On the geoepidemiology of multiple sclerosis and environmental & infectious determinants of its clinical course

By

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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Declaration of originality

This thesis contains no material which has been accepted for a degree or diploma by the University of Tasmania, nor any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief, no material previously published or written by another person except where due acknowledgement is made in the text of the thesis.

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______________________________  ________________________________
Steve Simpson, Jr.               Date
Statement of Co-authorship

This thesis includes papers for which Steve Simpson, Jr. (SSJ) is not sole author. SSJ took the lead in this research, developing and implementing the analyses included herein under the supervision of Leigh Blizzard (LB), writing manuscripts, and in the case of the meta-analysis of multiple sclerosis prevalence, designing and implementing the research project. In this process, however, he was assisted by co-authors to varying extent. Following then, the contributions of each co-author are detailed for each respective project.

1. The paper reported in Chapter 2:


- SSJ contributed to the data collection for the 2009 prevalence data along with Bruce Taylor (BT), management of the 2009 prevalence data and consolidation with the 2001 prevalence data, calculation of the 2001-2009 incidence and mortality rates; along with LB, statistical analysis of temporal trends in prevalence, incidence and mortality was done by SSJ under supervision by LB. SSJ composed drafts of the manuscript and coordinated revision.

- Fotini Pittas (FP) was involved in the development and acquisition of funding for both the 2001 and 2009 prevalence studies along with BT and Ingrid van der Mei (IvM); FP contributed to the data collection for the 2001 prevalence data along with BT; FP was involved in the conception of some of the analyses used in the study and contributed to the critical revision of the manuscript.

- LB provided guidance and supervision for all statistical analyses undertaken in this study, and was involved in the initial drafting and critical revision of the manuscript.
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2. The paper reported in Chapter 3:


- SSJ conceived the project and collected all prevalence data required, from published manuscripts, conference proceedings and/or direct correspondence with study authors. In concert with and under guidance of LB, Petr Otahal (PO) and BT, SSJ developed and implemented all statistical analyses. SSJ composed the drafts of the manuscript and coordinated revision. SSJ consolidated the data and composed the table in Appendix 4A. SSJ consolidated the data and composed the initial draft and critical revision of Appendix 4B. SSJ composed the initial draft and critical revision of Appendix 4C. SSJ consolidated the data and composed the table in Appendix 4D.

- LB provided guidance and supervision for all statistical analyses undertaken in this study, and was involved in the initial drafting and critical revision of the manuscript.
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- PO worked in concert with SSJ, LB and BT to develop statistical analyses undertaken in this study, and was involved in critical revision of the manuscript.

- IvM was involved in the initial drafting and critical revision of the manuscript.

- BT worked in concert with SSJ, PO, and PO to develop analyses undertaken in this study, and was involved in the initial drafting and critical revision of the manuscript.

3. The paper reported in Chapter 4:


- SSJ undertook the literature review for the background and immunological actions of vitamin D and its metabolites, epidemiology of personal UV exposure, vitamin D intake and circulating levels of vitamin D and their relationship with multiple sclerosis risk and clinical course, and the role of vitamin D in manifesting or modulating other causal pathways in multiple sclerosis risk and clinical course. SSJ composed the initial draft of these sections and coordinated critical revision of the manuscript.

- Kate Greenhill (KG) undertook the literature review for the background and intracellular and genetic actions of 1,25-dihydroxyvitamin D. KG composed the initial draft of these sections and contributed to the critical revision of the manuscript.

- IvM contributed to the critical revision of the manuscript.

- Jim Stankovich (JS) provided guidance for KG and contributed to the critical revision of the manuscript.

- Jac Charlesworth (JC) provided guidance for KG and contributed to the critical revision of the manuscript.

- BT contributed to the critical revision of the manuscript.
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4. The paper reported in Chapter 5:


- SSJ was involved in the development and implementation of statistical analyses undertaken, under supervision by LB. SSJ composed the drafts of the manuscript and coordinated revision.

- BT was involved in the development and acquisition of funding for the MS Longitudinal Study from which the data for this analysis was drawn, along with A-LP, FP, Terence Dwyer (TD), Peter Gies (PG), and IvM; BT was involved in the data collection for the MS Longitudinal Study, along with FP, PG, and IvM. BT was involved in the initial drafting and critical revision of the manuscript.

- LB provided guidance and supervision for all statistical analyses undertaken in this study, and was involved in the initial drafting and critical revision of the manuscript.

- A-LP was involved in the development and acquisition of funding for the MS Longitudinal Study, along with BT, FP, TD, PG, and IvM; A-LP contributed to the critical revision of the manuscript.

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- Helen Tremlett (HT) was involved in the conception and implementation of the analyses used and contributed to the critical revision of the manuscript.
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5. The paper reported in Chapter 6


- SSJ was involved in the development and implementation of statistical analyses undertaken, under supervision by LB. SSJ composed the drafts of the manuscript and coordinated revision.

- NS initiated project and was involved in initial drafting and critical revision of the manuscript.

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- Darryl Eyles (DE) was involved in measurement of 1,25-dihydroxyvitamin D and was involved in critical revision of the manuscript.

- Pauline Ko (PO) was involved in measurement of 1,25-dihydroxyvitamin D and was involved in critical revision of the manuscript.

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- LB provided guidance and supervision for all statistical analyses undertaken in this study, and was involved in the initial drafting and critical revision of the manuscript.

- TD was involved in the development and acquisition of funding for the MS Longitudinal Study, along with BT, A-LP, FP, and IvM. TD contributed to the critical revision of the manuscript.

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6. The paper reported in Chapter 7:

Statement of Co-authorship

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- BT was involved in the development and acquisition of funding for the MS Longitudinal Study from which the data for this analysis was drawn, along with A-LP, FP, TD, and IvM; BT was involved in the data collection for the MS Longitudinal Study, along with Dominic Dwyer (DD), Janette Taylor (JT), FP and IvM. BT was involved in the initial drafting and critical revision of the manuscript.

- DD was involved in the data collection for the MS Longitudinal Study, specifically the measurement of anti-human herpesvirus IgG titres, along with JT. DD was involved in the critical revision of the manuscript.

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7. The paper reported in Chapter 8:

Simpson, Jr. SL, Taylor B, Dwyer D, Taylor J, Blizzard L, Ponsonby A-L, Pittas F, Dwyer T, van der Mei, I. “Serological reactivation of human herpesvirus 6 is not associated with clinical outcomes in multiple sclerosis.” (unsubmitted manuscript)

- SSJ was involved in the development and implementation of statistical analyses undertaken, under supervision by LB. SSJ composed the drafts of the manuscript and coordinated revision.

- BT was involved in the development and acquisition of funding for the MS Longitudinal Study from which the data for this analysis was drawn, along with A-LP, FP, TD, and IvM; BT was involved in the data collection for the MS Longitudinal Study, along with Dominic Dwyer (DD), Janette Taylor (JT), FP and IvM. BT was involved in the initial drafting and critical revision of the manuscript.

- DD was involved in the data collection for the MS Longitudinal Study, specifically the measurement of anti-human herpesvirus IgG titres, along with JT. DD was involved in the critical revision of the manuscript.
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- JT was involved in the data collection for the MS Longitudinal Study, specifically the measurement of anti-human herpesvirus IgG titres, along with DD. JT was involved in the critical revision of the manuscript.

- LB provided guidance and supervision for all statistical analyses undertaken in this study, and was involved in the initial drafting and critical revision of the manuscript.

- A-LP was involved in the development and acquisition of funding for the MS Longitudinal Study, along with BT, FP, TD, and IvM; A-LP contributed to the critical revision of the manuscript.

- FP was involved in the development and acquisition of funding for the MS Longitudinal Study, along with BT, A-LP, TD, and IvM. FP was involved in the data collection for the MS Longitudinal Study, along with BT, DD, JT, and IvM. FP contributed to the critical revision of the manuscript.

- TD was involved in the development and acquisition of funding for the MS Longitudinal Study, along with BT, A-LP, FP, and IvM. TD contributed to the critical revision of the manuscript.

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Abstract

Multiple sclerosis (MS) is a chronic, demyelinating condition of the central nervous system, manifesting in alteration or loss of motor, sensory and cognitive function. The causes of MS are unclear but include genetic and environmental factors. This thesis presents several epidemiologic analyses, examining MS geoepidemiology, locally and globally, as well as evaluating key environmental and infectious determinants of clinical course.

The first analysis chapter examines MS epidemiology in the Greater Hobart region of Tasmania over the interval 1951 to 2009. This analysis found a significant increase in prevalence, this mediated by a significantly decreased mortality and increased longevity, as well as evidence of an increasing female/male sex ratio.

Next is a meta-analysis of MS prevalence and its association with latitude. This work, utilising the largest collection of MS prevalence studies, found a significant positive association between MS prevalence and latitude. This provides evidence in favour of the latitudinal gradient hypothesis and for environmental factors underlying the gradient, most particularly personal ultraviolet radiation (UVR) exposure and vitamin D.

The association between serum 25-hydroxyvitamin D (25(OH)D) and relapse was examined in a prospective cohort with clinically-definite MS followed for 2.3 years. This analysis found a significant inverse association between higher levels of 25(OH)D and subsequent hazard of relapse. This study provides key evidence that is needed to justify conducting randomised clinical trials of vitamin D supplementation in reducing relapse frequency in MS.

In this MS cohort, it was also found that persons on interferon-β (IFN-β) therapy had significantly higher 25(OH)D levels and that the association between personal sun exposure and 25(OH)D was stronger compared to those not on IFN-β. Importantly, the above association between 25(OH)D and relapse was only observed for those on IFN-β therapy.
Abstract

Last is an examination of the role of antibodies to Human Herpesvirus 6 (HHV-6) and Epstein-Barr virus (EBV) in MS clinical course. This analysis found a significant positive association between anti-HHV-6 IgG and relapse. This effect persisted on adjustment for the anti-EBV IgGs, indicating the effect was specific for HHV-6 antigen, or host antigen resembling it. There was no evidence of frequent serological HHV-6 reactivation, suggesting that the observed association between anti-HHV-6 IgG and relapse was not being mediated by serologically-detectable peripheral reactivation of HHV-6. No associations were observed between anti-HHV-6 and anti-EBV IgGs and progression in clinical disability.

This thesis presents a range of studies which add significantly to the literature on MS geoepidemiology, as well as the associations of environmental and infectious factors on MS clinical course. This work will be useful in the scientific community; both for hypothesis generation and providing strong evidence in support of existing hypotheses, and hopefully be of benefit to people with this debilitating disease.
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Conference presentations arising from work in this thesis

Oral presentations


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Poster presentations

“Increasing levels of vitamin D are associated with decreased hazard of relapse in multiple sclerosis”, Multiple Sclerosis Research Association Progress in MS Research Scientific Conference, Sydney, 14-17 Oct 2009.
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<tr>
<td>μg</td>
<td>Micrograms</td>
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<tr>
<td>1,25(OH)_2D</td>
<td>1,25-dihydroxyvitamin D</td>
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<td>25(OH)D</td>
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<td>95% CI</td>
<td>95 percent Confidence Interval</td>
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<td>ABS</td>
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<td>AHR</td>
<td>Adjusted Hazard Ratio</td>
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<td>Antigen Presenting Cell</td>
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<td>Cerebrospinal fluid</td>
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<td>Dissemination in space</td>
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<td>Helper T-lymphocyte class 17</td>
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<td>T_{reg}</td>
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<tr>
<td>UVR</td>
<td>Ultraviolet radiation</td>
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<td>Epstein-Barr Virus Viral Capsid Antigen</td>
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<td>VDBP</td>
<td>Vitamin D binding protein</td>
</tr>
<tr>
<td>VDR</td>
<td>Vitamin D receptor</td>
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<td>VDRE</td>
<td>Vitamin D receptor element</td>
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