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Current Review and Next Steps for Artificial intelligence in Multiple Sclerosis risk research

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Abstract

In the last few decades, the prevalence of multiple sclerosis (MS), a chronic inflammatory disease of the nervous system, has increased, particularly in Northern European countries, the United States, and United Kingdom. The promise of artificial intelligence (AI) and machine learning (ML) as tools to address problems in MS research has attracted increasing interest in these methods. Bayesian networks offer a clear advantage since they can integrate data and causal knowledge allowing for visualizing interactions between dependent variables and potential confounding factors. A review of AI/ML research methods applied to MS found 216 papers using terms “Multiple Sclerosis”, “machine learning”, “artificial intelligence”, “Bayes”, and “Bayesian”, of which 90 were relevant and recently published. More than half of these involve the detection and segmentation of MS lesions for quantitative analysis; however clinical and lifestyle risk factor assessment and prediction have largely been ignored. Of those that address risk factors, most provide only association studies for some factors and often fail to include the potential impact of confounding factors and bias (especially where these have causal explanations) that could affect data interpretation, such as reporting quality and medical care access in various countries. To address these gaps in the literature, we propose a causal Bayesian network approach to assessing risk factors for MS, which can address deficiencies in current epidemiological methods of producing risk measurements and makes better use of observational data.

Current Review and Next Steps for Artificial intelligence in Multiple Sclerosis risk research

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8 March 2021

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Abstract

In the last few decades, the prevalence of multiple sclerosis (MS), a chronic inflammatory disease of the nervous system, has increased, particularly in Northern European countries, the United States, and United Kingdom. The promise of artificial intelligence (AI) and machine learning (ML) as tools to address problems in MS research has attracted increasing interest in these methods. Bayesian networks offer a clear advantage since they can integrate data and causal knowledge allowing for visualizing interactions between dependent variables and potential confounding factors. A review of AI/ML research methods applied to MS found 216 papers using terms “Multiple Sclerosis”, “machine learning”, “artificial intelligence”, “Bayes”, and “Bayesian”, of which 90 were relevant and recently published. More than half of these involve the detection and segmentation of MS lesions for quantitative analysis; however clinical and lifestyle risk factor assessment and prediction have largely been ignored. Of those that address risk factors, most provide only association studies for some factors and often fail to include the potential impact of confounding factors and bias (especially where these have causal explanations) that could affect data interpretation, such as reporting quality and medical care access in various countries. To address these gaps in the literature, we propose a causal Bayesian network approach to assessing risk factors for MS, which can address deficiencies in current epidemiological methods of producing risk measurements and makes better use of observational data.

Keywords: Bayesian networks, AI decision making, risk factors, multiple sclerosis

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the nervous system that causes lesions to form in the brain, brain stem, optic nerve, and/or spinal cord [1]. Since 1990, the prevalence of MS has increased by 10% with increasing incidence reported in the United States, Canada, and Norwegian countries [2]. It is thought that improved diagnostic accuracy and physician understanding may be partially responsible for this effect, although it is unlikely that this fully explains the observed increase. This general increase in MS cases, particularly in women, along with uncertainty regarding the underlying causal mechanisms of MS, has increased research interest and efforts into the study of potential causes and triggers. The increasing availability of large datasets has enabled the study of potential causal pathways in MS, a relatively rare disease. For many other chronic diseases there has been significant research applying artificial intelligence (AI) or machine

learning (ML) techniques to help identify risk factors, early identification categories and predict disease progression.

This paper reviews the literature relating to AI/ML methods in current MS research with a focus on risk classification and risk factors. We found very few publications with this focus and those that did address this area largely failed to examine causal explanations beyond simple correlation calculations. It is increasingly widely recognized within the AI community that graphical causal models [3] provide a powerful way of understanding the limitations of observational data and enhancing this data with causal knowledge. A particularly powerful graphical causal model – the Bayesian network –which combines expert causal knowledge with Bayesian probability theory has been used to improve risk assessment in a range of medical conditions [4] [5] [6] [7] [8]. We propose a causal Bayesian network approach to supplement classical data-driven epidemiological methods. In Section 2 we present a background on the empirical studies of possible risk factors for MS. In Section 3 we present our review of current AI methods in MS research, which reveals a need for more risk-related research. In Section 4 we explain how a causal approach using Bayesian networks helps avoid common problems (including the impact of confounding factors and bias through colliders) in interpreting the effect of risk factors from observational studies. We also present a prototype causal Bayesian network that can provide a systemic structure for future research in MS risk assessment and prediction. Our conclusions and recommendations are presented in Section 5.

2. Background on MS Risk

Much work has been done to determine factors that appear to contribute to the development of MS. The causal pathway leading to MS is hypothesized to include a combination of environmental and genetic factors, but few have been confirmed, and potential interactions have proved extremely challenging to study. Since 1970, there has been a pronounced relative and absolute increase in prevalence of MS in women, which could conceivably be caused by genetic susceptibility to risk, lifestyle changes, or increased diagnosis. When observing ratio of female to males affected in Denmark over a period from 1950 to 2000, there was an increase from 1.3:1 to approximately 2:1 [9]; this change over a short period of time suggests it is more likely to be environmental factors that are driving this increase in MS female prevalence.

It is now established that there is a genetic element underlying MS susceptibility. Approximately 12% of MS patients have a relative affected by the disease [10]. A specific human leukocyte antigen (HLA) type, DBR1* 1501, is linked to increased susceptibility to MS; heterozygosity increases an individual's odds of developing MS by a factor of 3 [11]. Some ethnic groups are also less likely to have MS, due to either early life influences in different countries or genetic effects. One study found that African American populations in the United States had a 40% lower risk than their White counterparts [12]. However, when the same authors repeated the survey years later, they found that although risk had increased for this group, relative risk remained 33% lower in African American males compared to White males [13]. This study included a possible confounding variable, geographic residence, but the genetic makeup of each population and the reduced access to healthcare and/or lower suspicion of the diagnosis on the part of healthcare providers in minorities may also play a role. Other groups like the Mongolian, Japanese, Chinese, and Native American populations have significantly lower risk [14]. To date, there are no sufficiently powered genome-wide susceptibility studies in Black and Minority Ethnic (BAME) populations. Accounting for the interaction(s) between ethnicity, genetics and socioeconomic influences on both risk factors and access to healthcare for diagnosis means that

distinguishing risk associated with ethnicity from other potential causes of differential risk remains extremely challenging.

In addition to genetic factors, it is believed that there are environmental triggers or influences that may affect the risk of developing MS. The hope is that, if interventions are developed to change these, MS may be prevented. Observational studies suggest that MS incidence is highest in those countries furthest from the equator, but there remain pockets of populations in northernmost areas that are almost unaffected by MS; one such example is the Eskimo community in Canada [15]. This suggests there might be a genetic component or cultural influence, such as the high Vitamin D diet of oily fish, still at play. A similar effect is observed in the Arctic Circle of Norway where the incidence of MS is much lower in the coastal fishing locations versus more inland areas [16]. However, again cultural factors, access to healthcare and diagnostic testing, and reporting bias may explain why there are fewer recorded cases. Many Scandinavian countries also benefit from a centralized medical system and have had relatively consistent recording of incident cases due to registry systems, which may account for at least some of the higher reported rates. The general increase in cases in at least some countries could also be due to improved survival rates or increased reporting. In Iran, which has seen a sharp increase in MS cases, prevalence is variable across geographic locations which suggests an ethnic or lifestyle factor may also be contributing in a variable way [17].

Infectious agents have been considered as a potential cause of MS. Several studies have found that risk of developing MS increases to 2-3-fold in individuals with a history of EBV infection. [18] [19]. Modern lifestyle habits might increase susceptibility, such as smoking, high BMI in childhood [20], vitamin D deficiency [21], or high stress levels [22]. A Swedish study found that smoking increases the odds of developing MS by around 1.4 to 1.7, depending on the presence of genetic risk factors [23]. Based on a similar study of risk factors conducted in Iran, 64% of patients with MS reported having endured a stressful or traumatic event in their lifetime [24], but extensive retrospective studies such as these have some issues regarding recall bias whereby patients may over-report negative life events occurring close to disease onset. As we will explain in Section 4, there may also be explanations purely due to the way the data are collected and analyzed. In particular, many of the empirical studies of MS risk factors may fail to properly account for confounding factors in the analysis and biases in the data collected.

Our core hypothesis it that most studies are compromised due to the way the data are collected and analyzed, and in particular that many conclusions are flawed because of a failure to take full account of causal explanations for observed data. As explained by Pearl [3], true AI cannot be achieved by 'learning from data' alone even though machine learning techniques are usually classified as AI. True AI requires causal modelling, and Bayesian networks (BNs) provide both the graphical formalism for modelling causality together with an inference algorithm for prediction and diagnostics beyond that which can be achieved from standard statistical analyses of experimental data. Moreover, BNs also enable us to simulate interventions and counterfactual reasoning on observational data alone. This will be explained in Section 4. In what follows, we explore this, but first we present our review of the use of AI and ML methods applied to MS data.

3 Literature Review of AI/ML methods in MS Research

The relevant papers in the AI/ML literature review were found by using the following search terms in IEEE, IET, PubMed, and other available journals: "Multiple Sclerosis" + "machine learning", "artificial intelligence". We did not include names of specific ML techniques and algorithms, but did add:

"Bayes", "Bayesian", "expert learning" because of our particular interest in this area. The search resulted in 216 papers. After an initial review, 126 papers were rejected for any of the following reasons: they were published before 2010, did not relate specifically to MS, were review papers, contained a meta-analysis, or only discussed simple methods of producing risk, like fixed weights rather than unsupervised or supervised forms of machine learning.

The remaining 90 papers, listed in Appendix A, can be classified as shown in Figure 1 The green box in this figure is highlighted to show that only one paper presented an AI technique that related to determining MS clinical risk factors. We next consider the three top level classifications in detail. These are separated based on the type of information that each AI method uses to make either a prediction or assessment of MS prognosis, treatment effect, or disability level.

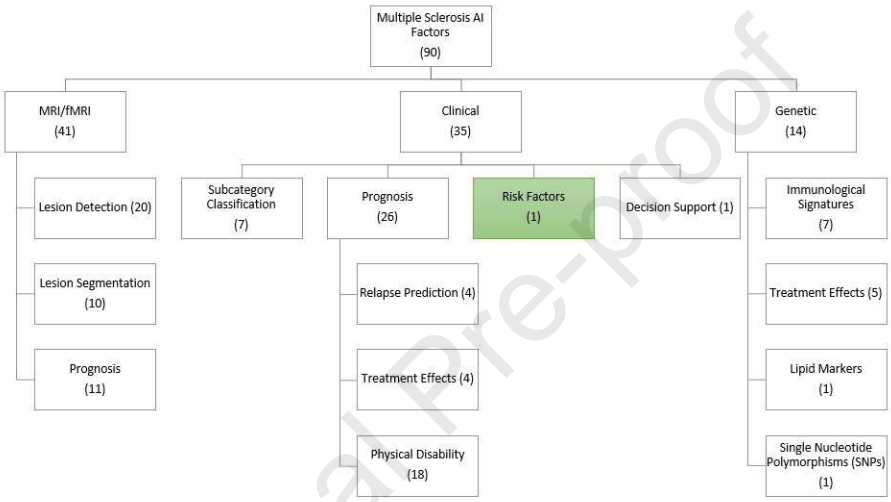

Figure 1 Classification of reviewed papers

3.1 Magnetic Resonance Imaging (MRI) and functional magnetic resonance imaging (fMRI)

Forty-one papers involve lesion detection and segmentation and seek to assess prognosis using MR imaging. The input to the machine learning (ML) models is a combination of MRI images and clinical and/or demographic data. Common ML techniques for classifying MRI images that might contain MS lesions include support vector machine (SVM), regression [25] [26] [27] [28] [29] [30] [31] [32], Random Forest [33] [34], KNN [35], Naïve Bayes (NB), multilayer perceptron (MLP) [36], and convolutional neural network (CNN) [37] [38] [39]. Deshpande et al used a supervised classification method called adaptive dictionary learning, where models decompose an input signal using MRI data given [40]. Some works focused on comparing different methods for their accuracy in detecting MS lesions [41] [42] [43]. Often before classifying MRI images, segmenting parts of an MRI image into specific areas of interest is required. Several novel automation tools have been developed for this purpose [44] as well as the application of neural networks [45] [46] and other methods of learning [47] [48] [49]. A transfer learning technique from van Opbroek et al segmented images while also compensating for differences in imaging protocols [50]. Another compensation method was presented by Falvo et al for diagnosing MS in under sampled MRI images [51]. A regression approach used by Goldsmith, Huang, and Crainiceanu attempted to find a correlation between MRI images of lesions in a certain part of the brain and a decrease in cognitive function in MS patients

[52]. Functional MRI (fMRI) data has also been tested as input to machine learning algorithms for the diagnosis of MS [53] [54]

3.2 Clinical

Clinical records may be used for machine learning studies around diagnosis [55] [56] [57]. Chase et al [56] developed an approach for detecting early cases of MS through electronic health record analysis. They found higher frequencies of certain reported symptoms, such as numbness in limbs, higher in the group that contained MS patients.

Thirty-five of the papers focused on clinical data to predict the progression of MS in terms of MS type, disability scale ranking, or risk of relapse. Fiorini et al [58], Ruggiero et al [59], and Brichetto et al [60] test an assortment of linear classifiers, including least squares and multi-layer perceptron (MLP), on their ability to predict MS course type (relapsing remitting, primary or secondary progressive) based on data from a clinical questionnaire. Fiorini's classifier performed best when distinguishing between remitting relapsing (RR) type from all other MS types. A similar study using MLP was performed by Kocevar et al to classify MS type from an input of MRI metrics obtained by graph theory-based analysis [61].

The most common metric used to measure the physical impact of MS is the Expanded Disability Status Scale (EDSS). The EDSS is an ordinal scale in 0.5 increments from 0 (no symptoms) to 10 (death due to MS). Sustained change in EDSS is a common primary outcome measure in clinical trials of MS disease modifying treatments. This metric is used in four similar studies that input clinical data into SVM [62] [63] and random forest [64] [65] models to predict the level of disability several years after initial MS onset. Disability can also be measured in terms of cognitive ability, which is how Kiiski et al quantify the effects of MS two years in advance using EEG data [66]. Eventually MS may affect a patient's ability to walk or speak, which motivated Sun, Hsieh, and Sosnoff to develop a sway metric that can predict individuals who are at high risk of falling [67]. Prediction of progression when observing early signs of MS, called clinically isolated syndrome (CIS), in MRI scans is another area of interest [68] [69]. MS patients often have periods of time when symptoms might ease, only to relapse later. This is why Engler et al develop a machine learning method to predict which cases are most likely to have relapses in the future [70]. Prognosis can potentially be determined using a variety of data sources.

The use of cytokine [71], motor function [72] [73], cognitive function [74] [75] [76], disability status [77], optical [78] [79] [80], and EEG [81] measurements in conjunction with artificial intelligence classifiers can point towards symptoms of MS. Although clinical data is used extensively for prognosis and prediction of MS course, only one dealt with analyzing clinical and environmental risk factors. An extensive case-control study outlined potential environmental exposures that might be partially responsible for patients to develop MS [82]. The only strong odds indicator that was found in this study was pesticide exposure, but only in males that had a specific genetic risk.

Incorporating expert knowledge when creating a model for diagnosis or disease progression is essential but was rarely found in papers contained in this review. This is especially important when considering clinical variables that are important for decision-making, but for which very little historical data are found [83]. One study that did incorporate clinician knowledge elicited language used by radiologists when describing lesions on an MRI scan [84]. The result was a classification of lesion load for each patient using a fuzzy rule-based system that was coded with this language. A similar study also used fuzzy concepts combined with knowledge about MS symptoms to advise physicians for whether to perform an MRI on a given symptomatic patient [85]. However, this was

not created with the help of a neurologist and relied on information taken from internet sources. Another clinician knowledge-driven study [86] involved the development of an automated system to predict the EDSS value that radiologists might give to MS patients. A combination of knowledge from medical students and machine learning algorithms yielded a higher predictive ability compared to a machine learning alone when asked to predict the progression of patients from relapsing-remitting to secondary progressive [87].

3.3 Genetic

Fourteen of the papers relate to the discovery of genetic attributes and immunological signatures common to MS patients or ones that could predict patient treatment response. A random forest approach was developed by Jackson et al to find common characteristics of MS patients most likely to have a progressive form of MS with the goal of aiding clinicians in diagnosis and treatment [88]. Similarly, an MLP method developed by Flauzino et al found immunological signatures that predict higher EDSS in MS patients [89]. Karmonik, Boon, and Khavari focused on centers of the brain that might be targets for treatment in muscle malfunction in MS patients [90]. Many studies use pathway analyses to find potential genetic or immunological markers that may contribute to MS. Five such studies combine this approach with unsupervised learning [91] [92], logistic regression [93], random forest [94], and clustering-based [95] methods to find common genetic attributes within MS populations. Using self-organizing maps, Lötsch et al found certain lipid markers that were present in MS patients versus healthy controls, thus presenting a possible target for drug development [96]. Assessing the effectiveness of medications on MS progression is another application of machine learning. For example, different studies predict drug response of MS patients using genetic signatures [97] [98] [99] [100] and CD4+ T cell biomarkers [101], and relapse data [102].

3.4 Bayesian approaches

Notably, we found no papers using a Bayesian approach to MS that incorporated causal knowledge and data. However, some work used purely data-driven Bayesian techniques. For example, a Causal Bayesian Network (CBN) was learned from data in Fleischer et al's work using fMRI connectivity data to predict disease progression markers, however only *r* and p-values from data were presented and any depiction of any Bayesian Network structure was lacking [103]. Similarly, Palacios et al applied structure learning to gene networks before establishing a Bayesian network for identifying drug targets [104].

In [105], a Bayesian classifier is used to detect potential lesions in MS patients' MRI scans. In developing a method for MRI image segmentation, Sudre et al used Bayesian Information Criterion (BIC) to calculate the trade-off between complexity and accuracy of potential models [106]. Another that involved MRI lesion segmentation used a Bayesian Generative Model, which is described as a convolutional neural network that is given Bayesian priors for transfer learning across domains of medical imaging data but does not have causal structure [107]. Forbes et al developed a Bayesian expectation-maximization (EM) framework for segmentation as well, where expert knowledge as prior distributions were entered into their Markov model [108]. Rodriguez et al expand their research objective to include predictions on both EDSS level and MS subtype. With a Bayesian network classifier, they were able to predict with up to 85% accuracy the time for patients to reach an EDSS level of 6 [109]. This network classifier included some causal structure but does not take into account additional confounding variables.

Another Bayesian approach was presented in the domain of MS treatment clinical trials [110]. They assess treatment effects on MS patients taking a certain drug based on disability progression from

input data from MRI lesions. Their work primarily focuses on a simple regression model. Three other papers involve the cost-benefit analysis of treatment effects [111] [112] [113] using similar regression methods.

Pozzi et al use a close relative to the Bayesian Network, called a decision tree, to calculate the lowest effective dosage for MS treatment [114]. A Bayesian latent-variable approach was used by Bergamaschi et al to predict the probability of an MS patient remaining free of disease progression based on early relapse data and demographic information [115] and extended this work to include a prediction of patients most likely to have long-term disability [116]. The authors mention that their motivation to use a Bayesian approach was due to the dynamic nature of the progression data. These papers all demonstrated the utility of Bayesian approaches or networks to aid in diagnosis and prediction. However, their work can be expanded further, which will be discussed next.

4. Proposed Bayesian Approach

One of the most contested risk factors studied in MS research best demonstrates the need for a Bayesian approach to medical risk that incorporate causal knowledge with data. This concerns the studies [117] [118] [119] [120] that suggested being born in spring months (April, May in the Northern hemisphere and Oct, November in the Southern hemisphere) increased the risk of MS by 13% [121]. However, Fiddes et al [122] demonstrated that this much hyped 'spring birth' risk factor may be explained by the simple fact these months are when there are more births. So, the 'birth rate' is a confounding variable. Another example of this type of problem is that the decreased vitamin D levels reported in MS patients versus controls could be confounded by a lifestyle factor that differs between patients and controls, even pre-diagnosis, such as decreased outdoor activity or exercise in people who subsequently develop MS as part of an "MS prodrome" [123]. It is conceivable that the development of national registries and reporting in different countries may also impact the incidence rates, with increased (or changing) ascertainment confounding the study of incidence. An unintended consequence of this could be highlighting an underlying environmental factor (or factors) specific to that country. Some countries (and communities within countries) have inequitable access to medical care, larger number of neurologists, and increased public awareness of MS which also affect the reported incidence rates [124]. Further analysis of immigration studies could also determine key intervals of exposure that lead to increased risk of MS.

A simple Bayesian network (BN) showing the 'birth rate' effect, which associates spring births with increased MS risk, is presented in Figure 2. Subsequent studies concur with what would seem like a spurious correlation. However, several causal explanations could account for this effect, including gestational vitamin D deficiency or ultraviolet B levels [125]. More generally we need to consider unobserved as well as observed factors and the causal relationships between them. These interactions can then be included as connected nodes in the BN. Circular nodes represent the variables that contribute to the structure, while the arrows show the directions of these effects.

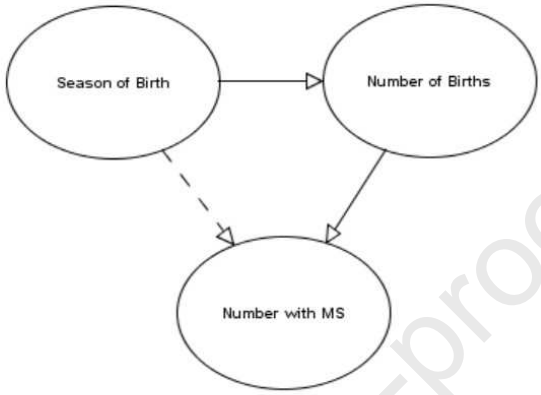

Figure 2. Month of Birth effect BN

Most MS risk literature involves case control studies that compare incidence of exposures or risks in the MS and control groups. This information is then used to calculate hazard ratio, odds ratio, or relative risk. Hazard ratios are used primarily in drug study outcomes to represent the odds of a treated group recovering in a treated after a given period compared to a control group [126]. Odds ratio, which is more prevalent in MS literature, is a measure that describes one's odds of contracting a disease given a certain exposure:

$$Odds\ Ratio\ (OR) = \frac{D_E/H_E}{D_N/H_N}$$

where D_E represents patients who have the disease and have had the exposure, H_E is number of patients who are healthy but have been exposed, D_N the patients who were not exposed and have a disease, and H_N the patients who are healthy and were not exposed. Relative risk is similar to this measure except that it compares the probability of an event happening in these two groups—unexposed and exposed:

$$Relative\ Risk\ (RR) = \frac{D_E/(D_E + H_E)}{D_N/(D_N + H_N)}$$

Given an odds ratio, a conditional probability table $B|A$ (see Table 1) can be populated, where A can symbolize the exposure and B the disease, and p and q the associated probabilities.

Table 1. Odds Ratio Probability Tables

	$B = True$	$B = False$
$A = True$	p	q
$A = False$	$1 - p$	$1 - q$

When extending a conditional probability table $B|A$ to multiple causes, such as $B|A_1, A_2$, where A_1 and A_2 are each a cause, it quickly becomes more complicated to calculate an odds ratio that has the same meaning as defined above if one of these variables are dependent on the other. A case-control or population-based study may not control for the confounding effect or may not measure the confounding variable at all.

The most dramatic effect of this can be seen when the 'correct' results are completely reversed due to overlooking the confounder; this is called Simpson's Paradox [127]. The causal explanation of this paradox – represented as a Bayesian network [128] [3] is shown in Figure 3. For example, there has previously been a reported connection between ethnicity and the risk of developing MS, as Northern European populations report a higher prevalence of the disease. However, many studies overlook the confounding variable or variables that affect study outcomes, which is this case may be access to medical care. Countries further from the equator generally tend to have higher access to healthcare for their populations. Hence, the 'true' impact of the risk factor on the outcome can only be assessed by 'breaking the link' from the confounder to the risk factor. BNs enable us to do this and hence simulate a controlled trial using only the existing observational data

Another common error in empirical risk studies arises from Berkson's Paradox, in which a vacuous or incorrect 'causal' relationship is inferred as a result of a biased dataset as shown in the BN structure of Figure 3. Graphical explanation of Simpson's Paradox and Berkson's Paradox [129]. Because of under- or over-sampling of subjects with a certain characteristic, the chance of developing a given disease is distorted. An example that relates to MS is the relationship of childhood obesity on later developing MS. An oversampling of patients who are not obese distorts evidence that obesity affects MS. The sample bias in the BN is explicitly modelled through the introduction of the Collider node. The biased results (which are the ones normally reported) are the results one would obtain by setting the 'Collider' variable to be 'true'. Once this constraint is removed the BN model is able to provide the true unbiased results.

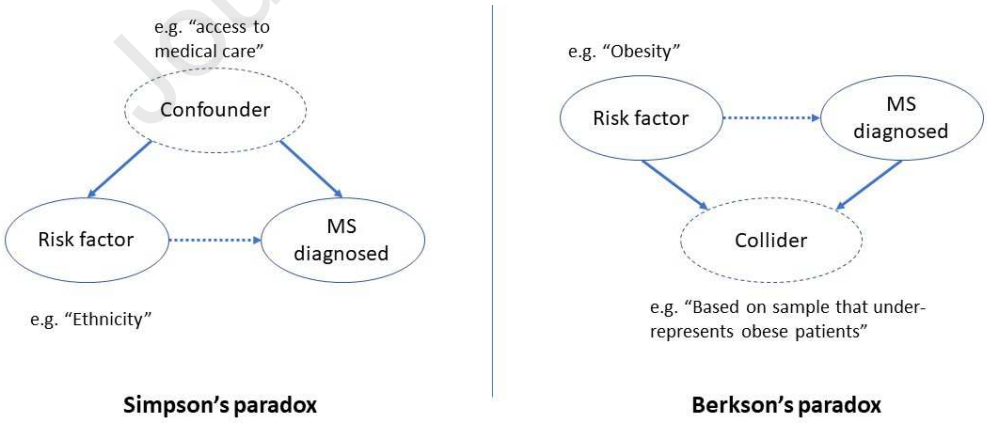

Figure 3. Graphical explanation of Simpson's Paradox and Berkson's Paradox

In practice, both confounding variables and colliders may jointly impact the results. It is not just the existence of potential confounding variables and colliders that can compromise the simple 'odds ratio' measure of risk factors. Figure 4 shows an example cause-effect situation, where a chain reaction of risk factors R_1, R_2, R_3, R_4 contribute to the development of MS. In general, the odds ratio cannot properly measure the impact of an individual risk factor when there are multiple causes and effects, or chain-type effects that have dependencies or other interacting variables. It assumes a

single explanation for the disease, namely, the exposure to a specific risk factor. This measure, however, is inappropriate in medical studies where it is impossible to control for all confounding factors. Odds ratios are particularly flawed in the case of MS, since it is agreed that MS does not have a single cause, and it is impossible to control for the huge combination of environmental and genetic factors that contribute to overall disease risk. To correctly model the effect of all the risk factors and their interactions on the development of MS, one must compute the joint probability distribution:

$$P(MS|R_1, R_2, R_3, R_4) = P(MS|R_2, R_4)P(R_2|R_1, R_3)P(R_4|R_3)P(R_1)P(R_3)$$

However, the odds ratio can only provide the individual and independent effects, namely:

$$P(MS|R_1), P(MS|R_2), P(MS|R_3), P(MS|R_4)$$

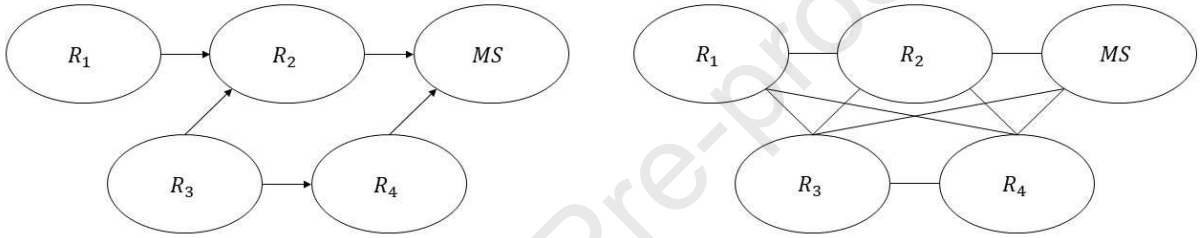

Figure 4. Bayesian structure that represents causal direction between variables compared to B) an odds ratio association structure

Multiple logistic regression, which is an extension of odds ratio, allows for more than one independent variable, but this also assumes independence between the variables, which may not always be the case. It also assumes a linear relationship between the independent and measured variable. Figure 5A shows this structure that contains only independent variables. Similarly, Naïve Bayes (Figure 5B) achieves reasonable accuracy by classifying an outcome given certain features. Due to the need for directionality and interdependence between involved variables, a new approach must be constructed to assess the relevant factors in MS development.

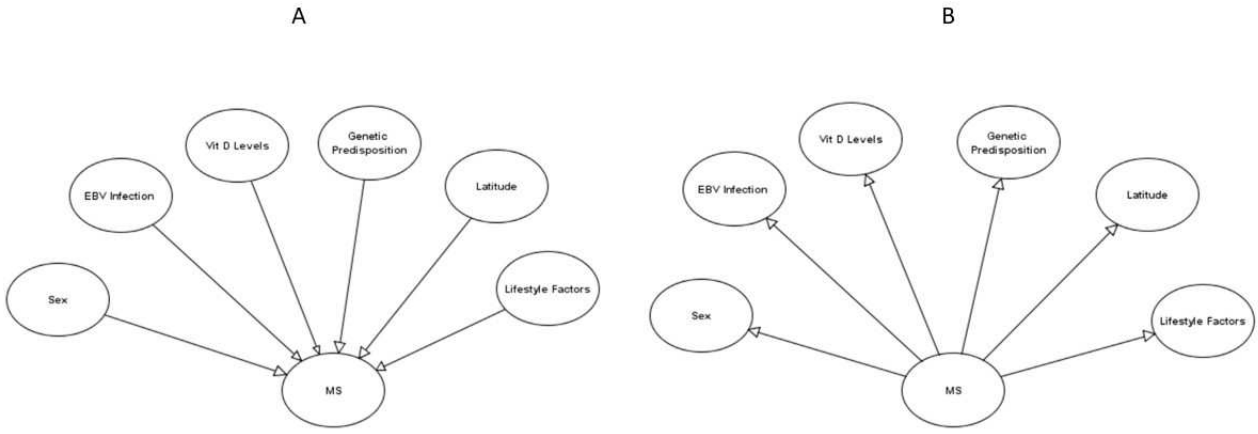

Figure 5. A) Regression model and B) Naive Bayes model

In the case of multiple sclerosis, causality is important. Based on MS literature, the initial risk of developing MS is genetic, followed by exacerbation by environmental effects on the physiology. Any appropriate model would show this effect. A researcher could choose to control for certain factors first, such as genetic markers and then test for certain environmental incidence. However, this causes information to be lost and reduces the number of subjects that can be included, especially when adding more categories of environmental exposures. The relative rarity of MS would reduce the number of test subjects further, which would have a more pronounced effect. Instead, these causal explanations should be modeled through expert domain knowledge and then probability distributions calculated. Using the Bayesian network, we are able to model these interventions and provide explanations for observed data.

Once simple causal interactions are modeled, a larger model that includes multiple dependencies in the case of MS can be created. Figure 6 shows a potential simplified causal structure for the explanation of increased MS prevalence in some areas, which can be explained by various forces. The arrows that connect factors such as EBV infection, vitamin D levels, and genetic predisposition to MS Prevalence node represent the causal link that most researchers believe exists. The strength of the arrow links is determined by conditional probabilities learned from data and/or expert knowledge, as explained in Section 3.3. The intermediary links between MS Prevalence and Latitude nodes shows how there can often be other explanations for observed phenomenon such as the increased number of cases in countries further away from the equator. A critical benefit of the model compared to alternative statistical approaches is that it explicitly distinguishes between “MS Prevalence” (which is not always directly observed or observable) and “Reported MS Prevalence,” since some factors might cause a reported value to differ from the true (but unobserved) value. As observations are added to the Bayesian network, updated probabilities on the most likely factor for increased prevalence in an area are calculated by a Bayesian inference algorithm. Widely available tools enable easy construction of BN models and automatically run the inference algorithm as observations are entered. Here we use the AgenaRisk tool [130].

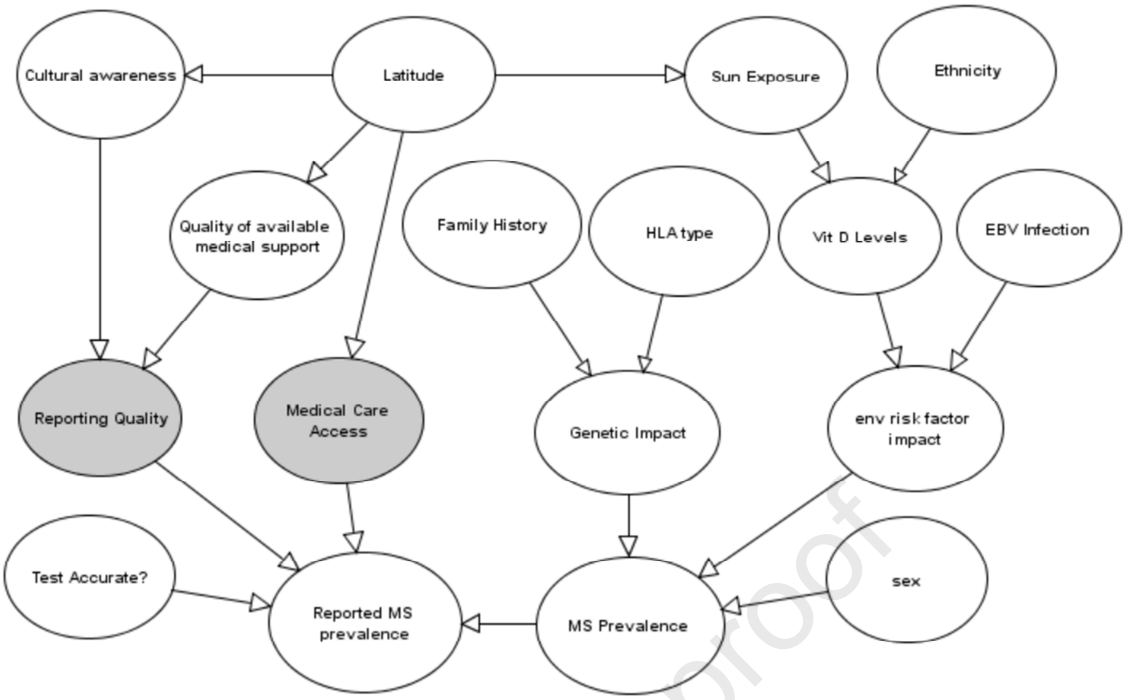

Figure 6. Bayesian network with causal explanations for MS prevalence

For example, let us imagine the scenario of an area, such as in Sardinia, which has high sun exposure, low latitude, but high prevalence of MS, as shown in Figure 7. This ***should*** reflect a low-risk area in the latitude gradient view of MS risk [131]. Due to the relatively high sun exposure in this population, it is less likely that an environmental risk is present. However, other environmental influences could still contribute, which can be reflected in the model. With these observations entered, the updated explanation for the high rates of MS is most likely due to a genetic predisposition in the population, which is consistent with current hypotheses about this effect.

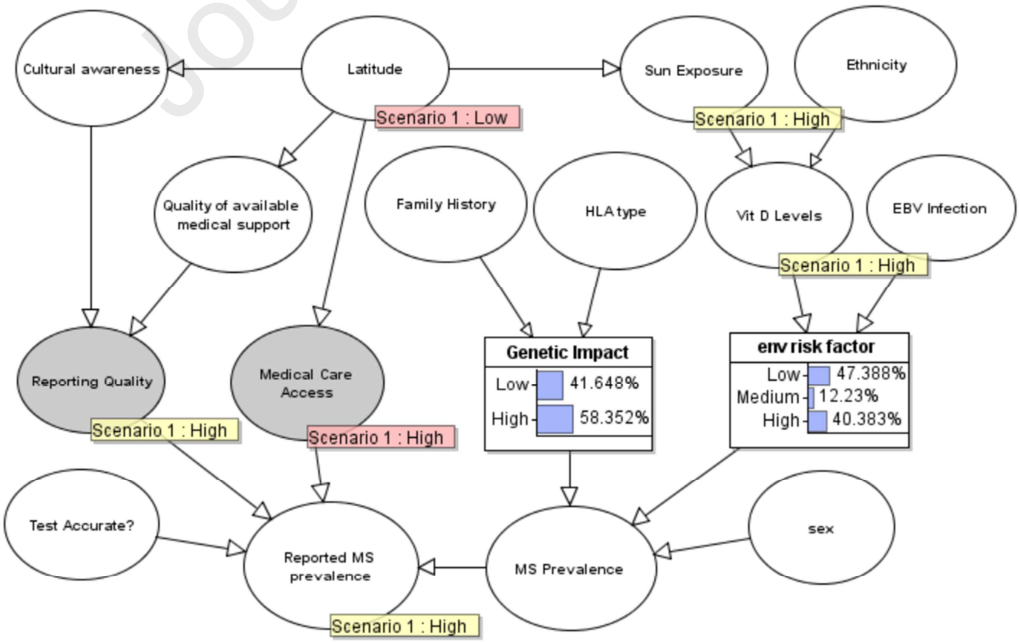

Figure 7. BN updated to show reasoning for high prevalence in a sunny, lower latitude location

To show a potential confounding effect on MS prevalence, we can observe how changing the variable “Reporting quality” can alter the true MS prevalence in an area. When observing that the reporting quality is high, the model predicts that the true MS prevalence can be generally trusted, with a small chance of error. When low quality reporting is included in the model instead, a greater discrepancy in reported MS versus true MS prevalence is observed. From this model (Figure 8), it is also clear that the dependency between latitude and reporting quality affects the results. By looking at the “Latitude” node, it is slightly more likely that the higher prevalence came from a Northern country.

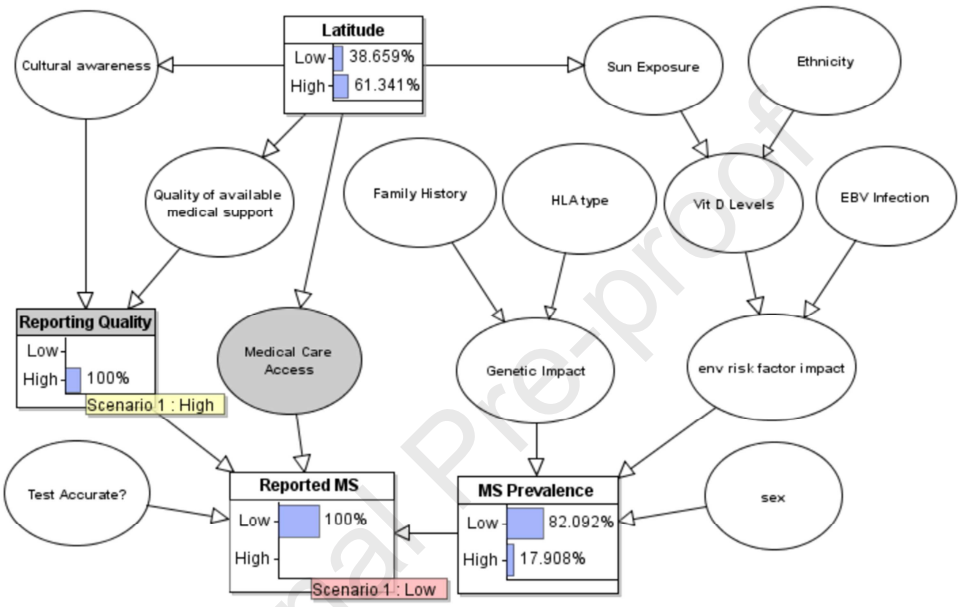

Figure 8. BN reflecting high reporting quality and resulting MS prevalence

The variability of factors over time can also be modeled in a Bayesian network. Gray nodes represent factors that have changed over time, such as increased quality of medical care or reporting, which would affect the number of MS cases reported in an area. This model could also be extended to include possible interventions that could alter the course of MS development, such as certain changes in lifestyle, like smoking cessation, or disease-altering medications. The proposed structure can also be modified to show the inclusion of factors that have yet to be determined, such as other lifestyle choices that affect MS triggering. The model presented in this section is available for download at http://www.eecs.qmul.ac.uk/~norman/Models/MS_prevalence and can be run in the free trial version of AgenaRisk (agenarisk.com).

Conclusions

The use of complex neural networks to help discoveri minute differences in MRI scans and predict the subtype or progression of MS is a promising start to AI usage in MS. But much more research is needed in risk assessment and decision making. There is great uncertainty about what the actual risk factors and causes of MS are , which is why there should be greater general interest in using AI/ML techniques to identify and understand these.. We have argued that Bayesian networks are a suitable (but as yet underused) AI technique to address this challenge. BNs can combine data and knowledge to provide causal explanations for epidemiological data. Using observational data alone, BNs enable

us to avoid the statistical errors arising from confounding variables and biased samples; they also enable us to simulate medical (or other) interventions and address counterfactual questions. Future work is needed in developing these models, especially for risk factors that have varying degrees of exposure, such as smoking or vitamin D levels.

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Appendix A: Sources Included in Literature Review

Title	Authors	Classification	Year
Fuzzy rule based expert system for diagnosis of multiple sclerosis	Ghahazi	Decision Support	2014
A Network Analysis of the Human T-Cell Activation Gene Network Identifies Jagged1 as a Therapeutic Target for Autoimmune Diseases	Ricardo Palacios, Joaquin Goni et al	Immunological Signatures	2007
Statistical classifiers for diagnosing disease from immune repertoires: a case study using multiple sclerosis	Jared Ostmeyer, Scott Christley et al	Immunological Signatures	2017
GM-CSF and CXCR4 define a T helper cell signature in multiple sclerosis	Edoardo Galli, Felix J. Hartmann et al	Immunological Signatures	2019
Machine learning approach identifies new pathways associated with demyelination in a viral model of multiple sclerosis	Reiner Ulrich, Arno Kalkuhl et al	Immunological Signatures	2010
An unsupervised machine learning method for discovering patient clusters based on genetic signatures	Christian Lopez	Immunological Signatures	2018
Disability in multiple sclerosis is associated with age and inflammatory, metabolic and oxidative/nitrosative stress biomarkers: results of multivariate and machine learning procedures	Tamires Flauzino, Andrea Name Colado Simão	Immunological Signatures	2019
Genetic model of MS severity predicts future accumulation of disability	Kayla C Jackson, Katherine Sun	Immunological Signatures	2020
Classification of radiologically isolated syndrome and clinically isolated syndrome with machine-learning techniques	Mato-Abad et al	Lesion Detection	2019
Temporally Consistent Probabilistic Detection of New Multiple Sclerosis Lesions in Brain MRI	Elliott, Colm et al	Lesion Detection	2013
Machine learning based compartment models with permeability for white matter microstructure imaging	Nedjati-Gilani, Gemma L et al	Lesion Detection	2017
Automated detection of white matter and cortical lesions in early stages of multiple sclerosis	Mário João Fartaria et al	Lesion Detection	2016
Validation of White-Matter Lesion Change Detection Methods on a Novel Publicly Available MRI Image Database	Lesjak, Žiga; Pernuš, Franjo et al	Lesion Detection	2016

A flexible mixed-effect negative binomial regression model for detecting unusual increases in MRI lesion counts in individual multiple sclerosis patients	Yumi Kondo, Yinshan Zhao, John Petkau	Lesion Detection	2015
Classification of multiple sclerosis lesions using adaptive dictionary learning	Deshpande, Hrishikesh; Maurel, Pierre; Barillot, Christian	Lesion Detection	2015
Multivariate prediction of multiple sclerosis using robust quantitative MR-based image metrics	Heiko Neeb, Jochen Schenk	Lesion Detection	2019
Bayesian inferences for beta semiparametric-mixed models to analyze longitudinal neuroimaging data	Xiao-Feng Wang, Yingxing Li	Lesion Detection	2014
Comparison of machine learning methods for stationary wavelet entropy-based multiple sclerosis detection: decision tree, k-nearest neighbors, and support vector machine	Yudong Zhang et al	Lesion Detection	2016
Multiple Sclerosis Detection Based on Biorthogonal Wavelet Transform, RBF Kernel Principal Component Analysis, and Logistic Regression	Shui-Hua Wang, Tian-Ming Zhan	Lesion Detection	2016
Multiple Sclerosis Identification Based on Fractional Fourier Entropy and a Modified Jaya Algorithm	Shui-Hua Wang, Hong Cheng	Lesion Detection	2018
Uncovering convolutional neural network decisions for diagnosing multiple sclerosis on conventional MRI using layer-wise relevance propagation	Fabian Eitel, Emily Soehler	Lesion Detection	2019
A supervised framework with intensity subtraction and deformation field features for the detection of new T2-w lesions in multiple sclerosis	Mostafa Salem, Mariano Cabezas	Lesion Detection	2018
CVSnet: A machine learning approach for automated central vein sign assessment in multiple sclerosis	Pietro Maggi, Mário João Fartaria	Lesion Detection	2020
Bayesian MS Lesion Classification Modeling Regional and Local Spatial Information	R Harmouche, L Collins, D Arnold	Lesion Detection	2006
A Multimodal Dense U-Net For Accelerating Multiple Sclerosis MRI	Antonio Falvo, Danilo Comminiello	Lesion Detection	2019
Classification of multiple sclerosis and non-specific white matter lesions using spherical harmonics descriptors	Yeqi Wang, Madison Hansen	Lesion Detection	2018
Adaptive weighted fusion of multiple MR	F Forbes, S	Lesion	2010

sequences for brain lesion segmentation	Doyle	Detection	
An ontology-based fuzzy decision support system for multiple sclerosis	Esposito	Lesion Detection	2011
Deep 3D Convolutional Encoder Networks With Shortcuts for Multiscale Feature Integration Applied to Multiple Sclerosis Lesion Segmentation	Brosch, Tom et al	Lesion Segmentation	2016
A toolbox for multiple sclerosis lesion segmentation	Eloy Roura et al	Lesion Segmentation	20115
Accurate, rapid and reliable, fully automated MRI brainstem segmentation for application in multiple sclerosis and neurodegenerative diseases	Laura Sander, Simon Pezold et al	Lesion Segmentation	2019
Bayesian Model Selection for Pathological Neuroimaging Data Applied to White Matter Lesion Segmentation	Carole H Sudre et al	Lesion Segmentation	2015
Transfer Learning Improves Supervised Image Segmentation Across Imaging Protocols	Annegreet van Opbroek	Lesion Segmentation	2015
Bayesian Generative Models for Knowledge Transfer in MRI Semantic Segmentation Problems	Anna Kuzina	Lesion Segmentation	2019
Subject-Specific Sparse Dictionary Learning for Atlas-Based Brain MRI Segmentation	Snehashis Roy	Lesion Segmentation	2015
A Comparison of Supervised Machine Learning Algorithms and Feature Vectors for MS Lesion Segmentation Using Multimodal Structural MRI	Elizabeth M Sweeney, Joshua T Vogelstein	Lesion Segmentation	2014
Population intensity outliers or a new model for brain WM abnormalities	X Tomas-Fernandez	Lesion Segmentation	2012
Interactive Lesion Segmentation with Shape Priors From Offline and Online Learning	Tony Shepherd, Simon J D Prince, Daniel C Alexander	Lesion Segmentation	2012
Machine-Learned Data Structures of Lipid Marker Serum Concentrations in Multiple Sclerosis Patients Differ from Those in Healthy Subjects	Jörn Lötsch, Michael Thrun et al	Lipid Markers	2017

Smooth Scalar-on-Image Regression via Spatial Bayesian Variable Selection	Jeff Goldsmith, Lei Huang, Ciprian M. Crainiceanu	Physical Disability	2014
Combined structural and functional patterns discriminating upper limb motor disability in multiple sclerosis using multivariate approaches	Jidan Zhong, David Qiziang Chen et al	Physical Disability	2017
Immunomodulatory therapies delay disease progression in multiple sclerosis	Roberto Bergamaschi, Silvana Quaglini	Physical Disability	2016
Exploration of machine learning techniques in predicting multiple sclerosis disease course	Yijun Zhao, Brian C Healy et al	Physical Disability	2017
A Bayesian hierarchical surrogate outcome model for multiple sclerosis	Luca Pozzi, Heinz Schmidli, David I. Ohlssen	Physical Disability	2016
Computer Aided Diagnosis System for multiple sclerosis disease based on phase to amplitude coupling in covert visual attention	Ahmadi, Amirmasoud; Davoudi, Saeideh; Daliri, Mohammad Reza	Physical Disability	2019
A machine learning approach for gait speed estimation using skin-mounted wearable sensors: From healthy controls to individuals with multiple sclerosis	Ryan S. McGinnis, Nikhil Mahadevan	Physical Disability	2017
Swept source optical coherence tomography to early detect multiple sclerosis disease. The use of machine learning techniques	Amaya Pérez del Palomar et al	Physical Disability	2019
A computer-aided diagnosis of multiple sclerosis based on mfVEP recordings	Luis de Santiago et al	Physical Disability	2019
Neural networks to identify multiple sclerosis with optical coherence tomography	Elena Garcia-Martin, Luis E. Pablo, Raquel Herrero	Physical Disability	2013
Modified connectivity of vulnerable brain nodes in multiple sclerosis, their impact on cognition and their discriminative value	Elisabeth Solana	Physical Disability	2019
Longitudinal penalized functional regression for cognitive outcomes on neuronal tract measurements	Jeff Goldsmith, Ciprian M Crainiceanu, Brian Caffo	Physical Disability	2012

Data-Driven Machine-Learning Quantifies Differences in the Voiding Initiation Network in Neurogenic Voiding Dysfunction in Women With Multiple Sclerosis	Christof Karmonik	Physical Disability	2019
Machine learning in secondary progressive multiple sclerosis: an improved predictive model for short-term disability progression	Marco TK Law, Anthony L Traboulsee	Physical Disability	2019
Machine Learning EEG to Predict Cognitive Functioning and Processing Speed Over a 2-Year Period in Multiple Sclerosis Patients and Controls	Hanni Kiiski, Lee Jollans	Physical Disability	2018
Model for Prediction of Progression in Multiple Sclerosis	Cristina Pruenza, María Teresa Solano	Physical Disability	2019
Machine learning analysis of motor evoked potential time series to predict disability progression in multiple sclerosis	Jan Yperman, Thijs Becker	Physical Disability	2020
An expert system for the evaluation of EDSS in multiple sclerosis	Gaspari, Roveda et al	Physical Disability	2002
Evaluation of machine learning algorithms performance for the prediction of early multiple sclerosis from resting-state FMRI connectivity data	Sacca, Valeria et al	Prognosis	2019
Characterization of relapsing-remitting multiple sclerosis patients using support vector machine classifications of functional and diffusion MRI data	Mariana Zurita et al	Prognosis	2018
The Differential Diagnosis of Multiple Sclerosis Using Convex Combination of Infinite Kernels	Yeliz Karaca, Yu-Dong Zhang et al	Prognosis	2017
Predicting conversion from clinically isolated syndrome to multiple sclerosis–An imaging-based machine learning approach	Haike Zhang, Esther Alberts et al	Prognosis	2019
Deep learning of joint myelin and T1w MRI features in normal-appearing brain tissue to distinguish between multiple sclerosis patients and healthy controls	Youngjin Yoo, Lisa YW Tang, Tom Brosch et al	Prognosis	2018
Predictive Value of Imaging Markers at Multiple Sclerosis Disease Onset Based on Gadolinium- and USPIO-Enhanced MRI and Machine Learning	Alessandro Crimi et al	Prognosis	2014

Collaboration between a human group and artificial intelligence can improve prediction of multiple sclerosis course: a proof-of-principle study	Andrea Tacchella et al	Prognosis	2017
Continuous reorganization of cortical information flow in multiple sclerosis: A longitudinal fMRI effective connectivity study	Vinzenz Fleischer et al	Prognosis	2020
SVM recursive feature elimination analyses of structural brain MRI predicts near-term relapses in patients with clinically isolated syndromes suggestive of multiple sclerosis	Viktor Wottschel	Prognosis	2019
Cross-Sectional and Longitudinal MRI Brain Scans Reveal Accelerated Brain Aging in Multiple Sclerosis	Einar A. Høgestøl	Prognosis	2019
Semi-supervised approaches to efficient evaluation of model prediction performance	Jessica L Gronsbell, Tianxi Cai	Prognosis	2018
Joint assessment of dependent discrete disease state processes	David Engler, Tanuja Chitnis, Brian Healy	Relapse Prediction	2017
Fall Risk Prediction in Multiple Sclerosis Using Postural Sway Measures: A Machine Learning Approach	Ruopeng Sun	Relapse Prediction	2019
Considering patient clinical history impacts performance of machine learning models in predicting course of multiple sclerosis	Ruggiero Seccia, Daniele Gammelli	Relapse Prediction	2020
Usefulness of Bayesian graphical models for early prediction of disease progression in multiple sclerosis	R Bergamaschi et al	Relapse Prediction	2000
Incorporating machine learning approaches to assess putative environmental risk factors for multiple sclerosis	Ellen M Mowry, Anna K Hedstrom	Risk Factors	2018
DeepWAS: Multivariate genotype-phenotype associations by directly integrating regulatory information using deep learning	Janine Arloth, Gökcen Eraslan	SNPs	2020
Graph Theory-Based Brain Connectivity for Automatic Classification of Multiple Sclerosis Clinical Courses	Gabriel Kocevar, Claudio Stamile	Subcategory Classification	2016

Computational Intelligence Technique for Prediction of Multiple Sclerosis Based on Serum Cytokines	Mehendi Goyal, Divya Khanna	Subcategory Classification	2019
Machine Learning Approach for Classifying Multiple Sclerosis Courses by Combining Clinical Data with Lesion Loads and Magnetic Resonance Metabolic Features	Adrian Ion-Mărgineanu, Gabriel Kocevar, Claudio Stamile	Subcategory Classification	2017
Using Multidimensional Bayesian Network Classifiers to Assist the Treatment of Multiple Sclerosis	Juan Diego Rodriguez, Aritz Perez, David Arteta	Subcategory Classification	2012
A machine learning pipeline for multiple sclerosis course detection from clinical scales and patient reported outcomes	Samuele Fiorini, Alessandro Verri	Subcategory Classification	2015
The hidden information in patient-reported outcomes and clinician-assessed outcomes: multiple sclerosis as a proof of concept of a machine learning approach	Giampaolo Brichetto	Subcategory Classification	2020
Early recognition of multiple sclerosis using natural language processing of the electronic health record	Chase, Mitrani, Lu, Fulgieri	Subcategory Classification	2017
A pharmacogenetic signature of high response to Copaxone in late-phase clinical-trial cohorts of multiple sclerosis	Colin J. Ross, Fadi Towfic et al	Treatment Effects	2017
Identification of CD4+ T cell biomarkers for predicting the response of patients with relapsing-remitting multiple sclerosis to natalizumab treatment	Paolo Fagone et al	Treatment Effects	2019
Cost-utility of First-line Disease-modifying Treatments for Relapsing-Remitting Multiple Sclerosis	Erkki Soini et al	Treatment Effects	2017
Is the risk of progressive multifocal leukoencephalopathy the real reason for natalizumab discontinuation in patients with multiple sclerosis?	Julia Krämer et al	Treatment Effects	2017
Patient-specific early classification of multivariate observations	Mohamed F Ghalwash et al	Treatment Effects	2015
Identification of Monotonically Differentially Expressed Genes for IFN-β-Treated Multiple Sclerosis Patients	Suyan Tian, Lei Zhang	Treatment Effects	2019

A Bayesian approach to probabilistic sensitivity analysis in structured benefit-risk assessment	Ed Waddingham, Shahrul Mt-Isa	Treatment Effects	2016
A Bayesian adaptive dose selection procedure with an overdispersed count endpoint	L Pozzi, H Schmidli, M Gasparini, A Racine-Poon	Treatment Effects	2013
A fast multivariate feature-selection/classification approach for prediction of therapy response in multiple sclerosis	S Mostafavi, S Baranzini	Treatment Effects	2006

Highlights

- Review of relevant and recently published artificial intelligence/machine learning methods applied to Multiple Sclerosis (MS) research
- Proposes Bayesian network approach of assessing risk factors for MS, which can address deficiencies in current epidemiological methods

Norman Fenton is a director of Agena Ltd.

Morghan Hartmann and Ruth Dobson have no conflicts of interest to declare.