels of disability as measured by the EDSS being less likely to report loss of work status. Jacobs et al. (1999) also identified progressive disease as being associated with loss of work, however the analysis combined both SPMS and PPMS into a single category and the MS population was not stratified by gender which may account for the variation in results³²⁰.

The study showed that after controlling for all other factors in the model, males were nearly one and a half times more likely to be working than females. Previous studies have found conflicting results with some finding male gender predictive of loss of work status^{302,321}, whilst others found male gender protective for loss of work status^{323,324}. Each of these studies differs in population size, sample source, study design and methods limiting the comparisons that can be made between them and the current study. In New Zealand there are policies for equal employment opportunities, tax payer funded education to the end of high school, and student loans for support during tertiary study available to all New Zealand citizens. As such it would appear that disease related factors rather than social or demographic reasons may be the drivers for males in New Zealand being more likely to remain in the work force than females. The observation that over half of females with early stage (relapsing-remitting) disease are not working, and that those with progressive forms of the disease are between 1.5 and 2 times more likely to be not working than females with RRMS has implications for people with MS, clinicians and

employers as females comprise 75% of the MS population. Clinically, there is a need to question whether the disease process for females is different to that of males; if the difference in disease between the genders manifests as specific symptoms which are the reason for females leaving the workforce, and if so what treatments or interventions are best utilised to minimise the MS symptoms which affect the female MS population's ability to work. Socially, there may be cultural reasons why females with MS leave the workforce. There may be fewer expectations for women to work, or they may have sufficient financial support from their partners that they do not need to work. If they had only been working part-time, the change in income from paid work to the invalids benefit may not be great enough for them to choose to stay in work. As three quarters of people with MS are female this represents a large proportion of the MS population who are not in the workforce, and are potentially being supported by their families and society.

A further observation was that males who were in the 5-9 years disease duration from diagnosis group had a higher percentage working than males in the 0-4 years and >10 years disease duration groups. This may indicate that males with medium duration disease course re-enter the workforce for a short period of time. A possible reason for increased work at this point is that they may have psychologically come to terms with the diagnosis of MS, possibly have fewer relapses, or have commenced on disease modifying therapy which is controlling their symptoms thereby better enabling them to work. Due to the cross-sectional nature of this study giving a 'snap shot' of people with MS in NZ at a point in time this is purely an observation and would need further study using prospective longitudinal methods to assess its validity.

Previous studies have identified higher levels of EDSS or disability in relation to occupation correlated with loss of work^{297,308,322}; with those in occupations with higher physical demands more likely to leave the workforce^{302,328,336}. In this study, the original occupation people were trained for was found to be an independent predictor of loss of work status after controlling for all other factors in the model. Sales, community work, machinery operator and labourer employment, occupations with moderate to heavy physical demands, had the highest odds ratio for not working. However, when stratified by sex the findings from this study showed females in occupations which require a higher cognitive input were significantly less likely to remain in the work force, whilst for males, it was those in more physical occupations; labourers, trades, and machinery operators who were more likely to leave the workforce. Verdier-Taillefer et al. (1995) had also stratified occupational demands by gender, finding that women had greater odds of

unemployment for work requiring physical strength whereas men were more affected by jobs with a rigid work schedule³³⁶. Using case-control methods and a sample size of 171 cases, this study compared employed people with MS with unemployed people with MS; it found that strenuous work was the greatest risk factor for loss of employment after controlling for all other factors. The differences between the two studies may be due to study design, sample size, or different occupational roles, cultures and composition as the studies were conducted in different countries and temporally a decade apart.

Disease related factors may affect people in occupations which have higher physical demands, reducing their ability to perform their role as levels of disability increase. Previous studies have identified physical disease related symptoms such as balance and walking difficulties³²⁷, physical disabilities³³¹, mobility problems³²¹, and type of work such as heavy physical work^{302, 335}, as key factors in loss of work status. Other studies using assessment tools other than the EDSS have identified fatigue^{331, 332}, upper limb motor skills³³², and cognitive deficits as predictors of loss of work status³²⁸. Fatigue, lower body motor function, multiple factors and cognition were the most frequently reported reasons for change in work status for the MS population, these findings having been previously been reported^{321,322,324,330}. However when the study's findings were stratified by sex, females were more likely to report fatigue and cognition as factors behind change in work status, whilst men stated lower body motor function and multiple factors were the main elements to their change in work status. These differences in reasons for change in job status are reflected in the occupations most affected for males and females in the study. Only the EDSS was used to measure levels of disability in this study, however based on occupational description it appears that both increasing physical disability and cognitively demanding roles are strong predictors for loss of work status in the New Zealand multiple sclerosis population. Future studies would benefit from using a measure of cognitive disability and fatigue to provide quantifiable data to elucidate these findings.

Cessation of employment and reduction of working hours were the most common reasons given for the most recent change in work status due to MS. Once again there was a significant difference between men and women, with men more likely to go onto some form of government benefit, whilst women were more likely to reduce their hours of work. One explanation for this may be that due to means testing in New Zealand, some women may not be eligible for a government benefit due to the level of income earned by their partner. Alternatively there may be fewer opportunities for men to negotiate part-

time or flexible hours, as men more commonly work full time throughout their careers, resulting in them leaving the workforce. One other study has reported a similar result, finding females were more likely to report staying employed in some capacity when compared with the males in the study³⁹⁶. This study was held in the USA where the health and welfare system is quite different to New Zealand. The authors suggest that this pattern of change in work status is likely to be linked to retirement and disability pensions which, in the USA, are based on continuous full-time employment histories which women are less likely to have as they tend to leave the workforce for periods of time to raise children. Unlike the USA, NZ does not have an early retirement option for most people, but there is support in the form of invalid and sickness benefits from government agencies. As the New Zealand study has similar findings to the USA study, despite contrasting health and welfare systems, the difference in change in work status between males and females may be more strongly linked to disease phenotype and disease symptoms such as fatigue and lower body motor function than socioeconomic factors.

Studies consistently record high levels of post high school qualifications in the MS population^{308,328,331,336}, a finding which is replicated in the current study with over 50% of the working age MS population holding a higher qualification. The results indicated that those who hold a higher qualification are more likely to retain workforce status. These findings are supported by other studies^{308,321,328,331} indicating that people with MS who hold a higher qualification may have a greater range of options available to them to assist maintaining work force status to some extent. Insight into these options is given by Smith and Arnett (2005) who observed that the group who had cut back their hours had significantly higher qualifications than those in the group who were not working³³¹. This would indicate that employers may be more amenable to negotiating alternative working arrangements with someone who has knowledge and skills that are in demand or difficult to replace.

The current study found that people with a higher education were more likely to report a change in employment status than those who did not hold a higher qualification, a finding also reported by Smith and Arnett (2005)³³¹. In contrast to previous studies, the current study further investigated this finding by sex, observing that the result was limited to the female MS population. This observation may reflect that females with higher degrees are more able to negotiate flexible hours or working arrangements to accommodate their disease-related needs. Working part-time is less common for males in society and this too may be reflected in the male MS population. Equally there may be

fewer expectations on women with MS to be the primary income earner, and as such they may have greater flexibility in negotiating their work commitments.

Marital status was found to be correlated with work status with people who were divorced, widowed or separated more likely to report that they were not working than those who were never married or married. Previous studies have found mixed results as to whether MS affects marital status; however none have published on work status in relation to marital status. Hammond et al (1996) found that there was a higher level of divorce or separation in people with MS who had higher levels of disability³⁰⁸. In two UK studies, no difference was found in divorce or separation rates between people with MS and the general population^{318,319}. In this study, people who have never been married were more likely to be younger, earlier in their life course, with lower levels of disability and as such more able to retain work status. Those who are in the married group were older, but were more likely to have the support of a partner to assist with the day to day demands of life, leaving more energy reserves for maintaining work status. In contrast those people in the divorced, separated or widowed group were older and had higher levels of disability; this with the added demands of coping without the support of a partner may mean they are less able to maintain their position in the work force. Alternatively they may have been unable to retain work force status due to the effects of the disease course, which placed added pressure on their marriage leading to its dissolution. As this is a cross sectional study, this is purely speculation as it is not possible to determine temporal cause and effect from descriptive observational data.

In summary, MS profoundly affects the workforce status of New Zealanders in the 25-64 year age group living with the disease. The effect occurs at a young age, early in the disease course and at low levels of disability. Age as a proxy for disease characteristics is the strongest predictor for loss of work after controlling for all other factors. Females are less likely to be working than males with MS, with females with progressive disease and higher levels of disability most affected. Despite a high proportion of people with MS holding a post high school qualification, over fifty percent of those with a higher qualification were not working. Departure from the workforce was reported by participants to be due to disease symptoms, in particular fatigue and cognitive function in women, and lower body motor skills in men. Females in occupations requiring higher levels of cognitive function and males in occupations requiring greater motor skills and strength are more likely to report loss of workforce status. The key factors predicting loss of work in the logistic regression model were age, original occupation, marital status,

sex and educational level. However as they only account for between 8.3% and 11.1% of the variance in work status, it must be surmised that a complex interaction of factors not tested for along with a confirmed diagnosis of MS is the strongest predictor for loss of work status in the New Zealand multiple sclerosis population. The interaction between demographic features, socioeconomic factors and disease characteristics in the analysis emphasise the complexity of multiple sclerosis and its effect on workforce status for those living with the disease.

Chapter Four

Income and multiple sclerosis

4.1

Background

Income from paid employment contributes to financial security for the individual and their family; and further, it contributes to society through payment of taxes and spending of disposable income. It is useful for addressing many kinds of situations ranging from finding affordable housing, feeding, clothing and caring for families, to paying the costs of healthcare. People with lower incomes will have more difficulty than the affluent in coping with costs of life, and these inequalities of income will affect their ability to access the healthcare and support services they require as a result of their illness.

This study explored the income status of people with MS aged between 25 and 64 years living in New Zealand on 7th March 2006. The information was collected through self-report responses to a questionnaire mailed to participants at home. Many of the questions were identical to those asked in the NZ national census questionnaire to enable direct comparison between the MS population and the general population of New Zealand (see Chapter 3). This chapter focuses on the level and sources of personal income in relation to a range of demographic variables and disease related characteristics. These variables included age, sex, marital status, region of residence, education, occupation, work status, MS phenotype, level of disability and duration of disease.

4.2

Objective

MS is associated with a significant change in an individual's physical and cognitive ability affecting their opportunity to be employed. We have shown in Chapter 3 that the disease effects of multiple sclerosis impact on employment status. In this chapter we examine how this change in work force status affects the income status of people with MS in New Zealand.

The aims of this chapter are firstly to report the income status of people with MS throughout New Zealand on the point prevalence date of March 7th 2006 (New Zealand census day), and to compare this with the income status of the general New Zealand

population based on the 2006 NZ national census data. Secondly, to identify the disease characteristics and demographic factors which determine low levels of income in the MS working age population.

4.3

Methods

This study was a cross-sectional descriptive study using capture-recapture methods which ensured participants were referred from a variety of sources enabling over 96% (by capture-recapture estimates) of the MS population in New Zealand to be located and invited into the study (see Chapter 2). The NZNMSPS achieved a moderately-high questionnaire response rate of 71.1% (2073 participants), with a relatively uniform distribution from throughout New Zealand, resulting in a representative sample of MS participants (see Chapter 3 for detailed discussion). All other details pertaining to the methods of this study have described previously in Chapters 2 and 3.

4.3.1

Participants

We used two populations for this study. The first group included all people with MS in New Zealand. The second group consisted of all people resident in New Zealand on census day. Participants with MS were identified and matched from various referral sources including regional MS Societies, hospital databases, neurologists' databases and the NZHIS discharge code list (see Chapter 2 for detailed explanation).

4.3.1.1

Working age population

As described in Chapter 3, there were too few participants with multiple sclerosis under 25 years of age ($n=45$) for robust statistical inference, and the universal superannuation (a national tax-payer funded retirement pension) is available for all people 65 years and over in New Zealand, which could confound the effect of disease on income for this group of people, as such, this study has limited its income analysis age group to a working age of 25-64 years (see Chapter 3 for definition of working age population).

4.3.2

Questionnaire

All participants with clinically definite MS who had consented to be part of the NZNMSPS were sent a questionnaire via post to self-complete, and a stamped return-addressed envelope in which to return the questionnaire (see Chapter 2). The questionnaire included questions on total personal income from the past 12 months, sources from which that income was obtained, and general demographic questions identical to those in the 2006 Statistics New Zealand Census questionnaire to enable comparison between the MS population and the general NZ population. A full list of variables that were recorded can be found in Chapter 3 (Table 3.1). The questionnaire is described in detail in Chapter 2.

4.3.3

Data management

Data was dual entered on each of two identical custom made Microsoft Access databases to collate the data from the questionnaires (see Chapter 2).

4.4

Statistical methods

Data was collated in the Microsoft Access database before being exported to the Statistical Package for Social Sciences (SPSS) version 17.0 for analysis³⁸⁷.

4.4.1

Statistical analysis

Descriptive analysis of the data included summary statistics of the raw data. Cross-sectional analysis of the relationship between socioeconomic factors, disease phenotype, disability and duration of disease was performed using the chi-square test for independence, with all results quoted as significant at the $p=0.05$ level, and the confidence intervals (CI) expressed at the 95% level. The variables assessed were; demographics including age, sex, region of residence and marital status; socioeconomic factors including income, education, occupational group and employment status; and disease characteristics including MS phenotype, EDSS, and years since diagnosis.

Direct bivariate logistic regression was performed to determine the effect of a number of factors on the likelihood that responders would report that their income was below the median annual individual income for people with MS. Bivariate logistic regression analysis is used when the dependent variable is dichotomous in nature³⁸⁹. In this model the dependent variable was dichotomised as below the median annual individual income for people with MS (<\$20,000 NZ) (1) and above the median annual individual income for people with MS (>\$20,000 NZ) (0).

A second model was tested to determine which factors would predict an income below the median annual individual income for the New Zealand working age population. In this model the dependent variable was dichotomised as below the median annual individual income for the NZ population (<\$34,750 NZ) (1) and above the median annual individual income the NZ population (>\$34,750 NZ) (0).

The models contained the same ten independent variables; age, sex, region of residence, education, marital status, original occupation, work status, MS phenotype, level of disability and duration of disease. Regression coefficients (Exp B in SPSS) are reported as odds ratios, indicating the strength of association between an independent variable and the dependent variable. A coefficient of greater than 1.00 indicates increased odds; a coefficient of less than 1.00 indicates decreased odds; and a coefficient of 1.00 represents no change in the odds of being in the predictor category of the variable under consideration. To determine if the likelihood of the odds ratio for individual predictors differing by greater than 1.00 was more than that which could be expected by chance, both a Wald test to assess statistical significance and confidence intervals for the effects are used³⁸⁹. Statistical significance was calculated to assess the likelihood of observing an association at least as large as the one found in the model, if in reality no association were present in the source population. It was quoted as significant with a p value ≤ 0.05 , indicating that there is a less than 5% probability that the observed result could have occurred by chance error. Confidence intervals were quoted at the 95% level indicating that there is a 95% probability that the true value lies within the confidence interval. When the confidence interval does not equal 1.00, this is similar to finding that the association is statistically significant with a p value ≤ 0.05 ^{100,101}. To investigate the dependence between independent variables, initial models were fitted with no interactions, and all 2-way interactions between lists and the saturated models. Care was taken to check for poorly populated covariate combinations, or cells, particularly due to

the relatively low numbers of males, and people with primary progressive disease hence higher order interactions were not included.

4.4.2

Statistical inference and multiple testing

Multiple comparisons or multiple testing can be of concern in very large data sets where multiple data points are compared between two or more groups simultaneously to assess whether they are different. A statistical test to adjust for multiple testing and minimise Type 1 errors, assumes that the responses are independent and provides a lower bound on likely p values. Type 1 errors are those which produce a false positive result or a result which is not actually there. In the case of multiple testing, the more terms that are put into the comparison, the greater the likelihood that one of those terms will be significantly different purely by random chance^{100,101}.

Multiple comparisons do not present a concern for the analyses in this thesis for several reasons. Firstly the study population is a census of the New Zealand MS population, not a sample of people with the disease, with an estimate of over 96% of the population being identified on capture-recapture analysis. On analysis, the population has been determined to be representative of people with MS in NZ, and there is no evidence of bias between responders and non-responders to the MS study questionnaire (See 3.5.1).

Secondly, the thesis tests three a priori hypotheses which by themselves are unique research questions. The statistical analyses are performed as there is a strong basis for expecting the result to be true; they are not used for repeated statistical testing to explore the data. The analyses test how each of the three hypotheses are modified or changed by other variables to describe the effects on the NZ working age MS population.

4.5

Results

4.5.1 Total annual personal income

The median annual personal income for both the MS respondents aged 15 years and over and the MS respondents in the working age group (25-64 years) was \$20,000. The median annual personal income for the New Zealand population aged 15 years and over

on census night was \$24,400, and for the working age (25-64 years) New Zealand population \$34,750 (Figure 4.1). All age groups over 30 years with MS earned less than their New Zealand peers until the 70 years and over age group, where there was a levelling out of income which can be attributed to universal access to the New Zealand Government Superannuation.

All results presented below apply to the working age population, those people aged between 25 and 64 years of age (see Chapter 2 for detailed explanation of this age group selection).

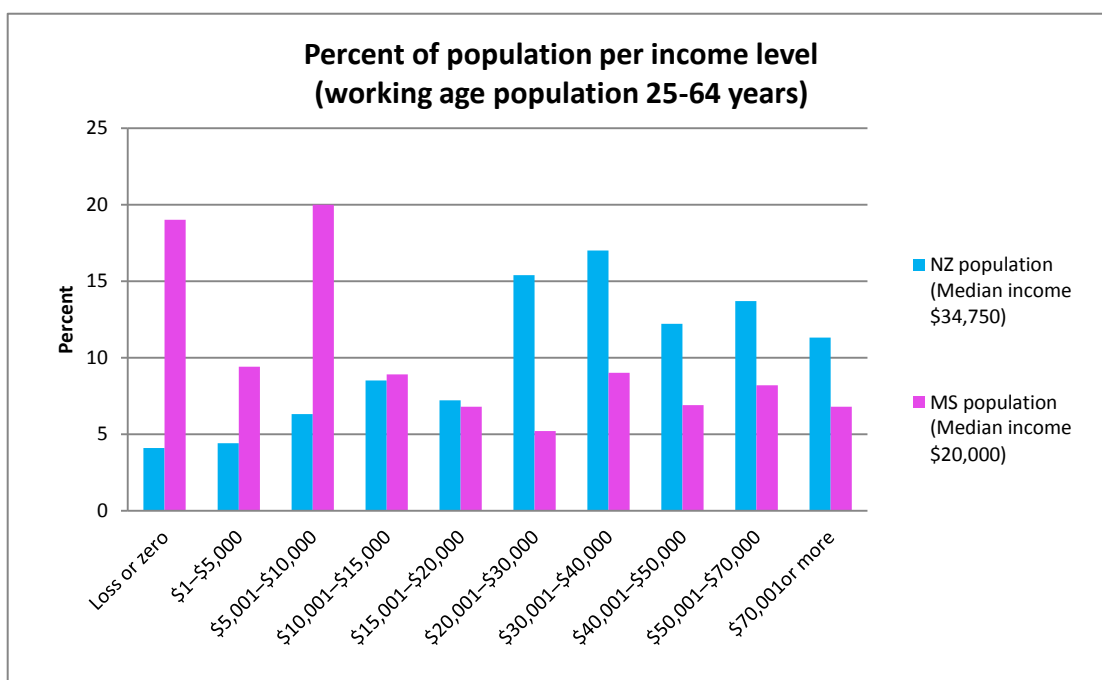


Figure 4.1 Proportion of MS and NZ working age population in each total annual personal income bracket

4.5.2

Total annual personal income by sex

As presented in Chapter 3, both men and women with MS are less likely to be working than the general New Zealand population which is reflected in the lower annual personal income they receive. The median annual personal income for New Zealand men aged between 25 and 64 years was \$41,100, whilst for men with MS of the same age range it was \$25,000. For women, the New Zealand population median annual personal income for this age group was \$25,600, and for the female MS population was \$15,000.

Similar to the general NZ population, there are more men than women with MS in the higher income bracket, and women are overly represented in the loss/zero to \$5,000 per annum income brackets. The higher income levels received by men in the general population can be explained by men being more likely to be in paid work, and to work full time than women. In the MS population, there is no significant difference in the proportion of males and females working ($p=0.17$), however for the group that are still working, the males ($n=168$) are three and a half times more likely to be in full time employment (OR 3.58, CI 2.31-5.55, $p<0.001$) than the females ($n=482$). Overall the MS population group has a proportionately higher representation in the lower income groups than their New Zealand peers (Figure 4.2a, 4.2b).

As this is the age group where people are earning an income to become established in a home, raise families, enjoy a lifestyle and save for retirement, the large gap between the MS population's median annual income and that of their NZ population peers indicates that their opportunities to achieve the same goals in life are likely to be limited due to reduced income levels. Furthermore, with lower levels of income their ability to meet the costs of daily living including home heating, healthy food and health care are likely to be reduced which may lead to poorer health outcomes, and further affect their ability to work and earn an income. As females with MS represent 75% of the MS population, their over-representation in the $< \$5,000$ income group, and underrepresentation in the full time work force represents a large proportion of people with MS who have low incomes and are likely to require some form of financial support from families and society.

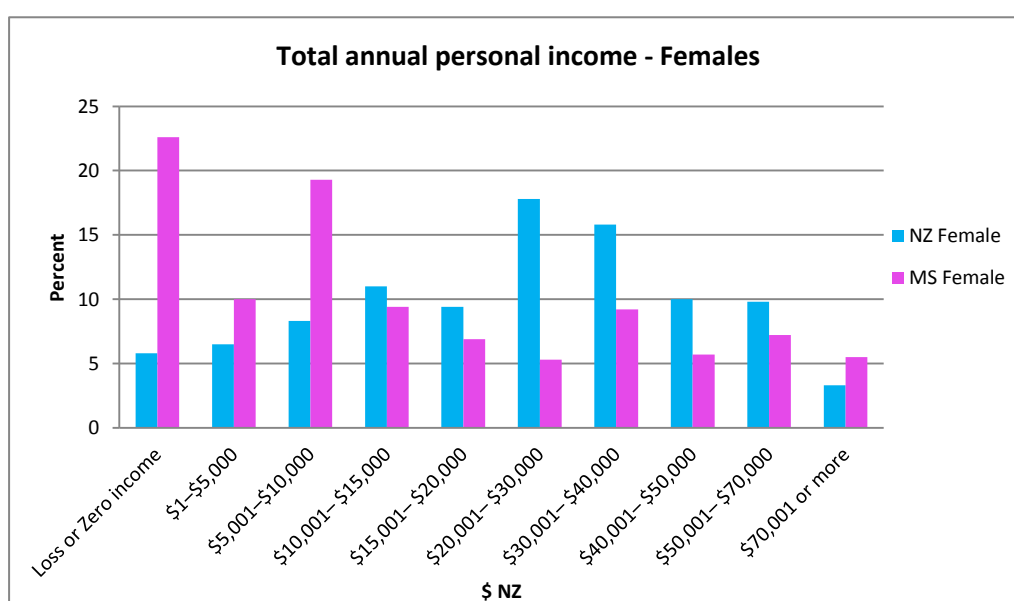


Figure 4.2a Proportion of MS and NZ female working age population in each total annual personal income bracket

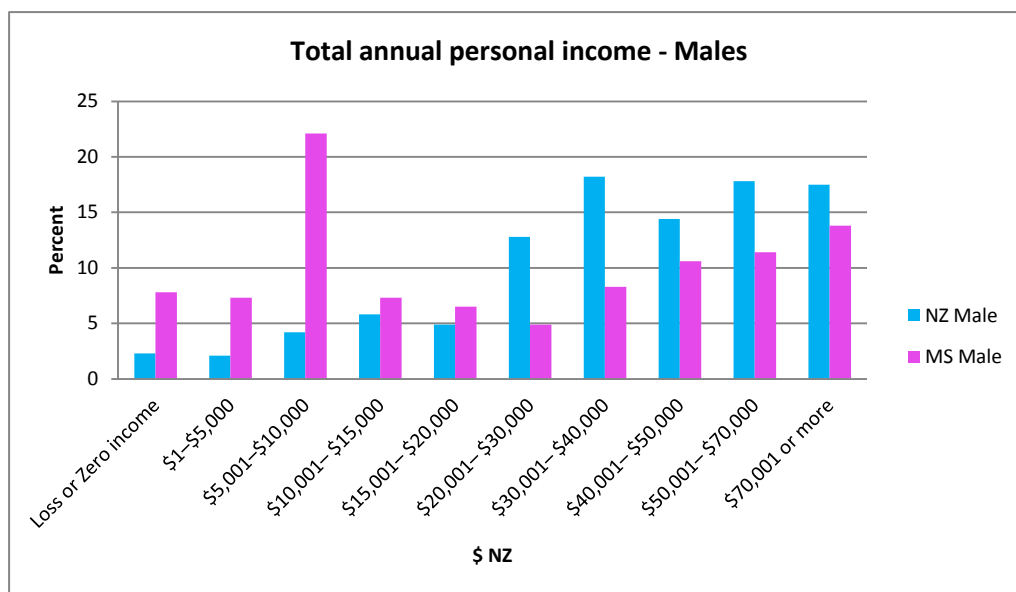


Figure 4.2b Proportion of MS and NZ male working age population in each total annual personal income bracket

4.5.3

Median annual personal income by age group

Income in the general New Zealand population differs by age. Those in the middle age groups tend to have higher median personal incomes than those in younger or older age groups, with men in the 40-49 years, and women in the 45-54 years age bands having the highest median annual individual incomes respectively.

In contrast, both men and women with MS experience their highest median annual personal income at an earlier age than the general NZ population, 30-34 years and 25-29 years respectively. People with MS aged 25-34 years have an OR 3.39 (CI, 2.35-4.90), indicating they are 3.4 times more likely to earn above the median annual personal income for the MS working age population (\$20,000) than people 55-64 years of age. For people with MS aged 35-44 years the OR was 1.86 (CI 1.41-2.45), and those aged 45-54 years the OR was 2.15 (CI 1.67-2.77) for earning an income above the MS working age median relative to people with MS aged between 55 and 64 years ($p < 0.001$).

When the median annual personal income for the NZ working age population (\$34,750) is substituted, people with MS aged 25-34 years have an OR 3.05 (CI, 2.10-4.45), indicating they are 3.1 times more likely to earn above the NZ median than people 55-64 years of age. For the other age groups, people with MS aged 35-44 years have an

OR 1.84 (CI 1.36-2.49) and people aged 45-54 years have an OR 2.02 (CI 1.53-2.67) for earning above the median relative to those people aged 55-64 years ($p < 0.001$). From the 35-44 year age group onwards, the income for people with MS rapidly falls below their age standardised peers in each age group, and remains below throughout all working lifespan age groups (Figure 4.3). This indicates that from a young age people with MS have the potential to earn as much as or more than their NZ population peers, however due to their loss of work status at an early age and early in the disease course, they experience a drop in income in an early working age group, and this decrease in income is observed through each successive age group.

When stratified by sex, females with MS ($n=1197$) in the youngest age group are 4.4 times (OR 4.40, CI, 2.87-6.73) more likely to earn above the median annual personal income for people with MS (\$20,000) and 3.8 times (OR 3.82, CI, 2.42-6.00) more likely to earn above the median annual personal income for the NZ working age population (\$34,750), than females in the 55-64 years age group ($p < 0.001$). Females aged 35-44 years had an OR 2.36 (CI 1.69-3.30), and those aged 45-54 years had an OR 2.46 (CI 1.81-3.35) for earning more than the MS median when compared with females aged 54-65 years. For the NZ population median, females aged 35-44 years had an OR 2.23 (CI 1.53-3.25) and those aged 45-54 years had an OR 2.36 (CI 1.66-3.36) for earning above the NZ median annual personal income when compared with females with MS aged 54-65 years.

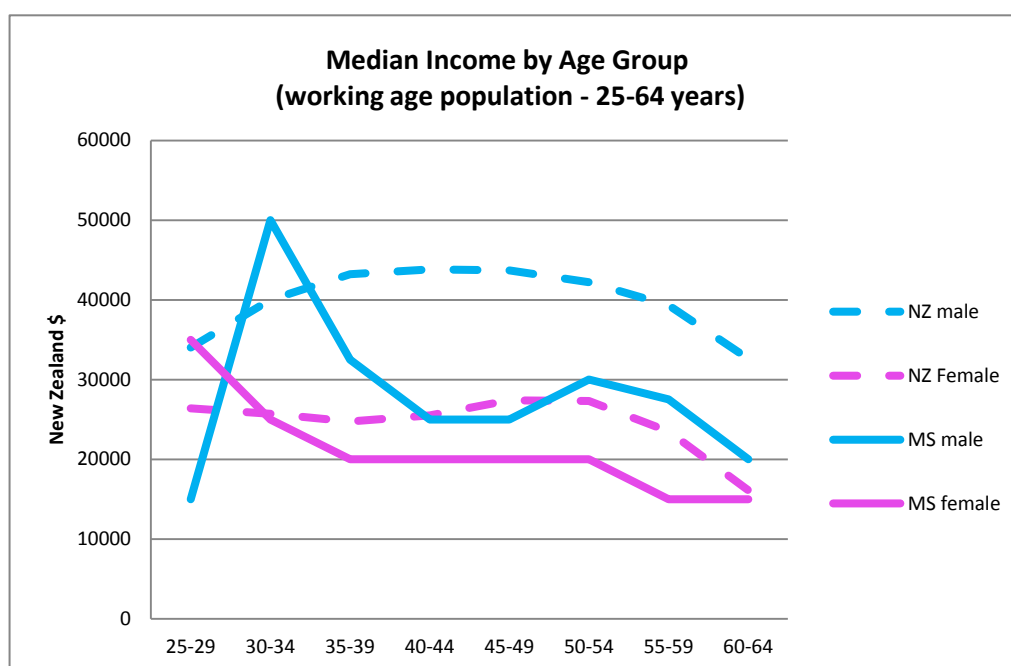


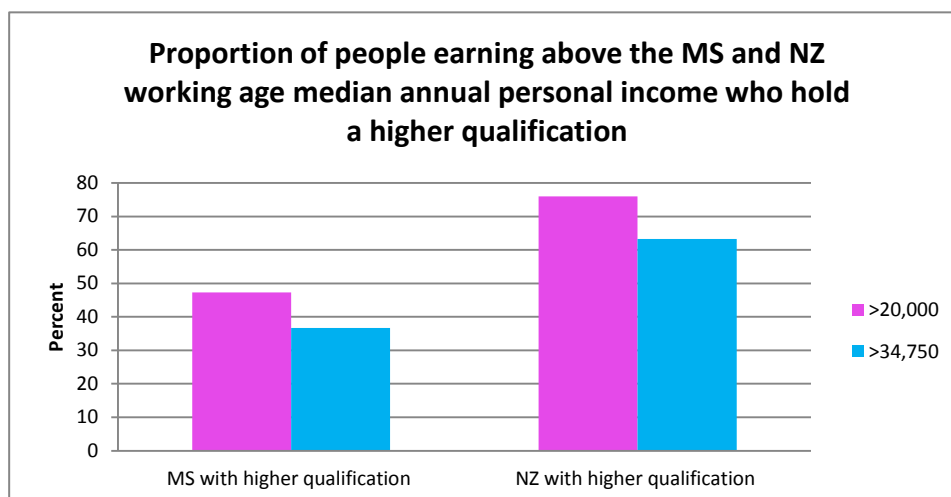
Figure 4.3 Median annual personal income for MS and NZ population by age group

In contrast, males with MS (n=385) in the 45-54 years age group were nearly twice as likely (OR 1.96, CI, 1.19-3.22) to earn above the median annual personal income for people with MS (\$20,000) than those in the 55-64 years age group (p=0.03). Results for males in both the 25-34 years and 35-44 years age groups included 1 in the confidence intervals indicating no significant differences between the median incomes of these age groups and males in the 55-64 years age group. However when analysed using the median annual personal income level of the NZ working age population (\$34,750), males 25-34 years had an OR 2.42 (CI, 1.13-5.15) and males in the 45-54 years age group had an OR 1.82 (CI, 1.10-2.99) indicating they were respectively 2.4 and 1.8 times more likely to earn above the median than males in the 55-64 years age group (p=0.04). The CI for males aged 35-44 years contained 1, indicating there was no significant difference in median income level between this group and those males aged 55-64 years. The small upward swing in income for males with MS in the 50-54 year age group reflects the effect from males with the PPMS phenotype entering the MS population. This group of people are more likely to have disease onset, and enter the MS population at a later age than other MS phenotypes^{392,393} when they are established in their careers, which moderates the effect of work and income loss in the secondary progressive group (Figure 4.3).

4.5.4

Personal income by qualification

In general, the level of income received by an individual is related to their level of education^{274, 398}. This trend is shown by both men and women in the general New Zealand working age population (Figure 4.4a). For the MS working age population, those with a post high school qualification are 1.4 times (OR 1.44, CI, 1.17-1.76) more likely to have an income greater than the median annual personal income for people with MS (\$20,000) than those who do not have a higher qualification (p<0.001) (Figure 4.4a). When analysed using the NZ median annual personal income, people with MS have an OR 1.72 (CI, 1.38-2.14, p<0.001) for earning above the NZ median if they hold a post high school qualification.



4.4a Proportion of MS and NZ working age populations with a post high school qualification earning above the MS and NZ median annual personal incomes

On stratification by sex, there was no significant difference in level of education for the male MS population with an income above MS median annual income (\$20,000), OR 1.40 (CI, 0.93-2.11, $p=0.11$). However, males with MS who hold a post high school qualification are 1.94 times (CI, 1.28-2.95, $p<0.01$) more likely to earn above the NZ median annual personal income than males who do not hold a higher qualification. This suggests that males with MS who report an income in the higher income bracket range are more likely to hold a higher qualification than those who report lower incomes; however the results indicate that compared with their NZ population peers their incomes as a group do not reflect their level of qualification. In New Zealand 51.7% of males with MS who have a post high school qualification earn over \$30,000, as do 68.5% of NZ males. However, 32.1% of males with MS who have a post high school qualification earn less than \$10,000 per annum compared with only 8% of males in the NZ population (Figures 4.4b & 4.4d & 4.4e).

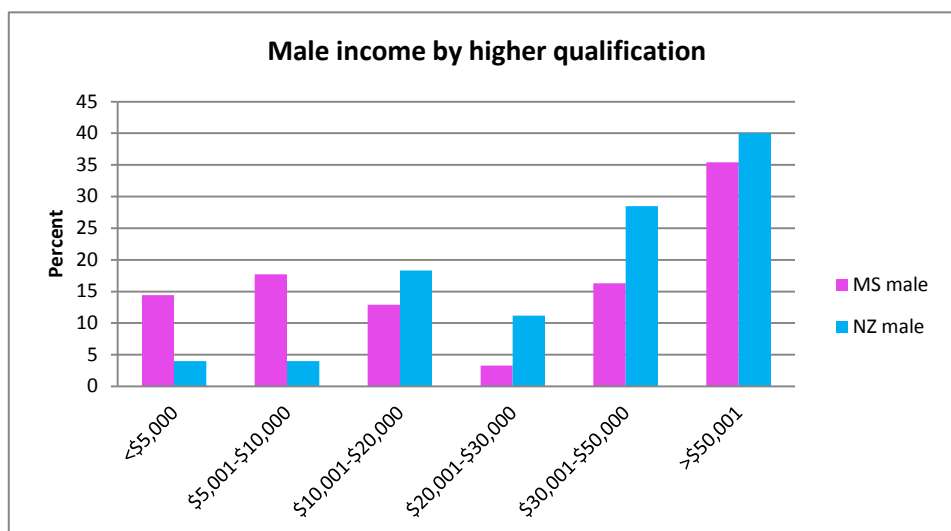


Figure 4.4b Median annual personal income of MS and NZ males who hold a post high school qualification

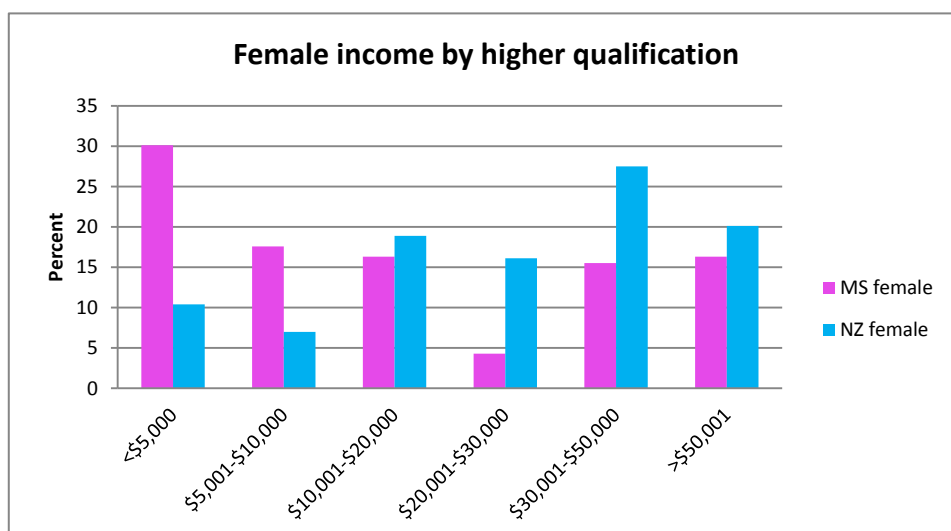


Figure 4.4c Median annual personal income of MS and NZ females who hold a post high school qualification

Females with MS show a similar result to the working age MS population, with an OR 1.44 (CI, 1.13-1.82, $p < 0.01$) when analysed using the MS population median annual personal income, and an OR 1.64 (CI, 1.26-2.13, $p < 0.001$) when analysed using the NZ median annual personal income, for the likelihood of earning above the median if they hold a higher qualification. This indicates that for females with MS having a post high school qualification is an important contributing factor to earning a higher income; however the results indicate that despite their level of qualification, females with MS are unable to earn an income commensurate with their NZ population peers. Of interest, only

31.8% of females with MS who hold a post high school qualification have an income over \$30,000 per annum, with 47.7% earning less than \$10,000. In the general NZ population 47.6% of females with a post high school qualification earn over \$30,000, with 17.4% earning less than \$10,000 per annum (Figures 4.4c & 4.4d & 4.4e).

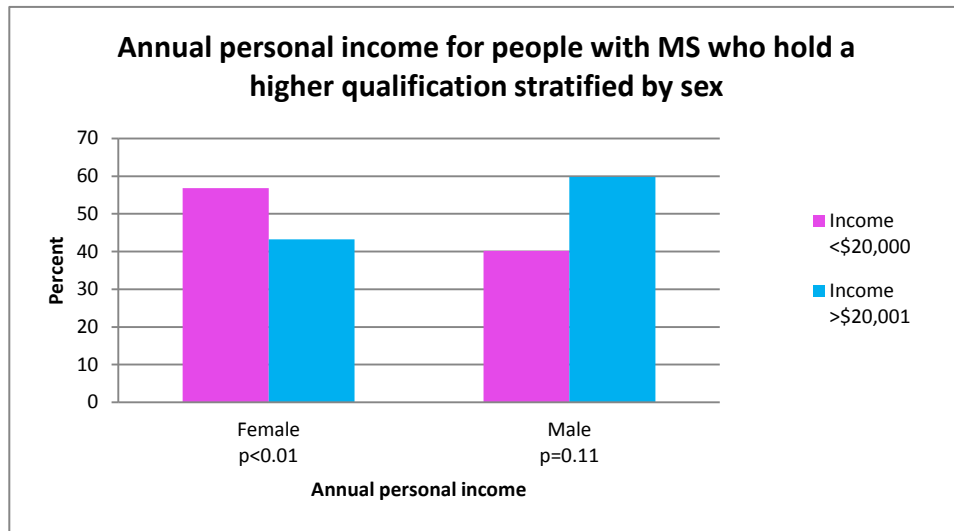


Figure 4.4d Proportion of MS males and females who hold a post high school qualification earning above the MS working age median annual personal income

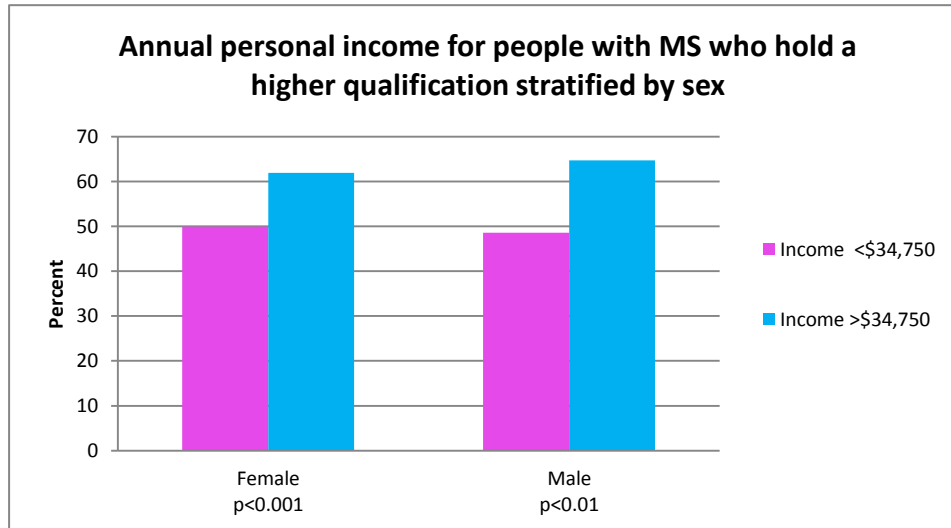


Figure 4.4e Proportion of MS males and females who hold a post high school qualification earning above the NZ working age median annual personal income

4.5.5

Personal income by workforce status

Total personal income is that which the individual receives from all sources not just wages and salary. An individual’s work force status, whether they are employed and if that employment is full or part time, affects their income. People who are employed full time usually work 30 hours or more per week. Those employed part time work 29 or less hours per week³⁸⁷. All other people in this analysis are classed as not working (see Chapter 3).

Analysis of income by workforce status indicated that people with MS who were working were 12 times more likely (OR 12.07, CI 9.51-15.33) to have an income above the median annual personal income for people with MS (\$20,000), and 10 times more likely (OR 10.02, CI 7.77-12.92) to have an income above the NZ median annual personal income (\$34,750) than those who were not working (p<0.001). As most income is received in the form of payment for work, the magnitude of this result is not unexpected.

People in the general NZ population and those with MS who are employed full time have higher incomes. The working age MS population who work full time have the same level of income as the working age NZ full time workforce in all age bands (Figure 4.5a).

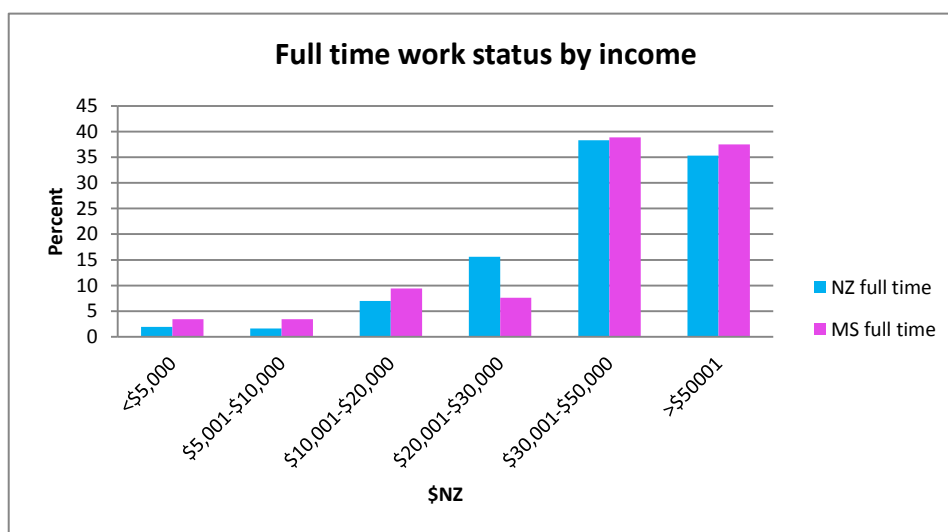


Figure 4.5a Median annual personal income for MS and NZ population working full time

A greater variation in income levels is found in the part time work force. In the general New Zealand population, 40.9% of the 25-44 year group and 43.9 % of the 45-64 year group working part time have an income over \$20,000 per annum. For the corresponding age groups, 22% and 29% of the MS part time working population have an income over \$20,000 per annum (Figure 4.5b).

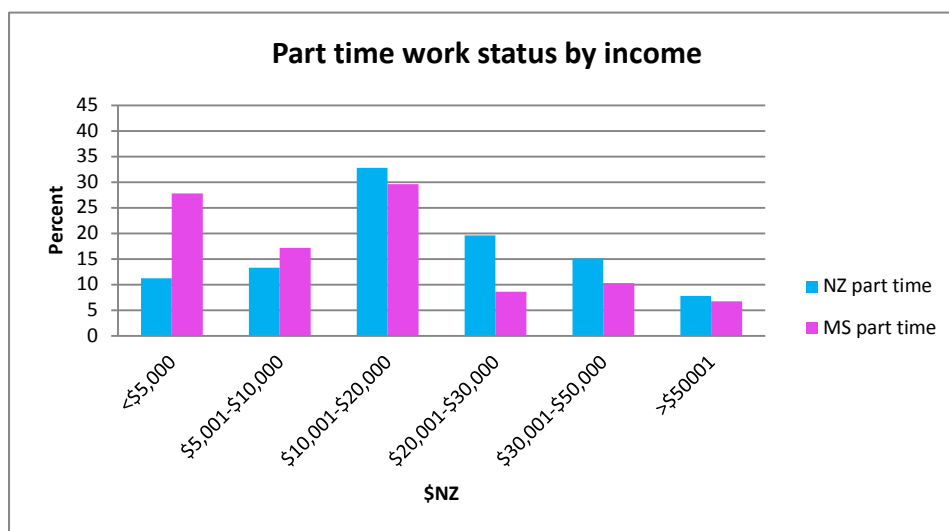


Figure 4.5b Median annual personal income for MS and NZ population working part time

Similarly, in the not working group the MS population was over represented in the under \$10,000 income bands for both age groups, with 71.1% of the 25-44 year group and 73.3% of the 45-64 year group having an income under \$10,000 per annum, compared with 52.7% and 42.2% of the respective general NZ population age groups (Figure 4.5c).

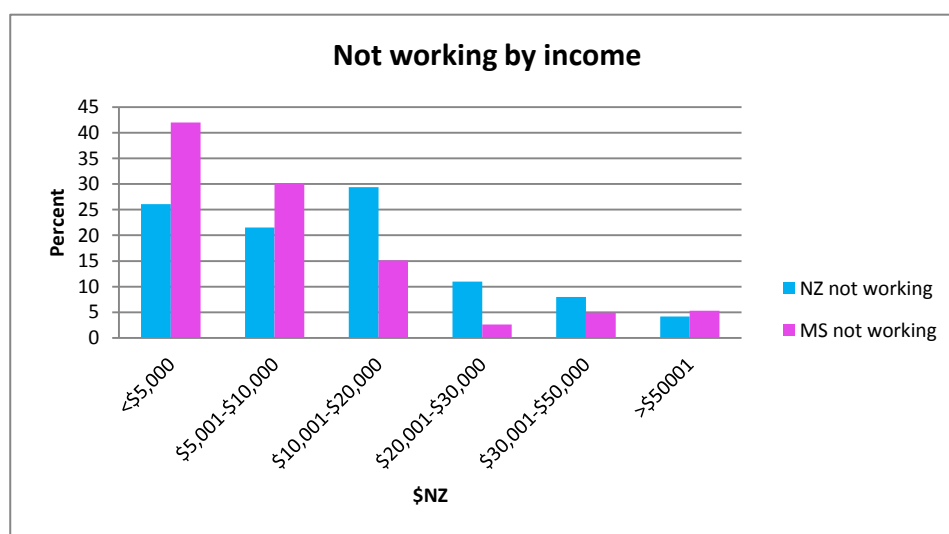


Figure 4.5c Median annual personal income for MS and NZ population not working on census day

When income by work status is stratified by sex, both the NZ general population, and the MS populations report similar income levels for their hours of employment. Of note, both females (31%), and males (50.4%), with MS have a slightly higher percentage of people in full time work earning over \$50,000 per annum than their NZ population peers, females (22.3%), and males (36.7%) (Figures 4.6a and 4.6b).

Females with MS who worked full-time were 11.6 times (OR 11.63, CI 7.41-18.26) more likely to have an income above the median annual personal income for people with MS (\$20,000), and 11.4 times (OR 11.36, CI 7.50-17.21) more likely to have an income above the NZ median annual personal income than those who worked part-time ($p < 0.001$). The effect was similar for males, with those in full time work 14.6 times more likely (OR 14.641, CI 5.850-36.644) to have an income above the MS median, and 17.5 times (OR 17.48, CI 7.15-42.71) to have an income above the NZ median than those who worked part-time ($p < 0.001$).

This indicates that for both males and females with MS if they are able to retain their full time work status they are likely to earn an income commensurate with that of their NZ working age population peers, and were significantly better off than people with MS who were working part-time hours.

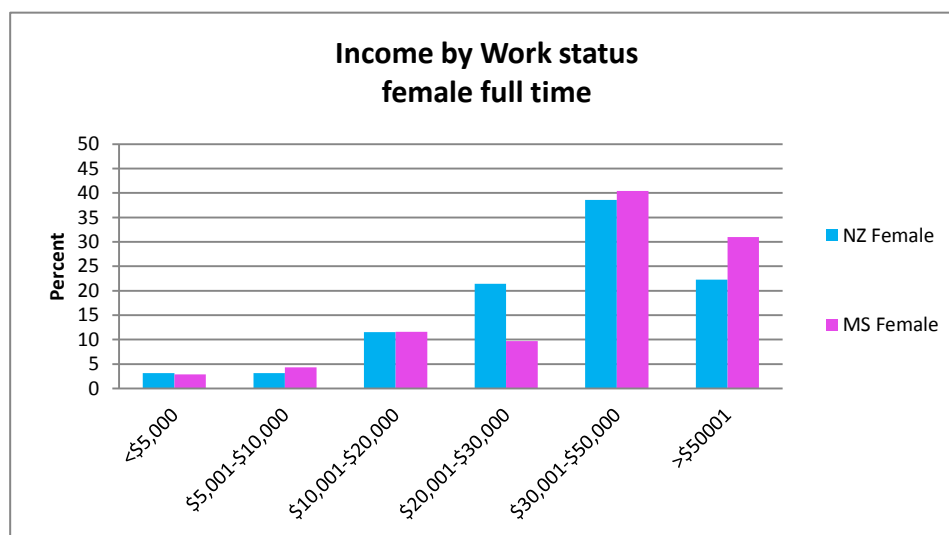


Figure 4.6a Median annual personal income for MS and NZ female population working full time

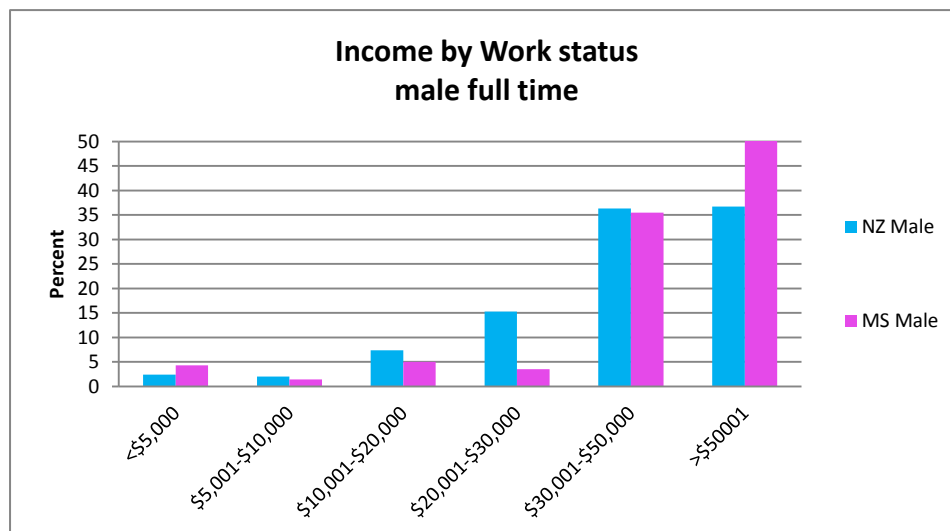


Figure 4.6b Median annual personal income for MS and NZ male population working full time

4.5.6

Personal income by occupation

Median annual personal income also varies by occupation. For the analysis, occupations were grouped by occupational descriptions. There were five main occupational groups, managers/professionals (Group 1), trades/technicians (Group 2), clerical/administration workers (Group 3), sales and community/service workers (Group 4), labourers/machinery operators and drivers (Group 5). Unsurprisingly, the occupational grouping with the highest median annual personal income was Group 1.

The questionnaire had requested data on the original occupation the participants had trained for as well as their occupation on census day. This enabled us to compare their census day income levels with; their census day occupation (for those who were still working), the occupation they had trained for, and the census day occupation of the New Zealand population (who were working on census day) as recorded in the census 2006 data.

The results showed no remarkable difference between income level and occupation for the MS population's original occupation or census day occupation, for those who were working, when compared with each other or with the working New Zealand population ($p=0.56$). This indicates that those people with MS who retain their workforce status are able to earn a similar level of income by occupation as their New Zealand population peers (Figure 4.7).

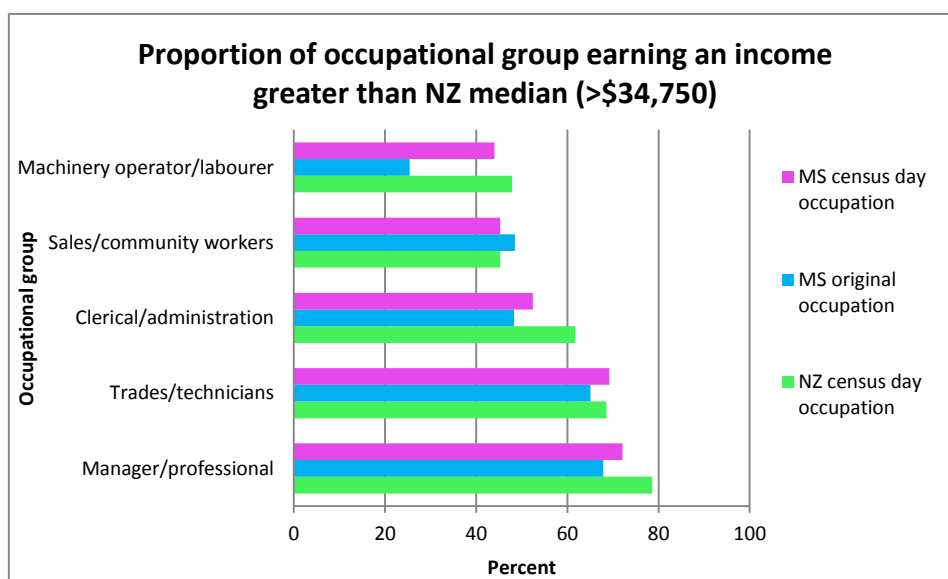


Figure 4.7 Proportion of NZ and MS census day working population and MS original occupation still working on census day who earn above the NZ median annual individual income

4.5.7

Sources of personal income

As with the NZ national census, people with MS were asked to record all sources of personal income for the previous 12 months. Any participants who recorded more than one source of income were counted in each category they recorded, therefore totals may add up to more than 100%. From our data we were unable to determine the main source of income for those people who recorded more than one source.

The most common sources of income for people in the New Zealand working age population were wages, self-employment and interest/dividends. For the MS working age population the main sources of income were wages, invalids benefit and interest/dividends. The proportion of people with no source of income in NZ was 3.7% whereas for the MS population it was 11% (Figure 4.8). This may be a reflection of the requirements for receiving a government welfare benefit in NZ. Welfare benefits are means tested, taking into consideration the household assets and income. If these are above a pre-determined threshold, then the individual who has applied for the benefit will be ineligible to receive government support, thereby being more likely to report no source of income.

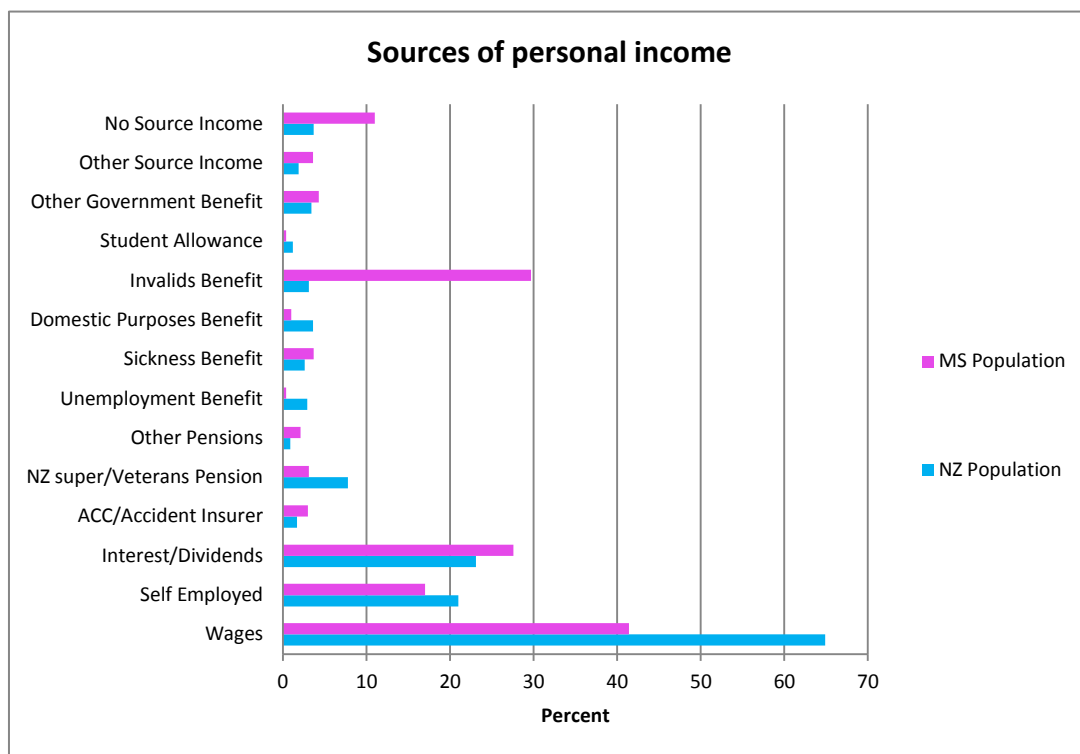


Figure 4.8 Sources of annual personal income for NZ and MS populations

4.5.7.1

Sources of personal income: government support

People with multiple sclerosis receive a higher percentage (42.6%) of income support from NZ government transfers than the general NZ population (24.6%). In particular, nearly 30% of their income support comes from a government invalids benefit. Of interest, 3.9% of the NZ population was receiving the unemployment benefit in 2006 compared with 0.4% of the MS population, indicating that people with MS are more likely to be not working due to disease-related disability rather than unemployment (Figure 4.9).

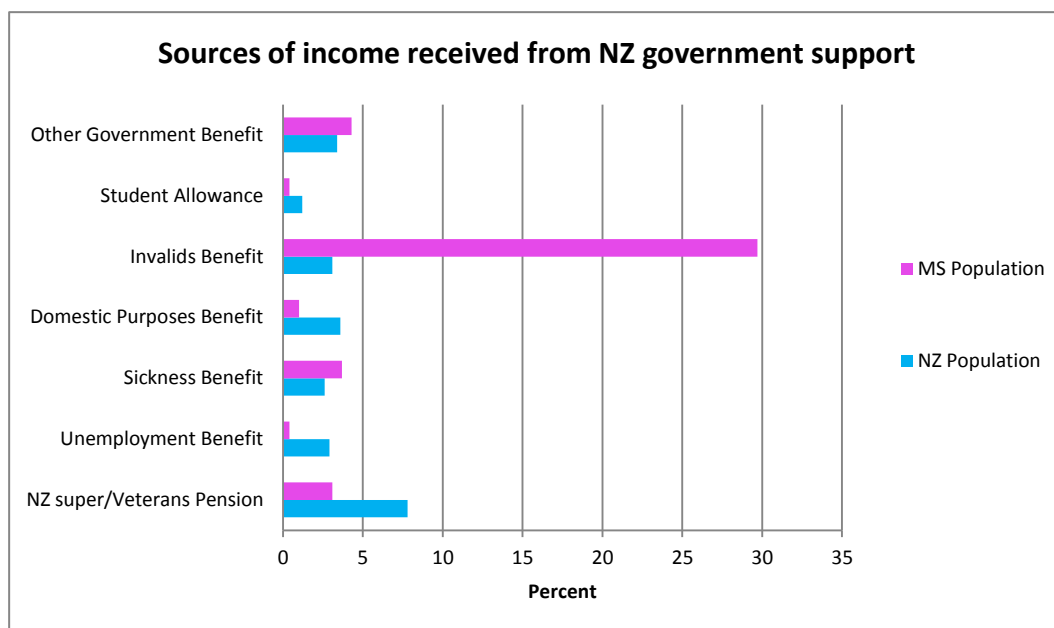


Figure 4.9 Sources of income from NZ government support for NZ and MS populations

4.5.7.2

Sources of personal income by age and sex

The main source of income for females in the 25-34 year age group in both the general NZ population and the MS population was from wages. Women in the general population maintained a fairly constant percentage of income from wages, self employment or interest/dividends throughout the working age period. In contrast, women with MS showed a steady decrease in percentage receiving income from wages and self employment and a corresponding increase in income from the invalids benefit and no source of income with each older age group (Figure 4.10a).

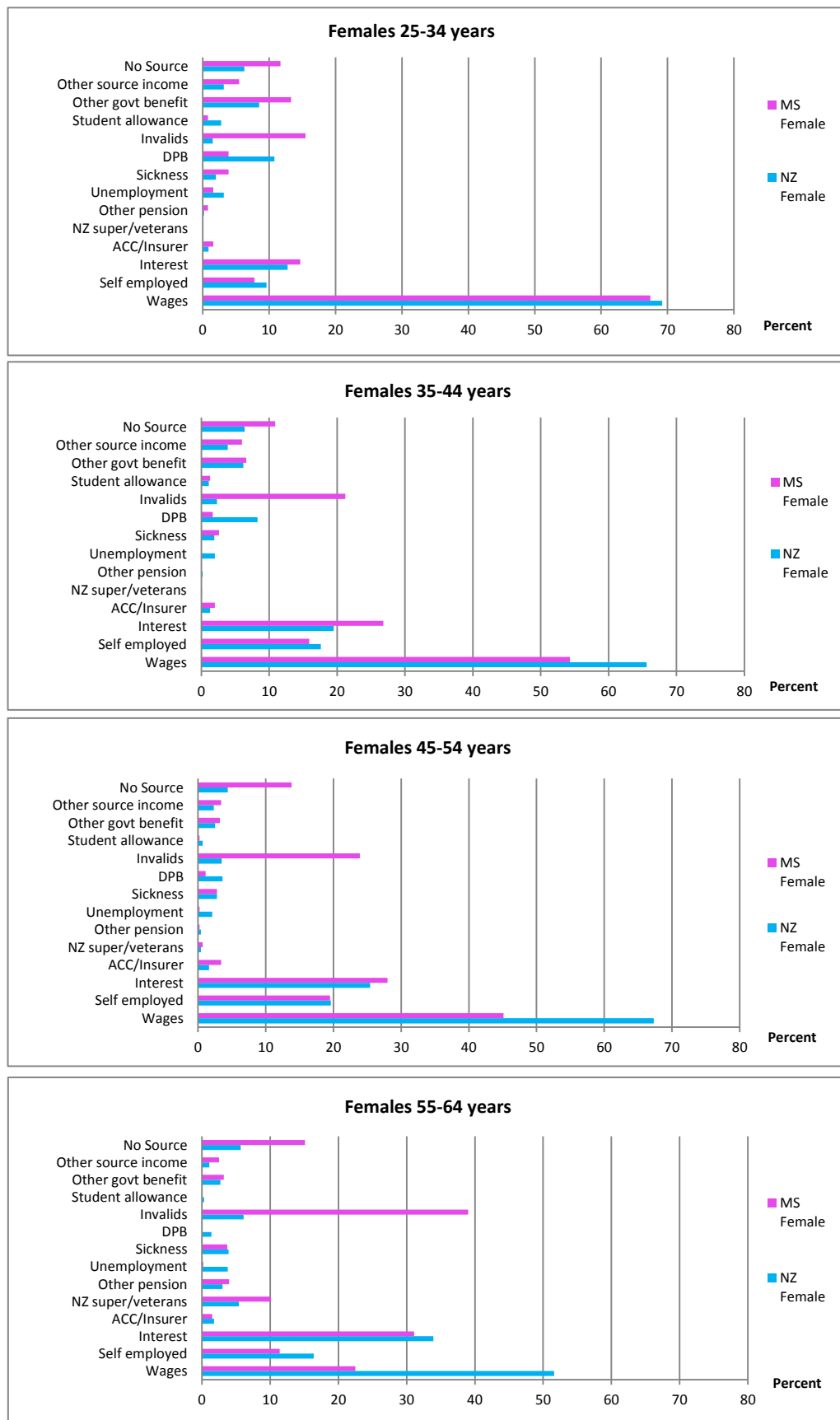


Figure 4.10a Change in female income sources for MS and NZ populations by age group

Males in the general New Zealand population receive a high percentage of their income from wages, self-employment and interest/dividends throughout the working age period, with the main change being a swing from working for wages to self-employment. Males with MS have a bimodal pattern to their source of income with higher percentages of income from wages, self-employment and interest/dividends received in the 25-34 year and 45-54 year age groups, and correspondingly higher levels receiving the invalids benefit in the 35-44 year and 55-64 year age groups. As PPMS tends to be diagnosed later in people's lives, these patterns may reflect the male PPMS patients entering the MS population (45-54 years), inflating the percentage of wage earners, and then their rapid accumulation of disability over the next decade resulting in them leaving the workforce and inflating the percentage of males receiving the invalids benefit (55-64 years) (Figure 4.10b).

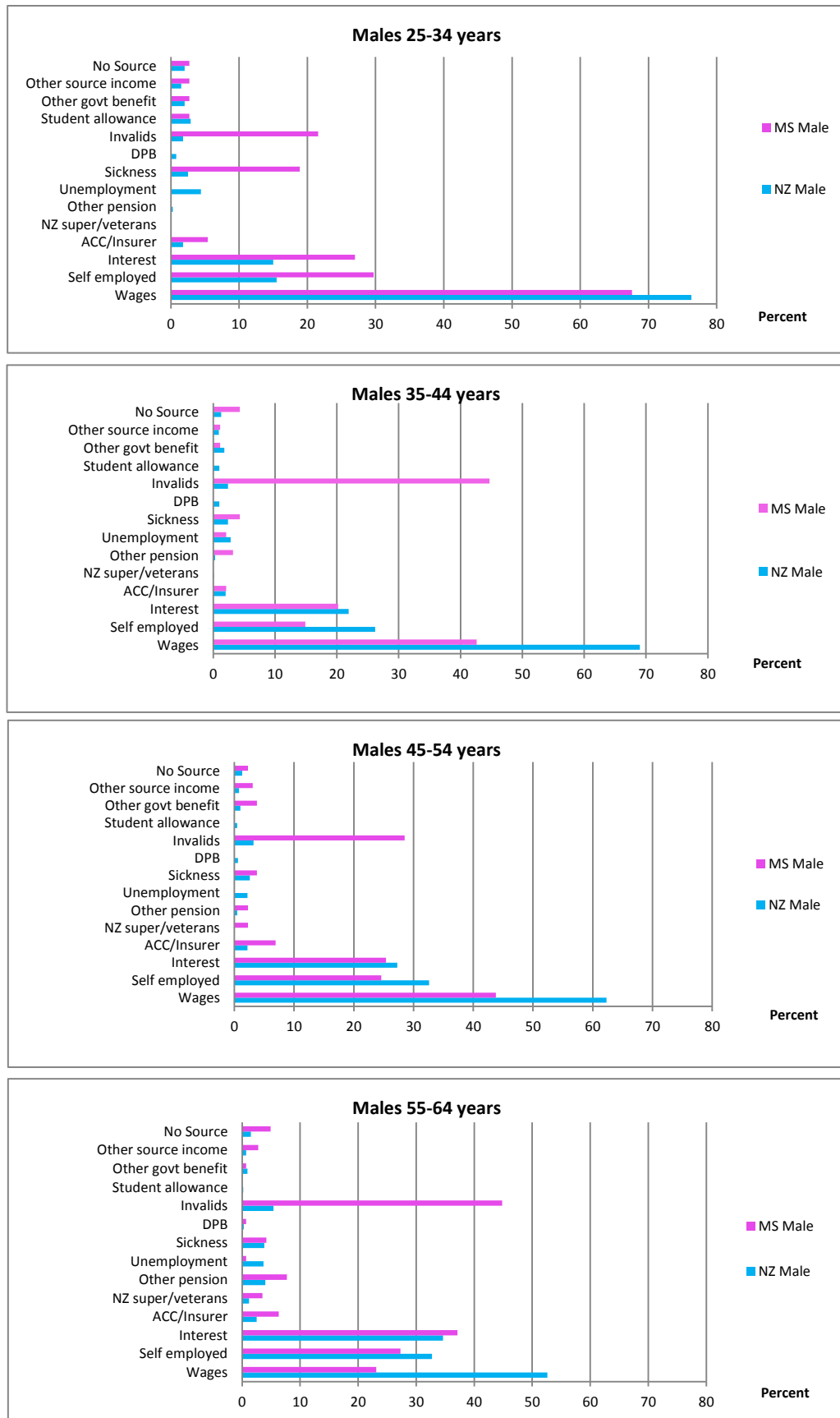


Figure 4.10b Change in male income sources for MS and NZ populations by age group

4.5.8

Income by disease characteristics

No significant difference in annual personal income was found between MS phenotypes ($p=0.30$), level of disability as measured by the EDSS ($p=0.61$), or duration of disease since diagnosis ($p=0.09$), (data not shown).

4.5.9

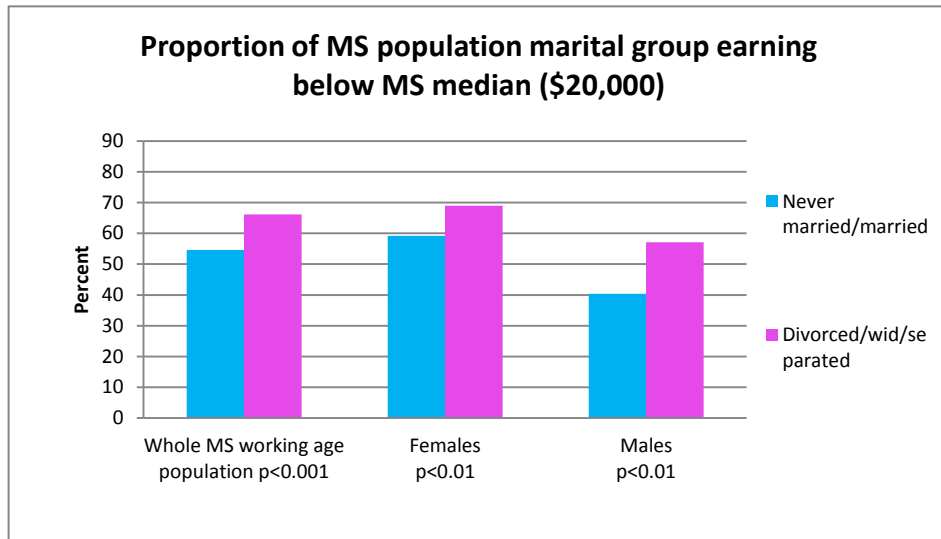
Income by marital status

People with MS who were in the divorced/widowed/separated group were 1.6 times more likely (OR 1.63, CI 1.27-2.08) to have an annual personal income less than the median annual personal income for people with MS (\$20,000), and 1.7 times more likely (OR 1.70, CI, 1.29-2.23) to have an annual personal income less than the NZ median annual personal income (\$34,750), than those who were in the never married/married group ($p<0.001$) (Figure 4.11a & 4.11b).

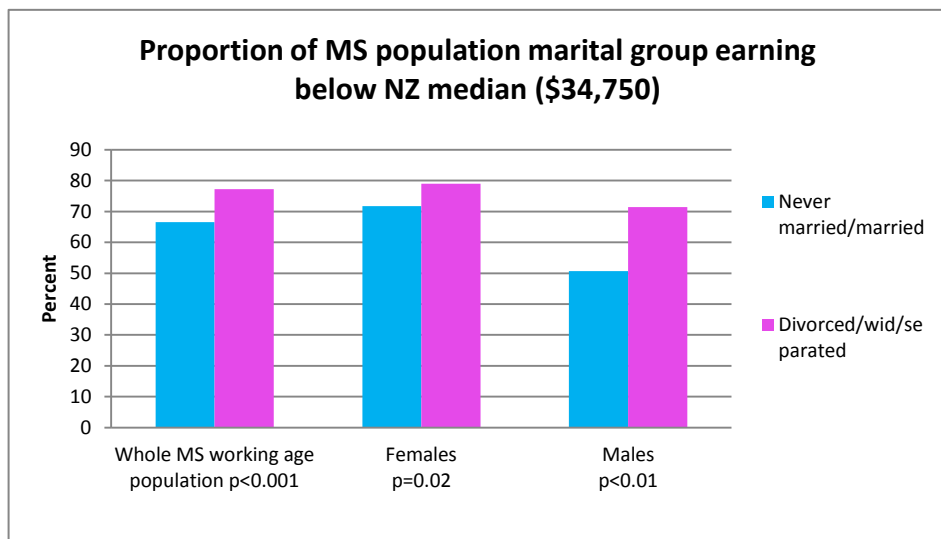
When stratified by sex, women show similar results to the general MS population with those who were divorced/widowed/separated having an OR 1.53 (CI 1.15-2.05, $p<0.01$) for having an income below the median annual personal income for people with MS (\$20,000), and an OR 1.48 (CI, 1.07-2.05, $p=0.02$) for having an income below the NZ median annual personal income when compared with those who have never been married/currently married (Figure 4.11a & 4.11b).

Males with MS who were divorced/widowed/separated were nearly twice as likely (OR 1.97, CI 1.20-3.21, $p<0.01$) to earn below the median annual personal income for people with MS (\$20,000), and 2.4 times more likely (OR 2.43, CI 1.44-4.12, $p<0.01$) to earn below the NZ median annual personal income (\$34,750) than those who were in the never married/married group (Figure 4.11a & 4.11b).

The observed effect of the interaction between marital status and reported income is greater for males with MS than for females with MS. Males who are in the divorced /widowed/separated group have a greater odds ratio for reporting an income below both the NZ and MS median personal income than females in the same marital status group. This may be a reflection of sample size (males in the divorced /widowed/separated marital group, $n=84$), or may indicate that men in this marital group have significant co-morbidities which affect their ability to earn an income.



4.11a Proportion of MS marital groups earning below the MS median annual personal income (\$20,000)



4.11b Proportion of MS marital groups earning below the NZ median annual personal income (\$34,750)

4.6

Factors predicting low income levels

Bivariate logistic regression was used to determine which factors relating to the working age multiple sclerosis population's clinical characteristics, demographic variables, and socioeconomic features predicted:

1. An income below the median annual personal income (NZ \$20,000) for people with MS of working age (25-64 years)
2. An income below the median annual personal income (NZ \$34,750) for the New Zealand working age population (25-64 years)

Modelling was run in steps which included the regions in six centroids, three regions, Auckland and the rest of New Zealand, and no regional breakdown. When divided into six and three regions, the confidence intervals became very wide due to the small numbers in some of the cells. When comparing the results from these models with the Auckland/rest of New Zealand model, the factors included in the final table were very similar indicating that the main region of influence was Auckland. However when comparison was made between the no regional breakdown model and the Auckland/rest of NZ model, the Auckland influence was not sufficient to alter the model effects. The final model was therefore run with no regional breakdown.

The final model for predicting an income below the MS population median can be seen in Table 4.1. The final model for predicting an income below the NZ population median can be seen in Table 4.2.

4.6.1

Model predicting low income using MS working age population median income \$20,000

The full model for low income, containing all predictors was statistically significant, Chi-square (10, N=1185) = 437.9, $p < 0.001$, indicating that the model was able to distinguish between respondents whose annual personal income was below the median and those whose income was higher than the median for people with MS aged 25-64 years. The model as a whole explained between 30.9% (Cox and Snell R Square) and 41.4% (Nagelkerke R Square) of the variance in level of income and correctly classified

77.8% of cases. The remaining variance shows that the individual and their circumstances play the largest part in determining income level.

As shown in Table 4.1, work status, sex, and original occupation were the independent variables which made a unique, statistically significant, contribution to the model. The strongest predictor of low income was work status, with participants who were not working having an odds ratio (OR) of 11.48 (CI 8.56-15.40, $p < 0.001$), indicating that people who are not working are 11.5 times more likely to report having an annual personal income below the median than those who are working after controlling for all other factors in the model. As most people receive income as remuneration for work, it is not surprising that the variable for not working was of a large magnitude and the strongest predictor for low income.

Males were nearly four times (OR 0.26, CI 0.18-0.39) more likely to report an income higher than the median annual personal income than females ($p < 0.001$).

The occupation people with MS were originally employed in made a significant contribution to the model ($p < 0.001$). People who were originally employed in sales and as community workers had an OR 2.12 (95% CI 1.30-3.43), and those who were labourers or machinery operators had an OR 2.64 (95% CI 1.72-4.07) for having an income below the median than those who originally worked in professional occupations. The confidence intervals for people in clerical/administration and trades/technicians occupations included 1 making the result not significant. This result suggests that people who originally qualified for professional occupations are either still able to work in those positions and earn a higher income, or have been able to adjust their working hours or type of work to help them maintain a level of income above the median.

Age did not reach significance ($p = 0.07$), however it did contribute to the model. The indication was that people with MS in the oldest age bracket (55-64 years) were more likely to report an income below the median than those in the youngest age group (25-34 years).

Two way interactions indicated that marital status in combination with sex contributed to predicting low income levels. Males who were divorced/widowed/separated were two and a half times (OR 2.54, CI, 1.24-5.21) more likely to report an income below the median than females who were in the married/never married group ($p = 0.01$). This result indicates that the interaction between marital status, income and sex is important, as people in the male MS group were four times more likely

to report an income above the median than females with MS, however when they are divorced/widowed/separated, males are two and a half times more likely to earn below the medium than females who are in the never married/married group. The lack of support from a partner, combined with older age group and more advanced disease are probably the contributing factors to the lower income in this group, however in the clinical context the interaction between the disease process of MS and marital status is an important aspect of a person with MS's life to consider as part of their overall well being.

Table 4.1 Model predicting Income below the MS median annual personal income (\$20,000)

Variables		Odds Ratio	95% Confidence Intervals for Odds Ratio		(p value)
			Lower	Upper	
Work status	Working Not working	11.48	8.56	15.40	<0.001
Sex	Female Male	0.26	0.18	0.39	<0.001
Original occupation	Professional	1.18	0.71	1.95	<0.001
	Trades	1.45	0.99	2.12	
	Clerical	2.12	1.30	3.43	
	Sales and community workers Machinery operators and labourers	2.64	1.72	4.07	
Age	25-34 years				0.07
	35-44 years	1.60	0.93	2.76	
	45-54 years	1.35	0.80	2.29	
	55-64 years	1.91	1.11	3.28	
Marital status by sex	Married or never married and female				0.01
	Divorced/widowed/separated and male	2.54	1.24	5.21	

4.6.2

Model predicting low income using NZ working age population median income \$34,750

The full model for low income, containing all predictors was statistically significant, Chi-square (13, N=1185) = 387.7, $p < 0.001$, indicating that the model was able to distinguish between respondents whose annual personal income was below the median and those whose income was higher than the median for the NZ working age population (25-64 years). The model as a whole explained between 27.9% (Cox and Snell R Square)

and 38.9% (Nagelkerke R Square) of the variance in level of income and correctly classified 77.9% of cases. The remaining variance shows that the individual and their circumstances play the largest part in determining low income levels.

As shown in Table 4.2, work status, sex, original occupation, age and disease duration from diagnosis were the independent variables which made a unique, statistically significant, contribution to the model. The strongest predictor of low income was work status, with participants who were not working having an odds ratio (OR) of 7.84 (CI 5.48-11.22, $p < 0.001$). This indicates that people who are not working are nearly eight times more likely to report having an annual personal income below the NZ median than those who are working after controlling for all other factors in the model. Once again this result is not unexpected as the majority of people receive income as remuneration for work therefore if they are not working they are more likely to have a lower income or no source of income depending on their circumstances.

Males were nearly seven times (OR 0.15, CI 0.08-0.26) more likely to report an income higher than the NZ median annual personal income than females ($p < 0.001$). This result reflects the earlier finding that men who remain in the work force are more likely to work full time therefore the income they earn will be significantly higher than women who have a higher proportion who work part time.

The occupation people with MS were originally employed in made a significant contribution to the model ($p < 0.001$). People who were originally employed in clerical and administration roles had an OR 1.84 (CI, 1.25-2.70), sales and community workers had an OR 2.36 (CI, 1.42-3.92), and those who were labourers or machinery operators had an OR 3.06 (CI, 1.93-4.85) for having an income below the median than those who originally worked in professional occupations. The confidence intervals for people in trades and technicians occupations included 1 making the result not significant. This result suggests that people who originally qualified for professional occupations are either still able to work in those positions and earn a higher income, or have been able to adjust their working hours or type of work to help them maintain a level of income above the median.

Age made a significant contribution to the model ($p = 0.02$), with people in the oldest age group (55-64 years) nearly 2½ times (OR 2.40, CI, 1.35-4.26) more likely to report an income below the NZ median than those in the youngest age group (25-34 years). The CI for all other age groups contained 1 making them not significant. The indication was that

all older age groups were more likely to report an income below the median than those in the youngest age group, however as only the oldest age group's CI did not include 1 little inference can be made from this result.

Disease duration from diagnosis indicated that those people who were >10 years post diagnosis were 1½ times more likely (OR 0.64, CI, 0.44-0.95, $p=0.04$) to report an income above the NZ median than those who were 0-4 years post diagnosis. The confidence interval for those in the 5-9 year post diagnosis group contained 1 making it not significant.

Two way interactions indicated that marital status in combination with sex contributed to predicting low income levels. Males who were divorced/widowed/separated were four and a half times (OR 4.48, CI, 1.95-10.29) more likely to report an income below the median than females who were in the married/never married group ($p<0.001$). Once again, this result suggests that the interaction between marital status, income and sex is important to consider when assessing the person with MS in the clinical setting. The interaction between the disease process of MS and marital status appears to have an effect on the person's work force status, and correspondingly their level of income, as the male MS group is more likely to earn above the median, however the divorced/widowed/separated male MS group is more likely to earn below the median than the never married/married female MS group. This would indicate that there is a protective aspect for work and income for those in the never married/married group for people with MS. The data analysed in this study is a descriptive picture of people with MS at one point in time in NZ, and causal associations cannot be made from these findings. It is however important to note that this interaction is present in the findings, and has clinical and social importance for the MS population.

Work status in combination with sex made a significant contribution to the model. Males who were not working were 2.6 times (OR 2.63, CI, 1.27-5.43) more likely to report an income below the NZ median than females who were working ($p<0.01$). Once again this result is not unexpected as people who work, whether male or female, are more likely to report a higher income than those who are not working.

Table 4.2 Model predicting income below the NZ median annual personal income (\$34,750)

Variables		Odds Ratio	95% Confidence Intervals for Odds Ratio		(p value)
			Lower	Upper	
Work status	Working Not working	7.84	5.48	11.22	<0.001
Sex	Female Male	0.15	0.08	0.26	<0.001
Original occupation	Professional Trades Clerical Sales and community workers Machinery operators and labourers	1.37 1.84 2.36 3.01	0.82 1.25 1.42 1.93	2.31 2.70 3.92 4.85	<0.001
Age	25-34 years 35-44 years 45-54 years 55-64 years	1.59 1.51 2.40	0.93 0.90 1.35	2.71 2.56 4.26	0.02
Disease duration from diagnosis	0-4 years 5-9 years >10 years	0.95 0.64	0.64 0.44	1.40 0.95	0.04
Marital status by sex	Married or never married and female Divorced/widowed/separated and male	4.48	1.95	10.29	<0.001
Work status by sex	Working and female Not working and male	2.63	1.27	5.43	<0.01

4.6.3

Goodness of fit – logistic regression model

The logistic regression model was assessed for best fit by changing one independent variable whilst keeping all other independent variables constant. The variables we tested were region; Auckland and the rest of NZ; Urban (Auckland, Wellington, Canterbury) and Rural (all other regions); Male and Female; working and not working. These variables were selected for further analysis for the following reasons:

- Auckland is New Zealand's largest city with around one quarter of the country's total population and had a lower response rate than the other regions, as such we wanted to ensure that there was no bias introduced by this region.

- Equally we wanted to ensure that the MS populations in urban and rural regions of New Zealand were not significantly different.
- As 75% of the MS population is female, and there was a lower response rate from males, it was important to investigate whether the female population was driving the model and concealing potentially different drivers of income levels in the male MS population.
- Finally, work status was a strong indicator of income level; as such we chose to test the models to see if there was a major difference when work status was omitted from the model.

All models produced similar results with marital status being the strongest predictor of low income in the models that did not contain work status as a variable, and work status being the strongest overall predictor of people with MS having a low income.

4.7

Discussion

An individual's annual personal income is, to a large extent, determined by their employment status. In economic terms loss of income due to reduced hours of work, or premature departure from the workforce are indirect costs of the illness. Cost of illness studies from Europe, Canada and the USA have estimated the indirect costs of multiple sclerosis to be between US\$5,600 and US\$31,000 per annum and account for up to 80% of the total MS costs^{297,300,302,304-306,341,399}. No other published study was found to have analysed the effects of demographic features and disease characteristics on the income of people with MS. This chapter examined the factors which predicted an annual personal income below the median (NZ \$20,000) for the working age (25-64years) MS population in New Zealand, and the median (NZ \$34,750) for the general NZ working age population.

The effect of loss of income due to loss of work status in the NZ multiple sclerosis population is profound, occurs in the youngest working-age group and increases with each older age group. This is in contrast to the general NZ working age population, whose income increases with each older age group, only diminishing in the age groups preceding retirement. The total personal annual income for both males and females with MS is significantly less than their general NZ population peers, with females in both the general

population and the MS population both earning less than their male counterparts. In New Zealand there remains a disparity in full-time work income levels between males and females, however the degree of disparity is well below that of the Organisation for Economic Co-operation and Development (OECD) 26-average. It is also one of the lowest in the OECD⁴⁰⁰ and therefore would be unlikely to fully explain the difference in annual personal income by sex. However, the difference in income levels by sex for the MS population can be partially explained by the results which show, that of those people with MS who are working, 79.2% of males work full time, whilst only 52.6% of females work full time. People who work full time were shown in the study results to report a higher income than those who work part time or were not working.

What is more difficult to explain is why men are more likely to remain in full time employment than women with MS. There were no significant differences between males and females by MS phenotype, level of disability or disease duration; level of education, age or marital status. However, there was a significant difference in current occupation, 33.3% of males and 30.1% of females were employed as managers and professionals (Group 1); 9.6% of males and 4.4% of females were employed trades and technicians (Group 2); 16.9% of males and 32% of females were employed as clerical and administration workers (Group 3); 11.3% of males and 22.6% of females were employed as community and service workers, and sales workers (Group 4); and 28.8% of males and 10.8% of females as labourers and machinery operators and drivers (Group 5). As these distributions show, there was a significantly higher proportion of men working in occupations requiring heavy physical work (Group 5), and of women in occupations requiring a mix of light physical and cognitively demanding work (Groups 3 and 4). This would indicate that people employed in occupations requiring a mix of cognitively demanding and light physical work are less likely to remain in full time work and therefore receive a lower annual personal income. It may also indicate that there are more opportunities for women to work part-time, with a corresponding lower income, either through type of occupation or support at home whereby they are not required to be the main income provider.

There was no difference found in the level of income received for full-time (>30hours/week) paid employment between the general NZ population and people with MS who were still employed full time. This indicates that those people with MS who are able to maintain full time employment receive equivalent incomes to the general population. The income for people with MS who work part-time (<30 hours/week) is

considerably lower than that of the general population part-time working group. This may indicate that people with MS who work part-time are employed for fewer hours than the part-time workers in the general population.

As expected, people with MS who were employed in professional positions earned higher incomes than those in trades/sales or machine operator/labourer occupations. Equally those people with MS who continued to work in the occupation they originally qualified for had incomes of the same level as the general New Zealand population employed in those occupations. These findings indicate that for people with MS, maintaining employment in the occupation for which they are qualified is an important factor in retaining income levels commensurate with those of the general population.

Educational achievement is generally associated with higher incomes^{274,396}, and this is reflected in the incomes of the general New Zealand population. Despite a higher percentage of people with MS (51.4%) holding post-high school qualifications compared with the general NZ population of the same age-group (41.6%); both men and women with MS are more likely to be in a lower income bracket than their NZ population peers. Within the working age MS population, those who hold a post high school qualification are more likely to earn above both the MS and NZ median annual personal income levels.

Females with MS, like the working age MS population, are about one and a half times more likely to earn above each of the medians if they hold a post high school qualification. For males with MS, there was no significant difference in level of education for an income above the MS median annual income (\$20,000), however, they were twice as likely to earn above the NZ median annual personal income (\$34,750) if they held a higher qualification. This would indicate that holding a higher qualification has more of an effect on the level of income earned by men than women with MS.

Attaining a higher education utilises a range of resources including time, money and personal commitment. As over half of people with MS have a higher qualification, considerable investment has been placed in this population. It is interesting to note that nearly 50% of men and 70% of women with MS who hold a higher qualification earn less than NZ \$30,000 (below the median annual personal income for the NZ working age population). Although this is not a burden of illness study, the potential cost to the individual, their families and society of lost educational investment through loss of income is worth considering. No published literature was found which discussed income in relation to education for MS, or other physically or cognitively disabling illnesses as

such it appears to be an area which would benefit from further study to support and expand on these observations.

International studies report that as the disease progressed people with MS received less income from salaries and increased support from state benefits³⁴¹, invalidity pensions³⁰⁰, and disability and retirement benefits²⁹⁷ depending on the country in which the study was located. New Zealand has a government-led taxpayer-funded welfare system which provides support in the form of benefits for those who need financial assistance for a variety of reasons including unemployment, illness and disability. Nearly half of people with MS received some form of income support through government transfers, with the main source being the invalids benefit. Although the invalids benefit offers a level of support to people with MS, the full annual individual benefit in 2006 was less than NZ \$14,000. With such a low level of income, people with MS who are on a benefit are likely to be at a financial disadvantage which may affect their ability to meet the basic costs of daily living. There are other hardship grants which can be applied for through the government to support people in need, however they do not dramatically increase the level of income received. Supporting a family with housing, clothing, food, health care and educational costs is likely to be challenging on a low budget, especially if the person has had to leave a job which paid a higher income. Studies have shown that loss of income can lead to a decline in standard of living and poorer health outcomes^{264,265}. Financial pressure on the individual, their partner and family should be considered in the broader health and social context by clinicians working with people with MS.

The MS population also reported a high percentage of people with no source of income. This may reflect the level of income earned by the partner of the person with MS. The invalids and sickness benefits in NZ are means tested, as such if their partner earns above the pre-determined threshold they become ineligible to receive a benefit and may have no source of personal income. In contrast, the general New Zealand population's main sources of government support in the working age group were the NZ superannuation/veterans pension, domestic purposes benefit and unemployment benefit. Of note less than half a percent of the MS population received the unemployment benefit indicating that disability due to disease rather than unemployment is the reason people with MS in NZ are not working.

The most striking observation was the difference in patterns of income sources between men and women with MS in each age group across the working age lifespan.

Women in the youngest age bracket received the highest proportion of their income from wages, and with each older age group, their source of income from wages decreased with a corresponding increase in income received in the form of the invalids benefit. Men however have a bimodal distribution with the highest levels of income from wages in the 1st and 3rd age brackets, and from the invalids benefit in the 2nd and 4th age brackets. The pattern for women can be explained by disease and disability progression with increasing age leading to loss of income through loss of ability to continue working. The pattern for males is more likely due to the entry of newly diagnosed PPMS males, who are still working and earning an income, into the MS population in their 40s (3rd age bracket), and then through the rapid accumulation of disability in the 4th age group leading to loss of income through loss of ability to continue working.

Marital status was found to be associated with individual annual income levels for the MS population, with people who were divorced/widowed/separated one and a half times more likely to have an income below each median than those who were in the never married/married group. This can be partially explained by age, as a higher proportion of people in the never married/married group are in the youngest age group (Figure 5.13a). This group are more likely; to be early in their disease course, have a non-progressive form of MS and lower levels of disability; and to have a post high school qualification and be currently working, which all correlate with receiving an income above the median annual personal income.

When stratified by sex, the effect for women was similar to that of the whole MS population, however for men, the effect was greater with them being two to two and a half times more likely to report an income below each median if they were divorced/widowed/separated than if they were in the married/never married group. The greater effect of change in income for men in the divorced/widowed/separated group compared with males who are in the never married/married group may be associated with males having a higher annual personal income as a population group from the outset. Thus when they experience a change in circumstances which affects their ability to earn an income the effect is greater. Other factors may also contribute to lower incomes for people who are divorced/widowed/separated, in particular the absence of support at home, and symptoms from the disease process which affect their ability to continue working.

Most findings in this study so far have indicated that the female population is negatively affected to a greater extent than the male MS population, particularly with

regards workforce participation and reported income levels, as such it is interesting to find that males who are divorced/widowed/separated report a much lower level of personal income than those who are never married/married. This may be a reflection of the number of males in this group (n=84), or an indication of an underlying factor which affects both their personal and professional lives. To investigate a causal association between marital status, disease characteristics and economic factors, which is beyond the scope of this cross-sectional study design, further studies would be needed, including prospective longitudinal studies and case-control studies. No published literature has been found describing income in relation to marital status for people with MS or any other chronic physically or mentally disabling condition of early adult onset.

The study found no association between level of income and disease phenotype, level of disability or disease duration since diagnosis.

In summary, multiple sclerosis profoundly affects the income status of New Zealanders in the 25-64 year age group living with the disease. The effect occurs at an early age and an increased effect is observed in the older age groups. Work status is the strongest predictor for loss of income after controlling for all other factors, with people who are not working more likely to report a lower income. As most people receive an income as remuneration for work, this result is not unexpected. Males are more likely to be employed full time, and as such receive higher incomes than females with MS.

Holding a higher qualification contributed to receiving a higher income for all people with MS, however the effect was greater for males than females. Despite a large proportion of people with MS having a higher qualification, a high percentage of this group reported an income below the medium annual NZ income, indicating that although having a higher qualification was protective for higher income; other factors such as loss of work force status had a greater effect on level of income.

Both men and women with MS who were in the divorced/widowed/separated marital group were more likely to report an income below the median annual personal income than those who were in the never married/married group however the effect was greatest for males. The interaction between marital status, sex and income is an interesting observation, and one which warrants further study to assess whether there is any causal association.

Finally changes in occupational status between the occupation people were original trained/educated for and their census day occupation was found to contribute to loss of

income. The results of this study indicate that the ability to continue working in the occupation that they were originally trained for was a key factor in people with MS retaining an income commensurate with their NZ population peers.

The key factors predicting an income below the median annual income for both the MS and NZ working age population logistic regression models were work status, sex, original occupation and age. However as they only account for between 27.9% and 41.4% of the variance in level of income, it must be inferred that a complex interaction of factors not tested for along with a confirmed diagnosis of MS is the strongest predictor for an income below the median (for both the MS and NZ populations) in the New Zealand multiple sclerosis population. The interaction between demographic features, socioeconomic factors and disease characteristics in the analysis emphasise the complexity of multiple sclerosis and its effect on level of income for those living with the disease.

Chapter Five

Socioeconomic status and multiple sclerosis

5.1

Background

Indices of socioeconomic status and deprivation are most commonly used by health and social services research to describe the relationship between socioeconomic position and health outcomes; or by community service providers and community groups to describe the populations they serve and to give support for applications for extra resources and funding^{401,266}.

There are two main tools for measuring socioeconomic status in New Zealand, the New Zealand Index of Deprivation (NZDEP) and the New Zealand Socioeconomic Index (NZSEI). The NZDEP has a focus on small area deprivation and is a tool more commonly used to assess people in the extremes of the socioeconomic spectrum, the very poor and the well off²⁸⁵. The NZSEI is an occupation based tool which measures the SES of those people who sit in the mid-range of the socioeconomic spectrum²⁶⁸. (For detailed discussion refer to Chapter 1.16.3). This study has used the NZSEI to assess and describe the socioeconomic status of people living with multiple sclerosis in the New Zealand population. The findings from this chapter will be discussed in the context of its implications for policy, clinical care and people and families living with MS.

5.2

Objective

MS is associated with a significant change in an individual's physical and cognitive ability, affecting their work and income status. A consequence of change in work status and the ability to earn an income may be a change in socioeconomic status.

The aim of this chapter is to determine the socioeconomic status of people with MS throughout New Zealand on the prevalence date of March 7th 2006 (New Zealand census day), which can then be compared with the socioeconomic status of the general New Zealand population based on the 2006 census data. The study aimed to describe the socioeconomic status in relation to the age, sex, education, location, marital status, occupation, work status, income, MS phenotype, duration of disease and disability levels

of the MS population, and determine which variables were most likely to predict a lower SES on the NZSEI.

5.3

Methods

The decision as to which measure of socioeconomic status, the NZSEI or the NZDEP, to use for this study was based on the data available for analysis and the demographic profile of the participants who were involved in the study.

The NZDEP, as a measure of small area deprivation, did not seem the best tool to use as this study is looking at a relatively small group of people, less than 1% of the New Zealand population, and as such, the numbers of people with MS in each small population area would be too small for stable estimates to be calculated. For targeting a specific group such as this, the area level socioeconomic effects on health are important, but probably not as important as the personal socioeconomic effects⁴⁰². Secondly, not all the variables required to calculate the small area deprivation had been collected in the study survey.

The philosophy on which the NZSEI, an occupation-based measure, is based fits with that of the study as the thesis argues that the disease process of MS directly affects people's ability to fill the occupational role they are qualified for and therefore their socioeconomic status is likely to be affected. The data collected during the NZNMSPS included both occupation at census and original occupation qualified for, education, number of hours currently working, income and general demographic data which met the criteria for using the NZSEI. Secondly the MS population is largely in the age group which would normally make up the occupational workforce in New Zealand.

One potential limitation to using the NZSEI (1991) is that a large proportion of the participants in our study are not working or are in part-time paid employment due to their disease, however as the data collected for the study included original occupation, education, number of hours currently working and income, we were able to use this data to impute for the missing data where necessary as per the 1996 modified NZSEI²⁷⁴. (For detailed discussion refer to Chapter 1.16.3).

5.3.1

Participants

We used two populations for this study. The first group included all people with MS in New Zealand. The second group consisted of all people resident in New Zealand on census day. Participants with MS were identified from various referral sources including regional MS Societies, hospital databases, neurologists' databases and the NZHIS discharge code list (see Chapter 2 for detailed explanation).

5.3.1.1

Working age population

The working age population is defined by Statistics New Zealand (2006) as the usually resident, non-institutionalised, civilian population over 15 years of age resident in New Zealand³⁸⁷. As the purpose of this chapter was to evaluate the socioeconomic status of people with MS in NZ, the population was restricted to the working-age population, those people aged over 15 years of age. However, as there were too few participants with multiple sclerosis under 25 years of age (n=45) for robust statistical inference, and the universal superannuation (a retirement pension) is available for all people 65 years and over in New Zealand, this could confound the effect of disease on socioeconomic status for this group of people, as such, this study has limited its cohort age group to a working age of 25-64 years (see Chapter 3 for detailed description).

5.3.2

Questionnaire

Participants with clinically definite MS who had consented to be part of the NZNMSPS were sent a questionnaire via post to self-complete, and a stamped return-addressed envelope in which to return the questionnaire (see Chapter 2). The questionnaire included questions on total personal income from the past 12 months, education, census day and original occupation, marital status, and general demographic questions identical to those in the 2006 Statistics New Zealand Census questionnaire to enable comparison between the MS population and the general NZ population. A full list of variables that were recorded can be found in Chapter 3 (Table 3.1). The questionnaire is described in detail in Chapter 2.

5.3.3

Data

The questionnaire collected socioeconomic information on; the participant's original occupation and their census day occupation, their educational level, qualifications and census day income. All participants in the working age group (25-64 years) had an original occupation recorded. The multiple sclerosis participants' occupations were manually coded into the New Zealand Standard Classification of Occupations 1999 (NZSCO99)²⁹³. These were then aggregated at the minor group level (97 occupational groups) as these were the groups on which the NZSEI 91 and 96 scoring systems were developed. These groups were selected for the NZSEI scoring system as they were considered to be detailed enough to be useful for social research and had sufficient numbers within each occupational category to provide stable estimates²⁶⁸. The scores in the NZSEI-96 scale have been calculated through a series of equations which include education, age, income and occupation in the model and are described in detail in the paper by Davis et al. (2004)²⁹⁴. For detailed discussion refer to Chapter 1.16.3.

The NZSCO99 occupational groups of the NZNMSPS study participants were then allocated an NZSEI-96 score between 10 (lowest socioeconomic level) and 90 (highest socioeconomic level), as per the NZSEI 1996 Users Guide²⁹⁴, which was used as the socioeconomic variable for the analysis. The NZSEI scores can be used as a continuous variable or for the development of discrete occupational classes depending on the research project requirements²⁶⁸. A combination of cluster and discriminant function analyses were used in the NZSEI design to determine the split points for the initial six discrete socioeconomic groups suggested by the NZSEI author²⁷⁴. Further categorical divisions of the NZSEI calculated by the author include quintiles and quartiles for use in research depending on the available data and research project²⁹⁴. For detailed discussion refer to Chapter 1.16.3.

The NZNMSPS participants were also asked if their work status had changed due to MS and if so in what way. This enabled us to identify those who were not working due to multiple sclerosis, as opposed to other reasons such as staying home to look after children. Those who were not working for reasons other than disease related effects were coded for their census day NZSEI score as per the original occupation they had qualified for and analysed as part of the working group. Those who were not working due to MS were coded as per their income level, most commonly the invalids benefit, for their

census day NZSEI score. Although the NZSEI scores can be used in the continuous form, due to the size of the study population they were divided into either two or six categorical socioeconomic groups, to enable the examination of differences in socioeconomic outcomes for people living with MS in New Zealand. The use of two or six categorical socioeconomic groups was dependant on the complexity of the statistical analysis and its effect on cell size and therefore the stability of the calculation. Wherever possible analyses were run using both two and six categorical groups to ensure there were no notable differences between the models, however in a number of cases p-values and CIs were only able to be calculated for the dichotomised group due to small cell sizes when the groups were subdivided further.

5.3.4

Data management

Data was dual entered on each of two identical custom made Microsoft Access databases to collate the data from the questionnaires (see Chapter 2).

5.4

Statistical methods

Data was collated in the Microsoft Access database before being exported to the Statistical Package for Social Sciences (SPSS) version 17.0 for analysis³⁸⁷.

5.4.1

Statistical analysis

Descriptive analysis of the data included summary statistics of the raw data. Cross-sectional analysis of the relationship between socioeconomic factors, demographic characteristics and disease phenotype, disability and duration of disease, was performed using the chi-square test for independence, with results quoted as significant at the $p=0.05$ value, and all confidence intervals (CIs) at the 95% level. The variables assessed were demographics including age, sex region of residence, and marital status; socioeconomic factors including income, education, original occupational group, census day occupational group and work status; and disease characteristics including MS phenotype, EDSS, and disease duration since diagnosis.

Direct bivariate logistic regression was performed to determine the effect of a number of factors on the likelihood that responders would report that they have had a change in socioeconomic status due to the effects of MS. Bivariate logistic regression analysis is used when the dependent variable is dichotomous in nature³⁸⁹. In this model the dependent variable was dichotomised as low socioeconomic status (NZSEI class 4,5,6) (1) and high socioeconomic status (NZSEI class 1,2,3) (0). The model contained ten independent variables; age, sex, marital status, original occupation, work status, income, education, MS phenotype, level of disability and duration of disease. Regression coefficients (Exp B in SPSS) are reported as odds ratios, indicating the strength of association between an independent variable and the dependent variable. A coefficient of greater than 1.00 indicates increased odds; a coefficient of less than 1.00 indicates decreased odds; and a coefficient of 1.00 represents no change in the odds of being in the predictor category of the variable under consideration. To determine if the likelihood of the odds ratio for individual predictors differing by greater than 1.00 was more than that which could be expected by chance, both a Wald test to assess statistical significance ($p < 0.05$) and confidence intervals (at the 95% level) for the effects are used³⁸⁹. Statistical significance was calculated to assess the likelihood of observing an association at least as large as the one found in the model, if in reality no association were present in the source population. It was quoted as significant with a p value < 0.05 , indicating that there is a less than 5% probability that the observed result could have occurred by chance error. Confidence intervals were quoted at the 95% level indicating that there is a 95% probability that the true value lies within the confidence interval. When the confidence interval does not equal 1.00, this is similar to finding that the association is statistically significant with a p value < 0.05 ^{100,101}. To investigate the dependence between independent variables, initial models were fitted with no interactions, and all 2-way interactions between lists and the saturated models. Care was taken to check for poorly populated covariate combinations, or cells, particularly due to the relatively low numbers of males, and people with primary progressive disease, hence higher order interactions were not included.

5.4.2

Statistical inference and multiple testing

Multiple comparisons or multiple testing can be of concern in very large data sets where multiple data points are compared between two or more groups simultaneously to assess whether they are different. A statistical test to adjust for multiple testing and minimise Type 1 errors, assumes that the responses are independent and provides a lower bound on likely p values. Type 1 errors are those which produce a false positive result or a result which is not actually there. In the case of multiple testing, the more terms that are put into the comparison, the greater the likelihood that one of those terms will be significantly different purely by random chance^{100,101}.

Multiple comparisons do not present a concern for the analyses in this thesis for several reasons. Firstly the study population is a census of the New Zealand MS population, not a sample of people with the disease, with an estimate of over 96% of the population being identified on capture-recapture analysis. On analysis, the population has been determined to be representative of people with MS in NZ, and there is no evidence of bias between responders and non-responders to the MS study questionnaire (See 3.5.1).

Secondly, the thesis tests three a priori hypotheses which by themselves are unique research questions. The statistical analyses are performed as there is a strong basis for expecting the result to be true; they are not used for repeated statistical testing to explore the data. The analyses test how each of the three hypotheses are modified or changed by other variables to describe the effects on the NZ working age MS population.

5.5

Results

5.5.1

Socioeconomic status of the multiple sclerosis population by census day NZSEI groups and original NZSEI groups

Davis et al. (2004) have calculated the predicted proportional distribution of the New Zealand population across the six categorical NZSEI classes developed from 1996 census data, with SES 1 being the highest SES level and SES 6 the lowest²⁷⁴. The socioeconomic status, as per the NZSEI, of people with MS in New Zealand was calculated for both their

census occupational group and the occupational group for which they had originally qualified. It is interesting to note that there is little difference in the predicted proportional distribution of the six NZSEI groups between the NZ working age population and the MS working age population original NZSEI score, indicating that based on the original occupation people with MS qualified for they have a similar SES distribution to their NZ population peers (Figure 5.1).

Over 90% of people with MS in the working age population had a work history, however more than 50% were not working on census day 2006 due to multiple sclerosis, thus a profound difference in socioeconomic status can be observed. No odds ratios or p values were able to be calculated at the six NZSEI categorical group level as the participant numbers in each cell became too small for analysis (Figure 5.1).

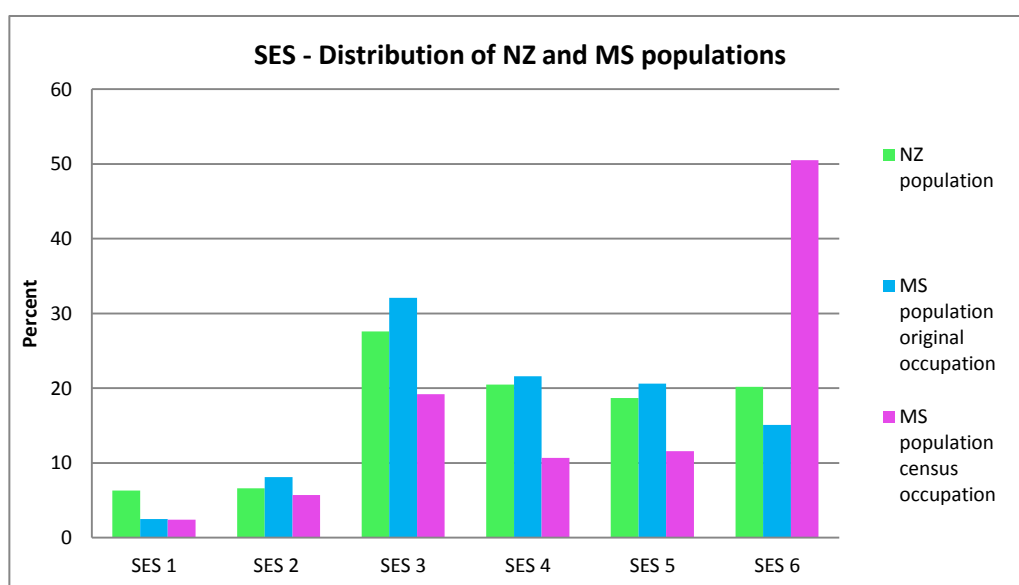


Figure 5.1 Socioeconomic distribution of NZ population, MS population original occupation, and MS population census day occupation

The NZSEI groups were then divided into two levels, with those in SES 1-3 being included in the high SES group and those in SES 4-6 being included in the low SES group. The analysis of the original NZSEI group in comparison with the census day NZSEI group for high and low SES was highly significant, with those participants who were originally in the low SES group being nine times (OR 9.29, CI, 7.19-12.00, $p < 0.001$) more likely to be in the lowest SES group on census day 2006 than those who were originally in the three highest SES groups. This indicates that although there is a change in SES for all NZSEI groups between their original group and their census day

group, the effect is most profound for those whose NZSEI score placed them in the lowest three SES groups for both their original and census day score (Figure 5.1).

5.5.2

Socioeconomic status of multiple sclerosis population by age group for census day NZSEI groups and original NZSEI groups

Socioeconomic status for the MS population was analysed by age group to assess whether there was any difference in SES with age. The results showed that if people with MS had stayed in the original occupation that they had trained for, there would have been a small change in SES with age ($p=0.02$), however the only significant difference was for people in the oldest age group. Compared with people who were 25-34 years of age, those in the 55-64 years age group were 1.7 times (OR 1.70, CI 1.20-2.40) more likely to be in the low SES group. The CIs for the 35-44 years and 45-54 years age groups contained 1 making them not significant.

When the analysis was performed using the census day NZSEI score, there was a significant change in SES with age ($p<0.001$). The analysis shows that when compared with the 25-34 years age group, each older MS population age group, has an increased proportion of people in the lower socioeconomic level, with people 35-44 years having an OR 1.91 (CI, 1.44-2.55), those 45-54 years had an OR 2.47 (CI, 1.82-3.34), and those 55-64 years had an OR 3.21 (CI, 2.20-4.69), indicating that the oldest age group in the working age population are over three times more likely to be in a lower SES group than the youngest age group (Figure 5.2a). The results show that each older age group has a higher proportion of people in the lower socioeconomic groups, however as the data from this cross-sectional study is descriptive, giving a picture of the MS population at one point in time, neither temporal change nor trend can be attributed to these results.

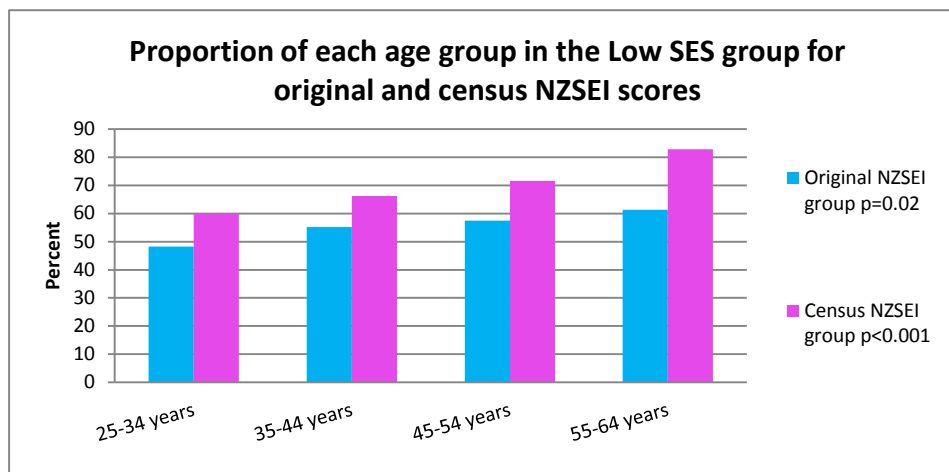


Figure 5.2a. Proportion of each age group, working age MS population, in the low SES group, p value is the difference between youngest and oldest age groups

When stratified by sex, the results for the female MS population were similar to the MS working age population (Figure 5.2b).

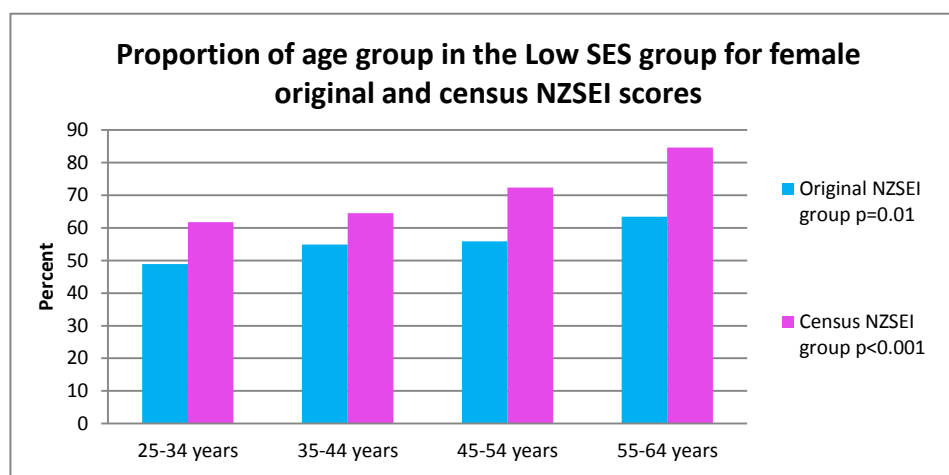


Figure 5.2b. Proportion of each age group in the low SES group for females with MS, p value is the difference between youngest and oldest age groups

For both original and census day NZSEI group, when compared with females aged 25-34 years, each older female MS age group, had a higher OR for being in a lower SES group, however the difference between age groups was more profound for the census day NZSEI scores. The results show that compared with females 25-34 years, those who were in the 55-64 years group were 1.8 times more likely to be in a lower socioeconomic group for their original occupation NZSEI score, but nearly twice as likely with an OR 3.4 to be in the lower SES group based on their census day NZSEI score (Table 5.1). Once again, it

must be noted that the data from this cross-sectional study is descriptive, giving a picture of the MS population at one point in time, therefore temporal change cannot be attributed to these results.

Table 5.1 Lower SES group for original and census day NZSEI score by age group for females with MS

Variables		Odds Ratio	95% Confidence Intervals for Odds Ratio		(p value)
			Lower	Upper	
Original occupation NZSEI group by age group	25-34 years				0.01
	35-44 years	1.37	1.04	1.80	
	45-54 years	1.42	1.05	1.92	
	55-64 years	1.81	1.22	2.69	
Census day NZSEI group by age group	25-34 years				<0.001
	35-44 years	2.11	1.50	2.97	
	45-54 years	3.04	2.12	4.34	
	55-64 years	3.43	2.21	5.32	

For males however, the results were more subtle, as there was no significant change in SES by age for the original NZSEI group ($p=0.28$), and only the oldest group reaching significance when compared with the youngest age group for the census day NZSEI group ($p=0.04$). The results for the census NZSEI showed that when compared with males in the 25-34 years age group, those who were 55-64 years had an OR 2.95 (CI 1.38-6.28) for being in the lower SES group. All other age group CIs contained 1, making them not significant (Figure 5.2c). These results indicate that males with MS in each age group are less likely to experience a change in their level of SES for both original and census day NZSEI score. Reflecting on the results of the previous two chapters, this may be due to males being more likely to remain in the workforce, work full time and earn a higher income than females with MS. If this finding was supported by evidence from future longitudinal prospective studies, it may indicate which factors contributed to males with MS remaining in the workforce, and if these were modifiable factors, whether there was a way manage the effects of these factors on females to enable them to remain in the workforce at a similar level to males with MS.

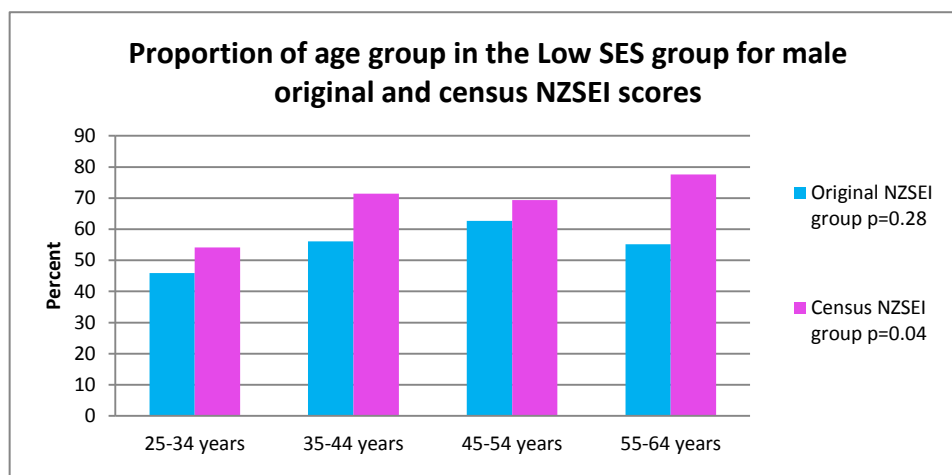


Figure 5.2c. Proportion of each age group in the low SES group for males with MS, p value is the difference between youngest and oldest age groups

5.5.3

Socioeconomic status of multiple sclerosis population by sex for census day NZSEI groups and original NZSEI groups

The model showed no significant difference between the sexes for change in socioeconomic status ($p=0.73$). However for both males and females there was a highly significant change in their SES when the NZSEI score for the original occupation they were trained for was compared with their census day NZSEI score.

Females had an OR 10.70 (CI, 7.89-14.51, $p<0.001$) and males had an OR 6.36 (CI, 3.94-10.27, $p<0.001$) indicating that females are 10 times and males 6 times more likely to be in a lower socioeconomic group in their circumstances on census day, than if they had remained in their original occupation and were earning the commensurate income for the position they had qualified for (Figure 5.3a & 5.3b).

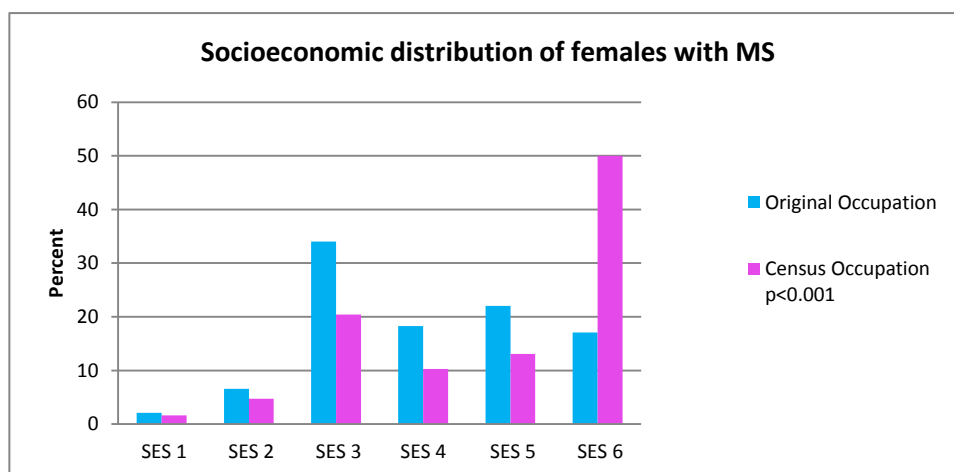


Figure 5.3a Proportion of females in each socioeconomic group based on their original and census day occupations

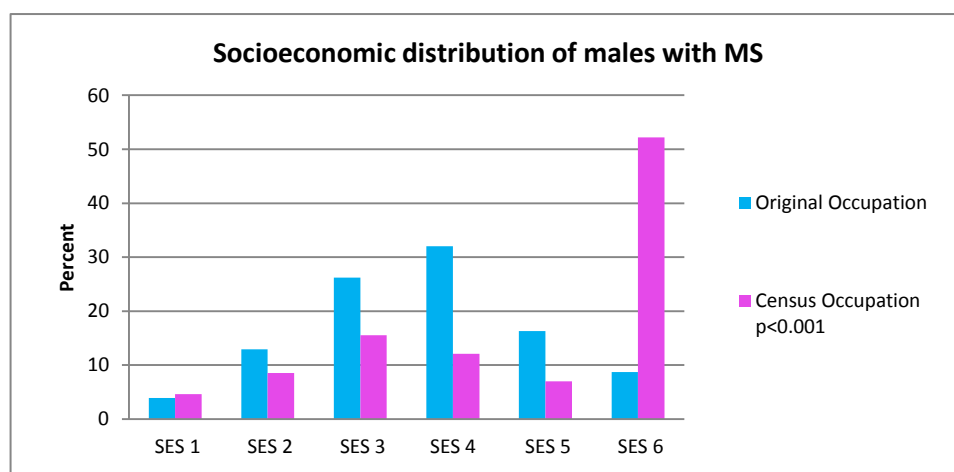


Figure 5.3b Proportion of males in each socioeconomic group based on their original and census day occupations

5.5.4

Socioeconomic status by multiple sclerosis phenotype

The results for original NZSEI group showed that there was no significant difference in SES by MS phenotype ($p=0.32$).

MS phenotype significantly contributed to SES for the census day NZSEI score. The model indicated that people with SPMS were 1.4 times more likely (OR 1.41, CI 1.06-1.86, $p=0.02$) to be in the lower socioeconomic group based on their census day NZSEI score than people with RRMS. The confidence level for the PPMS group included 1, making this result not significant (Figure 5.4a & 5.4b). The result indicates that MS phenotype makes a small contribution to SES for the census day NZSEI score with people

with SPMS having a higher percentage represented in the lowest SES group. As people with SPMS have more advanced disease with higher levels of disability, and tend to be older, they are less likely to be working and earning an income, factors which can be expected to affect SES.

When stratified by sex however, for both males and females, the census NZSEI groups (male $p=0.09$; female $p=0.07$) and the original NZSEI groups (male and female $p=0.50$) analyses did not reach significance. This reflects the small difference in magnitude of effect between MS phenotypes, with all phenotypes affected by change in socioeconomic status, and the differentiation in effect between MS phenotypes requiring the full MS working age population size to produce a statistically significant result.

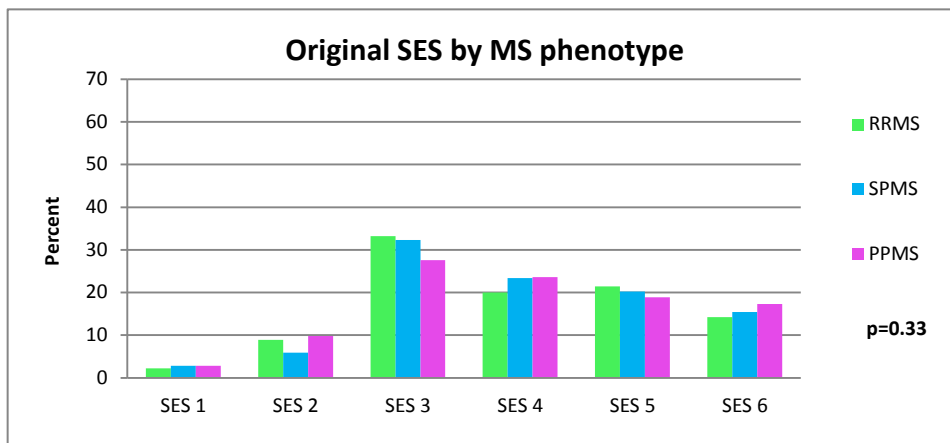


Figure 5.4a Effect of MS phenotype on SES, original NZSEI score, p value is SPMS, PPMS compared with RRMS

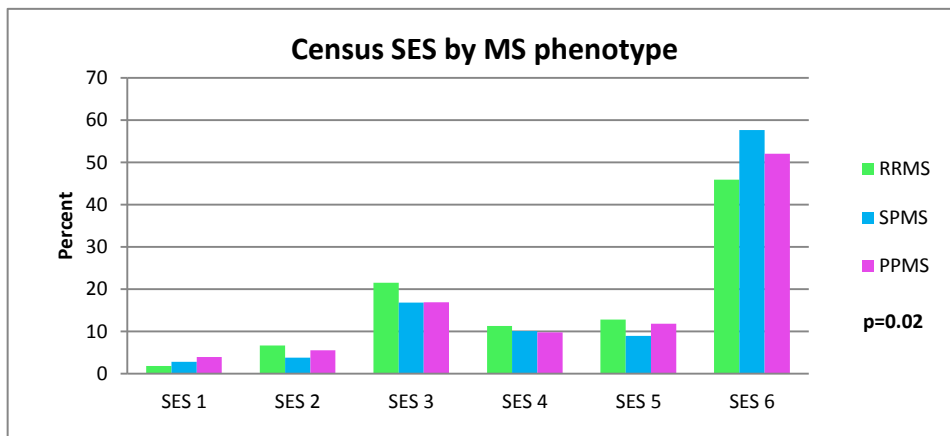


Figure 5.4b Effect of MS phenotype on SES, census day NZSEI score, p value is SPMS, PPMS compared with RRMS

5.5.5

Socioeconomic status by level of disability

There was no significant association between level of disability (EDSS) and SES. The analysis for original NZSEI score by EDSS had a level of significance of $p=0.18$, and the analysis for census day NZSEI score by EDSS had a level of significance of $p=0.08$. When comparing the two graphs, there is a higher percentage of people with both mild-moderate and moderately high-high levels of disability towards the lower end of the SES spectrum for census day NZSEI compared with original NZSEI, indicating that change in SES occurs in people with a low level of disability and the effect only marginally increases for people with a higher level of disability (Figure 5.5a, 5.5b). Once again these effects are a description of a population of people with MS at one point in time not an indication of trend as this is a cross-sectional study.

When stratified by sex, both census NZSEI groups (male $p=0.61$; female $p=0.20$) and original NZSEI groups (male $p=0.49$; female $p=0.12$) by disability remained non-significant.

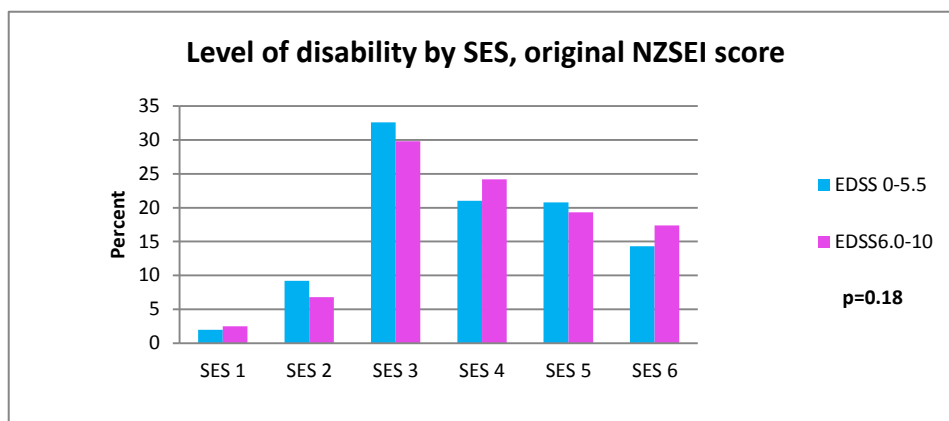


Figure 5.5a Socioeconomic status by level of disability (EDSS), original NZSEI score, p value indicates SES high EDSS group compared with low EDSS group

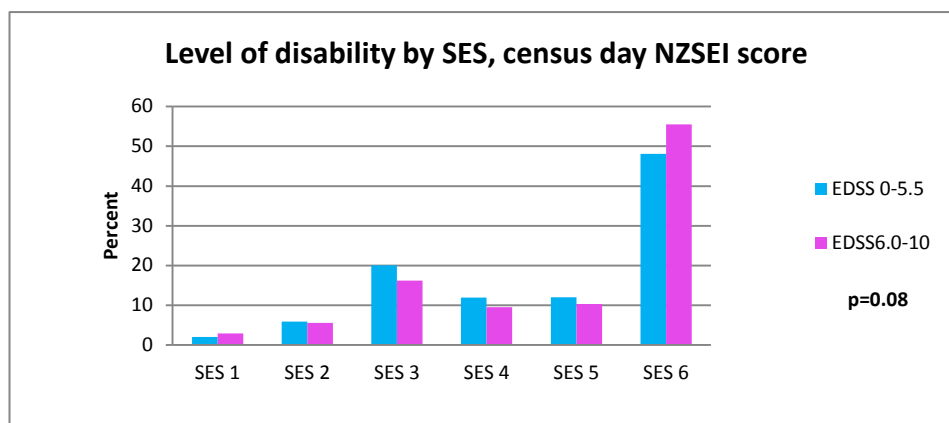


Figure 5.5b Socioeconomic status by level of disability (EDSS), census day NZSEI score, p value indicates SES high EDSS group compared with low EDSS group

5.5.6

Socioeconomic status by disease duration since diagnosis

There was no significant association found between disease duration from diagnosis and SES. The analysis for original NZSEI score by disease duration from diagnosis had a level of significance of $p=0.13$, and the analysis for census day NZSEI score by disease duration from diagnosis had a level of significance of $p=0.25$. When comparing the two graphs, there are a higher percentage of all levels of disease duration since diagnosis in the lower SES group for the census day NZSEI score compared with the original NZSEI score, indicating that loss of SES occurs early in the disease course and the effect only marginally increases with increased disease duration. (Figure 5.6a, 5.6b). This effect is observed for a population of people with MS at one point in time and is not an indication of trend as temporality cannot be assessed due to this being a cross-sectional study.

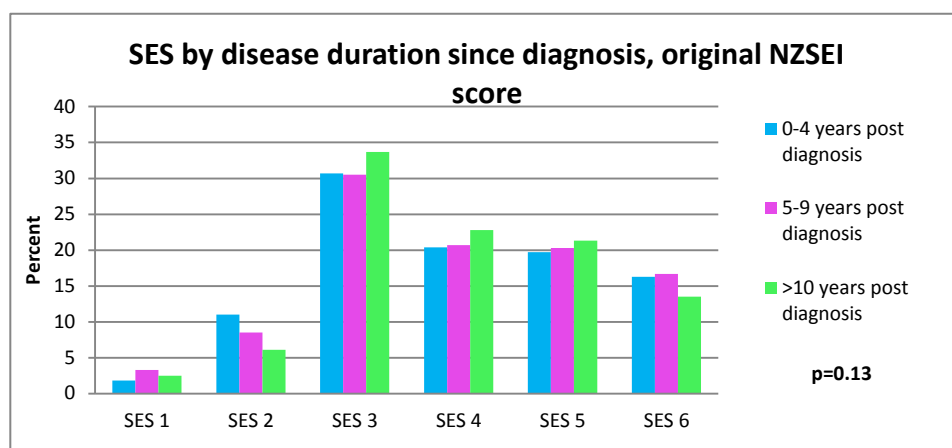


Figure 5.6a Socioeconomic status by disease duration since diagnosis, original NZSEI score, p value SES of longer disease duration compared with 0-4 yrs post diagnosis

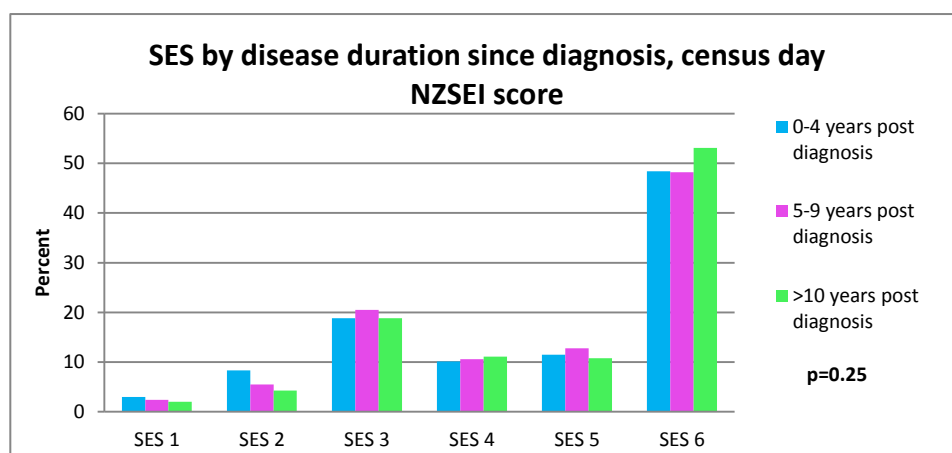


Figure 5.6b Socioeconomic status by disease duration since diagnosis, census day NZSEI score, p value SES of longer disease duration compared with 0-4 yrs post diagnosis

When stratified by sex, the original NZSEI group by disease duration analysis remains non-significant for both males ($p=0.51$) and females ($p=0.86$). There is no significant association for females between census day NZSEI group and disease duration from diagnosis ($p=0.83$), however for males a significant association was shown ($p=0.02$). The analysis found that males who are >10 years post diagnosis are twice as likely (OR 2.03, CI 1.20-3.42) to be in the lower socioeconomic group when compared with males who are 0-4 years post diagnosis. The confidence interval for males in the 5-9 year post diagnosis group contained 1, making it not significant. (Figure 5.6c).

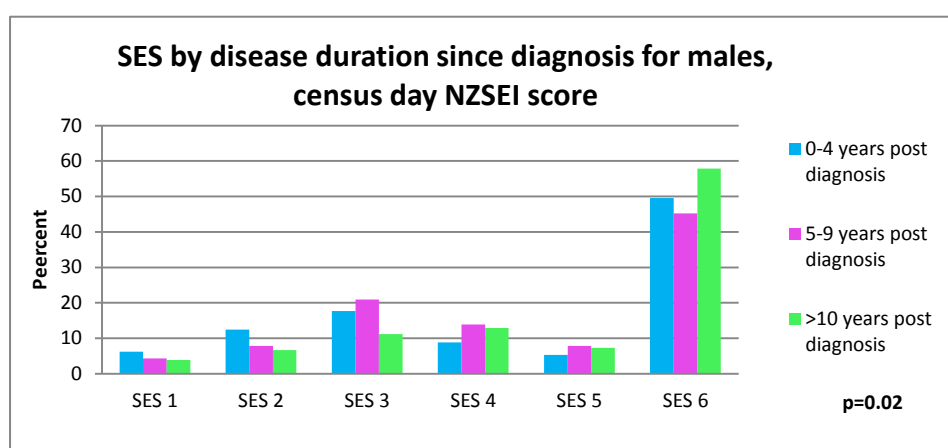


Figure 5.6c Male socioeconomic status by disease duration since diagnosis, census day NZSEI score, p value SES of disease duration >10 years compared with 0-4 yrs post diagnosis

5.5.7

Socioeconomic status by region of residence

Region of residence was associated with socioeconomic status for both original NZSEI group and census day NZSEI group. The initial analysis explored the data stratified by 6 centroids as described in Chapter 2, with the results indicating that for both original NZSEI ($p<0.01$) and census day NZSEI ($p<0.01$), people living in the Auckland region were significantly more likely to be in a higher socioeconomic group than people living in each of the other regions in NZ. However for each of the cells there were very small numbers of participants, and many of the confidence intervals contained 1, limiting inference from this result.

To simplify the picture, and increase the participant numbers in each cell, thus increasing the strength of the result, we then divided New Zealand into two regions, Auckland region and Rest of New Zealand, as it was evident that the Auckland region was the main region of difference. The model remained significant for both the original

NZSEI group and the census day NZSEI group. For census day NZSEI group, those who lived in the Rest of New Zealand had an OR 1.60 (CI, 1.25-2.05, $p < 0.001$) indicating they were 1.6 times more likely to be in a lower socioeconomic group when compared with people living in the Auckland region. For original NZSEI group, there was an OR 1.58 (CI, 1.25-1.98, $p < 0.001$) of being in a lower socioeconomic group for people living in the Rest of New Zealand when compared with those living in the Auckland region. The marginal differences in socioeconomic status between the two NZSEI group results indicate that difference in SES by region is unlikely to be entirely due to having a diagnosis of multiple sclerosis (Figure 5.7a, 5.7b). As the Auckland region includes Auckland, the largest city in New Zealand with approximately a quarter of the country's population, it is likely to have a greater number and variety of employment opportunities and attract more migrants to the region. As employment and income are associated with SES, it is not unexpected that this region has a slightly increased representation in the higher socioeconomic groups than the rest of New Zealand regions.

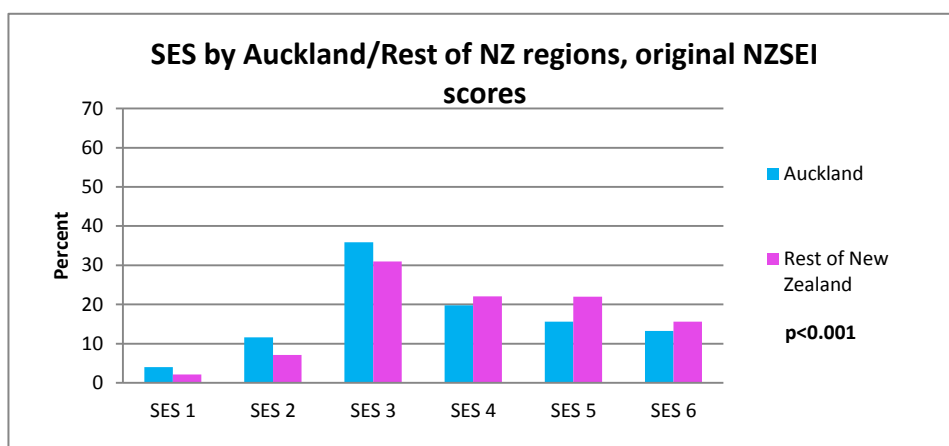


Figure 5.7a SES by region; Auckland and Rest of NZ, original NZSEI scores, p values SES group Rest of NZ when compared with Auckland

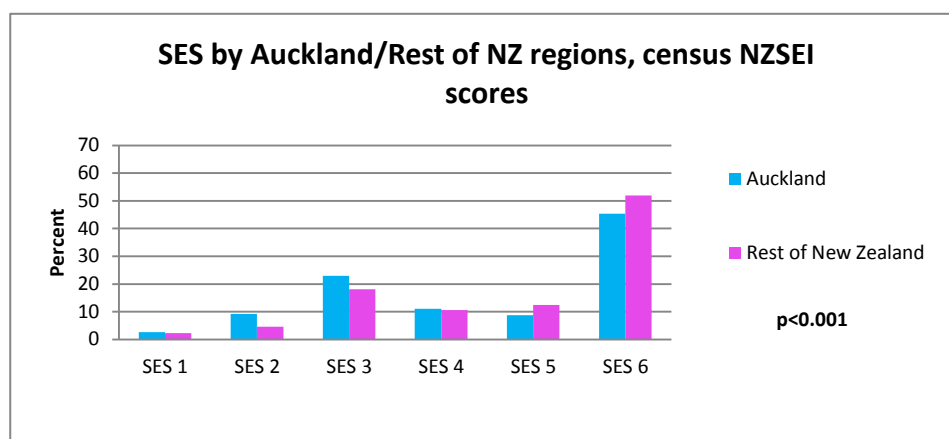


Figure 5.7b SES by region; Auckland and Rest of NZ, original NZSEI scores, p values SES group Rest of NZ when compared with Auckland

When stratified by sex, the results remain significant for males and females for both the census day NZSEI groups and the original NZSEI groups. Females who were in the Rest of NZ group were 1.5 times (OR 1.53, CI 1.16-2.03, $p < 0.01$) more likely to be in the lower socioeconomic group than those living in Auckland for census day NZSEI, and 1.4 times (OR 1.44, CI 1.11-1.86, $p < 0.01$) more likely to be in a lower socioeconomic group than those living in Auckland for original NZSEI (Figure 5.7c).

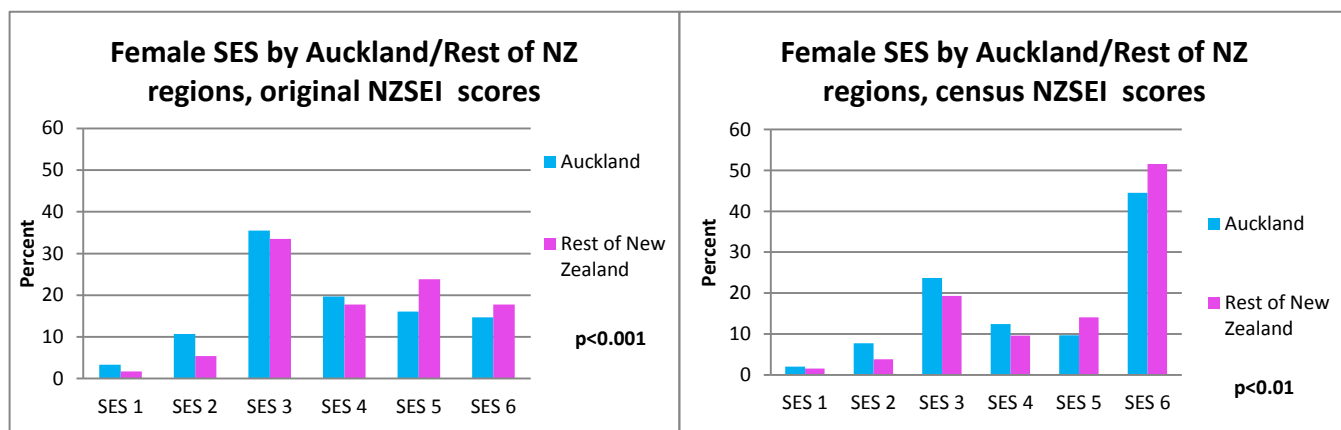


Figure 5.7 c. Female SES by region; Auckland and Rest of NZ, original NZSEI and census day NZSEI groups.

Males who were in the Rest of NZ group were 1.9 times (OR 1.91, CI 1.15-3.18, $p = 0.02$) more likely to be in the lower socioeconomic group for the census day NZSEI, and 2.2 times (OR 2.21, CI 1.35-3.64, $p < 0.01$) more likely to be in the lower socioeconomic group for original NZSEI than those living in the Auckland region (Figure 5.7d).

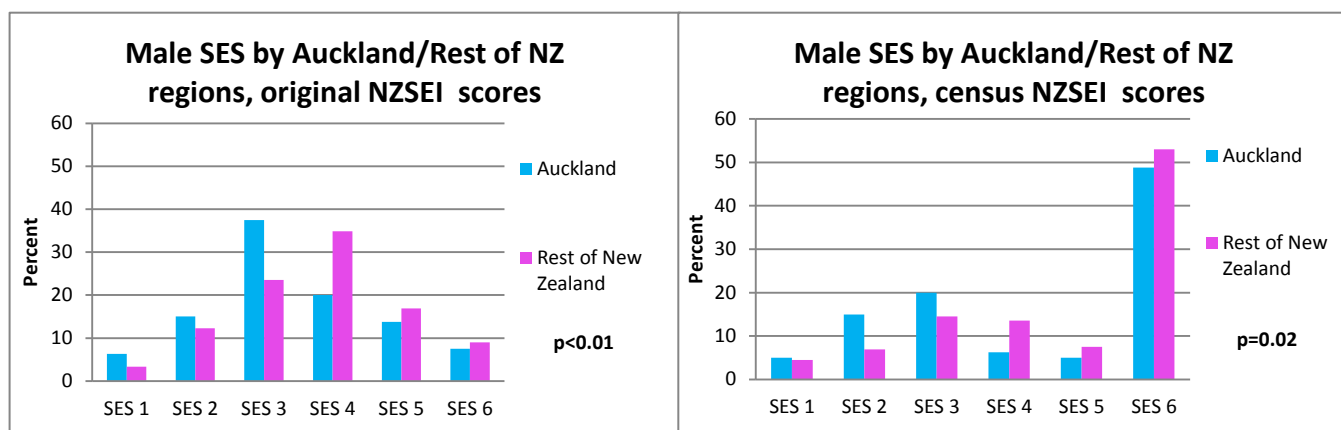


Figure 5.7d Male SES by region; Auckland and Rest of NZ, original NZSEI and census day NZSEI groups.

Once again the marginal differences in SES between census day NZSEI and original NZSEI results for males and females indicates that the difference in socioeconomic status

by region cannot be entirely explained by a diagnosis of MS, and will be a reflection of the influence of the Auckland region which includes the largest city in New Zealand with its particular characteristics of employment and migration as described above.

5.5.8

Association between census day NZSEI score and socioeconomic variables

Although the NZSEI algorithm includes occupation, income, and education; and controls for age in its model development, the scores are calculated from the 1996 census data for the entire NZ population over 15 years of age, and therefore represent that population's SES distribution. In the previous chapters the results have indicated significant differences between the MS and NZ population for education, work and income, as such we considered it important to analyse these factors by NZSEI score to fully describe the SES of the MS population on census day 2006. This section will describe the socioeconomic variables for the MS population in relation to their NZSEI score categorical SES groups.

5.5.8.1

Socioeconomic status by work status

Work status on census day was correlated with SES group with those who were not working more likely to be in a lower SES group OR 19.56 (CI 9.09-12.05, $p < 0.001$) (Figure 5.8a). When the SES groups are divided into two groups; top three and bottom three, the results remain significant for the census day NZSEI scores. Compared with people in higher SES group, those in the lower SES group were 9.8 times more likely to be not working (OR 9.82, CI 7.58-12.72, $p < 0.001$) (Figure 5.8b).

As over 50% of the census day MS population reported that they were not working, it is not surprising that there is a high proportion of this population in the lowest SES group. For most people, working in return for remuneration is their main source of income therefore if they are unable to work they are likely to have less or no income which in turn may affect their socioeconomic status.

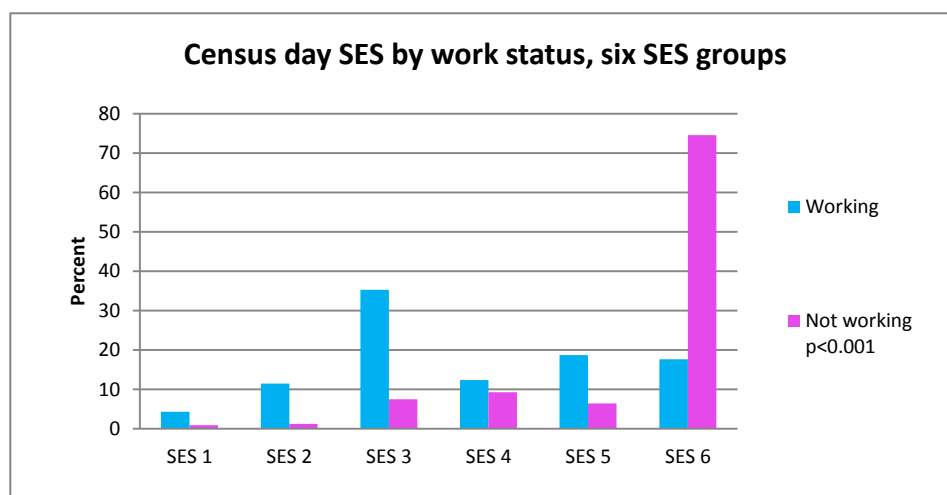


Figure 5.8a Census day socioeconomic status (6 groups) by work status, p value odds of not working for lower socioeconomic groups compared with SES1

When stratified by sex, using two SES groups as there were too few males for stable statistical analysis over six SES groups, females in the lower SES group were 7.6 times (OR 7.64, CI 5.75-10.16, $p<0.001$) more likely to be not working than those in the higher SES group (Figure 5.8b). For males the effect was greater, with males in the lower SES group 28.4 times (OR 28.45, CI 14.16-57.17, $p<0.001$) more likely to be not working than males in the higher SES group (Figure 5.8b). The magnitude of this effect may be partially due to smaller numbers of male participants, in particular for this analysis, in the high SES by not working cell ($n=10$).

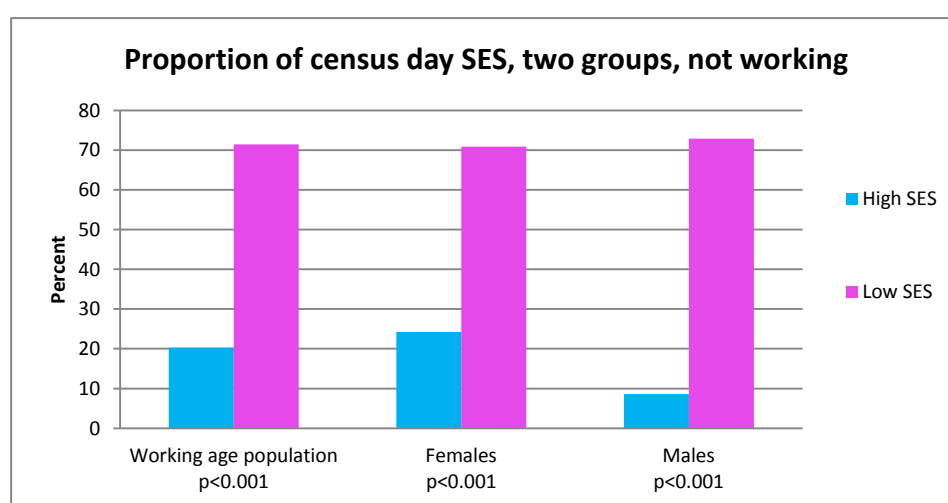


Figure 5.8b Census day socioeconomic status (2 groups), p value odds of not working for low socioeconomic group compared with high socioeconomic group

5.5.8.2

Socioeconomic status by income

Income level is highly correlated with SES using the census day NZSEI score, with the results indicating that compared with people in the SES 1 (highest) group, those in the SES 6 (lowest) group were 21 times (OR 21.20, CI 8.71-51.58, $p < 0.001$) more likely to have an income below the median annual personal income for people with MS (\$20,000) (Figure 5.9a). This result is not unexpected as 42% of the working age MS population reported receiving some form of government support as their source of income and 11% reported having no source of income.

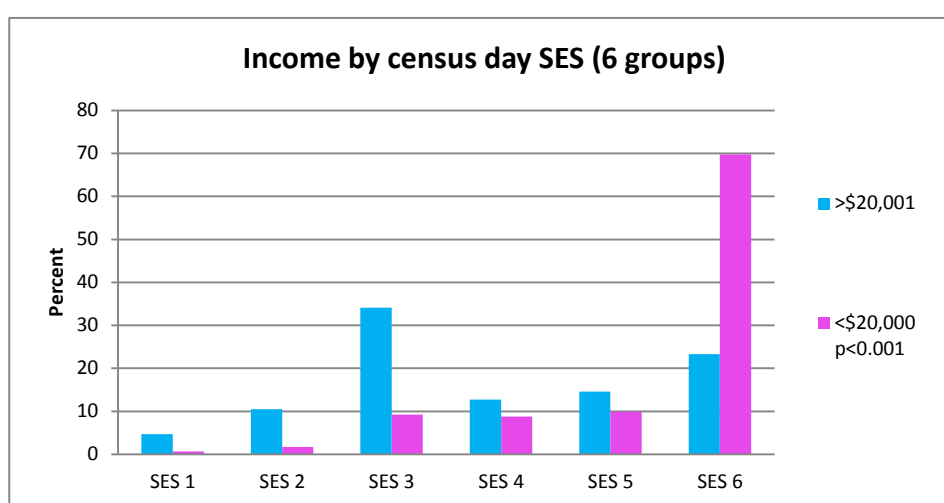


Figure 5.9a Census day socioeconomic status (6 groups) by level of income, p value lower socioeconomic groups reporting an income below median compared with SES1

When the SES groups were divided into top three and bottom three, the results were the same, but the effect was moderated and the confidence intervals narrower as there were greater numbers in each cell giving a more accurate result. There was a 7.5 times (OR 7.45, CI 5.78-9.61, $p < 0.001$) greater chance of having an income below the median annual personal income for people with MS (\$20,000), and a 7.9 times (OR 7.92, CI 6.19-10.14, $p < 0.001$) greater chance of having an income below the median annual personal income for NZ (\$34,750), for those in the lower SES group when compared with those people in the higher SES group based on the census day NZSEI score (Figure 5.9b).

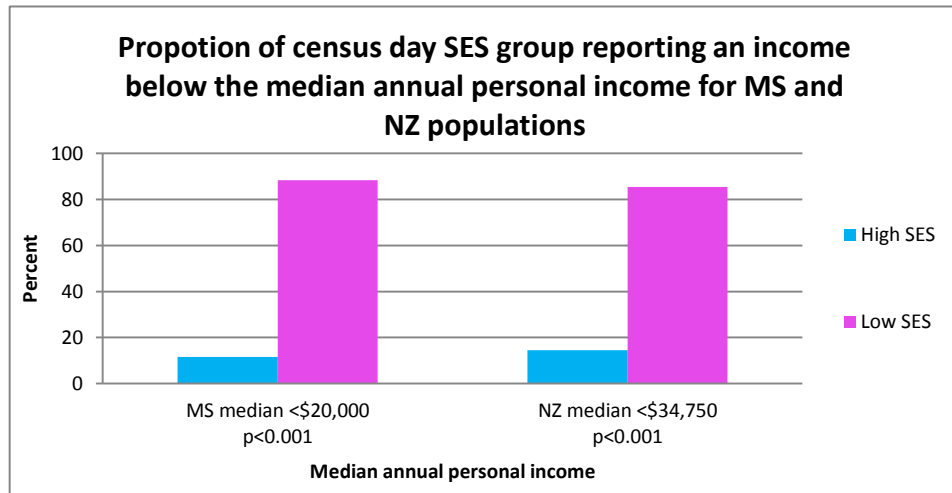


Figure 5.9b Census day socioeconomic status (2 groups) by level of income, p value low socioeconomic group reporting an income below MS or NZ median annual personal income compared with high socioeconomic group

When stratified by sex, females had an OR 6.50 (CI 4.91-8.60, $p < 0.001$) indicating that they were six and a half times more likely to be in the lower socioeconomic group if their income was below the MS median annual personal income (\$20,000), and 7.3 times (OR 7.27, CI 5.46-9.69, $p < 0.001$) more likely to be in the lower socioeconomic group if their income was below the NZ median annual personal income (\$34,750) (Figure 5.9c).

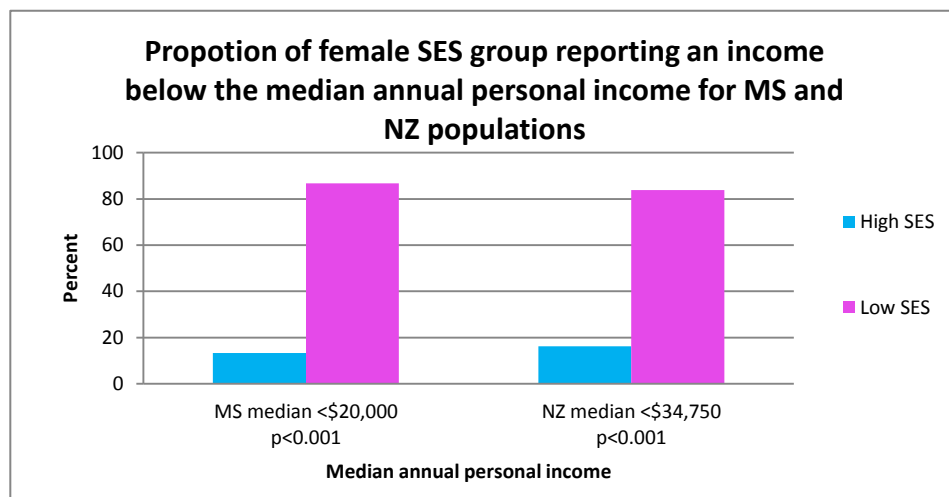


Figure 5.9c Female census day socioeconomic status (2 groups) by level of income, p value low socioeconomic group reporting an income below MS or NZ median annual personal income compared with high socioeconomic group

Males had an OR 21.61 (CI 9.68-48.22, $p < 0.001$) indicating that they were 21½ times more likely to be in the lower socioeconomic group if their income was below the MS median annual personal income (\$20,000), and 15.2 times (OR 15.23, CI 8.42-27.54, $p < 0.001$) more likely to be in the lower socioeconomic group if their income was below the NZ median annual personal income (\$34,750) (Figure 5.9d). Once again the results for the male MS population must be interpreted with caution as the population for this analysis is relatively small, with the high income by high SES group having a cell size of (n=10).

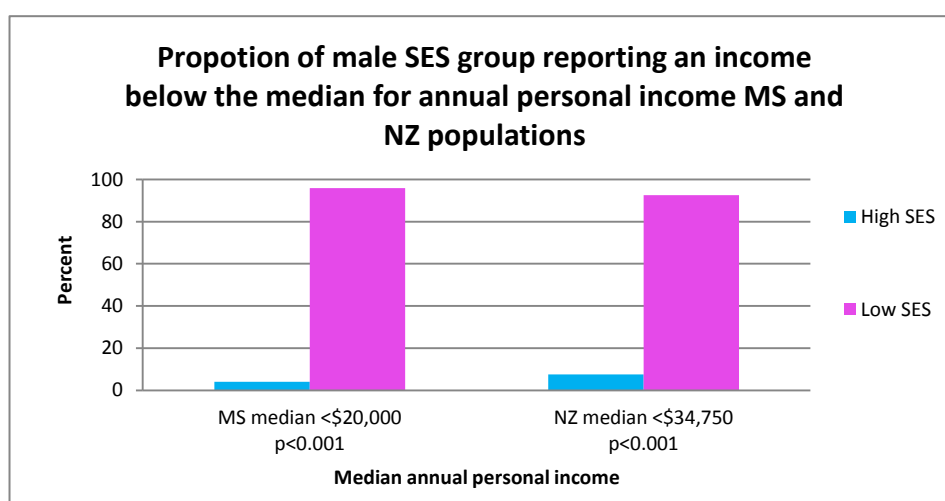


Figure 5.9d Male census day socioeconomic status (2 groups) by level of income, p value low socioeconomic group reporting an income below MS or NZ median annual personal income compared with high socioeconomic group

5.5.8.3

Socioeconomic status comparing original occupation with census day NZSEI score

Occupation was divided into five groups; managers/professionals, trades/technicians, clerical/administration, sales/community work, and machinery operators/labourers; based on a combination of statistics New Zealand occupational grouping and functional requirements of the occupations, and to enable large enough numbers in each group for robust statistical analysis.

The results for the comparison in SES between original occupational group and census day NZSEI showed that people who were originally qualified for the manager/professional group were more likely to be in the high socioeconomic group on census day when compared with all other occupational groups. People whose original

occupation was trades/technicians had an OR 1.97 (CI 1.36-2.85), clerical administration had an OR 4.78 (CI 3.51-6.52), sales and community workers had an OR 4.57 (CI 3.06-6.81) and machinery operators/labourers had an OR 9.47 (CI 6.40-14.02) for being in a lower SES group than people who were in the manager/professionals group ($p < 0.001$). This indicates that not only does the original occupational group the person with MS trained for locate them on the socioeconomic spectrum at the start of their careers, but it was also a strong predictor of socioeconomic status on census day with those people who were in occupations which require higher levels of education and offer greater remuneration more likely to have a higher level of SES (Figure 5.10). A number of factors could contribute to this observation. People in the manager/professional group may have earned an income which enabled them to save money, thereby giving them an income source from interest and dividends to support their SES. Secondly they may be in a better position to negotiate different working arrangements due to having knowledge and skills which are not easily replaced, enabling them to continue working, even if only part time, and maintain their SES.

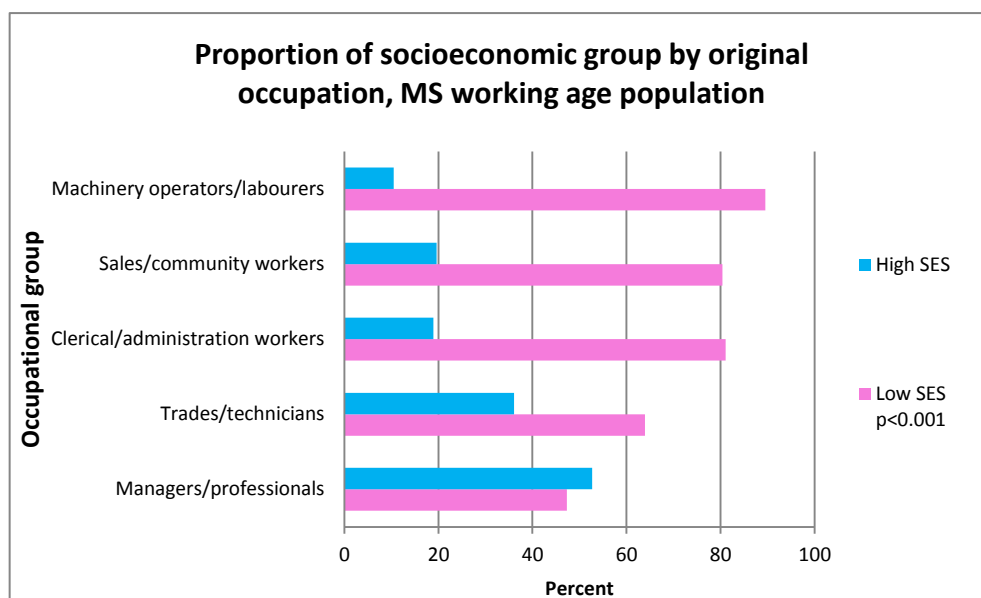


Figure 5.10 Census day socioeconomic group by original occupational group trained for MS working age population, p value odds of each occupational group being in the low socioeconomic group when compared with Managers/professionals

5.5.8.4

Socioeconomic status by education

Higher levels of education are generally associated with better jobs, higher income levels, and higher socioeconomic status²⁷⁰. The educational level of the MS working age (25-64 years) population differed from that of the New Zealand population of the same age group, with 51.4% of the MS population holding a post high school qualification as compared with 41.6% of their New Zealand population peers. However as discussed in Chapter 3.5.11 and Chapter 4.5.4, despite a higher proportion of people with MS holding a post high school qualification, a greater proportion were not working and reported an income below both the NZ and MS median annual individual income than their NZ population counterparts. The effect of low levels of income and work force participation despite a high level of education is reflected in the census day socioeconomic status of the working age MS population.

Post high school qualifications were significantly associated with socioeconomic status for the working age MS population. The analysis indicates that for their census day NZSEI group, the working age population with MS who do not hold a post high school qualification have a 3.3 times greater chance (OR 3.33, CI, 2.62-4.22 $p < 0.001$) of being in a lower socioeconomic group than those who have a higher qualification. However for original NZSEI group, those who did not hold a post high school qualification had a 5 times greater chance (OR 5.01, CI, 4.04-6.22, $p < 0.001$) of being in a lower socioeconomic group. This result indicates that more people with a post high school qualification were now, under their census day circumstances, included in the lower socioeconomic groups moderating the difference in SES status between those with and without a post-high school qualification (Figure 5.11a, 5.11b).

When stratified by sex the results remained significant for both males and females. Females were similar to the MS working age population, with those who did not hold a post secondary school qualification 3.6 times (OR 3.64, CI 2.76-4.81, $p < 0.001$) more likely to be in the lower socioeconomic group for the census day NZSEI score, and 6.6 times (OR 6.61, CI 5.12-8.53, $p < 0.001$) times more likely to be in the lower socioeconomic group for the original NZSEI score (Figure 5.11a, 5.11b).

Males had a more modest result, with an OR 2.52 (CI 1.58-4.03, $p < 0.001$) for the census day NZSEI score and an OR 2.28 (CI 1.51-3.44, $p < 0.001$) for the original NZSEI score, indicating that they are two to two and a half times more likely to be in the lower

socioeconomic group if they do not have a post high school qualification regardless of disease effects (Figure 5.11a, 5.11b).

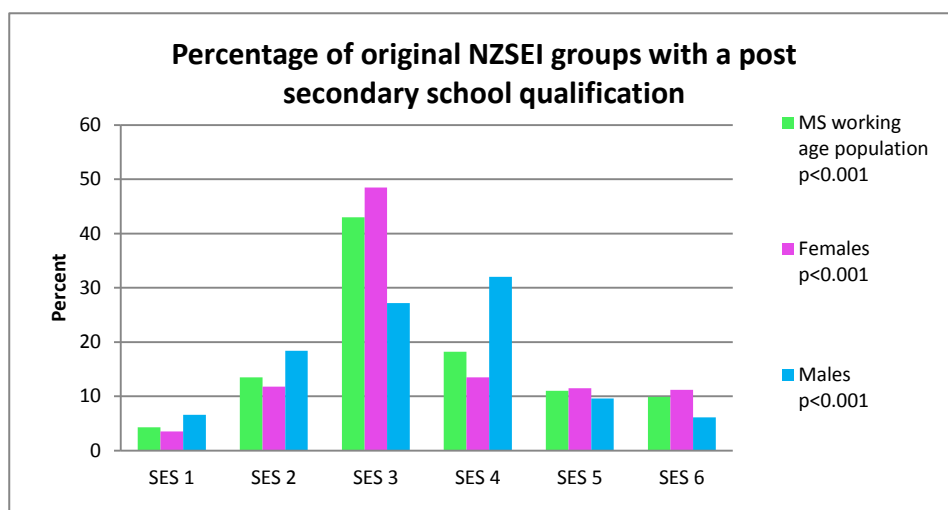


Figure 5.11a Proportion of original NZSEI group holding a post high school qualification, p value difference between higher and lower socioeconomic groups

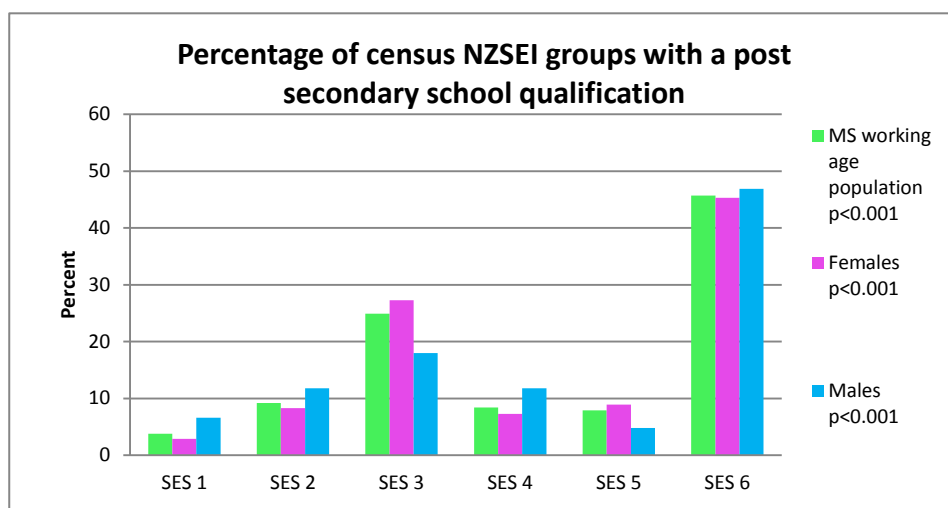


Figure 5.11b Proportion of census day NZSEI group holding a post high school qualification, p value difference between higher and lower socioeconomic groups

To assess whether any other factors were contributing to this effect, we analysed educational level in relation to disease characteristics and demographic factors, however the findings indicate that within the working age New Zealand MS population, the distribution of level of education is fairly uniform. There were no significant differences in education between the male and female working age MS population ($p=0.19$), or by marital status for either the whole MS population ($p=0.62$), or when stratified by sex; males ($p=0.83$), and females ($p=0.72$). There were no significant differences between educational level and MS phenotype ($p=0.62$), level of disability (EDSS) ($p=0.27$), or

disease duration since diagnosis ($p=0.11$). When stratified by sex the results remained non-significant for both males and females for all disease characteristics. These results indicate that educational level for people with MS is mostly attained prior to disease onset, however despite their level of education; they are unable to retain workforce status or level of income, the effect of which appears to flow on to socioeconomic status.

5.5.9

Socioeconomic status by marital status

The marital status of the MS working age (25-64 years) population differs from that of the New Zealand population of the same age band. Fourteen percent (14%) of the MS population have never been married as compared with 25% of the New Zealand population. Sixty three percent (63%) of the MS population and 58% of the New Zealand population were married and 22.6% of the MS population were divorced/widowed/separated as compared with 16.5% of the New Zealand population (Figure 5.12).

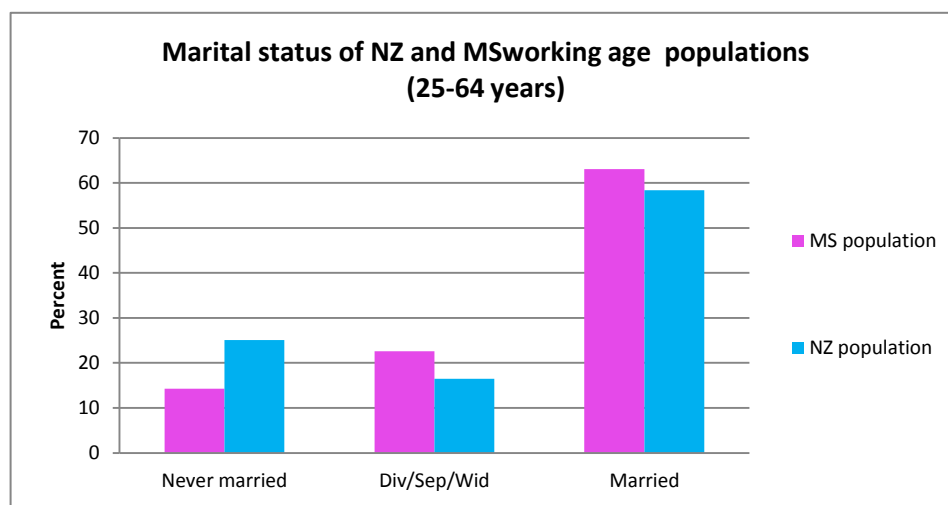


Figure 5.12 Marital status MS and NZ working age populations

When MS population data were analysed, the never married and married groups produced similar effects, whereas the effects for the divorced/widowed/separated were significantly different, as such the never married and married groups were combined to maximise numbers in the groups for the analyses.

Marital status was highly associated with change in SES for the working age MS population, with people who were in the divorced/widowed/separated group having a

greater chance of being in the lower SES group than people who were in the never married/married group for both their original NZSEI and their census day NZSEI. People who were divorced/widowed/separated had an OR 1.88 (CI, 1.42-2.53, $p < 0.001$) for being in the lower SES group for their census day NZSEI score and an OR 1.58 (CI, 1.24-2.00, $p < 0.001$) for being in the lower SES group for their original NZSEI score when compared with those in the never married/married group (Figure 5.13a). The results suggest that marital status has an effect on socioeconomic status with people who are in the divorced/widowed/separated group more likely to be in a lower SES group based on both their original NZSEI score and their census day NZSEI score. As the effect is greater for the census day NZSEI score this indicates that disease factors may be contributing to the interaction between marital status and SES, however the findings cannot entirely be attributed to a diagnosis of MS.

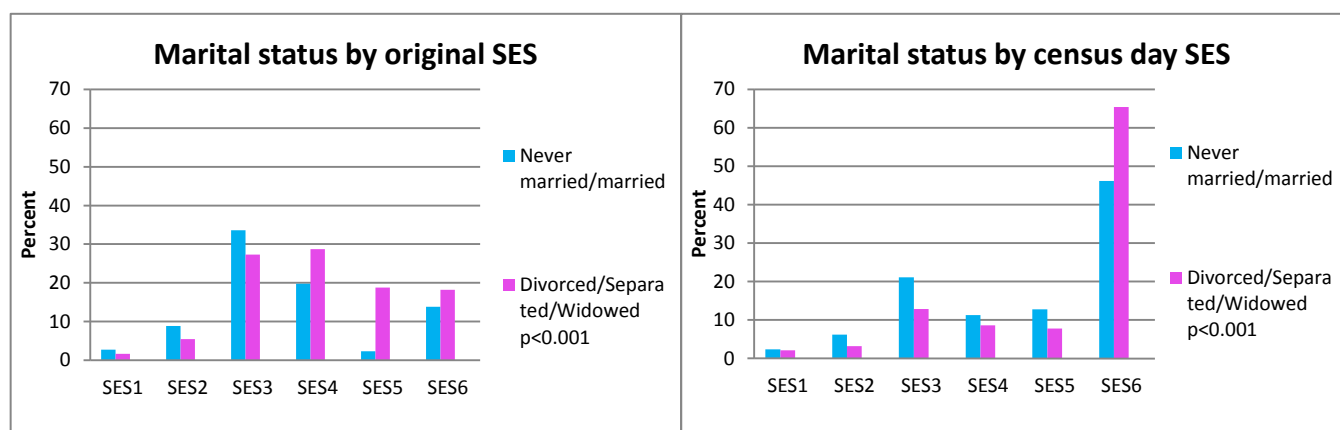


Figure 5.13a Original and census day 6 SES groups by marital status, p value divorced/widowed/separated group compared with never/married/married group SES

There were similar results for the female MS population. For their original NZSEI score, females who were divorced/widowed/separated were 1.5 times (OR 1.52, CI, 1.15-1.99) more likely to be in the lower SES group, and for their census day NZSEI score females who were divorced/widowed/separated were twice as likely (OR 2.18, CI 1.55-3.07) to be in the lower SES group than females who were in the never married/married group (Figure 5.13b).

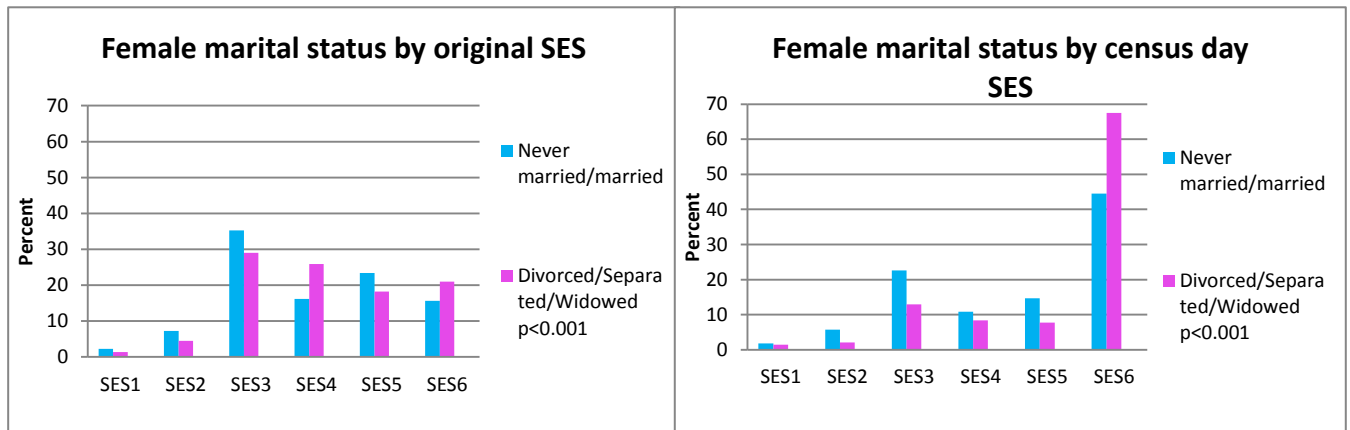


Figure 5.13b Female original and census day 6 SES groups by marital status, p value divorced/widowed/separated group compared with never/married/married group SES

The male working age MS population had a significant result for their original NZSEI, with those who were divorced/widowed/separated 1.8 times (OR 1.79, CI 1.08-2.95, $p=0.02$) more likely to be in the lower SES group than those who were in the never married/married group. The result lost significance for census day NZSEI group ($p=0.37$) indicating that on census day there was no significant difference in SES by marital group for the male MS population (Figure 5.13c).

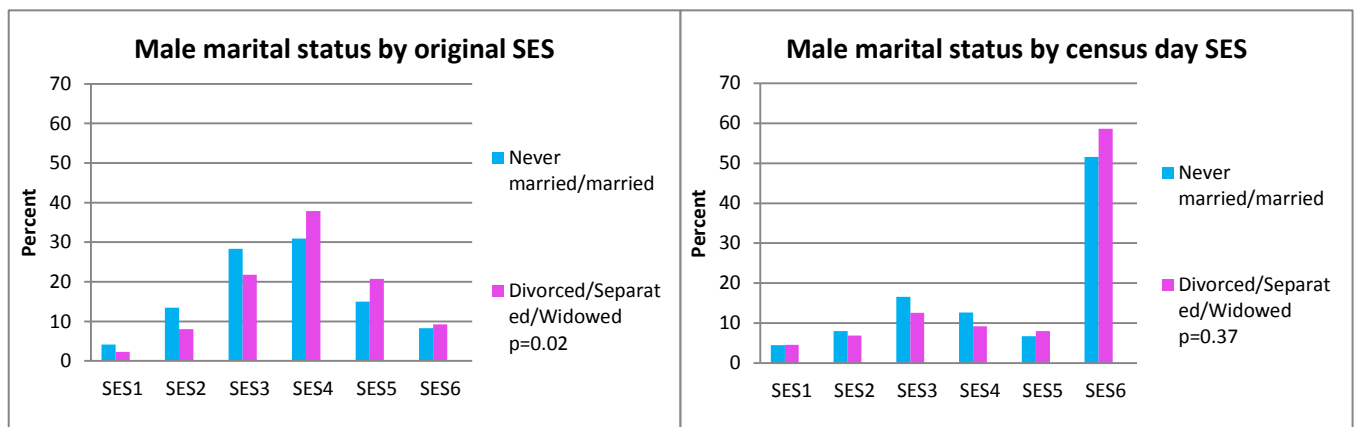


Figure 5.13c Male original and census day 6 SES groups by marital status, p value divorced/widowed/separated group compared with never/married/married group SES

5.5.9.1

Marital status by demographics and disease characteristics

To assess whether any other variables were contributing to the interaction between marital status and socioeconomic status we analysed marital status in relation to disease characteristics and demographic factors for the working age MS population. There was no significant difference in marital status by sex ($p=0.65$).

A significantly greater proportion of never married/married people were in the younger age groups, with a higher proportion of divorced/separated/widowed people in the older age groups. People who were 55-64 years were 4.8 times (OR 4.79, CI 2.58-8.87) more likely to be divorced/widowed/separated, those 45-54 years 3.8 times (OR 3.84-2.07), and those who were 35-44 years three times (OR 3.14, CI 1.66-5.95) more likely to be divorced/widowed/separated than people with MS who were 25-34 years of age ($p<0.001$) (Figure 5.14a).

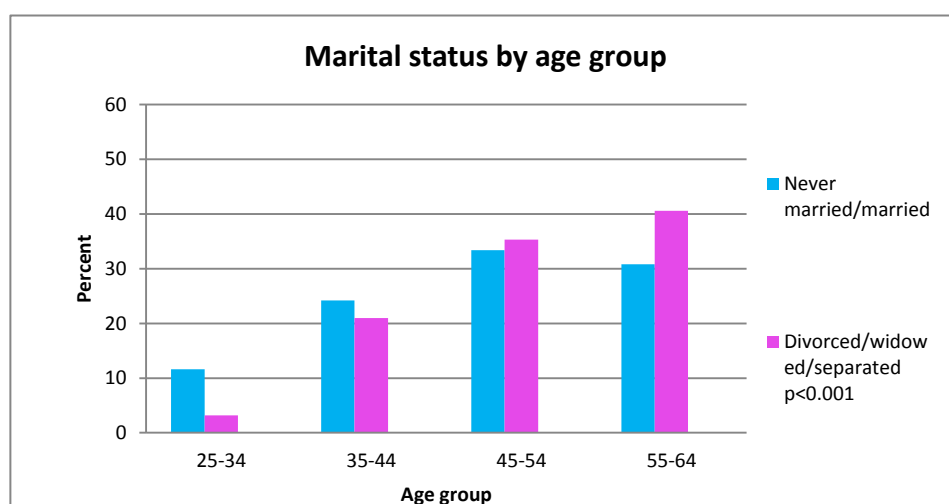
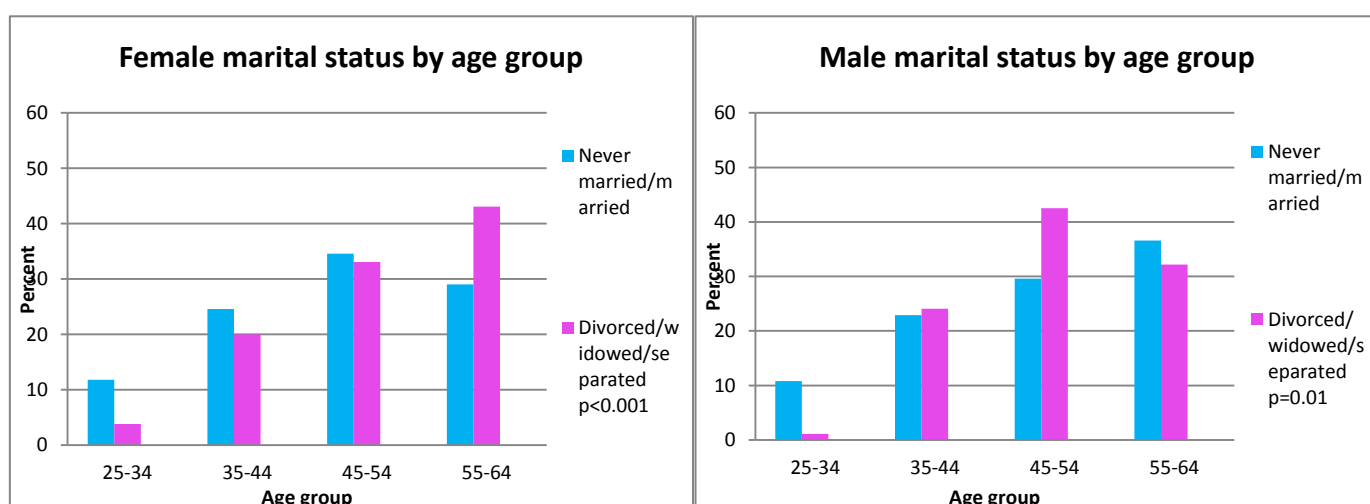


Figure 5.14a Marital status by age group for MS working age population

When analysed by sex, both females and males had a similar representation to the general MS population with a higher proportion of divorced/separated/widowed people in the older age groups, however the effect for the male MS population may be unreliable as indicated by the wide confidence intervals which can be attributed to the small sample size (Table 5.2, Figure 5.14b).

Table 5.2 Marital status by age group for females and males in the working age MS population

Variables		Odds Ratio	95% Confidence Intervals for Odds Ratio		(p value)
			Lower	Upper	
Females in the divorced/widowed/separated group by age group	25-34 years	2.53	1.28	4.99	<0.001
	35-44 years				
	45-54 years				
	55-64 years				
Males in the divorced/widowed/separated group by age group	25-34 years	9.92	1.28	63.10	0.01
	35-44 years				
	45-54 years				
	55-64 years				



Figures 5.14b Female and male marital status by age group for MS working age population

Analysis of the association between disease characteristics and marital status showed no correlation with disease duration since diagnosis for the working age MS population $p=0.87$, or for the female $p=0.98$, or the male working age MS population $p=0.75$. Marital status was correlated with disease phenotype and level of disability as measured by the EDSS.

Marital status was associated with MS phenotype, with people with SPMS 1.5 times (OR 1.54, CI, 1.19-1.99, $p<0.01$) more likely to be divorced/widowed/separated than people with RRMS. The CI for people with PPMS includes 1, making it not significant (Figure 5.15a).

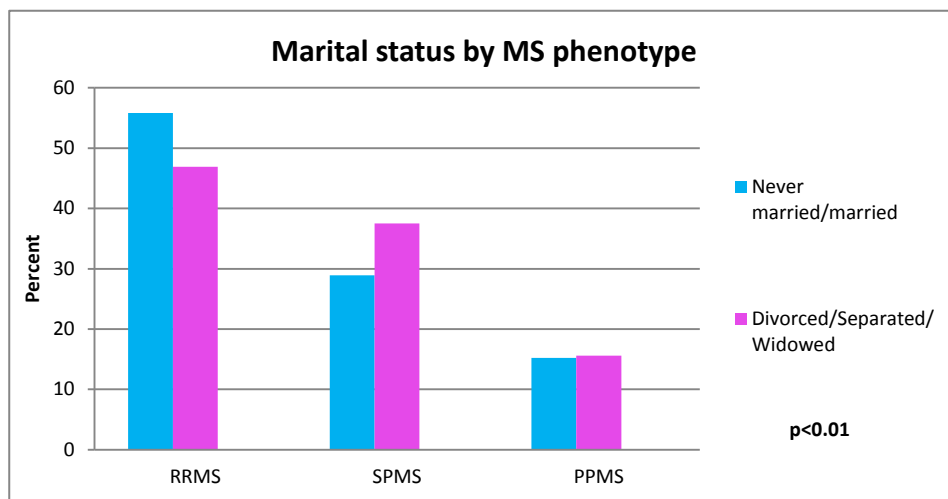


Figure 5.15a Marital status by MS phenotype, p value SPMS marital status compared with RRMS marital status

When analysed by sex, a similar result to the general MS population was obtained for the female MS population. Females with SPMS were 1.5 times (OR 1.54, CI 1.15-2.06, $p=0.01$) more likely to be divorced/widowed/separated than females with RRMS. The results for females with PPMS did not reach significance as the CI contained 1 (Figure 5.15b).

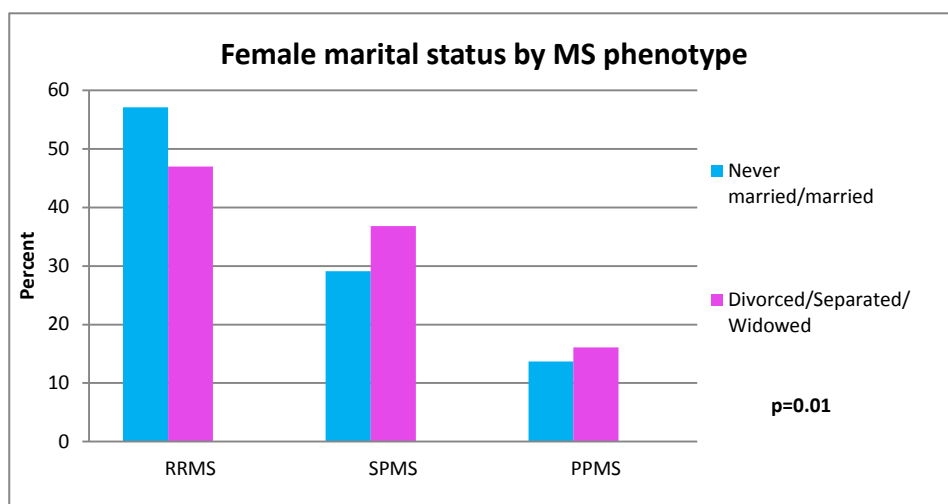


Figure 5.15b Female marital status by MS phenotype, p value SPMS, PPMS marital status compared with RRMS marital status

The analysis for males did not reach statistical significance ($p=0.11$), indicating no significant difference in marital status by MS phenotype for the male MS working age population, however it must be noted that the male population cell size for the divorced/widowed/separated by PPMS group is $n=12$, which may be too small for robust statistical analysis (Figure 5.15c).

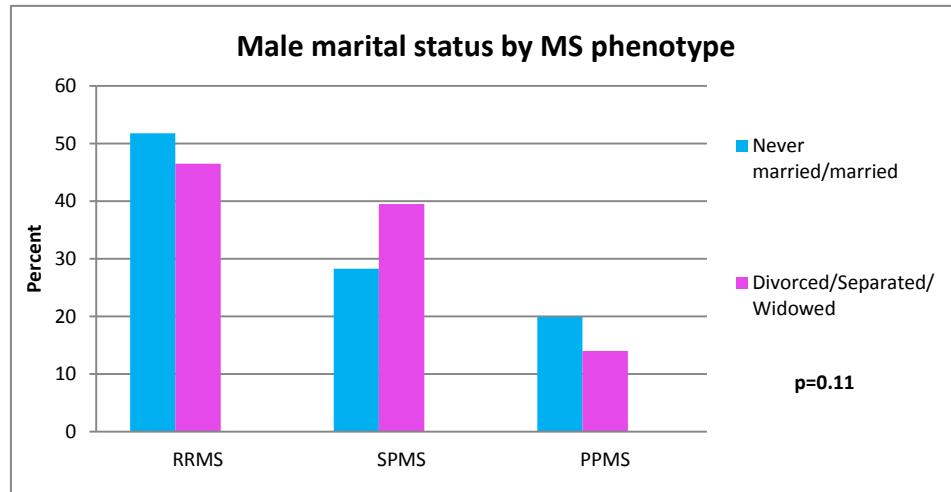


Figure 5.15c Male marital status by MS phenotype, p value SPMS, PPMS marital status compared with RRMS marital status

Level of disability as measured by the EDSS was statistically significant with higher levels of disability associated with being divorced/widowed/separated ($p=0.02$). People who had a disability score equal to or above EDSS 6.0 were 1.3 times (OR 1.36, CI, 1.06-1.76) more likely to be in the divorced/widowed/separated group than those with a lower level of disability (EDSS equal to or below 5.5) (Figure 5.16).

Once again a similar result was obtained for the female working age MS population, with females who had an EDSS ≥ 6.0 one and a half times (OR 1.49, CI 1.12-1.99) more likely to be divorced/separated/widowed than those with an EDSS ≤ 5.5 ($p<0.01$) (Figure 5.16).

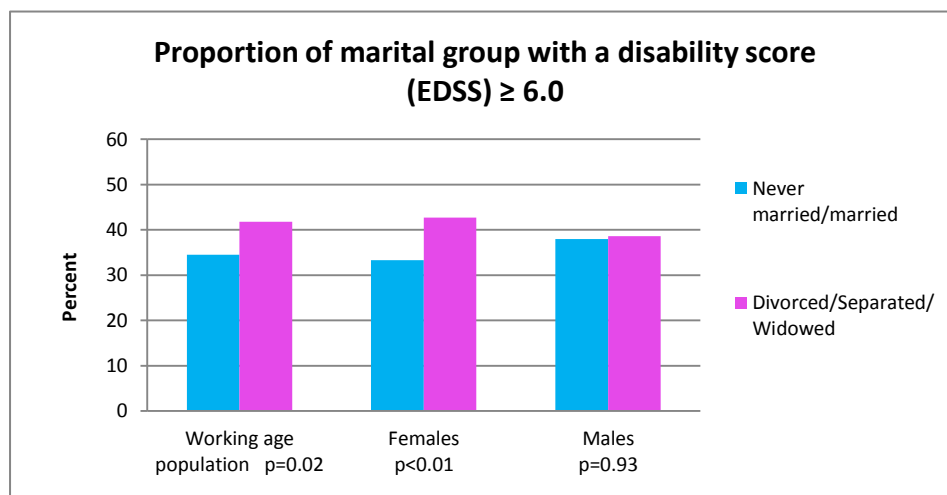


Figure 5.16 Marital status by level of disability \geq EDSS 6.0, p value divorced/widowed/separated group compared with never married/married group

For the male working age MS population there was no significant difference in marital status by level of disability ($p=0.93$), once again this result must be treated with caution as the cell for males who were divorced/separated/widowed and had an EDSS ≥ 6.0 contained a relatively small count $n=27$ (Figure 5.16).

Marital status in the working age MS population was associated with the SES indicators of work status, income, and NZSEI score, with people who were in the divorced/widowed/separated group more likely to be not working, in a lower income group and in a lower SES group. Disease characteristics and age were also associated with marital status with people who were in the divorced/widowed/separated group more likely to have a higher level of disability, SPMS phenotype, and be in the older age groups. Although these results indicate that people in the divorced/widowed/separated marital group are negatively affected in comparison with those in the never married/married group, temporality and causal association cannot be attributed to these findings as they are derived from descriptive data from a cross-sectional study.

5.5.9.2

Marital status by place of residence

Marital status was correlated with place of residence with those people who were in the divorced/widowed/separated group 4.4 times more likely (OR 4.42, CI, 2.90-6.74) to reside in a hospital/rest home facility than those who were in the never married/married group ($p<0.001$) (Figure 5.17).

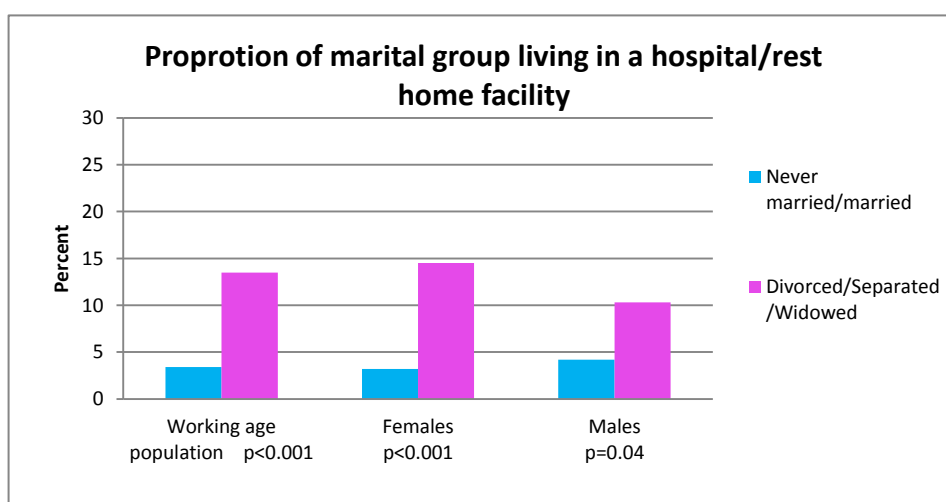


Figure 5.17 Census day place of residence by marital status, p value divorced/widowed/separated group residing in care compared with never married/married group

When stratified by sex, females who are in the divorced/widowed/separated group have an OR 5.15 (CI 3.17-8.37, $p < 0.001$), for residing in a hospital/rest home facility when compared with people in the never married/married group (Figure 5.17).

Whilst males who are in the divorced/separated/widowed group are 2.6 times (OR 2.66, CI 1.10-6.46, $p = 0.04$) more likely to reside in hospital/rest home facility than those in the never married/married group (Figure 5.17).

These findings may reflect the association between marital status and socioeconomic status noted in the previous section which presented people in the divorced/widowed/separated group as older, with more advanced disease and higher levels of disability; who were not working, had lower incomes and were in a lower socioeconomic group. This may indicate that people who are in the divorced/widowed/separated marital group have insufficient support at home to enable them to remain in their own environment as the disease progresses. Equally they may qualify more readily for government assistance to cover the cost of rest home/hospital level care whereas people who are in the never married/married group may have to pay for care under means testing and choose instead to manage in their own home with family and carer support.

5.5.10

Socioeconomic status by place of residence

Although only a small percentage of the working age population with MS in New Zealand were residing in a hospital or rest home facility on census day 2006 (5.6%), the analysis shows that they were most likely to be in the lower socioeconomic group. Based on the census day NZSEI scores, people in the lower SES group had an OR 4.86 (CI, 2.23-10.59, $p < 0.001$), indicating that they were nearly 5 times more likely to live in a hospital/rest home than those in the higher socioeconomic group (Figure 5.18a).

The data collected included place of residence 5 years prior to the census date. At that point 2.7% of the census day working age MS population lived in a hospital or rest home facility. Analysis of their SES groups based on census day NZSEI scores produced similar results, with the lower SES group having an OR 5.53 (CI, 1.71-17.90, $p < 0.001$) of living in a hospital/rest home when compared with the higher SES group (Figure 5.18b).

The multivariate analysis was run to determine the odds ratios for differences in place of residence by SES between males and females; however the numbers for males were

too small for accurate statistical evaluation. The model did however show that for women whether five years prior to census day 2006 (OR 3.62, CI, 1.10-11.97, $p=0.01$) or on census day 2006 (OR 3.54, CI, 1.61-7.81, $p<0.001$) there was a 3.5 times greater chance of residing in a hospital or rest home facility as compared with a house/flat/apartment if they were in the lower SES group (Figure 5.18a, 5.18b). The result for males in the cross tabulations indicated that all males with MS who were residing in a rest home or hospital, at either census day 2006 or 5 years prior to that, were in the lower socioeconomic group as shown in (Figure 5.18a, 5.18b).

As access to subsidised rest home/hospital level care in New Zealand is means tested, the higher proportion of people in the lower socioeconomic groups in residential care may be a reflection of the health care and social welfare systems. People in the higher SES groups may not qualify for financial support after means testing and may choose instead to care for the person with MS in their own home with family or carer support. Alternatively people who are in rest home/hospital level care are more likely to have advanced disease, be not working, and may have no income source which is also likely to affect their socioeconomic status. However, as this is a cross-sectional, descriptive study this is merely an observation as causal and temporal association cannot be established from the data.

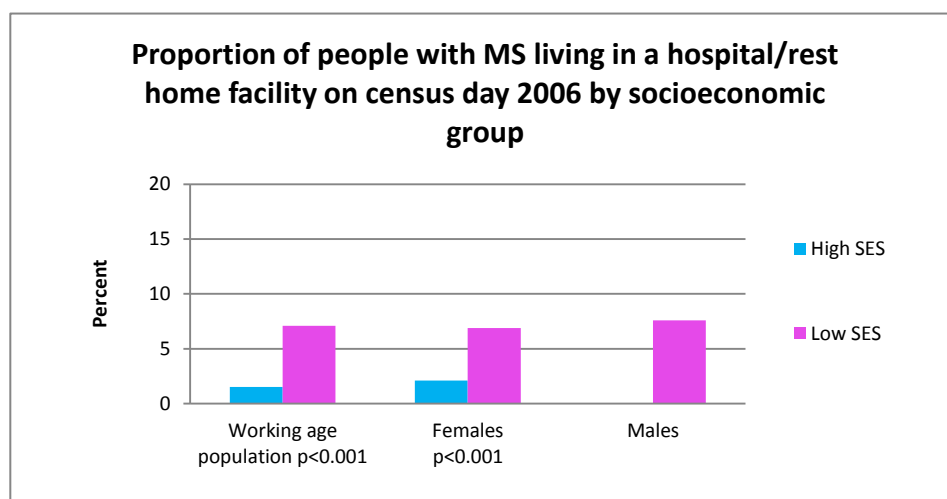


Figure 5.18a Proportion of MS population socioeconomic groups residing in a rest home/hospital facility on census day 2006

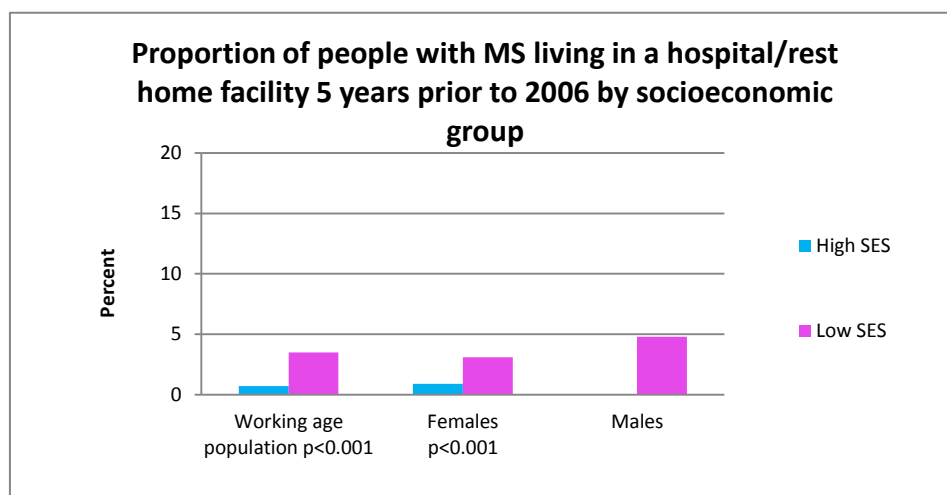


Figure 5.18b Proportion of MS population socioeconomic groups residing in a rest home/hospital facility 5 years prior to census day 2006

5.6

Factors predicting low socioeconomic status

Bivariate logistic regression was used to determine which factors relating to multiple sclerosis clinical characteristics and demographic features predicted low socioeconomic status for people in the working age group (25-64 years) with MS. Modelling was run in steps which included the regions in six centroids, three regions, Auckland and the rest of New Zealand, and no regional breakdown. When divided into six and three regions, the confidence intervals became very wide due to the small numbers in some of the cells. When comparing the results from these models with the Auckland/rest of New Zealand model, the factors included in the final table were very similar indicating that the main region of influence was Auckland. Comparison of results from the model with no regional break down and the Auckland/rest of NZ model indicated that the influence from the Auckland region was insufficient to change the model effect; as such the final model has no regional breakdown.

The models were also run in three steps for occupation: firstly, occupational groupings based on occupational demands (mainly cognitive, light physical and heavy physical); secondly, eight occupational groups as per the statistics NZ groupings, and finally five occupational groups (managers and professionals, trades and technicians, clerical and administration workers, sales and community workers, and labourers and machinery operators) to ascertain which aspect of the occupations were most likely to predict a lower

socioeconomic status. When divided by eight occupational groups, the confidence intervals became very wide due to the small numbers in some of the cells. The occupational groupings based on occupational demands gave specious results indicating that the composition of the groups did not reflect the true occupational effect. Using the five occupational groups described above, the results reflected those of the eight Statistics NZ described occupational groups, and there were sufficient numbers in the cells to give robust results.

The final model for predicting low socioeconomic status in the New Zealand working-age multiple sclerosis population can be seen in Table 5.3.

5.6.1

Model predicting low socioeconomic status

The full model for low SES, containing all predictors was statistically significant, Chi-square (12, N=1185) = 492.8, $p < 0.001$, indicating that the model was able to distinguish between respondents who were classified as being in the lowest three socioeconomic groups and those who were in the highest three socioeconomic groups for people with MS aged 25-64 years. The model as a whole explained between 34.0% (Cox and Snell R Square) and 48.9% (Nagelkerke R Square) of the variance in SES and correctly classified 82.9% of cases. The remaining variance shows that the individual and their circumstances play the largest part in determining loss of socioeconomic status.

As shown in Table 5.3, work status, income, original occupation, higher qualification, age and marital status were the independent variables which made a unique, statistically significant, contribution to the model. The strongest predictor of being in a lower socioeconomic group was work status with those people who were not working being 6.5 times more likely to be in a lower socioeconomic group (OR 6.47, CI 4.40-9.52, $p < 0.001$) than those people who were working.

Income made a significant contribution to the model with those people who reported an income below the median annual personal income for people with MS (\$NZ 20,000) being three times (OR 3.28, CI 2.27-4.75, $p < 0.001$) more likely to be in a lower socioeconomic group than those with an income above the median.

Original occupation made a significant contribution to the model with people working in professional occupations more likely to be in a higher socioeconomic group than any other occupational group. Trades workers were 1.9 times more likely to be in a lower

socioeconomic group (OR 1.91, CI 1.12-3.24); clerical workers had an OR 5.20 (CI, 3.26-8.29); sales and community workers an OR 4.09 (CI, 2.34-7.15); and labourers and machinery operators having an OR 11.46 (CI, 6.64-19.79) for being in a lower socioeconomic group when compared with professionals ($p < 0.001$).

People who did not hold a post high school qualification were twice as likely (OR 2.12, CI 1.46-3.09, $p < 0.001$) to be in a lower socioeconomic group than those who had a higher level of education after controlling for all other variables in the model.

Table 5.3 Model predicting low socioeconomic status for MS working age population

Variables		Odds Ratio	95% Confidence Intervals for Odds Ratio		(p value)
			Lower	Upper	
Work Status	Working	6.47	4.40	9.52	<0.001
	Not working				
Income	Median annual income >\$20,000	3.28	2.27	4.75	<0.001
	Median annual income <\$20,000				
Post secondary qualification	Post high school qualification	2.12	1.46	3.09	<0.001
	No post high school qualification				
Original occupation	Professional	1.91	1.12	3.24	<0.001
	Trades				
	Clerical				
	Sales and Community workers				
	Labourers and Machinery operators				
Age	25-34 years	1.02	0.58	1.81	0.01
	35-44 years				
	45-54 years				
	55-64 years				
Marital status	Never married/Married	1.59	1.03	2.46	0.04
	Divorced/Widowed/Separated				
Level of disability (EDSS)	Mild-moderate disability (0.0-5.5) Moderately severe-severe disability (6.0-10.0)	1.46	0.94	2.26	0.05

Age indicated that people in the 25-34 year age group were twice as likely (OR 2.09, CI 1.14-3.83) to be in a higher socioeconomic group than those who were in the 55-64 year age group; and 1.8 times more likely (OR 1.76, CI 1.01-3.09) to be in a higher SES group than those in the 45-54 year group ($p = 0.01$). There was no significant difference in SES group for the 35-44 year age group when compared with those in the 25-34 year group.

People who were in the divorced/widowed/separated marital group were one and a half times more likely (OR 1.59, CI 1.03-2.46, $p = 0.04$) to be in a lower socioeconomic

group than those who were in the never married/married group after controlling for all other variables in the model.

Level of disability contributed to the model, but did not reach significance ($p=0.05$).

Although all two way interactions were put into the analysis none were retained in the final model, indicating that the fitted interaction terms did not increase the model effect. This suggests that based on the evidence we have in this data set each variable outcome is acting independently from the others.

5.6.2

Goodness of fit – logistic regression model

The logistic regression model was assessed for best fit by changing one independent variable whilst keeping all other independent variables constant. The variables we tested were region; Auckland and the rest of NZ; Urban (Auckland, Wellington, Canterbury) and Rural (all other regions); Male and Female; Original socioeconomic group, Original occupational group based on role (mostly cognitive, light physical and heavy physical); original occupational group (eight groups); and original occupation (five groups). These variables were selected for further analysis for the following reasons:

- Auckland is New Zealand's largest city with around one quarter of the country's total population and had a lower response rate than the other regions, as such we wanted to ensure that there was no bias introduced by this region.
- Equally we wanted to ensure that the MS populations in urban and rural regions of New Zealand were not significantly different.
- As 75% of the MS population is female, and there was a lower response rate from males, it was important to investigate whether the female population was driving the model and concealing potentially different drivers of socioeconomic status in the male MS population.
- We investigated the effect of original socioeconomic group on the model to see what effect the MS populations' original SES had on their census day situation.
- Finally, we explored whether there was a difference in socioeconomic status based on the type of work performed in different occupations as the disability accumulated due to the disease process may affect the person's ability to fulfil their occupational requirements.

All models produced similar results with work status and original occupation being the strongest predictors of low socioeconomic status in the models that contained occupation variables, and original socioeconomic status and work status being the strongest predictors of people with MS being in a lower socioeconomic group in the models that contained the original socioeconomic status variable.

5.7

Discussion

Analysis of socioeconomic status is an important aspect of epidemiological studies as large differences in the occurrence of health problems, morbidity and mortality between people of higher and lower socioeconomic status have been previously identified²⁵⁶⁻²⁶³. Understanding the associations between disease characteristics, demographics and socioeconomic variables may contribute to understanding the disease effects and ways of minimising the impact of the disease^{258,264}. This chapter examined the factors which predicted being in a lower socioeconomic group, as determined by the NZSEI, in the working age (25-64 years) MS population in New Zealand. The findings from the analysis of the socioeconomic data for the New Zealand multiple sclerosis population provides new information as no data on this subject has previously been published from New Zealand.

When the socioeconomic distribution of the working age MS population is plotted against the proportionate socioeconomic distribution of the general New Zealand population in the same age groups, we find that based on the occupation for which they were originally trained and educated, people with MS have a similar socioeconomic distribution to the NZ population. However as over 50% of the working age MS population are no longer working and many of those who are still working have changed their roles, a significant difference in the socioeconomic status of people with MS can be noted. When the NZSEI score of the occupation for which they originally qualified is compared with their census day NZSEI score there is a significant increase in the proportion of the MS working age population at the lower end of the socioeconomic spectrum.

The greatest contributing factor to socioeconomic status identified in the analysis was a person's ability to work, and therefore earn an income. People with MS in the working age population (25-64 years) who were not working were nearly ten times more likely to

be in the lower socioeconomic group than those who were still able to work. Of note, the working group included both part time and full time employment, indicating that even those who are able to work in a limited capacity are significantly better off than people who are not working.

Income levels were reflected in the SES of people with MS with people in the lower socioeconomic group nearly seven and a half times more likely to have an income below the median annual personal income for people with MS (\$20,000), and nearly eight times more likely to have an income below the median annual personal income of the NZ working age population (\$34,750). Previous studies have identified lost productivity with its associated loss of earnings as accounting for up to 80% of the total indirect costs of MS. Research of other conditions such as depressive illness and other 'disorders of the brain' have also found time off work and reduced capacity at work as major contributors to the indirect costs associated with the illnesses²⁶⁵. As loss of work status has been identified as a major cost driver in burden of illness studies^{297,299,301,307}, the significance of loss of work status on SES for the working age NZ MS population cannot be understated.

The MS working age population has a high proportion of people with post-secondary school qualifications, 51.4% as compared with 41.6% of the NZ population in the same age group, with no significant difference in educational level by sex, marital status, or disease characteristics. This indicates that educational level for the MS working age population is attained prior to disease onset in most cases. As would be expected, people who did not hold a post high school qualification were more than three times as likely to be in the lower socioeconomic group when compared with those who did have a higher education when their census day NZSEI was analysed. What was more interesting was the result from the analysis of the original NZSEI score; people who did not hold a post high school qualification were five times more likely to be in a lower socioeconomic group if the MS population had remained in the original occupations they were educated for. This indicates that due to a change in occupational status most likely as a result of the effects of the disease process, a higher proportion of people who held a post high school qualification were in the lower socioeconomic group on census day.

Men and women are both affected by change in socioeconomic status, however the proportion of the effect is greater for women, with women ten times and men six times more likely to be in a lower socioeconomic group on census day than if they had retained their original occupation NZSEI score status. This may be a reflection of findings from Chapters 3 and 4 where it was observed that women were more likely to report a loss of

work status and lower incomes than men, and those women than did remain in the workforce were more likely to work part time. As women make up three quarters of the MS population, and tend to live longer than men in society, this has considerable financial implications for both the person with MS and society. In New Zealand lower income levels incur lower taxation levels which provides less societal revenue to support the government funded welfare system; furthermore, loss of workforce status may result in the person with MS requiring support in the form of welfare benefits which places further demands on the health and welfare systems.

Change in socioeconomic position was noted to occur at a young age in the NZ multiple sclerosis population, with an increased effect in the older age groups, a finding corroborated by international studies^{264,341,399}. This indicates that the impact on socioeconomic status due to the disease process may compound with age, however as this is a cross-sectional study temporal and causal associations cannot be made from the data analysis. If this observation was supported by future longitudinal studies it would have important implications for the financial security of people with MS leading into retirement and their ability to 'age in place' as recommended by the New Zealand Government strategy for the older person³⁴⁶.

Battaglia et al. (2000) identified hospitalisation, and in particular long term care as being the highest costs related to multiple sclerosis³⁰⁴. On census day 5.8% of the MS working age population (25-64 years) were residing in a hospital/rest home facility, with this group of people being five times more likely to be in the lower socioeconomic group. As this study is a cross-sectional study it is not possible to establish temporal relationships, therefore it is not possible to determine if those people who are residing in a residential care facility are there because they are from a lower socioeconomic group or whether they are in a lower socioeconomic group as a consequence of having to reside in a hospital/rest home due to MS. Previous international research has shown that people in lower socioeconomic groups tend to have increased exposure to health risks and a poorer health status^{317,349,350} which may in turn necessitate moving into a residential care facility.

In New Zealand, the system for provision of long term care offers a possible explanation. People have two options, they can choose to go into full time care in a private facility and pay the full costs themselves, or they can be assessed as needing full time care and be placed in a hospital/rest home facility with the potential for a level of financial support depending on their household situation. Financial support for long term care in NZ is means tested (income and assets), therefore if the household of a person

who requires long term care has assets and an income above the threshold, they have to pay all or a proportion of the costs of residing in that facility⁴⁰³. It is therefore reasonable to infer that people in the lower socioeconomic groups are more likely to go into a long term care facility when they are assessed as needing that level of care as they will be eligible for the maximum level of funding, whereas those in higher socioeconomic groups would probably try to manage with extra support at home as the cost is likely to be less than paying for full care in a hospital/rest home facility. Although this may reduce the financial burden on households with MS, it is likely to increase the burden of physical and psychological stress for families caring for the person with MS as has been shown in previous studies^{297,299,301,335}.

A further factor contributing to likelihood of residing in a hospital/rest home is marital status, with people who are in the divorced/widowed/separated group nearly four and a half times more likely to be living in a hospital/rest home than those who are in the never married/married group. The odds for females who are in the divorced/widowed/separated group increase to nearly five times that of females in the never married/married group, with males who are in the divorced/widowed/separated group two and a half times more likely to reside in a hospital/rest home than those in the never married/married group. People who are in the divorced/widowed/separated marital group are more likely to be older, have SPMS, a higher disability score (EDSS ≥ 6.0), lower incomes and to be not working. As such, they may have no support system at home to provide the care they need to remain in their own environment, and equally, they may qualify for maximum levels of funding under means testing to support their move into a residential care facility. What we cannot determine is temporality or causal effects from this data as it is from a cross-sectional study. That is, whether they are more likely to be living in a residential care facility because they are divorced/widowed/separated; or more likely to be in the divorced/separated/widowed group because they live in a hospital/rest home, and have more extensive disability and advanced disease which would have an impact on their relationship with their partner and place considerable strain on their marriage especially in the younger age groups.

Socioeconomic status was associated with disease characteristics, in particular having a diagnosis of SPMS and an EDSS ≥ 6.0 increased the likelihood of being in a lower socioeconomic group. Disease duration from diagnosis was not significantly associated with socioeconomic status for the working age population or females with MS, although males with disease duration ≥ 10 years were twice as likely to be in a lower

socioeconomic group as those 0-4 years post diagnosis. The indication for the working age MS population was that the loss of SES largely occurred early in the disease course with a marginally increased effect with disease progression. This may indicate that disease affects, other than physical disability, (the main aspect of MS assessed by the EDSS), are influencing the SES of people with MS in the earlier stages of the disease.

Regional influence was investigated to assess whether the difference in socioeconomic status could be explained by location of residence in New Zealand. For the whole NZ multiple sclerosis working age population, females, and males, there was a 1.5-2 fold difference in socioeconomic status for census day NZSEI between Auckland (higher SES), and the rest of New Zealand (lower SES). However a similar disparity in SES between Auckland and the rest of New Zealand was found on analysis of original NZSEI score, indicating that living in the Auckland region, may be a contributing factor to regional variation in SES separate from a diagnosis of multiple sclerosis.

In summary, multiple sclerosis profoundly influences the socioeconomic status of New Zealanders in the 25-64 year age group living with the disease. When compared with the NZSEI score based on their original occupation, there is a significant difference in socioeconomic status for their census day NZSEI score. The strongest predictor for being in the lower socioeconomic group is loss of work status, and loss of work status has been shown to predict loss of income in Chapter 4. Reporting an income below the median annual income of either the MS population or the NZ population on census day 2006 was also a strong predictor of being in a lower socioeconomic group. Education and occupational group are closely linked, with both having an effect on socioeconomic status. People who had no higher educational qualification were more likely to be in a lower socioeconomic group, as were people employed in all occupational groups in comparison to those employed as managers/professionals, the occupational group most likely to require a post high school qualification.

Females were affected to a greater extent than males, and as they make up three quarters of the MS population, consideration must be given to the flow on effects to family and society in the form of long term support and health service needs. People with MS in the lower socioeconomic group were shown to have a higher representation in residential care facilities. Whether they are in care because they are in the lower socioeconomic group or in the lower socioeconomic group because they have had to go into care cannot be inferred due to this being a cross-sectional study. People in residential

care were also more likely to be in the divorced/separated/widowed marital group, which in itself was a predictor for being in the lower socioeconomic group. The divorced/separated/widowed group were more likely to have SPMS and a higher level of disability in comparison to the never married/married group which would partially explain their higher representation in residential care.

A decrease in socioeconomic status is recorded for the 25-34 years age group, however with each successive older age group, the proportion in the lower SES group increases, with the greatest effect noted in people who are in the 55-64 years age group. As people who are older are more likely to have SPMS and higher levels of disability, their work status is more likely to be affected, which is reflected in their socioeconomic status.

There was some effect by region, with people who live outside the Auckland region more likely to be in a lower socioeconomic group, but as this effect was the same for both their original NZSEI score and their census day NZSEI score, it would indicate that the effect is due to other factors rather than purely a diagnosis of multiple sclerosis.

Although a number of variables have been shown to contribute to socioeconomic status in this chapter, the importance of being able to remain in work to retain socioeconomic status cannot be understated. The key finding of this chapter is that people in the working age (25-64 years) MS population in New Zealand with a confirmed diagnosis of multiple sclerosis who were not working experienced a loss of personal income and correspondingly were more likely to be in the lower socioeconomic group and that this effect was noted from an early age and early in the disease course.

Chapter Six

Summary, conclusions and recommendations

6.1

Overview

This chapter will provide a summary of the findings from this study followed by a detailed discussion of the implications of these findings. The strengths and limitations of this study will also be discussed. Finally areas for further research will be presented.

6.2

Summary

It is widely acknowledged that multiple sclerosis has a profound effect on the work status of people living with the disease. Over 90% of people with MS have a work history³²²⁻³²⁶ however unemployment rates as high as 80% have been reported^{307, 308, 324}. Burden of illness studies have identified loss of work as the major cost driver with some studies reporting the cost of MS to an individual to be as much as 40% of their lifetime earnings²⁹⁷. In New Zealand, the effect of MS on work status has never been formally investigated. There is also little published data, and none from New Zealand, on the income or socioeconomic status of people living with multiple sclerosis.

In 2006 the New Zealand National Multiple Sclerosis Prevalence Study was undertaken to ascertain the prevalence, distribution and profile of MS in New Zealand. The study also captured demographic data, disease characteristics and socioeconomic markers of New Zealanders living with MS in order to better characterise the effects of the disease on the socioeconomic status of the working age MS population. The overriding objective was to identify the predictors of change in work, income and socioeconomic status for people with MS, to enable strategies such as timely use of disease modifying therapies, and health and workplace support systems to increase and prolong workforce participation.

Applying the most appropriate tool to portray an accurate picture of the socioeconomic status of the NZ MS population was essential. As each country has its own health and welfare systems, and population and employment profiles it was necessary to use a socioeconomic evaluation tool specifically designed for the New

Zealand population. Two tools which had been widely tested and validated in health research in New Zealand were identified. One, the NZDep, was primarily designed to analyse deprivation in small area populations²⁸⁵. However due to the small size of the MS population, less than 1% of the NZ population, statistical inference was limited when using this measure. The NZSEI, an occupation based measure^{268,274}, provided a more accurate indication of the effect of the disease on work status, and therefore socioeconomic status, for the MS population, particularly those of working age (25-64 years). The results of these investigations have been reported and discussed in the preceding chapters, but the main findings are summarised here.

The NZNMSPS confirmed that there were 2917 cases of clinically definite multiple sclerosis in New Zealand on prevalence day, 7th March 2006. The coverage was estimated by capture-recapture methods to have identified over 96% of people with MS in New Zealand. All cases were sent a postal questionnaire with an overall response rate of 71.1%. Population representation analyses comparing key demographic features and disease characteristics of responders with non-responders confirmed that the responders for both the whole MS population and the working age MS population were largely representative of people living with MS in New Zealand.

The age standardised prevalence of MS in New Zealand on prevalence day was 73.1 per 100,000 population, confirming that NZ is a high risk region for the development of MS. Ethnically, New Zealanders of European descent have a significantly higher age standardised prevalence of MS (101.9 per 100,000 population) than those of Maori descent (24.2 per 100,000 population), and Pacific Island and Asian descent (78.7-82.4 per 100,000 population; see Table 2.7). This reflects findings from other countries with mixed populations consisting of both European and Non-European ethnic origins. The female to male ratio was 3:1, and further analyses by quintennial year of birth verified this ratio had remained stable since birth year 1940.

The NZMSPS confirmed previous findings of a latitudinal gradient associated with MS, with an increased prevalence with increasing latitude below 37° South. A unique finding of this study was that when the data was analysed by gender and MS phenotype, the latitudinal gradient was 3 times greater for females than males, and 7.2 times greater for the RRMS/SPMS phenotype than that of the PPMS phenotype. A linear model of prevalence demonstrated that females with the RRMS/SPMS phenotype were the major drivers of the latitudinal gradient in New Zealand, indicating that the genetic and/or

environmental factors which influence the development of MS do not affect all MS cases equally.

This study found that MS profoundly influences the work force status of New Zealanders living with multiple sclerosis, with older age group being the strongest predictor for not working. On prevalence day (NZ national census day 2006), 54.6% of people with MS in the working age population (25-64 years) were not working despite over 90% of the working age MS population having a work history, as compared with 22% of the New Zealand working age population. Along with age; sex and disease characteristics were major drivers of loss of work status.

- Age was shown to be associated with a number of disease characteristics. In particular increasing age was associated with higher levels of disability, longer disease duration, and more progressive forms of the disease.
- Loss of work status was found to occur early in the disease course affecting; 55.1% of working age people 0-4 years since diagnosis, at a low to moderate level of disability, 54.5% of people with an EDSS \leq 5.5, and in 53.5% of people with RRMS.
- Progressive forms of the disease, higher levels of disability and longer disease duration all contributed to loss of work status, however further analysis demonstrated that these findings were limited to the female MS population.
- Females were more likely to experience loss of work status than males.

Consistent with other international studies^{303,306}, a higher proportion of people with MS held post high school qualifications than the general New Zealand population.

- Those who held a higher qualification were more likely to retain some form of work status however they were also more likely to report a change in their work status. Once again, further analysis revealed this finding was limited to the female MS population.

Gender, occupational group and disease characteristics were also associated with change in work status.

- Females in occupations requiring greater cognitive input and light physical work were more likely to report a change in work status, in particular a reduction in

their hours of work. They reported fatigue and change in cognitive function as being the major drivers for their change in work status.

- Males who reported a change in work status were more likely to be in physically demanding occupations. They were more likely to cease work, commence a government benefit, and report that the change in their work status was due to decreased lower body motor function or multiple factors due to MS.
- Males who remained in work were more likely to be in full time employment, whereas females who remained in work were more likely to be employed part-time.

Work status was the strongest predictor of level of income, with those people who were not working significantly more likely to report an income below both the NZ and MS median annual personal incomes. Gender, occupational group, age and marital status were all major contributors to level of income reported. The median annual personal income for the working age (25-64 years) MS population on prevalence day (NZ national census day 2006), was NZ\$20,000, compared with NZ\$34,750 for the general NZ population of the same age group.

- Males and people working in professional occupations were more likely to report an income greater than either the MS or NZ median annual personal income.
- People who were in the older age groups and those who were in the divorced/widowed/separated marital group were more likely to report an annual personal income below the median.

Income sources showed that over 30% of the working age (25-64 years) NZ multiple sclerosis population were receiving the invalid's benefit compared with just 3% of the NZ population of the same age group.

- Of note, less than 0.5% of the same MS population were receiving the unemployment benefit, indicating that disease related factors rather than unemployment were the reason people with MS were not working at that time.
- Males were more likely to receive income from wages, self employment and the invalid's benefit, however females with MS reported their income sources to be wages, invalid's benefit or no source of income, which may reflect the country's policies regarding allocation of government support (Chapter 4).

With respect to socioeconomic status, using the NZSEI classification model (Chapter 5), work status was once again the strongest predictor, with those people who were not working significantly more likely to be in a lower socioeconomic group. Both males and females experienced a decrease in socioeconomic status however the effect was significantly greater for females.

- When stratified by age, a decrease in socioeconomic status was observed for each successive older age group, with the oldest group (55-64 years) being three times more likely to be in a lower socioeconomic group than the youngest group in the working age population.
- Although holding a higher qualification was predictive of being in a higher socioeconomic group, the effect was diminished between original SES group and census day SES group, indicating a higher proportion of people with a post secondary qualification were in the lower SES groups on prevalence day.
- Only a small proportion of working age people with MS in NZ were living in a hospital or rest home, however as a group, they were significantly more likely to be in a lower socioeconomic group.

Overall the working age MS population (25-64 years) had a higher proportion of people who were divorced/widowed/separated (22.6%) than that of the general NZ working age (25-64 years) population (16.5%).

- People with MS who were divorced/widowed/separated were more likely to be in the older age groups, have SPMS and a higher level of disability. When analysed further the findings associating marital status with disease phenotype and level of disability were limited to the female MS population.
- Marital status was also related to place of residence with a significantly higher proportion of people who were divorced/widowed/separated residing in a hospital or rest home.

The study found people with MS living in the Auckland region had a higher socioeconomic status than those who lived outside of the Auckland region, however the size of the effect remained the same for both their original socioeconomic status and their SES on prevalence day, indicating that this is more likely to be related to the influence of the region in which they reside than to disease effects. Equally, this effect was limited to

the Auckland region, as no difference in SES was found when rural and urban centres were compared, and once again only the Auckland region differed when the population was divided into six centroids (See Chapters 2 and 3).

Taken together these findings strongly support the hypothesis that MS has a significant effect on the socioeconomic status of people living with the disease. Despite being a well educated and highly employable group of people, the effects of the disease process and its associated accumulation of disability, appear to lead to a reduced capacity for work. The loss of work status is associated with a diminished income, the outcome of which indicates a decrease in socioeconomic status.

The remainder of this chapter will provide a more detailed discussion of the implications of these findings. The strengths and limitations of this study will be discussed. Finally areas for further research will be presented.

6.3

Discussion and implications of findings

There have been few published studies exploring the association between socioeconomic variables and multiple sclerosis, and none have previously been published from New Zealand. This is the only study thus far to have a census of the working age MS population from an entire country as the study population and to simultaneously have a national population census as the comparative working age population group. A significant finding of this study is that loss of workforce status with a corresponding decrease in income appears to result in a lower socioeconomic status for people with MS in New Zealand. This occurs at an early stage in the disease course and at low levels of disability as assessed by the EDSS. These study findings have significant implications for patients and their families, clinicians, policy makers and researchers.

6.3.1

Patients and their families

This study found a greater change in work status, income and socioeconomic status for females than for males. As 75% of people with MS are females, the implications of

these findings have importance for people living with MS and their families. A number of demographic factors and disease characteristics may contribute towards this finding.

In this study 67% of the working age MS population stated that they had changed their work status due to the effects of MS. One other study observed that people with MS reported changing their workload as their disease progressed, with up to 82% of the severe disease group having changed their work situation at some point²⁹⁷. The results of this thesis indicated that men were less affected by loss of work than females, and that men who continued to work were more likely to work fulltime, whereas women who worked were more likely to work part time. People with MS who worked full time continued to earn incomes commensurate with their working age NZ population peers; however those who worked part time or left the workforce earned significantly less than their peers. Few published studies have explored change in work status by sex however those that have found no differences between the sexes in work status³²⁸ or working hours³³¹. These studies suggested that this may be due to women being brought up with the expectation to work³³¹, or that local factors such as the availability of certain jobs or stage of the economic cycle may be contributing factors³²⁸.

As this study was conducted at a time when unemployment was low (4%) in New Zealand, and less than 0.5% of the working age MS population were receiving the unemployment benefit, it is unlikely that job availability or stage of the economic cycle were contributing to loss of work status for either sex. Equally as over 90% of the NZ working age MS population had work histories the difference between males and females is unlikely to be entirely due to gender related expectations of work. The contrasting results from the previously published studies may be explained by the small sample sizes (n=50³³¹ and n=102³²⁸), and the sample for each study being selected from single regions in the USA limiting their representation of the wider MS population. Data on personal perceptions of factors which contributed towards a change in work status was also collected from the NZ MS population and provide some insight into this finding.

Participants in this study cited different reasons related to disease symptoms for changes to work status depending on their sex. Males identified reduced lower body motor function and multiple factors as the main reasons for change in work status, whilst for females fatigue, multiple factors and reduced cognitive function were highlighted. This information may indicate that MS affects the sexes in different ways, or may reflect the different roles men and women commonly experience in society. Despite women actively participating in the workforce there are still cultural expectations that men should

be working and work full time, and if they are not working then physical or cognitive disability is a legitimate reason for leaving the work force³²⁴. For women, leaving the workforce to raise children and work part time while the children are young, is a commonly accepted norm, the difficulty then is for them to return to work when the children are older³²⁴. Women have traditionally tended to do household and child care roles alongside full or part time employment and due to fatigue or disease progression women with MS may find it hard to continue to do both. Equally if the person with MS is able to be supported by an income from their partner they may choose to leave paid employment and just manage the home³²⁴. Despite progress in pay equality, women still tend to earn less than their male counterparts⁴⁰⁰, which may mean there are fewer opportunities for men to choose early departure from the workforce and still retain adequate financial support from their partners.

No published studies were found which explore differences in MS symptoms between males and females affecting work status. However, MS symptoms including reduced motor function, fatigue, and reduced cognitive function are the most commonly cited factors contributing to loss or reduction of work status^{304,321,327,328,330,331}. In studies, fatigue was found to affect concentration and thinking, requiring more effort to perform these tasks which in turn exacerbated the fatigue³³⁰. Participants interviewed stated that fatigue tended to be variable and unpredictable, and as it could not be seen by colleagues and employers was less well tolerated than a visible physical disability³³⁰. Published studies indicated that fatigue, even in people with low levels of disability, was the most common symptom experienced by people who cut back their hours and worked part time, whereas people who had stopped working stated their symptoms were mainly loss of motor function or broad neurological symptoms^{259, 331}.

People with MS and their families can use the information from published research to adapt their lifestyles and better manage the symptoms and effects of MS on work force participation. The opportunity cost of remaining in employment may be a reduction of activities outside of work due to reduced demands on endurance and energy. This is of particular importance for women, as during this life phase they may be managing a combination of employment and domestic demands including reproduction and raising children. They are also more likely to be in the active phase of the disease with relapsing remitting symptoms which may create a drain on their available energy for managing the disease symptoms, work life and home life. The complex demands on their time and energy may impact on their decisions regarding continuation of work. Furthermore if they

do leave the work force for extended periods of time, they may lose confidence in their ability to return to their former occupation especially if a period of retraining is required. A supportive environment at home and work, along with flexible or fewer hours may help people with MS to manage their symptoms and remain in work.

6.3.2

Clinical

The findings of this study reflected international profiles of people with MS, with most of the New Zealand MS population being diagnosed in the early adult years, and experiencing the accrual of increasing levels of disability with increased disease duration. As a result of the disease process and disability accumulation, 54.6% of people with MS in the workforce age group (25-64 years) are not working.

A significant finding of this study was that loss of workforce status in this age group was found to occur early in the disease course and at a low to moderate level of disability affecting; 54.5% of people with an EDSS <5.5, and 55.1% of people whose disease duration from diagnosis was less than 4 years. These findings are reflected in the published literature, with one Canadian study finding that people with MS who had mild disease severity had an unemployment rate almost three times that of the Canadian population unemployment rate, and that only 37% of the mild-moderate disease severity group in that study worked full time²⁹⁷. Clinical implications of these findings include identification of the disease-related factors triggering departure from the workforce early in the disease course, and early intervention to manage them, thereby limiting their impact on workforce participation.

The largest proportion of people with MS (80-85%), are diagnosed with the relapsing-remitting MS phenotype. Early departure from the workforce could be related to emotional burden and distress at diagnosis⁴¹¹, or to the unpredictable nature of the RRMS disease course. Exacerbations in the relapsing-remitting phase of the disease can be frightening and affect the ability of the person with MS to make decisions about important issues such as continuing to work. Studies suggest health professionals should support the patient through the acute phase and encourage them to delay important decisions until they have recovered from the exacerbation^{330,412}.

Although quality of life was not evaluated in this study, international quality of life studies have indicated that the psychological impact of a diagnosis of MS may affect the

QOL of patients in the early phase of the disease⁴¹³. The study used the SF36 to assess quality of life in people with MS, with the scores indicating QOL was significantly reduced in early stages of disease. Furthermore, people with an SF36 disability score equivalent to a low EDSS score were found to have low overall QOL scores when compared to those of the normal population. The domains which were most pronounced were self perceived poor physical health, decreased energy and increased fatigue⁴¹³.

People with MS are often diagnosed at a time when they are developing their careers, starting families and looking to the future. The diagnosis may result in them being more focussed on their loss of health leading to a poorer perception of their general health; equally they may be experiencing concern and anxiety about the future including the potential accumulation of disability and its impact on their life and families. In the clinical setting, education and appropriate support soon after diagnosis can assist patients and their families with an understanding of the natural history of the disease, modify expectations, and address concerns about what future support might be needed and how it is to be met. Assessment of the cognitive and emotional state of the newly diagnosed MS patient is suggested to elicit whether counselling and further support would be beneficial.

Cognitive changes and fatigue were identified by participants, particularly females, in this study as factors which affected their workforce status. Cognitive changes, in particular information processing speed, memory and sustained attention, are noted to affect people earlier in the disease course, and be more prevalent than previously thought, affecting 40-65% of people with MS^{321, 328,330,333}. Fatigue is also frequently reported as impacting on work status by people with MS^{330,331,321}. Research suggests cognitive disability and fatigue interact to compound the effects of each other³³⁰. It has been reasoned that as people with MS notice the effects of fatigue in the workplace, they compensate by increasing their cognitive focus, this in turn creates an increase in levels of fatigue. A meta-analysis of studies of the effects of neurocognitive impairment on employment in people with HIV, Epilepsy, Severe Traumatic Brain Injury, and various other disorders [sic] affecting cognitive function, found that cognitive disability is associated with a greater probability of being unemployed, with the association being strongest in the domains of executive systems functioning, intellectual functioning, and memory⁴¹⁴. The authors suggest that as these are the areas which enable the person to organise, process and remember loss of function in these areas is likely to affect their capacity to remain employed. A further study of people with post polio syndrome and spinal cord injury identified fatigue as an important factor in determining their work force

status³⁵⁴. Both cognitive changes and fatigue can be subtle changes with the potential to be overlooked unless health professionals are systematic in their assessment of all aspects of MS at the clinical review. Strategies to manage fatigue should be considered, including balancing work around cognitive performance and fatigue. The use of written communication as well as verbal helps to compensate for reduced performance in information processing speed and memory. Early, accurate identification of clinical problems with effective interventions may be a means of managing the symptomatic effects of MS on workforce participation.

Published research indicates that not only do people with MS experience an early departure from the workforce, very few appear to re-enter the workforce at a later time³²¹. This study did not explore the concept of re-entry to the workforce, however on stratification by age and disease characteristics, the indications were that as well as early departure from the workforce, an increased percentage of people in the older age groups and those with longer disease duration and progressive disease were not working. For people who have prematurely left the workforce, the longer they are not working, the harder it may be to return to work even if their disease course has stabilised³²⁴. Alternatively it may be that as the disease course progresses the accumulated physical and cognitive disability precludes re-entry to the workforce. This is supported by several studies which identified an association between progressive disease, higher levels of disability and unemployment^{302,331}.

One further factor which may affect employment is the workplace environment. Physical or social barriers may limit the opportunities for a person with MS to work. Less than 5% of people in this study self-reported workplace issues as reasons for a change in employment status, however other studies have indicated it may be a greater contributing factor to unemployment, with access at work (39%), and travel to work (48%) being barriers identified by respondents in a study from the UK³³². Knowledge about the factors relating to disease and disability which affect access to or function in the workplace may enable the healthcare team to be more responsive in assisting the MS patient remain in the workplace with timely flexible rehabilitation expertise specific to the individual.

The results of this study indicated that people with MS in NZ who were not working had a lower income and socioeconomic status than those who remained in the workforce. Several international studies have found an association between lower socioeconomic status and a greater burden of illness in the general population^{256,258-263}. A study using in-depth interviews of people with MS indicated the consequences of unemployment for

them included poverty, lack of healthcare benefits, loss of professional identity, social isolation, and an increased focus on their disease³³⁰. This is supported by a study exploring quality of life in people with MS which noted that unemployment was associated with negative health perceptions³⁴⁸. They also found a higher EDSS and reliance on disability pensions were negatively associated with HRQOL; and higher education and income were predictors for improved HRQOL. There are some circumstances where people's employment options may be affected by the financial support available to them. In America, a study suggested that people with MS may try to remain in the workforce for a longer duration if their insurance coverage is insufficient to allow early retirement, alternatively if they have a good level of coverage they may be in a position to retire earlier³³¹. In New Zealand there is a government funded welfare system which provides an income in the form of an invalids benefit to people assessed as being too disabled to work. It is unlikely that people with disabilities in NZ will leave work early purely because the benefit is available as the income from the benefit is very low, less than NZ\$14,000 per annum before tax (in 2006).

Early departure from the workforce may also have social consequences, including isolation from colleagues and friends. The wider implications of MS are the effects on the partner and families of the person living with the disease. The findings of this study identified a higher percentage of the working age MS population who were divorced, widowed or separated (22.6%) than the general NZ population of the same age group (16.5%). Higher levels of divorce among the MS population have been identified in other studies³⁰⁸. Studies indicate people ageing with MS experience normal physiologic changes, however the progressive accumulation of disability from the disease leads to some of those changes occurring at an earlier age, which may need accommodations which would not normally be considered for that age group³⁵⁵. With the accrual of disability, the person with MS may require higher levels of care. If the partner of the person with MS has to give up work to care for them, the family will have lost both incomes, potentially reducing the household socioeconomic status further²⁵⁹. The cost of treatment, disability aids, home and car adaptation, not covered by public health or insurance, add financial pressure to the family. Limited resources for supporting children including schooling, extramural activities, and holidays can add strain to the marriage²⁵⁹. Some people with MS experience changes in bladder, bowel and sexual function affecting intimacy between partners, especially if the partner is now also the primary carer^{259,301}.

Physical disability can also lead to social isolation if access to social venues does not accommodate wheel chairs or people with limited walking distance due to disabilities.

Quality of life studies have indicated that as disease duration increases quality of life decreases for people with MS³⁰⁷. An awareness of the complexity of MS and its wider implications is important for the management of the physical and mental health of the person living with the disease. Clinicians can act as intermediaries or advocates for patient, linking people with MS to broader community services such as MS societies, counselling services, gyms etc to increase opportunities to engage in community activities, meet more people, decrease isolation and increase coping skills. A mail survey to people with cerebral palsy, MS, spinal cord injury, rheumatoid arthritis and osteoarthritis identified access to health care and support, and in particular specialty care from specialists in the field as important for the adequate management of complex conditions²⁶³. The expert input helped to prevent secondary complications, preserve health and overall functioning, which in turn helped to maintain their independence by avoiding institutionalisation or hospitalisation. They suggest that access to rehabilitation specialists was necessary to limit the accumulation of functional deficits²⁶³. The aim of the multidisciplinary health care team should be to minimise the accrual of disability that impacts on the work capacity of the person with MS.

6.3.3

Policy

Burden of illness studies have shown that multiple sclerosis is a costly disease due to its early onset, long duration and significant effects on employment³⁰⁴. A systematic review of cost of illness studies identified direct costs; such as hospitalisation and pharmaceuticals, as accounting for between 26%-87% of total costs, and indirect costs including; short and long term absence from work, change in type of work and early retirement, as accounting for 13%-74% of total costs³⁰¹. The costs paid by the healthcare sector and social services accounted for approximately half of the total cost per patient across a range of European countries participating in one study²⁹⁹. In another study, the highest component of MS-related costs was identified as indirect costs, in the form of lost time and lost productivity, with loss of earnings accounting for up to 80% of the total indirect costs²⁹⁷. Furthermore, the burden of MS on patients and caregivers was evident from the large costs attributable to lost time from both work and leisure. Productivity

losses have been identified as the highest societal costs; with lost productivity (or indirect costs) being related to work cessation which occurred early in the disease course, and both increasing direct and indirect costs associated with progressive disease^{299,307}.

Studies of other illnesses have found similar results; a systematic literature review of cost of illness studies of depression found that depressive illness was associated with an increase in both direct and indirect costs. The greatest contributor to direct costs was hospitalisation and indirect costs were time off work or reduced capacity at work⁴¹⁵. A systematic review of cost of illness studies of a range of disorders of the brain including addiction, affective, anxiety, brain tumour, dementia, epilepsy, migraine and other headaches, MS, Parkinson's disease, psychotic disorders, stroke, and trauma was completed to assess the burden of brain disorders in Europe²⁶⁵. The average cost per case for each disorder was calculated and ranged from 600 Euros per case for migraines and 1700 Euros per case for addiction disorders, to 24,000 Euros per case for MS and the highest being 39,000 Euros per case for brain tumours. Direct costs for all brain disorders made up 35%, with indirect costs due to lost work days and lost production estimated to be 46% of costs. Indirect costs for people with MS in this study were mainly due to lost work days from early retirement. No other brain disorder had sufficient published research data to provide comparable estimates, however the results indicated that in most other conditions studied indirect costs came largely from days lost from work due to illness as opposed to early retirement²⁶⁵.

This study found that 63.1% of all people with MS in NZ are not working. For the working age MS population (25-64 years) 54.6% are not working compared with 22% of NZ population of the same age group, although over 90% of the MS working age group have a work history. Loss of workforce status occurs in the youngest age group (25-34 years), with a corresponding decrease in work force participation with each successive older age group. A significant outcome from loss of workforce status for the individual with MS and their family is loss of disposable income.

New Zealand government policy proposes equity for people who are ageing, or have a chronic condition or disability³⁴⁷. There is a tax-payer funded government welfare system in NZ which provides means-tested financial support for people unable to work due to illness or disability. A large proportion of the working age MS population in NZ receive some form of government support payments 42.6%, compared with 24.6% of the same age group in the NZ population. The government support for the MS population is mostly in the form of an invalids benefit received by 30% of the MS working age population, as

opposed to 3% of the NZ working age population. It could be argued that people with disabilities due to MS may choose not to work as they have the option of financial support from the NZ government in the form of the invalid's benefit, this is unlikely however as the level of income from the invalids benefit is a very low, unlike early retirement pensions internationally.

A study of people with a variety of disabling conditions including cerebral palsy, MS, spinal cord injury, rheumatoid arthritis and osteoarthritis, identified loss of income as a limitation for access to extra support and health care not covered by the public system²⁶³. The cross-sectional self-report mail survey indicated that people in the poorest health state were those who needed the most input but were least able to afford or access it. The authors suggested that the consequences could be declining physical and mental health, and social participation. The study indicated that illnesses with a higher prevalence such as arthritis may have a higher profile among healthcare providers and community agencies, and as such may receive greater resources in a timelier manner. Illnesses that have a lower prevalence and are not as well understood may receive less resources and support due to lack of understanding about the disease or condition²⁶³.

An interesting finding was that 11% of the working age MS population reported having no source of income compared with 3.7% of the same NZ population group. This is likely to be a reflection of means testing in New Zealand, whereby a person's entitlement to a government benefit is assessed on the income of their partner. If the income received by their partner is above a pre-determined threshold then the person who is unable to work is not entitled to receive the benefit. If however the disability was received through an accident, in NZ through the ACC, the individual receives 80% of their income at the time of the accident for the rest of their life if they are unable to return to work. This funding is guaranteed regardless of the family assets or other sources of income. Furthermore, the ACC will fund the majority of modifications to the home and other accident-related costs to assist the person to remain in their own home with appropriate support. There is a level of funding available through the health care system to assist people with disabilities due to illness to receive equipment and modifications to their homes, however this is means tested and may not always cover the cost of the support required. This dichotomy in the welfare system in New Zealand is such that it may not always provide equity for people with chronic conditions such as MS and others with non accident associated disability.

This study observed that people with MS in the working age population were well educated with 51.4% having a post high school qualification compared with 41.6% of the NZ working age population. However 54.5 % of those with a higher qualification were not working compared with 14.8% of their NZ population peers. Previous studies have found that people with MS who held higher qualifications were more likely to be working than those with no higher education^{308,321,328,331}. This study concurred with those findings, and noted that a higher qualification was also associated with an income greater than the median annual income and being in a higher socioeconomic group. Despite these findings, it was interesting to note that 32.1% of males and 47.6% of females with MS who held a post high school qualification reported a median annual personal income below (NZ) \$10,000. Furthermore the study indicated that a greater proportion of people with a post high school qualification were in the lower SES groups based on their census day SES coding when compared their original occupation SES coding. This suggests that despite a high percentage of people with MS in New Zealand completing their education to a higher level prior to disease onset, they are unable to retain their workforce status, income or SES to a level commensurate with their age stratified NZ population peers.

In people with psychosis in Australia career disruption was reported to occur in 61-78% of people with psychotic disorders⁴¹⁶. This population-based study of people aged 15-64 years, found that 75% of people with psychotic disorders in this age group were not working, with 65.6% stating that their health and disability prevented them from working. The study indicated that this group of people were affected earlier in life with 11.3% leaving school before 14 years of age and only 24.2% completing post high school qualifications after psychosis onset⁴¹⁶. The earlier onset of disease affecting educational attainment may have influenced their opportunities for securing employment and their ability to retain it. The study observed that none of the people with a psychotic illness who left school before 14 years of age were employed, whereas those with a post high school education were more likely to be employed. Most participants in this study stated the only help they needed in the workplace was a support person to help them get and keep a job⁴¹⁶.

This study found very few people with MS received the unemployment benefit 0.4%, compared with 3.9% of the NZ population, indicating they were not working due to the disease process rather than from lack of work. Multiple sclerosis is a complex disease to manage due to its unique mix of physical and mental disabilities and considerable variability in presentation and progress between patients. No other illness has been

identified which can serve as a model on which to manage the effects of MS on work status. A key factor appears to be the fit of the individual with MS to the requirements of the occupation. These can apply to the physical and cognitive demands of the work and equally to the physical environment of the workplace and the expectations and attitude of the employer and colleagues of the person with MS³²⁴. Increased knowledge of the symptoms of MS in the individual and how these affect their capacity for meeting the job requirements may offer the opportunity to accommodate them in the work place through role modification, retraining, change of position, change of hours or more flexibility in the hours worked. A collaborative approach between employment services and health care services with some form of government funding to support people with MS to stay in work, including modifications to the work environment if needed would be preferable to early departure from the workforce.

As in other developed countries, New Zealand is experiencing a significant increase in the proportion of the population that is elderly. Equally with improved health care and support services people with chronic diseases and disabilities are surviving longer. The WHO views disablement as a societal issue, and argues that society must take responsibility to modify its outlook to enable persons with disabilities to reach their full potential and participate in all aspects of life³⁴².

In New Zealand, government strategies have been developed to address concerns regarding issues specific to the ageing population, those with chronic conditions and those living with disability^{346,343,347}. These policies, despite addressing the needs of a diverse group of people, have several common themes and goals. They include: a focus on self-management or empowerment of people to make choices which result in a healthy satisfying life; opportunities to be fully integrated in society and to participate in family and community life; equitable access to health, support and social services, with integrated care from support services along the continuum of life and disease process, and the opportunity to age in place.

This study found that unlike the general NZ working age population, each successive older age group in the MS working age population had smaller proportion of people participating in the workforce. In contrast other studies have indicated that age was either protective for working³²² or not a factor in their study as they had removed people who were not working for other reasons from the sample³³¹. Both of these studies had small samples drawn from one locality which may limit the generalisability of the results. The majority of published studies have found an association between increasing age in people

with MS; longer disease duration, increased disability and progressive disease; and loss of work status^{302,321,324}. Studies have suggested that the implication of this is that the earlier interventions are put in place the more effective they will be in limiting the effects of the disease on the work and family lives of people with MS^{302,324}.

For society, premature departure from the workforce takes an economic toll due to indirect costs including reduced work hours, temporary absences, early retirement, premature death, taxation revenue foregone and welfare transfer payments; and through direct costs including hospitalisation, and medical care.

This study found that 8.1% of the New Zealand MS population and 5.6% of the working age MS population were living in a rest home or hospital. These people were more likely to be in the lower socioeconomic groups, older age groups, have a higher level of disability and progressive disease. They were also more likely to be in the divorced/widowed/separated marital group. A cross-sectional study of people with MS in New South Wales, Australia, found 5% of people with MS were living in hospital or rest home, and similar to the current NZ study, they were more likely to have higher levels of disability³³⁵. Supported accommodation in a rest home or aged care facility with hospital level care for people under 65 years of age can be a difficult living situation. Studies have shown that people with MS can feel out of place due to the large gap in age, however there may be no alternative place of residence suitable to accommodate both their level of disability and age^{335,355}. The largest proportion of direct costs for MS are associated with long term hospitalisations^{297,304}. Hospitalisation due to disease exacerbation, and long term supportive care for people with higher levels of disability, is costly to society as well as MS patients and their families. As such, any reduction in burden of illness costs due to MS through effective treatments will benefit both patients and society. Studies have shown benefit from treatments can be achieved if initiated early in disease course^{248-254, 404-410}. As the onset of multiple sclerosis occurs at an early age, productivity savings can be gained by slowing the progress of the disease, reduced hospital admissions, and improved quality of life for people with MS and their families; with the cost of the DMD offset by decreased direct and indirect costs associated with the illness.

Finally, but most crucially, the access to disease modifying therapy for people with MS in New Zealand needs to be reviewed and addressed. With only 22% of people in the 25-64 years age group ever having been treated with disease modifying therapy, this is largely a natural history cohort. The findings show that half of New Zealanders with MS in this age group with an EDSS of <3 are not working, and yet they are not eligible to

receive disease modifying therapy until their disability level is an EDSS of 2.5. This would indicate that the effects of the disease which lead to loss of workforce status occur prior to them becoming eligible for treatment under current PHARMAC protocols.

A key component to improved outcomes for any condition is getting the right treatment to the right people at the right time. There is now considerable research-based evidence on the efficacy of disease modifying therapy early in the disease course for people with RRMS. A number of trials have found a clinical benefit in early treatment for patients with clinically isolated syndrome^{248-254,404-410}.

The trials demonstrate a delay in treated patients converting to clinically definite MS (McDonald criteria), and reduced disease activity recorded on successive MRI scans when compared with those receiving a placebo. Some studies extended their trials, placing those patients who had been receiving the placebo onto treatment after a designated period of time. The findings demonstrated that the clinical benefits for those people who received the early intervention were sustained and that delaying commencement of treatment was not as beneficial for the patients who had originally received the placebo. The effects of disease modifying therapy on people with RRMS included significant reductions in annual relapse rates, cumulative relapse rates, and disability progression.

The evidence from clinical trials shows that early and aggressive treatment delays and reduces the onset of disability accumulation in people with MS. Early treatment may be a cost-effective way of preventing the disability accumulation which leads to loss of income and loss of tax revenue whilst increasing the overall welfare burden on the New Zealand Government. Furthermore the range of disease modifying therapies available in New Zealand is far narrower than those available to people with MS in Australia, Europe and North America. In conclusion, if people with MS in New Zealand are not given the opportunity to receive the right treatment at the right time they cannot benefit from it. A review of both the criteria for commencement of disease modifying therapy, and the available therapeutic agents for people with MS in NZ is strongly recommended.

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6.3.4

Research

The findings from this cross-sectional study are limited to providing a descriptive picture of the MS population of New Zealand at a specific point in time. Although this

provides new information regarding the work status, income and socioeconomic status of the working age (25-64 years) MS population of New Zealand, a longitudinal prospective incident cohort study is needed to assess cause and effect and progression over time. Collection of socioeconomic data along with disease characteristics and demographic data will assist in identifying the factors which enable people with MS to remain in the workforce as well as those which contribute to premature departure. Longitudinal data with regular repeated measures is valuable for the determination of when change occurs and to what extent. A longitudinal prospective study will also inform strategies and measures for support and intervention to better manage the effects of the disease on employment.

Although the EDSS is a well recognised and extensively used measure of disability in research and clinical settings, it is limited to assessing physical disability, in particular lower body motor function. Pairing the EDSS with measures of cognitive change, upper body function and fatigue is suggested as the study findings indicate that these contribute to change in employment circumstances for people with MS.

This study found that over 90% of people with MS in New Zealand have a work history, a finding supported by international research³²²⁻³²⁶. Despite experience in the workforce, employment skills and in some cases considerable career experience, people with MS are unlikely to be familiar with managing employment difficulties arising from disability, therefore research exploring job retention and workforce re-entry strategies which target these areas would be useful. Support in the workplace is an area currently being studied in the UK³³². The programme is designed to work with the person with MS and their employer to develop strategies and support in the workplace to enable the person with MS to maintain their workforce status. Less than 5% of people in the NZ working age MS population reported work place difficulties as factors which contributed to change in work status. However, anecdotal feedback during this study indicated that for some people, lack of support and in some cases overt victimisation in the work place were factors which affected their employment. Others felt they could not tell their employer they had MS for fear of losing their job. Although these are reflections of a small number of individuals with MS, they do indicate that workplace support is an important aspect of integrated care which should be considered when planning allied health input into a package of care for the person newly diagnosed with MS. Co-ordinated early intervention by a multidisciplinary team may be the key to limiting premature departure from the workforce for people with MS.

This study found that departure from the workforce occurred early in the disease course and in 54.5% of people with mild to moderate levels of disability. As people in NZ with MS who have mild disability (EDSS 0-2.5) are not currently treated with disease modifying therapies, there is an opportunity to conduct an economic evaluation to assess the cost benefit of providing disease modifying therapy for a currently untreated MS population of working age. The study would be able to assess whether the cost of treatment is offset by reduced indirect costs including absence from work, and premature workforce departure and reduced direct costs such as hospitalisations.

An interesting finding of this study is the differences between men and women with MS in workforce participation. Further exploration of this interaction between sex, disease characteristics including symptoms, and workforce status in terms of their association and strength is warranted. A longitudinal study enrolling and following newly diagnosed patients would help clarify the influence of sex and disease characteristics on employment, income, and socioeconomic status. The finding of this association indicates that sex is an important factor to consider when assessing the affect MS has on the work status, income and socioeconomic status of persons with MS whether for clinical, policy or research purposes.

6.4

Strengths

To the best of our knowledge this is the first nationwide study of the effects of multiple sclerosis on work, income and socioeconomic status. The strengths of this study include the study population being a census; estimated at over 96% (on capture – recapture analysis), of the New Zealand MS population, with the comparison population being a census of the New Zealand population.

Furthermore, as the study was designed to occur at the same time as the New Zealand national census, and used a number of questions pertaining to socioeconomic data directly from the census questionnaire, we were able to make a direct comparison of socioeconomic and demographic features between people with MS in New Zealand and their general population peers at that point in time.

The study population was sourced from the full spectrum of MS contacts, including community groups, public and private health care providers, self referrals and hospital discharge codes. This ensured the full spectrum of the disease characteristics and

population demographics were represented in the data. All cases had their diagnosis of MS and disease history confirmed by a neurologist, and the disability score (EDSS) was calculated by the study neurologist at the time of study entry.

A further strength of this study was its size and representation of the NZ MS population. The response rate to the postal survey questionnaire was good with over 71% of people with MS in New Zealand responding (2073 individuals). Comparison of responders and non-responders by age, sex, region and MS characteristics indicated that the responders were largely representative of the whole MS population (see Chapter 3).

Finally, whereas most previous published studies were based on specific MS populations, or small sample sizes which can skew results or limit generalisability, this study was able to describe the characteristics of a whole nation's MS population including the full spectrum of MS phenotypes and disease stages. This study has extended previous work, as we were able to compare the MS population with their general NZ population peers, and within the MS population we were able to analyse the results between sexes, disease phenotypes, and a number of other disease characteristics and demographic variables due to the size of the population in the study and completeness of data. The results of this study have provided original descriptive information of the work status, income and socioeconomic status of people living with MS in New Zealand.

6.5

Limitations

The study also has several limitations. Firstly, this is a cross-sectional prevalence study which describes the characteristics of a population at a point in time. This type of descriptive study does not allow temporal relationships to be established between variables. The study is therefore unable to evaluate the variability of MS disease, or explore the relationships between disease variation symptoms and work status, or cause and effect as would be possible with a longitudinal study.

Level of disability was measured using the EDSS which has the recognised limitation of mainly being a measure of physical disability. Participant responses indicated that along with physical disability, cognitive impairment and fatigue were important factors in determining their workforce status. No measure of cognitive impairment or fatigue was used, and this may limit some of the findings of this study.

The study data was collected by postal questionnaire which is reliant on self report potentially introducing recall bias into the study. Most of the questions were taken directly from the 2006 New Zealand National Census Questionnaire, had simple tick box responses, and requested information pertaining to their current situation or the previous 12 months, a relatively short time-frame for recall. Furthermore, the use of tick box response options may limit the depth of information able to be collected from participants. To accommodate this we provided open ended response options after tick boxes for a number of questions and included a page at the end of the questionnaire for patients to write freelance on anything they felt related to them living with MS. Qualitative analysis of this data has not been included in this thesis.

Evaluation of work status, income and socioeconomic status was limited to the individual with MS, and gave no indication of the effects of multiple sclerosis on their immediate or extended family, which may have further ramifications for service planning and health policy in New Zealand.

Finally the study findings may be limited in their application outside of the New Zealand context as the tool used to assess socioeconomic status (NZSEI) has been designed for the New Zealand population. Equally, the health and welfare systems in New Zealand will be different to those in other countries which may result in different outcomes for people with MS between countries of residence.

6.6

Future research

The findings of both the New Zealand National Multiple Sclerosis Prevalence Study (see published papers Appendix 2) and this study investigating the effects of multiple sclerosis on the socioeconomic status of people living with the disease in New Zealand have provided robust platforms for future studies in New Zealand. All people who participated in this study were asked if they would be prepared to participate in future MS research with 75% responding that they would be interested.

Since then New Zealand people with MS through the MS study group, have participated in the ANZGene study which used genome wide association study techniques to replicate several known MS associations and identified two novel loci for MS which have previously been associated with other autoimmune diseases. This paper, published in *Nature Genetics* is referenced in the body of the thesis²⁴⁶.

Areas for future research should include an incident case study which would identify all newly diagnosed cases of MS in New Zealand over a 2-5 year period and to follow this cohort longitudinally. A full longitudinal cost of illness study should be run in association with the incidence study to investigate the effects of disease progression and disability accumulation, on work, socioeconomic status and the burden of illness resulting from MS in New Zealand. Disability assessment in this study should include cognitive testing and fatigue assessment alongside the assessment of physical disability to determine when cognitive changes occur and the effect of cognition and fatigue on changes in work status, marital status and ultimately socioeconomic status.

Longitudinal research is necessary to fully understand the multifaceted nature of MS and the effects of ageing with the disease. Data on ageing with a disability provides valuable information to support planning for services and programmes including: rehabilitation services; independent living support to age in place; provision of long-term residential care; and financial support through to retirement, especially if the age of eligibility for NZ national superannuation is raised as proposed by the current government. Outcomes from a longitudinal study would provide new knowledge and understanding of the needs and methods of supporting people with MS in the workplace, home and community at different stages of the disease. A nested case-control study could compare outcomes for those people who are eligible for disease modifying therapy with those who are not to assess the difference in disease progression and effect on work status between the two groups.

Other studies could include a pragmatic nested case-control study investigating the effect of early work place support and interventions as compared with standard care by an allied health team such as that being trialled in the UK³³² to assess whether raised awareness and specific support programmes facilitate improved workforce retention for people with MS.

Finally, the results of this study account for between 8.3% and 11.1% of the variation in work status, 27.9% and 41.4% of the variation in income, and 31% and 44.8% of the variance in socioeconomic status for the NZ working age MS population. Therefore around 90% of the variation in work status, 60% of the variance in income, and 55% of the variance in socioeconomic status remain unaccounted for. As the models included common demographic factors and disease characteristics of people with MS, most of the variation is likely to be due to the coping style, personality, symptomatic effects of MS, and other environmental factors not accounted for. Qualitative in-depth interviews with

people from the nested case-control study who change workforce roles or leave the workforce will offer insight into living with the disease, the circumstances surrounding their decisions to change or stop employment, and what aspects of the interaction with employers, health professionals and other community services contributed to the process⁴¹². Factors identified during these interviews may produce common themes which contribute to loss of workforce status in people with MS. Identification of the key triggers for change in workforce status for people early in the disease course may enable targeted treatments or interventions to be implemented with the desired outcome being work force retention for the MS population.

6.7

Conclusion

The studies that have been presented here help to characterise the demographic features and disease characteristics of people living with multiple sclerosis in New Zealand. The findings confirm New Zealand as a high risk region for developing multiple sclerosis. Females, in particular those with the RRMS/SPMS form appear to be the main drivers of the latitudinal gradient of MS in New Zealand, indicating that MS does not affect all cases equally, and confirming the hypothesis that genetic and environmental factors in combination contribute to developing MS.

The findings strongly support the hypothesis that multiple sclerosis significantly affects the socioeconomic status of people with the disease. Importantly, it has been shown that loss of work status which results in decreased levels of income is the key driver of change in socioeconomic status for people in the working age (25-64 years) NZ MS population. Loss of work was found to occur early in the disease course and at a low level of disability as measured by the EDSS. With over 50% of people in the working age MS population not working there is a significant loss of skills, education and knowledge from the employment market, with the flow-on effect of loss of disposable and taxable income affecting not only the individual with MS but also their family and the society in which they live.

Strategies to improve workforce retention of people with MS warrant investigating along with a review of the access to and availability of disease modifying therapies for people with MS in New Zealand. Longitudinal studies which follow the progression of MS from diagnosis may also lead to a better understanding of the key aspects of MS

which affect the work and socioeconomic status of people living with multiple sclerosis in New Zealand.

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Appendices

Appendix 1

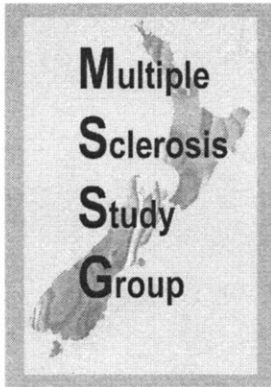
Notification Form

Information Sheet

Consent Form

Questionnaire

Neurological Assessment Form



New Zealand Multiple Sclerosis Prevalence Study Notification Form

Thank you for completing the enclosed notification form. The form is divided into two sections. Please read the following instructions carefully before completing this form.

Section One:

We ask you to **notify** us of **any** person within your records with a **possible** diagnosis of multiple sclerosis. In order to maintain the confidentiality of the person we request that you generate a unique number for each person notified using the following format.

The first eight digits of the number should be the person's date of birth in the format dd/mm/yyyy.

The next box indicates the person's gender. Please enter **F** for **female**; or **M** for **male**.

The final two boxes should include the person's initials. The **FIRST** letter of the persons **FIRST (Christian)** name should be entered first followed by the **FIRST** letter of their **SURNAME**.

For example, if you were notifying us about a female named Mary-Jane Kathryn Brown born on the first of April 1964 then you would enter 01041964FMB.

To complete this section we ask that you provide us with your own details including your name, address and designation i.e. MS caseworker, nurse, GP, person with MS, neurologist.

Section Two:

This section provides us with personal information about the person. This section should only be completed with the person's agreement. Completion of this section will allow us to identify and contact the person to request their participation in our study the details of which are outlined in the accompanying information brochure. We are obviously keen for as many people as possible to participate in this part of the study and would greatly appreciate your assistance with recruitment of the person.

Unique Identification Number (UIN) of Potential Participant

d d m m y y y y **G F S**

DOB

dd - date
mm - month
yyyy - year

Gender - Male /Female

First - **first** initial of **FIRST** (Christian) name

Surname - **first** initial of **SURNAME**

Notification

Complete in full for the first patient you notify to us thereafter we only require your name.

Full Name of person **completing this form** (Your name)

Address

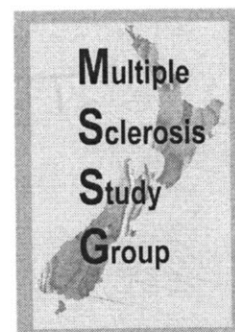
Phone Number

_____ (Area Code) _____ Number

E-mail Address

- Source: MS Society - Specialist - GP - NZHIS -
Hospital - Self Referral - Maori Health worker -

Other (state).....



Participant information sheet. New Zealand multiple sclerosis prevalence study.

You are invited to take part in a research project that aims to determine the number of people in New Zealand with the neurological disease multiple sclerosis, and to find clues to factors that may cause multiple sclerosis.

Your participation in this study is completely voluntary and deciding not to participate will not affect your care in any way. Please take time to review the information provided below. If you need an interpreter one can be provided. If you require any further information please do not hesitate to call the study centre on 0800 MS STUDY (0800 677 8839), or e-mail: mstudy@chmeds.ac.nz. You are also welcome to discuss the study with a friend, family or whanau.

If we have not heard from you in 2 weeks you will be contacted again by letter.

Background

Multiple sclerosis is a chronic inflammatory condition affecting the central nervous system. It is thought to be the most common cause of disability among young New Zealanders although the exact number of people living with MS is not currently known. What causes MS is still not clear; we do know however that the number of people within the population who have MS (the prevalence) varies significantly between countries and even between different geographical locations within the same country. For these reasons MS is thought to result from a complex interplay between both genetic and environmental factors. It has been shown for example that certain groups of people, because of their ancestry, are more prone to develop MS whereas others are protected from developing the disease. Genes on their own however do not cause MS; environmental factors also seem to play a role. One possible environmental factor that has been implicated and one that has particular relevance to New Zealanders is the amount of sunshine a person is exposed to.

It is hoped that through a better understanding of both the genetic and environmental factors associated with MS, researchers will be able to plan specific research projects to investigate potential therapies or preventive strategies for people at risk of developing MS.

Aims of the Study

The specific aims of the study are:

1. To accurately determine the number of people in New Zealand with multiple sclerosis.
2. To ascertain the level of disability experienced by those with MS.
3. To determine whether the prevalence of MS differs according to a person's ethnic background or ancestry.
4. To determine whether there is a link between latitude, (how far north or south a person lives) and the prevalence of MS.
5. To establish whether there is a link between the amounts of time a person spends outdoors and the prevalence of MS.
6. To determine the level of interest among participants in establishing a New Zealand multiple sclerosis register.

What is involved?

The study is an observational study consisting of two parts.

Part 1. Confirming the diagnosis of MS:

This part of the study will be done by your doctor (neurologist, physician or GP) and **will not** require you to do anything or to have any additional tests. **We will only receive medical information from your doctor directly related to the diagnosis of MS. The information the doctor provides will not identify you in any way.** Your doctor will be asked to fill out a form detailing how and when you were diagnosed with MS and, what symptoms you experienced. We will also ask your doctor about how MS limits your daily activities. This will be done using a specially designed scale (the Extended Disability Status Scale) that grades the level of disability experienced by people with MS.

If your doctor is **unable to** complete any part of the form, **and you agree**, you may be invited to attend a research clinic in your area. At the clinic you will be seen by a study doctor for the specific purpose of completing a form detailing how and when you were diagnosed with MS and to grade the level of disability you experience. This will involve you undergoing a brief neurological examination that is not painful or intrusive. No additional tests will be performed. For some persons this assessment may be conducted over the telephone. **Because we are not involved in your ongoing care we cannot provide advice regarding your care or diagnosis at this clinic.**

Part 2. Completing a questionnaire:

The second part of the study consists of a questionnaire that takes approximately 45 minutes to complete: The first part of the questionnaire asks questions about you such as education and marital status. These questions are derived from the recent New Zealand census and enable us to compare study participants with the New Zealand population as a whole so as to establish factors which may be unique to those with MS. The second part of the questionnaire asks about where you have lived and worked as well as the amount of sunlight you have been exposed to at different times in your life. The calendars included in this section ask you to record (in chronological order) where you have lived and worked or studied, and for how long you stayed at each location. This section of the questionnaire is quite comprehensive and may require you to talk to family members or friends about your early life. Further information on how to complete the questionnaire is included with the questionnaire.

Privacy Protection and Ethical issues

1. This is purely an observational study and we will not be involved in any way with your care or management. We will not suggest or advocate treatments or medications. No aspects of your care will be altered by participation in this study.
2. Many of the questions ask for personal information. We would like to reassure you that we take the privacy of all volunteers in this research project very seriously.
3. You will not be able to be identified in any report or publication of the results of this study.
4. Personal and family information will not be released, passed on to a third party or made public for any reason.
5. When analysing the study we will be using only identification numbers. Each person's personal details will remain strictly confidential.
6. You **do not** have to complete any question you do not wish to and may stop the questionnaire at any time.
7. All personal details will be kept in a password protected computer database in a locked office. The only persons who can access this information are the research staff (listed below) of the study.
8. On the completion of this study this database will be kept secure in a password protected computer with a separate backup set in hard copy in a locked filing cabinet.
9. We will keep only the details of persons who agree to us contacting them again if further studies of MS are conducted. Those who consent only to participate in this study will have their personal details deleted at the completion of the study.
10. If you decide at any stage to withdraw from the study we will remove your details from our database. This will not affect your future care or treatment in any way.

Who is conducting the study

This is a multi-centre study involving neurologists and physicians from throughout New Zealand. The study centre will be based in Christchurch and coordinated by the New Zealand Multiple Sclerosis Study Group within the Universities of Otago and Canterbury.

The chief investigator is:

Associate Professor Bruce Taylor
Department of Medicine
Christchurch School of Medicine and Health Sciences
P.O Box 4345
Christchurch
New Zealand
Phone 03 364 0929
Fax 03 364 0935

The principal investigators are:

Associate Professor Chris Frampton

Dr Deborah Mason
Dr Ann Richardson

Dr Clive Sabel
Dr Ernest Willoughby

Christchurch School of Medicine and Health Sciences
Christchurch Public Hospital
Christchurch School of Medicine and Health Sciences
Canterbury University
Auckland Hospital

The study coordinator is:
Glynnis Clarke

Christchurch School of Medicine and Health
Sciences

The study will be housed at the MS Research Centre Department of Medicine Christchurch School of Medicine & Health Sciences, at 45 Cambridge Terrace Christchurch.

If you have any questions or queries regarding your rights as a participant in this study you may wish to contact a Health and Disability Advocate:

- Northland to Franklin 0800 555050
- Mid and lower North Island 0800 423638
- South Island except Christchurch 0800 377766
- Christchurch 03 3777501

Funding

This study has been jointly funded by the Health Research Council and the New Zealand Multiple Sclerosis Society.

Feedback/Results

The population results arising from this study will be published in medical journals and made available to service providers such as the MS Society. Participants who have requested information regarding the results of the study will receive these at the completion of the study.

Statement of Approval

This study has received ethical approval from the Multi-region ethics Committee that reviews National and Multi-regional studies.

Compensation

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, please contact your nearest ACC office or the investigator.

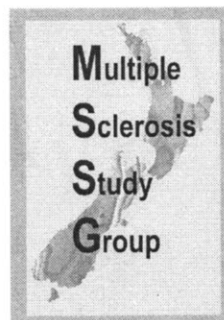
Thank you for taking the time to read this information sheet and considering participation in this study.

UNIVERSITY
of
OTAGO



Te Whare Wānanga o Otago

CHRISTCHURCH SCHOOL OF
MEDICINE AND HEALTH
SCIENCES
Te Kura Rata o Otautahi



New Zealand Multiple Sclerosis Prevalence Study

CONSENT FORM

REQUEST FOR INTERPRETER

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Cook Island	Ka inangaro au i tetahi tangata uri reo.	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai
Samoan	Ou te mana'o ia i ai se fa'amatala upu.	Ioe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai

NZMS Prevalence Study

1. I have read and I understand the information sheet dated 8th March 2006 for volunteers taking part in the study designed to find out about Multiple Sclerosis in New Zealand. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
2. I have had the opportunity to use family/whanau support or a friend to help me ask questions and understand the study.
3. I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my future health care.
4. I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.
5. I have had time to consider whether to take part.
6. I know who to contact if I have any questions about the study.
7. I wish to receive a copy of the results (*please circle the appropriate answer*)

YES

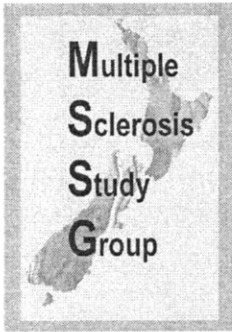
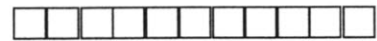
NO

8. I _____ (full name)
hereby give/do not give consent to take part in this study.

Signature _____ Date _____

Full names of Researchers:
Associate Professor Bruce Taylor
Dr Clive Sabel, Dr Deborah Mason
Dr Ernest Willoughby
Associate Professor Chris Frampton
Associate Professor Ann Richardson
Mrs Glynnis Clarke

**Contact Phone Number for researchers:
0800 MS STUDY (0800677 8839)**



New Zealand Multiple Sclerosis Prevalence Study Questionnaire.

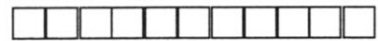
Thank you for taking the time to answer this questionnaire about MS in New Zealand. The first section of the questionnaire is about you. Many of the questions are standard questions about education, marital status, housing and income, derived from the New Zealand census. We need this information to find out how people with MS compare with the New Zealand population as a whole.

Some of the questions ask for personal information. We can assure you that this information will be kept completely confidential. You will not be able to be identified in any report or publication of the results of this study. If you do not wish to answer a particular question please put a line through it rather than leaving it blank, to let us know that you do not wish to answer that question. Please remember however, that the more complete the information we receive, the better the information we will be able to produce.

A number of questions ask about your heritage. We are interested in knowing about your ancestry because some ethnic groups appear to be protected from developing MS. We are interested in knowing if this is true within the New Zealand population.

A number of environmental factors have also been identified as possibly increasing the likelihood of developing MS. For this reason, we would like to know about the places you have lived and worked. The calendars in the second section of the questionnaire are designed to find out about this. You may wish to ask your family for help with this section, especially your earliest addresses and outdoor activities. An example of how to fill out each calendar is given at the top of each page.

If you require help with any part of the questionnaire please do not hesitate to contact the study team on phone number: **0800 MS STUDY (0800 677 8839)**, or e-mail: **msstudy@chmeds.ac.nz** . We would be happy to assist you.



Section 1: Who you are

1. What age group are you in?
 (Please tick the appropriate box)

- Less than 20 years
- 20-24
- 25-29
- 30-34
- 35-39
- 40-44
- 45-49
- 50-54
- 55-59
- 60-64
- 65-69
- 70-74
- 75 and older

For office use

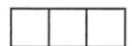
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13

2. a. Where did you live at the time of the 2006 census (March 2006)?
 (Please print the suburb, city or town, and region below)

Suburb _____

City or town _____

Region _____



14 15 16

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b. Where were you born ? *(Please print the suburb, city or town, and region if born in NZ or town/city and country if overseas)*

Suburb _____

City or town _____

Region (or country) _____

--	--	--	--

3. a. What **year** were you first diagnosed with MS? _____

--	--	--	--

17 18 19 20

b. Where were you living? *(Please print the suburb, city or town, and region if born in NZ or town/city and country if overseas)*

Suburb _____

City or town _____

Region (or country) _____

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4. a. What **year** did you first have symptoms of MS? _____

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21 22 23 24

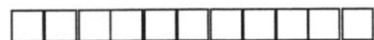
b. Where were you living? *(Please print the suburb, city or town, and region if born in NZ or town/city and country if overseas)*

Suburb _____

City or town _____

Region (or country) _____

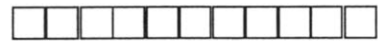
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Many of the following questions relating to ethnicity, occupation and living situations are identical to those in the 2006 census enabling us to make comparisons between people with MS and the general population of NZ.

5. Which ethnic group do you belong to?
(Please tick the box or boxes which apply to you)
- | | | |
|-------------------------------------------------------------------------|-----------------------------------------------|-----------------------------|
| <input type="checkbox"/> 1. NZ European | <input type="checkbox"/> 2. Maori | <input type="checkbox"/> 25 |
| <input type="checkbox"/> 3. Samoan | <input type="checkbox"/> 4. Cook Island Maori | <input type="checkbox"/> 26 |
| <input type="checkbox"/> 5. Tongan | <input type="checkbox"/> 6. Niuean | <input type="checkbox"/> 27 |
| <input type="checkbox"/> 7. Chinese | <input type="checkbox"/> 8. Indian | <input type="checkbox"/> 28 |
| <input type="checkbox"/> 9. Other (such as Dutch, Japanese, Tokelauan). | | <input type="checkbox"/> 29 |
| | | <input type="checkbox"/> 30 |
| | | <input type="checkbox"/> 31 |
| | | <input type="checkbox"/> 32 |
| | | <input type="checkbox"/> 33 |
- Please state: _____

6. What is your ancestral group? This refers to your ancestral origins (heritage) and may be different from your ethnic group.
(Please tick as many boxes as you need).
- | | |
|----------------------------------------------------------|-----------------------------|
| <input type="checkbox"/> 1. European | <input type="checkbox"/> 34 |
| <input type="checkbox"/> 2. Maori (Iwi/Hapu: _____) | <input type="checkbox"/> 35 |
| <input type="checkbox"/> 3. Samoan | <input type="checkbox"/> 36 |
| <input type="checkbox"/> 4. Cook Island Maori | <input type="checkbox"/> 37 |
| <input type="checkbox"/> 5. Other
Please state: _____ | <input type="checkbox"/> 38 |



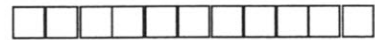
7. As best you can, please give your grandparents' ancestry
 (Please tick the box or boxes which apply to each grandparent)

Maternal Grandparents (your mother's parents)

	Your Mother's Father	Your Mother's Mother	
European	<input type="checkbox"/>	<input type="checkbox"/>	MF <input type="checkbox"/> 39
Maori	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 40
Samoan	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 41
Cook Island Maori	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 42
Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 43
Please state: _____			MM <input type="checkbox"/> 44
			<input type="checkbox"/> 45
			<input type="checkbox"/> 46
			<input type="checkbox"/> 47
			<input type="checkbox"/> 48

Paternal Grandparents (your father's parents)

	Your Father's Father	Your Father's Mother	
European	<input type="checkbox"/>	<input type="checkbox"/>	FF <input type="checkbox"/> 49
Maori	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 50
Samoan	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 51
Cook Island Maori	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 52
Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 53
Please state: _____			FM <input type="checkbox"/> 54
			<input type="checkbox"/> 55
			<input type="checkbox"/> 56
			<input type="checkbox"/> 57
			<input type="checkbox"/> 58



8. What is your highest secondary school qualification?

- 1. None
- 2. NZ School Certificate in one or more subjects, *or* National Certificate level 1 *or* NCEA Level 1
- 3. NZ Sixth Form Certificate in one or more subjects, *or* National Certificate level 2 *or* NZ UE before 1986 in one or more subjects *or* NCEA Level 2
- 4. NZ Higher School Certificate, *or* Higher Leaving Certificate *or* NZ University Bursary / Scholarship *or* National Certificate Level 3 *or* NCEA Level 3 *or* NZ Scholarship level 4
- 5. Other secondary school qualification **gained in NZ**.
Print what it is:

or

- 6. Other secondary school qualification **gained overseas**
Print what it is:

59

9. Apart from secondary school qualifications, do you have another completed qualification? *DON'T count qualifications that take less than 3 months of full-time study to get*

- Yes
Please go to question 10
- No
Please go to question 11

60

10. Print your highest qualification, and the main subject, for example:

Qualification *TRADE CERTIFICATE*
Subject *ELECTRICAL ENGINEERING*

Qualification (and level, if applicable)

Subject _____

61

□ □ □ □ □ □ □ □ □ □

11. In the last 7 days, which of these did you do?
(Tick as many boxes as you need to answer this question)

I worked for pay, profit or income
Please go to question 12

62

I worked in a family business or family farm **without pay**
Please go to question 12

63

None of these. *Please go to question 14*

64

12. In that job, what was your occupation, for example:
*PRIMARY SCHOOL TEACHER, CLOTHING MACHINIST,
MOTEL MANAGER, RECEPTIONIST?*

65

13. How many hours, to the nearest hour,
in all your jobs (for profit or unpaid in
a family business/farm) do you usually
work each week? _____ hours

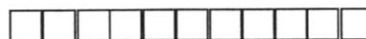
66 67 68

14. Has your job (occupation or hours of work) ever changed as a result of MS?

Yes *If yes, please explain why:*

No *If no, please go to question 16*

69

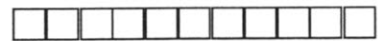


15. Please specify how your job has changed for the most recent time as a result of MS (*Tick as many boxes as you need*)

- Changed jobs 70
- Ceased working 71
- Reduced number of working hours worked per week 72
- Increased number of hours worked per week 73
- Commenced sickness benefit 74
- Commenced invalids benefit 75
- Became student 76
- Other (please specify _____) 77

16. What was the occupation you were **originally** trained for?
 For example: *PRIMARY SCHOOL TEACHER, CLOTHING MACHINIST, MOTEL MANAGER, RECEPTIONIST?*

_____ 78



17. Tick as many boxes as you need to show all the ways you yourself got income in the 12 months ending today
(DON'T count loans because they are not income):

- Wages, salary, commissions, bonuses, etc, paid by my employer 79
- Self-employment, or business I own and work in 80
- Interest, dividends, rent, other investments 81
- Regular payments from ACC or a private work accident insurer 82
- New Zealand Superannuation or Veterans Pension 83
- Other superannuation, pensions, or annuities (other than NZ Superannuation, Veterans Pension or war pensions) 84
- Unemployment Benefit 85
- Sickness Benefit 86
- Domestic purposes benefit 87
- Invalids Benefit 88
- Student Allowance 89
- Other government benefits, government income support payments, war pensions, or paid parental leave 90
- Other sources of income, counting support payments from people who do not live in my household 91
- or
- No source of income during that time 92

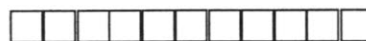
--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

18. From all the sources of income you marked in question 17, what was the total income that you yourself got before tax or anything was taken out of it, in the 12 months ending 31 March 2006?

- 1. Loss
- 2. Zero income
- 3. \$1 - \$5,000
- 4. \$5,001 – \$10,000
- 5. \$10,001 – \$15,000
- 6. \$15,001 – \$20,000
- 7. \$20,001 – \$25,000
- 8. \$25,001 – \$30,000
- 9. \$30,001 – \$35,000
- 10. \$35,001 – \$40,000
- 11. \$40,001 – \$50,000
- 12. \$50,001 – \$70,000
- 13. \$70,001 - \$100,000
- 14. \$100,001 or more

--	--

93 94



19. Which of these statements is true about your legal marital/civil union status? *(If you have had more than one legal marriage/civil union, answer for your most recent).*

- 1. I have never been legally married and I have never been legally joined in a civil union
- 2. I am divorced or my marriage has been dissolved
- 3. I am a widow / widower / bereaved civil union partner
- 4. I am permanently separated from my legal husband / wife / civil union partner
- 5. I am legally married
- 6. I am legally joined in a civil union

95

20. Where do you live at present?
(Please tick one box)

- 1. A house or flat
- 2. Boarding house
- 3. Hospital
- 4. Rest home
- 5. Other (please state: _____)

96



21. Where did you live 5 years ago?
(Please tick one box)

- 1. A house or flat
- 2. Boarding house
- 3. Hospital
- 4. Rest home
- 5. Other (please state: _____)

97

22. At present, do you receive services from any of the following?
(Please tick as many boxes as you need)

- District nurse
- Physiotherapist
- Home care
- Meals on wheels
- Multiple Sclerosis Society
- Other (please state: _____)
- None

98

99

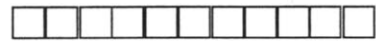
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101

102

103

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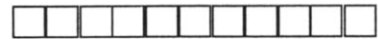


23. Does anyone in your immediate family (parents, siblings, half-siblings) have, or has anyone had multiple sclerosis?

(Please tick as many boxes as you need. If you have more than one brother or sister with MS please write the number of brothers or sisters with MS in the space provided below)

- | | | | | |
|--------------------------|-----------------|---------------------------------------|--------------------------|-----|
| <input type="checkbox"/> | No | | <input type="checkbox"/> | 105 |
| <input type="checkbox"/> | Mother | | <input type="checkbox"/> | 106 |
| <input type="checkbox"/> | Father | | <input type="checkbox"/> | 107 |
| <input type="checkbox"/> | Brother(s) | Number of brothers with MS _____ | <input type="checkbox"/> | 108 |
| <input type="checkbox"/> | Sister(s) | Number of sisters with MS _____ | <input type="checkbox"/> | 109 |
| <input type="checkbox"/> | Half-Brother(s) | Number of half-brothers with MS _____ | <input type="checkbox"/> | 110 |
| <input type="checkbox"/> | Half-Sister(s) | Number of half-sisters with MS _____ | <input type="checkbox"/> | 111 |

Thank you, this concludes section 1



Section 2: Residence Calendar

There has been some suggestion that the likelihood of developing MS may be related to where a person has lived in their lifetime. For this reason, we would like to know more about the places where you were brought up and have lived. The calendar on the following pages asks you to record these locations. By combining the data from all the participants in this study, we hope to identify patterns that will help us understand MS better.

- The calendar asks you to describe (in chronological order) where you have lived, and for how long you stayed at each location. An example of how to fill out the calendar is included at the top of each page.
- Please include all places you have lived, **from the start of your mother's pregnancy with you (your conception) to the date at which you were first diagnosed with MS**. Only include places where you have lived for more than 6 weeks. Please make every effort to ensure completeness, especially in your early life. If possible we would encourage you to consult other family members to help fill in details.
- Please start a new row for each time you moved, and continue on a separate page if you need more rows.

From & To section:

Please include **both** the month and the year. If you can't recall the exact month, please estimate. Don't leave blanks.

Where you have lived section:

For urban areas, fill in the **suburb and city**. For rural areas, fill in **the closest town and district**. If the address is **not in NZ** just fill in the **town and the country**. Please don't use PO Box numbers.

Sunlight exposure section:

For each place you have lived we would like to estimate how much sunlight you have been exposed to. This has probably changed at different times during your life. We therefore ask that for each place you have lived, separately for summer and winter, you tick the box that best estimates how many hours a week, on average you would normally have spent in the sun.

For each period of your life we are trying to capture an overall measure of how much time you spent in the sun. If you are unsure about your average sun exposure during any period, it may help to think about where you were and what you were doing at that time. For example, when you were at school maybe you played outside after school or at lunchtime; if you were working, did your job involve being indoors or outdoors a lot. During weekends or holiday periods did you spend more time indoors or outdoors.

You may wish to check with your family, particularly parents or siblings, about your sunlight exposure for ages before 6 as these are often difficult to recall.

If you are truly unsure and cannot find the information out, put a line through the sun exposure questions. **DO NOT LEAVE BLANK.**

Sunburn section:

For each period (each row), how many times were you sunburnt, **where the pain lasted two or more days?**



Office use only	From (Month and year)	To (Month and year)	Where you've lived		Sunlight Exposure														Sunburn						
					Suburb and city, or nearest town and district		Average hours per week spent in the sun Place tick ✓ in appropriate box														Number of times sunburnt Place tick ✓ in appropriate box				
					Suburb / Town	City / District (or country)	Winter				Summer					0	1	2-5	6-10	> 10					
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19							
example	6 / 1962	12 / 1975	Highbury	Wellington																					
R1	Conception	— / —																							
R2	— / —	— / —																							
R3	— / —	— / —																							
R4	— / —	— / —																							
R5	— / —	— / —																							
R6	— / —	— / —																							
R7	— / —	— / —																							
R8	— / —	— / —																							
R9	— / —	— / —																							
R10	— / —	— / —																							
R11	— / —	— / —																							
R12	— / —	— / —																							
R13	— / —	— / —																							
R14	— / —	— / —																							
R15	— / —	— / —																							



Section 3: Job Calendar

For all jobs where you have worked for more than 6 weeks up **until the time you were diagnosed with MS**, please could you:

- List the dates you worked in that job
- Tell us what the job was, and
- Indicate whether it was largely an indoor or outdoor job.

<i>Office use only</i> Period	From (Month and year)	To (Month and year)	Occupation	Indoor or Outdoor Job?	
	1 Until diagnosis	2 Until diagnosis		3	4 Largely Indoor
example	6 / 1962	12 / 1975	cleaner	✓	
J1	__ / __	__ / __			
J2	__ / __	__ / __			
J3	__ / __	__ / __			
J4	__ / __	__ / __			
J5	__ / __	__ / __			
J6	__ / __	__ / __			
J7	__ / __	__ / __			
J8	__ / __	__ / __			
J9	__ / __	__ / __			
J10	__ / __	__ / __			
J11	__ / __	__ / __			
J12	__ / __	__ / __			
J13	__ / __	__ / __			
J14	__ / __	__ / __			
J15	__ / __	__ / __			



Confirmation of the diagnosis of MS

As the diagnosis of MS is sometimes difficult some participants may need to be seen in a research clinic in their area. At that clinic you will be seen by a study doctor. This clinic visit will involve a neurological examination that is not painful or intrusive. No additional tests will be performed. Some people will not need to attend a clinic, but we may need further information, which we could obtain by telephone.

If you would be prepared to be contacted please write your contact details below. This information will be kept separate from the rest of the questionnaire to maintain your confidentiality.

Name: _____

Preferred Name: _____

Address: _____

Telephone: _____

E-mail: _____

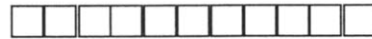
Preferred Means of contact: _____

Preferred day/time of contact: _____

Specialists Name: _____

Name of GP: _____

PTO.



MS Research and Register

We would like to contact people with MS to find out if they would be prepared to take part in future research into MS and/or for their names to be included on a confidential national register of people with MS.

Would you be prepared to take part in future research into MS?

Yes No

Would you be prepared to be contacted if a confidential national register of people with MS is established?

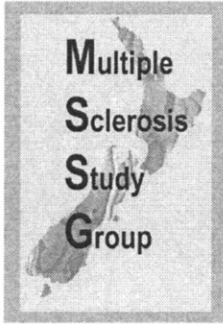
Yes No

(Your contact details will be used only for the purpose you agreed to.)

Finally, we would be very interested in any thoughts or opinions you may have as to the cause of your MS *(If you have any thoughts or opinions about this, please write them below)*

PTO

--	--	--	--	--	--	--	--	--	--	--	--



Neurological Assessment and EDSS

This section **should only** be completed by a neurologist or physician involved in the care of the person. **If you are not the person's neurologist or physician please leave this section blank.** If you are the person's neurologist or physician please complete this section on **each** person notified.

Full Name of person completing this form (Your name):
(Complete in full for the **first patient you notify** to us thereafter we only require your **name**, or stamp **and the date.**)

Date Form Completed: _____

Address: _____

Phone Number : _____
(Area Code) Number

E-mail Address: _____

Designation: _____

Neurological Assessment

1. Year of MS Diagnosis

--	--

2. Year of onset of 1st symptoms

--	--



3. Nature of 1st symptoms *((please tick one box only))*

- Optic neuritis
- Spinal cord
- Brainstem/cerebellar
- Sensory only
- Polysymptomatic
- Other please state _____

4. Type of MS *(please tick one box only)*

- Single demyelinating event
- Relapsing/Remitting
- Secondary Progressive
- Progressive since onset
- Not MS

5. How has the diagnosis been confirmed at any stage? Please include **all** events and tests performed up to and including March 6th 2006 *(please tick the appropriate box or boxes)*

a) Relapses
(Symptoms lasting more than 24 hrs)

2 or more attacks.
(Greater than 30 days apart)

Or

Single attack

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------	--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

b) Progressive Neurological Signs Greater than or equal to 12 months
(include both primary or secondary progression) Or Less than 12 months

c) Clinical signs Single clinical lesion
 Or 2 or more separate clinical lesions

d) Oligoclonal Bands Not done Positive Negative

e) Visual Evoked Potentials Not done Abnormal Normal

f) MRI	Not Done	Consistent with demyelination single lesion	Consistent with demyelination 2 or more lesions	Normal	
Brain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Spinal Cord	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. Has the patient been assessed in the last 12 months?

Yes. Please go to Question 7.
 No. **No more questions thank you.**

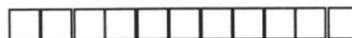
--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

7. At the time of the last assessment which of the following **best** fits the patient's level of disability. (Please **do not** include assessments done at the time of a relapse. If only assessed at the time of a relapse please leave this question blank).

Date of neurological assessment _____

- 0. Normal findings on neurological examination
- 1. No disability. Minimal signs on neurological examination.
- 2. Minimal and non ambulation-related disability. Able to run.
- 3. Unlimited walking distance without rest, but unable to run; or a significant non ambulation-related disability.
- 4. Walks without aid. Limited walking distance but **greater than or equal to** 500 metres without rest.
- 5 Walks without aid. Walking distance **less than** 500 metres
- 6A. Walks with permanent **unilateral** supported **less than** 100 metres without resting.
- 6B. Walks with permanent **bilateral** support **less than** 100 metres without resting.
- 7. Home restricted. A few steps with wall or furniture assistance. Walking distance **less than** 20 metres.
- 8. Chair restricted. Unable to take a step. Some effective use of upper limbs.
- 9. Bedridden and totally helpless.
- 10. Death due to MS

--	--



8. If completed in the last 12 months please indicate the patients Extended Disability Scale Score. (See attached sheet).

(Please **do not** include assessments done at the time of a relapse. If only assessed at the time of a relapse please leave this question blank).

Date of latest EDSS assessment _____

EDSS .

Thank you for completing this form

Appendix 2

Journal publications arising from the NZMSPS

1. Taylor, BV., Pearson, JP., Clarke, G., Mason, DF., Abernethy, DA., Willoughby, E, Sabel, C. (2010). MS prevalence in New Zealand, an ethnically and latitudinally diverse country. *Multiple Sclerosis*. 12: 1422-1431.
2. Richardson, AK., Clarke, G., Sabel, C., Pearson, JP., Mason, DF., and Taylor, BV. (2012). Method for identifying eligible individuals for a prevalence survey in the absence of a disease register or population register. *Internal Medicine Journal*. onlinelibrary.wiley.com/doi/10.1111/j.1445-5994.2012...x/pdf.

Multiple Sclerosis

<http://msj.sagepub.com/>

MS prevalence in New Zealand, an ethnically and latitudinally diverse country

Bruce V Taylor, John F Pearson, Glynnis Clarke, Deborah F Mason, David A Abernethy, Ernie Willoughby and Clive Sabel

Mult Scler 2010 16: 1422 originally published online 2 September 2010

DOI: 10.1177/1352458510379614

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MS prevalence in New Zealand, an ethnically and latitudinally diverse country

Bruce V Taylor¹, John F Pearson², Glynnis Clarke², Deborah F Mason³, David A Abernethy⁴, Ernie Willoughby⁵ and Clive Sabel⁶

Abstract

Background: The prevalence of multiple sclerosis (MS) is not uniform, with a latitudinal gradient of prevalence present in most studies. Understanding the drivers of this gradient may allow a better understanding of the environmental factors involved in MS pathogenesis.

Method: The New Zealand national MS prevalence study (NZMSPS) is a cross-sectional study of people with definite MS (DMS) (McDonald criteria 2005) resident in New Zealand on census night, 7 March 2006, utilizing multiple sources of notification. Capture–recapture analysis (CRA) was used to estimate missing cases.

Results: Of 2917 people with DMS identified, the crude prevalence was 72.4 per 100,000 population, and 73.1 per 100,000 when age-standardized to the European population. CRA estimated that 96.7% of cases were identified. A latitudinal gradient was seen with MS prevalence increasing three-fold from the North (35°S) to the South (48°S). The gradient was non-uniform; females with relapsing–remitting/secondary-progressive (RRMS/SPMS) disease have a gradient 11 times greater than males with primary-progressive MS ($p < 1 \times 10^{-7}$). DMS was significantly less common among those of Māori ethnicity.

Conclusions: This study confirms the presence of a robust latitudinal gradient of MS prevalence in New Zealand. This gradient is largely driven by European females with the RRMS/SPMS phenotype. These results indicate that the environmental factors that underlie the latitudinal gradient act differentially by gender, ethnicity and MS phenotype. A better understanding of these factors may allow more targeted MS therapies aimed at modifiable environmental triggers at the population level.

Keywords

ethnicity, gender ratio, latitude, multiple sclerosis, prevalence

Date received: 22nd March 2010; revised: 16th June 2010; accepted: 24th June 2010

Introduction

One of the most striking features of the epidemiology of multiple sclerosis (MS) is the significant variability in prevalence and incidence seen throughout the world.^{1,2} This geographical distribution is thought to be driven by two main factors: genetics and the environment acting at the population level.^{3–6} MS is predominantly a disease of persons of Northern European origin although it is recognized in almost all ethnic groups around the world.² In admixed populations the rates of MS differ, with the coexisting European population always having a higher prevalence.²

The most notable geographical variation described is the latitudinal gradient of MS prevalence seen in

genetically susceptible populations. This has been demonstrated in Australia,⁷ USA,⁸ France,⁹ and New Zealand.¹⁰ However, other studies in Sardinia¹¹ and

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Email: bruce.taylor@utas.edu.au

Patagonia¹² have not supported this observation. Others¹³ have suggested that the latitudinal gradient is largely due to a failure to standardize prevalence rates by age, or lack of ethnic stratification of the populations being studied.² A recent meta analysis of incidence studies¹⁴ has documented a consistent incidence latitudinal gradient with some reduction in strength since 1980. Causative environmental factors that have been postulated and extensively studied include decreased winter ultraviolet radiation (UVR)^{15,16} and subsequent decreased vitamin D levels,¹⁷ and geographical variation in late onset Epstein Barr virus infections.¹⁸

A national study of MS prevalence can be used to better understand this geographical variation and the contribution of factors such as ethnicity, clinical variables and environmental exposures acting at the population level. New Zealand (NZ) is ideally suited to such a study as it is latitudinally diverse, extending from 35°S to 48°S with a widely dispersed population, largely of Northern European origin. The NZ health system is highly developed with equitable access to neurological care throughout the country. In addition significant ethnic minorities are present including people of Polynesian origin, principally NZ Māori and Pacific Island peoples, allowing for the study of the role of ethnicity in the development of MS in an admixed population in an environment associated with a high risk of MS.¹⁰ In addition, there is a significant awareness of MS in the NZ healthcare system and the general population, due to the well established high prevalence of the disorder.¹⁰ A national MS prevalence study in NZ was therefore undertaken with the specific aims of:

- Measuring the crude, and age and sex adjusted prevalence (ASP) of DMS in NZ
- Determining if a latitudinal gradient of DMS is present in NZ.
- Determining whether a latitudinal gradient is influenced by age, gender, MS phenotype, or ethnicity.

Methods

The NZ national MS prevalence study (NZMSPS) was jointly funded by the NZ Health Research Council and the National MS Society of NZ. It was established with the specific aims of determining the national prevalence of MS in NZ on census day, 7 March 2006. Ethical approval for this study was obtained from the NZ multi-regional ethics committee. All persons who provided a questionnaire response signed an informed consent form. All other data was de-identified.

Inclusion and exclusion criteria

Inclusion criteria:

- Definite multiple sclerosis as defined by the McDonald criteria 2005.¹⁹
- Resident in NZ on census day (prevalence day).

Exclusion criteria:

- Probable, possible or not MS diagnosis
- Clinically isolated syndromes
- Devic's disease (neuromyelitis optica).
- Deceased before census day.

Recruitment

The NZMSPS recruited cases of MS from multiple sources, including MS societies' databases, hospital databases, NZ government health information statistics services, neurologist databases, MS care providers, and direct advertising through the media. For privacy reasons all cases were assigned by the notifier with a unique identifier number encompassing the person's date of birth, sex and initials. If upon receipt by the study the notification was unique the notifier was asked to contact the patient and invite them to participate. Informed consent was sought at this point including access to medical records. If the person could not be contacted or declined to participate the neurologist involved with the patient's care was asked to complete a de-identified neurological assessment that confirmed the diagnosis of MS including all investigations, year of onset and diagnosis, MS phenotype and current disability level. A neurological assessment form was completed for all unique notifications and the diagnosis of DMS verified by a study neurologist.

If a notified case had not been reviewed by a neurologist within 12 months or the diagnosis of DMS could not be confirmed, they were directly reviewed by a study neurologist to confirm the diagnosis. All cases were confirmed as being resident in NZ on census day by questionnaire or by NZ health information statistics.

Questionnaire

All unique individuals with DMS were sent a questionnaire based on the NZ national census 2006, responses were monitored and if no questionnaire was received the person was contacted by the notifier or, if they had consented, by the study centre. This process was performed at least twice for each case. Where the person was incapacitated relatives were utilized to complete the questionnaire; research staff also completed questionnaires over the phone and in person.

Data entry

All data was dual entered by two independent research assistants and then cross referenced to identify discrepancies, with all detected errors directly corrected from the paper copy.

Ethnicity

NZ is an ethnically diverse society with people of European origin comprising the majority in all regions. Ethnicity was assessed using the same self defined ethnicity question used in the 2006 NZ population census. Prior to this census being undertaken there was a campaign in NZ to declare ethnicity as 'New Zealander' under 'Other' ethnicity. Approximately 10% of respondents took this option, thus the grouping of 'Others' is greater than in previous NZ censuses. Statistics NZ do not provide individual breakdowns by age and sex for 'New Zealanders'; however, their analysis shows that 'New Zealanders' are over represented among males, middle age, and rural and southern regions and that they are more likely to be born in New Zealand and mono-lingual.²⁰ As the proportion of the population with 'New Zealander' self-defined ethnicity varied throughout the country we consistently took a scenario that would minimize ethnically defined gradients to eliminate any inflationary bias that this ambiguous response may generate.

When describing the 'European' population in NZ many assumptions have to be made, particularly in assuming that the majority of those responding 'Other' should be included as European. Therefore in this study the population defined as Non-Māori/Pacific People is the best approximation to European from those available from the census. The NZNMSPS study participants were asked about ethnicity of all four grandparents, allowing us to define ethnicity by descent and also self reported ethnicity.

Population denominators

All population denominators, including age, gender and ethnicity denominators, were obtained from the national census undertaken on the 7 March 2006 downloaded from Statistics NZ²⁰ on 22 January 2009.

Analysis and statistical methods

Analysis of latitudinal data. NZ census regions were aggregated into six broad latitudinal regions from North to South (Figure 1). These regions each contain sufficient MS cases to allow meaningful stratification by ethnicity, age, gender and MS phenotype. For each region a population weighted latitude and longitude centroid (PWC) was calculated and this centroid was

taken as the latitudinal reference point for that region (Figure 1). The latitude gradient was estimated by calculating ASPs and their confidence intervals for each of the six regions and fitting this to the PWCs.

Capture–recapture analysis. Capture–recapture analysis (CRA) is an established method for assessing population size²¹ that has been widely used in the estimation of MS prevalence²² worldwide and in the estimation of disease incidence and prevalence in NZ.²³ In this study six sources of notification were utilized. These six sources were not totally independent for various reasons. While simple capture–recapture estimates assume list independence, we fitted log-linear models to assess the dependence between lists thus explicitly adjusting for non-independence.²⁴ Log-linear models were fitted to the national dataset and to the data stratified by region. For each initial model the Akaike Information Criterion (AIC) was used to select the model with the best fit, as it produces less bias and more accurate estimates than competing measures of fit.²⁵ For the national dataset, models were fitted with and without covariates of age, sex and region. The estimates of the number of missing cases and population totals are based on the model including covariates for age, sex and region with minimum AIC. The large number of possible models prohibited a comprehensive model averaging approach.

All models and analysis were done using version 2.8.1 of the R language for statistical computing. Confidence intervals for modeled parameters use the profile likelihood method; confidence intervals for the two list analysis are by goodness of fit.

Results

Notifications and response rates

The NZNMSPS received a total of 13,803 notifications for 5901 unique individuals from which 2917 cases of DMS were identified as resident in NZ on prevalence day. Table 1 displays the notification data for all cases and response rates.

Capture–recapture analysis

Table 2 shows the best fitting models for the national dataset, with and without covariates and for the regionally stratified datasets, with the statistically 'best model' estimating that 91 cases (95% confidence interval [CI] 34–147) were missed, bringing the MS population to 3008 (95% CI 2951–3064). The predicted breakdown by gender, age and region is shown in Table 3, indicating that the missed cases were evenly distributed by region, age group and gender. Tables 2 and 3 illustrate

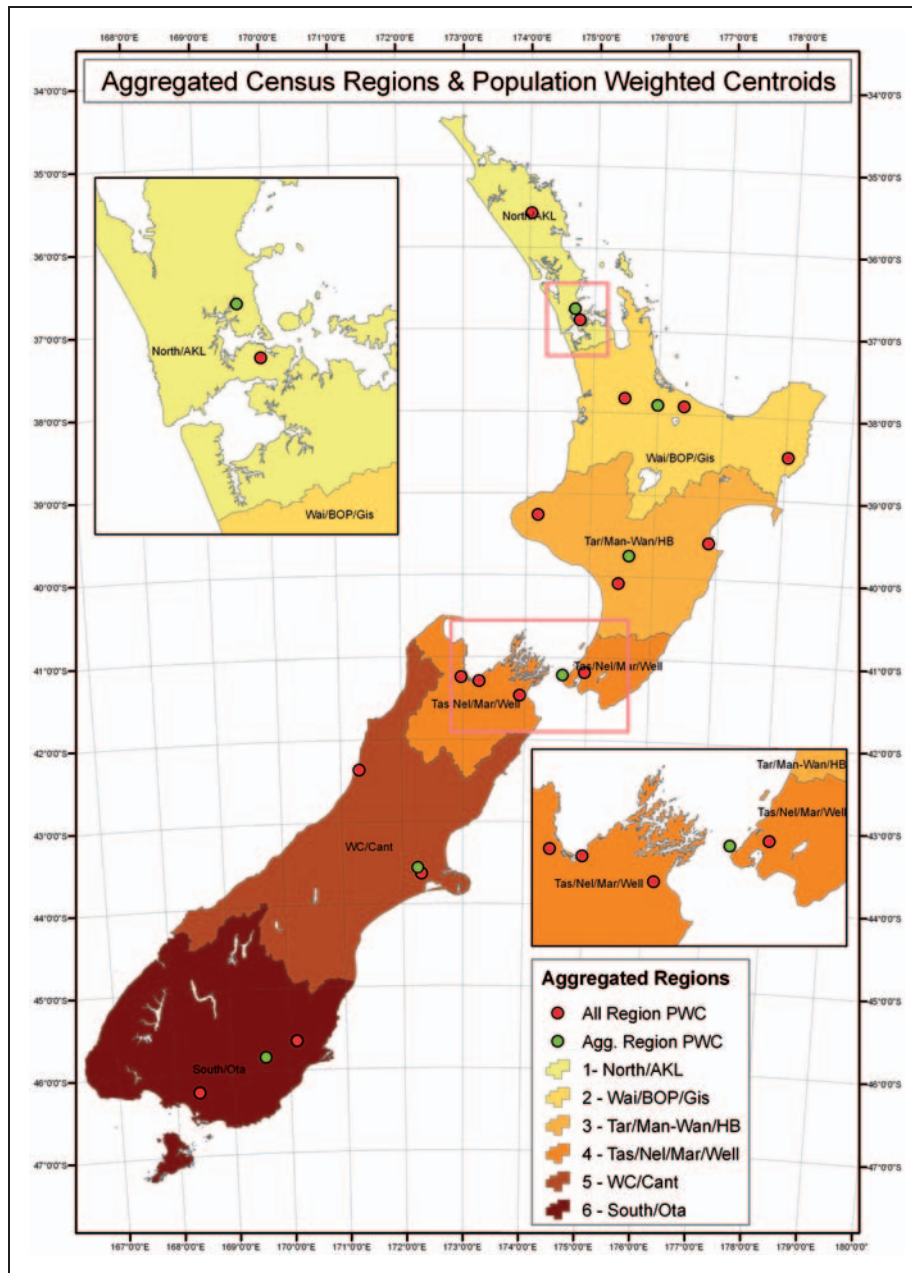


Figure 1. Aggregated census regions for New Zealand (NZ), all region population weighted centroids (PWCs) refer to the NZ statistical regions; aggregated PWCs refer to the combined regional PWCs as defined by the NZNMSPS.

that the chosen model produces estimates representative of models with good fit even though it may not be the 'true' model.

National age and sex standardized prevalence rates

The NZNMSPS identified 2917 cases of DMS amongst the NZ population of 4,027,950 on census day giving a crude MS prevalence of 72.4 per 100,000 population. When age-standardized to the standard European population this gives a prevalence of 73.1 per 100,000

population (CI 70.5–75.8). Figure 2 demonstrates the age and sex breakdown of DMS cases in NZ when compared with the overall NZ population.

Ethnicity and MS prevalence

Prevalence rates by ethnicity are displayed in Table 4. Table 5 gives the ethnic breakdown of the NZ population as determined by the self reported ethnicity question in the census. This data is divided into the six NZNMSPS geographical regions. In the NZNMSPS

Table 1. New Zealand national MS prevalence study demographics

Unique notifications	13,803			
Unique individuals	5901			
Mean notifications per individual	(Mean 2.5 + range 1–9, SD 1.5)			
Confirmed DMS cases	2917/5901 (49.4%)			
Not included reasons	2984/5901 (50.4%)			
Not confirmed/located	547 (9.3%)			
Deceased before census	1086 (18.4%)			
Possible MS	173 (2.9%)			
CIS	393 (6.7%)			
Not in NZ on census day	62 (1.1%)			
Diagnosed post census	24 (0.4%)			
Not MS	699 (11.8%)			
Questionnaire response rates (<i>n</i> , %)	2073, 71.1%			
Gender ratio M:F	728:2189 1:3			
Age	Mean	Max	Min	
Overall	51.74	93	9	
Male	51.14	82	16	
Female	51.94	93	9	
MS clinical phenotypes and disability levels	N	Mean age	M:F ratio	Mean Expanded Disability Status Scale
RRMS	1541	48.6	1:3.6	2.5
SPMS	918	59.6	1:4.5	6.4
PPMS	458	69.7	1:1.47	6.3

MS, multiple sclerosis; DMS, definite MS; NZ, New Zealand; RRMS, relapsing–remitting MS; SPMS, secondary progressive MS; PPMS, primary progressive MS.

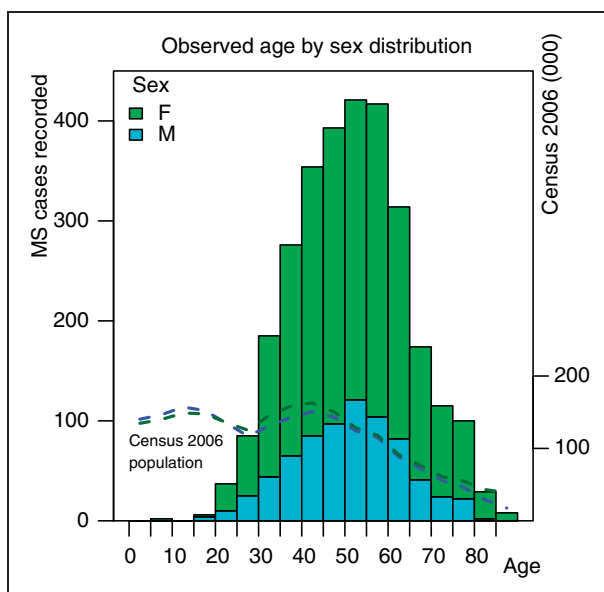
Table 2. Capture–recapture analysis log-linear modelling

Region	<i>n</i>	95% CI	<i>N</i>	AIC	Deviance	<i>df</i>	Zeros	List interaction terms		
								2way	3way	4way
National										
Saturated model	336	(–,–)	3253	405.9	0	0	2	15	20	15
Best model	64	(33,117)	2981	383.9	15.5	19	2	15	16	6
Best model with age, sex and region	91		3008	2669.2	857.1	1388	1013	14	12	4
Regional stratification (best model)										
R1	45	(23,82)	864	273.5	49.4	38	17	12	6	0
R2	17	(10,45)	351	192.5	52.5	48	30	8	0	0
R3	2	(0,8)	281	204.0	3.4	23	26	15	16	2
R4	45	(27,71)	550	235.3	31.5	43	14	10	3	2
R5	4	(1,11)	602	231.2	21.5	37	18	14	5	2
R6	44	(23,79)	426	203.0	24.9	39	23	12	5	6
Total	157	(84,296)	3074							

n, estimated number of cases missed; CI, confidence interval; *N*, population; AIC, Akaike Information Criterion; *df*, degrees of freedom.

Table 3. Missing cases as estimated by capture–recapture analysis by NZMSPS defined region (R1–R6), age and gender

Sex	Age	Estimate of missing cases						Sum
		R1	R2	R3	R4	R5	R6	
F	(0,60)	16.02	5.98	3.97	12.21	4.13	11.00	53.30
M	(0,60)	7.00	2.61	1.73	5.33	1.80	4.80	23.28
F	(60,100)	3.12	1.16	0.77	2.38	0.80	2.14	10.37
M	(60,100)	1.14	0.42	0.28	0.87	0.29	0.78	3.78
Sum		27.27	10.17	6.75	20.78	7.02	18.72	90.72

**Figure 2.** Age and sex breakdown of multiple sclerosis (MS) cases in New Zealand (NZ) compared with standardized population percentages from NZ census.

only one respondent listed ‘New Zealander’ as their ethnicity.

Table 4 demonstrates that the ASP of MS in NZ differs significantly between ethnic groups. Most notably persons who define themselves ethnically as Māori have a significantly lower prevalence of MS than the European population. Similarly, a low MS prevalence is seen in those of Pacific and Asian origin with a combined 15 cases identified. Due to low numbers no further analysis was undertaken on these two groups. Prevalence rates by ethnicity were not affected by region (data not shown).

MS prevalence variation by latitude and ethnicity

Using the defined six latitudinal regions of NZ (Figure 1) MS prevalence was plotted against the latitude of the population weighted centroid of each

region. Figure 3 demonstrates that there is a clear increase in MS prevalence with increasing latitude south of 37°. To assess the relationship between MS prevalence and latitude a linear model has been fitted to the southern five regions. The linear model has not been fitted to the northernmost region as it appears to go against the linear trend. The northernmost centroid includes Auckland, the largest city in NZ, with around one-quarter of the total population and the highest concentration of recent migrants. The increase in cases of MS found in Auckland compared with the neighboring region, Waikato, could be due to a number of factors, including ethnic mix, internal migration, external migration and availability of services and personal support. While Waikato has the largest population of Māori in NZ this is not the determining factor in the Auckland/Waikato difference as seen by the prevalence for the Māori and non-Māori/Pacific People groups. Similarly when the Northern region is split into its smaller constituents Northland and Auckland, Northland has the same prevalence as the Waikato region. This would indicate that the elevated prevalence in Auckland is due to local factors as outlined above.

MS prevalence for the total population increases by 10.7 ± 0.9 per 100,000 population per degree of latitude south of 37°S ($p < 0.002$). There is no difference in prevalence gradients between the total and non-Māori/Pacific People’s populations, supporting the assertion that the non-Māori/Pacific People’s group best represents the European population in this study. In the Māori population there is no evidence for a latitude gradient in the North Island; however, in the South Island the latitude gradient is similar to the total population (but not statistically significant due to low numbers), at 11.7 ± 1.4 increase in prevalence per degree of latitude ($p = 0.07$).

MS prevalence variation by latitude, gender and MS phenotype

There were highly significant differences in the latitudinal gradient of MS prevalence by gender ($p < 0.00007$,

Table 4. Prevalence age-standardized to European standard population for major ethnic groups in New Zealand

Ethnic group	Population	MS cases	Prevalence	ASP	ASP CIs
Total	4,027,950	2917	72.4	73.1	70.5–75.8
Māori	565,323	90	15.9	24.2	18.9–29.5
Non-Māori	3,462,606	2827	81.6	78.7	75.7–81.6
Non-Māori/ Pacific Peoples	3,215,667	2823	87.8	82.4	79.4–85.5
European	2,609,586	2699	103.4	101.9	98–105.8

MS, multiple sclerosis; ASP, age and sex adjusted prevalence; CI, confidence interval.

Table 5. Ethnic breakdown of the NZ population by self report from the NZ national population census 2006

Ethnicity responses for total ethnic groups (Thousands (000)) (%) by region							
Ethnicity	R1	R2	R3	R4	R5	R6	NZ
European	792(54.6)	445(65.0)	332(70.0)	404(69.8)	417(75.4)	219(76.8)	2610(64.8)
Māori	181(12.5)	164(24.0)	92(19.3)	66(11.5)	40(7.2)	23(8.0)	565(14.0)
Other	115(7.9)	76(11.1)	59(12.3)	66(11.4)	75(13.6)	40(14.1)	431(10.7)
Asian	237(16.3)	27(3.9)	14(2.9)	39(6.7)	30(5.3)	9(3.1)	355(8.8)
Pacific Peoples	182(12.5)	20(2.9)	13(2.6)	36(6.3)	11(2.0)	5(1.6)	266(6.6)
Peoples NEI	77(5.3)	32(4.6)	16(3.3)	19(3.3)	15(2.7)	9(3.2)	168(4.2)
MELAA	19(1.3)	3(0.5)	29(0.4)	6(1.0)	3(0.6)	1(0.5)	35(0.9)
Total stated	1375(94.7)	653(95.4)	458(96.7)	560(96.7)	538(97.3)	276(96.8)	3860(95.8)
Total	1452	685	474	579	553	285	4028

NZ, New Zealand; NEI, no ethnicity indicated; MELAA: Middle Eastern Latin American African.

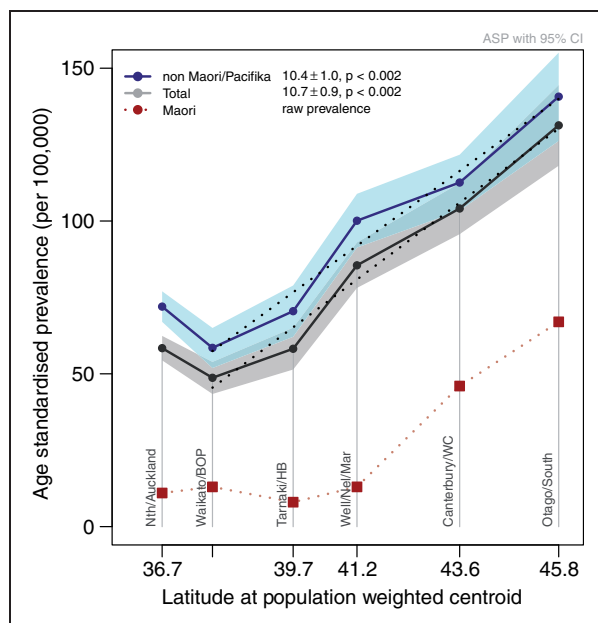


Figure 3. Multiple sclerosis (MS) prevalence by latitude and major ethnic groups in New Zealand (NZ), MS prevalence by region age-standardized to the NZ population with 95% confidence intervals is shown for the total and Non-Māori/Pacific Peoples populations. Raw prevalence is shown for the Māori population as there are insufficient numbers of cases for a valid age standardization.

Figure 4a) and by MS clinical course phenotype (relapsing–remitting/secondary-progressive MS [RRMS/SPMS] and primary-progressive MS [PPMS]) ($p < 0.0001$, Figure 4b) and when combined (Figure 4c). ANOVA of a linear model of prevalence with independent slopes and intercepts for each of the four groups shown in Figure 4c, RRMS/SPMS (M or F) and PPMS (M or F), shows evidence for different gradients ($p < 1 \times 10^{-7}$) and that this difference in gradients is driven by the female RRMS/SPMS population.

Gender ratios and age at onset

Neither gender ratios nor age at onset varied by latitude (data not shown). When sex ratios were calculated by quintennial year of birth as per Orton et al.²⁶ there was no evidence for an increase in gender ratios, with the F:M ratio remaining at or around 3:1 since birth year, 1940.

Discussion

The NZNMSPS has successfully recruited and acquired neurological information on nearly 3000 people living with MS in NZ on census day, 7 March 2006. This is by

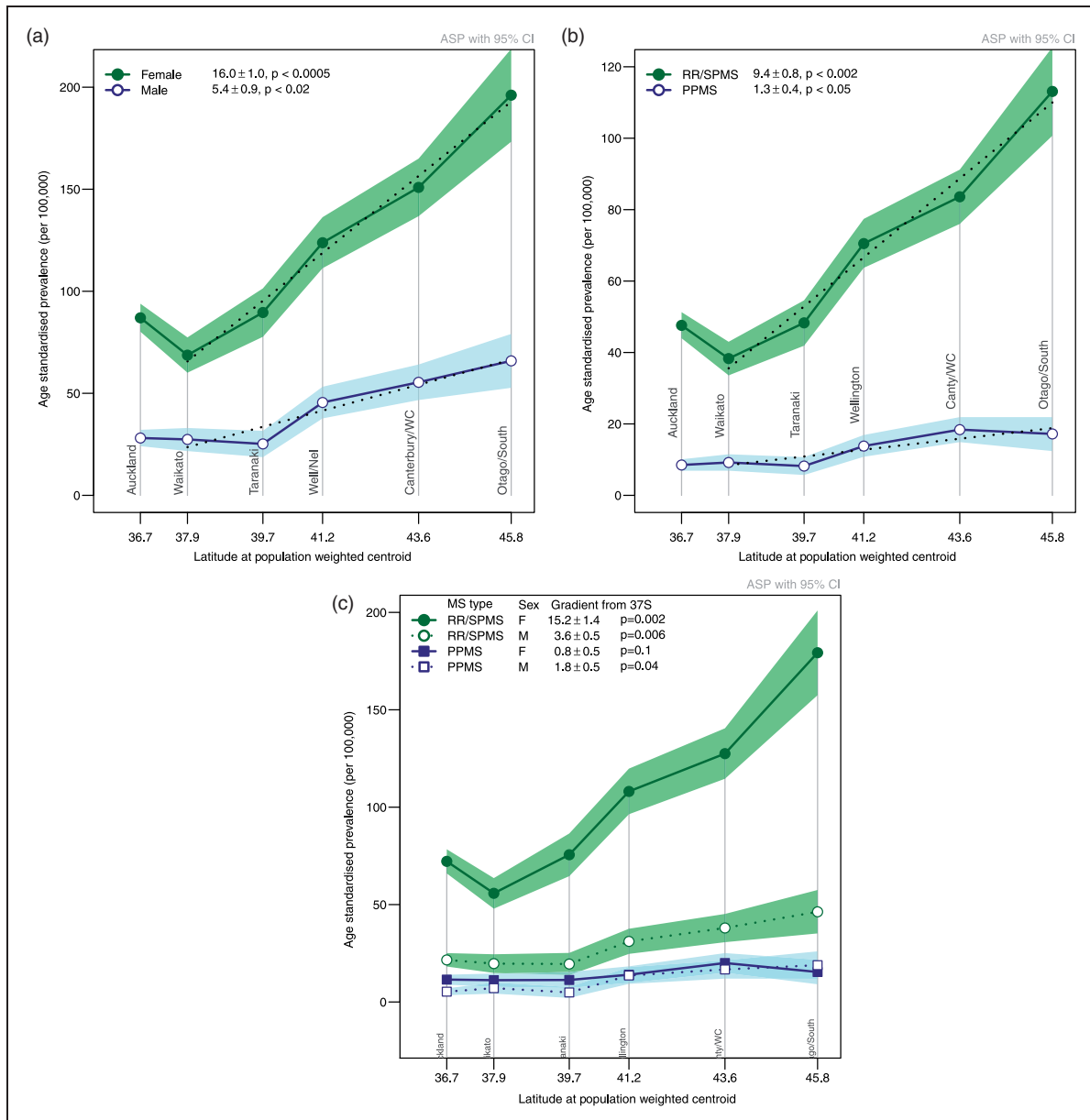


Figure 4. (a) Multiple sclerosis (MS) prevalence latitudinal gradient by gender. A linear model of prevalence on latitude and MS type shows that the gradient for females was about three times that for males ($p < 0.00007$). (b) MS prevalence gradient by clinical course phenotype, a linear model of prevalence on latitude and MS type shows that the gradient for relapsing–remitting (RR)/secondary progressive (SP)MS is 8 ± 0.9 times higher than for primary progressive (PP)MS ($p < 0.0001$). (c) MS prevalence latitudinal gradient by gender and MS clinical course. A linear model of prevalence on latitude, gender and MS type shows that the latitudinal gradient depends on both sex and MS type ($p < 1 \times 10^{-7}$).

far the largest stand-alone cross-sectional MS prevalence survey ever undertaken. CRA indicates that we have detected and phenotyped almost 97% of all individuals with DMS in NZ. The completeness of our data set allows us to undertake detailed analyses of the factors that drive the geographical variability of MS prevalence in NZ, a country ideally suited to research of this type.

The most significant finding from this study is the unequivocal confirmation of a highly significant latitudinal gradient of MS prevalence in NZ, with prevalence increasing threefold between the North and South of the country. The gradient is notable below 37° S. Previous studies have suggested that the factors that drive the latitudinal gradient become significant only above latitude 37° N.²⁷ In contradistinction to previous

observations¹³ the gradient persisted when the population was age and sex standardized. Similarly, ethnic stratification² did not influence the latitudinal gradient, with the gradient being strongest amongst those of European origin.

People of Māori origin have a much lower prevalence of MS in NZ: the overall prevalence in people with self defined Māori ethnicity was 30% of that seen in Europeans. No-one with MS and Māori origin had all four Māori grandparents (the majority had one or two Māori grandparents). MS was an uncommon disease among those of Pacific People origin or Asian origin, indicating that these populations may be protected from developing MS. There is, however, a latitudinal prevalence gradient for Māori that mirrors that seen for the European population but appears to start at higher latitudes, indicating that the environmental factors that apply to European populations may also apply to the genetically admixed Māori population.

The MS prevalence gradient was also non-uniform, with gender and MS phenotype significantly affecting the gradient. RRMS/SPMS cases had a latitudinal gradient 7.2 times greater than PPMS cases ($p < 0.0002$), and females had a gradient three times greater than males ($p < 0.00007$). Multiple regressions analysis indicates that females with RRMS/SPMS are the major drivers of the latitudinal gradient ($p < 1 \times 10^{-7}$).

The finding that the latitudinal gradient is non-uniform with females with RRMS/SPMS being the major drivers indicates that the environmental and/or genetic factor(s) that drive the gradient do not act uniformly on all MS cases. There are two possible explanations for the differential gradients.

If the baseline risk is driven by genetic factors and these factors are influenced by sex, with females being more susceptible, then the baseline genetic risk should not vary with latitude. Therefore the observed gradient indicates that there is either a protective factor operating at lower latitudes or a detrimental factor with higher latitude. If the natural rate of occurrence of MS is that seen at higher latitudes then the protective effect of decreasing latitude exerts a greater influence on females and on the inflammatory forms of MS (RRMS). Conversely the natural incidence may be that seen at lower latitudes and the detrimental factors may influence females and inflammatory forms of MS more with increasing latitude.

There are currently two biologically plausible explanations for the latitudinal gradient: decreased ambient winter UVR and subsequent decreased vitamin D levels, and latitudinal variation in susceptibility to late EBV infection,¹⁸ which have been well discussed elsewhere.^{3-5,28}

Of note, the gender ratio did not alter with latitude in NZ and there is no evidence that the gender ratio has

changed over time. This is in contradistinction to changes noted in Canada.^{26,29} This may reflect the latitudinal differences between the two studies or other environmental or genetic differences between the populations.

The finding of differential gradients of MS prevalence by gender and MS phenotype may open up significant areas of research interest and may assist in the development of therapies and intervention strategies at the population level, aimed at reducing the incidence of MS.

Funding

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Method for identifying eligible individuals for a prevalence survey in the absence of a disease register or population register

(Short title: Prevalence survey method)

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Abstract

Background

Identifying eligible individuals for a prevalence survey is difficult in the absence of a disease register or a national population register.

Aim

To develop a method to identify and invite eligible individuals to participate in a national prevalence survey while maintaining confidentiality and complying with privacy legislation.

Methods

A unique identifier (based on date of birth, sex, and initials) was developed so that database holders could identify eligible individuals, notify us, and invite them on our behalf to participate in a national multiple sclerosis prevalence survey, while maintaining confidentiality and complying with privacy legislation.

Results

Several organisations (including central government, health, and non-government organisations) used the method described to assign unique identifiers to individuals listed on their databases, and to forward invitations and consent forms to them. The use of a unique identifier allowed us to recognise and record all the sources of identification

for each individual. This prevented double-counting or approaching the same individual more than once, and facilitated the use of capture-recapture methods to improve the prevalence estimate. Capture-recapture analysis estimated that the method identified over 96% of eligible individuals in this prevalence survey.

Conclusions

This method was developed and used successfully in a national prevalence survey of multiple sclerosis in New Zealand. The method may be useful for prevalence surveys of other diseases in New Zealand, and for prevalence surveys in other countries with similar privacy legislation and lack of disease registers and population registers.

Key Words

Prevalence

Data Collection

Confidentiality

Epidemiologic Methods

Population

Introduction

The number of people with multiple sclerosis (MS) and the extent of disability experienced by people with MS in New Zealand had been unknown until 2010, when the findings of a national prevalence study were reported.¹ Earlier studies had provided regional prevalence estimates²⁻³ but there had never been a national prevalence study of MS in New Zealand. Accurate prevalence estimates were needed to facilitate the appropriate allocation of resources and planning of services, support, and treatment for people with MS in New Zealand.

This paper describes the method we developed to identify and invite eligible individuals to participate in the national prevalence survey of MS in New Zealand. The purpose of the paper is to describe this method in case it might be useful for prevalence surveys of other diseases in New Zealand or for prevalence surveys in other countries with similar privacy legislation and without disease registers or population registers.

Methods

In countries with national population registers it is possible to identify people with a disease and to estimate the prevalence of that disease using record-linkage between the population register and health services databases. A disease register can also provide an estimate of prevalence provided the register is complete and up-to-date. New Zealand does not have a national population register, and there is no MS disease register. Information about people with MS in New Zealand is held by the Ministry of Health (routinely collected hospital discharge data), in private and public consultant neurologists' records, and by the Multiple Sclerosis Society (databases at local and

national level), but no single organisation holds complete information on all people with MS.

To identify eligible people to participate in the New Zealand MS prevalence survey, we needed information from as many sources as possible to help us identify people with MS. New Zealand privacy legislation meant that the holders of information about people with MS were not permitted to provide us with the names and addresses of people on their databases.^{4,5} Instead we asked the holders of the databases to assign each individual an ID number for the prevalence study. The ID number incorporated each person's date of birth [dd/mm/yyyy], sex [M or F], and the initials of the person's first given name and surname. Thus, the ID number for a woman with MS named Mary-Jane Katherine Brown who was born on 2 June 1965 was 02061965FMB. We asked the holders of the databases to assign ID numbers in this way, and to forward a list of the ID numbers to us. We recorded the ID numbers, and asked the holders of the databases to forward a letter from us or make a telephone call to each individual inviting him/her to take part in a confidential survey about MS (the survey was designed to elicit information about demographic characteristics, place of residence at different ages, and sunlight exposure). Consultant neurologists who assigned ID numbers also completed a neurological assessment form for each ID number notified, to confirm the diagnosis of MS where possible. If the diagnosis of MS could not be confirmed or the person had not been seen by a neurologist within 12 months, they were directly reviewed by a study neurologist to confirm the diagnosis.

Initially we had designed the unique identifier to include ethnic group as well as date of birth, sex and initials. Apart from the Ministry of Health hospital discharge database, other databases did not include this information, or held incomplete information on ethnic group, so the final version of the unique identifier used in the MS prevalence survey included date of birth, sex and initials only. Questions on ethnic group (using the same questions as the New Zealand census) were included in the questionnaire, so this information was obtained from all participants in the survey. No other changes needed to be made to the design of the unique identifier.

The use of ID numbers meant that people with MS could be invited to take part in the prevalence study without their identities being revealed to us. It also allowed us to recognise when an individual was included on more than one database. This meant we could avoid approaching the same person twice. When we received an ID number which had already been forwarded to us from another source, the second or subsequent provider of the ID number was asked not to forward a letter to that individual.

We asked the holders of datasets to identify same-sex twins with MS, since this could create duplicate ID numbers if the twins also had the same initials. If this situation occurred, we planned to assign an adjusted ID number (day of birth plus 1 day) for one of each pair of twins, and record the existence of the twin-pair in our study database. Similarly, in the rare instance of different (non-twin) individuals with identical identifiers, we planned to increase the date of birth by 1 day for one of the individuals, and keep a record of this. Neither of these situations occurred in the MS prevalence survey.

In addition to approaching the holders of databases we advertised the prevalence survey in regional and community newspapers and on local and national radio stations, to raise awareness about the survey and to ask people with MS who had not already been approached about the survey, to contact us directly using a freephone number. People with MS who contacted us themselves, in response to these advertisements, were assigned an ID number by the study coordinator. The ID number was then used for all study records and data collected, including the questionnaire (see ethical considerations below).

Ethical considerations - Each individual identified from one or more of the sources described above was assigned an ID number and then either telephoned or sent a letter by the holder of the database, to explain the study, asking if they would be prepared to take part in the survey and clinical review if needed. An information sheet and informed consent form was included with each letter (or sent to each person who had agreed to provide their contact details by telephone), and each person contacted was asked to provide his/her name and address and return a signed consent form to the investigators in a prepaid envelope if he/she wished to participate. A separate form asked for permission to contact participants about future research projects and for their views on the establishment of a national register for people with MS.

People who did not wish to participate in the survey were asked to return a confidential form stating that they wished to decline (or for people contacted by telephone, to state that they did not wish to take part). In order to maintain confidentiality, this “decline”

form or telephone refusal did not identify the individual, other than by the ID number. If no reply to the initial letter was received within four weeks, and a “decline” form had not been received, we asked the relevant database holder to either forward a follow-up letter or telephone the participant on our behalf. If no reply to the second letter was obtained we asked the database holder to directly contact the person by phone if this was possible and deemed appropriate by the database holder.

Those who gave informed consent to participate in the survey were sent a self-administered questionnaire. They were also asked for permission for their medical records to be assessed by a consultant neurologist (preferably a neurologist they had seen). If an individual had not been seen by a neurologist within 12 months or the diagnosis of definite MS could not be confirmed, they were reviewed by a study neurologist to confirm the diagnosis. The results of the review were recorded and linked to other study data using the unique ID number, so the study neurologists who had made initial notifications from their databases or assessed individuals did not have access to identifying information once the data had been collected, thus maintaining patient confidentiality.

Information linking the names and addresses of study participants with their ID numbers was securely stored in a password protected computer only accessible to the study investigators and kept in a locked office. Participants were given an assurance that no individual with MS would be able to be identified from any presentations, reports, or other publications arising from the research. Approval for the study was obtained from the New Zealand National (Multi-Region) Ethics Committee.

Calculating the prevalence estimate – The point prevalence of MS in New Zealand was estimated by dividing the number of people with clinically definite MS according to the McDonald criteria⁶ on “the prevalence date” of 7 March 2006 (the date of the 2006 New Zealand population census) by the number of people usually resident in New Zealand on that date. The resident population was obtained from Statistics New Zealand. It took more than a year to collect information from and assess people with MS in New Zealand, but only those living with clinically definite MS on the prevalence date were included in the prevalence estimate.

Even the most rigorous prevalence surveys fail to identify all people with MS, so capture-recapture methods have been used in other prevalence surveys of MS.^{7,8} Capture-recapture methods utilise multiple data sources to calculate an estimate of the number of people with MS not identified from an individual data source. This allows a more accurate estimate of prevalence to be made, taking into account missing people.^{9,10} The unique ID number developed for the MS prevalence survey allowed us to identify multiple sources of identification for each individual, so we could use capture-recapture methods to improve our estimate of the prevalence of MS in New Zealand.

Results

We found this method worked very well in practice. Five sources (New Zealand government health statistics, District Health Board databases, consultant neurologists’ databases, MS care providers, and the MS Society databases) used the method described to assign unique identifiers to individuals listed on their databases. ID numbers were

also assigned by the Study Coordinator to individuals who self-notified. The method allowed us to recognise individuals who were listed on more than one database, and to include self-referred individuals by assigning unique identifiers to them. The unique identifier allowed us to recognise and record all the sources of identification for each individual, which facilitated the use of capture-recapture methods to improve the prevalence estimate.

The population of New Zealand at the 2006 census was 4,027,950 and we received 13,803 notifications for 5,901 individuals (including individuals with definite MS, possible MS, not MS, clinically isolated syndrome, and individuals who had died before or were not resident in New Zealand on census day). Of these notifications 2,917 were people with definite MS resident in New Zealand on census day; a prevalence of 72.4 per 100,000 (detailed results including age and sex-standardised prevalence estimates are provided elsewhere).¹ The remaining 2,984 of the 5,901 individuals notified were not located (547 individuals), had died before census date (1,086), were not in New Zealand on the census date (62), had been diagnosed after the census date (24) or did not have definite MS (173 had possible MS, 393 had clinically isolated syndromes, and 699 did not have MS). We received notification from more than one source for 80.6% of individuals in the study. Capture-recapture analysis estimated that the study had identified 96.7% of people with MS.¹

A number of individuals in the study had identical dates of birth and sex, but in each instance the given and surname initials were different, allowing assignment of a unique ID number to each individual. There were no same sex twins with the same initials.

Occasionally a patient was approached more than once because of an incorrect ID number, and invariably they let us know of the error, which meant we could correct it. We did not find any potential duplicates or errors of this nature among non-respondents.

Some incorrect dates of birth were detected; these were due to database error or transcription error by the database holder when assigning ID numbers. In most cases we were able to correct this through cross checking with another source. For researchers using this ID assignment method in future we recommend asking participants to write their date of birth on the questionnaire (we asked for age-group only in the questionnaire, since we thought we would already have the date of birth in the ID number) as this would help to verify the correct date of birth for each participant.

Discussion

This method allowed us to identify individuals with MS for a national prevalence survey, while maintaining confidentiality, complying with privacy legislation, and avoiding double-counting. Identification of all the sources of identification for each individual with MS also allowed us to use capture-recapture methods to obtain an accurate estimate of the prevalence of MS in New Zealand.

The advantages of assigning unique ID numbers for the study were:

- It avoided double-counting, given that some individuals could be identified from more than one source

- It prevented us sending multiple letters to people who were listed on more than one database
- Confidentiality was maintained, so that people who decided not to participate in the survey could not be identified (only those who wished to participate would provide us with their contact details)
- It ensured that those who had already declined to participate did not receive follow-up letters
- It allowed us to determine whether there were any significant age or sex differences between those who took part in the survey and those who declined (this could be determined because the ID numbers incorporated date of birth and sex)
- It facilitated the use of capture-recapture methods to obtain the most accurate estimate of the national prevalence.

The use of unique ID numbers based on date of birth, sex, and initials is appropriate for a prevalence survey, provided the prevalence of the disease or the number of individuals identified is not too high. If the prevalence of a disease, or the number of individuals identified is high it is likely that problems with duplicate ID numbers will occur (since in this situation several individuals with the disease could be expected to have the same sex, date of birth, and initials).

In the case of a small study, concerns that the unique identifier described here would make it possible to identify individuals (through knowing their initials, sex, and date of birth) could be addressed by encrypting the unique identifier or assigning a study ID

number to each unique identifier. The encrypted or study ID number would have no identifiable components such as initials or date of birth, and this would provide a further level of confidentiality.

A similar but not identical method of assigning unique ID numbers has been used in New Zealand and other countries to maintain confidentiality in the routine notification of cases of AIDS¹¹, but to our knowledge this method has not been used before in prevalence surveys. We believe this method could be useful for researchers wishing to undertake prevalence surveys of other diseases in New Zealand, and for researchers in other countries with similar privacy legislation and lack of disease registers and national population registers.

Acknowledgements

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Author contributions

Ann Richardson developed the method for identifying eligible individuals used in the prevalence survey and wrote the first draft of the manuscript.

Glynnis Clarke was the study coordinator of the prevalence survey, and implemented and refined the method.

Clive Sabel contributed to the design of the prevalence survey and carried out the geospatial analysis of the MS prevalence survey.

John Pearson carried out the capture-recapture analysis of the MS prevalence survey.

Deborah Mason was a study neurologist and contributed to the design of the prevalence survey.

Bruce Taylor was a study neurologist and the principal investigator for the prevalence survey.

All the authors contributed to the preparation of this manuscript.

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Figure 1

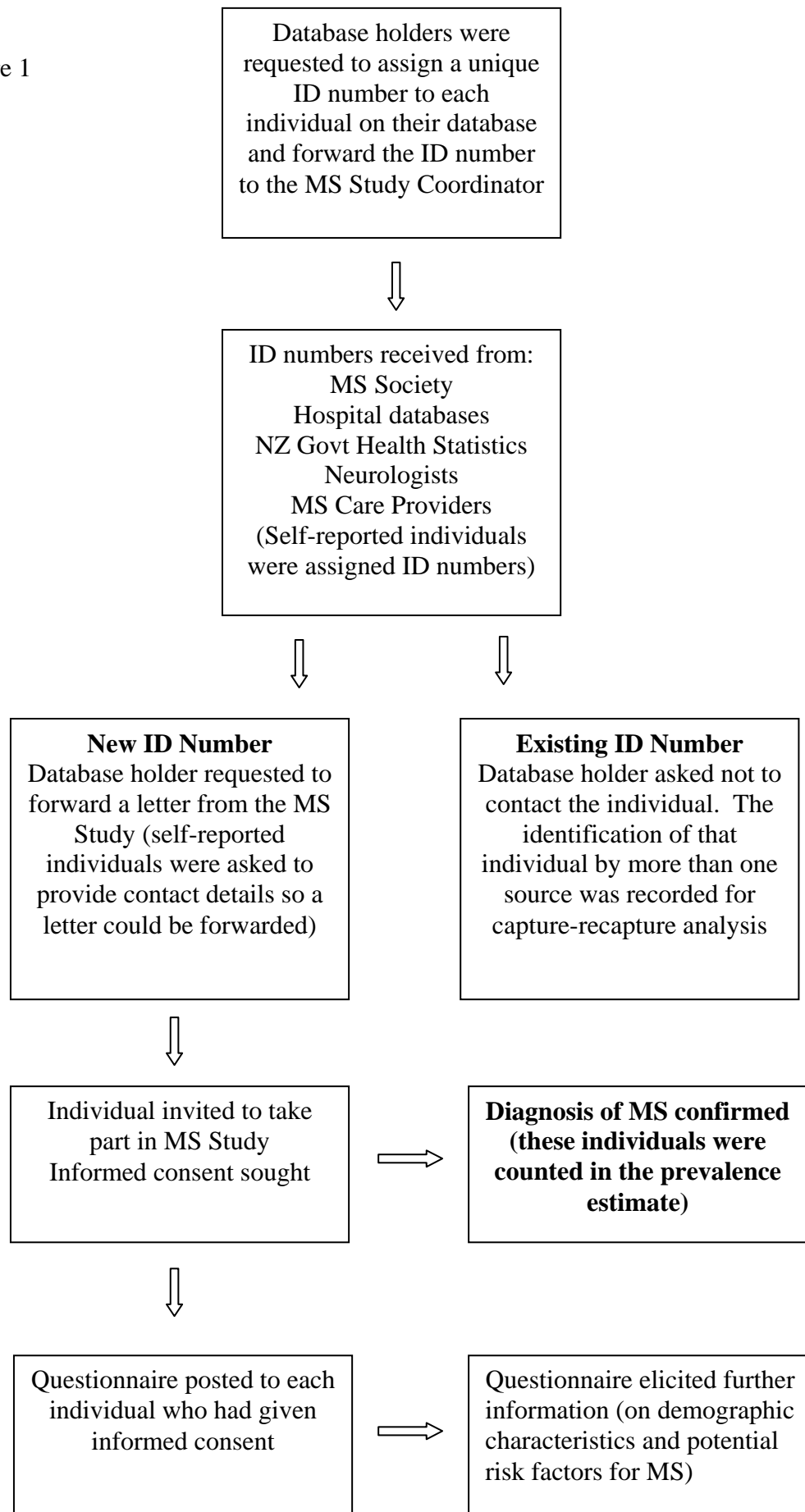


Figure 2

