Sun Exposure during Childhood and the Etiology of Multiple Sclerosis:
Measurement and Analysis

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ABSTRACT

Introduction: The ultraviolet radiation (UVR) emitted by the sun has both beneficial and detrimental effects on human health. Low levels of sun exposure have been suggested to play a role in susceptibility to multiple sclerosis (MS). MS is a chronic, immune-mediated, degenerative disease of the brain and spinal cord. Sunlight is an interesting hypothesis given the many interactions between UVR and the immune system. To date, most epidemiological research has been focused on adults with MS, as pediatric-onset MS (onset≤18 years of age) has only recently been recognized and studied. The overall goal of this research is to advance our understanding of the relationship between sun exposure and the risk of MS. The research presented is divided into two methodological themes: (1) *measurement* and (2) *analysis*.

Theme 1: The research on *measurement* of sun exposure focused on the development of the Pediatric MS Tool-Kit (Tool-Kit). The Tool-Kit is a measurement framework that will facilitate questionnaire design and data harmonization of pediatric MS etiological studies. I first designed and carried out a systematic review of measurement property studies that evaluated self-report questionnaires to assess children's sun related behaviours. I then performed an international Delphi study that I used to define a minimal set of core variables to assess sun exposure in pediatric MS case-control studies. Studies included in the systematic review assessed sun protection (71%), sun exposure (34%), and host characteristics (31%; e.g. sun sensitivity), and focused on current (45%) or usual (45%) behaviours. I did not identify a validated questionnaire that was designed for a case-control study. Six core variables that measure sun exposure behaviours in children are included in Tool-Kit, and can be accessed at www.maelstrom-research.org/mica/network/tool-kit.

Theme 2: The research on *analysis* of sun exposure focused on using novel analytical strategies to further elucidate the etiological model for MS. I used data collected in the Environmental Risk Factors in MS (EnvIMS) Study, a frequency matched case-control study that included adult MS cases and population-based controls from Canada, Italy and Norway (2251 cases and 4028 controls). Sun exposure behaviours, for 5-year age intervals, from birth to age 15 years were examined. I compared two life course epidemiology conceptual models (i.e. the critical period and accumulation models), to select the most etiologically relevant model. I also characterized

latent sun exposure behaviour groups and compared risk across groups. The accumulation model was selected as the best model, and demonstrated a 47% increased risk of MS, comparing low summer sun exposure from birth to age 15, to high levels during the same period. Relative to sun-seekers (i.e. high exposure in summer and in winter, and rare use of sun protection), sun-avoiders (i.e. low exposure in summer and winter, and frequent use of sun protection) had a 76% greater risk. Interestingly, sun-avoiders had a 40% higher risk, when compared to a sun exposure behaviour group that had similar sun exposure levels, but that rarely used sun protection.

Conclusions: Sun exposure is a modifiable risk factor that we can intervene on that may reduce burden of adult MS at the population level; and future studies, using the Tool-Kit variables, will be able to determine if sun exposure is also associated with risk of pediatric-onset MS. Targeted public health messages, which emphasize the benefits of sun exposure and how to maximize these benefits, while maintaining current recommendations aimed at reducing skin cancer, need to be tested.

RESUMÉ

Introduction : Les rayons ultraviolets (UV) émis par le soleil ont des effets bénéfiques, mais aussi néfastes sur la santé humaine. Il a été suggéré que les faibles niveaux d'exposition au soleil jouent un rôle dans la susceptibilité à la sclérose en plaques (SP). La SP est une maladie chronique et dégénérative, attribuable au système immunitaire affectant le cerveau et la moelle épinière. La lumière du soleil est une hypothèse intéressante compte tenu des nombreuses interactions entre les rayons UV et le système immunitaire. À ce jour, la plupart des recherches épidémiologiques ont porté sur les adultes atteints de SP, car ce n'est que récemment que l'apparition de la SP chez les enfants (à ≤ 18 ans) a été reconnue et étudiée. L'objectif général de cette recherche est de faire progresser notre compréhension de la relation entre l'exposition au soleil et le risque de développer la SP. La recherche présentée se divise en deux thèmes méthodologiques : (1) *la mesure* et (2) *l'analyse*.

Thème 1 : Les recherches sur la *mesure* de l'exposition au soleil ont porté sur le développement du Tool-Kit pour la SP pédiatrique (Tool-Kit). Ce Tool-Kit offre un cadre de mesure qui facilitera la conception de questionnaires et l'harmonisation des données issues d'études étiologiques de la SP pédiatrique. J'ai d'abord conçu et réalisé une revue systématique d'études portant sur les propriétés de mesures qui ont examiné les questionnaires d'auto-évaluation pour évaluer les comportements liés au soleil chez les enfants. J'ai ensuite effectué une étude internationale Delphi que j'ai utilisée pour définir un ensemble minimal de variables de base pour évaluer l'exposition au soleil dans les études cas-témoins sur la SP pédiatrique. Les études incluses dans la revue systématique ont évalué la protection contre le soleil (71 %), l'exposition au soleil (34 %) et les caractéristiques de l'hôte (31 %, telle que la sensibilité au soleil) et se sont concentrées sur les comportements actuels (45 %) ou habituels (45 %). Je n'ai pas trouvé de questionnaire validé conçu pour une étude cas-témoins. Six variables de base mesurant les comportements d'exposition au soleil chez les enfants ont été retenues pour le Tool-Kit et il est possible de les consulter au www.maelstrom-research.org/mica/network/tool-kit.

Thème 2 : Le volet d'*analyse* de l'exposition au soleil a porté sur l'utilisation de nouvelles stratégies d'analyse pour mieux comprendre le modèle étiologique de la SP. J'ai utilisé les

données recueillies dans une étude sur les facteurs de risque environnementaux de la SP (EnvIMS). Cette étude cas-témoins appariée en fréquence comprenait des cas d'adultes atteints de SP et des témoins représentatifs provenant du Canada, de l'Italie et de la Norvège (2251 cas et 4028 contrôles). Les comportements d'exposition au soleil de la naissance à l'âge de 15 ans ont été examinés par intervalle de 5 ans. J'ai comparé deux modèles conceptuels d'épidémiologie du parcours de vie (le modèle de période critique et le modèle d'accumulation) pour sélectionner le modèle le plus pertinent sur le plan étiologique. J'ai également décrit les groupes latents associés au comportement d'exposition au soleil et j'ai comparé le risque entre ces groupes. Le modèle d'accumulation a été sélectionné comme le meilleur modèle. Ce modèle démontre une augmentation de 47 % du risque de SP en comparant la faible exposition au soleil d'été de la naissance à l'âge de 15 ans à des niveaux élevés d'exposition pendant la même période. Par rapport aux amateurs de soleil (ceux qui ont une exposition élevée en été et en hiver, et qui utilisent rarement une protection solaire), les personnes qui évitent le soleil (celles qui ont une faible exposition en été et en hiver et qui utilisent fréquemment une protection solaire) ont un risque plus élevé de 76 %. Il est également intéressant de constater que les personnes qui fuient le soleil ont un risque plus élevé de 40 % comparativement à un groupe qui avait des niveaux d'exposition au soleil similaires, mais qui utilisait rarement une protection solaire.

Conclusions : L'exposition au soleil est un facteur de risque modifiable sur lequel nous pouvons intervenir pour réduire le fardeau de la SP chez les adultes au niveau de la population. En utilisant les variables du Tool-Kit, les études seront dorénavant en mesure de déterminer si l'exposition au soleil est également associée à un risque de SP pédiatrique. Il faudra développer et évaluer des campagnes de communication en santé publique et éducation à la santé qui mettent l'accent sur les avantages de l'exposition au soleil et la façon de maximiser ces avantages, tout en conservant les recommandations actuelles visant à réduire les taux de cancer de la peau.

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The research that is presented in Manuscript 1 and Manuscript 2 was funded by an operating grant that I prepared and submitted to the US National MS Society (NMSS Grant # 5986412) and an International Meeting Grant that I prepared and submitted to the MS International Federation (MSIF). The policies of these granting agencies allowed me to be listed as the Co-Principal Investigator on the NMSS grant, and the Principal Investigator on the MSIF grant, I was primarily responsible for managing the research outlined in grant.

STATEMENT OF ORIGINALITY

The research presented in this thesis makes several significant contributions towards advancing our understanding of the link between sun exposure and the risk of MS, and specifically with regard to *measurement* and *analysis* of sun exposure data. While the research examines pediatric and adult MS separately, the findings of this thesis are interlinked and thus apply to MS in general.

My research interests are in disease etiology, and when I became involved in pediatric MS research, I was quickly fascinated by the epidemiology of MS. In my previous research I had first-hand experience with the limitations of using measurement tools with poor measurement properties. One example includes the analyses I conducted for my MSc thesis. The exposure measurement tool was a very poor measure, which given my naiveté I had not appreciated at the start of my graduate studies. Realizing too far into my MSc, I was stuck using the data that had been collected, and left to justify my results based on this limitation.

The design of good measurement tools is not easy, and requires a particular skill set. Given that I had developed this skill set through my training, and my research experiences, I wanted to make this contribution to the field of pediatric MS research. This is the reason I developed the Pediatric MS Tool-Kit. The timing is ideal, given that not much research has been performed to date. The Tool-Kit has the potential to shape research in the field of pediatric MS, and will keep a focus on the importance of good exposure measurement in pediatric MS etiological research.

A natural consequence of proposing a measurement framework for a research area is that the data collected will be similar, thus enhancing the potential to combine data for pooled analyses. For rare diseases this presents an incredible opportunity to be able to have enough statistical power in an analysis to be confident in the result obtained. The Pediatric MS Tool-Kit has the potential to serve as the cornerstone for pediatric MS etiological research, and to dramatically enrich our understanding of MS etiology in general, given the methodological advantages that will be gained from investigating etiology in pediatric populations, as compared to adults.

I am also very interested in statistics and the use of statistics with epidemiology to inform our understanding of disease etiology. Based on questions I had when initially reading the literature on sun exposure and MS risk, I developed a novel analytical strategy to investigate and

further elucidate the etiological model of MS. My research examined childhood as the etiologically relevant period. The modelling approaches I used improved model specification, as models that included accumulation of exposure over childhood had better model fit criteria than critical period models. Two previous studies had alluded to the fact that accumulation may be a better hypothesis for the role that sun exposure plays in determining MS risk. My research was the first to use statistical methods to formally compare the ability of these two models to predict MS risk. My research findings strongly advocate that the accumulation model be used in future analyses that examine sun exposure and MS risk, including analyses performed using data from pediatric MS studies.

My research also highlights a high risk sub-group that public health should target in an attempt to reduce the burden of MS. My research suggests that chronically low sun exposure levels appear to be linked to MS risk. While this sub-group represents a small proportion of the population; the risk of MS in this group was increased by 76%. Childhood (≤15 years) is a time that parents have more control over their children's sun related behaviours, relative to adolescence, so this may be the ideal opportunity to teach parents how to maximize benefits, while minimizing the harms; and these healthy behaviours may be passed on to the next generation.

Overall this thesis research contributes to advancing knowledge of the association between sun exposure and MS risk across the life span. While I received guidance throughout the process of conducting this research from my supervisor, committee members and collaborators, I was the lead on the research presented in this thesis and take full responsibility for its conception, execution and presentation.

CONTRIBUTION OF AUTHORS

The research presented in this manuscript-based thesis includes three manuscripts that each represent original scholarship and distinct contributions to knowledge, and will be submitted for publication to peer-reviewed journals, after I defend my PhD thesis. While I obtained substantial input from my supervisor, committee members, and collaborators, I was principally responsible for conceptualizing and carrying out the research presented in each manuscript.

For the research related to pediatric MS, I conceived the Pediatric MS Tool-Kit (Tool-Kit). I designed the methodology to develop the Tool-Kit, which required me to apply for operating grant funding, and thus I assembled a team of seven researchers to serve as co-applicants. The research team included my supervisor, Dr. Christina Wolfson; my committee members, Drs. Maura Pugliatti and Isabel Fortier; as well as three active pediatric MS researchers, Drs. Brenda Banwell, Amit Bar-Or and Heather Hanwell, with whom I had worked with prior to starting my PhD studies. I wrote and submitted five operating grant applications: two to the MS Society of Canada, two to the Canadian Institutes of Health Research, and one to the US National MS Society (NMSS) between 2011 and 2012; and in March 2013 was awarded 3-years of funding from the NMSS. I was Co- Principal Investigator and primarily responsible for the research and managed all administrative aspects of the grant including hiring, annual progress reports and ethics submissions.

The first two objectives of this thesis research were also the objectives of the operating grant; while the research presented in this thesis focuses on sun exposure as part of the grant, I completed similar research for environmental tobacco smoke (ETS) and vitamin D intake (VDI). I designed and carried out a systematic review, which included writing the protocol, developing and running the search strategy, screening abstracts, reviewing full-texts for inclusion, data extraction, quality assessment, summarizing and interpreting the findings, and writing the manuscript presented chapter 4 (Manuscript 1). The operating grant funding allowed me to hire two research assistants: Dr. Catherine Tansey, who served as the second reviewer for the sun exposure and ETS systematic reviews; as well as Paul K Schneider, MSc., who served as the second reviewer for the VDI review. I also established a formal connection with the International Pediatric MS Study group, and designed and carried out a Delphi study to obtain expert input to develop the Tool-Kit. I invited an additional six

collaborators to participate in the Delphi study including three pediatric neurologists active in pediatric MS research, Drs. Ming Lim, Rinze Neuteboom, and Evangeline Wassmer, and three content experts, Drs. David L. O'Riordan (sun exposure), Jörg E. Matt (ETS), and Bryna Shatenstein (VDI). I planned and organized three research meeting (January 2014, November 2014 and November 2015). I also prepared the final Tool-Kit proposal for online presentation. I wrote the manuscript presented in chapter 5 (Manuscript 2). I also presented one oral and two poster presentations at international scientific conferences and two poster presentations at local student symposiums, on the research presented in Manuscript 1 and 2.

For the research related to adult MS I used data collected in the Environmental Risk Factors in MS (EnvIMS) Study. In addition to my supervisor, Dr. Christina Wolfson, Drs. Kjell-Morten Myhr, Maura Pugliatti and Trond Riise are the Principal Investigators of the EnvIMS study. I decided to focus on data that were related to sun exposure. I conceptualized my research questions and developed the analytical plan. I sought input from Dr. Antonio Ciampi in developing the fourth objective of this thesis, which involved the use of latent class analysis. I cleaned the data, ran all analyses and wrote the manuscript presented in chapter 6 (Manuscript 3). I also presented this research as a poster presentation at two international scientific conferences and two poster presentations at two local student symposiums.

The specific contributions of the authors are detailed below.

Ph.D. thesis (excluding Manuscript 1, Manuscript 2, and Manuscript 3)

Sandra Magalhaes: Conception, design, and analysis and interpretation of data. Drafting and revising the thesis.

Christina Wolfson: Revision of the thesis.

Manuscript 1: Sun Related Behaviours in Children: A Systematic Review of the Measurement Properties of Self-Report Questionnaires

Sandra Magalhaes: Conception, study design, and analysis and interpretation of data; and drafting the article and revising it critically for important intellectual content.

Catherine Tansey: Study design, data extraction and interpretation of data; and revising the article critically for important intellectual content.

Brenda Banwell, Amit Bar-Or, Isabel Fortier, Heather L. Hanwell, and Maura Pugliatti: Study design; and revising the article critically for important intellectual content.
Christina Wolfson: Study design, and analysis and interpretation of data; and revising the article critically for important intellectual content.

Manuscript 2: A Framework for Measurement and Harmonization of Pediatric Multiple Sclerosis Etiologic Research Studies: The Pediatric MS Tool-Kit

Sandra Magalhaes: Conception, study design, and analysis and interpretation of data; and drafting the article and revising it critically for important intellectual content.
Brenda Banwell, Amit Bar-Or, Isabel Fortier, Heather E. Hanwell, Ming Lim, Georg E. Matt, Rinze Neuteboom, David L. O'Riordan, Maura Pugliatti, Bryna Shatenstein, and Evangeline Wassmer: Study design, and analysis and interpretation of data; and revising the article critically for important intellectual content.
Paul K. Schneider, Catherine Tansey: Second reviewers for the measurement property reviews. Participated and helped in organizing the Delphi study meetings.
Christina Wolfson: Conception, study design, and analysis and interpretation of data; and drafting the article and revising it critically for important intellectual content.

Manuscript 3: Shedding Light on the Link between Early Life Sun Exposure and Risk of Multiple Sclerosis: The EnvIMS Study

Sandra Magalhaes: Conception, study design, and analysis and interpretation of data; and drafting the article and revising it critically for important intellectual content.
Maura Pugliatti, Trond Riise, Kjell-Morten Myhr: Conception and study design; and revising the article critically for important intellectual content.
Antonio Ciampi: Study design and interpretation of data; and revising the article critically for important intellectual content.
Christina Wolfson: Conception, study design, and interpretation of data; and revising the article critically for important intellectual content.

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CHAPTER 1: INTRODUCTION

1.1 Background

Multiple sclerosis (MS) is a chronic autoimmune disease affecting the brain and spinal cord, and as a result of the disease process people living with MS can have significant physical and cognitive disabilities. While MS can be defined as a rare disease (i.e. <10% of the population), MS prevalence varies globally and is suggested to be highest in Canada, Italy and Norway (e.g. >200 per 100,000).[1-3] MS is most commonly diagnosed in adults; however, MS onset in the pediatric age range has recently been recognized and studied. Pediatric-onset MS, which is defined as onset prior to age 18 years, represents less than 10% of those with MS.[4]

MS etiology is suggested to involve the complex interplay between genetic susceptibility and environmental/lifestyle factors.[5] MS susceptibility is suggested to be determined in childhood and early adolescence. Several factors have been implicated in MS etiology, though most MS etiological research has been conducted in adult populations. Evaluating risk factors in a pediatric population has several advantages because they are younger and thus: (i) provide a shorter time frame during which to identify risk factors; and (ii) are closer in time to pertinent exposures consequently have less exposure misclassification, as the exposures occurred more recently in time and are easier to recall. However, studies that include pediatric MS cases are likely to be limited by small sample sizes and consequently low statistical power.

Sun exposure is one of the factors that have been implicated in risk of adult MS. MS prevalence has been shown to be positively correlated with latitude,[6, 7] and inversely correlated with ultraviolet radiation (UVR).[8-10] Several case-control studies have reported an association at the individual level, and suggest that individuals who spend less time outdoors have an increased risk of MS.[11-21] No studies were identified that examined the association between sun exposure and risk of pediatric-onset MS.

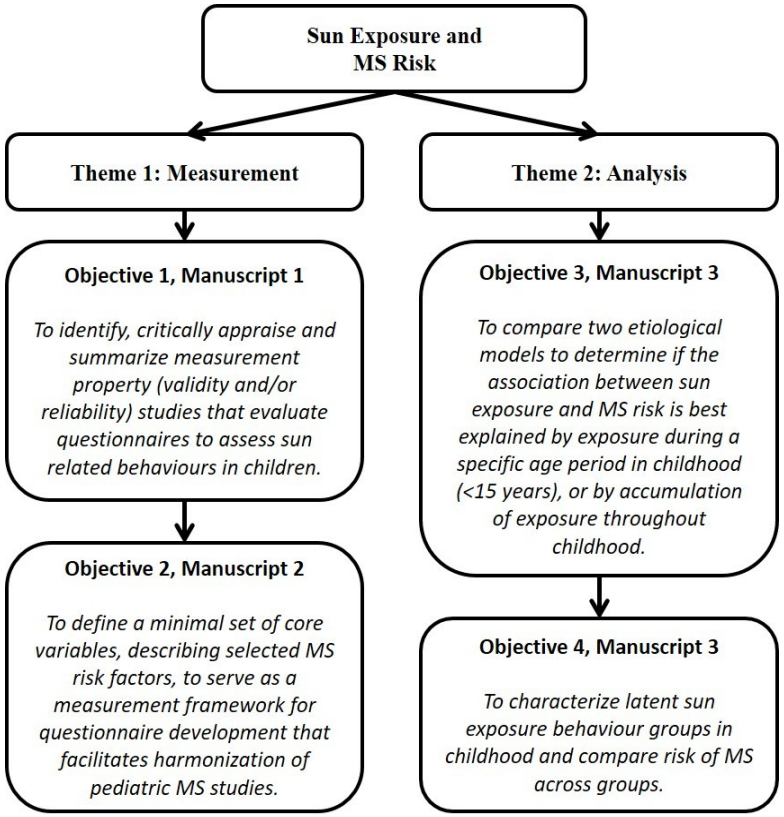
Sun exposure is an attractive hypothesis as the sun is directly responsible for several biological processes including: vitamin D synthesis, melatonin regulation, immune system function, and endorphin production. [22, 23] Due to its varied effects, both too much sun exposure and too little sun exposure can have negative effects on health. A World Health Organization report that examines the global burden of disease from solar UVR suggests that 1.5 million disability adjusted life years (DALYs) were lost in 2000 due to excessive UVR exposure, but

that the number lost if UVR exposure were below levels required to maintain vitamin D levels is 3.3 billion DALYs.[24] The link between sun exposure and the risk of MS is the focus of the research presented, and the overall goal is to advance our understanding of the etiological model of MS.

1.2 Themes and Objectives

The research is divided into two themes: (1) *measurement* and (2) *analysis*. Both themes are focused on sun exposure, but theme 1 relates to pediatric MS and theme 2 to adult MS. The first theme focuses on the measurement of sun exposure, with particular interest in measurement in the context of pediatric MS case-control studies. The second theme focuses on analysis of sun exposure, and uses two novel analytical approaches to examine the association with risk of adult MS. I developed this research around four objectives; two objectives relate to the first theme and two objectives relate to the second theme. The flow diagram below outlines the two themes, four objectives and three manuscripts that encompass the research presented. (Figure 1.1)

Figure 1.1 Flow diagram outlining the organization of the research presented: themes, objectives and manuscripts



1.2.1 Objective 1

The first objective was completed to develop a knowledge base for the research completed for objective 2. I completed this step to identify, critically appraise and summarize studies that examine the measurement properties (validity/reliability) of questionnaires to assess sun related behaviours in children, such as sun exposure, sun protection and host characteristics (e.g. sun sensitivity). Appraising the measurement properties of available questionnaires is a valuable methodological step in designing a new study; either to identify a validated questionnaire that can be borrowed and tested for use, or to develop and test a new questionnaire that builds on the available measurement property literature for the construct of interest. I wanted to determine if there were any self-report questionnaires that had been validated for use in pediatric case-control studies, and if no such questionnaires were available, I wanted to use the evidence on the measurement properties of measuring sun related behaviours to inform on the development of a measurement framework that can be used to develop questionnaires for pediatric MS case-control studies (Objective 2).

1.2.2 Objective 2

The second objective was to develop a measurement framework, that I named the Pediatric MS Tool-Kit. The Tool-Kit includes a rigorously defined set of exposure variables for three priority risk factors (i.e. sun exposure, environmental tobacco smoke and vitamin D intake). I used the evidence obtained in objective 1 to develop an international Delphi study to obtain expert input in defining a set of core variables for each risk factor. The Tool-Kit can be used by pediatric MS researchers to design study-specific questionnaires. The short-term goals of the Tool-Kit are to improve exposure measurement in individual pediatric MS studies, and to enhance the comparability of study results across studies. The long-term goal is to facilitate harmonization of pediatric MS studies in the future.

1.2.3 Objective 3

The third objective focuses on examining different life course epidemiology conceptual models in relation to the risk of MS. I tested two models: the critical period model and the accumulation model. I used self-reported sun exposure during summer as the main exposure variable, given that UVR is highest during the summer months. Risk of MS associated with the frequency of outdoor summer sun exposure, during three age intervals (birth-5 years, 6-10 years, 11-15 years), was estimated separately (critical period model), and combined to estimate a

cumulative effect (accumulation model). Previous MS sun exposure case-control studies have assumed a critical period model. However, in two Australian studies MS risk was estimated using both models and the accumulation model had effect estimates that were larger in magnitude than estimates obtained from the critical period models; though the two models were not directly compared.[18, 20] I extend previous analyses and use an analytical framework, proposed for binary exposures,[25] to directly compare these two life course epidemiology conceptual models, and to determine which model is better at explaining the risk of MS.

1.2.4 Objective 4

The fourth objective builds on the analyses completed in objective 3. However, in objective 4 I characterized sun exposure using multiple variables, including frequency of outdoor summer sun exposure, outdoor winter sun exposure[13, 18, 20] and sun protection use.[12-14] In addition to low summer sun exposure,[13, 14, 17, 18, 20] studies suggest that low sun exposure during winter[13, 18, 20] and high levels of sun protection use[12-14] are also associated with higher risk of MS. I wanted to characterize sun exposure behaviour groups, using these three variables, to understand how combinations of these behaviours contributed to the risk of MS. The exposure variables were defined using the conceptual model that was found, in objective 3, to best explain risk of MS. Risk of MS was compared across groups to understand how MS risk changes depending on different sun exposure behaviours.

1.3 Thesis Outline

In chapter 2, I present a background on MS and on sun exposure. I then introduce the two themes in my thesis: (1) *measurement* and (2) *analysis*. Theme 1 focuses on etiology of pediatric-onset MS and contains two manuscripts (derived from objectives 1 and 2); and theme 2 focuses on etiology of adult-onset MS and contains one manuscript (derived from objectives 3 and 4). In chapter 3 I present more detailed methods, than is possible in the manuscripts, to supplement the methods presented in each manuscript. Chapters 4 and 5 contain the first two manuscripts, which are focused on measurement of sun exposure in children. Chapter 4 (Manuscript 1) presents a systematic review of the measurement property studies. Chapter 5 (Manuscript 2) presents the development of the Tool-Kit. Chapter 6 (Manuscript 3) is focused on analysis of sun exposure and risk of adult MS. Chapter 7 provides an overall discussion of the

research in the context of previous research and strengths and limitations, followed by the biological and public health implications of the research, and opportunities for future research.

CHAPTER 2: BACKGROUND

2.1 Preface to Chapter 2

In chapter 2 I present the background to orient the research presented in this thesis. I first introduce multiple sclerosis (MS), describe its clinical features and diagnostic criteria, present incidence and prevalence estimates, an etiological model of MS and risk factors implicated in MS etiology. As the focus of the research presented in this thesis is on the link between sun exposure and MS risk, I then introduce sun exposure generally, and summarize the literature that supports this link. In the last part of the chapter, I introduce the two overriding methodological themes that this thesis research was developed around: *measurement* and *analysis*. In the section on *measurement*, I introduce exposure measurement in epidemiology, and harmonization methods. In the section on *analysis*, I introduce life course epidemiology generally, and in the context of MS sun exposure research, and present the evidence on the role that sun related behaviours have on the risk of MS. The purpose of chapter 2 is to provide a more comprehensive background, than is possible in the individual manuscripts (Chapters 4-6).

2.2 Multiple Sclerosis

MS is a chronic disease that has an interesting epidemiology. Rates of MS vary by age, sex and geography. Incidence rates of MS increase as age increases, with a peak between 30-50 years of age, and then decreases with increasing age. [26-28] MS is more commonly diagnosed in females than in males, with female to male ratios ranging in magnitude between studies, but most suggest a two to one sex ratio, which has been reported to be increasing over time.[6, 29-31] MS incidence and prevalence have been shown to increase with increasing distance from the equator[6, 7] and to be highest in Canada,[1] although exceptions have been noted (i.e. Sardinia, Italy[2]). The etiology of MS is not understood, though it is suggested to involve a complex interplay between genetic predisposition, and environmental and lifestyle factors.[5] The strongest and most consistently identified genetic risk factor is the human leukocyte antigen (HLA) DR1*1501 allele.[32] Seropositivity to Epstein-Barr virus nuclear antigen (EBNA), infectious mononucleosis, and smoking were found, in a recent umbrella review of systematic reviews, to be the environmental/lifestyle risk factors that are most consistently associated with MS.[33]

Most etiological research has focused on adult MS populations; however, pediatric-onset MS has recently become increasingly studied. It has been estimated that 3-10% of all MS patients are under the age of 18 years.[4] Pediatric MS (<18 years of age) has been defined with respect to age, which is further divided into two groups: *children* under age 10 years, and *adolescents* between 10 to 18 years.[34] Incidence rates of MS are higher in adolescents than in children, and the female to male predominance that has been observed in adults is also true in adolescents, but not for children, as rates are similar for males and females.[35]

For the research presented in this thesis it is important to make the distinction between pediatric MS, adult MS, pediatric-onset MS and adult-onset MS. Pediatric MS is defined as an MS diagnosis in childhood or adolescence, whereas after this age it is defined as adult MS. In those classified as adult MS, onset could have occur prior to, or after, the age of 18 years. Adult-onset MS refers strictly to a diagnosis after the age of 18 years.

2.2.1 Clinical Features of Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune and neurodegenerative disease. Autoimmune diseases are characterized by the immune system mounting an immune response against a certain organ (or multiple organs). The organ that is targeted in MS is the central nervous system, specifically the myelin sheath surrounding the neurons in the brain and spinal cord. The underlying biological mechanisms leading to this process have not yet been firmly established, but are thought to involve interactions between the different components of the immune system (e.g. T-cells, T-regulatory cell, B-cell, macrophages).[36] As a result of the disease process, brain atrophy is also observed in longitudinal MRI studies of individuals with MS, demonstrating the neurodegenerative component of MS.[37]

In adult MS, the disease most commonly follows a relapsing remitting course (90%).[38] Relapsing remitting MS (RRMS) is characterized by periods of clinical symptoms (an MS attack) followed by periods of remission that vary in length. An MS attack is defined as '*patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection.*'[39]

Due to the pathological disease process individuals can suffer a variety of symptoms; impaired mobility, vision problems, fatigue, cognitive deficits, bowel/bladder incontinence, spasticity, pain, and tremors, have been noted in studies of adult MS patients.[40] MS patients are

also more likely to suffer from depression and/or anxiety than the general population[41] Over time the disease can leave those living with MS needing help with mobility;[42-46] for example one study estimated that the median age at which adult MS patients require a cane to ambulate was 55 years (95% CI 54-56) and require a wheelchair was 63 years (95% CI 61.0-65.1).[46] Life expectancy in individuals with MS is lower than the general population; a recent study in Norway reported median life expectancy of 74.7 years for MS and 81.8 years for the general population.[47]

Pediatric-onset and adult-onset MS share similar clinical features, although differences have been noted. Studies have shown that pediatric MS follows a similar disease course as adult-onset MS, as the vast majority of children (95%) have RRMS.[48, 49] While children have been shown to have higher relapse rates than adults,[50] which is used as a marker of disease activity, the time to marked disability is suggested to be slower in children,[51, 52] but because the disease process begins earlier in life, this happens at an early age.[48]

2.2.2 Diagnostic Criteria for Multiple Sclerosis

With widespread accessibility to MRI, MS is now most often diagnosed using the McDonald criteria.[39, 53] The McDonald criteria are validated clinical and MRI criteria that can be used to diagnose MS at first clinical presentation. Prior to the establishment of the McDonald criteria, the Poser criteria were used to diagnose MS, which required two clinically separate MS attacks (i.e. clinically definite MS).[54] While most MS patients have a second attack within 2 years of their first attack, use of MRI criteria to diagnose MS earlier improves clinical care and prognosis. The McDonald criteria were established in 2001 and after two revisions (in 2005 and 2010), the most recent criteria have been shown using retrospective patient cohorts of clinically definite MS to have sensitivity in the range of 68% to 84%, and specificity 60% to 93%.[55-58] The McDonald criteria, which were developed in adults, have also been shown to have very good measurement properties for diagnosing children.[59, 60] In a Canadian sample, among children over the age of 11 years, Sadaka et al (2012) reported a high sensitivity (100%) and specificity (86%).[59]

2.2.3 Incidence and Prevalence of Adult Multiple Sclerosis

The incidence and prevalence of MS vary globally. In Table 2.1 and Table 2.2 I provide relevant estimates of prevalence and incidence that I extracted from the MS literature. With

regards to adult MS, of particular interest to the research presented in Manuscript 3 (Chapter 6) are prevalence (Table 2.1) and incidence (Table 2.2) in Canada, Norway and Italy, as the data that were used were collected in these three countries.

Table 2.1 Prevalence of adult multiple sclerosis in Canada, Italy and Norway

Location	Year(s)	Prevalence per 100,000 (95%CI)
Canada		
Nationwide[1]		240 (210-280)
Stratified Estimates		
Prairies	2000-2001	*340 (240-440)*
Quebec		*180 (90-260)*
British Columbia		*240 (160-320)*
Atlantic		*350 (230-470)*
Manitoba[26]	2006	226.7 (218.1-235.3)
British Columbia[27]	2008	179.9 (176.0-183.8)
Nova Scotia[61]	2010	266.9 (257.1-277.1)
Italy		
Ferrara[62]	2004	120.9 (110.1-134.2)
Republic of San Marino[63]	2005	166.7 (123.7-220.0)
Sardinia[2]	2007	210.4 (186.3-234.5)
Norway		
Nationwide[3]	Jan 1, 2012	203 (199-207)
Hordaland County[64]	2013	211.4 (198.3-224.2)
Buskerud County[65]	Jan 1, 2014	213.8 (196.4-231.1)

Table 2.2 Incidence rates of adult multiple sclerosis in Canada, Italy and Norway

Location	Year(s)	Incidence per 100,000 person-years (95%CI)
Canada		
Manitoba[26]	1998-2006	11.4 (10.7-12.0)
British Columbia[27]	1996-2008	7.8 (7.6-8.1)
Nova Scotia[61]	2010	5.2 (3.8-6.6)
Italy		
Ferrara[62]	2004	4.4 (3.8-5.0)
Republic of San Marino[63]	1990-2005	7.9 (5.3-11.1)
Sardinia[2]	2003-2007	9.7 (3.4-13.2)
Norway		
Hordaland County[64]	2003-2007	8.5 (7.3-9.7)
Buskerud County[65]	2003-2013	11.8 (10.6-13.1)

Canada is thought to have the highest prevalence of MS in the world. The only nationwide study was conducted in 2000-2001 using the Canadian Community Health Survey (CCHS), which relied on self-report of MS.[1] In the CCHS, the prevalence of MS in Canada was estimated to be 240 per 100,000 (95%CI: 210-280); and was found to be lower in Quebec, but higher in the Prairie and Atlantic provinces.[1] More recent studies, each of which used administrative data and the same validated case definitions to estimate incidence and prevalence, have been conducted in Manitoba,[26] Nova Scotia[61] and British Columbia. [27] All three studies support the notion of high prevalence in Canada, as well as regional differences, although the prevalence estimates obtained were lower than those that were reported in the CCHS.(Table 2.1) Incidence rates in Canada ranged from 5.2 per 100,000 person-years in Nova Scotia in 2010,[61] to 11.4 per 100,000 person-years in Manitoba between 1998 and 2006.[26] (Table 2.2) Changes in incidence and prevalence over time were also assessed; incidence rates have remained stable over time, whereas prevalence has increased, which is suggested to be due to the aging population and longer survival in individuals with MS.[26, 27, 61]

Incidence and prevalence of MS vary by country throughout Europe,[29] but have also been suggested to be highest in both Norway and Italy, comparable with those in Canada. A nationwide study in Norway, which used established MS registries, estimated prevalence on

January 1, 2012 to be 203 per 100,000 population, which was lower than was reported for Hordaland County, western Norway[64] in 2013 and for Buskerud County, southeastern Norway on January 1, 2014.[65] Annual incidence was estimated for the Hordaland County (2003-2007) [64] and Buskerud County (2003 and 2013),[65] and was also in line with incidence rates in Canada. (Table 2.2)

While no nationwide prevalence or incidence studies have been conducted in Italy, a recent systematic review of MS incidence and prevalence studies suggested that Italy has been well studied.[29] Of particular interest for the research presented in this thesis are the regions of Sardinia, Ferrara and Republic of San Marino, as the study participants described in Manuscript 3 (Chapter 6) were sampled within these three geographic regions in Italy. The prevalence in Sardinia was estimated to be 210.4 per 100,000 (95%CI: 186.3-234.5) in 2007, in line with estimates reported in Canada and Norway; however MS appears to be less common in the Republic of San Marino[63] and in Ferrara.[62] (Table 2.1) Annual incidence (2003-2007) in Sardinia was also similar to rates in Canada and Norway (9.7 per 100,000 (95%CI: 3.4-13.2);[2] as was annual incidence (1990-2005) in the Republic of San Marino (7.9 per 100,000 (95%CI: 5.3-11.1)).[63] However, as may be anticipated based on lower prevalence, annual incidence was lowest in Ferrara.[62] (Table 2.2)

2.2.4 Incidence and Prevalence of Pediatric Multiple Sclerosis

To date, the majority of descriptive epidemiology studies have focused on adult populations; however, a small number of studies have specifically reported incidence and prevalence of pediatric MS. Two studies estimated prevalence of pediatric MS, one conducted in Sardinia, Italy[66] and another in Kuwait,[67] but reported very different estimates; the prevalence in Sardinia on December 31, 2012 was 26.9 per 100,000 pediatric population (95%CI: 26.6-27.2), whereas the prevalence in Kuwait in 2013 was 6.0 per 100,000 (95%CI: 4.2–8.5).

Several studies have estimated the incidence of pediatric MS. (Table 2.3) The annual incidence of pediatric MS in Sardinia (2001-2011) was 2.9 per 100,000 children (95%CI: 2.8-2.9), higher than is reported in other incidence studies. In the Kuwaiti study mentioned above, incidence in 2013 was 2.1 per 100,000 children (95%CI: 1.1–3.7); while rates reported in incidence studies performed in Germany,[68, 69] Iceland,[70] Japan[71] and the USA,[70] were lower than 1 per 100,000 person-years. (Table 2.3)

Table 2.3 Incidence rates of pediatric multiple sclerosis

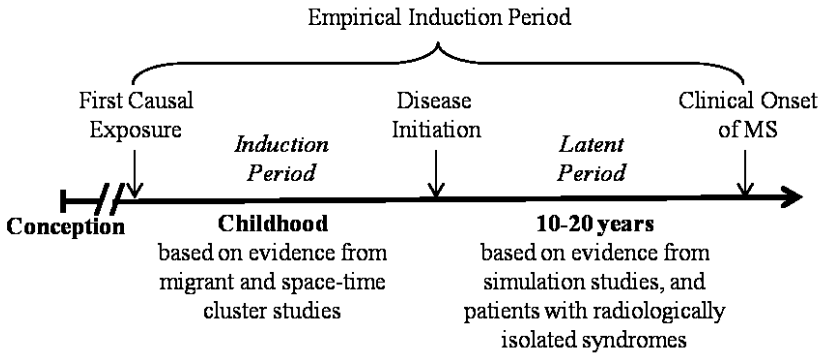
Location	Year(s)	Age (years)	Incidence per 100,000 person-years (95%CI)
Sardinia[66]	2001-2011	<18	2.9 (2.8-2.9)
Kuwait[67]	2013	<18	2.1 (1.1–3.7)
Japan[71]	2005–2007	<16	0.69 (0.58-0.80)
Germany[69]	2009-2011	<16	0.64 (0.56-0.73)
USA[72]	2004-2009	<18	0.51 (0.33-0.75)
Iceland[70]	1990-2009	<18	0.45
Germany[68]	1997-1999	<16	0.3

Several studies have demonstrated an effect of age,[68, 69, 73] and overall suggested that incidence increases markedly with age.[68, 69] For example, a recent German study that estimated annual incidence rates (2009-2011) for children under 16 years, found the lowest rates in those under age 10 years (0.09 per 100,000 children (95%CI: 0.06-0.14)); whereas in children between 14-15 years incidence was much higher (2.6 per 100,000 children (95%CI: 2.2-3.1).

2.2.5 An Etiological Model of Multiple Sclerosis

The etiological model of adult MS has been developed using several different study designs, which suggest that MS has a long empirical induction period. The empirical induction period includes both the induction and latent periods. The induction period for MS has been suggested to be in childhood, including the time period between birth and 15 years of age, based on evidence from migrant studies and space-time clustering studies; followed by a long latent period, between 10 to 20 years, based on evidence from simulation studies and patients with radiologically isolated syndromes. I created Figure 2.1 based on this evidence, to illustrate a potential etiological model for MS. Given that childhood is an etiologically relevant time period, the analyses presented in Manuscript 3 (Chapter 6) were restricted to sun exposure prior to the age of 15 years.

Figure 2.1 An etiological model of MS



Migrant studies conducted in the early to mid to late 20th century in South Africa,[74] Israel,[75] USA[76] and Australia[77] compared MS incidence as a function of age at migration, and suggest MS risk is determined in the first two decades of life.[78] A recent re-analysis of data from Australia, on migrants from the United Kingdom and Ireland,[79, 80] supported previous findings that risk of MS was greater in those who migrated after age 15 years, than those who migrated prior to age 15 years.

Clustering of exposure prior to MS onset has been suggested based on evidence from space-time clustering studies; individuals with MS have been found to be geographically clustered prior to onset. In particular, these studies imply that the induction period is during childhood. An early study conducted in the Shetland Islands, UK found significant clustering more than 20 years prior to clinical onset.[81] Subsequent analyses by Riise et al[82] in Norway found that clustering peaked at age 18 years; and by Pugliatti et al,[83, 84] in Sardinia suggested clustering of MS cases between one year and 15 years of age.[83, 84]

Wolfson et al[85, 86] performed two simulation studies to estimate the distribution of the latent period for MS, and point to a susceptibility period between 10-15 years, and a latent period of 20 years. Incidental findings on MRI that are suggestive of MS in asymptomatic individuals with a normal neurological exam, termed radiologically isolated syndrome (RIS),[87, 88] provides clinical evidence that MS has a long latent period. Longitudinal MRI studies following individuals with RIS, report time to clinical conversion upwards of 10 years.[88]

2.2.6 Risk Factors Implicated in the Etiology of Multiple Sclerosis

Although the etiology of MS is not understood, several risk factors have been implicated.[5, 33] As part of the background work for Manuscript 2 (Chapter 5), I conducted a structured literature review to get a sense of the non-genetic risk factors that had been implicated

in MS etiology. The risk factors that I identified include: smoking[89, 90] and environmental tobacco smoke exposure,[91] antibiotic use,[92] body mass index (BMI),[93] daycare/sibling exposure,[94] older onset of puberty,[95] physical activity,[96] prenatal and perinatal factors,[97] residential history, stressful life events/childhood trauma,[98] ***sun exposure***,[13, 20] vaccinations,[99] viral infections (Epstein-Barr Virus (EBV)[100] and infectious mononucleosis in particular[101]), and vitamin D intake.[102, 103] To date, MS etiologic research has been focused on adult MS populations; however publications that report on etiology of pediatric MS are growing in number. For example, risk of pediatric MS has been shown to be associated with environmental tobacco smoke exposure,[104] BMI,[105] and viral infections.[106]

An important goal of etiological research is to identify modifiable factors that we can intervene on to reduce the burden of disease at the population-level. While cohort studies are the preferred observational study design to examine etiological risk factors, given that MS is rare (i.e. <0.2%) and has a long latent period, the case-control study is, therefore, the most efficient and commonly used design to study MS etiology. Repurposed cohort studies have, however, been used to assess MS etiology. For example, studies using the Nurses' Health Study data have reported an inverse association with vitamin D intake,[102, 103] and positive associations with cigarette smoking,[90] BMI,[93] and EBV.[100] Alternative cohort designs, such as nested-case-control studies, have also been used and report a positive association with penicillin use,[92] and an inverse association with neonatal vitamin D status.[107]

While findings from case-control studies can be impacted to a greater extent by some forms of bias than those from cohort studies, such as misclassification due to inaccurate recall or systematic difference in reporting (i.e. recall bias), it is reassuring that case-control study designs have provided consistent evidence for the role of certain risk factors, such as cigarette smoking,[108] EBV[100, 101] and body size.[93, 109] The research presented in Manuscript 3 (Chapter 6) uses data that were collected using a case-control study design; however several strategies were used in an attempt to reduce the impact of bias on the study results. For example, the study materials were identical for cases and controls; the case series included cases with disease duration less than 10 years (focusing on more recent onset cases); controls were sampled to be representative of the study base, using population-based sources; cases and controls were frequency-matched on key confounders and more than one control was enrolled per case. Specifically, to improve reporting accuracy of exposure information, study participants were

encouraged to seek help from their parents in completing the questionnaire and, whenever possible the items in the questionnaire were those with measurement properties that had been assessed and/or that had been shown to work well in previous research studies.

2.3 Sun Exposure

Sun exposure is a potentially modifiable factor, and is the focus of the research presented in this thesis. The sun emits ultraviolet radiation (UVR). Of interest are the UV-A (315-400nm) and UV-B (280-315nm) rays, as these are the two rays that reach the earth's surface. The amount of UVA and UVB rays reaching the earth's surface depends on a number of factors, including the position of the earth relative to the sun, the density of the ozone layer, cloud cover and altitude.[110] Not surprisingly, more rays reach the earth's surface when it is physically closer to the sun (e.g. highest at the equator, higher during summer than winter, and mid-day exposure is greatest at any location), when the ozone layer is thinner, when there is less cloud cover, and at higher altitudes.

In addition to factors affecting the amount of UV rays reaching the earth's surface, there are other factors that can alter the amount of sun that individuals, in the same geographic area, are exposed to. Snow, sand and water reflect UV rays and therefore increase the amount of exposure;[111] whereas the use of sunscreen creams, protective clothing (e.g. hats, sunglasses, protective clothing, umbrella), staying in the shade or indoors during high exposure times, all decrease the amount of exposure.[112] Other personal factors such as sun practices (e.g. time spent in the sun, sun tanning), skin colour, sun sensitivity, sunburn history, cultural beliefs, and history of melanoma may be linked to behaviours that modify exposure.[112]

Sunlight has both beneficial and detrimental effects on human health.[22-24] UVR plays a role in several biological processes including: vitamin D synthesis, melatonin regulation, immune system function, and endorphin production.[22, 23] However, excessive sun can lead to sunburns, eye damage, photoaging, immunosuppressant, and skin cancer.[113] Due to the varied effects that the sun has, both too much sun exposure and too little sun exposure can have negative effects on health. For example, too much sun exposure leads to sunburns, and a greater number of sunburns are a determinant of melanoma risk.[114] Alternatively, too little sun exposure is closely linked to lower levels of circulating vitamin D, and lower levels of vitamin D have

been linked to many diseases such as osteoporosis, cancer, heart disease and autoimmune disease,[115] including MS. [102, 103]

2.3.1 Sun Exposure and the Etiology of Multiple Sclerosis

Sun exposure has been suggested to play a role in the etiology of MS. Overall, evidence from ecological studies and case-control studies have suggested that lower levels of sun exposure increase the risk of MS. The distribution of MS is suggested to follow a latitude gradient, as MS is more common with increasing distance from the equator.[6, 7, 116] Simpson et al (2011) [7] conducted a meta-analysis that included 321 published prevalence estimates and reported a significant non-linear association, as they did not observe an association between latitude and prevalence at high latitudes. Alonso et al (2008)[6] evaluated age- and sex- specific incidence rates, and found a positive association with latitude, although the association was attenuated after 1980; [6] They suggested that the observed attenuation was due to increasing incidence at lower latitudes.

UVR is correlated with latitude, and overall, ecological studies have demonstrated an inverse association with MS prevalence, in both the northern and southern hemisphere.[8-10] A North American study found a strong correlation between MS prevalence and the UV index (a marker of ground-level strength of UVR);[8] and an Australian study, by van der Mei et al (2001)[9] found a very strong association with satellite-derived UVR measurements ($r = -0.91$).[9] Orton et al (2011)[10] specifically examined UVB and also reported strong associations with MS prevalence (annual mean UVB irradiation: $r = -0.80$; average winter UVB: $r = -0.87$).

Sloka et al (2008)[117] conducted an ecological study that examined the effects of both latitude and UVR in a multivariable model. While there were studies from all continents, only four studies were available for the southern hemisphere. Multivariable models showed that UVR and latitude were independently associated with MS prevalence; however, UVR had the strongest impact. The association between UVR and MS prevalence was strengthened when eight studies from the most northern locations (i.e. Scandinavia and the Faroe Islands) were removed; which is in line with the non-linear association, reported by Simpson et al.[7]

Sloka et al (2011)[118] performed in an incidence study (1998- 2002) in Newfoundland, Canada, and found that after accounting for satellite derived measures of average daily erythemal UVR, there was no longer an association between latitude and incidence. They also examined age-specific exposure, and associations were more pronounced for UVR exposure in the first

year of life, weaker when considering the first ten years of life, whereas no association was observed at time of first attack.[117] This evidence provides support that childhood is an etiologically relevant period to consider in examining the link between sun exposure and the risk of MS. Together these studies provide evidence for a role of sun exposure in the etiology of MS, however, ecological fallacy is always a concern, and requires replication at the individual level.

While, I did not identify any cohort studies that examined the association between individual-level sun exposure and MS risk, evidence from several case-control studies support a link.[11-14, 17-20] Case-control studies conducted in European countries (i.e. Italy (mainland, Sardinia and Sicily) and Norway),[13, 14, 17] the Middle East (i.e. Iran and Kuwait),[11, 12, 19] Australia,[18, 20] and in the Caribbean (i.e. Cuba and Martinique),[14] suggest that lower levels of sun exposure increase the risk of MS.

Case-control studies that examined age-specific sun exposure suggest that the first two decades of life are an etiologically relevant period.[13, 14, 17, 18, 20] Our group previously published results[13] from Italy and Norway using the same sun exposure data presented in Manuscript 3 (Chapter 6). We found that lower frequency of outdoor sun exposure during summer between birth and 5 years of age produced the largest effect estimate in Italy, whereas the largest effect estimate in Norway was found for lower sun exposure between 13 to 15, and 16 to 18 years of age. In an Australian study, van der Mei et al (2003)[20] suggested summer sun exposure between 6 to 15 years of age was most strongly predictive of MS risk.[20] Two other case-control studies, conducted in northern Norway,[17] and in Cuba, Martinique and Sicily,[14] also provide evidence that sun exposure during childhood or adolescence is associated with increased MS risk.

2.4 Guiding Methodological Themes

The research in this thesis is grouped into two methodological themes: *measurement* and *analysis*. Both themes focus on sun exposure and MS. The first is focused on the measurement of sun exposure using self-report questionnaires, with particular attention to measuring and harmonizing sun exposure data in pediatric MS studies. The second is focused on exploring the link between sun exposure and risk of adult MS, using two novel analytical approaches: the first uses life course epidemiology theory, and the second uses latent class analysis to characterize sun exposure behaviours.

2.4.1 Methodological Theme 1: *Measurement* of Sun Exposure

The goal of the research related to *measurement* was to develop a measurement framework to guide the design of questionnaires for pediatric MS case-control studies. Manuscript 1 focuses on measurement of sun exposure in pediatric populations in general. In the next section (2.4.1a), I introduce the importance of good measurement in epidemiological studies. The research presented in Manuscript 1 (Chapter 4) was conducted to provide an evidence-base to inform the research presented in Manuscript 2 (Chapter 5). Manuscript 2 focuses on the development of the Pediatric MS Tool-Kit (Tool-Kit). The Tool-Kit is a measurement framework that can be used by pediatric MS researchers to design study-specific questionnaires to examine the link between sun exposure and the risk of pediatric-onset MS. The short-term goals of developing the Tool-Kit are to improve exposure measurement in pediatric MS etiological studies, and to enhance the comparability of results across studies. The long-term goal is to facilitate harmonization of pediatric MS studies in the future. In section 2.4.1b I present some background on harmonization methods and terminology.

2.4.1a Measurement in Epidemiology

Exposure measurement is a key consideration in the design of an epidemiological study, and the use of measurement tools that are valid and reliable is imperative. Validity is defined as the extent to which the measurement tool measures the construct(s) it was designed to measure; and reliability as the extent to which the measurement tool is free from measurement error.[119] Well designed measurement property studies are necessary to assess validity and reliability. While objective measures tend to have better measurement properties than subjective measures, they are often not feasible in certain contexts, such as to assess history of sun exposure in case-control studies. In this context, exposure measurement often requires use of self-report questionnaires.

The quality of self-report questionnaires, however, varies greatly. Gaffney et al[120] performed a systematic review to document questionnaires used to assess infant exposure to environmental tobacco smoke in studies published between 1996 and 2002. Among the 60 studies that Gaffney et al[120] identified, none used the same questionnaire, the validity of the questionnaire was only assessed in 30% , and no investigations reported on reliability. In this research area, questionnaires were specifically developed for the purposes of the particular study/investigation (i.e. developed "in-house").[120] While "in-house" questionnaires may appear

to serve their purpose, their use has limitations, and thus it is preferable whenever possible to use questionnaires that have been shown to be valid and reliable, so that researchers are confident that what is being captured is the best reflection of the construct they wish to measure.

One methodological approach to appraise the quality of available questionnaires is a systematic review of measurement property studies.[121] A systematic review of measurement property studies can be used to identify, critically appraise and compare the measurement properties, validity and/or reliability, of available questionnaires. This approach can also be used to select a questionnaire, or to identify questionnaires that warrant validation. The popularity of systematic review of measurement property studies is increasing; for measurement tools that measure health status or (health-related) quality of life the number of reviews increased from 0-1 per year in the early 1990s, to 31 in 2005,[121] and up to 85 in 2013.[122] I used a systematic review of measurement property studies for the research presented in chapter 4 (Manuscript 1). I completed this research to enhance questionnaire design and help minimize information bias in pediatric epidemiological studies; and with regards to the Tool-Kit, I specifically wanted to identify self-report questionnaires that had been validated for use in pediatric case-control studies.

2.4.1b Harmonization

The Tool-Kit was developed to provide a methodology that can facilitate harmonization of pediatric MS studies in the future.[123] Harmonization is an attractive approach to use to study diseases with very low incidence, such as pediatric MS, as individual studies have small sample sizes and consequently low statistical power. The combining of data from multiple studies is an obvious solution when larger sample sizes are required, but it is not straightforward to implement and should not be attempted without a clear and reproducible approach.

Harmonization is an emerging methodology that is used to systematically combine data that are collected in two or more studies. Harmonization is the methodological process of assessing the compatibility of information collected in two or more studies. The methods of harmonization are based on the use of a common set of core variables that describe key exposures, outcomes and covariables.[124] The key to harmonization is the critical appraisal of the study design, data collection methods and tools, to determine if the information obtained in each study can be integrated meaningfully.[124-126] If information is deemed compatible, the statistical

analysis of the harmonized dataset is equivalent to an individual-level participant data meta-analysis.[127]

The Tool-Kit was developed for prospective harmonization. Prospective harmonization requires collaboration during the study design phase, to determine what information should be collected to enable data pooling in the future. Investigators may decide to use identical measurement tools and procedures; which is referred to as stringent prospective harmonization.[128] Stringent prospective harmonization simplifies the harmonization process; however it is not always possible or ideal in epidemiologic research since it allows no flexibility and no context-specific modification should be made to study questionnaires. Flexible-prospective harmonization, however, allows for some loosening of the rules in the data collection of participating studies.[128] Flexible harmonization allows context-specific modifications to be made to study questionnaires, in order to meet the specific needs of the investigator, the population or the cultural context. Flexible harmonization involves the use of a measurement framework that is shared across studies, so that the data that are collected can be used to derive a common set of variables that can be combined for pooled analyses. Although flexible harmonization is less straightforward than stringent prospective harmonization, is often more realistic and perhaps even more appropriate for etiological research.

The need to combine data across multiple studies, using prospective harmonization, has been recognized by the research community. The National Institute of Neurological Disorders and Stroke (NINDS) developed standardized research methods for data collection to monitor the clinical course of several neurological diseases, including MS.[129, 130] The Canadian Partnership for Tomorrow (CPT) study includes five prospective cancer cohort studies across Canada. The questionnaire used in each study includes a core set of variables that are common across the five studies.[131] Another example which has similarities with the Tool-Kit is the EURODIAB study.[132] The EURODIAB study included an environmental exposure component to assess the role of infections, vaccinations and vitamin D supplementation in risk childhood type 1 diabetes.[133, 134] Eight centers across Europe used a common set of variables to develop center specific questionnaires. While different measurement approaches were used across centers, as the data were equivalent, they were harmonizable and pooled for analysis.

Taking advantage of the growing interest and research activity in pediatric MS, I developed methods for flexible prospective harmonization of pediatric MS studies. The Tool-Kit

provides a framework for the measurement of risk factor data. The Tool-Kit proposes a set of core variables for MS researchers to use in designing their questionnaires, so that study data are harmonizable. The Tool-Kit is a valuable resource for researchers who are planning studies, and will enhance measurement in individual studies and facilitate the process of harmonization of studies in the future. Developing methods for flexible harmonization also provides the opportunity for ongoing studies to participate in harmonization projects.

2.4.2 Methodological Theme 2: *Analysis* of Sun Exposure

The goal of the research related to *analysis* was to extend previous analyses that have been used to examine the association between sun exposure and MS risk, to explore the association in greater depth and further inform the etiological model of MS. Two questions that really interested me were: (i) whether risk was determined at a particular age, or if sun exposure behaviour throughout childhood was a better predictor; and (ii) how different sun exposure behaviours, taken together, relate to MS risk. I used life course epidemiology theory to address my first question, and I used latent class analysis to address my second question.

2.4.2a Life Course Epidemiology

Life course epidemiology has been defined as "*the study of long term effects on later health or disease risk of physical or social exposures during gestation, childhood, adolescence, young adulthood and later adult life*."[135, 136] The idea is that exposure during key developmental periods has long term effects on the risk of chronic diseases in adulthood, through the mechanism of "biological programming." This paradigm fits well with the etiologic model of MS given the evidence that risk is determined in childhood, followed by a long latent period.

Life course epidemiology theory is based on several conceptual models that are used to explain the link between exposure over the life span, and disease risk.[25, 135, 136] The two conceptual models that are relevant to the research presented in this thesis are (i) the critical period model and (ii) the accumulation model. The critical period model suggests that there is a time period during which an individual is susceptible to exposures that determine disease risk. This could be a certain age, age period, a developmental process (e.g. puberty) or other distinct event (e.g. pregnancy). The accumulation model suggests that the longer the length of time an individual is exposed, the greater the risk of disease, irrespective of when exposure occurs. While a cohort study is clearly the best study design to use to examine life course epidemiology

models, data collected in a case-control study can be used to derive the necessary exposure variables to develop the appropriate models.[25] The ability to better understand the window of risk for MS is important to target both interventional and basic science research.

I identified four studies that assessed sun exposure at multiple age intervals during childhood.[13, 17, 18, 20] The same questionnaire was used in each of these four studies. In two Australian studies, by van der Mei et al[20] and Lucas et al,[18] the risk of MS was estimated for exposure at different age intervals separately (i.e. critical period model) as well as by combining exposure in multiple age intervals (i.e. accumulation model).[18, 20] The study by van der Mei et al[20] was based on prevalent MS cases, and found that risk was greatest for exposure between the age of 6-10 years and 6-15 years, but was attenuated when examining exposure between age 6-20 years, and was null when exposure between 6-25, 6-30 or 6-35 years was combined.[20] The study by Lucas et al,[18] was based on incident MS cases, and found a significant effect for exposure in the last three years, but the effect was more pronounced when exposure between 6 years and current age was combined.[18]

However, these studies did not directly compare these different exposure models to determine which, if any, predicts MS risk better. In our previous analyses of the sun exposure data from Italy and Norway, that are used in research presented in chapter 6 (Manuscript 3), we assumed a critical period model and examined various age intervals from birth to age 30 years.[13] We found that effect estimates for some 5-year age intervals were larger than effect estimates for other intervals. However, we did not examine the accumulation model. To extend previous analyses, I conducted analyses to directly compare the two life course epidemiology models (i.e. critical period model and accumulation model), to determine which of these models is best at explaining the link between sun exposure and MS risk.

2.4.2b Sun Exposure Behaviours and Risk of Multiple Sclerosis

Most MS studies have examined sun exposure during summer, given that the sun is strongest during this time of the year. However, three studies also assessed winter exposure and found significant associations with MS risk.[13, 18, 20] In our previous publication[13] we found a clear association between winter sun exposure and MS in Italy from birth to 10 years, but no evidence of an association in Norway.[13] Sun protection use is an important behaviour that can greatly impact the amount of sun to which an individual is personally exposed. Greater levels of sun protection have been shown to be associated with MS risk.[12-14] The interaction between sun

exposure and sun protection has only been reported on in our previous analyses.[13] We did not find a significant interaction between summer sun exposure and sun protection in Italy or Norway. To extend these analyses I used latent class analyses to identify latent sun exposure behaviours groups characterized by varying levels of sun exposure during summer, during winter and sun protection use. Using this approach, multiple indicators can be examined simultaneously, and group membership can be related to MS risk.

2.5 Summary

Sun exposure is a modifiable risk factor that we can intervene on at the population-level to reduce risk of disease. The sun has several important roles in maintaining human health. Both excessive and insufficient sun exposure have been shown to increase the risk of several diseases. MS is linked to low levels of sun exposure. MS prevalence is positively correlated with latitude and inversely correlated with UVR, and individual-level studies provide evidence of an association between low levels of sun exposure and the risk of adult MS. To date, no studies have reported on sun exposure and pediatric-onset MS.

CHAPTER 3: METHODS

3.1 Preface to Chapter 3

In chapter 3 I describe the methods I used to address the four thesis objectives. Herein, I provide a more detailed description of some of the methods that are presented in each of the manuscripts (Chapters 4, 5 and 6). I first present the methods that I used to address objective 1 (Manuscript 1, Chapter 4); and provide more details about the (i) systematic review protocol, (ii) search strategy, (iii) COSMIN initiative, (iv) data extraction and quality assessment forms, and (v) scoring of study quality. I then describe the methods I used to address objective 2 (Manuscript 2, Chapter 5); which includes (i) the Pediatric MS Tool-Kit, (ii) assembling a research team, (iii) submitting operating grant applications, (iv) engaging the pediatric MS research community, (v) developing and implementation of a risk factor survey, (vi) literature reviews of measurement properties, and (vii) a Delphi study. I end this chapter with a description of the methods I used to address objectives 3 and 4 (Manuscript 3, Chapter 6); and provide more details on the (i) EnvIMS study design and setting, (ii) study participants, (iii) questionnaire, (iv) variables (exposure, outcome and confounders), and (v) statistical analyses. The methods outlined in this chapter are presented to supplement those described in each individual manuscript.

3.2 Manuscript 1 Methods

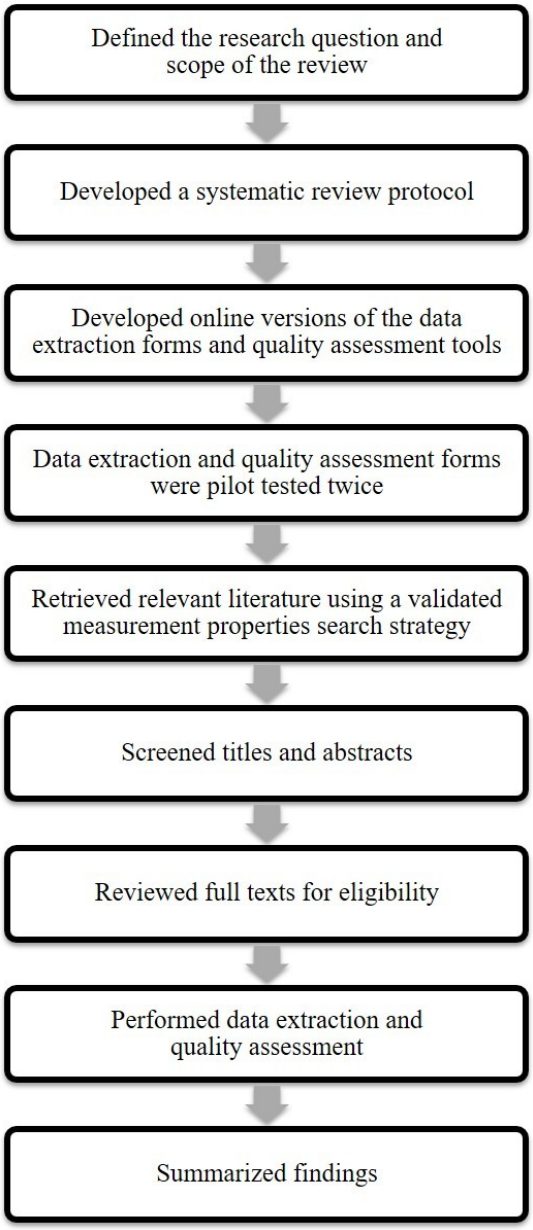
Manuscript 1 (Chapter 4) presents the research related to the first objective of this thesis: *to identify, critically appraise and summarize measurement property (validity and/or reliability) studies that evaluate questionnaires to assess sun related behaviours in children*. The flow chart below outlines the methods I used to complete the review (Figure 3.1); some methods are described in this section, while others are described in Manuscript 1 (Chapter 4)

3.2.1 Systematic Review Protocol

The research question guiding this review was: *what are the measurement properties (validity/reliability) of self-report questionnaires that can be used to ascertain information about sun related behaviours in children?* A review protocol was prepared in advance of performing the systematic review; the protocol is presented in an appendix of Manuscript 1 (Chapter 4,

Appendix 4.1) The protocol was reviewed by my supervisor, Dr. Christina Wolfson; and by Dr. Catherine Tansey, a research assistant hired to serve as an independent reviewer for the systematic review. I was the primary reviewer for each article and Dr. Tansey was the second reviewer; any discrepancies in our responses were resolved by consensus.

Figure 3.1 Flow chart of methods used to conduct the systematic review of measurement property studies.



3.2.2 Search Strategy

I constructed search strategies to search MEDLINE (PubMed, 1946-current), EMBASE (1947-current) and Cumulative Index to Nursing and Allied Health Literature (CINAHL, 1937-current), using a validated PubMed search strategy.[137] Terwee et al., (2009)[137] described a search strategy developed to identify publications that report on the measurement properties of measurement tools. The search strategy was validated, and was shown to have high sensitivity (>94%), but low specificity (11%-75% depending on the validity study).[137]

The validated search strategy has four search components: (i) *construct* search, (ii) *population* search, (iii) *instrument* search and (iv) *measurement properties* search. I consulted with a McGill Life Sciences librarian on several occasions, and worked closely with her, to fine-tune the review-specific search terms. The *construct* search includes review-specific terms, which were related to sun exposure. For the *population* search component, I used another validated search strategy that was developed to identify pediatric studies in PubMed.[138] The *instrument* search component is optional and is intended to narrow the search results; I included terms to focus the search on questionnaires, as opposed to objective measures of sun exposure. The *measurement properties* search component was developed by Terwee et al.,[137] and provides a very comprehensive list of keywords related to measurement properties, and was used as is presented in their publication.[137] I contacted the corresponding author, Dr. Caroline Terwee in February 2014, to obtain similar search strategies for EMBASE and CINHAL. While the EMBASE and CINHAL search strategies that Dr. Terwee provided me with had not been validated, they had been developed using similar search terms to those used in the validated PubMed search strategy. Therefore, this was the best approach to identify relevant publications in EMBASE and CINHAL.

3.2.3 COSMIN Quality Assessment Checklist

I mention the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) throughout Manuscript 1, and in Manuscript 2. COSMIN was developed in response to the need to improve the quality of reporting of measurement property studies and, to provide guidelines to perform rigorous reviews of these studies.[121] COSMIN provided me with an excellent set of methodological tools to use to perform my research. However, COSMIN was developed for health status measurement. Since exposure measurement is the focus of my research, I examined the COSMIN literature, and while some aspects were not relevant to

exposure measurement, it provided the best available methodology to follow to conduct this review.

Mokkink et al.[119, 139-142] conducted a Delphi study that they used to reach international consensus on taxonomy, terminology and definitions of measurement properties for health-related patient-reported outcomes;[119] and developed the COSMIN checklist. The COSMIN checklist is a tool designed to evaluate the methodological quality of studies on the measurement properties of health status measurement instruments.[139-141] The checklist can be used to improve conduct and reporting of measurement property studies, or to perform quality assessment of published studies.[139, 142] I used the checklist to do both. In Manuscript 1 I used it to perform quality assessment, as described below in section 3.2.4. In Manuscript 2, I used the checklist to design a content validity study (section 3.3.8).

3.2.4 Data Extraction and Quality Assessment Forms

In Manuscript 1, due to space constraints I was only able to briefly mention the use of DistillerSR (Evidence Partners, Ottawa, Canada), which is the software I used to conduct the review electronically. DistillerSR is an online systematic review software that automates several steps, greatly enhancing the quality and consistency of the review. We created electronic versions of the data extraction form that I developed, and the COSMIN quality assessment checklist.[142] We were able to control data entry, such as ensuring all data fields were completed prior to moving on to the next form. All the electronic forms were pilot tested. First on two publications that met three of the four inclusion criteria, but the study populations were adults and not children. Dr. Tansey and I met to discuss our experience reviewing these publications, which helped to refine and streamline the data collection process. We then pilot tested the data extraction forms that were modified based on the first pilot, using two publications that met all our inclusion criteria, which I identified through the background work for the review. Only minor changes were made following the second pilot.

Citations and abstracts, from the three electronic databases, were imported into DistillerSR from the referencing software EndNote (Clarivate Analytics, Philadelphia, PA) and checked for duplicates. Each record was indexed and kept track of in DistillerSR. An initial screening form was used to quickly exclude irrelevant publications. (Appendix A.1) The title and abstracts of potentially relevant publications were then screened using a form that included one question for each of the inclusion criteria. (Appendix A.2) The response options for these

questions were: *yes*, *no* or *unsure*. The record was automatically moved to full review if we both answered *yes* to all four questions. When either of us was *unsure*, we each reviewed the full text, independently, to make a final decision. A question was also added to the screening form to select studies that used a sun exposure questionnaire, but for which the assessment of the measurement properties was not mentioned in the abstract; and we reviewed the methods of each of these studies to determine if the measurement properties of the sun exposure questionnaire had been assessed.

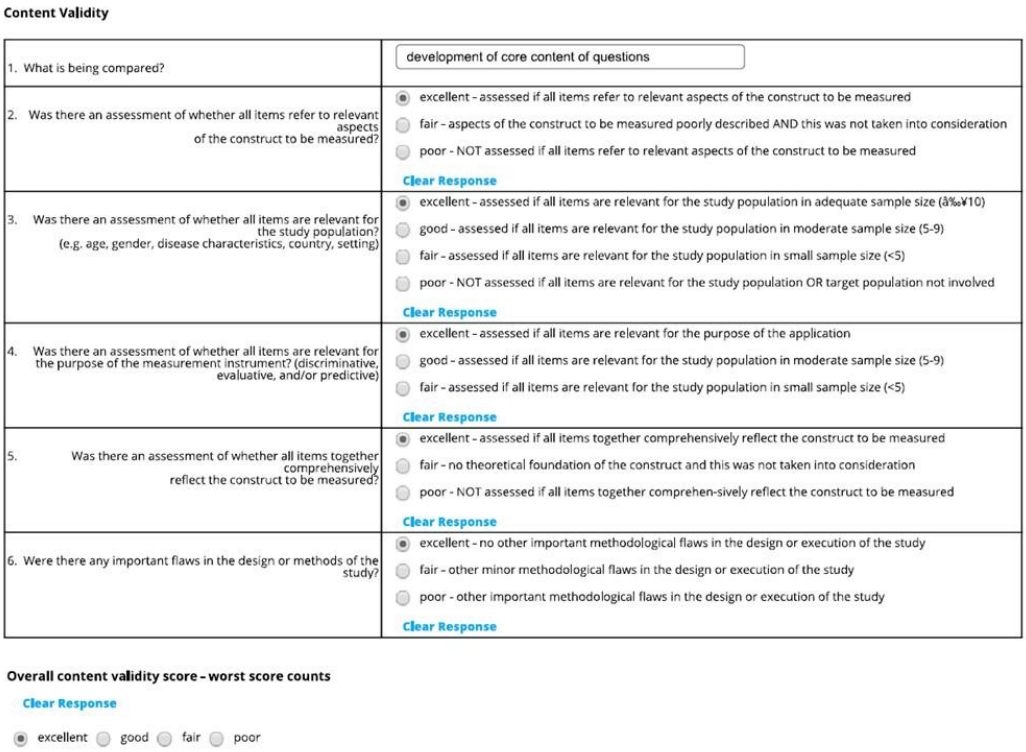
The full text of each publication that met the inclusion criteria was uploaded into DistillerSR. A background form that I developed to extract general information about the publication and the questionnaire was then completed. (Appendix A.3) A COSMIN measurement property domain form was used to determine which measurement properties were assessed in each publication. (Appendix A.4) The responses on this form were compared and discrepancies discussed prior to completing quality assessment. A separate form was created for each of the seven measurement properties in the COSMIN checklist:[139, 142] internal consistency, reliability, content validity, criterion validity, hypothesis testing, structural validity and cross-cultural validity. The COSMIN checklist also includes two data extraction forms focused on interpretability and generalizability of the study. In summary, for each publication included in this review, the following forms were completed: a background form, COSMIN measurement property domain form, the relevant COSMIN measurement property checklist forms, COSMIN interpretability form and COSMIN generalizability form.

3.2.5 Scoring of Study Quality

I used the scoring tool developed for the COSMIN checklist.[140, 143] The checklist includes five to 15 questions for each measurement property, and each question is rated using one of four response options (*excellent, good, fair* and *poor*). The response options for each question include a brief description, and this information helps to assign the score. COSMIN suggests using the 'worst score counts' algorithm to assign a quality rating to each measurement property.[143] The score is equivalent to the lowest rating for any of the questions in the checklist. The developers of the scoring system note that a poor response option is only provided for questions that reflect important methodological flaws.[143] In Figure 3.2 I provide a screenshot from DistillerSR of the COSMIN checklist for content validity. This study received an excellent rating, however, had

any one of these five questions been instead rated poor, the study would have received a poor quality assessment rating.

Figure 3.2 Screenshot from DistillerSR of the COSMIN Content Validity Checklist.



Content Validity

1. What is being compared?	development of core content of questions
2. Was there an assessment of whether all items refer to relevant aspects of the construct to be measured?	◉ excellent - assessed if all items refer to relevant aspects of the construct to be measured ○ fair - aspects of the construct to be measured poorly described AND this was not taken into consideration ○ poor - NOT assessed if all items refer to relevant aspects of the construct to be measured Clear Response
3. Was there an assessment of whether all items are relevant for the study population? (e.g. age, gender, disease characteristics, country, setting)	◉ excellent - assessed if all items are relevant for the study population in adequate sample size (â‰¥10) ○ good - assessed if all items are relevant for the study population in moderate sample size (5-9) ○ fair - assessed if all items are relevant for the study population in small sample size (<5) ○ poor - NOT assessed if all items are relevant for the study population OR target population not involved Clear Response
4. Was there an assessment of whether all items are relevant for the purpose of the measurement instrument? (discriminative, evaluative, and/or predictive)	◉ excellent - assessed if all items are relevant for the purpose of the application ○ good - assessed if all items are relevant for the study population in moderate sample size (5-9) ○ fair - assessed if all items are relevant for the study population in small sample size (<5) Clear Response
5. Was there an assessment of whether all items together comprehensively reflect the construct to be measured?	◉ excellent - assessed if all items together comprehensively reflect the construct to be measured ○ fair - no theoretical foundation of the construct and this was not taken into consideration ○ poor - NOT assessed if all items together comprehen-sively reflect the construct to be measured Clear Response
6. Were there any important flaws in the design or methods of the study?	◉ excellent - no other important methodological flaws in the design or execution of the study ○ fair - other minor methodological flaws in the design or execution of the study ○ poor - other important methodological flaws in the design or execution of the study Clear Response

Overall content validity score – worst score counts

Clear Response

◉ excellent ○ good ○ fair ○ poor

3.3 Manuscript 2 Method

Manuscript 2 (Chapter 5) presents the research related to the second objective of this thesis: *to define a minimal set of core variables, describing selected MS risk factors, to serve as a measurement framework for questionnaire development that facilitates harmonization of pediatric MS studies.*

3.3.1 Pediatric MS Tool-Kit

Manuscript 2 focuses on the development of the Pediatric MS Tool-Kit (or Tool-Kit). Given that etiologic research in pediatric MS is a relatively recent area of research, developing a measurement framework for prospective harmonization is highly relevant to enhance this research area. The Tool-Kit includes a set of core variables and is intended to be used by

researchers to develop questionnaires that are harmonizable. In the following sections I describe the methodology that I used to develop the Tool-Kit.

3.3.2 Assembling a Research Team

To develop the Tool-Kit I assembled a research team of seven investigators, which included epidemiologists and pediatric and adult MS neurologists. My supervisor, Dr. Christina Wolfson, and I invited five researchers, who we had previously worked with, to collaborate on the project. I organized and led teleconferences between our research team members as well as a full day face-to-face planning meeting held in Montreal in January 2014.

3.3.3 Operating Grant Applications

In order to complete the tasks required to develop the Tool-Kit I prepared five grant submissions. In 2011-2012 I applied for operating grant funding from the MS Society of Canada (two applications submitted, both not awarded), Canadian Institutes of Health Research (two submitted, both not awarded) and the US National MS Society (NMSS) (one submitted, and was awarded). In January 2013 we received notification from the NMSS that our application had been funded for three years (March 2013-2016; $131,143 USD). The objectives of the operating grant coincide with the first two objectives of this thesis. In the grant we committed to developing Tool-Kit resources for three MS risk factors. However, the research presented in this thesis focuses on one risk factor: *sun exposure*. In addition to the NMSS operating grant, I also applied for, and received, an International Meeting Grant from the MS International Federation (November 2014, £4675). This funding supplemented the funding we received from the NMSS, and was primarily used for the first Delphi face-to-face meeting held in Montreal in November 2014.

3.3.4 Engaging the Pediatric MS Research Community

As the Tool-Kit was being developed for the pediatric MS research community I engaged members of this community early in the process. In fall 2012, prior to receiving grant funding, I presented an overview of the Tool-Kit at the International Pediatric MS Study Group (IPMSSG) Committee meeting which was held in conjunction with the 2012 European Congress on Treatment and Research in MS in Lyon, France. The IPMSSG committees includes active researchers in the field of pediatric MS, from around the world.[144] At this meeting the group endorsed the development of the Tool-Kit, agreed to facilitate distribution of a Risk Factor

Survey (described in the next section and in presented in Appendix B) that I developed, and in addition, individual committee members provided input and advice, which I incorporated as I developed the Tool-Kit methods. Following the 2012 meeting I worked with the IPMSSG coordinator to organize the distribution of the Risk Factor Survey.

3.3.5 Development and Implementation of the Risk Factor Survey

The purpose of the Risk Factor Survey was to obtain input from members of the IPMSSG, in order to help select three risk factors. To develop the Risk Factor Survey content I completed a literature review using a structured approach. The purpose of the review was to identify risk factors that had been previously implicated in the risk of MS. I searched PubMed in March 2013 using MeSH and keyword search terms: "risk factor", "etiology", "cause" and "causality". To be included the publication had to: (i) assess etiology of MS; (ii) examine an environmental risk factor (i.e. genetic factors were excluded); and (iii) use an analytical study design with a comparison group (i.e. cohort or case-control study). There were 88 relevant publications identified. As the goal was to select risk factors that were measured using self-report questionnaires and were relevant for pediatric populations, I narrowed the list of risk factors using the following set of predefined criteria: (i) must be suggested to be an etiologic risk factor for MS in at least one high quality study that is sufficiently free of bias, including adequate control for confounding factors;[145] (ii) the time period of exposure associated with the risk factor is relevant for pediatric populations; (iii) the risk factor can be measured through interview or self-report questionnaire. Twelve risk factors were selected: body size/BMI; environmental tobacco smoke; head injury/traumatic brain injury; infectious mononucleosis; penicillin use; physical activity; prenatal/perinatal factors; exposure to other children (siblings/attending daycare); stressful life events; sun exposure; vaccinations; and vitamin D intake.

The Risk Factor Survey was designed and administered online using SurveyMonkey (San Mateo, California, USA). (Appendix B.1) The survey listed the 12 risk factors detailed above. In the survey I briefly described the purpose of the survey; provided links to documents that contained a summary of the review methods (Appendix B.2); and the set of predefined criteria. The findings of the review were summarized in tabular form, and provided key information about the 12 risk factors. (Appendix B.3)

Survey respondents were asked to prioritize risk factors; for each of the 12 risk factors they were asked to indicate whether they viewed each risk factor as (i) *a priority*, (ii) *important,*

but not a priority, (iii) *not important for future research*, or (iv) *I don't have an opinion*. An open-ended question was included to give the opportunity for respondents to list risk factors that were not included in the survey, but that they felt were a priority. The survey was completed anonymously. An email with a link to the online survey was distributed in May 2014 to 138 IPMSSG members. The email introduced the Tool-Kit project and its goals, the risk factor survey and our research team. A reminder email, that included the original email, was sent two weeks later. There were 48 IPMSSG members who responded to the risk factor survey (35% response rate).

Responses were summarized using two approaches. First the proportion of respondents that indicated the risk factor was *a priority* or *important, but not a priority* were calculated separately; followed by the proportion combining these two response options. Proportions were compared across the 12 risk factors to help select three risk factors. The two risk factors that were most highly endorsed by IPMSSG members as *a priority* for future research were sun exposure and vitamin D intake (85% and 81%, respectively). Infectious mononucleosis was also ranked highly (73%). When I combined the response options *a priority* and *important, but not a priority*, both sun exposure (96%) and vitamin D intake (94%) remained highly endorsed. Using this latter approach, environmental tobacco smoke (ETS) ranked third (93%). While only 35% rated ETS as *a priority* for future research, it was most highly endorsed as being important for future research. Based on the challenges surrounding collection of information about ETS exposure using questionnaires, ETS was selected as the third risk factor, in addition to sun exposure and vitamin D intake. Following the survey a one page summary of the survey results was sent by email to all IPMSSG members.

3.3.6 Literature Reviews of Measurement Property Studies

The systematic review of measurement property studies presented in section 3.2 and chapter 4 was performed to provide an evidence-base to inform the development of the Tool-Kit variables. I also conducted similar reviews to identify validated questionnaires to assess vitamin D intake and ETS; but do not present the methods and results of these reviews in this thesis. The objective of the systematic review, which was specific to the Tool-Kit, was to identify validated questionnaires to assess children's sun related behaviours in case-control studies. The findings of the three measurement property reviews were used in designing the Delphi study rounds, and

were also summarized in tabular format to facilitate face to face discussions during the third round of the Delphi study.

3.3.7 Delphi Study

As is suggested in the harmonization literature, I used an iterative expert consensus seeking process to select core variables.[124, 126] I designed a Delphi study with four rounds, to obtain input from researchers in the field. The Delphi method was developed by the RAND Corporation in the 1950s, to use expert input to forecast the impact of technology on warfare.[146] They note that "*its object is to obtain the most reliable consensus of opinion of a group of experts. It attempts to achieve this by a series of intensive questionnaires interspersed with controlled opinion feedback."* There are several advantages of a Delphi study, including the ability to obtain input from individuals who are geographically dispersed, which was important in developing the Tool-Kit. Given that the process is meant to be anonymous, this avoids forms of open group biases, such as the bandwagon effect or group-think. [147] However, I modified the process. In addition to providing anonymous input, experts also met face-to-face for the third Delphi round. I felt that a combined approach was more effective to meet the research objectives, as I wanted to actively engage experts in group discussions.

I designed a Delphi study with four rounds. The rounds were developed using knowledge gained from the systematic reviews. A feedback report with a summary of responses from the previous round was included in the subsequent round, which allowed experts to provide input on the collective responses. I used SurveyMonkey (San Mateo, California, USA) for rounds one and two, round three was completed face-to-face through guided discussions, and in round four I circulated a Word document via email. Rounds 1, 2 and 4 were anonymous.

Round one had two purposes: (i) to define a research question, for each of the risk factors, to guide future research; and (ii) to select a set of criteria to guide the selection of the Tool-Kit core variables. The primary purpose of Delphi round two was to select, for each risk factor, three constructs; which was completed to help focus the process of selecting core variables in round three. Constructs represent various sun related behaviours, such as summer sun exposure, winter sun exposure, or skin characteristics. Within each construct different variables can be conceptualized (i.e. *frequency* of sun exposure during summer or *duration* of sun exposure during summer). The purpose of round three was to select and define the core and ancillary variables. The purpose of round four was to provide additional comments on the

selected variables and provide final approval on the Tool-Kit variables that were selected in round three.

3.3.7a Assembling a Working Group

To complete the Delphi study I first assembled a working group (WG) of eleven researchers. My supervisor, Dr. Christina Wolfson, and I provided oversight, which included designing each round, incorporating and summarizing expert input, and providing feedback to our expert WG. The other nine WG members participated in each round of the Delphi study; and included epidemiologists, pediatric MS neurologists, adult MS neurologists and content experts for each risk factor. Three WG members were co-applicants on our operating grant (Drs. Brenda Banwell, Heather Hanwell and Maura Pugliatti), and six were invited external experts; three pediatric neurologists and three content experts, one for each risk factor. Invited experts were contacted by email, and had to be available to attend an initial face-to-face meeting in Montreal, as well as agree to participate in all four rounds of the Delphi study. The initial meeting that I planned, organized and led was held in November 2014, and provided the WG with important background information for participation in the Delphi study.

Three of the invited experts were pediatric neurologists selected from among the members of the IPMSSG, using a snowball sampling strategy. I sent electronic invitations to three pediatric neurologists who were actively involved in pediatric MS research; two of them were unable to participate, and were asked to suggest another, whom they felt would be a good candidate to participate in this research. The pediatric neurologists who agreed to participate all practiced in Europe; and included Drs. Ming Lim and Evangeline Wassmer from the United Kingdom and Dr. Rinze Neuteboom from the Netherlands.

The three content experts were identified from among authors of publications included in the systematic reviews of measurement properties. For sun exposure and ETS, I created a ranked list of authors, based on the number of publications they had authored. For sun exposure, the author that had published the most was unavailable, the second did not respond to my email, and the third, Dr. David L. O'Riordan, agreed to participate. For ETS the author I contacted first, Dr. Jörg E. Matt, agreed. For vitamin D intake, my supervisor and I invited a nutrition researcher, Dr. Bryna Shatenstein, who is located in Montreal, with whom I consulted when developing the vitamin D intake review; she had also authored one of the publications in the vitamin D review.

3.3.7b Risk Factor Working Groups

The WG was divided into 'risk factor working groups', one for each risk factor, with four experts in each group. Drs. Banwell (ETS and vitamin D intake), Hanwell (sun exposure and vitamin D intake) and Pugliatti (sun exposure and ETS), each served on two groups, based on their research experience and interests. The three content experts (Drs. Matt, O'Riordan and Shatenstein) served on the group they were selected for. I asked Drs. Lim (ETS), Neuteboom (sun exposure) and Wassmer (vitamin D intake) to rank their preference for the risk factor they preferred, and conveniently they each selected a different risk factor.

3.3.7c Delphi Round One

One research question for each risk factor was presented, and experts were asked to comment on the research questions and provide suggestions for improvements. The WG was also presented with 13 criteria and asked to what extent they agreed (*strongly agree* to *strongly disagree*) that the criteria should be used; they were also asked to list additional criteria, they felt were important, but that were not listed. Individual criteria were selected if the majority of experts responded that they *agreed* or *strongly agreed* that the criteria should be included; as a result of the WG input eight criteria were selected. (Chapter 5, Table 5.2)

3.3.7d Delphi Round Two

Experts were presented with a list of constructs, and were asked to indicate if variables related to the construct: (1) *must* be included; (2) are *important*, but represent *supplementary* information; (3) are *not required* to address the research question. For sun exposure the constructs were: summer sun exposure; winter sun exposure; sun exposure during holidays; travel to sunny destinations; sun protection; sun sensitivity; skin characteristics; phenotypic characteristics (e.g. eye colour); residential history; and meteorological data. The three constructs that were most highly ranked were selected, and were focused on in round three.

3.3.7e Delphi Round Three

I had initially planned for all rounds to be online, however given that selecting the core variables was a complex process, which was difficult to fully represent online, I decided it was best to actively engage experts in face-to-face discussions. I planned, organized and led a one and a half day meeting in Montreal. At this meeting the WG participated in guided discussions to select and define a set of core variables for each risk factor. The meeting was divided into three break-out sessions: (i) to orient discussions about the exposure; (ii) to select the core variables;

(iii) to define the selected core variables. Given that the goal was to limit the number of core variables, experts were also asked to select and define ancillary variables; which I defined as important supplementary information about exposure, but that was not deemed core by the WG. The meeting was audio recorded, which I summarized following the meeting, and used to prepare the final proposal presented in round four.

3.3.7f Delphi Round Four

WG members used the Track Changes function in Word, to provide input on each variable; and they were also asked to answer specific methodological questions that were needed to fine-tune the Tool-Kit variables. The content validity of the Tool-Kit core variables was also assessed in round four. The Tool-Kit is a proposal for a common measurement framework that outlines a set of exposure variables, their definitions, harmonizable response options and data coding.

3.4 Manuscript 3 Methods

Manuscript 3 (Chapter 6) presents the research related to the third and fourth objectives of this thesis: *(i) to compare two etiological models to determine if the association between sun exposure and MS risk is best explained by exposure during a specific age period in childhood (<15 years), or by accumulation of exposure throughout childhood; and (ii) to characterize latent sun exposure behaviour groups in childhood and compare risk of MS across groups.*

3.4.1 EnvIMS Study Design and Setting

The data used to address objectives 3 and 4 were collected in the Environmental Risk Factors in MS Study (EnvIMS). The goal of EnvIMS was to identify environmental risk factors for MS and evaluate their interactions. The EnvIMS study design and methodology is presented in a publication that I was first author on.[148] EnvIMS is a frequency matched case-control study that enrolled cases and controls in Canada, Italy, Norway, Serbia and Sweden. In my thesis I only used data collected in Canada, Italy and Norway as these countries had the largest sample sizes. Study coordination took place at major academic institutions in each country (McGill University, University of Bergen, and University of Sassari). The study was conducted between 2009 and 2010 in Italy, between 2009 and 2011 in Norway, and between 2012 and 2013 in Canada.

3.4.2 Study Participants

EnvIMS study participants were over the age of 18 years at the time of sampling; and thus the case series includes some cases of pediatric-onset MS. Cases had to have a clinically confirmed diagnosis of MS based on the established Poser[54] or McDonald diagnostic criteria.[39] To limit to more recent onset cases, cases had to have clinical disease onset within 10 years at the time of sampling. Cases and controls were frequency matched on year of birth (within 5 years), sex and area of residence. The goal of EnvIMS was to obtain 4 controls per case, however, as response rates were low, 3 to 4 controls were available per case in Italy and Norway, and 2 controls per case in Canada. Response rates were highest in Canada (cases: 83%, controls: 59%), followed by Norway (cases: 70%, controls: 36%), and lowest in Italy (cases: 43%, controls: 21%).

Cases and controls were sampled from: Sardinia, Ferrara and Republic of San Marino in Italy; throughout Norway in Norway; and the Greater Montreal Area, Greater Toronto Area and city of Winnipeg in Canada. Case selection was completed using regional MS registries in Italy, and the national MS registry in Norway. As there are no registries in Canada, cases were selected from large MS clinics in three major Canadian cities (Montreal, Toronto and Winnipeg). In Canada, the MS clinic nurse or coordinator identified eligible cases, and introduced the study during the patient's next clinic visit.

Control selection was completed using regional healthcare databases in Italy and Statistics Norway in Norway. The distribution of year of birth, sex and area of residence in cases was used by database custodians to select controls from these population-based databases. In Canada, no equivalent was available, and random digit dialling was used to identify controls living in the same regions as cases (based on telephone area code). A survey company provided a list of randomly selected telephone numbers and addresses (ASDE Survey Sampler, Inc., Montreal, Canada). Trained interviewers contacted each telephone number to identify eligible controls. As cases and controls were enrolled concurrently, research staff attempted to ensure overlap in the distribution of age and sex between cases and controls.

3.4.3 Questionnaire

EnvIMS investigators developed a 10-page questionnaire, the EnvIMS-Q.[149] The primary goal of the questionnaire was to collect information from study participants about their exposure,

from birth, to several factors that had been previously implicated in MS risk (e.g. sun exposure, passive and active tobacco smoking, infections, diet etc.). (Appendix C)

The questionnaire also collected key information on demographic characteristics and potential confounding variables. The questionnaire included a core set of questions which were common across all questionnaires; as well as country-specific questions. The EnvIMS-Q was originally drafted in English. It was translated into Italian, Norwegian and Canadian-French. The layout and appearance of the EnvIMS-Q was identical across countries, designed to be optically scanned and thus data were read electronically.

The EnvIMS-Q was pilot tested in all five counties, and was found to have cross-cultural acceptability, to be feasible and to be reliable.[149] An EnvIMS-Q was addressed to each study participant and mailed to their home address. An identical package was sent to cases and controls. In addition to the EnvIMS-Q, the package also included an introductory letter detailing the study goals, a pre-addressed postage-paid return envelope, a study brochure and post-it notes with country-specific sentences to motivate participation.[150] A colorful logo created specifically for the study was included on all documents. Two reminders were sent to non-responders in Italy and Norway and three reminders were sent in Canada.

3.4.4 Variables

This section presents the measurement and coding for the exposure, outcome and potential confounding variables that are used in the statistical analyses.

3.4.4a Exposure Variables

Sun exposure during the summer was the main exposure used in objective 3. In addition to summer sun exposure, winter sun exposure and use of sun protection were used as main exposures in objective 4. Sun related questions were adapted from those that have been used in previous MS sun exposure studies[13, 17, 18, 20] and have been tested for reliability in Australia (11 week interval, kappa=0.51-0.70).[151] They were also found to have acceptable test-retest reliability in pilot testing of the EnvIMS-Q.[149]

Both summer and winter sun exposure was assessed using a question about frequency of outdoor activities. Summer and winter were not strictly defined. Summer sun exposure was ascertained using the following question: *"In the past, <u>in summer,</u> how often did your activities (playing, participating in sports, watching sports, gardening, walking, work activities, etc.) take*

you outside at the following ages?" Winter sun exposure was ascertained using the question: *"In the past, in winter, how often did your activities (playing, participating in sports, watching sports, shovelling snow, walking, work activities, etc.) take you outside at the following ages?"* Both questions offered four response options: *not that often, reasonably often, quite often and virtually all the time.* The question about frequency of sun protection use was asked generally: *"How often did you use sun protection (sunscreen or protective clothing such as hats, long sleeves) at the following ages?"* This question also had four response options: *never/seldom, sometimes, quite often and almost always.*

Each of these questions was asked for five-year age intervals from birth to age 30 years, as well as in the last 3 years. My analyses focus on the first three age intervals (birth to age 15 years). In Norway the first three age intervals differed from those used in Canada and Italy (birth-5 years, 6-10 years, 11-15 years), as the Norwegian EnvIMS investigators wanted the age intervals to follow the Norwegian schooling system, to aid with recall (birth-6 years, 7-12 years and 13-15 years). Although age intervals were slightly different in Norway, given that there was substantial overlap, I combined them with the similar age interval used in Canada and Italy (i.e. birth-5 years combined with birth-6 years). In Canada, an additional response option, *don't know*, was provided for age intervals 0-5 years and 6-10 years, for all three exposure variables. For objective 3, summer sun exposure was dichotomized. *Not that often* and *reasonably often* were combined and defined as the lower sun exposure group; and *quite often* and *virtually all the time* were combined and defined as the higher sun exposure group. To estimate the increase in risk associated with lower sun exposure, the lower sun exposure group was coded as 1 and the higher sun exposure group was coded as 0.

For objective 4, winter sun exposure and sun protection use were also dichotomized. Winter sun exposure was coded using the same approach that was just described for summer sun exposure, with higher values representing lower levels of sun exposure. For sun protection those reporting *almost always,* and *quite often* were coded as 1, and those reporting *never/seldom* and *sometimes* were coded as 0.

3.4.4b Outcome Variable

MS cases were coded as 1 in the analysis and controls coded as 0.

3.4.5c Potential Confounding Variables

A large number of variables that were selected using background knowledge of MS and sun exposure were examined as possible confounders. Age was centered and modelled continuously. In Italy and Norway, participants' sex was also ascertained from the respective registries, whereas in Canada a question was included in the EnvIMS-Q. For the analyses, females were coded as 1 and males coded as 0.

In addition to age and sex, I also examined confounding by: family related variables (parent's education, ethnicity, and number of siblings), health related variables (physical activity, body size, and environmental tobacco smoke (ETS) exposure from mother, father or both), sun related variables (winter sun exposure and sun protection) and phenotypic related variables (skin, eye and hair colour and tanning reaction to sun), and other disease related variables (infectious mononucleosis, indoor allergies, outdoor allergies and autoimmune disease).

The highest level of education attained by the participant's mother and father was reported by the study participant; and depending on the country, different response options were provided, but I was able to classify parent's education into three levels: less than high school, completed high school, and any post-secondary education. The highest education level of either parent was used in the analysis, modelled using indicator variables, with any post-secondary education used as the reference.

Participants were asked to report their birth parents' ethnic background. However, response options for parents' ethnicity also differed by country, which made it difficult to combine this variable across countries. Data on parents' ethnicity that were collected in Canada and Norway enabled me to create a variable that classified ethnic background as European and non-European. However, in Italy, the response options designated various regions of Italy (e.g. northern Italy, central Italy, etc.) and provided an option for non-Italian ethnicity; although most participants were Italian. Therefore, when assessing confounding by parents' ethnicity analyses were restricted to Canada and Norway. European ancestry was coded as 1 and non-European ancestry coded as 0.

In Canada participants recorded the total number of brothers and sisters they have, the sex of their siblings, as well as the year their siblings were born. In Italy and Norway, participants only recorded year of birth and sex of siblings. A variable indicating the total number of siblings was created using these data. Participants reporting more than 6 siblings were

combined into the same category. The total number of siblings was treated as a continuous variable, but truncated at 6.

I classified physical activity, body size and ETS exposure as health related variables. The question on physical activity asked participants to report their frequency (*none, <once /week, 1-2 times/week or 3+ times/week*) of (i) light and (ii) vigorous physical activity, when they were between the ages of 13 and 19 years. Although this variable does not directly coincide with the age periods included in my analyses, physical activity is an important variable to consider as it is related to MS and to amount of sun exposure. I combined the two physical activity variables, to create a three-level variable that classified physical activity as no physical activity, light physical activity only, or both light and vigorous physical activity; indicator variables were modelled with 'both light and vigorous physical activity' as the reference category.

Body size at age 5, 10 and 15 years was ascertained using body shape silhouettes.[152, 153] There were nine body shape silhouettes to select from, and one version was used for males and another for females. Data were coded 1 to 9, 9 indicating the largest body size, and were treated continuously in the analysis. Participants reported if their mother and/or father smoked inside the house when they were a child. I examined confounding by ETS exposure from mother, father as well as a variable characterizing any parental exposure. ETS exposure was coded as 1 and no exposure coded as 0.

The sun related variables, winter sun exposure and sun protection, were examined as main exposures in objective 4, but for objective 3 these variables were examined as confounders. The phenotypic related variables that I examined were skin colour, eye colour, hair colour and tanning reaction to sun. To quantify skin colour the questionnaire included a colour chart, coded from 1 to 10, with 10 indicating darkest skin colour.[154] Participants were instructed to compare the colour chart against the inner part of their arm, between the elbow and the armpit, and to select the best number to represent the colour of their untanned skin. Skin colour was modelled continuously.

Response options for eye colour differed slightly between countries. In Italy and Norway four response options were provided that I classified into dark (black or brown eyes) and light (blue or green) eye colour; whereas in Canada there was an additional response option for hazel eye colour. I grouped hazel with brown eyes, into the dark eye colour category. Light eyes were coded as 1 and dark eyes coded as 0. There were five response options for hair colour in each

country: black, dark brown, brown, blonde, red. I created a three level variable, grouping black or dark brown hair colour together, as well as blonde or red hair colour. Indicator variables were created and the darkest hair colour category was used as the reference. Tanning reaction to the first sun was ascertained using a Fitzpatrick type scale,[155] and included four ordinal response options from *'always burn, never tan'* (coded as 3) to *'rarely burn/more than average tan'* (coded as 0).

I also considered confounding by history of other diseases, such as infectious mononucleosis, indoor allergies, outdoor allergies and autoimmune disease. The age of onset for each of these was also ascertained in the questionnaire, and participants were only classified as 'yes' if onset was prior to or during the age interval under examination. Thus if onset was after age 15, the participant was classified as 'no'; whereas if age at onset was, for example, 7 years the participants was classified as 'yes' for age intervals 6-10 year and 11-15 years, but not birth-5 years. Yes was coded as 1 and no coded as 0.

Participants were asked if they had had infectious mononucleosis (also known as "mono" or "the kissing disease"). A history of allergy to pollen was classified as outdoor allergies and history of allergy to house dust was classified as indoor allergies. An 'other' category was also included in the questionnaire, which asked participants to specify the type of allergy. Some participants noted hay fever for the other category, but did not check yes for pollen allergy, and were thus included in the outdoor allergy group. The autoimmune diseases that were considered include systemic lupus erythematosus (lupus), rheumatoid arthritis, hypothyroidism, hyperthyroidism, Crohn's disease, ulcerative colitis, type I diabetes mellitus (juvenile diabetes), celiac disease, psoriasis. If the participants reported having been diagnosed with one or more of these, they were classified as yes.

3.4.5 Statistical Methods

3.4.5a Sample Size Considerations

The EnvIMS study was originally designed to enrol a combined number of 3,000 cases and 12,000 controls across the five countries. With the planned sample size and using conservative estimates for exposure prevalence and differences between cases and controls, sample size calculations suggested that odds ratios as small as 1.2 could be identified with over 90% power. While the targeted sample size, and control to case ratio was not achieved, updated power analysis[156] demonstrated that with the sample sizes obtained there is over 80% power to

identify odds ratios as low as 1.2, and over 90% power to identify odds ratios as low as 1.5. (Appendix D)

3.4.5b Objective 3 Analyses

The modelling approach I used to identify the most etiologically relevant model for MS was based on an analytical approach that had been proposed to compare the plausibility of various life course epidemiology models, in order to select the one that is most consistent with the data.[25] As this analytical approach was developed to model binary exposures,[25] summer sun exposure was dichotomized as described in section 3.4.4a. I used Stata 11.0[157] to complete the analyses. A generalized linear model, with a logit link and binomial family, was used to estimate the risk of MS associated with lower levels of outdoor sun exposure during summer, for the various models. Fixed effects for country were included in all regression models. A saturated regression model is used as the base model; this model estimates effects estimates for all possible exposure patterns. A series of nested regression models, that are developed to represent the different life course epidemiology conceptual models, are then compared to the saturated regression model, using model fit criteria. I used the Bayesian Information Criterion (BIC) and likelihood ratio test (LRT) to select the best model. The goal of the model selection process is to identify a more parsimonious model (or models) that characterize the data best (i.e. have similar model fit as the saturated model). The best model was one that had the lowest BIC and for which the LRT with a p-value $\geq$0.05. I examined the critical time period and accumulation model.[25, 135, 136] A description of the model parameters that are estimated by the regression models that were used is provided in an appendix in Manuscript 3 (Chapter 6; Appendix 6.1)

Critical Period Model: The critical period model suggests that there is a critical period during which an individual is susceptible to exposures that determine disease risk. This period could be a certain age, age period, a developmental process (e.g. puberty) or other distinct event (e.g. pregnancy). I estimated the risk of MS associated with having low levels of summer sun exposure, compared with having higher levels of summer sun exposure for three five-year age intervals, before the age of 15 years. I hypothesized that there is a five-year critical period, before the age of 15 years, during which low levels of sun exposure best predict risk of MS.

Accumulation Model: The accumulation model suggests that the longer the length of time that an individual is exposed (or not exposed in the case of low sun exposure), the greater the risk of disease, irrespective of when exposure occurs. I estimated the risk of MS associated with the sum of the number of the age intervals (0, 1, 2 or 3) that an individual reported low levels of sun exposure, compared to individuals who reported high levels, in all three age intervals. I modelled the accumulation of exposure using an ordinal variable, as well as indicator variables, with 0 as the reference group. I hypothesize that MS risk is greatest in individuals who are exposed to low levels of summer sun exposure for a greater number of age intervals before the age of 15 years.

3.4.5c Accounting for Confounding

Cases and controls were frequency matched on age and sex, and these variables were included in all regression models. To enable comparisons across models the same set of confounders were used in all adjusted models. The list of potential confounders was generated using background knowledge. Bivariate associations between the potential confounding variable and each critical period exposure variable, and outcome variable were first explored. Logistic regression was used to complete all bivariate analyses. Variables were deemed possible confounders if they were associated ($p<0.05$) with exposure in controls and associated with outcome in both exposed and unexposed groups. If a variable was deemed to be a possible confounder in any age interval, the variable was examined in a multivariable model. A backward deletion, with a greater than 10% change in estimate approach was used to select the confounder set to include in all models.[158] To do this I used the saturated model, and if the magnitude of any of the exposure estimates changed by more than 10%, the variable was included as a confounder. To present the most robust estimates, I also performed a backward deletion approach, again, on the model that had the best model fit criteria.

3.4.5d Missing Data

Missing data are not a significant problem in this dataset. By design there was no missing information for the outcome, sex, age and country. For outdoor sun exposure during summer the amount of missingness ranged from 3.4% to 7.1%. Among the confounders examined the other sun related behaviour variables, sun exposure during winter (range: 6.3%-9.4%) and sun protection use (range: 5.1%-12.9%), had the largest amount of missing data in the dataset. However, information on other confounders was, overall, complete; missing data ranged from 1.3% for hair colour to 9.6% for parents highest level of education. While the missing data

mechanism cannot be known with certainty, I used multiple imputation (MI) models to explore the effects of missing data on the final selected model.

3.4.5e Sensitivity Analysis

I completed three types of sensitivity analyses to assess the robustness of the final results: (i) to assess the potential impact of time since exposure, I restricted the sample to those under (i) 30, (ii) 40 and (iii) 50 years of age; (ii) to examine more incident cases, I restricted analyses to those with disease duration less than five years; and (iii) to assess the potential impact of misclassification I restricted analyses to study participants who reported that they received help completing the questionnaire.

3.4.5f Objective 4 Analyses

The analyses I performed for objective 4 were exploratory, and were used to compare risk of MS across latent sun exposure behaviour groups. I used Latent Class Analysis to create sun exposure behaviour groups using three exposure variables: sun exposure during summer, sun exposure during winter and use of sun protection. To complete these analyses I used the bias-adjusted Step3 procedure in Latent GOLD 5.0 (Statistical Innovations, Belmont, MA, USA). [159] The process involves three steps. First, a cluster model is developed for a set of response variables. I tested models that had 1 to 7 clusters, and I used the BIC to select the model with the number of sun exposure behaviour groups that best characterize the data. Age and sex were included as covariates in the cluster model. A profile plot was used to visualize the distribution of the classes, and the estimated class means for each response variable (re-scaled to range from 0 to 1).

The second step in the three step procedure involves assigning individuals to the different clusters. Using the best cluster model selected in the first step, individuals where assigned to each clusters based on their posterior class membership probabilities, using proportional class assignment. The final step involves estimating the association between cluster and an outcome, case status (MS or control), using logistic regression. Two different estimation methods are available in Latent GOLD; I used both. Maximum likelihood estimation has been suggested to underestimate the association between cluster and the outcome, and thus a corrected version was developed, called the Bolck-Croon-Hagenaars (BCH) method.[160]

Latent GOLD provides odds ratio estimates that either use effects coding or dummy coding. I used both approaches as they provide slightly different information. I first used effects

coding, which compares each cluster to the average of all clusters, to estimate risk of MS for each sun exposure behaviour group, and to compare risk across clusters. I also used dummy coding to estimate the risk of MS as compared to the cluster with the highest risk of MS. I used this approach because I was interested in the high risk groups, and wanted to determine how this group compared to the others.

3.5 Summary

In this chapter I presented an overview of the methods I used to perform this thesis research, which was intended to expand on the methods sections included in each individual manuscript. In the next three chapters, I present the three manuscripts that make up this research.

CHAPTER 4: SYSTEMATIC REVIEW OF MEASUREMENT PROPERTIES

4.1 Preface to Manuscript 1

In chapter 4 I present the first of the two manuscripts that are related to the first methodological theme of this thesis research: *measurement*. Specifically, Manuscript 1 focuses on measurement properties of self-report questionnaires that can be used in epidemiologic research to measure sun related behaviours in children. I designed and performed a systematic review of measurement property studies using existing guidelines, a validated search strategy and a standardized quality assessment tool. The research presented in this chapter was completed as the first stage in the development of the Tool-Kit core variables, which is presented in the next chapter (Manuscript 2). The goal of Manuscript 1 was to summarize and critically appraise existing evidence on the validity and reliability of questionnaires designed to ascertain information about sun exposure, use of sun protection, or host characteristics, such as sun sensitivity or skin colour. This manuscript will be submitted to the *International Journal of Epidemiology.*

4.2 Manuscript 1 - *Sun Related Behaviours in Children: A Systematic Review of the Measurement Properties of Self-Report Questionnaires*

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ABSTRACT

In observational studies, self-reported questionnaires are often used to measure sun related behaviours, such as sun exposure or sun protection. Appraising the measurement properties of questionnaires is an essential step in study design. We conducted a systematic review of measurement properties to identify, critically appraise, and summarize the validity and/or reliability of self-reported questionnaires that can be used to ascertain information about sun related behaviours in children, with the goal of enhancing questionnaire development and ultimately minimizing information bias in pediatric epidemiological studies. Publications were included in this review if they: (i) reported on a questionnaire that assesses a sun related behaviour(s), (ii) assessed measurement properties, (iii) included children, and (iv) were written in English. PubMed, EMBASE and CINAHL were searched in February 2014 using a validated search strategy. Two reviewers independently extracted data from each publication, and performed quality assessment using the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) checklist. Of the 4538 abstracts screened, 35 publications were included. Twenty-two questionnaires were identified; six were assessed in more than one study. The measurement properties of questions about sun protection (71%), sun exposure (34%), and host characteristics (31%) were assessed, and questions mainly focused on current

(45%) and usual (45%) behaviours. Four studies examined both validity and reliability, 14 examined validity only and 17 examined reliability only. Half of the studies were rated as poor quality, primarily due to incomplete reporting or improper statistical analyses. While the measurement properties of the 22 questionnaires varied, collectively there is evidence of validity and reliability. The results of this review provide an evidence-base for the selection of questionnaires that can be used to assess sun related behaviours in pediatric populations.

BACKGROUND

The ultraviolet radiation (UVR) emitted by the sun plays an important role in several human physiological processes such as, vitamin D synthesis, melatonin regulation, immune system function, and endorphin production.[22] However the sun is also responsible for sunburns, eye damage, photoaging and skin cancer.[113] Due to the varied effects that the sun has, both too much sun exposure and too little sun exposure can have negative effects on health. [22-24] For example, too much sun exposure leads to sunburns, and a greater number of sunburns is a determinant of melanoma risk.[114] Alternatively, too little sun exposure is closely linked to deficient vitamin D levels, and lower levels of vitamin D have been linked to many different diseases included osteoporosis, cancer, heart disease and autoimmune diseases, including multiple sclerosis.[115]

It has been estimated that half of the total sun exposure up to age 60 years is acquired during early life, thus childhood is an important etiologic exposure period to consider.[161] Compared to other sun related risk factors, sunburns are recallable events, and exposure measurement may be associated with less misclassification. Measurement of sun exposure and use of sun protection, however, are much more difficult constructs to quantify. The amount of sun a child is exposed to is difficult to measure and is dependent on environmental factors,[112] sun-seeking or sun-avoidance behaviours, skin characteristics (e.g. pigmentation), use of sun protective measures, as well as cultural factors.[112]

Self-report questionnaires are often used in epidemiological studies to examine the effects of sun exposure. While self-report questionnaires are known to have a substantial amount of measurement error, they are often the most appropriate approach given the time and resources required for more intensive methods, such as direct observation or UV dosimeters. In certain contexts, such as a case-control study, self-report may be the only realistic approach to obtain

exposure information. Before a decision is made to use a questionnaire, the measurement properties (validity and reliability) of the questionnaire should be assessed. This includes consideration of previous measurement property studies, as well as testing the questionnaire's measurement properties in the population of interest, if not already done. Validity is defined as "*the degree to which a questionnaire measures the construct it is designed to measure*"; reliability is defined as "*the degree to which the questionnaire is free from measurement error",* assuming it is valid.[119]

A systematic review of measurement property studies can be used to identify, critically appraise and compare the measurement properties of available questionnaires. [121] This approach can be used to select a questionnaire, or to identify questionnaires that warrant validation. The use of systematic reviews of measurement property studies has been increasing in popularity; for questionnaires measuring health status or (health-related) quality of life, the number has increased from 0-1 review per year in the early 1990s, to 31 in 2005,[121] and 85 in 2013.[122] The COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) were developed in response to the need to improve the quality of reporting of original measurement property studies and, to provide guidelines to perform rigorous systematic reviews of such studies. [121] The COSMIN taxonomy, terminology and checklist were developed using an international Delphi study.[119, 162] The Delphi study included forty-three experts in epidemiology, statistics, psychology and clinical medicine who provided input to develop a set of standards and methodological resources to facilitate the conduct and reporting of systematic reviews of measurement property studies.

We conducted a systematic review of measurement property studies, using the COSMIN guidelines, to examine available questionnaires that could be used to ascertain information about children's sun related behaviours. The goal was to identify, critically appraise and summarize the measurement properties of validated questionnaires, and ultimately to provide a resource to help guide the design and/or selection of questionnaires for future pediatric epidemiological studies.

METHODS

Systematic Review Protocol

A review protocol was prepared in advance of performing the review. (Appendix 4.1) This systematic review was designed to investigate the following research question: what are the

measurement properties (validity/reliability) of self-report questionnaires that can be used to ascertain information about sun related behaviours in children?

Eligibility Criteria

To be included in the review a publication had to report on the measurement properties (validity/reliability) of a questionnaire designed to measure sun related behaviours in children (birth to 18 years of age) and be written in English. The sun related behaviours of interest were sun exposure (e.g. current, recent, cumulative, and history of exposure), use of sun protection, and host characteristics (e.g. sun sensitivity). Both self-administered and interview-based questionnaires, that used either child- or proxy-report (e.g. the child's parent) were considered.

Information Sources

MEDLINE (PubMed, 1946-current), EMBASE (1947-current) and Cumulative Index to Nursing and Allied Health Literature (CINAHL, 1937-current) were searched in February 2014. The reference lists of key review papers and included publications were also searched. If the actual questionnaire was not included in the publication, in an appendix or in an online supplement, and could not be found using Google, we emailed the corresponding author to request a copy.

Search Strategy

Our search strategy was based on one that had been developed and validated in PubMed by the COSMIN research group (97% sensitivity and 75% specificity).[137] The search strategy was structured using four search components: (i) construct, (ii) population,[138] (iii) instrument and (iv) measurement properties.[137] (Appendix 4.1) We consulted with a McGill University librarian to help us develop our search terms. We obtained similar, but not yet validated, search strategies to use to search EMBASE and CINAHL. (Dr. Caroline Terwee, personal communication, 2014)

Study Selection

The search results were imported into DistillerSR (Evidence Partners, Ottawa, Canada), an online systematic review software. The titles and abstracts were screened independently by two reviewers (SM and CT). DistillerSR automatically identifies discrepant responses.

Discrepancies were resolved through discussion between the two reviewers and another author was consulted (CW) as needed.

Quality Assessment of Measurement Properties

The COSMIN checklist was used to complete quality assessment.[139, 142, 162] The checklist includes a variety of close-ended questions used to assess the quality of measurement property studies. We developed an online version of the checklist in DistillerSR. Forms were created for the following measurement properties: (i) internal consistency, (ii) reliability, (iii) content validity (including face validity), (iv) criterion validity, (v) hypothesis testing, (vi) cross-cultural validity, and (vii) structural validity.[119] The COMSIN checklist also includes two data extraction forms that focus on interpretability and generalizability of the study. Each question in the checklist is rated as: excellent, good, fair or poor. We used the 'worst score counts' scoring system.[143] This scoring system assigns a score that is equal to the lowest rating given for any of the questions in the checklist. This scoring system is recommended by its developers and a poor rating reflects critical methodological flaws in the study design or reporting.

Data Collection Process

An online data extraction form was developed in DistillerSR, and was pilot tested twice, independently, by two reviewers (SM and CT). The COSMIN quality assessment checklist includes data items (e.g. age, sex, sampling method, setting etc.) which were included in our online data extraction form. An additional list of items that were selected from previous systematic reviews of measurement property studies and through discussions with our research team, were also extracted from each publication. The data items that were collected are listed in the appendix (Appendix 4.1).

Summary Measures

We also extracted the result of key analyses. The summary measures of interest were dependent on the measurement property being examined, and primarily included: correlation and measures of association for construct validity studies; intra-class correlation, kappa and/or weighted kappa for studies examining agreement or reliability; testing the unidimensionality of the scale, followed by calculation of Cronbach's α for internal consistency studies.

Synthesis of Results

We provide a summary of the measurement properties studies that were identified. Descriptions of study results are focused on the studies that had an adequate quality assessment rating (i.e. fair, good and excellent); although studies that received a poor rating are mentioned. The sun-related questions that were included in the questionnaires were classified into three groups: sun exposure, sun protection and host characteristics. Questions about sun exposure quantify the amount of sun the child was exposed to, such as the time spent outdoors daily. Those about sun protection characterize the amount and/or type of sun protection used, such as wearing hats or sunscreen when outdoors. Those about host characteristics are related to the child's phenotype, such as sun sensitivity or the child's skin colour. A summary of the questionnaires that are examined in more than one study is also presented.

RESULTS

Study Selection

The PRISMA[163] study flow diagram is presented in Figure 4.1. There were 8,739 records obtained through electronic database searching (PubMed=3,253; EMBASE=4,102; CINAHL=1,384) and 6 records identified by hand searching reference lists. After records were de-duplicated, 4,538 publications were screened for inclusion, and 4194 were excluded. We reviewed 344 full-texts and 305 were excluded. The primary reason for exclusion was that the article did not report on the validity and/or reliability of a questionnaire (n=266). We completed data extraction on four publications that were subsequently excluded: two publications combined children and adults in the analysis, and child-specific results could not be isolated (the sample included 111 adults and 27 children);[164, 165] one publication had insufficient information about content validity to conduct a proper review;[166] and one publication examined *beliefs* about sun exposure and not sun exposure *behaviours*.[167] There were 35 publications that met the inclusion criteria.[161, 168-201]

Early in the screening process we realized that measurement property studies performed and reported in the publication were sometimes not specifically mentioned in the abstract as it was not the aim of the study. We thus modified the screening process and recorded if the abstract mentioned the use of a sun exposure questionnaire in a pediatric population, with no mention of whether measurement properties were assessed. There were 185 abstracts that met these criteria

and 178 were excluded. Therefore, seven of the 35 publications (20%) that are included in this review would have been missed, had this modification not been made to the screening strategy.[170, 176, 180, 187, 190, 191, 197]

Study Characteristics

Study characteristics are presented in Table 4.1. Studies were published between 1991 and 2013, and 60% were published since 2000. Over 80% of studies were carried out in the USA (18 studies[161, 170-172, 174, 177, 180-185, 189, 191, 193, 194, 200, 201]) or in Australia (11 studies[168, 169, 173, 175, 178, 179, 186-188, 192, 198]), and the rest were performed in New Zealand[195, 199], Colombia[196], Germany[197], Singapore[176] and the UK.[190] The setting was most often a school (57%)[170, 171, 173, 175, 177-179, 184, 186-188, 190, 195-200], a swimming pool (14%)[180, 182, 183, 193, 194] or the community (11%).[168, 181, 189, 192] The most frequent sampling method used was convenience sampling (51%);[161, 168, 170-172, 174, 175, 177, 181-183, 187, 188, 190, 191, 193-195] random (14%)[173, 178, 199] and consecutive (14%)[169, 185, 198] sampling were used less often. Two studies used a two-stage sampling approach;[182, 198] first sampling a larger unit, such as a school or swimming pool, followed by sampling of participants (i.e. children or their parents) within the larger unit. In nearly 30% of studies the methods used to sample study participants were not reported or not clearly described.[176, 179, 184, 186, 189, 192, 196, 197, 200, 201]

The sample size ranged from 10 to 4,721. Age mainly ranged from primary-school to high-school age, although one study included babies (7-11 months).[192] In three studies the sample also included adults.[181, 195, 198] In two, the child-specific results could be isolated from those for adults.[181, 198] The other used a sample of university students who ranged in age from 16-49 years; and while the results were not restricted for those under 18 years, the median age was 18 and thus the results are likely generalizable to our target population.[195] Most studies included an equal mix of boy and girls; in 74% of studies the proportion of girls ranged from 40-60%.

Questionnaire Characteristics

Characteristics of the 22 questionnaires identified are presented in Table 4.2. Ten questionnaires were named.[161, 170-172, 174, 176, 179-189, 191, 193-196, 200] Nineteen questionnaires were developed and tested in English. The majority of questionnaires were self-administered (84%). Self-report was most commonly provided by children (86%), whereas parent report was used in

36%. Forty-five percent of questionnaires assessed current behaviours,[169, 176, 178, 179, 181-183, 186-189, 193-197, 199-201] and 45% measured usual behaviours.[170-175, 177, 181-183, 185, 190, 191, 193, 194] Sun protective behaviours were most commonly measured. Questions about sun protection were included in 14 questionnaires, [161, 169-172, 174, 175, 177, 179-187, 189-191, 193, 194, 197, 199, 200] questions about sun exposure in 8 questionnaires [176, 178, 181-183, 189, 192, 193, 198-201] and host characteristics in 8 questionnaires.[168, 173, 175, 178, 181, 182, 188, 189, 195, 196, 198]

Measurement Properties

Four studies assess both validity and reliability;[178, 184, 185, 195] 14 studies assessed validity only[169, 176, 179, 181-183, 189, 192-194, 196, 199-201] and 17 reliability only.[161, 168, 170-175, 177, 180, 186-188, 190, 191, 197, 198] Two studies assessed three measurement properties,[178, 184] five studies examined two measurement properties,[175, 179, 185, 191, 195] and the majority (80%) assessed only one measurement property. A total of 44 measurement properties were assessed for quality using the COSMIN checklist. (Figure 4.2)

COSMIN Quality Assessment Checklist

The 'worst score' scoring system suggested that half of the measurement properties studies were of poor quality (49%). Among studies that examined validity, 42% were assigned a poor rating, as were 54% of those that examined reliability. In most cases a poor score was recorded for only one question in the checklist. For construct validity the most common reason for a poor score was that the measurement properties of the comparator instrument were not adequately described; while for test-retest reliability it was because correlation coefficients, rather than a measure of agreement, such as kappa or weighted-kappa, were used to quantify agreement; for inter-rater reliability because test conditions were not similar; and for internal consistency because the unidimensionality of items was not assessed.

Validity

Two studies assessed content validity[179, 181] and 17 assessed construct validity.[169, 176, 178, 179, 182-185, 189, 192-196, 199-201]

Content Validity: Content validity was the only assessed in two studies; one which received an excellent quality assessment rating;[181] and a second that received a poor rating due to incomplete reporting of study methods.[179] The study that received an excellent rating reported on a consensus-based set of core questions that were developed to measure both sun exposure and sun protection habits for skin cancer prevention research. [181] In that research, a working group was assembled to evaluate existing sun exposure questionnaires; and together they devised a core set of seven questions for children (via parent report) and eight questions for adolescents. Cognitive interviews were then used to refine the questions and response options.

***Construct Validity*:** Construct validity was demonstrated using several different comparators. A summary of these studies is presented in Table 4.3. Questions about sun exposure were examined in nine studies,[176, 178, 183, 189, 192, 193, 199-201] questions about sun protection in eight[169, 179, 182, 184, 185, 193, 194, 199] and host characteristics in two.[195, 196] Self-report of sun exposure was most often compared to UV exposure measured using a polysulfone dosimeter or similar device. Self-report of sun protection use was most often compared to direct observation. Correlation coefficients were most commonly used to quantify the association between measures.

Nine studies that reported on construct validity were rated as fair,[176, 178, 179, 183, 189, 195, 196, 200, 201] and one was rated as good.[199] The study that received a good rating was conducted in New Zealand and used a portable electronic UV monitor, worn by the child, to collect time-stamped UV exposure data.[199] The questionnaire assessed sun exposure and sun protection over one week. Zero UV exposure was greatest when children were indoors or in a vehicle, and exposure was highest when outdoors or outdoors in shade.

Three studies used polysulfone dosimeters and examined associations with reports of time in the sun (range: r=0.18-0.64).[178, 183, 201] One of these studies examined both sun exposure and vitamin D production, and reported correlation coefficients between time outdoors and polysulfone dosimeter measurements (r=0.64) that were adjusted for % daily UVB peak (i.e. a measure that captures the changes in UVB intensity throughout the day).[201] Other comparators that were used include UV sensitive stickers,[200] chromameter[189] and a light meter;[176] and these studies reported similar estimates of validity for questions about sun exposure, as was reported in the studies that used polysulfone dosimeters.

One study used direct observation to test the validity of sun protection questions included in the Solar Protection Behaviour Diary.[179] Agreement with a child's self-report ranged from k=0.30 (in the shade) to k=0.70 (wearing a hat).[179] The two studies on host characteristics used the Fitzpatrick scale. The Fitzpatrick scale focuses on sun sensitivity (i.e. if unprotected skin tends to burn or tan). One study used a spectrophotometer and found a strong inverse correlation between measured skin colour (with lower measured values indicating darker skin colour) and self-reported skin colour (Spearman's ρ=-0.75) and self-reported skin photosensitivity (ρ=-0.64).[195] The other used medical examination and only found 50% agreement with responses provided by high school students; adolescents tended to report less sun sensitive skin types.[196]

Reliability

Internal consistency analyses were performed in 11 studies,[161, 170-172, 175, 178, 180, 185, 190, 191, 197] intra-rater reliability (test-rest) in ten[168, 173-175, 178, 184, 186, 188, 191, 195] and inter-rater reliability in four.[177, 184, 187, 199] A summary of these studies is presented in Table 4.4. Three studies examined both internal consistency and test-retest reliability;[175, 178, 191] and one study examined both test-retest and inter-rater reliability.[184]

Internal Consistency (IC): Nearly all the studies that assessed IC examined items about sun protection behaviours. These studies were mostly skin cancer prevention intervention studies. The items focus on frequency of using various sun protective measures when outdoors in the sun, such as a hat, clothing or sunscreen; as well as sun-avoidance behaviours such as limiting time outside or using shade. Cronbach's α was reported in ten of the 11 studies. Overall, questionnaire items about sun protection behaviours were found to be internally consistent. Seven studies received a poor quality assessment rating. The primary reason for a poor rating was that it was unclear if unidimensionality of items was checked. However, all studies that received a poor rating reported large Cronbach's α values (range: 0.54 to 0.78).

Four studies received a fair or good rating.[170-172, 175] Three of these studies examined the Sunshine and Your Skin Questionnaire, although slight modifications were made to the questionnaire between studies.[170-172] The questionnaire has 14 questions about sun protective behaviours, and was found to consist of three factors (sunscreen use, lip balm use, and hat use), with two items in each factor, and 8 individual items. In each study IC was examined at three

time points (6 months apart) and Cronbach's α ranged from 0.52 to 0.84. In addition to these items, the questionnaire also included eight items on parent's preventive behaviours, which were also found to be unidimensional, and internally consistent (α range: 0.76 to 0.84). The fourth study with an adequate quality assessment rating that assessed IC reported on a behaviour scale with six items, four of which were found to be unidimensional with a Cronbach's α=0.54.[175]

Intra-Rater Reliability*:* Ten studies examined intra-rater reliability, or test-retest, of nine questionnaires. The Fitzpatrick scale was assessed in two studies.[188, 195] Questions about host characteristics were included in five questionnaires,[168, 173, 175, 188, 195] and sun protection in four questionnaires.[174, 175, 177, 184, 186, 188, 191, 195] The time interval between administrations ranged from 6 hours to 8-18 years. All nine questionnaires were based on child-report, and in one both the child and their parents completed a questionnaire separately.[184] In eight studies categorical response options were used, however, kappa was only estimated in five.[168, 174, 186, 188, 195] Three studies used ordinal response options but treated the data as continuous, and Pearson's correlations were estimated, which was the primary reason for a poor score.

Five studies were of fair or good quality,[168, 174, 188, 191, 195] and of these, three assessed host characteristics.[168, 188, 195] The two studies that assessed the test-retest reliability of the Fitzpatrick scale each used different questions and response options.[188, 195] One questionnaire asked two questions, one about skin reaction to mid-day sun exposure without any protection and another about skin colour;[195] whereas, in the other questionnaire, skin reaction and skin colour were incorporated into a single question.[188] Despite these differences, both studies found similar estimates for weighted kappa. For a 1-week test-retest, the weighted kappa was 0.77 for sun reaction and 0.78 for skin colour.[195] For a 6-month test-retest, on three separate occasions, weighted kappa ranged from 0.76 to 0.81 for the single question.[188] The other questionnaire that included questions on host characteristics examined long-term reliability of responses that were provided by participants in a study they had participated in 8-18 years earlier.[168] For questions on phenotypic characteristics (e.g. skin colour, hair colour) kappa ranged from 0.37 for children and 0.30 for adolescents for a question about shoulder freckling, to 0.76 and 0.78 (respectively) for a question about eye colour.

The other two studies that received a fair or good quality assessment rating examined test-retest reliability of sun protection questions.[174, 191] The Sun Protection Behaviour Scale, a 7-

item scale that ascertains frequency of sun-protective behaviours, had an ICC=0.70 for a 1-week interval.[191] The other study examined a question on sunscreen use, that is included in the Centers for Disease Control and Prevention Youth Risk Behaviour Surveillance System questionnaire, which had a kappa=0.61 for a 2-week interval. [174]

Child-Parent Agreement (Inter-Rater Reliability): We used the term inter-rater reliability to define studies that examined agreement between responses from child and their parent. Four studies examined inter-rater reliability.[177, 184, 187, 198] Two assessed sun protection behaviours only,[184, 187] one assessed sun protection and host characteristics,[177] and another assessed both sun exposure and host characteristics,[198]

Two studies received a fair rating.[177, 184] One study examined questions about phenotypic characteristics (skin colour and frequency of sunburn) and frequency of using various sun protection measures.[177] Questions about skin colour (k_w =0.73), sunscreen use (k_w=0.52) and number of sunburns over the past summer (k_w =0.55) had the highest level of agreement, whereas weighted kappa values were lower for questions about limiting time in the sun between 10 AM and 4 PM (k_w =0.44), frequency of wearing sunscreen outdoors (k_w =0.36). Questions about frequency of sitting in the shade, wearing a shirt or hat, had the lowest agreement (range: k_w=0.08 to 0.26). [177] The other study examined agreement between responses to a question about frequency of hat use, and reported a strong correlation (r=0.57).[184]

Validated Questionnaires

There were four questionnaires that were examined in more than one study. (Table 4.5) Those with the most support for validity/reliability are the Sun Habits Survey/Diary[161, 180-183, 193, 194] and the Solar Protection Behaviour Diary.[179, 186, 187, 189, 200] Both questionnaires include questions about sun exposure and sun protection, and the Solar Protection Behaviour Diary also includes questions about host characteristics. The Sun Habits Survey and Sun Habits Diary are available for use online.[202]

The Sun Habits Survey and Sun Habits Diary are two separate questionnaires; the survey records usual behaviours, and the diary records daily behaviours. The construct validity of the Sun Habits Survey and Sun Habits Diary were assessed in four studies.[182, 183, 193, 194] Each questionnaire has been compared to sun exposure measured using a polysulfone dosimeters in

two studies,[183, 193] with sun protection measured using direct observation in two,[193, 194] and with sunscreen use measured using a sunscreen swabbing method in two.[182, 193] The responses from the 4-day diary and the survey, provided by the same participants, were also compared in all four studies. Collectively, the results support the validity of these questionnaires. These studies suggested that the diary and survey have comparable validity, and that self-reported sun exposure and protection use on weekdays was more valid than on weekends. There were two studies that assessed the reliability of the Sun Protection Habits score, the predecessor to the Sun Habits Survey/Diary.[161, 180] Both studies received a poor rating as the unidimensionality of the scale was not examined, however, questionnaire items characterizing sun protection practices were internally consistent (Cronbach's $\alpha>0.50$).

Reporting Issues

There were several data items that were of interest, that we had difficulty collecting. Some information was either not reported or not clearly reported in the publication. Details about missing data were most often not reported. The response rate was not reported in 43% of publications. The proportion of missing items, either for the entire questionnaire or for individual questions, was not reported in 67%. Nearly half of the studies did not provide a description of how missing data were handled in the analysis. In those that did, complete cases analysis was most often used; in 14% we determined that complete case analysis was used, based on numbers in tables and figures, but it was not specifically mentioned in the text. In two-thirds of studies a score was calculated, but in half, the details of how the score was calculated were not provided. For questionnaires that had a score, the distribution of scores was often not provided, nor was the proportion of participants with the highest and lowest scores. Confidence intervals were often not provided. The exact questions that were examined were not provided in over 60% of studies. In a small subset, details on how to access the questionnaire were provided. However, in the majority of cases we found the questionnaire by searching Google or contacting the corresponding author. Corresponding authors were very receptive to our requests.

DISCUSSION

Overview and Discussion of Findings

We conducted a systematic review of measurement property studies to summarize evidence on the validity and/or reliability of questionnaires that ascertain information about a child's sun related behaviours. Thirty-five publications were identified that reported on 22 questionnaires and included 44 measurement property assessments (18 on validity and 21 on reliability) of these questionnaires. Four questionnaires were examined in more than one study. These are important to consider further, as in the absence of a gold standard, the consistency of findings demonstrating validity and/or reliability, in different populations, is necessary to be confident in the quality of a questionnaire.

Several of the included studies reported summary measures that were quite large in magnitude. For example, a Pearson's r=0.82 (95%CI: 0.73-0.92) was reported between sun exposure self-report and a UV sensitive sticker placed on the leg;[200] a kappa estimated using quadratic weights, k_w=0.76 (95%CI: 0.66–0.83) to 0.81 (95%CI: 0.66–0.89) for a 6 month test-retest of the Fitzpatrick scale;[188,] or Cronbach's α that ranged from 0.52-0.84 for sun protection questions in Sunshine and Your Skin Questionnaire.[170] Overall, studies that examined reliability tended to have larger summary measures. There is no available gold standard to quantify sun exposure, thus validity estimates are expected to be lower due to differences in the measurement errors of the constructs being compared.

Questions on current behaviours were most commonly assessed, as questionnaires were often used in studies designed to examine the effects of interventions to modify children's sun exposure in the context of skin cancer prevention; as were questions to assess sun protection. We only identified one study in infants.[192] Infancy represents a key developmental period, and thus is important to examine in etiologic research; future research should examine this age group. Only one study examined reliability of response over long periods of time (i.e. 8-18 years).[168] There is also a need for studies to assess questionnaires requiring longer-term recall of information, as is often necessary in case-control studies.

Quality assessment using the COSMIN checklist indicated that half of the studies were rated as poor quality; the number was greater for studies that examined reliability than validity. The COSMIN checklist can be used to improve the conduct and reporting of new studies. Our impression was that the 'worst score counts' scoring system did not adequately represent the

quality of the studies included. A poor response was most often recorded for only one of five to 15 questions that made up the score. The main reason for a poor rating among the validity studies was because the comparator instrument was not adequately described. In the absence of a gold standard, any statements about validity are dependent on the quality of the comparator used. Thus their measurement properties should be sufficiently described to enable the reader to appraise its quality; as well as references to provide more information. This highlights an area that should be improved in the reporting of future studies.

Among reliability studies, a poor rating was most common because the incorrect analysis was used. To receive a good or excellent score, continuous data had to be analyzed using intra-class correlations (ICC), binary data using kappa, and ordinal data using weighted kappa. Pearson's or Spearman's correlation coefficients we often reported in place of the ICC. This is problematic given correlation coefficients fail to account for systematic deviations in measurements. Only one study reported an ICC, whereas five studies reported correlation coefficients. Ordinal data, with 4 or 5 levels were often treated as continuous data and Pearson's correlations were estimated, rather than weighted kappa. Weighted kappa statistics use more information about the discrepancies in agreement and account for chance agreement, and are thus more appropriate measures for ordinal data.

We found three reviews, published in 1997, 2004 and 2005, that had also discussed the use of self-report questionnaires to measure sun related behaviours in children.[203-205] Relative to these reviews, ours includes more recent studies (i.e. those published after 2005), focuses specifically on studies that examined the measurement properties of questionnaires and uses systematic review methods. In the previous reviews objective measures to quantify sun exposure, such as polysulphone dosimeters or direct observation, were also described; whereas our review is focused on self-report questionnaires.

Strengths and Limitations

Our review has several strengths, primarily related to the rigorous systematic review methods used. The design and conduct of the review followed guidelines provided in the PRISMA Statement[163] and by the COSMIN initiative. A protocol was developed in advance, and two independent reviewers were involved in each stage of the review. We searched three electronic databases. We used an online automated software to conduct the review, which helped

to streamline the process and reduce errors. We performed quality assessment using standard measures that were developed through an international research initiative (the COSMIN checklist).

A potential limitation of the review relates to the search strategy. We used the validated COSMIN search strategy, which was validated to identify measurement property studies on patient-reported outcome measures; while our focus was on exposure measurement. However, we are confident that the measurement property component of the COSMIN search is also applicable to exposure measurement studies, as the list is comprehensive and includes terms that are applicable to measurement properties in general. Our search focused on sun related behaviour therefore studies on host characteristics, such as skin colour may have been missed.

The COSMIN checklist was used to assess study quality, however some the questions in the checklist were not relevant to exposure measurement (e.g. Minimal Important Change (MIC) or Minimal Important Difference (MID)), because the checklist was developed for outcome measures. Thus a quality assessment checklist that is specific to exposure measurement is necessary. Measurement property studies that were not mentioned in the abstract of a publication may have also been missed. To increase sensitivity, we modified our screening strategy to isolate abstracts that included mention of the use of a questionnaire in children; however if a measurement property term was not included in the title, abstract or as an index term, the record would not have been captured in our search results. Seven eligible publications were identified because of the modification we made in the screening process; but it required each reviewer to independently examine the full-texts of 185 publications.

CONCLUSIONS

We identified 22 validated self-report questionnaires that measure children's sun related behaviours. A total of 44 measurement properties were assessed and collectively provided evidence for the validity and reliability of measuring sun related behaviours in children. We critically appraised the quality of each measurement property study using established standards, and this process highlighted the need for improved conduct and, particularly, reporting of measurement property studies. We recommend that new measurement property studies are developing using COSMIN, as these standards were developed to enhance both study design and reporting.

The goal of this research was to provide a resource to help guide the design and selection of questionnaires to assess sun related behaviours in future epidemiological studies. In fact, we used the evidence collected in this systematic review to guide the development of a measurement framework, which we call the Pediatric MS Tool-Kit. The knowledge gained through this systematic review provided a strong evidence-base to select and define a set of variables to measure sun exposure behaviours in pediatric MS studies. A systematic review of measurement property studies is an underutilized methodology and is a useful step when designing a questionnaire. In particular, there is a need to increase the number of systematic reviews of measurement property studies for exposure measurement. The evidence provided by this type of review may help to reduce misclassification, and thus has the potential to enhance measurement in epidemiological studies.

TABLES

Table 4.1 Characteristics of studies evaluating the measurement properties of questionnaires that measure sun related behaviours in children

First Author (year published)	Country	Setting	Sampling Method	Age	Sex (% female)	Sample Size
Baxter (2008)[168]	Australia	community	convenience	children: <15 yrs, adolescents: 15-19 yrs	children: 46, adolescents: 53	188
Bennetts (1991)[169]	Australia	beach	consecutive	8-12 yrs	38	50
Blizzard (1997)[173]	Australia	school	random	14-15 yrs	53	364
Brener (2002)[174]	USA	school	convenience	median (range): 16 yrs (13-18)	53	4691
Broadstock (1996)[175]	Australia	school	convenience	12-17 yrs	44	138 (test-retest), 4721 (internal consistency)
Buller (1994)[170]	USA	school	convenience	grades 4-6	nr	139
Buller (1996)[171]	USA	school	convenience	grades 4-6	50	447
Buller (1997)[172]	USA	school	convenience	grade 4	56-58	232 (time 1), 216 (time 2), 159 (time 3)
Dharani (2012)[176]	Singapore	community	not reported	mean (sd): 8.3 yrs (1.6)	49	117
Dusza (2005)[177]	USA	school	convenience	11-14 yrs	55	52
Dwyer (1996) [178]	Australia	school	random	14-15 yrs	42	125
Girgis (1993)[179]	Australia	school	not reported	9-11 yrs	nr	108
Glanz (1999)[161]	USA	recreation centre	convenience	mean (sd): 7.0 yrs (1.1)	49	756

First Author (year published)	Country	Setting	Sampling Method	Age	Sex (% female)	Sample Size
Glanz (2002)[180]	USA	swimming pool	random (pools), consecutive (parents)	mean (sd): 6.6 yrs (1.5)	47	1172
Glanz (2008)[181]	USA	community	convenience	1-17 yrs	72	28
Glanz (2009)[182]	USA	swimming pool	convenience (pools), consecutive (parents)	mean (sd): 7.2 yrs (1.7)	53	564
Glanz (2010)[183]	USA	swimming pool	convenience	mean (sd): 7.2 yrs (1.7)	48	180
Hunter (2010)[184]	USA	school	not reported	grade 4	not reported	27 (test-retest), 79 (construct validity), 102 (inter-rater)
Lescano (1997)[185]	USA	beach	consecutive	mean (sd): 5.0 yrs (1.7)	not reported	88
Lower (1998)[186]	Australia	school	not reported	mean (sd): 13.8 yrs (1.0)	49	99
Lower (1998)[187]	Australia	school	convenience	mean (sd): 13.7 yrs (0.9)	49	115
Magin (2012)[188]	Australia	school	convenience	mean (sd): 15.2 yrs (1.2)	65	244
Mayer (1997)[189]	USA	community	not reported	6-9 yrs	53	58
Mewse (2011)[190]	UK	school	convenience	mean (sd): 14.5 yrs (1.3)	51	201
Norman (2007)[191]	USA	primary care clinic	convenience	mean (sd): 12.7 yrs (1.3)	54	33 (test-retest), 819 (internal consistency)
O'Riordan (2000)[192]	Australia	community	not reported	mean (range): 9.6 months (7-11)	57	not reported
O'Riordan (2008)[193]	USA	swimming pool	convenience	mean (sd): 6.5 yrs (1.8)	30	10
O'Riordan (2009)[194]	USA	swimming pool	convenience	mean (sd): 7.7 yrs (1.7)	48	201
Reeder (2010)[195]	New Zealand	school	convenience	median (range): 18 (16-49)	61	289

First Author (year published)	Country	Setting	Sampling Method	Age	Sex (% female)	Sample Size
Sanclemente (2008)[196]	Colombia	school	not reported	>15 years	58	91
Schüz (2013)[197]	Germany	school	not reported	mean (sd): 15.7 yrs (0.7)	55	207-253
Sullivan (2003)[201]	USA	existing study	not reported	mean (sd): 12 yrs (1.8)	100	35
Whiteman (1997)[198]	Australia	school	consecutive (cases), random (controls)	median (range): 16 yrs (10-24)	39	202
Wright (2007)[199]	New Zealand	school	random	8 yrs & 12 yrs	53	345
Yaroch (2006)[200]	USA	school	not reported	grades 6-8	50	527

Table 4.2 Characteristics of questionnaires that have been validated to measure sun related behaviours in children

First Author (year published)	Name of Questionnaire	Constructs Assessed	Time Frame	Language	Administration Mode	Respondent
Dharani (2012)[176]	Child Development Supplement-III 2007	sun exposure	current	Chinese	self-admin	child
Hunter (2010)[184]	Child's Sun Protection Behavior Survey	sun protection	not reported	English	self-admin	child & parent
Magin (2012)[188] Reeder (2010)[195] Sanclemente (2008)[196]	Fitzpatrick	host characteristics	current	English, Spanish[196]	self-admin	child
Girgis (1993)[179] Lower (1998)[186] Lower (1998)[187] Mayer (1997)[189] Yaroch (2006)[200]	Solar Protection Behaviour Diary	sun exposure, sun protection, host characteristics	current	English	self- & interview-admin	child & parent
Glanz (2008)[181] Glanz (2009)[182] Glanz (2010)[183] O'Riordan (2008)[193] O'Riordan (2009)[194]	Sun Habits Survey & Sun Habits Diary[1]	sun exposure, sun protection, host characteristics	usual, current	English	self-admin	child & parent
Glanz (1999)[161] Glanz (2002)[180]	Sun Protection Habits score[1]	sun protection	usual, current	English	self-admin	parent
Norman (2007)[191]	Sun Protection Behavior Scale	sun protection	usual	English	self-admin	child
Lescano (1997)[185]	Sun Safe Behaviors Questionnaire	sun protection	usual	English	interview-admin	parent
Buller (1994)[170] Buller (1996)[171] Buller (1997)[172]	Sunshine and Your Skin Questionnaire	sun protection	usual	English	self-admin	child

First Author (year published)	Name of Questionnaire	Constructs Assessed	Time Frame	Language	Administration Mode	Respondent
Brener (2002)[174]	Youth Risk Behavior Survey	sun protection	usual	English	self-admin	child
Questionnaires that were not named						
Baxter (2008)[168]		host characteristics	history	English	interview-admin	child
Bennetts (1991)[169]		sun protection	current	English	interview-admin	child
Blizzard (1997)[173]		host characteristics	usual	English	self-admin	child
Broadstock (1996)[175]		sun protection, host characteristics	usual	English	self-admin	child
Dusza (2005)[177]		sun protection	usual, last summer	English	self-admin	child & parent
Dwyer (1996)[178]		sun exposure, host characteristics	cumulative, last summer & current	English	self-admin	child
Mewse (2011)[190]		sun protection	usual	English	self-admin	child
O'Riordan (2000)[192]		sun exposure	last weekend	English	self-admin	parent
Schüz (2013)[197]		sun protection	current	German	self-admin	child
Sullivan (2003)[201]		sun exposure	current	English	self-admin	child
Whiteman (1997)[198]		sun exposure, host characteristics	lifetime	English	self- & interview-admin	child & parent
Wright (2007)[199]		sun exposure, sun protection	current	English	self-admin	child

1. There was significant overlap between questionnaire items in the Sun Protection Habits score and the Sun Habits Survey and Sun Habits Diary.

Table 4.3 Measurement property studies that examined the construct validity of self-report questionnaires to assess sun related behaviours in children

First Author (year)	Name of Questionnaire	Constructs linked with results	Comparator(s)	Statistics Used	Summary of Results	Construct Validity QA Score
Bennetts (1991)[169]	not named	sun protection	direct observation	χ^2 test	p<0.05 for sunscreen, hat & shirt use	poor
Dharani (2012) [176]	Child Development Supplement-III 2007	sun exposure	light meter	Pearson correlation	weekday school holidays: r=0.34 (95% CI 0.05, 0.58); weekday school 0.17 (0.14, 0.45); weekday school: 0.07 (0.16, 0.29); weekend school: 0.25 (0.02, 0.46)	fair
Dwyer (1996)[178]	not named	sun exposure	polysulfone dosimeter	Pearson correlation	r=(-0.05) to 0.38	fair
Girgis (1993)[179]	Solar Protection Behaviour Diary	sun protection	direct observation	Kappa	head=0.70, shoulders= 0.34, legs=0.35, shade or not= 0.31	fair
Mayer (1997)[189]	Solar Protection Behaviour Diary	sun exposure	Chroma Meter (dimensions: skin colour & tan)	Pearson correlation	lighter skin colour: r=-0.21 to -0.33; & more tan: r=0.28 to 0.37	fair
Yaroch (2006)[200]	Solar Protection Behaviour Diary	sun exposure	UV sensitive sticker	Kendall's tau	leg: τ=0.82 (95%CI: 0.73, 0.92); face:0.54 (0.45, 0.64); hand: 0.42 (0.30, 0.53) arm: 0.40 (0.23, 0.56);	fair
Glanz (2009)[182]	Sun Habits Survey & Sun Habits Diary	sun protection	(i) sunscreen swab; (ii) diary & survey responses	Method of triads validity coefficient range & Kappa	(i) diary: 0.28, 0.75 survey: 0.14, 0.39; (ii) r=0.30	poor
Glanz (2010)[183]	Sun Habits Survey & Sun Habits Diary	sun exposure	(i) polysulphone dosimeter; (ii) diary & survey responses	Pearson correlation	(i) diary r=0.18 (weekday) and 0.34 weekend); (ii) r=0.35–0.53	fair

First Author (year)	Name of Questionnaire	Constructs linked with results	Comparator(s)	Statistics Used	Summary of Results	Construct Validity QA Score
O'Riordan (2008)[193]	Sun Habits Survey & Sun Habits Diary	sun exposure & sun protection (location)	(i) polysulfone dosimeter; (ii) direct observation; (iii) sunscreen swab; (iv)diary & survey responses	Pearson correlation & kappa	(i) sun exposure: diary r=0.32, survey: weekend (we) r=0.30, weekday (wd) r=0.45; (ii) sun protection: diary wd k=0.48-0.84, we k=0.31-0.70, survey: r=0.29-0.57; (iii) sunscreen use: diary k=0.36, survey k=0.16; (iv) sun exposure: we r=0.50, wd r=0.67, sun protection: r=0.21-0.81, sunscreen use: r=0.30	poor
O'Riordan (2009)[194]	Sun Habits Survey & Sun Habits Diary	sun protection	(i) direct observation; (ii) diary & survey responses	Pearson correlation & kappa	(i) diary k=0.12-0.45, survey r=0.10-0.52; (ii) r=0.27-0.52	poor
Hunter (2010)[184]	Child's Sun Protection Behavior Survey	sun protection	pedometer-affixed hat	Pearson correlation	r=0.27	poor
Lescano (1997)[185]	Sun Safe Behaviors Questionnaire	sun protection	direct observation	Pearson correlation	r=0.36	poor
O'Riordan (2000)[192]	not named	sun exposure	polysulfone dosimeter	Pearson correlation	r=0.34	poor
Reeder (2010)[195]	Fitzpatrick	host characteristics	Spectrophotometer (lighter skin higher values)	Spearman correlation	ρ=(-0.64)-(-0.75)	fair
Sanclemente (2008)[196]	Fitzpatrick	host characteristics	medical examination	Concordance (%)	Overall: 50%; by skin type: I 50%, II 82%, III 45%, IV 15%, V & VI 0%	fair
Sullivan (2003)[201]	not named	sun exposure	polysulfone dosimeter	Pearson correlation	adjusted for % UV-B peak r=0.64; without adjustment r=0.57	fair

First Author (year)	Name of Questionnaire	Constructs linked with results	Comparator(s)	Statistics Used	Summary of Results	Construct Validity QA Score
Wright (2007)[199]	not named	sun exposure & sun protection	electronic UV monitor	Concordance (%)	Zero UV exposure: indoors (36%) & in vehicle (31%); compared to highest UV exposure: outside (61%) & outside in shade (60%)	good

k=kappa; r=Pearson's correlation coefficient; ρ=Spearman's Rho; τ=Kendall's Tau; UV=ultraviolet radiation; UVB=ultraviolet B radiation

Table 4.4 Measurement property studies that examined the reliability of self-report questionnaires to assess sun related behaviours in children

First Author (year)	Name of Questionnaire	Constructs Assessed	Interval	Reliability Summary	Reliability QA Score	IC Summary	IC QA Score
Inter-Rater Reliability Studies							
Dusza (2005)[177]	n/a	sun protection behaviour	n/a	k_w=0.08-0.73	fair		
Hunter (2010)[184]	Child's Sun Protection Behaviour Survey	sun protection behaviour	n/a	r=0.57	fair		
Lower (1998)[187]	Solar Protection Behaviour Diary	sun protection behaviour	n/a	sen: 59-98%; spec: 61-87%	poor		
Whiteman (1997)[198]	n/a	sun exposure, host characteristics	n/a	k_w=0.11-0.88	poor		
Test-Retest Studies							
Baxter (2008)[168]	n/a	host characteristics	8 to 18 yrs	children: k=0.37-0.76 & r=0.19-0.46; adols: k=0.30-0.90 & r=0.36-0.50	fair		
Blizzard (1997)[173]	n/a	host characteristics	4 months	r=0.47-0.75	poor		
Brener (2002)[174]	Youth Risk Factor Survey	sun protection behaviour	2 weeks	k=0.61	good		

First Author (year)	Name of Questionnaire	Constructs Assessed	Interval	Reliability Summary	Reliability QA Score	IC Summary	IC QA Score
Hunter (2010)[184]	Child's Sun Protection Behaviour Survey	sun protection behaviour	1 week	children: r=0.42; parents: r=0.59	poor		
Lower (1998)[186]	Solar Protection Behaviour Diary	sun protection behaviour	not reported	k=fair to good	poor		
Magin (2012)[188]	Fitzpatrick	host characteristics	6 months	k_w=0.76 (95%CI: 0.66–0.83) to 0.81 (0.66–0.89)	good		
Reeder (2010)[195]	Fitzpatrick	host characteristics	1 week	k=0.77-0.78	good		
Test-Retest and Internal Consistency Studies							
Broadstock (1996)[175]	n/a	host characteristics	6 hours	r=0.80	poor	Cronbach's α=0.54¥	fair
Dwyer (1996)[178]	n/a	host characteristics	5 months	r=0.03-0.47	poor	r=0.30-0.52¥	poor
Norman (2007)[191]	Sun Protection Behavior Scale	sun protection behaviour	1 week	ICC=0.70	fair	Cronbach's α=0.78	poor
Internal Consistency Studies							
Buller (1994)[170]	Sunshine and Your Skin Questionnaire	sun protection behaviour				Cronbach's α=0.52-0.84	fair
Buller (1996)[171]	Sunshine and Your Skin Questionnaire	sun protection behaviour				Cronbach's α=0.69	good

First Author (year)	Name of Questionnaire	Constructs Assessed	Interval	Reliability Summary	Reliability QA Score	IC Summary	IC QA Score
Buller (1997)[172]	Sunshine and Your Skin Questionnaire	sun protection behaviour				Cronbach's α=0.54-0.76	fair
Glanz (1999)[161]	Sun Protection Habits Score	sun protection behaviour				Cronbach's α=0.70[¥]	poor
Glanz (2002)[180]	Sun Protection Habits Score	sun protection behaviour				Cronbach's α=0.54[¥]	poor
Lescano (1997)[185]	Sun Safe Behaviours Questionnaire	sun protection behaviour				Cronbach's α=0.69	poor
Mewse (2011)[190]	n/a	sun protection behaviour				Cronbach's α=0.66	poor
Schüz (2013)[197]	n/a	sun protection behaviour				Cronbach's α=0.70-0.83	poor

adols=adolescents; QA=quality assessment; IC=internal consistency; ICC=intraclass correlation; k=kappa; k_w=weighted kappa; r=Pearson's correlation; sen=sensitivity; spec=specificity

[¥]scoring system provided in the publication

Table 4.5 Measurement properties and quality assessment scores for questionnaires that were examined in more than one study

Questionnaire Name	Construct Validity	Content Validity	Internal Consistency	Reliability
Sun Habits Survey & Sun Habits Diary	1 fair [183], 3 poor [182, 193, 194]	1 excellent [181]	2 poor* [161, 180]	
Solar Protection Behaviour Diary	3 fair [179, 189, 200]	1 poor [179]		2 poor [186, 187]
Fitzpatrick	2 fair [195, 196]			2 good [188, 195]
Sunshine and Your Skin Questionnaire			1 good [171], 2 fair [170, 172]	

*Internal consistency measurement property studies evaluated the Sun Protection Habits score, a questionnaire that was the predecessor to the Sun Habit Survey and & Sun Habits Diary.

FIGURES

Figure 4.1 PRIMSA Study Flow Diagram

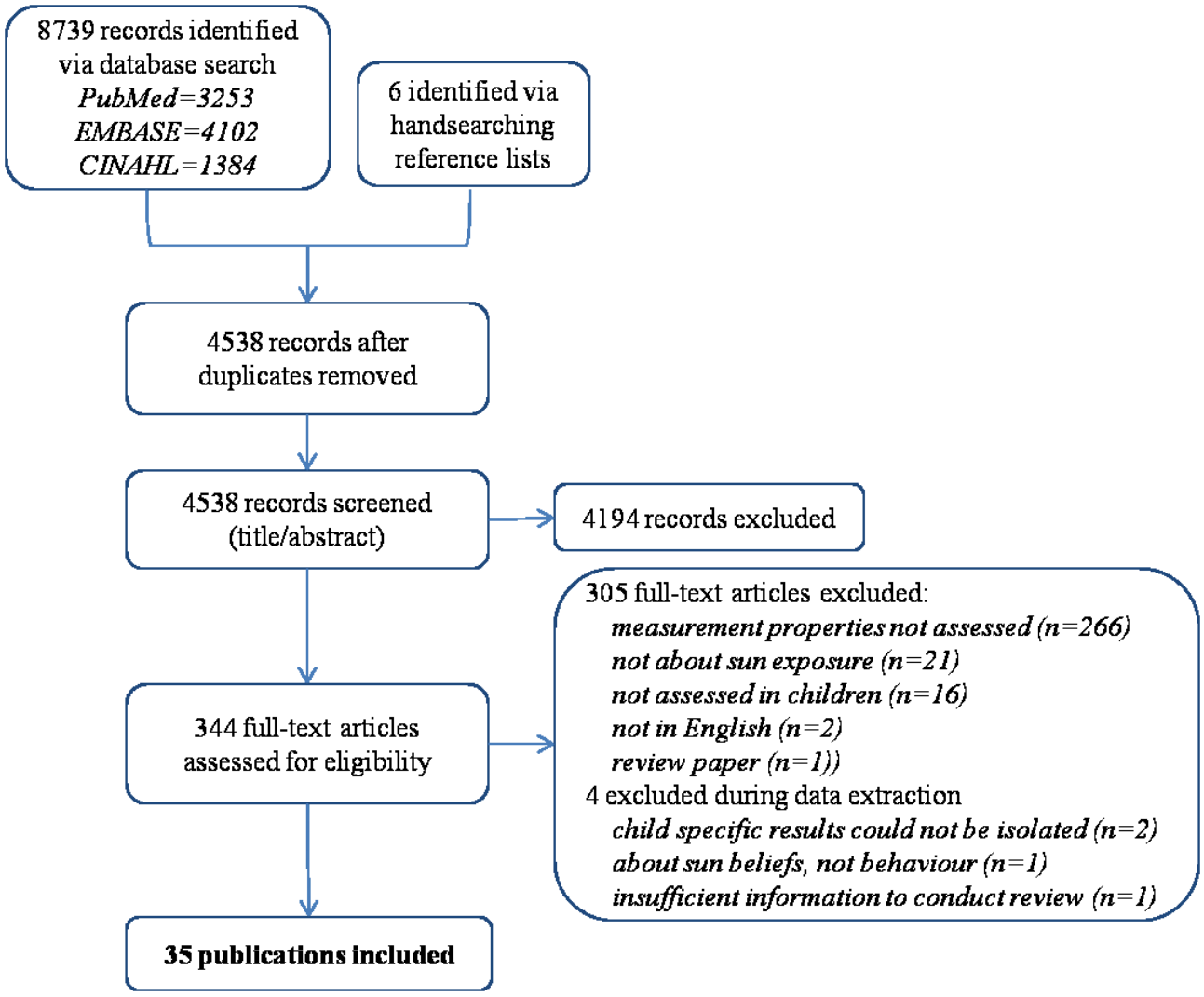
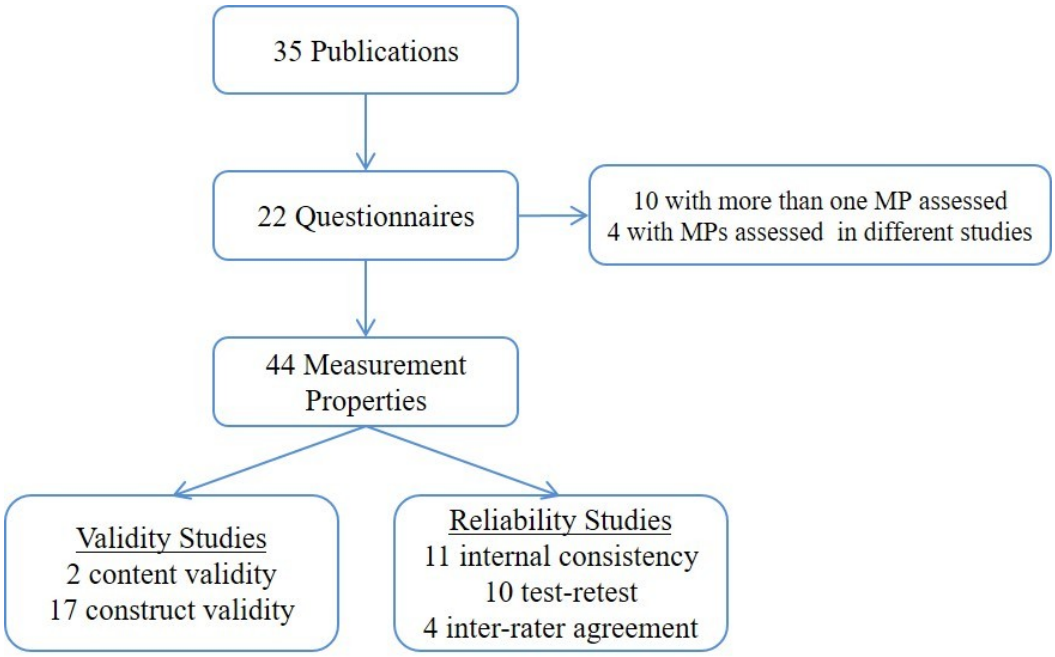


Figure 4.2 Flow diagram of publications, questionnaires and measurement properties (mp).



APPENDIX 4.1: Systematic Review Protocol

Background

In observational studies, elucidating the role of etiologic risk factors requires, among other things, the use of good measurement tools. Measurement tools are defined here as any method of ascertaining information about a study participant. The measurement tools of interest in this review are self-report questionnaires. Questionnaires can be a validated scales, a set of questions or even a single question. The "quality" of questionnaires, however, varies greatly. A systematic review documented questionnaires that were used in studies assessing infant exposure to environmental tobacco smoke exposure, for example, found that the majority were specifically developed for the purposes of the particular study/investigation (i.e. developed "in-house").[120] While "in-house" questionnaires may appear to serve their purpose, this approach has its limitations. Firstly, it is preferable whenever possible to use questionnaires that have undergone some validation so that researchers are confident that what is being captured is the best reflection of the construct they wish to measure. Furthermore, comparability of studies is hampered when each study uses a different questionnaire to measure the same construct, and it is challenging to determine whether differences in study findings are the result of true differences or due to the use of different questionnaires. The process of validation allows researchers to determine whether the questionnaire accurately captures the exposure of interest, reflects the key aspects of exposure and ascertains consistent and reproducible information.

Rationale

Our goal is to provide researchers with information about available self-report questionnaires that have undergone validation, thus helping minimize information bias in pediatric observational studies. Information bias is defined as bias in estimating an effect caused by measurement errors in the required information.[206] The choice of questionnaires and measurement strategies is thus a critical component of study design. Critical appraisal of the properties of the different questionnaires available is important, but is often overlooked. This is not surprising since a comprehensive review of the many questionnaires available to collect information on exposure is a time consuming task that requires a particular expertise. We will complete this legwork for the research community, providing an evidence-base from which to select questionnaires to use in studies examining sun related behaviours in children. The sun

related behaviours that we were interested in included sun exposure, sun protection and host characteristics, such as sun sensitivity.

Research Question

What are the measurement properties (validity/reliability) of self-report questionnaires that can be used to ascertain information about sun related behaviours in children?

Objectives

1. To identify, critically appraise and summarize measurement property (validity and/or reliability) studies that examined questionnaires to assess sun related behaviours in children.
2. To provide an evidence-base for the development and selection of questionnaires to assess sun related behaviours in children.

Information Sources

Electronic literature databases will be searched for relevant publications: MEDLINE (PubMed, 1946-current), EMBASE (1947-current) and Cumulative Index to Nursing and Allied Health Literature (CINAHL, 1937-current). The reference lists of key review papers and included publications will also be searched.

Search Strategy

We will use a search strategy that has been validated in PubMed to identify publications that report on the measurement properties of questionnaires. We will contact the authors who developed the search strategy to obtain complementary search strategies to use in EBMASE and CINAHL. The search has four components: construct search, population search, instrument search and measurement properties search. The first three search components use review-specific search terms. A McGill University librarian will help us develop the search strategy for components one and three. The search strategy will be developed first in PubMed, and then translated into search terms for the other two databases. For the population search we will use a validated PubMed search strategy identify studies that include children;[138] we will translate the search strategy using similar search terms in EMBASE and CINAHL.

PubMed Search Terms:

1. *Construct search:* "Sunlight"[Mesh] OR "Vitamin D"[Mesh] OR sun[tiab] OR sunlight[tiab] OR “vitamin D”[tiab] OR outdoor*[tiab] OR UV[tiab] OR UVB[tiab]

2. *Population search*[138]*:* Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school [tiab] OR school*[tiab] OR prematur* OR preterm*

3. *Instrument search:* "Questionnaires"[Mesh] OR questionnaire* OR "Case-Control Studies"[Mesh] OR “case control study”[tiab] OR "Retrospective Studies"[Mesh] OR retrospective*[tiab] "Mental Recall"[Mesh] OR "Reproducibility of Results"[Mesh] OR "Self Disclosure"[Mesh] OR "Research Design"[Mesh] OR "Epidemiologic Research Design"[Mesh] OR "Time"[Mesh] OR "Data Collection"[Mesh] OR "Epidemiologic Methods"[Mesh]

EMBASE Search Terms:

1. *Construct search:* sunlight/ OR ‘vitamin D’.tw OR sun*.tw OR sunlight.tw OR ultraviolet radiation/ OR ultraviolet b radiation/ OR outdoor*.tw. OR uv.tw. OR uvb.tw.

2. *Population search:* Infan*.mp. OR newborn*.mp. OR new-born*.mp. OR perinat*.mp. OR neonat*.mp. OR baby*.mp. OR babies.mp. OR toddler*.mp. OR minors*.mp. OR boy.mp. OR boys.mp. OR boyfriend.mp. OR boyhood.mp. OR girl*.mp. OR kid.mp. OR kids.mp. OR child*.mp. OR schoolchild*.mp. OR adolescen*.mp. OR juvenil*.mp. OR youth*.mp. OR teen*.mp. OR under age*.mp OR underage*.mp. OR pubescen*.mp. OR exp pediatrics/ OR pediatric*.mp. OR paediatric*.mp. OR peadiatric*.mp. OR school*.tw OR prematur*.mp. OR preterm*.mp.

3. *Instrument search:* exp questionnaires/ OR questionnaire*.tw OR exp ‘Case-Control Studies’/ OR ‘case control study’.tw OR ‘Retrospective Study’/ OR retrospective*.tw OR recall/ OR recall.tw. OR exp reproducibility/ OR reproducib*.tw. OR ‘Self Disclosure’/ OR ‘self disclosure’.tw. OR methodology/ OR method*.tw. OR Epidemiology/ OR epidemiolog*.tw. OR Time/ OR time.tw. OR ‘information processing’/ OR (data adj collect*).tw. OR survey.tw OR exp health survey/

CINAHL Search Terms:

1. *Construct Search*: (MH "Sunlight") OR "sun*" OR (MH "Vitamin D") OR "vitamin d" OR "UV" OR "UVB" OR (MH "Recreation") OR "outdoor*"

2. *Population Search:* (Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby* OR babies OR toddler* OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child* OR adolescen* OR juvenil* OR youth* OR teen* OR underage* OR

under age* OR pubescen* OR pediatric* OR paediatric* OR peadiatric* OR school* OR prematur* OR preterm*)

3. *Instrument search:* (MH "Questionnaires+") OR (MH "Structured Questionnaires+") OR questionnaire* OR (MH "Case Control Studies+") OR TI "case control study" OR AB "case control study" OR (MH "Retrospective Panel Studies") OR (MH "Revolving Panel Studies") OR (MH "Retrospective Design") OR TI retrospective* OR AB retrospective* OR (MH "Memory+") OR TI recall OR AB recall OR (MH "Recall Bias") OR (MH "Reproducibility of Results") OR TI reproducib* OR AB reproducib* OR (MH "Self Disclosure") OR (MH "Self Report") OR (MH "Study Design") OR (MH "Epidemiological Research") OR TI epidemiolog* OR AB epidemiolog* OR (MH "Time Factors") OR (MH "Time") OR TI time OR AB time OR (MH "Data Collection Methods") OR (MH "Data Collection")

Inclusion Criteria

1. The publication must report on a questionnaire that ascertains information about sun related behaviours (e.g. sun exposure, sun protection).
2. The publication must assess the validity and/or reliability of a questionnaire.
3. The publication must assess a questionnaire in a pediatric population (children from birth to 18 years of age; or parents of children under the age of 18 years)
4. The publication must be written in English

Data Collection and Quality Assessment

Two reviewers will perform data extraction and quality assessment independently. Titles and abstracts will be screened for relevance using the inclusion criteria noted above. Assessment of methodological quality will be completed using the COSMIN Initiative checklist.[139, 142] The four-point scale will be used to score each publication (excellent, good, fair, or poor). We will develop an electronic data extraction form in DistillerSR (Evidence Partners, Ottawa, Canada), an online systematic review software. Information that will be extracted from each publication includes:

(i) *questionnaire*: name, type of measurement questionnaire (scale, set of questions, single question), exposures measured (sun exposure, sun protection, host characteristics), recall period, number of items and response categories, language, administration (self-administered, interview-administered), scoring and scores, prior uses, publication year, copyrights and corresponding author information;

(ii) *sample*: sampling methods, response rate, sample size, sample characteristics (e.g. age, sex, disease status)

(iii) *study design*: setting, location, outcome studied, responsiveness/missing data;

We will contact individual authors to obtain the exact questionnaire and any additional information as needed. Discrepancies identified between the two reviewers will be resolved through consensus. When consensus is not reached a third reviewer, who is a member of our research team, will be asked to provide an additional independent review. The process will be piloted on two publications, and the modified process will be piloted tested again on another two publications.

Data summary

We will summarize the information collected into tables that will be included in the publication of this review. Reporting will follow the PRISMA guidelines.[163]

CHAPTER 5: DEVELOPMENT OF THE PEDIATRIC MS TOOL-KIT

5.1. Preface to Manuscript 2

In chapter 5 I present the second of two manuscripts that are related to the first theme of this thesis: *measurement*. Specifically, Manuscript 2 focuses on the development of a set of core variables that can be used to measure exposure to risk factors of use in pediatric MS case-control studies. The core variables are part of the Pediatric MS Tool-Kit. The Tool-Kit can be used by the study investigator(s) to design study specific questionnaires. Use of a common measurement framework, to ascertain exposure information, enhances the opportunity to combine individual-level data collected in multiple studies. In the grant that my supervisor and I obtained to complete this research, we committed to developing a set of core variables for three risk factors. I solicited input from the pediatric MS research community, through the International Pediatric MS Study Group, to select three priority risk factors. One of the selected risk factors is *sun exposure*, and thus fits with the topic area of this thesis. The other two risk factors that were selected are environmental tobacco smoke exposure and vitamin D intake. The manuscript that is presented in this chapter also mentions these two risk factors. This manuscript will be submitted to the journal *Multiple Sclerosis*; and will be open-access as I have ear-marked funds for this purpose from the International Meeting Grant that I received from the Multiple Sclerosis International Federation in November 2015.

5.2 Manuscript 2 - *A Framework for Measurement and Harmonization of Pediatric Multiple Sclerosis Etiologic Research Studies: The Pediatric MS Tool-Kit*

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ABSTRACT

Studying multiple sclerosis (MS) etiology in children has several methodological advantages compared to studying etiology in adults. Using a rigorous methodological process we

developed the Pediatric MS Tool-Kit. The short-term goals of the Tool-Kit are to improve exposure measurement in individual pediatric MS studies, and to enhance the comparability of study results across studies. In the long-term the use of the Tool-Kit will facilitate harmonization of pediatric MS studies, which is one methodological approach to circumvent issues of small sample sizes. The Tool-Kit proposes a minimal set of core variables that can be used to assess MS etiological risk factors among children from birth to 18 years of age. We solicited input from the International Pediatric MS Study Group to select three risk factors: environmental tobacco smoke (ETS) exposure, sun exposure, and vitamin D intake (VDI). We used a two-stage methodology to develop the Tool-Kit core variables: (i) literature reviews on measurement properties of relevant questionnaires; and (ii) a Delphi study involving a working group of epidemiologists, neurologists and content experts from North America and Europe. The content validity of the core variables was assessed. Literature reviews yielded 152 publications on measurement properties of ETS questionnaires, 35 on sun exposure and 13 on VDI. The Tool-Kit includes six core variables to measure ETS, six to measure sun exposure and six to measure VDI, which were found to have good content validity. The Tool-Kit resources are available online (www.maelstrom-research.org/mica/network/tool-kit). We believe the Tool-Kit will prove to be a valuable resource to guide pediatric MS researchers in developing study specific questionnaires.

BACKGROUND

Multiple Sclerosis (MS) is primarily a disease of adulthood, with peak incidence between 30 and 50 years of age,[26-28] although MS in children has recently become increasingly studied. Pediatric MS cases are a small proportion (3-10%) of all those diagnosed with MS.[35] Two studies have estimated the prevalence of pediatric MS, one conducted in Sardinia, Italy[66] and another in Kuwait,[67] but reported very different estimates. The prevalence in Sardinia on December 31, 2012 was 26.9 per 100,000 pediatric population (95%CI: 26.6-27.2), whereas the prevalence in Kuwait in 31 December, 2011 was 6.0 per 100,000 (95%CI: 4.2–8.5). Whereas MS prevalence in adult populations was estimated to be 210 per 100,000 (95%CI: 186.3-234.5) in 2007 in Sardinia,[2] and 85 per 100,000 persons (95%CI: 82.8-87.0) in 2011 in Kuwait.[207]

While etiological risk factors identified in studies of adult-onset MS[91, 93] have also been shown to be associated with pediatric-onset MS,[104, 105] there are few publications that report on

the etiology of pediatric MS. Although MS etiology has been mainly studied in adults, examining etiology in children has the potential to provide important insights. Pediatric MS provides a unique opportunity to study MS etiology because cases are younger, and thus (i) onset is closer in time to when key exposures occur, and (ii) the time period in which to search for risk factors is shorter. In addition, since studies suggest that MS risk is determined in childhood and early adolescence, [74, 75, 83-86, 208] this time period is highly relevant.

A common methodological problem faced in epidemiological studies examining etiology of pediatric MS is small sample sizes. Because pediatric MS is rare, the number of cases that can be obtained in individual studies is low and requires long periods of time to accrue to have sufficient statistical power to precisely estimate main effects, or to explore interaction between risk factors. Harmonization, a methodology used to combine data collected in multiple studies, provides a potential solution to small sample sizes. The methodology used for harmonization focuses on the use of a common set of core variables, which serve as a framework to conduct pooled analyses.[124]

We developed the Pediatric MS Tool-Kit (Tool-Kit) for pediatric MS researchers to design study-specific questionnaires based on variables which: (i) have been selected using a rigorous methodological process; (ii) enhance comparability of results across studies; and (iii) are amenable to future harmonized analyses. This paper describes the methodology that was used to develop the Tool-Kit, and provides an overview of how the Tool-Kit can be used in pediatric MS research.

METHODS

Risk Factor Survey

In order to select which risk factors to include in the Tool-Kit we engaged members of the International Pediatric MS Study Group (IPMSSG). The IPMSSG is a global network that includes members from 41 countries, with the unifying vision to optimise worldwide healthcare, education and research in pediatric MS.[209] We developed a risk factor survey to solicit input from members of the IPMSSG.

The risk factor survey focused on risk factors that have been previously shown to be associated with MS risk. We searched PubMed in March 2013 using the search terms: “risk factor”, “etiology”, “cause” and “causality”. The goal was to identify studies that: (i) assessed

the etiology of MS; (ii) examined an environmental risk factor (i.e. excluding genetic factors); (iii) used an analytical study design with a comparison group (e.g. cohort or case-control study); and (iv) were published in English. To focus on the most recent evidence, only articles published after 2000 were included. One author (SM) screened all abstracts and extracted basic details to generate a list of risk factors. The list was then filtered using the following predefined criteria: (i) an association was found with the risk of MS, in at least one high quality study; (iii) the timing of exposure is relevant to pediatric MS; and (iv) the risk factor can be measured using a self-report questionnaire.

This filtered list was included in an online survey that was distributed to 138 members of the IPMSSG in May 2014. For each risk factor, the survey asked IPMSSG members to report whether, in their view, the risk factor was: (i) *a priority*, (ii) *important, but not a priority*, (iii) *not important for future research*, or (iv) *I don't have an opinion*. The proportion of respondents indicating that the risk factor was *a priority* was calculated, as well as the proportion combining the top two response options (i.e. either *a priority* or *important, but not a priority*). These proportions were compared across the risk factors and used to select three risk factors. We started with three risk factors in order to develop a Tool-Kit methodology which can then be used to add additional risk factors to the Tool-Kit.

Developing the Took-Kit

For each of the risk factors included in the Tool-Kit we used a two-stage methodology to select the common set of core variables. The first stage was a literature review of measurement property studies and the second stage was a Delphi study.[146, 210] The Tool-Kit is a measurement framework which provides necessary information that can be used to design a harmonizable study-specific questionnaire.

Stage One – Literature Reviews of Measurement Properties

The purpose of the literature reviews was to summarize the available evidence on the measurement properties of relevant questionnaires, in order to inform the development of the Tool-Kit variables. One review was performed for each risk factor; the findings of the reviews are being written up for publication. Briefly, we used methodology that had been proposed to conduct a systematic review of measurement property studies.[163] We searched three electronic

databases (PubMed, EMBASE and CINHAL) using a validated measurement properties search strategy.[137] We selected studies that examined validity and/or reliability of a questionnaire to assess children's exposure to each of the risk factors. Quality assessment of each study was performed using the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) checklist; a set of rigorously developed tools to facilitate the evaluation of the quality (i.e. excellent, good, fair or poor) of measurement property studies.[139, 142]

Stage Two – Delphi Study

A Delphi study was conducted to obtain expert input to select a set of core variables for each risk factor. A working group (WG) of 11 researchers from Canada, the USA, the UK, the Netherlands, and Italy was assembled, including epidemiologists, pediatric MS neurologists, adult MS neurologists, and content experts. (Appendix 5.1) The WG included researchers actively involved in MS research, who are also members of the IPMSSG. We also invited three content experts, one for each risk factor. Content experts were selected from among authors of the publications found in the literature reviews. The WG was divided into three sub-groups with some overlapping membership, one for each risk factor, with six members in each group. Prior to the start of the Delphi study, the WG met for a two-day face-to-face meeting in Montreal, Canada for an introduction to the study and background knowledge to facilitate participation.

The Delphi study had four rounds. The knowledge gained from the measurement property literature reviews, conducted in stage one, was used to develop each round. Each round also incorporated the input provided by the WG in the previous rounds. The responses given in each round were summarized and WG members commented on the summary. Delphi rounds one, two and four were completed anonymously online and round three was a face-to-face meeting. Round one focused on defining a research question for each risk factor. In round one, the WG was also presented with 11 criteria, and members were asked to select those that should be used to guide the selection of core variables. The purpose of round two was to select the three top constructs for each risk factor, which allowed us to focus the variable selection process conducted in round three.

We initially planned for all rounds to be online, however, because selection of core variables proved to be a complex process and we wanted to actively engage experts in discussion, round three was completed at a face-to-face meeting held in Montreal, Canada. The

WG participated in guided discussions to select and define the core variables. Given that the goal was to limit the number of core variables, experts were also asked to select ancillary variables; these were defined as variables that provide important supplementary information about exposure, but were not deemed core by the WG. In round four, the WG provided approval for the proposed Tool-Kit variables. As a result of the Delphi study, we developed a measurement framework that includes a set of core and ancillary variables for pediatric MS studies, a description for each variable, harmonizable response options and data coding.

In round four, we also evaluated the content validity of the core variables. The COSMIN checklist was used to design the content validity study.[139, 142] Using a three-level Likert scale (highly relevant, somewhat relevant, not relevant) each WG member independently rated whether the core variables: (i) refer to relevant aspects of the construct being measured, (ii) are relevant for the target study population (e.g. age, sex, disease characteristics, country, setting), (iii) are relevant for the purpose of the measurement instrument (e.g. predicting exposure), and (iv) together comprehensively reflect the construct being measured. Variables that were rated as relevant (highly or somewhat) remained as core variables, those that were rated as 'not relevant' were subsequently classified as ancillary variables.

RESULTS

Risk Factor Survey

Over 1400 abstracts were identified, and risk factor information was extracted from 88 relevant publications. Forty-two risk factors were initially identified, and subsequently reduced to 12 using our predefined filter: body size or body mass index; environmental tobacco smoke (ETS); head injury or traumatic brain injury; history of infectious mononucleosis; penicillin use; physical activity; prenatal and perinatal factors; sibling exposure and attending daycare; stressful life events; sun exposure; vaccinations; and vitamin D intake (VDI).

These 12 risk factors were then included in the risk factor survey that was completed by 48 IPMSSG members (35% response rate). The results of the survey are displayed in Figure 5.1. Sun exposure and VDI were most highly endorsed as priorities for future research (85% and 81% of respondents, respectively). Mononucleosis infection and vaccinations also ranked highly as a priority for future research (73% and 56% of respondents, respectively). However, when the responses 'a priority' and 'important' were combined, sun exposure (96%) and VDI (94%)

remained highly endorsed in addition to ETS (93%). Using the results of the survey, we selected three risk factors for which we developed a common set of core variables: ETS, sun exposure, and VDI.

Developing the Tool-Kit: Literature Reviews of Measurement Properties

Three measurement property reviews were performed, one for each risk factor. The reviews yielded 152 publications on measurement properties of ETS questionnaires, 35 on sun exposure and 13 on VDI. For VDI we also carried out a search on the grey literature, which focused on searching country-specific food composition databases and government reports; to identify country-specific food options that are good sources of vitamin D. Much of the extant measurement property literature focused on questionnaires that measure current or recent exposure, which is relevant for cohort and cross-sectional studies; however, we did not identify validated questionnaires to assess long-term exposure histories, which is required for case-control studies.

Developing the Tool-Kit: Delphi Study

Three research questions were proposed to guide future research to examine ETS, sun exposure, and VDI and risk of MS. (Table 5.1) More than half of working group members agreed that eight criteria should be used to guide the selection of the core variables. (Table 5.2) For ETS the constructs selected were sources and locations of smoke exposure as well as smoking rules in the home. For sun exposure, summer sun exposure, use of sun protection and residential history were selected. For VDI, the selected constructs were vitamin D supplementation, infant feeding practices and vitamin D rich foods. Core variables were selected in round three and refined in round four of the Delphi study.

Overall, the Tool-Kit core variables were shown to have good content validity. The expert WG agreed that the core variables refer to relevant aspects of exposure, are relevant for the target study population, and that for the purpose of the study, the core variables, together, comprehensively reflect exposure. However, several modifications were made as a result of the content validity study. An ancillary variable to assess duration of travel to sunny destination during winter months was added to the set of sun exposure variables. A core variable was re-classified as an ancillary variable in the set of VDI variables (i.e. use of dietary supplements was

recommended by a health care professional). In the final Tool-Kit there are six core and three ancillary variables for ETS; six core and six ancillary variables for sun exposure; and six core and five ancillary variables for VDI. (Table 5.3) The final proposed Tool-Kit variables can be accessed online (www.maelstrom-research.org/mica/network/tool-kit). An example of a core variable is provided in Table 5.4.

The WG also defined age epochs for the Tool-Kit variables. Differences in the potential for exposure based on the child's main activities and changes in activities that represent potential changes in exposure were considered; but we also wanted to select a small number of age epochs, to ensure questionnaires were not too long. We selected the following age epochs: (i) baby (birth-1 year), (ii) toddler/preschool (2-4 years), (iii) child/primary- or elementary-school age (5-12 years), and (iv) teenager/high-school age (13-18 years). Several WG members suggested that in utero was also an important age epoch. However, given the need to modify the variable definitions, to define mother's activities/behaviours, we did not include this epoch, but highlight it as an important time period to examine, that will require additional methodological work.

DISCUSSION

We developed the Pediatric MS Tool-Kit, which aims to enhance the methodological rigour of pediatric MS etiologic studies by proposing a measurement framework to facilitate the design of study-specific questionnaires. The short-term goals of the Tool-Kit are to enhance the validity of exposure measurement in individual pediatric MS studies, by proposing a set of rigorously selected and defined variables that measure priority risk factors; as well as to enhance comparability of study results, by proposing the use of a common measurement framework. The long-term goal of the Tool-Kit is to enhance the potential for collaboration through data sharing and consequently larger sample sizes in harmonized analyses. The Tool-Kit provides a set of core and ancillary variables that are intended to be used to measure children's exposure to sun, exposure to environmental tobacco smoke and intake of vitamin D. The core variables are those that were selected for harmonized analyses. As the working group proposed a number of important variables to comprehensively measure exposure, these additional variables are provided as ancillary variables. The Tool-Kit will reduce the time and resources required to design study-specific questionnaires.

The Tool-Kit can be considered as a common measurement framework for pediatric MS research. Researchers can use the information in the Tool-Kit to create a questionnaire that is specific to their target population. The exact questions, however, are not provided in the Tool-Kit. We chose to provide information about the variable to develop the questions, rather than of exact wording of individual questions. This approach is referred to as flexible prospective harmonization.[128] We could have proposed a questionnaire for use in all studies; however, we felt this approach was too stringent. While the use of flexible prospective harmonization may hamper comparability among studies, it may be more appropriate for etiological research given study investigator(s) are most knowledgeable about their study context and target population.

The Tool-Kit makes an important methodological contribution to pediatric MS research. The need for, and value of, prospective harmonization has been recognized by the research community, and is demonstrated by several examples of large prospective harmonization initiatives such as: the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDE);[129, 130] European Prospective Investigation into Cancer and Nutrition (EPIC) study;[211] the PhenX Tool-Kit;[212] and Canadian Partnership for Tomorrow project.[131] The NINDS has recently developed CDE for MS that include variables focused on demographics, clinical assessments, imaging, and neuropsychology/cognition.[129, 130] The NINDS also used a working group model to select and define the MS CDE. The MS CDE also include a core set of variables, which they define as *essential information applicable to any study*; but have also defined a set of CDE which they classify as supplemental - highly recommended, supplemental, or exploratory. Researchers who received funding from the NINDS are asked to use the CDE to design their data collection tools.

Using the Tool-Kit

The Tool-Kit variables can be accessed online at www.maelstrom-research.org/mica/network/tool-kit. The information presented online includes the proposed Tool-Kit variables (i.e. name, type, description), response options and data coding. To be harmonizable we recommend that this information be used to develop individual questions to include in study-specific questionnaires. Ideally, at least one question should be developed for each variable, and the question should be worded so that it links to the variable description in the

Tool-Kit. If multiple questions are used, it will be important to ensure the Tool-Kit variables can be generated from the questions used.

The proposed response options that correspond to each variable are meant to be used as is, although modification is possible; however, for data to be harmonizable researchers should ensure the response options in the Tool-Kit can be generated from modified response options. For example, if deemed more appropriate by the study investigators, additional response options may be added, but the new response options should be collapsible into those provided in the Tool-Kit. We do not recommend that investigators exclude any response options proposed in the Tool-Kit, as they form the basis for harmonization, and were developed through a rigorous methodological process.

In addition to retaining the response options as proposed in the Tool-Kit, the age epochs should also be used as is outlined in the Tool-Kit, in order for data to be harmonizable. However, unlike the response options, collapsing age epochs is much more methodologically difficult, and may render the data non-harmonized. The key is to ensure the Tool-Kit variables and response options can be generated from the data collected in a study.

Once the questionnaire is developed, we recommend that the actual questions and their response options be compared to the variable definitions and response options in the Tool-Kit by an individual who was not involved in developing the study questionnaire; and if the questionnaire is used in a language other than English, this individual should be fluent in English and in the language used in the questionnaire.

As the long-term goal of the Tool-Kit is to provide the opportunity for collaboration through harmonization, researchers using the Tool-Kit variables will be asked to provide us with some basic information about their study (e.g. study name, sample size, variables used) to be displayed on the Tool-Kit webpage. An additional condition of use is to cite this publication in any manuscripts that have used the Tool-Kit. The Tool-Kit is a methodological resource for questionnaire design, and is not a repository of data. While we will maintain an inventory of studies that have used the Tool-Kit variables, the decision to share data, at the time of a proposed harmonized analysis, is left to the discretion of the individual study investigators. IT infrastructure has been recently developed to enable remote and confidential analysis of sensitive research data (i.e. DataSHIELD),[213] which is important given legal, ethical and logistical issues surrounding the sharing of data that contain personal information.

The main limitation, in light of the rigorous process used to select the core variables, is the possibility that the variables selected have poor measurements properties. We were unable to identify a validated questionnaire to use in a case-control study, and thus we used an expert consensus seeking approach to select the Tool-Kit variables. The Tool-Kit has not yet been tested in a 'real-life' research setting. While we show that the core variables have good content validity, continued evaluation of the measurement properties of the Tool-Kit variables will be imperative to its utility and success. We are open to collaborating with researchers wanting use and assess the measurement properties of the core variables in their specific research settings.

CONCLUSIONS

We believe the Tool-Kit will prove to be a valuable resource to guide pediatric MS researchers in developing study specific questionnaires. Rigorous epidemiological and expert consensus methods were utilized to develop the Tool-Kit variables and the pediatric MS research community was involved in our work to ensure that what we developed is in line with the needs of, and relevant for, the research community. We invite content area experts to take the opportunity to expand the Tool-Kit to develop additional core variables for the other priority MS risk factors.

TABLES

Table 5.1 Research Questions for the three risk factors that are included in the Tool-Kit

Risk Factor	Research Question
Environmental Tobacco Smoke	Everything else being equal, are children who have been exposed to higher levels of environmental tobacco smoke at increased risk of MS compared with children who have been exposed to lower levels of environmental tobacco smoke?
Sun Exposure	Everything else being equal, are children who have been exposed to lower levels of sun at increased risk of MS compared with children who have been exposed to higher levels of sun?
Vitamin D Intake	Everything else being equal, are children with lower intake of vitamin D (through supplementation) at increased risk of MS compared with children with higher intake of vitamin D (through supplementation)?

Table 5.2 Eight criteria for selecting the core variables to be included in the Tool-Kit

Selection Criteria
The variable is necessary to answer the research question.
The variable helps to better interpret or understand the level of exposure to the risk factor.
The variable is a potential confounder or effect modifier.
The variable can be collected using proxy-report (i.e. parent/guardian) via self-administered and/or interview-administered questionnaire.
The variable can be collected in a valid and reliable way, given the required retrospective nature of the data collection.
The level of detail that is asked to recall is reasonable given the retrospective nature, time and resources available.
The variable is of high enough prevalence in the source population to ensure sufficient statistical power.
The variables and response options should be selected to enhance cross-cultural validity

Table 5.3 Tool-Kit core and ancillary variables for the three risk factors

Core Variables	Ancillary Variables
Environmental Tobacco Smoke Exposure	
1. Home ETS Exposure Ladder[1] 2. Childcare ETS Exposure Ladder[1] 3. Frequency of Smoking by the Child's Mother 4. Frequency of Smoking by the Child's Father 5. Frequency of Smoking by Others who Lived with the Child 6. Residential History	1. Evidence that Previous Smoker(s) Lived in Child's Home 2. Smoking Status of Close Family Members and/or Friends 3. Type of Tobacco Products Consumed by Individuals who Lived with the Child
Sun Exposure	
1. Residential History 2. Frequency of Daily Outdoor Activities during Daylight Hours 3. Duration of Time Outdoors on Weekends during Summer 4. Duration of Time Outdoors on Weekdays during Summer 5. Duration of Time Outdoors on Weekdays during Winter 6. Duration of Time Outdoors on Weekends and School Holidays during Winter	1. Frequency of Travel to Sunny Destinations during Winter 2. Skin Colour 3. Sun Sensitivity 4. Frequency of Sun Protection Use: Sunscreen 5. Frequency of Sun Protection Use: Wearing a Shirt with Sleeves 6. Frequency of Sun Protection Use: Staying in the Shade or Under an Umbrella
Vitamin D Intake	
1. Child's Use of Dietary Supplements 2. Frequency that the Child Used Dietary Supplements 3. Duration of Time that the Child Used Dietary Supplements 4. Child's Use of Dietary Supplements that Contain Vitamin D 5. Frequency that the Child Used Dietary Supplements that Contain Vitamin D 6. Duration of Time that the Child Used Dietary Supplements that Contain Vitamin D	1. Brands of Dietary Supplements that were Commonly Used by the Child 2. Use of Dietary Supplement was Recommended by a Health Care Professional 3. Child's Use of Cod Liver Oil 4. Frequency that the Child's Used Cod Liver Oil 5. Duration of Time that the Child Used Cod Liver Oil

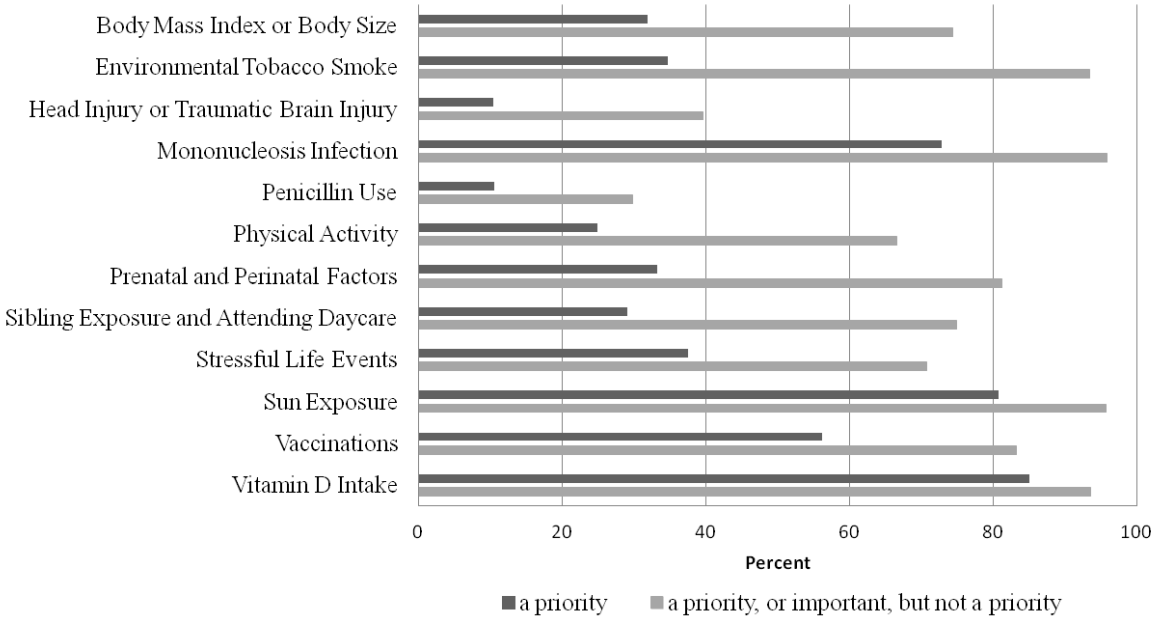
[1] The ETS Exposure Ladders incorporate sources and locations of exposure, as well as smoking rules in the home.

Table 5.4 Example of a core variable included in the Tool-Kit

Table	Sun Exposure
Variable name	Frequency of Daily Outdoor Activities during Daylight Hours
Label	Frequency of outdoors activities
Description	• Classifies the frequency of the child's usual daily outdoor activities during daylight hours. • Self-report by parent or both child and parent. • Ask for all relevant age epochs.
Value type	Text
Missing	9999
Unit	*not applicable*
Categories codes and labels	3: Almost always outdoors 2: More often outdoors 1: More often indoors 0: Almost always indoors 9999: Don't know/can't recall

FIGURES

Figure 5.1 Results of the Risk Factor Survey, indicating the percent of respondents that rated each risk factor as (i) *a priority,* and either (ii) *a priority*, or *important, but not a priority.*



APPENDIX 5.1: Pediatric MS Tool-Kit Delphi Study Working Group Members

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CHAPTER 6: EXPLORING THE LINK BETWEEN SUN AND MS RISK

6.1 Preface to Chapter 6

In chapter 6 I present the third manuscript which is related to the second theme of this thesis: *analysis*. Manuscript 3 addresses objectives 3 and 4, both of which are focused on analysis of sun exposure data. The research presented in this chapter builds on the analyses conducted in previous sun exposure MS case-control studies. My goal was to advance our understanding of the MS etiologic model, and I used two novel modelling approaches to gain additional insights. Life course epidemiology theory provides a set of conceptual models that are used to describe disease susceptibility. The critical period and accumulation models are two examples that may be relevant to MS susceptibility. I used a life course epidemiology analytical approach to examine these two models to determine which best explained the association between sun exposure and MS risk. I also used latent class analysis to characterize latent sun exposure behaviour groups, using three exposure variables, and compared risk of MS across groups. This manuscript will be submitted to the *International Journal of Epidemiology.*

6.2 Manuscript 3 - *Shedding Light on the Link between Early Life Sun Exposure and Risk of Multiple Sclerosis: The EnvIMS Study*

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ABSTRACT

Multiple sclerosis (MS) is believed to have a long latent period with an etiologically relevant period in childhood or early adolescences. Lower levels of sun exposure in childhood have been suggested to be associated with increased risk of MS. We extend previous analyses, using two novel analytical strategies, to further elucidate the etiological model. Data collected in the Environmental Risk Factors in MS (EnvIMS) Study, a case-control study that included MS cases and population-based controls from Canada, Italy and Norway, were used. Participants reported on sun exposure behaviours for five-year age intervals from birth; we focus on the first three age intervals (<15 years). We tested two different life course epidemiology conceptual models, critical period and accumulation; and used latent class analysis to estimate MS risk for different sun exposure behaviour groups. The analysis included more than 2000 cases and 4000 controls. The accumulation model had the best model fit; and demonstrated a nearly 50% increased risk of MS when comparing lowest reported sun exposure to highest (RR=1.47 (95% CI: 1.24, 1.74)). The latent sun exposure behaviour group characterized by low sun exposure during summer and winter and high sun protection use had the highest risk of MS; this group had a 76% increased risk as compared to the group with the opposite exposure pattern (RR=1.76 (95%CI: 1.27, 2.46)). Our analyses provide additional insights about the link between sun exposure and MS, in three countries with high prevalence of MS. We demonstrate that longer duration of time indoors during childhood is strongly linked with MS risk.

BACKGROUND

Multiple sclerosis (MS) is a chronic immune-mediated disease affecting the central nervous system. MS is suggested to have a long latent period [85, 86] with disease risk determined in childhood or early adolescences.[82-84, 214] The etiology is suggested to involve an interplay between genetic and lifestyle and environmental factors.[5] The prevalence of MS varies globally, though it is generally higher in northern countries, such as Canada [26, 27, 61] and Norway [3, 64] (e.g. prevalence>200 per 100,000 population). However, there are exceptions, as similar estimates have been reported in Italy,[2, 63] a more southern country.

Several ecological studies have shown that MS prevalence is inversely correlated with latitude [6, 7, 116] and ambient ultraviolet radiation. [8, 9, 117, 118] Case-control studies have consistently found an inverse association between sun exposure levels and risk of MS at the individual-level.[11-14, 17-20] Some case-control studies have measured sun exposure, generally, over the lifetime (i.e. time spent outdoors), while others have examined sun exposure behaviours in greater depth. Several studies have also estimated MS risk across a number of different age periods, which is consistent with assessing a critical period model.[13, 17, 18, 20] The critical period and accumulation models are two conceptual life course epidemiology models that can be used to explain disease etiology.[25, 135, 136] Two case-control studies performed in Australia examined both the critical period model, as well as exposure over longer periods of time, which is referred to as the accumulation model.[18, 20] These two studies showed that accumulation of exposure, or lack thereof in the case of sun exposure, during childhood or early adolescences is an etiologically relevant model to consider.

We extend previous analyses and use two novel analytical approaches to further explore the link between sun exposure and the risk of MS. The first objective of this study was to directly compare two different etiologic models, critical period and accumulation. The second objective was exploratory, and considered three sun behaviours simultaneously (i.e. summer sun exposure, winter sun exposure, and sun protection use), to understand how these sun related behaviours, taken together, may contribute to MS risk. Our goal was to further develop the etiological model of MS, to advance our understanding of the association between sun exposure and risk of MS.

METHODS

Study Design

The analyses presented build on those previously reported by members of our research group.[13] A detailed description of the study design and methodology of the Environmental risk factor In MS study (EnvIMS study) is presented elsewhere, [148] and is described briefly here. EnvIMS was a case-control study that included MS cases and population-based controls in five countries, but only data collected in Canada, Italy and Norway are used here, as these countries enrolled the largest number of study participants. The study was conducted from 2009-2014. A self-administered questionnaire, the EnvIMS-Q, [149] was mailed to participants' homes. Participants were 18 years of age or older at the time of sampling. Two to four controls were frequency matched with cases on year of birth (within 5 years), sex and area of residence. Power analyses [156] suggested that, with the available sample size and α=0.05, the main analyses has 80% power to identify odds ratios of 1.2 as statistically significant, and 90% power for odds ratios of 1.5.

Variables

***Exposures Variables*:** The sun related questions in EnvIMS were similar to those used in previous studies; [17, 18, 20] and those that had undergone measurement property assessment for test-retest reliability in Australia.[151] Outdoor sun exposure during summer was the main exposure for the first objective, and was captured using a question about frequency of time spent outdoors in summer; the interpretation of summer was self-perceived and not strictly defined. Participants completed a matrix with one of four response options (i.e. *'not that often'*, *'reasonably often'*, *'quite often'* and *'virtually all the time'*), for the each age interval. In Canada and Italy five-year age intervals were used (i.e. 0-5, 6-10 and 11-15 years); whereas, in Norway age intervals were based on the schooling system, with a view to aiding recall (i.e. 0-6 years, 7-12 years, and 13-15 years). While intervals were slightly different, they were combined, given the substantial overlap. For objective 2, variables characterizing frequency of outdoor sun exposure during winter (same response options as summer exposure) and use of sun protection when outdoors ('*almost always*', '*quite often*', '*sometimes*' and '*seldom/never*') were also used.

***Outcome Variable*:** MS diagnosis was defined based on McDonald[39] or Poser[54] criteria for clinically and laboratory-supported definite or probable MS. Cases were required to have clinical disease onset within 10 years of the time of sampling.

Potential Confounding Variables: Age and sex were included in all models. The following variables were selected based on their potential to confound the relationship between sun exposure and MS risk: parent's education, ethnicity, number of siblings, physical activity, body shape, environmental tobacco smoke exposure (mother and/or father), sun related variables (winter sun exposure, sun protection) and skin related variables (skin, eye and hair colour, tanning reaction to sun), and associated diseases (mononucleosis infection, indoor allergies, outdoor allergies, autoimmune disease).

Statistical Methods

Objective 1 Analyses: We used an analytical framework that is used to compare life course epidemiology conceptual models, to examine how consistent the models are with the data.[25] A series of regression models were created to represent the different conceptual models, which were then compared to a saturated regression model, using model fit criteria. Model selection was based on the Bayesian Information Criterion (BIC) and likelihood ratio test (LRT). The saturated model includes all possible parameters. The goal was to identify a more parsimonious regression model or models that characterize the data, and had a similar model fit to the saturated regression model.

A generalized linear regression model, with a logit link and binomial family, was used to estimate the risk of MS associated with lower levels of outdoor sun exposure during summer. Analyses were completed in Stata 11.0.[157] Data from all three countries were combined; and fixed effects for country were included in all models. The same confounders were used in all models. Bivariate analyses were used to select potential confounders and a backward deletion approach, using a greater than 10% change in estimate, was used in a multivariable model.[158] Sun exposure during summer was dichotomized to compare those with lower levels ('not that often' or 'reasonably often') to those with higher levels ('quite often' or 'virtually all the time'). The following two models were examined: (i) the critical period model and, (ii) the accumulation model.

The critical period model suggests that there is a time period during which an individual is susceptible to exposures that determine disease risk. This could be a certain age, age period, a developmental process (e.g. puberty) or other distinct event (e.g. pregnancy). We estimated the risk of MS associated with having low levels of outdoor sun exposure during summer compared with having higher levels, for three age intervals (i.e. 0-5, 6-10 and 11-15 years). We hypothesized that there is a five-year critical period before the age of 15 years during which lower levels of sun exposure best predicts risk of MS.

The accumulation model suggests that the longer the length of time an individual is exposed the greater the risk of disease, irrespective of when exposure occurs. We estimated the risk of MS associated with the sum of the number of the age intervals (0, 1, 2 or 3) that an individual reported lower levels of sun exposure, compared to individuals who reported higher levels, over the three age intervals. We hypothesize that MS risk is greatest in individuals who are exposed to lower levels of sun exposure for a greater number of age intervals before the age of 15 years. A description of the model parameters is presented online. (Appendix 6.1)

Several sensitivity analyses were completed to assess the robustness of the results. To assess the effect of time since exposure the sample was restricted to those under (i) 30, (ii) 40 and (iii) 50 years of age. To examine more incident cases, analyses were restricted to those with disease duration less than five years. To assess the possible impact of misclassification of exposure, analyses were restricted to those who had help completing the questionnaire. Complete case analysis was used for all analyses; however, we also assessed the potential impact of missing data using multiple imputation models.

Objective 2 Analyses: Objective 2 builds on objective 1. Objective 2 analyses were performed using the exposure variables for the life course epidemiology model that was found, in objective 1, to be most consistent with the data. Latent class analysis was used to identify latent classes, which we call *sun exposure behaviour groups*, using indicators for frequency of summer sun exposure, winter sun exposure and sun protection use when outdoors. We then estimated the relative risk of MS across the sun exposure behaviour groups. Analyses were completed in Latent Gold 5.0 using the Step3 procedure.[159] The Step3 procedure is completed in three steps; first a cluster model is used to identify latent classes, study participants are then assigned to clusters, and the association between cluster membership and a dependent variable is estimated.

A cluster model was used to determine the number of latent classes that fit the data best. Given the large dataset the number of latent classes that were tested ranged from one to seven, and BIC was used to select the best model. Age and sex were included as covariates. Participants were proportionally assigned to sun exposure behaviour groups, and group membership was regressed on MS status, using logistic regression. Risk was estimated using effects coding, which compares risk in each sun exposure behaviour group to the average risk across all groups. We also used dummy coding to estimate risk in the sun exposure behaviour group with the highest risk relative to each of the other groups, given the high risk group was of primary interest.

RESULTS

Data from 6279 study participants are included in the present analyses: 2251 cases and 4028 controls. Demographic characteristics of the participants are presented in Table 6.1. Cases had mean age of 41.9 years and 69% were female, and controls had mean age of 44.4 years and 70% were female. Average disease duration in cases was 6.5 years. Characteristics of sun exposure behaviours are presented in Table 6.2. By design there was no missing information about the outcome, age, sex and country. For the main exposure, the amount of missing data, across the three age intervals, ranged from 3.4% to 7.1%; and when these variables were combined to create the accumulation exposure variable, 8.4% were missing. The variable with the largest amount of missing information was sun protection use between birth and 5 years of age, with 12.9% missing data.

Objective 1 Results

There were 5750 study participants with non-missing data on frequency of summer sun exposure. The majority (64%) reported a high frequency of outdoor sun exposure during summer at all three age intervals, and 10% reported a low frequency at all three age intervals. (Table 6.3) Compared to the saturated model, the accumulation model was found to be most consistent with the data, although the critical period models for age intervals 0-5 years and 11-15 years also had good fit criteria. Model fit criteria for the models that were tested are presented in Table 6.4. The accumulation model was tested two ways, using (i) ordinal variables and (ii) indicator variables. Based on the LRT, both accumulation models had a $p>0.05$, indicating a similar fit to the saturated model. However, the first model had a lower BIC than the second model (-42318.59 vs.

-42304.23). Based on the LRT the critical period models for age intervals 0-5 years and 11-15 years also had p>0.05; the BIC for these models was larger but similar to the ordinal accumulation model (-42314.23 and -42311.88, respectively). Based on these results the ordinal accumulation model was selected as the best model.

Risk ratio (RR) estimates for the three top models are presented in Table 6.5. For the accumulation model, the RR comparing low sun exposure at all three age intervals, to high sun exposure at all three age intervals, suggested a 47% increased risk (RR=1.47 (95%CI: 1.24, 1.74)). Sensitivity analyses resulted in similar RR, except in the analysis that was restricted to participants who had help from their parent(s) completing the questionnaire, which produced a larger RR (2.14 (95%CI: 1.56-3.00). (Appendix 6.2)

Objective 2 Results

The accumulation model was used for objective 2. The model with six latent classes had the lowest BIC. Ordinal indicators for the number of age intervals participants reported having low sun exposure during summer and during winter, and having high sun protection use, explained a large amount of variance (R^2>65%). The profile plot in figure 6.1 displays the distribution of the six sun exposure behaviour groups. There were two groups that had high sun exposure in summer and in winter for all three age intervals (clusters 3 and 4); two with low sun exposure in summer and in winter for all three age intervals (clusters 5 and 6); and two with high sun exposure during summer, but lower sun exposure during winter (clusters 1 and 2). Among the pairs with similar sun exposure profiles, one frequently used sun protection, whereas the other rarely used sun protection.

Sun exposure behaviour groups were found to be significantly associated with MS (p=0.02). Cases were most likely to be classified into the group characterized by the low levels of sun exposure during summer and winter, and high levels of sun protection use (i.e. sun-avoiders). Compared to the average risk across groups, sun-avoiders had 20% increased risk of MS (RR=1.20 (95%CI: 1.05, 1.37)). (Table 6.6) Comparing sun-avoiders to all other groups, risk was greatest relative to sun-seekers (i.e. high sun exposure during summer and winter and low sun protection; RR=1.76 (95%CI: 1.27, 2.46)). Risk of MS in sun-avoiders was higher than in all other groups. (Table 6.7) Interestingly, when sun-avoiders were compared to the group that is

characterized by similar summer and winter sun exposure, but when outdoors they rarely used sun protection, the risk of MS was 40% greater (RR=1.40 (0.96, 2.04)).

DISCUSSION

Our analyses suggest that lower levels of sun exposure accumulated from birth to age 15 years are associated with increased risk of MS. We first used an analytical approach to examine the plausibility of two life course epidemiology models. We found that MS risk was nearly 50% greater in individuals who spent the least amount of time outdoors before the age of 15 years, compared to those who spent the most amount of time outdoors. In life course epidemiology terminology this describes the accumulation model. The greater time an individual is exposed, or not exposed in our case, the higher the risk of disease. The accumulation model was compared to the critical period model, for three age intervals. The critical period models for the age intervals, (i) birth to 5 years of age and (ii) 11 to 15 years, also had good model fit, perhaps suggesting an increased susceptibility to MS during both these age periods.

The results obtained in objective 1 are consistent with previous literature. Several case-control studies have demonstrated a link between sun exposure and MS risk.[11-14, 17-20] Our study is the largest case-control study, to date, to examine sun exposure and MS risk, and it includes three countries with high MS prevalence (i.e. Canada, Norway and Sardinia and mainland Italy). Studies that examined risk in childhood or adolescence reported higher risk in relation to less time in the sun.[13, 14, 17, 18, 20] In studies that estimated age specific effects, the analyses were structured using a critical period model.[13, 17, 18, 20] Two of these studies also estimated risk using an accumulation model, and although the models were not directly compare, the effect estimates obtained for the accumulation models were larger than for critical period models.[18, 20] Collectively the evidence suggests that accumulation of low sun exposure during childhood best explains the risk of MS. It would also be interesting to develop life course epidemiology models for other MS risk factors.

We also wanted to explore how various sun behaviours were related to MS risk. Studies have shown that lower levels of sun exposure during summer, [13, 14, 17, 18, 20] during winter, [13, 17, 18, 20] and higher levels of sun protection use are associated with increased risk of MS.[11-13] Our analyses identified six distinct sun exposure behaviour groups, with different levels of summer

and winter sun exposure, and of sun protection use; and we explored the relationship between these sun related behaviours and MS risk.

Lowest risk of MS was found in the sun-seeking group (i.e. high summer sun exposure, high winter sun exposure and rarely using sun protection for all three age intervals; cluster 3 in figure 6.1); whereas highest risk was found in sun-avoiders (e.g. low summer and winter exposure, and almost always using sun protection for all three age intervals; cluster 6 in figure 6.1). When comparing sun-avoiders to sun-seekers, we estimated a more than 75% increase in the risk of MS. The risk of MS was 40% greater in sun-avoiders than in the group that had similar low summer and winter sun exposure, but didn't use sun protection, in their limited time outdoors. Interestingly, among the sun exposure behaviour groups with higher sun exposure, the use of sun protection did not appear to impact MS risk; which supports the importance of using sun protection when spending more time in the sun.

The ultraviolet rays emitted by the sun play a number of important roles in human physiology; including several that have been implicated in MS such as production of vitamin D and immune system function (e.g. T- lymphocytes, B-lymphocytes, regulatory T-cells).[215, 216] Our results also indicate that early childhood (birth and 5 years) and early adolescence (11 and 15 years) may be sensitive periods.[136] Childhood is an important time in life during which the immune system develops, [217] making children particularly vulnerable to insults that predispose them to disease later in life. Key changes in immune system function during these two age periods may help point to the biological mechanisms underlying MS etiology; for example, early childhood is an important period in developing immunity, and early adolescence is marked by the onset of puberty.

We also found an important effect of sun protection. Sunscreen blocks UVB, however use of more protective measures, such as staying indoors or using an umbrella, block both UVA and UVB rays. Over time sun exposure practices have changed as a result of public health promotion programs to reduce skin cancer risk, and children are more likely to be protected when out in the sun, or kept indoors during high exposure periods of the day.[112] While these measures are critical, a WHO report suggests that diseases associated with low sun exposure (e.g. rickets, osteomalacia and osteoporosis), account for greater burden of disease than those associated with high levels of sun exposure.[24] Vitamin D has been the focus of a lot of MS research, however, vitamin D is only one of the many beneficial effects of the sun.[218] Both

human and animal studies suggest that there are effects of the sun on MS risk that are independent of vitamin D.[18, 219] It is thus imperative to provide balanced information about the sun's benefits.[23, 220] Such messages may include the need to obtain short amounts of daily sun, at certain periods of the day to maximize benefits; while at the same time maintaining the current recommendations to use sun protection and limit excessive exposure during high UVR periods. Sun safety messages must be tailored for the specific population, given geographic differences in weather patterns, distribution of skin pigmentation and cultural practices.

Several measures were used to reduce bias in this study. Data from a population-based case-control study were used to enhance generalizability of results. The EnvIMS study questionnaire was tested for feasibility, applicability and reproducibility;[149, 151] and the sun related questions have been shown to work well in other studies.[17, 18, 20] Nevertheless, misclassification remains likely, as sun exposure is difficult to measure using self-report questionnaires, in addition to the long duration from the time from exposure to data collection. Interestingly, effect estimates were stronger in the sensitivity analyses that were restricted to those who reported having help from their mother and/or father. However, recall bias cannot be dismissed given the study design; furthermore, heat negatively impacts MS patients,[221-223] and as current behaviours may impact reporting of past behaviours, cases may be more likely to inaccurately report lower levels of sun exposure than controls.

CONCLUSIONS

We used two novel analytical strategies to further explore the link between sun exposure and MS risk, in three countries with high rates of MS. We show that longer duration of time spent indoors during childhood is strongly linked with increased MS risk. There was an indication that specific age periods in early childhood (0-5 years) and early adolescence (11-15 years), may represent sensitive periods during which low sun exposure levels have a greater impact on MS risk. In addition, among children who spend less time in the sun, lower levels of sun protection may mitigate the negative effects that spending most time indoors have on the risk of developing MS in adulthood. However, among those who spent more time outdoors, sun protection did not appear to meaningfully affect MS risk. Thus, even when high levels of sun protection are used, enough sun is able to reach the body. These finding provide support for promoting balanced safe sun practices to reduce disease burden. Simple changes in sun exposure

behaviour may have an important impact on incidence of MS and other diseases related to low sun exposure, and should be explored further, especially in countries and cultures where children spend a lot of time indoors.

TABLES

Table 6.1 Characteristics of study participants (cases and controls) enrolled in the Environmental Risk Factors in MS (EnvIMS) Study

Participant Characteristics	Cases (n=2251)	Controls (n=4028)
Country of Residence *% (n)*		
Canada	26.1 (587)	24.3 (978)
Italy	31.4 (707)	33.1 (1333)
Norway	42.5 (957)	42.6 (1717)
Age at Study (years) *mean (sd, range)*	41.9 (10.7, 18-80)	44.4 (11.5, 18-86)
MS Disease Duration (years) *mean (sd, range)*	6.5 (2.8, 0-11)	n/a
Sex *% female (n)*	69.4 (1563)	70.3 (2,832)
Ethnicity (Canada and Norway only) *% (n)*		
At least one parent is European	94.0 (1451)	93.0 (2507)
Both parents non-European	3.2 (50)	4.9 (132)
Missing	2.8 (43)	2.1 (56)
Participant Education *% (n)*		
Less than high school	12.0 (271)	8.9 (357)
Completed high school	29.5 (663)	27.0 (1088)
Post-secondary education	51.4 (1158)	54.5 (2195)
Missing	7.1 (159)	9.6 (388)
Highest Level of Education of Parents *% (n)*		
Less than high school	52.1 (1172)	54.5 (2195)
Completed high school	19.1 (429)	18.7 (755)
Post-secondary education	20.0 (451)	17.4 (700)
Missing	8.8 (199)	9.4 (378)
Number of Siblings *% (n)*		
Only child	5.0 (203)	6.4 (143)
1	28.3 (1139)	30.0 (675)
2	27.5 (1109)	29.0 (652)
3	16.4 (662)	15.7 (353)
4	8.8 (353)	7.7 (173)
5	5.1 (206)	3.6 (80)
6+	8.0 (324)	6.1 (138)
Missing	1.6 (37)	0.8 (32)

Participant Characteristics	Cases (n=2251)	Controls (n=4028)
Physical Activity between age 13-19 years *% (n)*		
Light and heavy physical activity	84.3 (1897)	85.3 (3441)
Light physical activity only	8.4 (189)	7.4 (296)
No physical activity	2.8 (63)	2.6 (103)
Missing	4.5 (102)	4.7 (188)
Mother Smoked during Childhood *% (n)*		
Yes	44.6 (1004)	41.2 (1660)
No	52.2 (1175)	56.3 (2266)
Missing	3.2 (72)	2.5 (102)
Father Smoked during Childhood *% (n)*		
Yes	59.6 (1342)	59.2 (2386O
No	36.8 (829)	37.9 (1525)
Missing	3.6 (80)	2.9 (117)
Body Shape @ age 5 years		
mean (sd, range)	2.4 (1.5, 1-9)	2.3 (1.5, 1-8)
Missing, % (n)	7.3 (164)	7,1 (287)
Body shape @ age 10 years		
mean (sd, range)	2.6 (1.5, 1-9)	2.4 (1.5, 1-9)
Missing, % (n)	7.0 (158)	6.5 (262)
Body shape @ age 15 years		
mean (sd, range)	2.9 (1.4, 1-9)	2.7 (1.4, 1-8)
Missing, % (n)	6.3 (142)	6.0 (242)
Mononucleosis Infection before age 15 years *% (n)*		
0-5 years	0.4 (10)	0.2 (7)
6-10 years	1.4 (31)	0.6 (25)
11-15 years	5.4 (121)	2.2 (90)
Outdoor allergies before age 15 years *% (n)*		
0-5 years	2.2 (49)	2.0 (79)
6-10 years	5.3 (119)	4.6 (185)
11-15 years	8.3 (186)	7.0 (280)
Indoor allergies before age 15 years *% (n)*		
0-5 years	1.9 (43)	1.6 (64)
6-10 years	4.0 (89)	3.3 (131)
11-15 years	5.5 (124)	4.8 (192)

Participant Characteristics	Cases (n=2251)	Controls (n=4028)
Autoimmune disease before age 15 years (not including MS) *% (n)*		
0-5 years	1.0 (22)	0.7 (27)
6-10 years	1.5 (34)	1.3 (54)
11-15 years	2.0 (45)	1.8 (74)

Table 6.2 Sun related behaviours and phenotypic characteristics of study participants (cases and controls) enrolled in the Environmental Risk Factors in MS (EnvIMS) Study

Characteristic, % (n)	Cases (n=2251)	Controls (n=4028)
Sun Related Behaviours		
Outdoor Activities during Summer		
0-5 years of age		
Not that often	5.8 (131)	4.5 (183)
Reasonably often	21.1 (475)	18.7 (755)
Quite often	41.1 (924)	42.0 (1692)
Virtually all the time	25.0 (562)	28.8 (1158)
Missing	7.1 (159)	6.0 (240)
6-10 years of age		
Not that often	1.6 (35)	1.5 (60)
Reasonably often	13.8 (310)	11.6 (467)
Quite often	43.9 (989)	43 (1733)
Virtually all the time	37 (832)	40.3 (1623)
Missing	3.8 (85)	3.6 (145)
11-15 years of age		
Not that often	2.6 (58)	2.9 (88)
Reasonably often	20.5 (461)	17.1 (687)
Quite often	45.5 (1024)	46.8 (1886)
Virtually all the time	27.9 (629)	30.6 (1231)
Missing	3.5 (79)	3.4 (136)
Outdoor Activities during Winter		
0-5 years of age		
Not that often	17.6 (397)	15.9 (641)
Reasonably often	32 (721)	33.6 (1354)
Quite often	30.8 (694)	30.4 (1226)
Virtually all the time	10.1 (228)	11 (442)
Missing	9.4 (211)	9.1 (365)
6-10 years of age		
Not that often	8.2 (185)	7.7 (310)
Reasonably often	29.2 (658)	27.9 (1124)
Quite often	40.9 (921)	41.6 (1676)
Virtually all the time	15.3 (345)	16 (646)
Missing	6.3 (142)	6.8 (272)
11-15 years of age		
Not that often	7.9 (177)	7.8 (314)
Reasonably often	35.7 (804)	33 (1328)
Quite often	39 (878)	39.9 (1608)
Virtually all the time	11 (247)	12.9 (519)
Missing	6.4 (145)	6.4 (259)

Characteristic, % (n)	Cases (n=2251)	Controls (n=4028)
Sun Protection Use		
0-5 years of age		
Seldom/never	36.6 (823)	40.5 (1632)
Sometimes	17.7 (399)	17 (684)
Quite often	14 (316	12.9 (519)
Almost always	18.8 (423)	17.6 (709)
Missing	12.9 (290)	12.0 (484)
6-10 years of age		
Seldom/never	36.4 (820)	40.1 (1617)
Sometimes	22.5 (507)	21.2 (855)
Quite often	15.3 (345)	14.1 (567)
Almost always	15.5 (349)	15.2 (611)
Missing	10.2 (230)	9.4 (378)
11-15 years of age		
Seldom/never	35.7 (804)	37.8 (1522)
Sometimes	33.7 (759)	31.7 (1276)
Quite often	15.3 (344)	14.4 (581)
Almost always	10 (226)	11 (444)
Missing	5.2 (118)	5.1 (205)
Phenotypic Characteristics		
Skin Colour		
mean (sd, range)	4.0 (1.7, 1-10)	4.0 (1.7, 1-10)
missing	3.4 (74)	3.0 (119)
Natural Hair Colour		
Black or Dark Brown	42.3 (951)	43.3 (1744)
Light Brown	33.6 (757)	34.5 (1389)
Blonde or Red	22.7 (510)	20.9 (843)
Missing	1.5 (33)	1.3 (52)
Natural Eye Colour		
Darker (Black, Brown or Hazel)	46.7 (1052)	46.8 (1884)
Lighter (Grey/Green or Blue)	50.7 (1142)	51.3 (2068)
Missing	2.5 (57)	1.9 (76)
Tanning Reaction to First Sun		
Always burn, never tan	9.8 (221)	8.4 (339)
Usually burn/sometimes tan	26.7 (600)	25.1 (1009)
Tan average/sometime mild burn	39.7 (894)	42.9 (1727)
Rarely burn/more than average tan	19.5 (438)	19.7 (795)
Missing	4.3 (98)	3.9 (158)

Table 6.3 Trajectories of frequency of outdoor sun exposure during summer in early life

Frequency of Outdoor Sun Exposure during Summer			% (n)[1]
Birth to 5 years	**6 to 10 years**	**11 to 15 years**	
High	High	High	63.6 (3658)
Low	High	High	11.3 (651)
Low	Low	Low	9.6 (550)
Low	Low	High	3.6 (204)
Low	High	Low	1.6 (89)
High	Low	Low	0.9 (54)
High	Low	High	0.2 (13)
High	High	Low	9.2 (531)

1. The were 528 (8.4%) study participants with missing data.

Table 6.4 Bayesian information criterion (BIC) and likelihood ratio test (LRT) for the life course epidemiology models with the best model fit criteria

Model[1]	**BIC**	**LRT (χ^2, p-value)**
Saturated	-42271.19	--
Critical Time Period		
0-5 years	-42314.23	8.90, 0.18
6-10 years	-42308.63	14.51, 0.03
11-15 years	-42311.88	11.26, 0.08
Accumulation		
Ordinal variable	-42318.59	4.55, 0.60
Indicator variables	-42304.23	1.59, 0.81

[1] Models include exposure variables and adjustment for age, sex and country.

Table 6.5 Risk ratio estimates, for the three life course epidemiology models with the best model fit criteria, comparing the risk of MS in individuals reporting the lowest levels of summer sun exposure to those reporting highest levels of summer sun exposure

Model	Risk Ratio[1] (95%CI)
Accumulation Model *Ordinal (0 to 3 age intervals)*	1.47 (1.24, 1.74)[2]
Critical Time Period Model *Age interval 0-5 years*	1.29 (1.14, 1.45)
Critical Time Period Model *Age interval 11-15 years*	1.29 (1.13, 1.47)

[1] Estimates adjusted for age, sex and country.
[2] Estimate is for a three unit change in exposure (three age intervals with low summer sun exposure compared to three age intervals with high summer sun exposure).

Table 6.6 Risk ratio estimates for the six latent sun exposure behaviour groups, relative to average risk across all groups

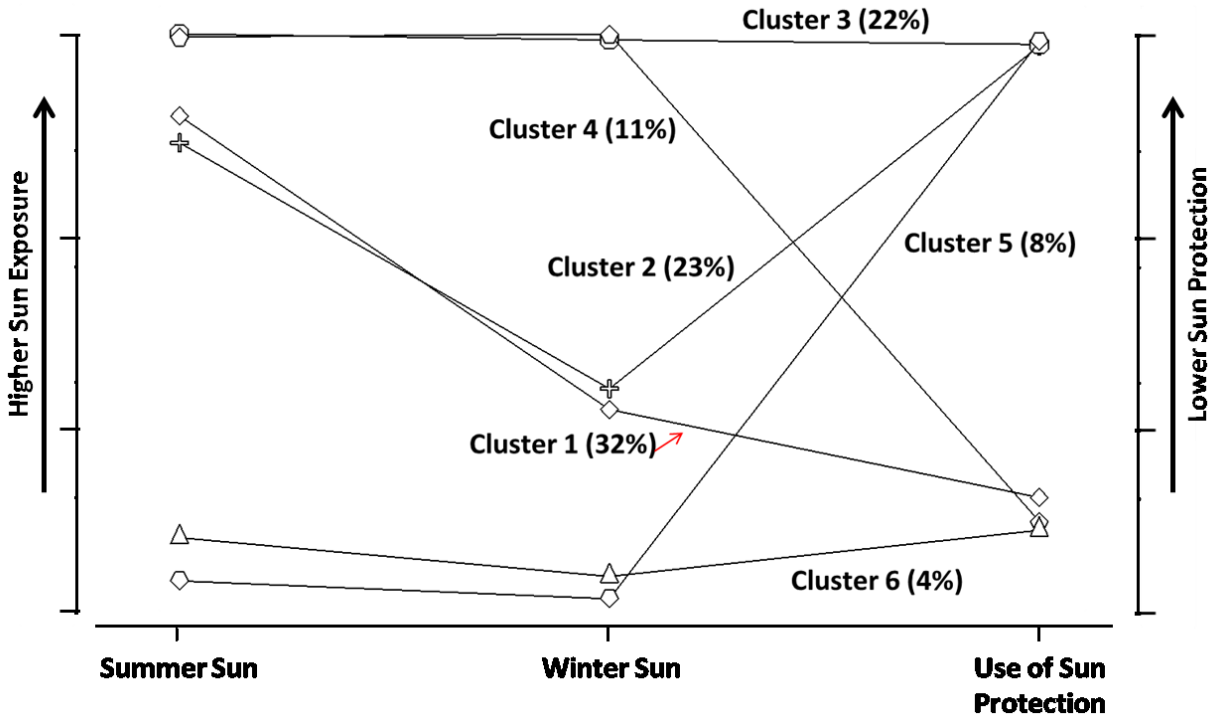
Cluster Number	Risk Ratio (95%CI)
1	0.95 (0.90, 1.01)
2	0.97 (0.90, 1.04)
3 (sun-seekers)	0.90 (0.84, 0.96)
4	0.99 (0.91, 1.08)
5	1.01 (0.92, 1.12)
6 (sun-avoiders)	1.20 (1.05, 1.37)

Table 6.7 Risk ratio estimates comparing the risk of MS in sun-avoiders (cluster six), relative to the other latent sun exposure behaviour groups

Cluster Comparisons	Risk Ratio (95%CI)
6 vs. 1	1.57 (1.13, 2.17)
6 vs. 2	1.53 (1.09, 2.15)
6 vs. 3	1.76 (1.27, 2.46)
6 vs. 4	1.46 (1.02, 2.08)
6 vs. 5	1.40 (0.96, 2.04)

FIGURES

Figure 6.1 Profile plot for the cluster model with six latent classes (the proportion of the sample in each cluster)



APPENDIX 6.1: Description of the model parameters for life course epidemiology models

The modelling approach proposed by Mishra et al (2009) can be used to examine life course epidemiology models using binary exposure variables. They suggest using a saturated regression model, which estimates values for all possible exposure patterns in the dataset. The saturated model fit criteria are compared to model fit for a series of regression models that represent different relevant life course epidemiology models. The critical period and accumulation models were examined in these analyses. Both the Bayesian Information Criterion (BIC) and likelihood ratio test (LRT) were used to identify the model with the best fit. The goal of this process is to identify a more parsimonious model (or models) that characterize the data best and have similar model fit as the saturated model.

Frequency of summer sun exposure was the main exposure examined. Frequency of sun exposure during summer (i.e. how often they were outdoors) was measured using a four level ordinal variable, but was dichotomized for these analyses. Risk in those with low sun exposure levels (*'not that often'* or *'reasonably often'*; coded as 1), were compared to those with higher sun exposure levels (*'quite often'* or *'virtually all the time'*; coded as 0), for each of the three age intervals assessed (0-5 years, 6-10 years, and 11-15 years).

Notation

X_j = frequency of outdoor sun exposure during summer at age interval *j*.

j = age intervals (0-5 years, 6-10 years, 11-15 years)

Z_i = confounding variables

Saturated Model*:*

$$\text{Logit}(p) = \alpha + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_1{*}X_2 + \beta_5X_1{*}X_3 + \beta_6X_2{*}X_3 + \beta_7X_1{*}X_2{*}X_3 + \Sigma\beta_iZ_i + \varepsilon$$

β_1 = log-odds of MS associated with reporting low sun for the 0-5 year age interval and high sun for all other age intervals, relative to reporting high sun for all age intervals.

β_2 = log-odds of MS associated with reporting low sun for the 6-10 year age interval and high sun for all other age periods, relative to reporting high sun for all age intervals.

β_3 = log-odds of MS associated with reporting low sun for the 11-15 year age interval and high sun for all other age periods, relative to reporting high sun for all age intervals.
β_4 = log-odds of MS associated with reporting low sun for the 0-5 and 6-10 year age intervals and high sun for 11-15 years, relative to reporting high sun for all age intervals.
β_5 = log-odds of MS associated with reporting low sun for the 0-5 and 11-15 year age intervals and high sun at 6-10 years, relative to reporting high sun for all age intervals.
β_6 = log-odds of MS associated with reporting low sun for the 6-10 and 11-15 year age intervals and high sun at 0-5 years, relative to reporting high sun for all age intervals.
β_7 = log-odds of MS associated with reporting low sun for all intervals, relative to reporting high sun for all age intervals.

Two life course epidemiology models were then compared to the saturated model.

Critical Period Model: This model suggests that there is a critical period during which an individual is susceptible to particular exposures that determine disease risk. We estimated the risk of MS associated with having low levels of outdoor sun exposure during summer, compared with having higher levels of outdoor sun exposure during summer, for each of the three age intervals (*j*). We hypothesize that there is a critical period before the age of 15 years during which the risk of MS is most strongly associated with low levels of outdoor sun exposure during summer.

Three models were tested:
$\text{Logit}(p) = \alpha + \beta_1 X_1 + \Sigma\beta_i Z_i + \varepsilon$
$\text{Logit}(p) = \alpha + \beta_2 X_2 + \Sigma\beta_i Z_i + \varepsilon$
$\text{Logit}(p) = \alpha + \beta_3 X_3 + \Sigma\beta_i Z_i + \varepsilon$

β_1 = log-odds of MS associated with reporting low sun for the 0-5 year age interval, relative to reporting high sun for the 0-5 year age interval, irrespective of exposure in other age intervals.
β_2 = log-odds of MS associated with reporting low sun for the 6-10 year age interval, relative to reporting high sun for the 6-10 year age interval, irrespective of exposure in other age intervals.

β_3 = log-odds of MS associated with reporting low sun for the 11-15 year age interval, relative to reporting high sun for the 11-15 year age interval, irrespective of exposure in other age intervals.

Accumulation Model: This model suggests that the longer the duration of time an individual is exposed the greater the risk of disease, irrespective of when exposure occurs. The variable used in this model was created by summing the values for the dichotomous summer sun exposure variables for the three age intervals. The exposure variable ranged from 0 to 3; zero represents individuals who reported high sun levels for all three age intervals, and 3 represents those who reported low sun exposure levels for all three age intervals. The exposure variable was treated two ways in the analysis; as an ordinal variable and as indicator variables. We estimated the risk of MS associated with the total number of the age intervals (0, 1, 2 or 3) an individual was exposed to lower levels of outdoor sun exposure during summer compared to individuals who were exposed to higher levels of outdoor sun exposure during summer, before the age of 15 years. We hypothesize that MS risk is greatest in individuals who are exposed to low levels of outdoor sun exposure during summer for a greater number of age intervals.

(i) Ordinal variable model:

Logit $(P|X, Z) = \alpha + \beta_1(\Sigma_j Xj) + \Sigma\beta_i Z_i + \varepsilon$

β_1 = log-odds of MS associated with reporting low sun for each additional age interval, relative to reporting high sun for all age intervals.

(ii) Indicator variable model:

Logit $(p) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \Sigma\beta_i Z_i + \varepsilon$

β_1 = log-odds of MS associated with reporting low sun for one age interval, relative to reporting high sun for all age intervals.

β_2 = log-odds of MS associated with reporting low sun for two age intervals, relative to reporting high sun for all age intervals.

β_3 = log-odds of MS associated with reporting low sun for three age intervals, relative to reporting high sun for all age intervals.

APPENDIX 6.2: Results of sensitivity analyses for the accumulation model

Model	Risk Ratio (95%CI)[1]
Main model (n=5750)	1.48 (1.26-1.73)
Under 30 years (n=765)	1.48 (0.94-2.41)
Under 40 years (n=2450)	1.37 (1.06-1.77)
Under 50 years (n=4197)	1.44 (1.19-1.77)
Had help completing questionnaire (n=1673)	2.15 (1.56-2.99)
Disease duration <5 years (n=1863)	1.48 (1.09-1.95)

1. Risk is those reporting low sun for all age intervals compared to reporting high sun for all age intervals.

CHAPTER 7: DISCUSSION

7.1 Preface to Chapter 7

In chapter 7 I discuss the results and implications of my findings. The chapter is divided into two main sections. Findings related to the first methodological theme, *measurement*, are discussed in section 7.2; and those related to the second methodological theme, *analysis*, are discussed in section 7.3. Within each of these sections, I first present an overview of the main results (sections 7.2.1 and 7.3.1), followed by a discussion of the results (sections 7.2.2 and 7.3.2) and end each section by describing some strengths and limitations of the research (sections 7.2.3 and 7.3.3). I then discuss the biological and public health implications of the findings (section 7.4), and directions for future research (section 7.5). The chapter ends with the overall conclusions of my research (section 7.6).

7.2 Methodological Theme 1: *Measurement*

The first methodological theme is *measurement* of sun related behaviours. Given the increasing interest in the etiology of pediatric MS and that, to date, there have been few studies conducted, I developed the first theme of my research around *measurement* of exposure. This research is presented in Manuscript 1 (Chapter 4) and Manuscript 2 (Chapter 5). The research presented in chapter 4 was undertaken to develop an evidence base to inform the research presented in chapter 5. In chapter 4 I presented the research I conducted to identify and critically appraise evidence on the measurement properties of self-report questionnaires to assess children's sun related behaviours. In chapter 5 I presented the research I carried out to develop a measurement framework for pediatric MS etiologic research, the Pediatric MS Tool-Kit. The Tool-Kit is a collection of methodological resources that were developed for pediatric MS researchers to facilitate the design of study specific questionnaires.

7.2.1 Overview of Results

7.2.1a Systematic Review of Measurement Property Studies (Manuscript 1, Chapter 4)

The research presented in chapter 4 was conducted to identify validated questionnaires that could be used in pediatric case-control studies. However, in order to get an overall sense of assessing sun related behaviours using self-report questionnaires, I did not restrict the inclusion

criteria to measurement property studies that evaluated questionnaires for use in case-control studies. I identified 22 questionnaires that had been evaluated for validity and/or reliability; however, nearly all questionnaires were designed to ascertain information about current (45%) or usual (45%) behaviours. Questions that measured past exposures (e.g. last summer, cumulative lifetime exposure) were included in five questionnaires; though only one study examined long term reliability (e.g. an 8 to 18 year test-retest interval).[168] The lack of studies on the measurement properties of long term recall of exposure, which is required in case-control studies, is a major gap in the measurement property literature.

A coincidental finding, which I identified as a result of a modification that I made in the screening methodology for the systematic review, was that a large proportion of questionnaires, in this research area, had not been validated. I had to modify the screening methodology because in a subset of publications, the measurement properties of the questionnaire were assessed, and reported on in the body of the publication, but this was not specifically mentioned in the abstract; we identified all abstracts in our search results that mentioned using a self-report questionnaire to assess sun related behaviours in children. This required us to review the full text of 185 publications, to assess them for eligibility; in fact, seven publications that were included in the systematic review were identified this way. However this step also highlighted an important finding: in 176 out of the 185 studies (96%) that used a self-report questionnaire, the measurement properties of the questionnaire had not been examined. Therefore, questionnaires used in this research area tend to be developed 'in house', specifically for the purposes of the study.

7.2.1b Pediatric MS Tool-Kit Development (Manuscript 2, Chapter 5)

The Tool-Kit *core variables* are the main result of the research presented in chapter 5. A set of *ancillary variables*, to more comprehensively characterize exposure, are also included. The Tool-Kit core and ancillary variables are presented for use by the research community on a dedicated webpage. There are six sun exposure core variables that are included in the Tool-Kit, and they were found to have good content validity. One variable defines the child's residential history, another defines the location of the child's daily activities (e.g. indoors/outdoors), and the others define the usual duration that the child spent outdoors daily, between 10am and 4pm, on weekdays, and on weekends, in the summer, and in the winter. With the data that are collected using the Tool-Kit variables, both cumulative and age-specific UVR dose can be derived.

Residential history information can be used to obtain corresponding estimates of ambient ultraviolet radiation using NASA's Total Ozone Mapping Spectrometer; which can then be combined with usual duration of time outdoors between 10am and 4pm. Cumulative UVR dose has been estimated in previous adult MS case-control studies.[18, 20, 224] A specific algorithm for the Tool-Kit variables has not yet been developed.

In addition to the core variables, six ancillary sun exposure variables were also proposed. The ancillary variables focus on host characteristics (i.e. sun sensitivity and skin colour) and use of sun protection (i.e. sunscreen, wearing a shirt with sleeves and staying in the shade or under an umbrella). An ancillary variable about the usual number of weeks, during the winter months, that the child travelled to a sunnier destination was also included.

One strategy to enhance the success of the Tool-Kit is to make it accessible to the research community. I took advantage of the resources provided by Maelstrom Research, a research initiative that develops and tests harmonization methods.[126] The Tool-Kit variables are organized using their '*standard for harmonized variable dissemination*'. For the time being this is presented in a fixed format, as Maelstrom Research is currently developing a web platform for prospective harmonization projects; and once implemented the Tool-Kit webpage will be interactive and user friendly. I will request that researchers who use the Tool-Kit provide basic information about their study design and the variables that they use, which will be displayed online and will enhance opportunities for collaboration.

7.2.2 Discussion of Results

My research highlights the need for research to inform the development of valid and reliable questionnaires to assess children's sun related behaviours that can be used in case-control studies. I did not find a validated questionnaire for this purpose. Two case-control sun exposure studies from the adult MS literature examined the measurement properties of their questionnaire;[149, 151] one of these questionnaires was the EnvIMS-Q, the questionnaire used in chapter 6 (Manuscript 3). The same questions were used in both studies[149, 151] and both found acceptable test-retest reliability over 2 weeks,[149] and 11 weeks.[151] The reliability of the Tool-Kit variables will need to be examined; however, I would expect that responses provided by parents about their child's sun related behaviours (i.e. as is required in a pediatric MS case-control study), will be more reliable than responses provided by adults about their own behaviours during childhood (i.e. as is required in an adult MS case-control study). Pugliatti et al.,[149] also

found that the sun exposure questions included in the EnvIMS-Q were cross-culturally acceptable and feasible in Norway and Italy;[149] although not included in the publication, the EnvIMS-Q used in Canada was also found to be acceptable and feasible.(Dr. Christina Wolfson, personal communication) The cross-cultural validity of the Tool-Kit variables will need to be examined.

In my research I observed that a large number of questionnaires were developed specifically for the purposes of the particular study/investigation (i.e. developed "in-house"). This is in line with the findings of a systematic review of questionnaires to assess environmental tobacco smoke in infants.[120] While questionnaires developed "in-house" may appear to serve their purpose, this approach has its limitations, as the quality of the questionnaire has not been examined. The Tool-Kit can help to reduce the use of 'in-house' questionnaires in pediatric MS research, as it proposes a measurement framework, to guide the design of questionnaires, which has been developed using a rigorous methodological approach.

The first short-term goal of the Tool-Kit is to enhance measurement of sun exposure in pediatric MS case-control studies. There are three important reasons why the Tool-Kit is a better option than using questionnaires that are developed 'in-house'. First, the exposure variables contained in the Tool-Kit were selected by an expert working group, which included MS epidemiologists, pediatric and adult MS neurologists, and sun exposure researchers, working in North America and in Europe. The Tool-Kit needs to be cross-culturally valid, thus it was pivotal that the working group included representation from different countries. For logistical reasons I only invited researchers from North America and Europe. The diversity of the research expertise also helped to enhance the content validity of the Tool-Kit variables.

Second, as a result of the rigorous methods used to develop the Tool-Kit, I am encouraged that the variables have good content validity; and this was supported by the results of the content validity study. The Tool-Kit includes a comprehensive, yet minimal set of variables that will enhance measurement in individual studies.

Finally, as the Tool-Kit variables are a resource for the research community, I have made them available online. This will provide an opportunity to evaluate them on a broader scale. In fact, this 'post-marketing' evaluation will be very important, and I look forward to providing guidance to researchers who want to use the Tool-Kit, and to continue evaluating the

measurement properties of the variables. My research will also keep the focus on good quality measurement in this emerging area of etiologic research.

My research will enhance the comparability of study results; the second short-term goal of the Tool-Kit. Comparability of studies is hampered when each study uses different variables to measure the same construct, and thus it is challenging to determine whether differences in study findings are the result of true differences or of the use of different questions. Consistency across studies will be important to increase confidence that sun exposure is a risk factor for pediatric MS.

The long-term goal of the Tool-Kit is to enhance the opportunity for, and value of, future harmonized analyses. Harmonization is an attractive methodology to use to study rare diseases, such as pediatric MS.[123] However, harmonization is difficult when different variables are used to measure exposure.[125] To enhance the value of, and ability to perform harmonized analyses, future pediatric MS studies should use the variables and response options provided in Tool-Kit, as they form the basis for harmonization.

For pediatric MS, harmonized analyses have the potential to address the issue of small sample sizes in individual studies. The analysis of harmonized data is referred to as an individual-level patient data meta-analysis (IPD-MA). IPD-MA is preferred to the traditional meta-analysis of aggregate data, as it allows for more flexibility in the analysis, however, IPD-MA require a lot of time and resources to perform.[127] The Tool-Kit is a resource for prospective harmonization. Prospective harmonization is preferred over retrospective harmonization;[125, 225, 226] however, it requires collaboration at the study design stage, so that the data collected can be meaningfully combined in the future.

The Pediatric MS research community is very collaborative, as is demonstrated by the creation of the International Pediatric MS Study Group (IPMSSG), a global network that includes 155 members from 41 countries. (Jon Temme, Coordinating Consultant for the IPMSSG, personal communication, 2017). The unifying vision of the IPMSSG is to optimise worldwide healthcare, education and research in pediatric MS. I engaged the IPMSSG in several ways, as I wanted to ensure the Tool-Kit was relevant for the research community. Sharing measurement methods is already practiced in adult MS research. Similar exposure variables have been used in several adult MS sun exposure studies.[13, 14, 17, 18, 20] In fact, the EnvIMS-Q, the questionnaire used in chapter 6, has recently been translated into Persian[227] and Spanish. I am

confident that MS researchers will use the Tool-Kit and that it will be a valuable resource for the research community.

The Tool-Kit is a model for flexible prospective harmonization, and as the name implies, it allows for some flexibility in measurement. [13, 14] This approach allows researchers to make context-specific modifications, in order to meet the particular needs of the study, the population or the cultural context. The key, however, is to ensure that the core variables detailed in the Tool-Kit can be created using the data collected. Although flexible prospective harmonization is less straightforward than using the exact same questionnaire across studies (i.e. stringent prospective harmonization), it is often more realistic and perhaps more appropriate for etiological research.

The research related to the first methodological theme, *measurement*, proposes a measurement framework that will facilitate the design of harmonizable questionnaires to examine the link between sun related behaviours and the risk of pediatric MS. The Pediatric MS Tool-Kit has the potential to greatly advance our understanding of MS etiology.

7.2.3 Strengths and Limitations

The main strength of this research is the rigorous methodology that I used to develop the Tool-Kit variables. I used systematic review methods to appraise the measurement properties of relevant questionnaires, and expert input to select and define a core set of exposure variables. I completed the foundational work that is required to design a sun exposure questionnaire for a pediatric MS case-control study. My research will not only save time and resources required to design the questionnaire, but will also improve measurement in individual studies, over the use of questionnaires developed 'in-house.'

The main limitation, in light of the rigorous process used to select the core variables, is the possibility that the variables selected have less than optimal measurements properties. While I did examine their content validity, the same group of researchers who were involved in developing the Tool-Kit assessed its content validly. Thus it is likely that they would rate the variables favourably; therefore content validity will need to be assessed further by an independent group of researchers. The construct validity and reliability of the Tool-Kit variables have not been examined. Ongoing evaluation of the measurement properties of the Tool-Kit variables is essential.

7.3 Methodological Theme 2: *Analysis*

The second methodological theme is *analysis* of sun related behaviours. This research is presented in chapter 6. There were two questions I investigated. The first was whether there was a specific age period in childhood, during which sun exposure determined MS risk, or if it was sun exposure behaviours over childhood that increased susceptibility to MS. The second was how sun related behaviours, taken together, relate to the risk of MS.

7.3.1 Overview of Results

7.3.1a Life Course Epidemiology Analyses (Manuscript 3, Chapter 6)

I used life course epidemiology theory to tackle the first question. I developed exposure variables to represent two life course epidemiology conceptual models: the critical period model and the accumulation model.[25, 135, 136] The accumulation model was found to be the best model: sun exposure throughout childhood, from birth to age 15 years, being the best predictor of MS risk. The model suggested that MS risk was nearly 50% higher in those with the lowest frequency of summer sun exposure, compared to those with the highest frequency. The 95% confidence interval for this estimate ranged from 25% to 75%, supporting the conclusion that low levels of sun exposure throughout childhood is associated with greater risk. Interestingly when the main analysis was restricted to study participants who reported receiving help completing the questionnaire, the risk of MS was more than double, and the upper limit of the 95% confidence interval suggested as much as a three-fold increase in the risk of MS.

My results also suggest that low sun exposure between birth to age 5 years, and 11 to 15 years, may also be important determining MS risk. The risk ratio estimates for these two models were nearly identical. I estimated a nearly 30% increased risk of MS when those with the lowest frequency of summer sun exposure, in the specific age period, were compared to those with the highest frequency; and the 95% confidence intervals were also indicative of greater risk (range: 13% to 47%).

7.3.1b Sun Exposure Behaviour Groups Analyses (Manuscript 3, Chapter 6)

I used latent class analysis to investigate my second question. I extended previous analyses and examined the effect of three sun related behaviours, simultaneously, to understand how they contribute to the risk of MS. There are two key results. First, the risk of MS was greatest in those who were exposed to the least amount of sun, and lowest in those exposed to the greatest amount

of sun. Second, among those who reported spending the least amount of time outdoors, the level of sun protection modified the risk of MS.

I characterized six latent sun exposure behaviour groups: two with high sun exposure in summer and in winter; two with low sun exposure in summer and in winter; and two with high sun exposure during summer, but lower sun exposure during winter. Among the pairs with similar sun exposure profiles, one frequently used sun protection, whereas the other rarely used sun protection. The lowest sun exposure group (i.e. *sun-avoiders*: low summer and low winter sun exposure and high sun protection) was the smallest group (4%); whereas the most common group (32%) had high sun exposure during summer, lower sun exposure during winter and low sun protection use. When I compared sun-avoiders, to the highest sun exposure group (i.e. *sun-seekers*: high summer and high winter sun exposure and low sun protection), I found a 76% increased risk of MS in sun-avoiders. Interestingly, when sun-avoiders were compared to a group with similarly low sun exposure levels, but with infrequent used of sun protection, I estimated a 40% increased risk of MS in sun-avoiders.

7.3.2 Discussion of Results

The analyses that I used generated several new insights about the link between sun exposure and the risk of MS. My results suggest that among individuals living in Canada, Italy and Norway the accumulation of exposure throughout childhood, or lack thereof in the case of sun exposure is the best model to use to explain MS risk. However, the results are also indicative of a sensitive period between birth and 5 years of age, and 11 to 15 years of age. I demonstrated an important effect of sun protection on the risk of MS; and the effect depends on the level of sun exposure. Among individuals who spend a lot of time indoors, their risk of MS was markedly increased if they reported frequently using sun protection, in their limited time out in the sun.

My results suggest that there may be a sensitive periods from birth to age 5 years and from 11 to 15 years. While the models that I tested were critical period models, the results of my analyses suggest that they are sensitive periods, not critical periods. As these two terms had been used interchangeably in the epidemiology literature, Ben-Shlomo and Kuh (2002) provided definitions that highlight differences.[136] These authors define a critical period as '*a limited time window in which an exposure can have adverse or protective effects on development and subsequent disease outcome. Outside this window, this developmental mechanism for mediating*

exposure and disease risk is no longer available.' Whereas, a sensitive period is defined as *'a time period when an exposure has a stronger effect on development and hence disease risk than it would at other times; in other words the same exposure outside this time period may still be associated with increased risk but this association is weaker than during the sensitive period.'* Therefore, because I found an important effect in more than one age period, and that accumulation of exposure best predicted MS risk, these age periods, in life course epidemiology terms, fit the definition of sensitive periods.

My results are consistent with those that have been reported in previous studies, further supporting the hypothesis that lower levels of sun exposure are associated with higher risk of MS.[13, 14, 17, 18, 20] Most case-control studies that have reported age-specific effect estimates, have structured their analyses using a critical period model. There are two Australian studies that modelled exposure using both the critical period and accumulation models.[18, 20] The study by van der Mei et al.,[20] included prevalent MS cases and found that spending less time outdoors (<1-2 vs. ≥2-3 hours) was associated with a two-fold greater risk of MS, for age period 11 to 15 years; but in contrast to my findings they report a three-fold increase in risk for the age period 6 to 10 years. Exposure prior to age 6 years was not assessed. Although the critical period and accumulation models were not directly compared, the effect estimates from the accumulation model were larger in magnitude than those from the two critical period models. The study by Lucas et al[18] included incident cases at the time of the first MS attack, and did not find evidence of an association for exposure from 6 and 18 years of age, or for the critical period models for 6 to 10 years and for 11 to 15 years; however they did observe an effect when they examined exposure from age 6 years to current age.

To my knowledge, my study was the first to use latent class analysis to study MS etiology. I selected this analytical approach, because I was interested in developing exposure variables that included multiple sun related behaviours. Sun behaviours are interrelated and do not occur in isolation. Cluster models provided some interesting insights about sun related behaviours generally. As I expected, *a priori*, there was a group that were sun-seekers (e.g. high summer sun, high winter sun and low sun protection), and a group that were sun-avoiders (e.g. low summer sun, low winter sun and high sun protection).

I also anticipated that the sun-avoiders would have the highest risk of MS, and that sun-seekers would have the lowest risk; and my results provide evidence to support this hypothesis.

An interesting observation I made was that the risk of MS may depend on the level of *sun protection* used, among those who spend a lot of time indoors. I identified a group that had similar sun exposure levels as the sun-avoider group, but when outdoors they rarely used sun protection; and compared to this group the risk of MS was 40% greater in the sun-avoider group. This suggests that sun protection can modify the risk of MS in those who spend the most time indoors; and that among these individuals, sun protection may not be needed, as these individuals spend a limited amount of time outdoors and thus will not be exposed to enough sun to increase their risk of diseases linked to excessive exposure. In fact, the use of sun protection may be increasing their risk of disease associated with low sun exposure, such as MS.

I used latent class analysis to model exposure. I could have also developed exposure variables using interaction terms between the three sun related variables. However, using this approach I would not have identified which sun exposure behaviour groups fit the data best, as I would have had to specify the groups myself. Also I would have estimated a larger number of effect estimates, when considering a three-way interaction with variables that each has four levels. Using latent class analysis, I only estimated effects for the latent groups that were best represented in the data. I found this approach helpful and I recommend that it be used to examine exposures that are described using multiple related variables, such as sun exposure.

Previous research also suggests an important effect of sun exposure during winter, and of sun protection use on the risk of MS. The two Australian case-control studies that I mentioned above, both found that low sun exposure during winter is associated with increased risk of MS. van der Mei et al.[20] included summer and winter exposure in the same model and the effect of summer exposure was attenuated and 95% confidence intervals included the null, whereas winter exposure remained significant. Lucas et al., [18] consider a measure of lifetime UV dose and sun protection in the same model, and reported no change in the effect of UV dose on MS risk; which was consistent with results reported in another study performed in Cuba, Martinique and Sicily.[14] In our previous analyses of the EnvIMS sun exposure data from Italy and Norway, we did not find an interaction between summer exposure and sun protection.[13] I did not identify any studies that considered all three sun exposure variables, simultaneously.

In the research that is related to the second methodological theme, *analysis,* I used novel analytical strategies to advance our understanding of MS etiology. The results are in line with previous research, but provide some additional insights about the association, which should be

used as a model for future statistical analyses in this research area; in particular, that the accumulation model be used to represent exposure and that sun protection use needs to be considered when examining the effects of outdoor sun exposure on MS risk.

7.3.3 Strengths and Limitations

An important contribution of my research is that I examined the link between sun exposure and MS risk in greater depth than has been previously reported. There are also strengths specific to the EnvIMS study design. It is the largest MS case-control study conducted to date; my analyses included 2251 cases and 4028 controls. Case and controls were frequency matched on age and sex, and were recruited from population-based sources. Sun exposure was measured using questions that were shown to work well in previous studies,[13, 14, 17, 18, 20] to be reliable,[149, 151] and to be cross-culturally feasible and acceptable in Canada, Italy and Norway.[149]

There are several limitations that need to be considered in interpreting the results. Ideally, case-control studies should focus on enrolling incident cases, and if possible, should enrol cases as soon as possible after diagnosis. Given that MS is rare and to obtain the targeted number of cases in a reasonable amount of time, the inclusion criteria for EnvIMS required cases to have disease duration of less than 10 years. However, these cases are in fact prevalent cases. A common bias related to enrolling prevalent cases is survival bias, although this is unlikely to be a major issue given that life expectancy for MS is greater than 70 years of age.[47] However, the disease process can impact cognition, which may lead to systematic differences in responses provided by cases relative to controls. Reassuringly, the results obtained in sensitivity analyses restricted to cases with disease duration of less than 5 years were similar to those found for the entire sample. Differences in cognitive ability may lead to differential misclassification, as the sensitivity/specificity of responses provided by cases would be lower than those provided by controls.

While the sun exposure questions had undergone some validation[149, 151] and been used in previous studies,[13, 14, 17, 18, 20] the measurement properties of these questions require further assessment. Qualitative response options were used for the sun exposure questions, which may lead to non-differential misclassification; and may in part explain why effect estimates were lower than expected, based on the results reported in previous sun exposure studies. While the questionnaire was pilot tested for interpretability in all three countries, and found to be comprehensible, the correspondence between the qualitative response options and actual time

(i.e. in minutes/hours) was not assessed. It is possible that response options were interpreted differently by participants in different countries, and within the same country. For example, depending on the amount of time participants spent outdoors, their interpretation of being outdoors *reasonably often* may differ; those who spend more time outdoors may attribute more time (i.e. *reasonably often*=4 hours per day), to the same response option, as those who spend less time outdoors (i.e. *reasonably often*=1 hour per day). I included fixed effects for country, which helps to account for similarity of responses within each country. Nevertheless, data on the correspondence between qualitative and quantitative responses would have been useful to formally assess the impact of misclassification. In addition, incorporating frequency and time outdoors would have enabled the derivation of a more comprehensive exposure variable; and with more detailed residential history data, an estimate of UVR dose could also be calculated and used in the analysis.[224]

Non-differential misclassification is expected if the interpretation of the qualitative response options was similar between cases and controls, which would imply the reported effect estimates are attenuated. However, if cases and controls interpreted the qualitative response differently, the results would be impacted by differential misclassification. If cases tended to under estimate their time outdoors, in the ranking of the response options, then my results may be explained by the differences in the accuracy of the responses provided, and not by the actual time spent outdoors. Recall bias is also possible due to disease related factors among cases. Individuals with MS often report having increased sensitivity to heat,[221-223] which makes spending time in the sun difficult. As current behaviour can influence the reporting of past behaviours, it is possible that MS cases may underestimate sun exposure.

Selection bias is also a concern, as the EnvIMS study had low response rates, especially in Italy (Canada: 83% cases, 59% controls; Norway: 70% cases, 36% controls; Italy: 43% cases, 21% controls).The effect estimates that I reported were a weighted average of the effect across countries, and thus the impact of lower response rates in Italy may have biased the overall estimate, if the association obtained for Italy differed markedly from that found for other countries. To assess this I examined heterogeneity of effects across countries, however, the interaction term in the regression model was not statistically significant.

Methods of recruitment also differed between countries, which may have resulted in differences in response rates, and selection into the study. In Norway and Italy population-based

registries were used to identify both cases and controls; whereas in Canada population-based registries are not available to recruit either cases or controls. Cases were selected from three MS clinics located in tertiary health care centres. Thus the case series in the Canadian sample, may differ from the case series in the Italian and Norwegian samples, and may represent more aggressive or difficult MS cases. In Canada population-based registries from which to sample controls are also not available. Random digit dialling (RDD) was the primary source of control recruitment. In the past, RDD was considered a gold standard for control recruitment; however, the utility of RDD has decreased due to increased use of cell phones and telemarketing (i.e. receiving unwanted calls).[228]

Controls who participate in research studies tend to be healthier than those who refuse;[229] healthier individuals are generally more physically active and thus may be more likely to spend time outdoors. In an attempt to assess the representativeness of the EnvIMS controls, a member of our research team compared the distribution of selected variables to similar estimates taken from country-specific population-based data sources (e.g. Statistics Canada in Canada). Distribution of weight, height and smoking characteristics (e.g. daily smokers, ever smokers) in controls were found to be similar to the general population, however, EnvIMS controls were found to have a higher level of education. While Italy and Norway used population-based registries to sample controls, preliminary analyses suggest that controls enrolled in Canada are more similar to the general population. (Dr. Christina Wolfson, personal communication)

Selection bias requires that selection into the study is associated with both the exposure and the outcome. Information to formally assess the impact of selection bias was not available, given I did not have access to information about early life sun exposure in those who did not participate. While I was unable to formally assess the impact of selection bias, my study results may have been spurious if the cases who participated were more likely to have had low sun exposure in childhood, and/or the controls who participated had higher levels than those who declined participation.

While I examined a comprehensive set of confounding variables, which I selected based on background knowledge, residual confounding is always a concern. This may result from poor quality measurement of measured confounders, or from unmeasured confounding. Among measured confounders, for example, level of physical activity was only collected for the age period 13 to 19 years, therefore it is likely that physical activity was not adequately adjusted for

in my analyses. Physical activity is suggested to reduce the risk of MS, and is positively associated with the frequency of outdoor activities. Therefore positive confounding would be expected, and thus with the lack of a more robust measure of physical activity the association that I observed, between sun exposure and MS risk, may be explained by differences in physical activity between cases and controls. The EnvIMS-Q included a large set of factors that have been implicated in MS risk, including infectious mononucleosis, smoking, body size, vitamin D intake; thus it is unlikely that a confounder, which is a strong predictor of MS, was missed.

7.4 Implications of Research

7.4.1 Biological Implications

The sun plays a role in several biological processes that have been linked to MS, including vitamin D synthesis, melatonin regulation, and immune system functioning. Studies also demonstrate that UVR drastically suppresses clinical signs of experimental autoimmune encephalomyelitis, an animal model of MS, independent of vitamin D.[219] My research provides further support for the role of the sun in the development of MS, and highlights childhood as an important risk period. Childhood is marked by many key developmental periods, and therefore the mechanism of 'biological programming' may be operating to determine risk. For example, chronically low UVR levels can have adverse effects on immune system development, and may permanently shift the immune system's balance toward a more pro-inflammatory state. The two sensitive periods that I identified may also be mapped to specific events in immune system change and development, such as infancy and puberty,[230] that can be explored further in basic science research.

7.4.2 Public Health Implications

Of relevance for public health is the identification of modifiable environmental and/or lifestyle factors that we can intervene on to reduce the number of individuals that are diagnosed with MS. Sun exposure is clearly a modifiable factor, and it has been the focus of public health programs since the early 1980's, to reduced incidence of diseases associated with excessive exposure (e.g. skin cancer).[231] Sun protection is an important preventive strategy to reduce excessive exposure.[112] However, my results suggest that among those who spend a lot of time indoors, using sun protection when outdoors, may have negative effects on health. My results suggest that sun safety public health message may need to be revised to provide a more balanced

message, which emphasizes the sun's benefits,[22, 23] and how to maximize these benefits, especially in countries and cultures where children spend a lot of time indoors.[232]

7.5 Future Research

7.5.1 Measurement of Sun Exposure

Developing validated questionnaires that can be used in case-control studies is an essential activity to enhance future research. In regards to pediatric MS, future research should evaluate the measurement properties of the Tool-Kit variables. Next steps include: (i) a content validity study, by an independent group of researchers; and (ii) designing a template questionnaire that links to the Tool-Kit variables, and pilot testing this questionnaire, which will include using cognitive interviewing techniques.

7.5.2 Analysis of Sun Exposure

Data collected in previous studies that have examined the link between sun and MS risk, can be used to derive exposure variables to represent accumulation of sun exposure. Thus, the reanalysis of previously collected data, using the same analytical approaches that I used in my research, is an opportunity for future research. Retrospective harmonization of the data collected in previous sun exposure and MS studies is another opportunity for future research.

A cohort study to examine sun exposure and the risk of MS should also be carried out. The design of a prospective cohort study to specifically examine MS etiology is restricted by low incidence and a long latent period. Re-purposed cohort study such as the Nurses' Health Study have been used to examine several risk factors, such as cigarette smoking, [90] vitamin D intake[102, 103] and body size.[93] As my research shows that childhood is an etiologically relevant period, one approach would be to link data collected in existing birth cohort studies, with national MS registries. Given the low incidence of MS, retrospective harmonization of birth cohorts might also be needed to acquire a sufficient number of cases.

7.6 Conclusions

I used rigorous epidemiological methods to advance the field of MS etiological research. For pediatric MS my research proposes a measurement framework, the Pediatric MS Tool-Kit. The Tool-Kit will improve measurement in individual studies, increase comparability of results

across studies, and will enhance the opportunity for collaboration through the process of prospective harmonization. For adult MS, I used novel analytical strategies to further elucidate the etiological model of MS. I propose that the accumulation model is the etiologically relevant model, and should be used to model sun exposure in future research. I conclude that the longer the length of time children are exposed to low levels of sun during the summer, throughout childhood, the greater their susceptibility to MS. I also conclude that among sun-avoiders, the use of sun protection in their limited time outdoors, increases risk of MS. The Took-Kit can be used to investigate these etiological hypotheses in pediatric populations, which is methodologically advantageous, as compared to studying etiology in adults with MS, because the population is younger. My research contributes to the growing evidence which demonstrates the negative impact that low levels of sun exposure, during early childhood, have on the development of chronic diseases in adulthood.

APPENDIX A: Screenshot from DistillerSR of data extraction forms

Data Extraction Forms

Reference: Wright CY, Reeder AI, Bodeker GE, Gary A, Cox B. Solar UVR exposure, concurrent activities and sun-protective practices among primary schoolchildren. Photochemistry and Photobiology. 2007;83:749-758

A.1: Initial Form

Comprehensive measures of ultraviolet radiation (UVR) exposure, concurrent activities and sun-protective practices are needed to develop and evaluate skin cancer prevention and sun protection interventions. The UVR exposures of 345 primary schoolchildren at 23 schools around New Zealand were measured using electronic UVR monitors for 1-week periods over 12 weeks in 2004 and 2005. In addition, ambient UVR levels on a horizontal surface were measured on-site at each school. Children completed activity diaries during the period UVR measurements were made and provided information on their indoor and outdoor status and clothing and sun protection worn. Mean total daily UVR exposure (7:00-20:00 h NZST + 1) at the body location where the UVR monitors were worn was 0.9 SED (standard erythemal dose, 1 SED = 100 J m(-2)). This was 4.9% of the ambient UVR on a horizontal surface. Mean time spent outdoors was 2.3 h day(-1). Differences in children's UVR exposure could be explained in part by activity, where outdoor passive pursuits were associated with higher UVR exposure rates than outdoor active and outdoor travel pursuits. Compared with older children, the activities of younger children, although labeled the same, resulted in different UVR exposures, either as a result of reporting differences or a real difference in UVR exposure patterns. UVR exposure rates were generally higher on weekdays compared with the weekend, confirming the important role of school sun protection and skin cancer prevention programs. High UVR exposure activities included physical education, athletics and lunch break.

and go to

Initial Form

1. Should this article be included?
   - (•) yes
   - ( ) no
   - ( ) no abstract
   - ( ) unsure, need to see pdf

4. If initially unsure, why was it finally excluded?
   - ...

5. If not included, would this article be useful for background info?
   - ( ) yes
   - ( ) no

   Clear Response

6. Does this article seem to use a sun exposure questionnaire? (check all that apply)
   - [ ] yes
   - [ ] in children

A.2: Title and Abstract Form

Comprehensive measures of ultraviolet radiation (UVR) exposure, concurrent activities and sun-protective practices are needed to develop and evaluate skin cancer prevention and sun protection interventions. The UVR exposures of 345 primary schoolchildren at 23 schools around New Zealand were measured using electronic UVR monitors for 1-week periods over 12 weeks in 2004 and 2005. In addition, ambient UVR levels on a horizontal surface were measured on-site at each school. Children completed activity diaries during the period UVR measurements were made and provided information on their indoor and outdoor status and clothing and sun protection worn. Mean total daily UVR exposure (7:00-20:00 h NZST + 1) at the body location where the UVR monitors were worn was 0.9 SED (standard erythemal dose, 1 SED = 100 J m(-2)). This was 4.9% of the ambient UVR on a horizontal surface. Mean time spent outdoors was 2.3 h day(-1). Differences in children's UVR exposure could be explained in part by activity, where outdoor passive pursuits were associated with higher UVR exposure rates than outdoor active and outdoor travel pursuits. Compared with older children, the activities of younger children, although labeled the same, resulted in different UVR exposures, either as a result of reporting differences or a real difference in UVR exposure patterns. UVR exposure rates were generally higher on weekdays compared with the weekend, confirming the important role of school sun protection and skin cancer prevention programs. High UVR exposure activities included physical education, athletics and lunch break.

and go to

Title/Abstract Review

1. Is the article in English?
   (•) yes ( ) no

3. Is the main focus of the article a measurment tool?
   (•) yes ( ) no ( ) no, but measurement properties mentioned

4. Is reliability or validity evaluated in this article?
   (•) yes ( ) no ( ) unsure

5. Has it been used for children?
   (•) yes ( ) unsure ( ) no

A.3: Background Form

Background of Measurement Tool

1. What construct is being measured?	(•) Sun exposure ( ) Vitamin D intake ( ) Risk factor #3 **Clear Response**
2. If sun exposure, which category(ies) does the article include? check all that apply.	[ ] exposure-history (time specific) [ ] exposure-history (cumulative) [x] exposure-current [x] protection (behaviour) [ ] host reaction (burning, skin type)
3. Was the article published since 2000?	(•) yes ( ) no **Clear Response**
4. What is the name of the tool? (use not named or unsure if needed)	not named
5. any other pertinent information about the tool e.g. was it modified from elsewhere.	...
6. Is the exact measurement tool provided? If elsewhere, attach the other document. If no, then answer #7.	( ) yes (•) no ( ) unsure **Clear Response**
7. If measurement tool is elswhere, comment &/or copy/paste citation.	...
8. How many items in the scale?	( ) 1-5 ( ) 6-15 ( ) >15 ( ) unknown **Clear Response**
9. What type of measurement tool is this?	( ) scale ( ) set of questions ( ) single question (•) other **Clear Response**
10. Does the measurement tool have sub scales? How many?	activities grouped 7 high-level activities
11. Are response categories provided? (if any response categories given for any question, then answer yes)	( ) yes ( ) no ( ) unsure **Clear Response**
12. How is questionnaire administered? (check all that apply)	[ ] self administered [x] self administered (child) [ ] self administered (parent) [ ] interview [ ] can't tell [ ] other
14. What language was questionnaire developed in?	english
15. What languages/translations are mentioned in this article?	none
16. Should we go back to find articles with a detailed description of translation?	( ) yes (•) no **Clear Response**
17. Should we go back to find other articles about past & future use	(•) yes ( ) no **Clear Response**
18. Should we go back to find other references about characteristics of the measurement tool?	( ) yes (•) no **Clear Response**
19. Is the scoring system described?	( ) yes, scoring system is provided ( ) no, scores appear to be calculated, but method is not described (•) no, tool is not scored **Clear Response**
20. Please insert corresponding author contact info	Anthony I. Reeder - E-mail: tony.reeder@stonebow.otago.ac.nz

A.4: COSMIN Domain Form

COSMIN domains

1. Is internal consistency described in the article? ○ yes ◉ no ○ unsure	2. Is reliability discussed in the article? ○ yes ◉ no ○ unsure
3. Is content validity described in the article? ○ yes ◉ no ○ unsure	4. Is structural validity described in the article? ○ yes ◉ no ○ unsure
5. Is hypothesis testing described in the article? ◉ yes ○ no ○ unsure	6. Is cross-cultural validity described in the article? ○ yes ◉ no ○ unsure
7. Is criterion validity described in the article? ○ yes ◉ no ○ unsure	
8. Rate interpretability ◉ yes	9. Rate generalizability ◉ yes

APPENDIX B: Risk Factor Survey

B.1: Risk Factor Survey

Selecting Priority Risk Factor

By completing the following survey you will help us select priority etiologic risk factors for pediatric MS etiologic reseach.

Our goal is to use rigorous epidemiological methods to develop questionnaire standards that will facilitate the collection of information about exposure to etiologic risk factors in case-control studies of pediatric MS.

To develop the methodological process involved, we will start with three risk factors.

We completed a Scoping Review to generate a list of relevant risk factors (view methods) and applied pre-defined criteria (view criteria) to narrow the list. This resulted in the risk factors listed below. A summary of the information collected through the scoping review can be viewed here

Completion of the survey is anonymous.

For each risk factor listed below, please indicate whether in your view the risk factor is:
(i) a priority for future research,
(ii) important for future research, but not a priority, or
(iii) not important for future research.

In your decision, please consider the following:

- The results of our scoping review (view)
- Our focus is case-control studies in pediatric populations; assessment would thus be based on interview or self-report questionnaire completed by the child and/or their parent/guardian.
- Prioritize risk factors for which methodological development would help you, as a researcher, in the design of questionnaires.

	Priority	Important, but not a Priority	Not Important	I have no opinion
Body Mass Index and/or Body Size	○	○	○	○
Environmental Tobacco Smoke	○	○	○	○
Head injury and/or Traumatic Brain Injury	○	○	○	○
Mononucleosis Infection	○	○	○	○
Penicillin Use	○	○	○	○
Physical Activity	○	○	○	○
Prenatal and Perinatal Factors	○	○	○	○
Sibling Exposure and Attending Daycare	○	○	○	○
Stressful Life Events	○	○	○	○
Sun Exposure	○	○	○	○
Vaccinations	○	○	○	○
Vitamin D Intake	○	○	○	○

Other (Priority Risk Factor not listed, please specify)

B.2: Summary of the Review Methods

Purpose:

The main purpose of the review was to get a sense of the different risk factors implicated in MS etiology and to understand which of these are potentially relevant to study in pediatric MS populations.

Guiding Research Question:

1. What risk factors in the existing literature have been shown to be associated with MS etiology?
2. Of these risk factors which are relevant for pediatric MS etiology?

Identifying relevant studies:

Date range: 2000---2013 (search run in March 2013)

Languages: English articles will be reviewed in full; we will collect information on articles not in English (i.e. review abstracts)

Electronic databases: PubMed

Inclusion Criteria:

For inclusion articles should:

- ✓ Assess etiology of MS – therefore excluding prognostic papers
- ✓ Report on an etiologic risk factor that is an environmental exposure – therefore excluding genetic factors
- ✓ Use of an analytical epidemiologic study design with a comparison group (unexposed or control) – therefore excluding disease only studies

B.3: Summary of the Review Findings

Risk Factor	Adult (#) and/or Pediatric(#)	Years of Publication (range)	Study Designs	Locations of Studies	Results overview
Body Size and/or Body Mass Index	adult	2009, 2012	cohort, case-control	Sweden, USA	Two studies showed increased risk associated with higher BMI or larger body size
Environmental Tobacco Smoke	adult (1) & pediatric (1)	2007-2011	case-control	France, Sweden	Two studies showed increased risk associated with environmental tobacco smoke exposure
Head injury and/or Traumatic Brain Injury	adult	2009, 2012	cohort, case-cohort	Denmark, Taiwan	Two studies showed increased risk associated with head injury or traumatic brain injury
Mononucleosis Infection	adult	2004-2011	cohort (3), case-control (9)	Australia, Canada, Denmark, Gothenburg, Italy, Netherlands, Southern England, Sweden, UK	11 studies showed increased risk associated with Mononucleosis infection; one showed non-signficant findings
Penicillin Use	adult	2006, 2011	nested case-control, case-control	Denmark, UK	One study showed increased risk associated with Penicillin use while another showed decreased risk
Physical Activity	adult	2001	case-control	Canada	One study showed increased risk associated with being more active
Prenatal and Perinatal Factors	adult	2008-2011	cohort, case-control	Australia, Canada, USA	Four studies showed risk to be associated with particular pernatal or perinatal characterstics
Sibling Exposure and Attending Daycare	adult	2001-2011	cohort, case-control (5)	Australia, Canada, Denmark, Germany, Sweden	Four studies showed decreased risk asscoaited with increased exposure to other children; two studies show non-signficant findings
Stressful Life Events	adult	2004-2012	cohort, matched cohort, case-control (2)	China, Denmark, Germany, USA	Three studies showed increased risk asscoaited with stressfull life event; one showed non-signficant findings
Sun Exposure	adult	2003-2012	case-control	Australia, , Crete, Iran, North America	Five studies showed decreased risk associated with increased sun exposure; one study showed non-signficant findings
Vaccinations	adult (5) & pediatric (2)	2003-2009	case-control	Brazil, France, Gothenburg, Italy, USA	Two studies showed increased risk associated with being vaccinated; two showed non-signficant findings; one showed decreased risk with late vaccination (compared to early vaccination)
Vitamin D Intake	adult	2004, 2011	cohort	USA	Two studies showed decreased risk associated with increased vitamin D intake

APPENDIX C: EnvIMS Questionnaire (EnvIMS-Q)

This Questionnaire will be read by an automatic optical reader

- Please use a blue or black pen to indicate your answer choice. Participant ID: _____
- Put an X in the box which corresponds to your correct answer choice : ☒
- If you put an X in the wrong box, please fill in the whole box completely ■ and then select the correct answer by placing an X in the correct box ☒

By filling out this form and sending it back to us, you consent to be a part of the study.

Date: _____

SECTION 1: DEMOGRAPHICS

1. Year of birth: ☐☐☐☐ **Your age now:** ☐☐

Are you a woman ☐ **or a man** ☐

Please complete the following table with information about where you lived at the following ages:

	Town/City	Province/State & Country
At birth	_____	_____
	_____	_____
0-5 yrs	_____	_____
	_____	_____
6-10 yrs	_____	_____
	_____	_____
11-15 yrs	_____	_____
	_____	_____
16-20 yrs	_____	_____
	_____	_____
21-25 yrs	_____	_____
	_____	_____
26-30 yrs	_____	_____
	_____	_____

2. What is the highest level of education attained by you, your mother and your father?

	Yourself	Your mother	Your father
Some elementary school education	☐	☐	☐
Completed elementary school	☐	☐	☐
Some high school education	☐	☐	☐
Completed high school	☐	☐	☐
CEGEP or college diploma	☐	☐	☐
Technical or trade school diploma	☐	☐	☐
University degree (Bachelor's)	☐	☐	☐
Graduate studies	☐	☐	☐
▶(Specify level e.g. Masters, PhD, etc)	_____	_____	_____
Don't know	☐	☐	☐

3. What are your birth parents' ethnic backgrounds?

	Your father	Your mother
White	☐	☐
Chinese	☐	☐
Latin American	☐	☐
Arab	☐	☐
Aboriginal (e.g., North American Indian, Inuit)	☐	☐
West Asian (e.g., Iranian, Afghan)	☐	☐
Black	☐	☐
Japanese	☐	☐
Southeast Asian (e.g., Vietnamese, Cambodian)	☐	☐
Korean	☐	☐
South Asian (e.g., Indian, Sri Lankan)	☐	☐
Filipino	☐	☐
Other (Specify) _____	☐	☐

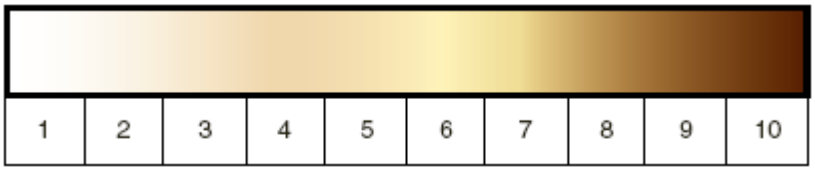
4. Please indicate in the box how many brothers and sisters you have. Include all children who lived with you during your childhood. If you are an only child, enter 0 in the box. ☐

Please indicate the years of their births and their genders.

	1	2	3	4	5	6
Year of Birth:	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐
Sex (M/F)	M ☐ F ☐	M ☐ F ☐	M ☐ F ☐	M ☐ F ☐	M ☐ F ☐	M ☐ F ☐

SECTION 2: SUN EXPOSURE

1. Please select the corresponding box below the colour that best matches the natural colour of your skin at the inner upper arm (without tanning). Set the colour chart against the inner part of your arm, between the elbow and the armpit, and select the number that corresponds best to the part of the figure that is closest to the colour of your skin.



2. What is the tanning reaction of your skin to its first sun exposure in the summer, with *no* use of sunscreen?

1. Always burn, never tan	☐
2. Usually burn, tan less than average (with difficulty)	☐
3. Sometimes mild burn, tan about average	☐
4. Rarely burn, tan more than average (with ease)	☐
5. Don't know	☐

3. What is the natural colour of your hair as a young adult?

1. Black	☐
2. Dark Brown	☐
3. Light Brown	☐
4. Blonde	☐
5. Red	☐

4. What colour are your eyes?

1. Black	☐
2. Brown	☐
3. Gray, green	☐
4. Blue	☐
5. Hazel	☐

5. In the past, in summer, how often did your activities (playing, participating in sports, watching sports, gardening, walking, work activities, etc.) take you outside at the following ages?

	Not that often	Reasonably often	Quite often	Virtually all the time	Don't know
0-5 yrs	☐	☐	☐	☐	☐
6-10 yrs	☐	☐	☐	☐	☐
11-15 yrs	☐	☐	☐	☐	
16-20 yrs	☐	☐	☐	☐	
21-25 yrs	☐	☐	☐	☐	
26-30 yrs	☐	☐	☐	☐	
In the past 3 years	☐	☐	☐	☐	

6a. In the past, in winter, how often did your activities (playing, participating in sports, watching sports, shovelling snow, walking, work activities, etc.) take you outside at the following ages?

	Not that often	Reasonably often	Quite often	Virtually all the time	Don't know
0-5 yrs	☐	☐	☐	☐	☐
6-10 yrs	☐	☐	☐	☐	☐
11-15 yrs	☐	☐	☐	☐	
16-20 yrs	☐	☐	☐	☐	
21-25 yrs	☐	☐	☐	☐	
26-30 yrs	☐	☐	☐	☐	
In the past 3 years	☐	☐	☐	☐	

6b. On weekends and holidays, how much time did you normally spend outside at the following ages:

	Never	Less than 1 hour/day	1-2 hours/day	3-4 hours/day	More than 4hours/day	Don't know
0-5 yrs	☐	☐	☐	☐	☐	☐
6-10 yrs	☐	☐	☐	☐	☐	☐
11-15 yrs	☐	☐	☐	☐	☐	
16-20 yrs	☐	☐	☐	☐	☐	
21-25 yrs	☐	☐	☐	☐	☐	
26-30 yrs	☐	☐	☐	☐	☐	
In the past 3 years	☐	☐	☐	☐	☐	

7. At the following ages, where have your work and occupational activities (including parenting, caregiving, etc.) been carried out:

	Mainly indoors	Mainly outdoors	Equal time spent indoors and outdoors
16-20 yrs	☐	☐	☐
21-25 yrs	☐	☐	☐
26-30 yrs	☐	☐	☐

8. How often did you go on vacation to sunny places during winter months at the following ages?

	Never/seldom	1week/year or less	1-2 weeks/year	4+ weeks/year
0-5 yrs	☐	☐	☐	☐
6-10 yrs	☐	☐	☐	☐
11-15 yrs	☐	☐	☐	☐
16-20 yrs	☐	☐	☐	☐
21-25 yrs	☐	☐	☐	☐
26-30 yrs	☐	☐	☐	☐
In the past 3 years	☐	☐	☐	☐

9. How often did you use sun protection (sunscreen or protective clothing such as hats, long sleeves) at the following ages?

	Never/Seldom	Sometimes	Quite often	Almost always	Don't know
0-5 yrs	☐	☐	☐	☐	☐
6-10 yrs	☐	☐	☐	☐	☐
11-15 yrs	☐	☐	☐	☐	
16-20 yrs	☐	☐	☐	☐	
21-25 yrs	☐	☐	☐	☐	
26-30 yrs	☐	☐	☐	☐	
In the past 3 years	☐	☐	☐	☐	

10. How often did you use sunlamps or tanning beds at these ages?

	Never/Seldom	Less than once/year	Less than once/month	Once or more/month
16-20 yrs	☐	☐	☐	☐
21-25 yrs	☐	☐	☐	☐
26-30 yrs	☐	☐	☐	☐

SECTION 3: DIET

We would like to ask you information about your diet when you were a **"teenager" (between 13 and 19 years old)**. If your diet changed substantially during this period of time, please try to report the average consumption for the period.

1. Please indicate in which season(s) you generally consumed the following foods while you were a *teenager (age 13-19 years)?*
(you may choose more than one checkbox per row)

	Winter	Spring	Summer	Fall	Never/ seldom
Cows' milk (liquid or reconstituted powdered)	☐	☐	☐	☐	☐
Other type of milk (Specify: _____)	☐	☐	☐	☐	☐
Yogurt	☐	☐	☐	☐	☐
Eggs (prepared any style)	☐	☐	☐	☐	☐
Fresh cheeses (e.g., fresh ricotta, cottage cheese, cream cheese)	☐	☐	☐	☐	☐
Aged cheeses (e.g., Parmesan, strong cheddar)	☐	☐	☐	☐	☐
Smoked cheeses (e.g., smoked gouda)	☐	☐	☐	☐	☐
Other cheeses (e.g., cheddar, marble, feta, havarti, mozzarella, Monterey Jack, gouda, pecorino, Gloucester, Cheshire)	☐	☐	☐	☐	☐
Red meat (e.g., beef, lamb, venison, bison) or cold cuts (of all types)	☐	☐	☐	☐	☐
Smoked meat & pork	☐	☐	☐	☐	☐
Hotdogs, frankfurters, weiners	☐	☐	☐	☐	☐
Fresh fish	☐	☐	☐	☐	☐
Frozen fish	☐	☐	☐	☐	☐
Preserved fish (in oil, in salt, dried)	☐	☐	☐	☐	☐
Smoked fish	☐	☐	☐	☐	☐
Shellfish...					
(i) Molluscs (cuttlefish, octopus, squid, mussels, clams, oyster, scallops, etc.)	☐	☐	☐	☐	☐
(ii) Crustaceans (prawns, scampi, lobster, shrimp, crab, etc.)	☐	☐	☐	☐	☐

2a. Please indicate how often you generally ate the following foods while you were a *teenager (age 13-19 years)*.
(Please select only one box per row)

	Never	Less than once/mth	1-3 times/mth	Once/ week	2-3 times/ week	More than 3 times/ week
Cow's milk (liquid or reconstituted powdered)	☐	☐	☐	☐	☐	☐
Other type of milk (Specify: _____)	☐	☐	☐	☐	☐	☐
Yogurt	☐	☐	☐	☐	☐	☐
Eggs (prepared any style)	☐	☐	☐	☐	☐	☐
Fresh cheeses (e.g., fresh ricotta, cottage cheese, cream cheese)	☐	☐	☐	☐	☐	☐
Aged cheeses (e.g., Parmesan, strong cheddar)	☐	☐	☐	☐	☐	☐
Smoked cheeses (e.g., smoked gouda)	☐	☐	☐	☐	☐	☐
Other cheeses (e.g., cheddar, marble, feta, havarti, mozzarella, Monterey Jack, gouda, pecorino, Gloucester, Cheshire)	☐	☐	☐	☐	☐	☐
Red meat (e.g., beef, lamb, venison, bison) or cold cuts (of all types)	☐	☐	☐	☐	☐	☐
Smoked meat & pork	☐	☐	☐	☐	☐	☐
Hotdogs, frankfurters, weiners	☐	☐	☐	☐	☐	☐
Fresh fish	☐	☐	☐	☐	☐	☐
Frozen fish	☐	☐	☐	☐	☐	☐
Preserved fish (in oil, in salt, dried)	☐	☐	☐	☐	☐	☐
Smoked fish	☐	☐	☐	☐	☐	☐
Shellfish:.						
(i) Molluscs (cuttlefish, octopus, squid, mussels, clams, oyster, scallops, etc.)	☐	☐	☐	☐	☐	☐
(ii) Crustaceans (prawns, scampi, lobster, shrimp, crab, etc.)	☐	☐	☐	☐	☐	☐

2b. We are particularly interested in how often you ate the following types of fish as a teenager *(age 13-19 years)*.

	Never	Less than once/mth	1-3 times/mth	Once/ week	2-3 times/ week	More than 3 times/ week
Fresh or frozen salmon (*not* including smoked or canned)	☐	☐	☐	☐	☐	☐
Canned salmon	☐	☐	☐	☐	☐	☐
Fresh or frozen tuna (*not* including canned)	☐	☐	☐	☐	☐	☐
Canned tuna	☐	☐	☐	☐	☐	☐
Trout, Carp	☐	☐	☐	☐	☐	☐
Halibut	☐	☐	☐	☐	☐	☐
Sardines, anchovies	☐	☐	☐	☐	☐	☐
Fresh or frozen mackerel	☐	☐	☐	☐	☐	☐
Cod	☐	☐	☐	☐	☐	☐
Herring	☐	☐	☐	☐	☐	☐
Grouper, swordfish	☐	☐	☐	☐	☐	☐
Flounder, sole, smelt	☐	☐	☐	☐	☐	☐
Pickerel, snapper, perch	☐	☐	☐	☐	☐	☐
Other: specify _____	☐	☐	☐	☐	☐	☐

3. What type of water did you usually drink when you were a *teenager (age 13-19 years)?* *(you can check more than one box per row)*

	No Consumption	For drinking	For cooking	To make coffee/ tea/ hot drinks
Well water, spring water.	☐	☐	☐	☐
Tap water	☐	☐	☐	☐
Bottled water	☐	☐	☐	☐
Don't know		☐	☐	☐

4. How often did you use the following condiments and oils as a *teenager (age 13-19 years)* including as dressings, or sauces, and for cooking?
(Please check only one box per row)

	Never	Less than once/mth	1-3 times/ mth	Once/ week	2-3 times/ week	4-5 times/ week	More than 5 times/week
Butter	☐	☐	☐	☐	☐	☐	☐
Margarine	☐	☐	☐	☐	☐	☐	☐
Lard	☐	☐	☐	☐	☐	☐	☐
Mayonnaise	☐	☐	☐	☐	☐	☐	☐
Vegetable oil…							
(i) Corn, sesame, walnut, sunflower, flaxseed, safflower oil	☐	☐	☐	☐	☐	☐	☐
(ii) Canola, peanut, olive, coconut, avocado, almond oil	☐	☐	☐	☐	☐	☐	☐
(iii) Other vegetable oils: Specify: _____	☐	☐	☐	☐	☐	☐	☐

5. Did you take any of the following dietary supplements when you were a *teenager(age 13-19 years)?*

	Yes	No	Don't know
Cod liver oil liquid	☐	☐	☐
Cod liver oil capsules	☐	☐	☐
Fish oil capsules	☐	☐	☐
Multivitamins	☐	☐	☐
Calcium	☐	☐	☐
Vitamin B12	☐	☐	☐
Vitamin C	☐	☐	☐
Vitamin D	☐	☐	☐

6. Please report what you were fed as a baby. (*You can select more than one box per column and line.*)

	Breast milk	Artificial formula	Other milk (e.g. cow, soy, etc.)	Don't know
From 1-3 mths	☐	☐	☐	☐
From 4-6 mths	☐	☐	☐	☐
From 7-9 mths	☐	☐	☐	☐
From 10 mths & older	☐	☐	☐	☐
Specify:			_____	

SECTION 4: MEDICAL HISTORY

The following questions concern illnesses that you may have had when you were younger.

1. Please indicate at what age you had the following illnesses or surgical interventions. To help you remember, think about which school grade you were in when you had the illness/surgery. Check all that apply.

	Didn't have	Don't know	Did have	Age at diagnosis: 0-5 yrs	6-10 yrs	11-15 yrs	16-20 yrs	21-25 yrs	26-30 yrs
Measles	☐	☐	☐→	☐	☐	☐	☐	☐	☐
Mumps	☐	☐	☐→	☐	☐	☐	☐	☐	☐
Rubella (German Measles)	☐	☐	☐→	☐	☐	☐	☐	☐	☐
Chicken pox	☐	☐	☐→	☐	☐	☐	☐	☐	☐
Tonsillectomy (tonsil removal)	☐	☐	☐→	☐	☐	☐	☐	☐	☐
Pneumonia *(check as many times as applies)*	☐	☐	☐→	☐	☐	☐	☐	☐	☐

2a. Have you had infectious mononucleosis (also called "mono" or "the kissing disease")?

Yes ☐ →go to question 2b

No ☐ Don't know ☐ → If no or don't know, skip to question **#4**

2b. If yes, did have a blood test to check the diagnosis?

Yes ☐ No ☐ Don't remember ☐

2c. At what *age* did you have mononucleosis?

0-5 yrs ☐ 6-10 yrs ☐ 11-15 yrs ☐ 16-20 yrs ☐ 21-25 yrs ☐ 26-30 yrs ☐

3a. Do you remember in which *month* you were diagnosed with mono?

No ☐ Yes ☐ if yes, in which month was it? ☐☐

→ If you *know* the month, skip to question **#4**.

3b. If you don't remember the exact month, can you recall in which *season* you had mono?

Spring	Summer	Fall	Winter	Don't Remember
☐	☐	☐	☐	☐

4. Have you ever had a urinary tract infection (UTI)? If yes, please give your best estimate of the age(s) when it/they occurred.

			Ages when UTI occurred. *(you can check more than one box in the same row)*					
No	Don't know	Yes	0-5 yrs	6-10 yrs	11-15 yrs	16-20 yrs	21-25 yrs	26-30 yrs
☐	☐	☐→	☐	☐	☐	☐	☐	☐

5. Have you ever had a parasitic infection (e.g., Tenia or tapeworm, ossiuri, ascarides, giardia, cryptosporidium, etc.)?
If yes, please give your best estimate of your age when it first occurred.

			Age of ***first*** infection					
No	Don't know	Yes	0-5 yrs	6-10 yrs	11-15 yrs	16-20 yrs	21-25 yrs	26-30 yrs
☐	☐	☐→	☐	☐	☐	☐	☐	☐

6. Do you have a history of allergy (such as conjunctivitis or red itchy watery eyes, rhinitis or runny nose, eczema, hives, asthma) to any of the following?
If yes, please estimate the approximate age at which you experienced the first symptoms (i.e., when did the allergies begin?).

				Age at ***first*** symptoms					
	No	Don't know	Yes	0-5 yrs	6-10 yrs	11-15 yrs	16-20 yrs	21-25 yrs	26-30 yrs
Pollens	☐	☐	☐→	☐	☐	☐	☐	☐	☐
House dust	☐	☐	☐→	☐	☐	☐	☐	☐	☐
Animal dander/fur	☐	☐	☐→	☐	☐	☐	☐	☐	☐
Any food	☐	☐	☐→	☐	☐	☐	☐	☐	☐
Other allergies Specify: _____	☐	☐	☐→	☐	☐	☐	☐	☐	☐

7. Has a doctor ever told you that you had any of the following disorders?

	No	Don't know	Yes	Age at diagnosis	Age at first symptoms
Systemic lupus erythematosus (Lupus)	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Rheumatoid arthritis	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Hypothyroidism	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Hyperthyroidism	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Multiple sclerosis	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Optic neuritis	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Crohn's disease	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Ulcerative colitis	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Type I diabetes mellitus (juvenile diabetes)	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Celiac disease	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Psoriasis	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Leukemia	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Hodgkin's lymphoma	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Non Hodgkin's lymphoma	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Melanoma skin cancer	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Non-melanoma skin cancer	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Kidney disorders	☐	☐	☐→	☐☐ yrs	☐☐ yrs
Other medical disorders, specify: _____	☐	☐	☐→	☐☐ yrs	☐☐ yrs

8. To your knowledge, does anyone in your family have a history of any of the following diseases?

	No	Father	Mother	Brother/Sister	Child	Don't know
Systemic lupus erythematosus (lupus)	☐	☐	☐	☐	☐	☐
Rheumatoid arthritis	☐	☐	☐	☐	☐	☐
Hypothyroidism	☐	☐	☐	☐	☐	☐
Hyperthyroidism	☐	☐	☐	☐	☐	☐
Multiple sclerosis	☐	☐	☐	☐	☐	☐
Optic neuritis	☐	☐	☐	☐	☐	☐
Crohn's disease	☐	☐	☐	☐	☐	☐
Ulcerative colitis	☐	☐	☐	☐	☐	☐
Type I diabetes mellitus (juvenile diabetes)	☐	☐	☐	☐	☐	☐
Celiac disease	☐	☐	☐	☐	☐	☐
Psoriasis	☐	☐	☐	☐	☐	☐
Leukemia	☐	☐	☐	☐	☐	☐
Hodgkin's lymphoma	☐	☐	☐	☐	☐	☐
Non Hodgkin's lymphoma	☐	☐	☐	☐	☐	☐

SECTION 5: SMOKING HABITS AND LIFESTYLE FACTORS

1. Have you ever been a regular smoker? ("regular" = smoked one or more cigarettes per day for 6 months or longer)

Yes ☐ No ☐ → If your answer is no skip to question **#5**.

2. If yes, how many cigarettes per day on average did you smoke at the following ages?

	0 cig./day	1-4 cig./day	5-10 cig./day	11-20 cig./day	21+ cig./day
11-15 yrs	☐	☐	☐	☐	☐
16-20 yrs	☐	☐	☐	☐	☐
21-25 yrs	☐	☐	☐	☐	☐
26-30 yrs	☐	☐	☐	☐	☐

3. At what age did you start to smoke cigarettes daily? (Age) ☐☐

3a. Do you still smoke? Yes ☐ No ☐

4. How many years have you smoked in total? (Number of years) ☐☐

5. Did your mother smoke while she was pregnant with you?

No ☐ Don't know ☐ Yes → ☐ How many cigarettes per day did she smoke? Less than 10 ☐ 10+ ☐

6. Did your <u>mother</u> smoke <u>inside the house</u> when you were a child?

She was a non-smoker ☐ No, she didn't ☐ Don't know ☐ Yes → ☐ If yes, how many cigarettes per day did she smoke inside the house? Less than 10 ☐ 10+ ☐

7. Did your <u>father</u> smoke <u>inside the house</u> when you were a child?

He was a non-smoker ☐ No, he didn't ☐ Don't know ☐ Yes → ☐ If yes, how many cigarettes per day did he smoke inside the house? Less than 10 ☐ 10+ ☐

8. Did you live with anybody else who smoked <u>inside the house</u> before you were age 21?

No ☐ Yes → ☐

Who?	How many cigarettes a day did he/she smoke inside the house?	
Brother ☐	Less than 10 ☐	10+ ☐
Sister ☐	Less than 10 ☐	10+ ☐
Other ☐	Less than 10 ☐	10+ ☐

9. Did you live with anybody who smoked <u>inside the house</u> when you were between the ages of 21-25 years?

No ☐ Yes → ☐ How many cigarettes per day were smoked inside the house? Less than 10 ☐ 10+ ☐

10. Did you live with anybody who smoked inside the house when you were between the ages of 26-30 years?

No ☐ Yes→ ☐ How many cigarettes per day were smoked inside the house?

Less than 10 ☐ 10+ ☐

11. Have you ever worked in an environment where someone regularly smoked inside your workplace?

No ☐ Yes ☐

12. What figure best depicts the shape of your body at the different ages.

At 5-years	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
At 10-years	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
At 15-years	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
At 20-years	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
At 25-years	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
At 30-years	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Today	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

13. What is your current weight? ☐☐☐ (Pounds) or ☐☐☐ (Kilograms)

14. How tall are you? ☐ (Feet) & ☐☐ (Inches) or ☐☐☐ (Centimetres)

15. What was your level of physical activity per week when you were a teenager (between 13 and 19 years old)? (For example, light physical activities refer to activities that require light physical effort such as walking leisurely, stretching, vacuuming or light yard work. Vigorous physical activities refer to activities that take heavy physical effort such as jogging, running, stair machine, sports (e.g. tennis, basketball, soccer, etc.)).

	None	Less than once/week	1-2 times/week	3 or more times/week
Light physical activity (your heart beats slightly faster than normal)	☐	☐	☐	☐
Vigorous physical activity (your heart rate increases a lot)	☐	☐	☐	☐

MEN – please **proceed to the last question (#14) on page 9**

SECTION 6: HORMONAL FACTORS

WOMEN ONLY. Men, please proceed to the last question (#14) on this page.

1. How old were you when you started getting your period? ☐☐ Age

2. Are you pregnant now? Yes ☐ No ☐

3. Have you ever been pregnant? Yes ☐ No ☐ → if no skip to question **#5**.

4. If yes, please provide the following information on the outcome of each pregnancy and the year(s).

	1st pregnancy	2nd pregnancy	3rd pregnancy	4th pregnancy	5th pregnancy	6th pregnancy
Born alive	☐	☐	☐	☐	☐	☐
Breastfed for at least 1 month	☐	☐	☐	☐	☐	☐
Lost pregnancy (spontaneous or induced abortion, interuterine death, still born)	☐	☐	☐	☐	☐	☐
Lost at # weeks:	_____	_____	_____	_____	_____	_____
Year of outcome:	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐

5. Have you ever undergone hormonal treatment for infertility?

Yes ☐ No ☐ → if no skip to question **#7**

6. If yes, please indicate the year(s) you received treatment and the number of cycles per year.

Year(s): ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐

No of cycles/year: ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

7. Have you ever used a birth control pill (not the "mini-pill" that contains progesterone only, but the type that is taken for 3 weeks, followed by 1 week replacement with "sugar-pills"), hormonal patches, vaginal hormonal rings, or *hormonal* inter-uterine devices (IUD)?

Yes ☐ No ☐ → if no skip to question **#10**

8. If yes, how old were you when you started using these contraceptives? ☐☐ Age

9. For how long did you/have you used these contraceptives?

Less than 1 year	1-3 years	4-5 years	6-9 years	10+ years
☐	☐	☐	☐	☐

10. Have you ever suffered from hirsutism, that is, from an excess of coarse hair in areas of the body where it is not normally found (e.g., face, chest, back, abdomen)?

Yes ☐ Don't know ☐ No ☐ → if no/don't know skip to last question **#14**

11. If yes, have you ever been given hormonal therapies to treat this? Yes ☐ No ☐ → if no skip to last question **#14**

12. At what age did you start these therapies? ☐☐ Age

13. For how long did you take these therapies?

Less than 1 year	1-3 years	4-5 years	6-9 years	10+ years
☐	☐	☐	☐	☐

14. Lastly, we would like to know if someone helped you fill out the questionnaire.

No ☐ Yes ☐ → Who? Mother ☐ Father ☐ Other ☐

Thank you for your participation!

If there is anything else that you would like to tell us about the survey, please do so in the space provided below.

Please return the questionnaire in the enclosed self-addressed envelope to the following address:

EnvIMS Study
Neuroepidemiology Research Unit
1025 Pine Avenue West, Suite P2.028
Montreal, QC H3A 1A1

APPENDIX D: Sample Size Considerations

The data used in Manuscript 3 was already collected, and thus the sample size was fixed. I used the following formula to calculate the minimal sample size required, to achieve a certain level of statistical power.[233]

$$n = \{Z_{1-\alpha/2}[P(1-P)/B]^{1/2} + Z_{1-\beta}[P1(1-P1) + P2(1-P2)(1-B)/B]^{1/2}\}^2 / [(P1-P2)^2(1-B)]$$

I estimated the sample size needed to attain 80% power (β); but also examined 85% and 90% power. I used an alpha of 0.05 and fixed the event rate at 50%. I varied the proportion of events in exposed (P2) and unexposed (P1) groups, using values coinciding to proportions obtained in previous studies.[14, 20] For these parameters I initially considered values ranging from 0.25 to 0.40 for the proportion of the outcome in the unexposed, and 0.45 to 0.65 for the proportion of the outcome in the exposed. As I included confounders in the final model the sample size needed to be inflated to account for the correlation between the main effect and the confounders; I selected a conservative R^2 of 0.20. Using the shortcut suggested by Hsieh et al,[233] $N_{multivariate}=N_{univariate}/(1-R^2)$, the sample size obtained from the sample size formula provided above was inflated. In my analysis I have 80% power to detect odds ratios as low as 1.2 with the total sample, and 90% power to detect odds ratios of 1.5. The required sample sizes for 80% power and odds ratios lower than 2.0 are provided in this table.

P=Pr(Y=1)	B=Pr(x=1)	P1=Pr(Y=1|x=0)	P2=Pr(Y=1|x=1)	OR	R^2	N	Inflated N
0.5	0.1	0.4	0.45	1.2	0.2	4691	5863
0.5	0.1	0.4	0.5	1.5	0.2	1173	1467
0.5	0.1	0.35	0.45	1.5	0.2	1145	1432
0.5	0.1	0.4	0.55	1.8	0.2	521	651
0.5	0.1	0.35	0.5	1.9	0.2	509	637
0.5	0.1	0.3	0.45	1.9	0.2	492	615

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