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Sclérose en plaques et emploi

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La sclérose en plaques est une maladie du jeune adulte, le plus souvent diagnostiquée entre 25 et 35 ans) avec une prépondérance féminine (3/4 de femme). Elle touche aujourd'hui 100 000 personnes en France, dont 700 enfants. Deux mille cinq cents nouveaux cas sont diagnostiqués chaque année. La SEP représente la première cause de handicap sévère non traumatique du jeune adulte. Elle affecte donc des adultes jeunes en pleine période de projet d'existence et bouleverse la vie personnelle, familiale et professionnelle. C'est une maladie auto-immune du système nerveux central (le cerveau et la moelle épinière). Le système de défense (système immunitaire), habituellement impliqué dans la lutte contre les virus et les bactéries, s'emballe et attaque la myéline, gaine protectrice des fibres nerveuses qui joue un rôle important dans la propagation de l'influx nerveux du cerveau aux différentes parties du corps. Les signes observés au début de la maladie varient selon l'emplacement des lésions dans le cerveau ou dans la moelle épinière : troubles moteurs, fourmillements, troubles de l'équilibre, troubles visuels ou urinaires… Ils sont souvent transitoires.
Dans 85% des cas, la sclérose en plaques débute par une forme à poussées. L'évolution et l'expression de la maladie sont extrêmement imprévisibles. Depuis 15 ans de nombreux progrès ont été réalisés dans la connaissance et la prise en charge de la SEP. De nouveaux traitements permettent aujourd'hui de ralentir l'évolution de la maladie grâce à une recherche active en France, et, en parallèle les professionnels de santé ont pris conscience qu'il était essentiel d'accompagner les malades dans leur vie quotidienne, prenant en charge leurs symptômes et en les aidant sur le plan social. Des consultations multidisciplinaires, une organisation en réseaux et un accès au soin individualisé à proximité du domicile sont aujourd'hui proposés aux malades.

Après un aperçu sur les aspects épidémiologiques et économiques de la maladie, l'objectif de cette bibliographie est de recenser de la littérature scientifique sur l'impact de la sclérose en plaques sur l'emploi et la situation professionnelle des patients qui souffrent de cette pathologie, pour la période allant de 2009 à mai 2020 avec quelques publications clefs antérieures à ces dates. Le périmètre géographique retenu concerne la France et les pays de l'OCDE.

Les recherches bibliographiques ont été réalisées sur les bases et les portails suivants : Medline, Science direct, Econlit, Banque de données en santé publque (BDSP) et et Cairn. Cette bibliographie ne prétend pas à l'exhaustivité. Les références sont classées par ordre alphabétique d'auteurs et de titres.

Stratégies de recherche

("multiple sclerosis"[MeSH Terms]) OR "multiple sclerosis"[Title/Abstract])

("labor market outcomes"[Title/Abstract]) OR "labor market participation"[Title/Abstract]) OR "absenteism"[Title/Abstract]) OR "sick leave"[Title/Abstract]) OR "sickness absence"[Title/Abstract]) OR "sick leave"[MeSH Terms]) OR "sick leave"[Title/Abstract]) OR "labor productivity"[Title/Abstract]) OR "labor productivity losses"[Title/Abstract]) OR "health productivity"[Title/Abstract]) OR "employment"[MeSH Terms]) OR "employment"[Title/Abstract]) OR "return to work"[MeSH Terms]) OR "return to work"[Title/Abstract]) OR "professional career"[Title/Abstract])

("prevalence"[Title]) OR (incidence[Title])) OR ((epidemiology[Title]) OR (multiple sclerosis /epidemiology"[MeSH Terms])

("cost of illness"[MeSH Terms]) or ("cost of illness"[Title])) OR ("economics"[Title])) OR ("economics"[MeSH Terms])

Sommaire

Aspects épidémiologiques et économiques

ÉTUDES FRANÇAISES

Blein, C., Chamoux, C., Reynaud, D., et al. (2018). "Diversité des prises en charge des patients atteints de sclérose en plaques entre régions françaises." Revue d'Épidémiologie et de Santé Publique **66**(6): 385-394.
http://www.sciencedirect.com/science/article/pii/S0398762018313440

> L'objectif de l'étude est d'observer et de comparer les prises en charge hospitalières sur l'année 2015 des patients pris en charge pour leur sclérose en plaques entre trois anciennes régions françaises de caractéristiques différentes en termes de prévalence, de nombre de centres de ressources et de compétences et de taille de la région. Méthodes L'ensemble des séjours hospitaliers de la base PMSI MCO 2015 présentant au moins un diagnostic principal ou relié (DP-DR) en G35* « sclérose en plaques » ont été extraits afin de recueillir l'ensemble des hospitalisations dont le motif de prise en charge est la sclérose en plaques. Nous avons également extrait les traitements de chimiothérapie administrés à l'hôpital via la recherche des séjours avec un diagnostic associé significatif (DAS) en G35* « sclérose en plaques » lorsque le DP ou le DR était codé en Z512 « chimiothérapie non tumorale ». Les régions analysées correspondent à celles de 2015, dont certaines ont fusionné depuis. Résultats On dénombre 95 359 séjours hospitaliers MCO de SEP au niveau national sur l'année 2015 pour une cohorte de 21 102 patients et un coût total de 54,1 M€ pour l'Assurance maladie. La prise en charge est principalement ambulatoire avec 88,5 % des séjours. La région Rhône-Alpes représente 7,6 % des séjours de SEP au niveau national, 9,6 % des patients, 14 % des journées en hospitalisation complète (HC) et 10,4 % du coût national ; 58,4 % des séjours ont lieu dans les deux principaux centres hospitaliers prenant en charge la SEP. La région Nord-Pas-de-Calais représente 9,8 % des séjours, 10 % des patients, 6,6 % des journées en HC et 9,1 % du coût national ; 29,8 % des séjours ont lieu dans le principal centre hospitalier prenant en charge la SEP. La région Centre représente 2,7 % des séjours, 2,8 % des patients, 3,1 % des journées en HC et 2,8 % du coût national ; 28,4 % des séjours ont lieu dans le principal centre hospitalier prenant en charge la SEP. Conclusion L'étude souligne la diversité des modèles de prise en charge hospitalière des patients SEP entre ces trois régions.

Bruno, D., Marc, D., Ouarda, P., et al. (2019). "Economic burden of multiple sclerosis in France estimated from a regional medical registry and national sick fund claims." Mult Scler Relat Disord **36**: 101396.

> BACKGROUND: Estimating direct healthcare costs of patients with multiple sclerosis (MS) and identifying risk factors of high costs including relapse are important drivers of public health decision making in France. METHODS: This is a longitudinal retrospective study based on patient charts (qualified registry of MS in Lorraine (ReLSEP)) and claims data (from the main compulsory health insurance and national hospital database estimated monthly. All patients with MS not deceased or lost to follow-up reported in the registry in 2013-2014 were included. Outpatient costs were those paid to the healthcare provider and inpatient costs were those related to national cost estimates. Mean total costs per patient by disease severity were estimated monthly, accounting for MS evolution over the study period. Costs of MS relapse were estimated using a general linear model. RESULTS: A total of 4373 patients were identified in the ReLSEP registry, and 2166 of these patients were included in the study. Among those, outpatient claims were available for 1366 and 627 were hospitalized at least once. The average annual direct costs for patients with MS were estimated to be €12,296 in 2014. Furthermore, ambulatory costs represented 87.8% out of those costs and were mainly

> driven by medications (60.6%) and paramedic visits (11.2%). Monthly direct costs were higher in patients with severe disease (€1249 for EDSS 7-9) compared to those with mild or moderate disease (€992 for EDSS 0-3; €953 for EDSS 4-6) (p < 0,006). Interestingly, drug costs were higher in patients with mild disease, whereas costs related to paramedical care, medical devices, and transportation were higher in those with severe MS. The unit cost of relapse was estimated between €1681 and €2193. CONCLUSIONS: Costs were mainly driven by medications and highly related to disease severity. Relapse cost was the main contributor to total cost.

Debouverie, M., Rumbach, L. et Clavelou, P. (2007). "Données épidémiologiques et analyse de‘l'offre de soins de la sclérose en plaques en France." Rev Neurol (Paris) **163**(6): 637-645.
http://www.sciencedirect.com/science/article/pii/S0035378707904725

> Plusieurs études d'incidence et de prévalence de la sclérose en plaques ont été conduites ces dernières années tant au niveau national (Assurance maladie) qu'au niveau régional. Le taux de prévalence est évalué de 65 à 125 pour 100 000 habitants avec un gradient progressif du Sud-ouest vers le Nord-est. Le taux annuel d'incidence standardisé prenant en compte les intervalles de confiance est compris, selon les régions, entre 4,1 et 8,2/100 000 habitants. Comme dans d'autres pays européens, une augmentation de l'incidence est constatée chez les femmes. Chez les hommes, cette augmentation n'a pas été observée. L'augmentation de l'incidence de la sclérose en plaques ne semble pas liée à un meilleur taux de diagnostic des formes bénignes. L'origine géographique d'Afrique du Nord des patients apparaît constituer une variable prédictive majeure et indépendante d'évolution rapidement péjorative de la maladie. Les personnes atteintes de sclérose en plaques expriment le besoin d'une prise en charge professionnelle et individualisée, prenant en compte les diverses dimensions médicales et médico-sociales de leur maladie. Les organisations actuelles, cliniques, réseaux de santé, centres de réadaptation, lits en centres identifiés, doivent être pérennisées, voire intensifiés.

Defer, G. et Debouverie, M. (2019). La sclérose en plaques : historique, épidémiologie et pathogénie. Paris : elesevier –Masson

> En France, la sclérose en plaques (SEP) touche plus de 80 000 personnes et plus de 3 000 nouveaux cas sont diagnostiqués chaque année. C'est la plus commune des maladies neurologiques de l'adulte jeune. La plupart des cas concernent une population de 20 à 40 ans, majoritairement féminine. Les manifestations neurologiques de la maladie sont secondaires à une destruction progressive des gaines de myéline qui entourent les fibres nerveuses, et dont le rôle est d'assurer leur protection et la bonne transmission de l'influx nerveux, et ceci en raison d'un dysfonctionnement du système immunitaire. La sclérose en plaques se présente sous deux formes : la forme avec poussées qui est la plus fréquente et la forme progressive où le risque de handicap est plus élevé. Les conséquences de cette affection peuvent être importantes en termes physiques et psychologiques mais aussi de vie sociale, professionnelle et familiale. Cet ouvrage pratique et synthétique, richement illustré, aborde successivement l'historique, l'épidémiologie et l'histoire naturelle puis la pathogénie de cette maladie. Il en décrit l'évolution des concepts, l'épidémiologie, l'anatomopathologie et l'immunologie et ouvre des perspectives sur les nouveaux traitements et les capacités de remyélinisation. Cet ouvrage, rédigé par un collectif d'experts biologistes et médecins travaillant dans les centres spécialisés sur la SEP, est destiné aussi bien aux neurologues confirmés souhaitant mettre à jour leurs connaissances, qu'aux autres professionnels de santé impliqués dans la prise en charge des patients et bien sûr aux médecins et paramédicaux en formation qui voudraient mieux comprendre ce que représente la sclérose en plaques.

Foulon, S., Maura, G., Dalichampt, M., et al. (2017). "Prevalence and mortality of patients with multiple sclerosis in France in 2012: a study based on French health insurance data." J Neurol **264**(6): 1185-1192.

> Data on the prevalence of multiple sclerosis (MS) in France are scarce. National and regional updated estimates are needed to better plan health policies. In this nationwide study, we provided estimates of the prevalence of MS in France in 2012 and mortality rate in 2013. MS cases were identified in the French national health insurance database (SNIIRAM-PMSI) using reimbursement data for disease-modifying treatment, long-term disease status for MS, disability pension for MS, and hospitalisation for MS (MS ICD-10 code: G35). We identified 99,123 MS cases, corresponding to an overall crude prevalence rate of 151.2 per 100,000 inhabitants [95% confidence interval (CI) 150.3-152.2]: 210.0 per 100,000 in women (95% CI 208.4-211.5) and 88.7 per 100,000 in men (95% CI 87.6-89.7). The overall prevalence rate was 155.6 per 100,000 inhabitants (95% CI 154.7-156.6) after standardization on the 2013-European population. We observed a prevalence gradient with a higher prevalence (190-200 per 100,000) in North-Eastern France and a lower prevalence in Southern and Western France (126-140). The crude mortality rate in 2013 was 13.7 per 1,000 MS cases (11.4 in women and 20.3 in men). The standardized mortality ratio was 2.56 (95% CI 2.41-2.72). Our results revise upwards the estimation of MS prevalence in France and confirm the excess mortality of MS patients compared to the general population.

Foulon, S., Weill, A., Maura, G., et al. (2015). "Prévalence de la sclérose en plaques en France en 2012 et mortalité associée en 2013 à partir des données du Sniiram-PMSI." Revue d'Épidémiologie et de Santé Publique **63**: S17-S18.
http://www.sciencedirect.com/science/article/pii/S0398762015000383

> L'actualisation des données de prévalence de la sclérose en plaques (SEP) et de la mortalité associée à cette pathologie est nécessaire dans le cadre du Plan de lutte contre les maladies neurodégénératives et pour une meilleure planification de l'offre de soins, au niveau national et local. Méthodes À partir des données du Sniiram 2011–2012 et du PMSI 2008–2012, nous avons identifié les cas de SEP à l'aide des quatre critères suivants : affection de longue durée (ALD) pour SEP (code CIM10=G35), remboursement d'un traitement spécifique (interféron bêta, acétate de glatiramère, fingolimod, natalizumab), versement d'une pension d'invalidité pour SEP ou hospitalisation pour SEP (diagnostic principal, relié ou associé). Pour être considéré comme un cas prévalent au 31 décembre 2012, une personne devait présenter au moins un des ces quatre critères, être consommant en 2012 et être toujours vivant au 31 décembre 2012. Un ratio standardisé de mortalité (SMR) a été calculé sur l'année 2013 chez les patients ainsi identifiés et affiliés au régime général (standardisation sur l'âge et le sexe). Résultats Au total, 99 123 personnes ont été identifiées comme ayant une SEP ; 68,4 % des cas ont été identifiés par au moins deux critères de sélection. L'ALD pour SEP a permis l'identification de 83,3 % des cas, suivie par l'hospitalisation (69,6 %), le remboursement d'un traitement spécifique (40,1 %) et le versement d'une pension d'invalidité (16,3 %). Le sex-ratio était de 2,5 femmes pour un homme. L'âge moyen (ET) était de 50,3 (14,2) ans. La prévalence France entière était de 151,2 pour 100 000 habitants (210,0 chez les femmes et 88,7 chez les hommes). La prévalence de la maladie était plus élevée dans les régions du Nord-Est de la France par rapport aux régions du Sud-Ouest. Les personnes identifiées comme ayant une SEP présentaient un sur-risque de décès en 2013 par rapport à la population générale avec un SMR à 2,56 (IC 95 % 2,41–2,72). L'âge moyen (ET) au décès était de 66,6 (13,9) ans. Discussion/conclusion Les résultats de notre étude sont cohérents avec les données de la littérature mais réévaluent à la hausse le nombre de patients atteints de SEP en France.

Fromont, A., Binquet, C., Clerc, L., et al. (2009). "Épidémiologie de la sclérose en plaques : la particularité française." Rev Neurol (Paris) **165**(8): 671-675.
http://www.sciencedirect.com/science/article/pii/S0035378709002525

> La France est considérée comme une zone de moyen à fort risque de sclérose en plaques. Plusieurs études d’incidence et de prévalence ont été réalisées, surtout au niveau régional et parfois au niveau national. La prévalence est évaluée entre 143 et 60 pour 100 000 habitants, avec une prévalence plus importante au nord-est de la France. Les taux d’incidence varient entre 4,1 et 8,2 pour 100 000 habitants en fonction des régions. Dans certaines régions comme la Lorraine, l’incidence semble augmenter chez les femmes. In France, the risk of multiple sclerosis is considered medium to high risk. Several incidence and prevalence studies have been performed at regional and national levels. Prevalence is evaluated between 143 and 60 per 100 000 inhabitants. Prevalence of multiple sclerosis is higher in northeastern France. Incidence varies between 4.1 and 8.2 per 100 000 inhabitants depending on the region. In certain regions such as Lorraine, incidence among women seems to be on the rise.

Fromont, A., Binquet, C., Sauleau, E. A., et al. (2010). "Geographic variations of multiple sclerosis in France." Brain **133**(Pt 7): 1889-1899.

> France is located in an area with a medium to high prevalence of multiple sclerosis, where its epidemiology is not well known. We estimated the national and regional prevalence of multiple sclerosis in France on 31 October 2004 and the incidence between 31 October 2003 and 31 October 2004 based on data from the main French health insurance system: the Caisse Nationale d'Assurance Maladie des Travailleurs Salaries. The Caisse Nationale d'Assurance Maladie des Travailleurs Salaries insures 87% of the French population. We analysed geographic variations in the prevalence and incidence of multiple sclerosis in France using the Bayesian approach. On the 31 October 2004, 49 417 people were registered with multiple sclerosis out of the 52 359 912 insured with the Caisse Nationale d'Assurance Maladie des Travailleurs Salaries. Among these, 4497 were new multiple sclerosis cases declared between 31 October 2003 and 31 October 2004. After standardization for age, total multiple sclerosis prevalence in France was 94.7 per 100,000 (94.3-95.1); 130.5 (129.8-131.2) in females and 54.8 (54.4-55.3) in males. The national incidence of multiple sclerosis between 31 October 2003 and 31 October 2004 was 7.5 per 100,000 (7.3-7.6); 10.4 (10.2-10.6) in females and 4.2 (4.0-4.3) in males. The prevalence and incidence of multiple sclerosis were higher in North-Eastern France, but there was no obvious North-South gradient. This study is the first performed among a representative population of France (87%) using the same method throughout. The Bayesian approach, which takes into account spatial heterogeneity among geographical units and spatial autocorrelation, did not confirm the existence of a prevalence gradient but only a higher prevalence of multiple sclerosis in North-Eastern France and a lower prevalence of multiple sclerosis in the Paris area and on the Mediterranean coast.

Fromont, A., Lehanneur, M. N., Rollot, F., et al. (2014). "Coûts de la sclérose en plaques en France." Rev Neurol (Paris) **170**(6): 432-439.
http://www.sciencedirect.com/science/article/pii/S0035378714008030

> La sclérose en plaques (SEP) appartient aux affections de longue durée (ALD) pour lesquelles les patients sont pris en charge à 100 % pour leurs dépenses de santé par la Caisse nationale d’assurance maladie des travailleurs salariés (CNAMTS). La CNAMTS assure 87 % de la population française. Les objectifs de cette étude étaient d’évaluer les coûts médicaux

directs et indirects de la SEP parmi la population assurée par la CNAMTS en France en 2004. Les données comprenaient les différents coûts liés à la SEP en 2004. Nous avons calculé le coût global direct et indirect de la SEP, le coût direct et indirect par patient et les différents postes de dépenses. En 2004, 49 413 patients bénéficiaient d'une ALD pour SEP. Le coût direct de la SEP représentait 469 719 967 €. Le coût direct par patient et par an était de 9506 €. Les différents postes de dépenses comprenaient les traitements (44,5 %), les hospitalisations (27,9 %), les soins infirmiers (5,8 %), la kinésithérapie (5,7 %), les transports (4 %), la biologie (1,1 %) et les autres dépenses (1,5 %). Les coûts indirects étaient estimés à 116 millions d'euros en 2004. L'impact économique de la SEP en France est important comparable à celui du VIH.

Ha-Vinh, P., Nauleau, S., Clementz, M., et al. (2016). "Geographic variations of multiple sclerosis prevalence in France: The latitude gradient is not uniform depending on the socioeconomic status of the studied population." Mult Scler J Exp Transl Clin **2**: 2055217316631762.

BACKGROUND: In France, two studies analysed multiple sclerosis prevalence nationwide: one was carried out in farmers, and the other one in employees. A south-north gradient of prevalence was found solely in farmers. OBJECTIVE: In order to better describe the latitude gradient in France, which is not uniform depending on the studied population, we assessed whether a gradient exists in another population than farmers and employees: independent workers. The same methods of case ascertainment have been used. METHODS: Altogether 4,165,903 persons insured by the French health insurance scheme for independent workers were included. We searched the database for (a) long term disease status 'multiple sclerosis', (b) domicile, (c) gender and (d) age. RESULTS: A total of 4182 cases of multiple sclerosis were registered giving a prevalence of 100.39/100,000. Adjustment by age and sex and spatial smoothing with a Bayesian analysis showed a gradual increase of prevalence from the southwest to the northeast of France. Standardised morbidity ratio was correlated with latitude and longitude (p<0.0001; p = 0.0031; adjusted R(2)= 0.3038). CONCLUSION: A discrepancy of geographic distribution between farmers and independent workers on the one hand and employees on the other cannot be attributable to environment. Assuming that socioeconomic status by itself is not associated with multiple sclerosis risk, employees' geographic mobility at adulthood for professional reasons could have interfered with the gradient effect.

Ha-Vinh, P., Nauleau, S., Clementz, M., et al. (2019). "Health care services and disease modifying therapies use in community-based multiple sclerosis patients: Evolution from 2013 to 2015 and demographic characteristics." Presse Med **48**(1 Pt 1): e1-e19.

INTEREST OF THE WORK: Multiple sclerosis (MS) disease modifying therapies (DMT) utilization increased during the last decade with the approval of new drugs. Symptomatic treatments also play an important role. Describing time trends and demographic characteristics for DMT and symptomatic treatments utilization in population-based MS patients will lead to a better knowledge of the resources distribution. METHODS: Repeated cross-sectional analysis on each calendar year were implemented retrospectively on the health insurance claims database in France from 2013 until 2015 regarding DMT, fampridine, fluoxetine, psychiatrist office visits, and Physical therapy sessions to calculate an utilization rate defined as the number of MS patients (whenever the date of diagnosis) who filled at least 1 prescription or service within the studied calendar year per cent MS patients covered the same calendar year (number of users per cent MS population per annum). Beneficiaries with MS were identified by their exemption of co-payment for long-term disease (ALD). RESULTS: DMT utilization rate increased from 34.22% in 2013 to 38.73% in 2015. The increase was due to recently developed DMT as first-generation DMT utilization rate decreased from 30.20% to 20.06%. Rates were not different between genders but significantly decreased with age. The average age of users was significantly lower for DMT than for symptomatic treatments (recently developed DMT: 43.63, first-generation DMT: 45.84, psychiatrist office visits: 49.08, Fampyra(®): 55.41, Physical therapy sessions: 55.88, fluoxetine: 58.26). Regional DMT utilization rates ranged from 31.68% in Auvergne-Rhône-Alpes to 42.58% in Normandie. They were not correlated to regional rates of MS prevalence (R-Square=0.0558; P=0.2556) nor to the presence of a MS reference centre in the region (Chi-Square=0.0190; P=0.8905). In 2015 the six DMTs with the highest rates were by decreasing orders: Tecfidera(®), Avonex(®), Gilenya(®), Aubagio(®), Copaxone(®), and Rebif(®). Half of them were recently developed orally-administered drugs. PERSPECTIVES: Complex factors may explain the interprovincial variability. Low DMT utilization rates in the most aged patients who also have the highest recourse rate to symptomatic treatments reflect the fact that the indication of disease modifying therapies do not address older patient's needs. New DMTs with medical indications for the late degenerative phase are needed.

Le Teuff, G., Abrahamowicz, M., Wynant, W., et al. (2015). "Flexible modeling of disease activity measures improved prognosis of disability progression in relapsing-remitting multiple sclerosis." J Clin Epidemiol **68**(3): 307-316.

OBJECTIVES: To illustrate the advantages of updating time-varying measures of disease activity and flexible modeling in prognostic clinical studies using the example of the association between the frequency of past relapses and occurrence of ambulation-related disability in multiple sclerosis (MS). STUDY DESIGN AND SETTING: Longitudinal population-based study of 288 patients from Burgundy, France, diagnosed with relapsing-remitting MS in 1990-2003. The end point was a nonreversible moderate MS disability (European Database for Multiple Sclerosis score >/= 3.0 derived from Extended Disability Status Scale). Alternative time-varying measures of attacks frequency included (1) conventional number of early MS attacks in the first 2 years after diagnosis; and two new measures, continuously updated during the follow-up; (2) cumulative number of past attacks; and (3) number of recent attacks, during the past 2 years. Multivariate analyses used Cox proportional hazards model and its flexible generalization, which accounted for time-dependent changes in the hazard ratios (HRs) for different attack frequency measures. RESULTS: HRs for all measures decreased significantly with increasing follow-up time. The proposed updated number of recent attacks improved model's fit to data, relative to alternative measures of attack frequency, and was associated with a statistically significantly increased hazard of developing ambulation-related MS disability in the next 2 years during the entire follow-up period. CONCLUSION: Updated measures of recent disease activity, such as frequency of recent attacks and modeling of their time-dependent effects, may substantially improve prognosis of clinical outcomes, such as development of MS disability.

Lebrun-Frenay, C., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for France." Mult Scler **23**(2_suppl): 65-77.

INTRODUCTION: To estimate the value of interventions in multiple sclerosis (MS) - where lifetime costs and outcomes cannot be observed - outcome data have to be combined with costs. This requires that cost data be regularly updated. OBJECTIVES AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting data on resource consumption and work capacity, health-related quality of life (HRQoL) and prevalent symptoms for patients with MS. Descriptive analyses are presented by level of severity, in the societal perspective, in EUR 2015. RESULTS: A total of 491 patients (mean age 47 years) participated; 82% were below retirement age, and of these 56% were employed. Employment was related to disease severity, and MS affected productivity at work for 90% of patients. Overall, 95% and 67% of patients experienced fatigue and cognition as a problem, respectively. The mean utility and annual costs were 0.735 and euro22,600 at Expanded Disability Status Scale (EDSS) 0-3, 0.500 and euro38,100 at EDSS 4-6.5, and 0.337 and euro48,100 at EDSS 7-9, respectively. The average cost of a relapse was estimated at euro2300. CONCLUSION: This study provides current data on MS in France that are important for developments of health policies and to estimate the value of current and future treatments.

Lefeuvre, D., Rudant, J., Foulon, S., et al. (2017). "Healthcare expenditure of multiple sclerosis patients in 2013: A nationwide study based on French health administrative databases." Mult Scler J Exp Transl Clin **3**(3): 2055217317730421.

BACKGROUND: Little is known about expenditure items of multiple sclerosis (MS) patients over recent years in France. OBJECTIVE: To describe healthcare expenditure among MS patients and identify the main expenditure drivers. METHODS: All healthcare expenditure reimbursed by French National Health Insurance to MS patients in 2013 was described on the basis of nationwide health administrative databases (SNIIRAM/PMSI). Expenditure was described globally and according to age and sex. RESULTS: The average expenditure among the 90,288 MS patients included was euro11,900 per patient. Pharmacy and hospitalisation accounted for 47% and 23% of healthcare expenditure, respectively (38% and 22% of MS patients were treated with disease-modifying therapies and hospitalised overnight or longer, respectively). Average expenditure did not differ according to age. However, pharmacy expenditure decreased with age (from 71% between the ages of 20 and 29 years to 18% between the ages of 70 and 79 years), whereas hospitalisation expenditure increased with age (from 15% to 35%). Paramedical fees accounted for 2% of expenditure between the ages of 20 and 29 years and 24% between the ages of 70 and 79 years. CONCLUSION: Overall, pharmacy expenditure was the main expenditure item, which decreased with increasing age, while hospitalisation and paramedical expenditure increased with increasing age.

Lefeuvre, D., Rudant, J., Foulon, S., et al. (2016). "Coût de la sclérose en plaques en France : description des différents postes de dépenses à partir des bases de données de l’assurance maladie." Rev Neurol (Paris) **172**: A84.
http://www.sciencedirect.com/science/article/pii/S0035378716002137

La sclérose en plaques est une maladie chronique invalidante nécessitant une prise en charge multidisciplinaire importante. Il existe peu de données récentes sur son coût, notamment en France. Objectifs Décrire les différents postes de dépenses des patients atteints de sclérose en plaques, du point de vue de l’assurance maladie. Patients et méthodes Les consommations de soins en 2013 des personnes atteintes de sclérose en plaques et affiliées au régime général, les montants correspondants remboursés par l’assurance maladie, ainsi que les prestations en espèces versées à ces patients (arrêts de travail et invalidité) ont été décrits à partir des données des bases de l’assurance maladie (SNIIRAM et PMSI). Résultats L’analyse a porté sur 90 288 patients. Un tiers des patients ont eu un traitement de fond en 2013, et 45 % ont été hospitalisés (22 % au moins une nuit). Le montant moyen des remboursements était de 11 920 euros par patient (dont médicaments : 5640 euros, hospitalisations : 2676 euros, honoraires médicaux/paramédicaux : 2065 euros). Par ailleurs, les prestations en espèces atteignaient 2815 euros par patient, en moyenne. Discussion La comparaison avec une précédente publication de 2004 indique que, parmi les patients en ALD, les montants ont augmenté de 4 % en dix ans (en euros constants). Le coût des médicaments a augmenté de 25 %, alors que les coûts hospitaliers et les prestations en espèces ont diminué respectivement de 23 % et 16 %. Conclusion L’augmentation du coût des médicaments sur une décennie, premier poste de dépense en 2013, a été en partie compensée par la baisse des coûts hospitaliers et des prestations en espèces.

Leray, E., Moreau, T., Fromont, A., et al. (2016). "Epidemiology of multiple sclerosis." Rev Neurol (Paris) **172**(1): 3-13.

Multiple sclerosis (MS) is the most frequently seen demyelinating disease, with a prevalence that varies considerably, from high levels in North America and Europe (>100/100,000 inhabitants) to low rates in Eastern Asia and sub-Saharan Africa (2/100,000 population). Knowledge of the geographical distribution of the disease and its survival data, and a better understanding of the natural history of the disease, have improved our understanding of the respective roles of endogenous and exogenous causes of MS. Concerning mortality, in a large French cohort of 27,603 patients, there was no difference between MS patients and controls in the first 20 years of the disease, although life expectancy was reduced by 6-7 years in MS patients. In 2004, the prevalence of MS in France was 94.7/100,000 population, according to data from the French National Health Insurance Agency for Salaried Workers (Caisse nationale d'assurance maladie des travailleurs Salariés [CNAM-TS]), which insures 87% of the French population. This prevalence was higher in the North and East of France. In several countries, including France, the gender ratio for MS incidence (women/men) went from 2/1 to 3/1 from the 1950s to the 2000s, but only for the relapsing-remitting form. As for risk factors of MS, the most pertinent environmental factors are infection with Epstein-Barr virus (EBV), especially if it arises after childhood and is symptomatic. The role of smoking in MS risk has been confirmed, but is modest. In contrast, vaccines, stress, traumatic events and allergies have not been identified as risk factors, while the involvement of vitamin D has yet to be confirmed. From a genetic point of view, the association between HLA-DRB1*15:01 and a high risk of MS has been known for decades. More recently, immunogenetic markers have been identified (IL2RA, IL7RA) and, in particular thanks to studies of genome-wide associations, more than 100 genetic variants have been reported. Most of these are involved in the immune response and often associated with other autoimmune diseases. Studies of the natural history of MS suggest it is a two-phase disease: in the first phase, inflammation is focal with flares; and in the second phase, disability progresses independently of focal inflammation. This has clear implications for therapy. Age may also be a key factor in the phenotype of the disease. In conclusion, France is a high-risk country for MS, but it only slightly reduces life expectancy. MS is a multifactorial disease and the implications of immunogenetics are major. Preventative approaches might be derived from knowledge of the risk factors and natural history of the disease (smoking, vitamin D).

Magy, L. (2018). "La sclérose en plaques, première maladie invalidante de l'adulte jeune." Actualités Pharmaceutiques **57**(573): 20-23.
http://www.sciencedirect.com/science/article/pii/S0515370017305177

La sclérose en plaques est une pathologie auto-immune et inflammatoire qui affecte le système nerveux central. Elle se présente sous différentes formes et entraîne des lésions qui provoquent des troubles moteurs, sensitifs, vésico-sphinctériens et cognitifs, qui peuvent progresser vers un handicap irréversible. Les premiers symptômes apparaissent le plus souvent chez l'adulte jeune.

McKay, K. A., Tremlett, H., Fisk, J. D., et al. (2018). "Psychiatric comorbidity is associated with disability progression in multiple sclerosis." Neurology **90**(15): e1316-e1323.

OBJECTIVE: Emerging evidence suggests that comorbidity may influence disability outcomes in multiple sclerosis (MS); we investigated the association between psychiatric comorbidity and MS disability progression in a large multiclinic population. METHODS: This retrospective cohort study accessed prospectively collected information from linked clinical and population-based health administrative databases in the Canadian provinces of British Columbia and Nova Scotia. Persons with MS who had depression, anxiety, or bipolar disorder were identified using validated algorithms using physician and hospital visits. Multivariable linear regression models fitted using an identity link with generalized estimating equations were used to determine the association between psychiatric comorbidity and disability using all available Expanded Disability Status Scale (EDSS) scores. RESULTS: A total of 2,312 incident cases of adult-onset MS were followed for a mean of 10.5 years, during which time 35.8% met criteria for a mood or anxiety disorder. The presence of a mood or anxiety disorder was associated with a higher EDSS score (beta coefficient = 0.28, p = 0.0002, adjusted for disease duration and course, age, sex, socioeconomic status, physical comorbidity count, and disease-modifying therapy exposure). Findings were statistically significant among women (beta coefficient = 0.31, p = 0.0004), but not men (beta coefficient 0.22, p = 0.17). CONCLUSION: Presence of psychiatric comorbidities, which were common in our incident MS cohort, increased the severity of subsequent neurologic disability. Optimizing management of psychiatric comorbidities should be explored as a means of potentially mitigating disability progression in MS.

Ongagna, J. C., Berthe, C., Collongues, N., et al. (2014). "Prévalence des comorbidités associées à la sclérose en plaques dans la base EDMUS alsacienne." Rev Neurol (Paris) **170**: A115.
http://www.sciencedirect.com/science/article/pii/S0035378714003440

Pivot, D., Debouverie, M., Grzebyk, M., et al. (2016). "Geographical Heterogeneity of Multiple Sclerosis Prevalence in France." PLoS One **11**(12): e0167556.

INTRODUCTION: Geographical variation in the prevalence of multiple sclerosis (MS) is controversial. Heterogeneity is important to acknowledge to adapt the provision of care within the healthcare system. We aimed to investigate differences in prevalence of MS in departments in the French territory. METHODS: We estimated MS prevalence on October 31, 2004 in 21 administrative departments in France (22% of the metropolitan departments) by using multiple data sources: the main French health insurance systems, neurologist networks devoted to MS and the Technical Information Agency of Hospitalization. We used a spatial Bayesian approach based on estimating the number of MS cases from 2005 and 2008 capture-recapture studies to analyze differences in prevalence. RESULTS: The age- and sex-standardized prevalence of MS per 100,000 inhabitants ranged from 68.1 (95% credible interval 54.6, 84.4) in Hautes-Pyrénées (southwest France) to 296.5 (258.8, 338.9) in Moselle (northeast France). The greatest prevalence was in the northeast departments, and the other departments showed great variability. DISCUSSION: By combining multiple data sources into a spatial Bayesian model, we found heterogeneity in MS prevalence among the 21 departments of France, some with higher prevalence than anticipated from previous publications. No clear explanation related to health insurance coverage and hospital facilities can be advanced. Population migration, socioeconomic status of the population studied and environmental effects are suspected.

Roux, J., Grimaud, O. et Leray, E. (2016). "Peut-on mesurer le niveau de handicap moteur lié à la sclérose en plaques à partir des bases de l'Assurance maladie ?" Revue d'Épidémiologie et de Santé Publique **64**: S199.
http://www.sciencedirect.com/science/article/pii/S0398762016303650

La sclérose en plaques (SEP) est une maladie chronique entraînant sur le long terme l'apparition d'un handicap moteur mesurable par l'échelle Expanded Disability Status Scale

(« EDSS »). Les bases de données de l'Assurance maladie ne contenant pas de données cliniques, cette étude vise à étudier la possibilité d'estimer le niveau de handicap moteur de patients atteints de SEP à partir de données de l'Assurance maladie en France. Méthode Au total, 650 patients atteints de SEP en 2007 ont été identifiés dans l'échantillon généraliste des bénéficiaires (1/97e de l'Assurance maladie). Les achats et locations de plus de quatre mois consécutifs d'aides techniques (canne, déambulateur, véhicules pour handicapé physique [VHP] manuel et électrique, lit médical et matériel anti-escarres de classe II) sur la période 2007–2013 ont été identifiés. Le taux d'incidence de chacune des aides techniques a été estimé au cours du suivi, ainsi que le niveau de handicap moteur aux dernières nouvelles et mis en regard du score EDSS correspondant. Résultats Au total, 266 (40,9 %) personnes ont eu la prescription d'au moins une aide technique sur la période 2007–2013. L'âge médian de délivrance de la première aide est de 52ans. À la date de dernière information, 83 (12,8 %) patients avaient une canne (EDSS estimé 5,5–6), 31 (4,8 %) un déambulateur (EDSS estimé 6,5) et 77 (11,8 %) un VHP manuel (EDSS estimé 7) ; 37 (5,7 %) patients possédaient un VHP électrique (EDSS estimé 7,5) et 38 (5,8 %) un lit médical avec un matériel antiescarres de classe II (EDSS estimé supérieur à 8,5). Discussion Cette étude permet de décrire sur un échantillon non biaisé de personnes atteintes de SEP en France les différentes aides techniques à la marche. Le niveau de handicap moteur peut ainsi être estimé à partir de données administratives pour pallier l'absence de données cliniques. Le handicap non moteur pourra également être étudié.

Roux, J., Grimaud, O. et Leray, E. (2018). "Étude des parcours de soins des patients ayant une sclérose en plaques en France sur la période 2007–2013 : une analyse des bases médico-administratives utilisant la méthode « Multichannel Sequence Analysis »." Revue d'Épidémiologie et de Santé Publique **66**: S25.
http://www.sciencedirect.com/science/article/pii/S0398762018300579

La sclérose en plaques (SEP) est une maladie chronique nécessitant une prise en charge pluridisciplinaire complexe. Cette étude vise à identifier et caractériser une typologie de parcours de soins des patients ayant une SEP en France. Méthodes Les patients SEP ont été identifiés en janvier 2007 dans l'échantillon généraliste des bénéficiaires (EGB) et le PMSI grâce au statut d'affection longue durée, aux prescriptions médicamenteuses spécifiques et aux diagnostics des séjours hospitaliers. L'ensemble de leurs prestations et séjours a été extrait sur la période 2007–2013. Les consommations d'intérêt étaient : les hospitalisations liées à la SEP et les recours à un généraliste, un neurologue libéral, un spécialiste libéral de médecine physique et de réadaptation et les soins infirmiers et de kinésithérapie. Ces six dimensions ont été analysées simultanément grâce à la méthode « Multichannel Sequence Analysis » et une classification ascendante hiérarchique. Résultats Au total, 543 patients (sex-ratio 2,8, âge médian en 2007 48 ans) ont été répartis dans une typologie à cinq clusters. Le cluster principal (n=271) correspondait à des patients jeunes, peu consommateurs donc probablement avec une maladie récente et peu active. Les 124 patients du second cluster étaient plus souvent traités à l'hôpital pour leur SEP et recouraient fréquemment à des kinésithérapeutes, reflétant probablement une maladie active et la présence de symptômes. Les patients du troisième cluster (n=61) étaient suivis régulièrement par des neurologues libéraux et étaient beaucoup sous traitement (85,2 %), témoignant sans doute d'une maladie contrôlée. Le quatrième groupe incluait 47 patients ayant un contact important avec des kinésithérapeutes, des infirmiers et des généralistes, probablement lié à une SEP progressive ou avancée. Les patients du dernier groupe (n=40), plus âgés avec plusieurs comorbidités, étaient tous décédés durant le suivi et recouraient fortement aux infirmiers. Discussion/Conclusion Ces résultats suggèrent qu'il est possible grâce à cette méthode appliquée sur des données médico-administratives de différencier plusieurs types de prise en charge (médicale, paramédicale et médicamenteuse) et de déterminer des profils cliniques de patients.

Roux, J., Le Meur, N., Grimaud, O., et al. (2016). "Consommations de soins des patients atteints de sclérose en plaques en France de 2007 à 2013 à partir des bases de données médico-administratives." Rev Neurol (Paris) **172**: A88.
http://www.sciencedirect.com/science/article/pii/S0035378716002228

La sclérose en plaques (SEP) est une maladie neurologique chronique affectant environ 100 000 personnes en France pour lesquelles la consommation précise de soins est peu connue. Objectifs Décrire les soins auxquels les personnes atteintes de SEP dans l'échantillon généraliste des bénéficiaires (EGB) ont recours et créer une typologie des modes de consommation. Patients et méthodes La population a été identifiée de 2007 à 2012 dans l'EGB (échantillon national au 1/97e) et le PMSI grâce au statut affection longue durée, aux prescriptions médicamenteuses et aux diagnostics des séjours hospitaliers. Les consultations annuelles de médecine générale (MG) et neurologues, les séjours hospitaliers liés à la maladie, et les prescriptions de traitements ont été décrits et traités par analyse de séquences. Deux algorithmes de classification ont permis de créer une typologie. Résultats Au total, 1000 patients SEP ont été identifiés et classés en trois groupes : les bénéficiaires ayant une consommation « faible » (14,5 %) avec un nombre annuel médian de 2,0 consultations MG et 0,0 consultation neurologue libéral, ceux présentant une consommation « intermédiaire » (67,8 %) avec 5,1 consultations MG et 0,1 consultation neurologue libéral, et les bénéficiaires ayant une consommation « élevée » (17,7 %) avec 13,7 consultations MG et 0,4 consultation neurologue libéral. Discussion Cette étude est la première sur le sujet en France réalisée à partir des bases de données médico-administratives sur un échantillon représentatif de la population française. L'exhaustivité des données de consommation en ville permettra d'intégrer les traitements, les consultations médicales et paramédicales, les examens biologiques et actes d'imagerie. Conclusion Cette étude fournit des informations objectives et quantifiées sur la consommation de soins liée à la SEP. Les modalités de consommation varient significativement entre patients et méritent d'être élucidées.

Sagnes-Raffy, C., Gourraud, P. A., Hannon, V., et al. (2010). "[Multiple sclerosis in Haute-Garonne: an important underestimation of case numbers]." Rev Epidemiol Sante Publique **58**(1): 23-31.
https://www.ncbi.nlm.nih.gov/pubmed/20106619

In France, the prevalence of multiple sclerosis is estimated between 65 and 125 patients per 100,000 inhabitants with a South-West towards North-East gradient. Nevertheless, the epidemiology of multiple sclerosis remains still imperfectly known, the recent studies being realized, either in a region of France, or from a single data source and thus suscepted not to be exhaustive. OBJECTIVE: Assessing the prevalence of the multiple sclerosis in 2005 in Haute-Garonne by matching several data sources completed by a capture-recapture method; estimating the exhaustivity of each of the sources. METHODS: The data sources were hospital data (DRG for the hospitalization, data of consultation), data of public health insurance system (main health insurance, agricultural health insurance, social welfare for self employed), and data from the MIPSEP network. The linkage was based on name, maiden name, first name, date of birth and sex and allowed a first estimation of the number of cases. Models of loglinear regression allowed estimating the total number of case and the sensitivity of each source. RESULTS: The total number of cases obtained by matching several sources of information amounted to 1549. The use of several data sources increased by 25.6 % the maximum number of patients identified with a single source of information (national health insurance, any insurance). According to the model used, the method of capture-recapture estimated the number of cases up to 1722. Therefore, this study estimated a prevalence of multiple sclerosis between 110 and 149 cases per 100,000 inhabitants in Haute-Garonne. CONCLUSION: The prevalence of the multiple sclerosis is largely underestimated in Haute-Garonne and questions the magnitude over the so-called gradient. Matching several sources of information is indispensable to improve collection of the total number of cases.

Trumbic, B., Zephir, H., Ouallet, J.-C., et al. (2018). "Pertinence des soins : le modèle Choosing wisely® (CW) est-il applicable à la prise en charge de la sclérose en plaques (SEP) en France ? Une étude pilote du GRESEP." Rev Neurol (Paris) **174**: S93.
http://www.sciencedirect.com/science/article/pii/S0035378718302467

La campagne CW vise à améliorer la pertinence des soins par la limitation des explorations et traitements superflus selon les sociétés savantes. Les préconisations sont discutées entre médecins et patients pour une décision partagée. Objectifs Évaluer la faisabilité et l'intérêt du modèle CW dans la prise en charge de la sclérose en plaques (SEP) en pratique quotidienne en France. Méthodes Préconisations élaborées par deux groupes de travail indépendants selon une méthode dérivée du consensus formalisé de la Haute Autorité de santé. Résultats Sept préconisations ont été retenues, relatives à la place des potentiels évoqués multimodaux dans le diagnostic, au traitement des poussées par corticoïdes (dose, voie, contexte d'administration), à la prise en charge anti-infectieuse des patients sous autosondage intermittent, au traitement de la fatigue. Par exemple : dans le traitement des poussées de SEP, il n'est pas indispensable d'administrer systématiquement une corticothérapie à forte dose par voie IV, si la voie orale peut être utilisée. Discussion L'acceptabilité de ces préconisations par des praticiens non spécialisés, ainsi que leur impact sur les pratiques réelles restent à évaluer. Conclusion Le modèle CW est contributif à l'analyse de la pertinence des soins de SEP en pratique quotidienne. Informations complémentaires BIOGEN France a apporté un soutien financier à l'organisation de la réunion entre le groupe de rédaction et le groupe de cotation, sans prendre part à la conception de l'étude, à la sélection des recommandations et à leur contenu.

ÉTUDES INTERNATIONALES

Barin, L., Kaufmann, M., Salmen, A., et al. (2019). "Patterns of care for Multiple Sclerosis in a setting of universal care access: A cross-sectional study." Mult Scler Relat Disord **28**: 17-25.

BACKGROUND: Current guidelines recommend regular neurological MS care in persons diagnosed with MS, but little is known about implementation of this recommendation or potential access barriers. This study examined disease-specific and sociodemographic differences between MS patients in Neurological Care (NeC), General Practitioner Care (GPC), or no Physician Care (NoPC) to identify group differences and characteristics that may suggest care access barriers. METHODS: Patient-reported data were analyzed from 1038 Swiss Multiple Sclerosis Registry participants by means of multivariable regression to identify systematic differences across the three care groups. Assessments included comprehensive data on clinical, sociodemographic, and geographic factors. RESULTS: 89% reported being in regular care by a neurologist (56% in private practices, 44% in hospitals), 5% were in GPC, and 6% reported No Physician Care (NoPC). Compared with the NeC group, patients not seeing a neurologist included two subgroups, one consisting of persons with a primary progressive MS (PPMS) and/or an extended MS history. The second subgroup included persons with a recent MS diagnosis within the last 2 years. Within the NeC group, the patients seen in private practices were of older age and more frequently female compared to those at clinics, but no differences were detected with regard to disability status, MS type, or treatment patterns. CONCLUSIONS: Access to neurological care is high in Switzerland. Given the emerging paradigm for early treatment and new drugs for progressive MS, regular neurology visits should be promoted among patient groups currently less in neurological care such as persons with PPMS or recently diagnosed.

Battaglia, M., Kobelt, G., Ponzio, M., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for Italy." Mult Scler **23**(2_suppl): 104-116.

INTRODUCTION: In order to estimate the value of interventions in multiple sclerosis (MS) - where lifetime costs and outcomes cannot be observed - outcome data have to be combined with costs. This requires that cost data be regularly updated. OBJECTIVES AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting data on resource consumption and work capacity, health-related quality of life (HRQoL) and prevalent symptoms for patients with MS. Descriptive analyses are presented by level of severity, from the societal perspective, in EUR 2015. RESULTS: A total of 1010 patients (mean age = 45 years) participated in Italy. In total, 94% were below retirement age, and of these, 56% were employed. Employment was related to disability, and MS affected productivity at work in 77% of the patients. Overall, 96% and 65% of the patients experienced fatigue and cognitive difficulties as a problem, respectively. Mean utility and total annual costs were 0.735 and euro22,900 at Expanded Disability Status Scale (EDSS) of 0-3, 0.534 and euro40,100 at EDSS of 4-6.5, and 0.135 and euro53,300 at EDSS of 7-9. The mean cost of a relapse was estimated to be euro2600. CONCLUSION: This study illustrates the burden of MS on Italian patients and provides current data on MS that are important for the development of health policies.

Berger, T., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for Austria." Mult Scler **23**(2_suppl): 17-28.

INTRODUCTION: In order to estimate the value of interventions in multiple sclerosis (MS) - where lifetime costs and outcomes cannot be observed - outcome data have to be combined with costs. This requires that cost data be regularly updated. OBJECTIVES AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting data on resource consumption and work capacity, health-related quality of life (HRQoL) and prevalent symptoms for patients with MS. Descriptive analyses are presented by level of severity, from the societal perspective, in EUR 2015. RESULTS: A total of 516 patients (mean age, 53 years) participated in Austria; 72% were below retirement age, and of these, 46% were employed. Employment was related to disability, and MS affected productivity at work for 77% of those working. Overall, 94% and 67% of patients experienced fatigue and cognition as a problem. Mean utility and total annual costs were 0.778 and 25,100euro at Expanded Disability Status Scale (EDSS) 0-3, 0.579 and 44,100euro at EDSS 4-6.5, and 0.244 and 73,800euro at EDSS 7-9. The mean cost of a relapse was estimated at 2563euro. CONCLUSION: This study illustrates the burden of MS on Austrian patients and provides current data on MS that are important for development of health policies.

Bezzini, D. et Battaglia, M. A. (2017). "Multiple Sclerosis Epidemiology in Europe." Adv Exp Med Biol **958**: 141-159.

Multiple sclerosis is characterized by a non-homogeneous distribution around the world. Some authors in past described a latitude gradient, with increasing risk from the equator to North and South Poles, but this theory is still controversial. Regarding Europe, there are many articles in the literature concerning the epidemiology of this disease but, unfortunately, they are not always comparable due to different methodologies, they do not cover all countries in the continent, and most of them reported data of small areas and rarely at a national level. In 2012 there were 20 national registries that could help to describe the epidemiology of the disease and, in addition, there is an European Register for Multiple Sclerosis that collect data from already existing national or regional MS registries and databases. Another valid alternative to obtain epidemiological data, also at national level, in a routinely and cost-saving way is through administrative data that are of increasing interest in the last years.

Birnbaum, H. G., Ivanova, J. I., Samuels, S., et al. (2009). "Economic impact of multiple sclerosis disease-modifying drugs in an employed population: direct and indirect costs." Curr Med Res Opin **25**(4): 869-877.

OBJECTIVE: The study objective is to compare the annual total medical and indirect costs of newly treated and untreated employees with multiple sclerosis (MS). RESEARCH DESIGN AND METHODS: A retrospective database analysis of employer medical, drug, and disability claims database (Ingenix Employer database, 1999-2005; 17 large US companies) was conducted for employees 18-64 years of age with > or =1 MS diagnosis after January 1, 2002. Employees with > or =1 MS disease-modifying drug (DMD) claim comprised the newly treated group; employees with MS but no DMD at any time comprised the untreated, comparison group. Index date was the day after the most recent claim (treated, DMD claim; untreated, MS claim) meeting the following requirements: continuous health coverage for 3 months before (baseline period) and 12 months after the index date (study period) and actively employed during baseline. MAIN OUTCOME MEASURES: Total medical costs and indirect (work loss) costs over the 1-year study period (2006 $US) were compared for DMD-treated and untreated MS employees, adjusting for baseline characteristics, including comorbidities. RESULTS: During the baseline, MS employees who became treated (n = 258) were younger (40.9 vs. 44.4 years, p < 0.0001) and had a higher proportion of women (72 vs. 62%, p = 0.007) than the untreated group of MS employees who never received DMD treatment (n = 322). The 3-month baseline MS-related medical costs were higher among treated MS employees ($2520 vs. $1012, p < 0.0001). There was a nonsignificant trend toward higher baseline non-MS-related medical costs in untreated versus treated MS employees. Risk-adjusted total annual medical costs ($4393 vs. $6187, p < 0.0001) and indirect costs ($2252 vs. $3053, p < 0.0001) were significantly lower for treated MS employees than for untreated MS employees. CONCLUSIONS: Initiation of MS disease-modifying drugs was associated with substantial significant medical and indirect savings for employees with MS. Study findings should be considered in the context of the study limitations (e.g., analytic focus on employees with at least 12-month follow-up; lack of clinical detail on MS severity).

Bishop, M. et Rumrill, P. D. (2015). "Multiple sclerosis: Etiology, symptoms, incidence and prevalence, and implications for community living and employment." Work **52**(4): 725-734.

BACKGROUND: This article presents an overview of multiple sclerosis (MS), one of the most common neurological disorders in the Western Hemisphere. We explore the impacts of MS on employment, career development, and community living, and the implications for rehabilitation professionals. OBJECTIVE: The objective in this article is to provide a current and comprehensive review of the etiology and symptoms, incidence and prevalence, and current treatment strategies for MS, and the effects of MS on vocational and psychosocial outcomes. METHODS: This analysis represents a comprehensive review of the relevant medical, vocational, community living, and rehabilitation research literature. RESULTS: Living with MS is associated with wide-ranging and unpredictable effects on employment, career development, and community independence. Effective responses by health and rehabilitation professionals require a comprehensive understanding of this progressive and complex condition and its psychosocial impacts. CONCLUSIONS: Customized interventions from allied health professionals and rehabilitation counselors that are grounded in the unique features of MS and that reflect current best practices in Vocational Rehabilitation are required to improve rehabilitation outcomes for people with MS.

Boyko, A., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for Russia." Mult Scler **23**(2_suppl): 155-165.

BACKGROUND: In order to assess the value of management strategies in multiple sclerosis (MS), outcome data have to be combined with cost data. This, in turn, requires that cost data be regularly updated. OBJECTIVE AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting current data on resource consumption, work capacity and health-related quality of life (HQoL). Descriptive analyses are presented by level of severity; costs are estimated in the societal perspective, in RUB 2015. RESULTS: A total of 208 patients (mean age: 38.5 years) participated in the Russian study; 97% were below retirement age, and of these, 49% were employed. MS was reported to affect productivity at work in 63% of patients. Overall, 87% and 41% of patients felt that fatigue and cognition were a problem. The mean utility and costs were 0.769 and 578,000 RUB at Expanded Disability Status Scale (EDSS) 0-3, 0.509 and 826,000 RUB at EDSS 4-6.5, and 0.071 and 1,013,000 RUB at EDSS 7-9. The average cost of a relapse was 33,000 RUB. CONCLUSION: This study illustrates the burden of MS on Russian patients and provides current data that are important for developing health policies.

Brook, R. A., Rajagopalan, K., Kleinman, N. L., et al. (2009). "Absenteeism and health-benefit costs among employees with MS." Curr Med Res Opin **25**(6): 1469-1476.

OBJECTIVE: The purpose of this analysis was to assess the differences in lost time and health-benefit costs (HBCs) among employees treated with disease modifying treatments (DMTs) for multiple sclerosis (MS). STUDY DESIGN: Employees with an MS diagnostic code (ICD-9 340.xx) and a DMT prescription claim (1/1/2001-6/30/2007) were identified from the HCMS Research Reference Database and assigned to DMT cohorts. The first prescription for the DMT was used as each person's index date. One-year outcomes included HBCs and absenteeism (lost time, comprising sick leave [SL], short- and long-term disability [STD/LTD], and workers' compensation). METHODS: Demographics were compared using t-tests for continuous variables and chi-square tests for discrete variables. Two-part multivariate regression modeling (logistic regression combined with generalized linear regression) was used to determine annual HBCs and absenteeism for each cohort controlling for age, gender, job-related variables, and Charlson Comorbidity Score. All cost variables were inflated to US$2007. RESULTS: Annual ranges among the DMTs were: HBCs $17,953-26,970 and absenteeism 7.33-20.67 days. Compared with glatiramer acetate ('C'), IFN-beta1a IM ('A') users had lower SL ($445, p = 0.0469) and STD ($969, p = 0.0164) costs; and IFN-beta1b ('B') users had lower medical costs ($2143, p = 0.0091). In addition, those treated with 'A' had 4.2 fewer SL days (p = 0.0101) compared with those treated with 'C'. CONCLUSIONS: Patients treated with 'A' reported significantly lower SL costs, SL days, and STD costs than patients treated with 'C', suggestive of greater real world benefits with 'A'. Despite small sample sizes and the retrospective nature, the study provides interesting insights into the use of DMTs in MS. The study also revealed important areas of future research, specifically the need for development of methods to determine which MS patient groups respond best to which DMT treatments.

Brundin, L., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for Sweden." Mult Scler **23**(2_suppl): 179-191.

> BACKGROUND: To assess the value of management strategies in multiple sclerosis (MS), outcome data have to be combined with cost data. This requires that cost data be regularly updated. OBJECTIVE AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting current data on resource consumption, work capacity and health-related quality of life (HRQoL). Descriptive analyses are presented by level of severity; costs are estimated in the societal perspective, in 2015 SEK. RESULTS: A total of 1864 patients (mean age 56 years) participated in Sweden; 74% were below retirement age, and of these, 55% were employed. MS was reported to affect productivity at work in 78% of patients. Overall, 94% and 72% of patients felt that fatigue and cognition were a problem, respectively. The mean utility and costs were 0.757 and 244,000SEK at Expanded Disability Status Scale (EDSS) 0-3, 0.563 and 384,000SEK at EDSS 4-6.5 and 0.202 and 888,000SEK at EDSS 7-9, respectively. The average cost of a relapse was 36,900SEK. CONCLUSION: This study illustrates the burden of MS on Swedish patients and provides current data that are important for the development of health policies.

Buijs, S., Krol, M. et de Voer, G. (2018). "Healthcare utilization and costs of multiple sclerosis patients in the Netherlands: a healthcare claims database study." J Comp Eff Res **7**(5): 453-462.

> AIM: To investigate the incidence and prevalence and healthcare costs of multiple sclerosis (MS) in the Netherlands by using healthcare claims data. MATERIALS & METHODS: A claims database was analyzed including 26% of the Dutch population. RESULTS: Average prevalence of MS in the Netherlands was 88 per 100,000 inhabitants (males 48, 127 females) and incidence nine per 100,000. Yearly per patient medication costs were highest in the year after the first MS claim and then decreased. Hospital costs were 30% higher in the first year of MS claims than after 3 years of MS claims. The patients often used co-medication, such as antidepressants and antibiotics. CONCLUSION: Dutch incidence and cost estimates based on claims were consistent with previous estimates. Prevalence estimates were somewhat higher. Drug and hospital costs were highest shortly after the diagnosis. Healthcare consumption related to comorbidities was in-line with the previously reported comorbidity estimates.

Calabrese, P., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for Switzerland." Mult Scler **23**(2_suppl): 192-203.

> INTRODUCTION: To estimate the value of interventions in multiple sclerosis (MS) - where lifetime costs and outcomes cannot be observed - outcome data have to be combined with costs. This requires that cost data be regularly updated. OBJECTIVES AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting data on resource consumption and work capacity, health-related quality of life (HRQoL) and prevalent symptoms for patients with MS. Descriptive analyses are presented by level of severity, from the societal perspective, in CHF 2015. RESULTS: A total of 721 patients (mean age 48 years) participated in Switzerland; 90% were below retirement age, and of these, 65% were employed. Employment was related to disease severity, and MS affected productivity at work for 69% of patients. Overall, 93% and 64% of patients experienced fatigue and cognition as a problem, respectively. The mean utility and annual costs were 0.799 and 29,600CHF at Expanded Disability Status Scale (EDSS) 0-3, 0.614 and 66,800CHF at EDSS 4-6.5 and 0.348 and 110,800CHF at EDSS 7-9, respectively. The mean cost of a relapse was estimated at 7600CHF. CONCLUSION: This study provides current data on MS in Switzerland

that are important for development of health policies and to estimate the value of current and future treatments.

Cárdenas-Robledo, S., Otero-Romero, S., Montalban, X., et al. (2020). "[Prevalence and impact of comorbidities in patients with multiple sclerosis]." Rev Neurol **71**(4): 151-158.

INTRODUCTION: Multiple sclerosis is a chronic, inflammatory and degenerative disease of the central nervous system. In most cases it is characterised by the recurring focal neurological deficit, which may become progressive over time. Given the chronic nature of the disease, patients may present with additional diseases (comorbidities), which affect the natural history of the disease and its treatment in different ways. AIM: To summarise the available evidence regarding the influence of comorbidities on the natural history of multiple sclerosis. DEVELOPMENT: Patients with multiple sclerosis are at greater risk than the general population of developing both acute and chronic comorbidities. It has been shown that comorbidities can delay the diagnosis of multiple sclerosis after clinical onset, increase the rates of relapses and of accumulation of disability. Comorbidities also influence aspects of the choice of treatment and therapy adherence. Finally, comorbidities also increase the mortality rate and reduce the quality of life of patients with multiple sclerosis. CONCLUSIONS: Screening, diagnosis and treatment of comorbidities are a key aspect of caring for patients with multiple sclerosis to improve their long-term prognosis in terms of disability, quality of life and mortality.

Carney, P., O'Boyle, D., Larkin, A., et al. (2018). "Societal costs of multiple sclerosis in Ireland." J Med Econ **21**(5): 425-437.

AIMS: This paper evaluates the impact of multiple sclerosis (MS) in Ireland, and estimates the associated direct, indirect, and intangible costs to society based on a large nationally representative sample. MATERIALS AND METHODS: A questionnaire was developed to capture the demographics, disease characteristics, healthcare use, informal care, employment, and wellbeing. Referencing international studies, standardized survey instruments were included (e.g. CSRI, MFIS-5, EQ-5D) or adapted (EDSS) for inclusion in an online survey platform. Recruitment was directed at people with MS via the MS Society mailing list and social media platforms, as well as in traditional media. The economic costing was primarily conducted using a 'bottom-up' methodology, and national estimates were achieved using 'prevalence-based' extrapolation. RESULTS: A total of 594 people completed the survey in full. The sample had geographic, disease, and demographic characteristics indicating good representativeness. At an individual level, average societal cost was estimated at €47,683; the average annual costs for those with mild, moderate, and severe MS were calculated as €34,942, €57,857, and €100,554, respectively. For a total Irish MS population of 9,000, the total societal costs of MS amounted to €429m. Direct costs accounted for just 30% of the total societal costs, indirect costs amounted to 50% of the total, and intangible or QoL costs represented 20%. The societal cost associated with a relapse in the sample is estimated as €2,438. LIMITATIONS AND CONCLUSIONS: The findings highlight that up to 70% of the total costs associated with MS are not routinely counted. These "hidden" costs are higher in Ireland than the rest of Europe, due in part to significantly lower levels of workforce participation, a higher likelihood of permanent workforce withdrawal, and higher levels of informal care needs. The relationship between disease progression and costs emphasize the societal importance of managing and slowing the progression of the illness.

Catic, T., Suljic, E., Gojak, R., et al. (2018). "How Cost-of-Illness (COI) Study Provides Direct and Indirect Costs of Multiple Sclerosis (MS) in Bosnia and Herzegovina ?" Mater Sociomed **30**(4): 270-275.

> BACKGROUND: This cost-of-illness (COI) study provides deep insight in direct and indirect costs of multiple sclerosis (MS) in Bosnia and Herzegovina (BH). AIM: Objective of this study was to analyze the costs and quality of life (QoL) of patients with MS in BH. PATIENTS AND METHODS: We applied the same methodology already used in study conducted across nine European countries. Sixty-two patients participated with EDSS score not higher than 6.5. Costs are collected using a questionnaire quality of life was measured by EQ-5D and MSQOL-54 questionnaires. RESULTS: Mean age of respondents was 39.8 The mean utility measured by EQ-5D-3L was 0.68 at the beginning and 0.63 at the end of the study. QoL measured by MSQoL-54 showed improvement at the end of the trial. Costs are presented from the societal and payer perspective. Cost of MS in Bosnia and Herzegovina annually amount 124.8 million BAM. Cost driver where indirect and DMDs costs, with significant differences among subgroups. CONCLUSIONS: This study provides an in-depth analysis of MS costs in BH providing data for health policies development and information for future cost-effectiveness evaluations of new therapeutic options as well as for comparison of MS costs with other countries.

Chalmer, T. A., Buron, M., Illes, Z., et al. (2020). "Clinically stable disease is associated with a lower risk of both income loss and disability pension for patients with multiple sclerosis." J Neurol Neurosurg Psychiatry **91**(1): 67-74.

> OBJECTIVE: To assess the risk of losing income from salaries and risk disability pension for multiple sclerosis patients with a clinically stable disease course 3 years after the start of disease-modifying therapy (DMT). METHODS: Data from the Danish Multiple Sclerosis Registry were linked to other Danish nationwide population-based databases. We included patients who started treatment with a DMT between 2001 and 2014. Patients were categorised into a clinically stable group (No Evidence of Disease Activity (NEDA-2)) and a clinically active group (relapse activity or 6-month confirmed Expanded Disability Status Scale worsening). Outcomes were: (1) loss of regular income from salaries and (2) a transfer payment labelled as disability pension. We used a Cox proportional hazards model to estimate confounder-adjusted HRs, and absolute risks were plotted using cumulative incidence curves accounting for competing risks. RESULTS: We included 2406 patients for the income analyses and 3123 patients for the disability pension analysis. Median follow-up from index date was ~5 years in both analyses. The NEDA-2 group had a 26% reduced rate of losing income (HR 0.74; 95% CI 0.60 to 0.92). HRs were calculated for 5-year intervals in the disability pension analysis: year 0-5: a 57% reduced rate of disability pension for the NEDA-2 group (HR 0.43; 95% CI 0.33 to 0.55) and year 5-10: a 36% reduced rate (HR 0.64; 95% CI 0.40 to 1.01). CONCLUSION: Clinically stable disease course (NEDA-2) is associated with a reduced risk of losing income from salaries and a reduced risk of disability pension.

Chen, A. Y., Chonghasawat, A. O. et Leadholm, K. L. (2017). "Multiple sclerosis: Frequency, cost, and economic burden in the United States." J Clin Neurosci **45**: 180-186.

> Multiple sclerosis (MS) is one of the most common neurological diseases, affecting young and middle-aged adults. The full economic cost of managing chronic MS is substantial. To investigate the recent trend of medical cost and economic burden of MS management in the United States (U.S.), we inquired for available data from the National Inpatient Sample database (NIS; from 1994 to 2013). The annual rates of changes were determined by linear regression analysis. We found an estimated half million increase in MS admissions, annually,

which was projected to exceed 43.5 million by the end of year 2017. We also found the charge and the costs associated with MS care increased at rates of US$ 40 million a year and US$ 8 million a year, respectively. We revealed a 1.6 fold increase in the inflation of medical bill in the past decade, and the inflation of medical bills was inversely correlated to the cost-to-charge ratios. In sum, we outline the national trends of medical care use and the expenditure of caring for patients with MS. Periodic reviews and characterizations of expenditure trends are critical for formulating future policy.

Cheraghmakani, H., Baghbanian, S. M., HabibiSaravi, R., et al. (2020). "Age and sex-adjusted incidence and yearly prevalence of multiple sclerosis (MS) in Mazandaran province, Iran: An 11-years study." PLoS One **15**(7): e0235562.

INTRODUCTION: The incidence rate of MS is a valuable indicator of the recent changes in the risk of this disease, and it is widely implicated for health planning purposes. OBJECTIVES: This study aims to determine the MS incidence over the past eleven years in Mazandaran province and to compare it with the other parts of Iran and the world. MATERIALS AND METHODS: This retrospective study is conducted in Mazandaran province by using registered data in the files of the patients with their consent. The yearly crude incidence rates, age, and sex-specific incidence rates and directly standardized incidence rates of this population are calculated, and the temporal changes in the incidence rates are analyzed. RESULTS: 662 (26%) male patients with the mean (SD) age of 32.6 (9.48) and 1884 (74%) female patients with the mean (SD) age of 31.9 (9.15) are studied. The direct standardized incidence rate of MS was 3.28 in 100.000 in 2008 and reached 4.17 in 100.000 in 2018, and this increase was significant ($p<0.05$). Also, the yearly prevalence of MS increased from 24.4 to 72.5 in this period. CONCLUSIONS: The MS incidence has increased in Mazandaran. The potential role of some genetic or environmental factors needs further investigation.

Chruzander, C., Tinghog, P., Ytterberg, C., et al. (2016). "Longitudinal changes in sickness absence and disability pension, and associations between disability pension and disease-specific and contextual factors and functioning, in people with multiple sclerosis." J Neurol Sci **367**: 319-325.

BACKGROUND: Even though it is well known that disability due to MS is highly associated with employment status, the long-term longitudinal perspective on sickness absence and disability pension over the MS trajectory is lacking. In addition, further knowledge of risk factors for future disability pension is needed. OBJECTIVES: To explore long-term longitudinal changes in the prevalence of sickness absence and disability pension in people with MS (PwMS), as well as to explore associations between disease-specific factors, contextual factors and functioning, and the outcome of future full-time disability pension. METHODS: A prospective, population-based survival cohort study, with a nine year follow-up, including 114 PwMS was conducted by combining face-to-face collected data and register-based data. RESULTS: The prevalence of full-time disability pension increased from 20% to 50%, however 24% of the PwMS had no disability pension at all at end of follow-up. Sex, age, disease severity and impaired manual dexterity were associated with future full-time disability pension. CONCLUSIONS: The large increase in prevalence of PwMS on full-time disability pension during the MS trajectory, calls for the development and implementation of evidence-based interventions, aiming at keeping PwMS in the work force. Modifiable factors, such as manual dexterity should be targeted in such interventions.

Dalla Costa, G., Leocani, L., Montalban, X., et al. (2020). "Real-time assessment of COVID-19 prevalence among multiple sclerosis patients: a multicenter European study." Neurol Sci **41**(7): 1647-1650.

> We assessed the prevalence and impact of COVID-19 among multiple sclerosis (MS) patients across Europe by leveraging participant data collected as part of the ongoing EU IMI2 RADAR-CNS major programme aimed at finding new ways of monitoring neurological disorders using wearable devices and smartphone technology. In the present study, 399 patients of RADAR-MS have been included (mean age 43.9 years, 60.7% females) with 87/399 patients (21.8%) reporting major symptoms suggestive of COVID-19. A trend for an increased risk of COVID-19 symptoms under alemtuzumab and cladribine treatments in comparison to injectables was observed. Remote monitoring technologies may support health authorities in monitoring and containing the ongoing pandemic.

Dubois, B., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for Belgium." Mult Scler **23**(2_suppl): 29-40.

> INTRODUCTION: In order to estimate the value of interventions in multiple sclerosis (MS) - where lifetime costs and outcomes cannot be observed - outcome data have to be combined with costs. This requires that cost data be regularly updated. OBJECTIVES AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting data on resource consumption and work capacity, health-related quality of life (HRQoL) and prevalent symptoms for patients with MS. Descriptive analyses are presented by level of severity, from the societal perspective, in EUR 2015. RESULTS: A total of 1856 patients (mean age: 54 years) participated in Belgium; 66% were below retirement age, and of these, 44% were employed. Employment was related to disease severity, and MS affected productivity at work in 85% of the patients. Overall, 95% and 72% of the patients experienced fatigue and cognitive difficulties, respectively, as a problem. Mean utility and annual costs were 0.703 and euro26,400 at Expanded Disability Status Scale (EDSS) 0-3, 0.478 and euro45,300 at EDSS 4-6.5, and 0.193 and euro62,000 at EDSS 7-9. The mean cost of a relapse was estimated to be euro3000. CONCLUSION: This study provides current data on MS in Belgium that are important for development of health policies and for estimating the value of current and future treatments.

Ernstsson, O., Gyllensten, H., Alexanderson, K., et al. (2016). "Cost of Illness of Multiple Sclerosis - A Systematic Review." PLoS One **11**(7): e0159129.

> BACKGROUND: Cost-of-illness (COI) studies of Multiple Sclerosis (MS) are vital components for describing the economic burden of MS, and are frequently used in model studies of interventions of MS. We conducted a systematic review of studies estimating the COI of MS, to compare costs between studies and examine cost drivers, emphasizing generalizability and methodological choices. MATERIAL AND METHOD: A literature search on studies published in English on COI of MS was performed in PubMed for the period January 1969 to January 2014, resulting in 1,326 publications. A mapping of studies using a bottom-up approach or top-down approach, respectively, was conducted for the 48 studies assessed as relevant. In a second analysis, the cost estimates were compared between the 29 studies that used a societal perspective on costs, human capital approach for indirect costs, presenting number of patients included, time-period studied, and year of price level used. RESULTS: The mapping showed that bottom-up studies and prevalence approaches were most common. The cost ratios between different severity levels within studies were relatively stable, to the ratio of 1 to 2 to 3 for disability level categories. Drugs were the main cost drivers for MS-patients with low disease severity, representing 29% to 82% of all costs in this patient group, while the main cost components for groups with more advanced MS symptoms were production losses due to MS and informal care, together representing 17% to 67% of costs in those groups. CONCLUSION: The bottom-up method and prevalence approach dominated in studies of COI of MS. Our findings show that there are difficulties in

comparing absolute costs across studies, nevertheless, the relative costs expressed as cost ratios, comparing different severity levels, showed higher resemblance. Costs of drugs were main cost drivers for less severe MS and informal care and production losses for the most severe MS.

Fernández, O., Calleja-Hernández, M. A., Meca-Lallana, J., et al. (2017). "Estimate of the cost of multiple sclerosis in Spain by literature review." Expert Rev Pharmacoecon Outcomes Res **17**(4): 321-333.

Multiple Sclerosis (MS) is a progressive disease leading to increasing disability and costs. A literature review was carried out to identify MS costs and to estimate its economic burden in Spain. Areas Covered: The public electronic databases PubMed, ScienceDirect and IBECS were consulted and a manual review of communications presented at related congresses was carried out. A total of 225 references were obtained, of which 43 were finally included in the study. Expert Commentary: Three major cost groups were identified: direct healthcare costs, direct non-healthcare costs and indirect costs. There is a direct relationship between disease progression and increased costs, mainly direct non-healthcare costs (greater need for informal care) and indirect costs (greater loss of productivity). The total cost associated with MS in Spain is €1,395 million per year, and that the mean annual cost per patient is €30,050. Beyond costs, a large impact on the quality of life of patients, with an annual loss of up to 13,000 quality-adjusted life years was also estimated. MS has a large economic impact on Spanish society and a significant impact on the quality of life of patients.

Flachenecker, P., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for Germany." Mult Scler **23**(2_suppl): 78-90.

INTRODUCTION: To estimate the value of interventions in multiple sclerosis (MS) - where lifetime costs and outcomes cannot be observed - outcome data have to be combined with costs. This requires that cost data be regularly updated. OBJECTIVES AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting data on resource consumption and work capacity, health-related quality of life (HRQoL) and prevalent symptoms for patients with MS. Descriptive analyses are presented by level of severity, from the societal perspective, in EUR 2015. RESULTS: A total of 5475 patients (mean age 52 years) participated in Germany. In all, 84% were below retirement age, and of these, 51% were employed. Employment was related to disease severity, and MS affected productivity at work for 80% of patients. Overall, 96% and 78% of patients experienced fatigue and cognitive difficulties as a problem, respectively. The mean utility and total annual costs were 0.786 and 28,200euro at Expanded Disability Status Scale (EDSS) 0-3, 0.586 and euro44,000 at EDSS 4-6.5 and 0.273 and euro62,700 at EDSS 7-9, respectively. The mean cost of a relapse was estimated at euro2500. CONCLUSION: This study provides current health economic data on MS in Germany that are important for the development of health policies and for estimating the value of the current and future treatments.

Garcia-Dominguez, J. M., Maurino, J., Martinez-Gines, M. L., et al. (2019). "Economic burden of multiple sclerosis in a population with low physical disability." BMC Public Health **19**(1): 609.

BACKGROUND: In multiple sclerosis (MS), half of affected people are unemployed within 10 years of diagnosis. The aim of this study was to assess the economic impact of MS in adult subjects with relapsing-remitting MS (RRMS) and primary progressive MS (PPMS). METHODS: A multicenter, non-interventional, cross-sectional study was conducted. The Expanded Disability Status Scale (EDSS) and the 23-item Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ-23) were used to assess disability and work performance, respectively. Only indirect costs were considered using the human capital method, including work costs. Professional support costs and informal caregivers' costs were also estimated. RESULTS: A total of 199 subjects were studied (mean age: 43.9 +/- 10.5 years, 60.8% female, 86.4% with RRMS). Median EDSS score was 2.0 (interquartile range: 1.0-3.5) and median MSWDQ-23 total score was 31.5 (15.2, 50.0). The number of employed subjects decreased after MS diagnosis from 70.6 to 47.2%, and the number of retired people increased (23.6%). Mean age of retirement was 43.6 +/- 10.5 years. Ten percent of the population had sick leaves (absenteeism was seen in 90.9% of the student population and 30.9% of the employed population). Professional support in their daily life activities was needed in 28.1% of subjects. Costs for sick leave, work absenteeism, premature retirement and premature work disability/pensioner were euro416.6 +/- 2030.2, euro763.4 +/- 3161.8, euro5810.1 +/- 13,159.0 and euro1816.8 +/- 9630.7, respectively. Costs for professional support and informal caregiving activities were euro1026.93 +/- 4622.0 and euro1328.72, respectively. CONCLUSIONS: MS is responsible for a substantial economic burden due to indirect and informal care costs, even in a population with low physical disability.

Gyllensten, H., Kavaliunas, A., Alexanderson, K., et al. (2018). "Costs and quality of life by disability among people with multiple sclerosis: a register-based study in Sweden." Mult Scler J Exp Transl Clin **4**(3): 2055217318783352.

Background: Population-based estimates of costs of illness and health-related quality of life, by disability levels among people with multiple sclerosis, are lacking. Objectives: To estimate the annual costs of illness and health-related quality of life, by disability levels, among multiple sclerosis patients, 21-64 years of age. Methods: Microdata from Swedish nationwide registers were linked to estimate the prevalence-based costs of illness in 2013, including direct costs (prescription drug use and specialised healthcare) and indirect costs (calculated using sick leave and disability pension), and health-related quality of life (estimated from the EQ-5D). Disability level was measured by the Expanded Disability Status Scale (EDSS). Results: Among 8906 multiple sclerosis patients, EDSS 0.0-3.5 and 7.0-9.5 were associated with mean indirect costs of SEK 117,609 and 461,357, respectively, whereas direct costs were similar between the categories (SEK 117,423 and 102,714, respectively). Prescription drug costs represented 40% of the costs of illness among multiple sclerosis patients with low EDSS, while among patients with high EDSS more than 80% were indirect costs. Among the 1684 individuals who had reported both EQ-5D and EDSS, the lowest health-related quality of life scores were found among those with a high EDSS. Conclusion: Among people with multiple sclerosis, we confirmed higher costs and lower health-related quality of life in higher disability levels, in particular high indirect costs.

Gyllensten, H., Kavaliunas, A., Murley, C., et al. (2019). "Costs of illness progression for different multiple sclerosis phenotypes: a population-based study in Sweden." Mult Scler J Exp Transl Clin **5**(2): 2055217319858383.

Background: Little is known of how the cost of illness and health-related quality of life changes over time after a diagnosis of multiple sclerosis. Objectives: The aim was thus to explore the progression of annual direct and indirect costs and health-related quality of life among people with multiple sclerosis of working ages, following diagnosis with relapsing-remitting multiple sclerosis (RRMS), primary progressive multiple sclerosis (PPMS) or conversion to secondary progressive multiple sclerosis (SPMS) after RRMS. Methods: Swedish nationwide registers were linked to estimate the annual cost of illness in 2006-2013 among people with a registered new multiple sclerosis phenotype, including: direct costs, indirect costs, and health-related quality of life. Results: Drugs and indirect costs for sick leave were the main cost drivers after diagnosis with RRMS. After conversion to SPMS, the

RRMS cost drivers were replaced by indirect costs for disability pension. The main cost driver in newly diagnosed PPMS was indirect costs for sick leave, later replaced by disability pension. Health-related quality of life scores were similar after RRMS and SPMS. Conclusions: After initial high indirect costs for sick leave, people with RRMS had higher drug costs compared to people with PPMS. Cost drivers during SPMS initially followed the pattern in the RRMS population, but were replaced by indirect costs for disability pension.

Gyllensten, H., Wiberg, M., Alexanderson, K., et al. (2018). "Comparing costs of illness of multiple sclerosis in three different years: A population-based study." Mult Scler **24**(4): 520-528.

BACKGROUND: Little is known about changes in the costs of illness (COI) among multiple sclerosis (MS) patients during recent years. OBJECTIVES: To compare the COI among MS patients and matched controls in 2006, 2009, and 2012, respectively, indicating the costs attributable to the MS disease. METHODS: Three cross-sectional datasets were analyzed, including all MS patients in Sweden aged 20-60 years and five matched controls for each of them. The analyses were based on 10,531 MS patients and 52,655 matched controls for 2006, 11,722 and 58,610 individuals for 2009, and 12,789 and 63,945 for 2012. Nationwide registers, including prescription drug use, specialized healthcare, sick leave, and disability pension, were linked to estimate the prevalence-based COI. RESULTS: Adjusted for inflation, the average difference in COI between MS patients and matched controls were Swedish Krona (SEK) 243,751 (95% confidence interval: SEK 239,171-248,331) in 2006, SEK 238,971 (SEK 234,516-243,426) in 2009, and SEK 225,923 (SEK 221,630-230,218) in 2012. The difference in indirect costs were SEK 170,502 (SEK 166,478-174,525) in 2006, SEK 158,839 (SEK 154,953-162,726) in 2009, and SEK 141,280 (SEK 137,601-144,960) in 2012. CONCLUSION: The inflation-adjusted COI of MS patients was lower in 2012 than in 2006, in particular regarding indirect costs.

Gyllensten, H., Wiberg, M., Alexanderson, K., et al. (2018). "Costs of illness of multiple sclerosis in Sweden: a population-based register study of people of working age." Eur J Health Econ **19**(3): 435-446.

BACKGROUND: Multiple sclerosis (MS) causes work disability and healthcare resource use, but little is known about the distribution of the associated costs to society. OBJECTIVES: We estimated the cost of illness (COI) of working-aged individuals with MS, from the societal perspective, overall and in different groups. METHODS: A population-based study was conducted, using data linked from several nationwide registers, on 14,077 individuals with MS, aged 20-64 years and living in Sweden. Prevalence-based direct and indirect costs in 2010 were calculated, including costs for prescription drug use, specialized healthcare, sick leave, and disability pension. RESULTS: The estimated COI of all the MS patients were SEK 3950 million, of which 75% were indirect costs. MS was the main diagnosis for resource use, causing 38% of healthcare costs and 67% of indirect costs. The distribution of costs was skewed, in which less than 25% of the patients accounted for half the total COI. CONCLUSIONS: Indirect costs contributed to approximately 75% of the estimated overall COI of MS patients of working age in Sweden. MS was the main diagnosis for more than half of the estimated COI in this patient group. Further studies are needed to gain knowledge on development of costs over time during the MS disease course.

Harirchian, M. H., Fatehi, F., Sarraf, P., et al. (2018). "Worldwide prevalence of familial multiple sclerosis: A systematic review and meta-analysis." Mult Scler Relat Disord **20**: 43-47.

BACKGROUND: Several studies have suggested that the existence of a history of multiple sclerosis (MS) in family, is one of the predisposing factors for MS. Based on our knowledge, the review and estimation of the prevalence of familial multiple sclerosis (FMS) in the world has not been reported up to now. This study is a systematic review and a meta-analysis of FMS prevalence in the world. METHODS: Two researchers searched "epidemiology" or "prevalence" or "incidence" and "familial multiple sclerosis" as relevant keywords in international databases such as PubMed, web of science and Scopus up to 2016. MedCalc Version 15.8 was used to estimate the pooled prevalence of FMS. (PROSPERO ID = CRD42016033016) RESULTS: From the 184 total articles found from 1954 to 2016, we pooled and analyzed the data of 17 final eligible studies, according to the inclusion criteria. The prevalence of FMS was estimated as 12.6% within a total sample size of 14,619 MS patients in the world as of 95% confidence interval (CI: 9.6-15.9). CONCLUSION: We detected significant heterogeneity from Hungary to Saskatchewan for FMS prevalence that was not latitude and ethnicity dependent. This highlighted the accumulation effects of genetic and environment on FMS prevalence. Pooled prevalence of FMS in MS population was calculated 12.6% by random effect in the world.

Havrdova, E., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results of the Czech Republic." Mult Scler **23**(2_suppl): 41-52.

INTRODUCTION: In order to estimate the value of interventions in multiple sclerosis (MS) - where lifetime costs and outcomes cannot be observed - outcome data have to be combined with costs. This requires that cost data be regularly updated. OBJECTIVES AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting data on resource consumption and work capacity, health-related quality of life (HRQoL) and prevalent symptoms for patients with MS. Descriptive analyses are presented by level of severity, in the societal perspective, in CZK 2015. RESULTS: A total of 747 patients (mean age 47 years) participated; 86% were below retirement age and of these, 49% were employed. Employment was related to disease severity, and MS affected productivity at work for 82% of those working. Overall, 92% and 66% of patients experienced fatigue and cognitive difficulties as a problem. Mean utility and annual costs were 0.832 and 257,000CZK at Expanded Disability Status Scale (EDSS) 0-3, 0.530 and 425,500CZK at EDSS 4-6.5 and 0.141 and 489,000CZK at EDSS 7-9. The average cost of a relapse was estimated at 12,600CZK. CONCLUSION: This study provides current data on MS in the Czech Republic that are important for the development of health policies.

Howard, J., Trevick, S. et Younger, D. S. (2016). "Epidemiology of Multiple Sclerosis." Neurol Clin **34**(4): 919-939.

The epidemiology of multiple sclerosis (MS) includes a consideration of genetic and environmental factors. Comparative studies of different populations have revealed prevalence and incidence rates that vary with geography and ethnicity. With a prevalence ranging from 2 per 100,000 in Japan to greater than 100 per 100,000 in Northern Europe and North America, the burden of MS is similarly unevenly influenced by longevity and comorbid disorders. Well-powered genome-wide association studies have investigated the genetic substrate of MS, providing insight into autoimmune mechanisms involved in the etiopathogenesis of MS and elucidating possible avenues of biological treatment.

Iljicsov, A., Milanovich, D., Ajtay, A., et al. (2020). "Incidence and prevalence of multiple sclerosis in Hungary based on record linkage of nationwide multiple healthcare administrative data." PLoS One **15**(7): e0236432.

OBJECTIVES: As there were only regional studies in Hungary about the prevalence of multiple sclerosis (MS), we aimed to estimate its epidemiological features using data of Hungary's single-payer health insurance system. METHODS: Pseudonymized database of claims reported by hospitals and outpatient services between 2004-2016 was analyzed and linked with an independent database of outpatient pharmacy refills between 2010-2016. We established an administrative case definition of MS and validated it on medical records of 309 consecutive patients. A subject was defined as MS-patient if received MS diagnosis (International Classification of Diseases, 10th edition, code G35) on three or more occasions at least in 2 calendar years and at least once documented by a neurologist. Patients were counted as incident cases in the year of the first submitted claim for MS. We allowed a 6-year-long run-in period, so only data between 2010-2015 are discussed. RESULTS: Sensitivity of the administrative case definition turned out to be 99%, while specificity was >99%. Crude prevalence of MS has increased from 109.3/100,000 in 2010 to 130.8/100,000 in 2015 (p-value = 0.000003). Crude incidence declined from 7.1/100,000 (2010) to 5.4/100,000 (2015) (p-value = 0.018). Direct standardization - based on European standard population and results of nationwide Hungarian census of 2011 - revealed that age standardized prevalence was 105.2/100,000 (2010), which has grown to 127.2/100,000 (2015) (p-value = 0.000001). Age standardized incidence rate declined from 6.7/100,000 (2010) to 5.1/100,000 (2015) (p-value = 0.016). The ratio of MS-patients receiving ≥1 prescription for disease modifying treatment increased from 0.19 (2010) to 0.29 (2015) (p-value = 0.0051). The female/male ratio of prevalent cases remained 2.6. DISCUSSION: The prevalence of MS in Hungary is higher than previously reported, the incidence rate is moderate. The prevalence is rising, the incidence rate shows decline. The proportion of patients receiving disease modifying treatment grows but was still around 30% in 2015.

Ivanova, J. I., Birnbaum, H. G., Samuels, S., et al. (2009). "The cost of disability and medically related absenteeism among employees with multiple sclerosis in the US." Pharmacoeconomics **27**(8): 681-691.

Studies have not previously reported the indirect cost burden of multiple sclerosis (MS) from an employer perspective. To compare annual indirect costs between privately insured US employees with MS and matched employee controls. A retrospective analysis of a privately insured claims database containing disability data from 17 US companies was conducted. Employees with >/=1 MS diagnosis (ICD-9-CM: 340.x) after 1 January 2002, aged 18-64 years, were selected. Employees with MS were matched by age and sex to employee controls without MS. All were required to have continuous health coverage 3 months before MS diagnosis (baseline) and 12 months after (study period). Main outcomes measures included study period annual indirect (disability and medically related absenteeism) costs. For completeness, we also included measures of direct (medical and drug) costs. Chi-squared tests were used to compare baseline co-morbidities and differences in indirect resource use (disability and medically related absenteeism) between employees with MS and controls. Wilcoxon rank-sum tests were used for univariate comparisons of disability and medically related absenteeism days and associated annual indirect and direct costs between employees with MS and controls. Generalized linear models, controlling for differences in baseline characteristics, were used to estimate risk-adjusted annual costs for employees with MS and controls. Employees with MS (n = 989) averaged 44 years of age, and 66% were female. Compared with employee controls, employees with MS had significantly higher rates of mental health disorders, other neurological disorders and physical disorders measured by the Charlson Co-morbidity Index. Employees with MS were more likely to have short-term or long-term disability than employee controls (21.4% vs 5.2%, respectively; p < 0.0001), resulting in a higher mean number of disability days per year (29.8 vs 4.5; p < 0.0001). Employees with MS also had a higher rate of medically related absenteeism and associated absenteeism days than employee controls. On average, annual costs (year 2006 values) for disability were significantly higher for employees with MS ($US3868) than employee controls

($US414; p < 0.0001). Annual medically related absenteeism costs were also higher for employees with MS than for controls ($US1901 vs $US1003, respectively; p < 0.0001). On average, total annual indirect costs for employees with MS were $US5769 compared with $US1417 for controls (p < 0.0001). MS is a chronic and debilitating disease that poses a substantial employer burden in terms of medically related absenteeism and disability costs. Indirect costs of employees with MS were >4 times those of employee controls.

Jennum, P., Wanscher, B., Frederiksen, J., et al. (2012). "The socioeconomic consequences of multiple sclerosis: a controlled national study." Eur Neuropsychopharmacol **22**(1): 36-43.

> Multiple sclerosis (MS) has serious negative effects on health-, social-, and work-related issues for the patients and their families, thus causing significant socioeconomic burden. The objective of the study was to determine healthcare costs and indirect illness costs in MS patient in a national sample. We used all national records from the Danish National Patient Registry (1998-2006), and identified 10,849 MS patients which were compared with 43,396 randomly age-, sex- and social matched citizens. Healthcare sector costs included frequencies and costs of hospitalizations and weighted outpatient use, frequencies of visits and hospitalizations and costs from primary sectors, and the use and costs of drugs. Productivity costs (the value of lost productivity from time off from work due to illness) and all social transfer payments were also calculated. Patients with MS had significantly higher rates of health-related contact and medication use and very low employment rate which incurred a higher socioeconomic cost. The income level of employed MS patients was significantly lower than that of control subjects. The annual total health sector costs and productivity costs were euro14,575 for MS patients vs. euro1163 for control subjects (p<0.001), corresponding to an annual mean excess health-related cost of euro13,413 for each patient with MS. In addition, the MS patients received an annual mean excess social transfer income of euro6843. MS present social and economical consequences more than eight years before diagnosis. We conclude that MS causes major socioeconomic consequences for the individual patient and for society. Productivity costs are a far more important economic factor, especially due to reduced employment, which are enhanced by the early age of diagnose onset.

Jones, E., Pike, J., Marshall, T., et al. (2016). "Quantifying the relationship between increased disability and health care resource utilization, quality of life, work productivity, health care costs in patients with multiple sclerosis in the US." BMC Health Serv Res **16**: 294.

> BACKGROUND: Multiple sclerosis (MS) is a chronic progressive condition affecting the central nervous system. Progression of MS results in increased level of disability and most patients will eventually experience some degree of functional impairment and impaired mobility. Costs and burdens escalate as MS disability increases. However, there is a lack of recent data on the impact of MS disability on the cost and burden among patients in the US. METHODS: Data for this study were drawn from a real world, cross-sectional survey undertaken between 2013 and 2014. Neurologists completed detailed patient report forms (PRF) for the most recent consulting patients with MS (age >18 years). Patient's perceptions of their diagnosis and health-related quality of life (HRQoL) were collected through a patient self-completion questionnaire (PSC). Regression analysis was used to evaluate the relationship between disability (determined by latest Expanded Disability Status Scale [EDSS] score) and current relapse and health care resource utilization, health care costs, HRQoL and work productivity. RESULTS: PRF data were collected for 715 patients (335 also completed a PSC). Patients with higher disability scores (EDSS 3-5 and >5 vs <3 points) and current relapse (vs no current relapse) reported significantly greater health resource utilization for physician visits (p < 0.05) and hospitalizations (p < 0.05) in the preceding 12 months. In addition, they had poorer HRQoL (p < 0.05), were significantly more likely to be unemployed (p < 0.05) and

to have had to stop working due to MS (p < 0.05). They also incurred significantly higher health care related costs, including costs for physician consultations, hospitalizations and therapy (p < 0.05). The total costs of care were $51,825, $57,889 and $67,116 for EDSS < 3, EDSS 3-5 and EDSS > 5 groups, respectively; $51,692 and $58,648 for non-relapse and relapse groups, respectively. CONCLUSIONS: For MS patients in the US, health resource utilization and healthcare care costs increase with progression of disability. As the disability worsens, patients also exhibit diminished HRQoL and lower work productivity. There is a need for treatments that slow down or delay disability progression among MS patients.

Kapica-Topczewska, K., Tarasiuk, J., Chorąży, M., et al. (2020). "The epidemiology of comorbidities among multiple sclerosis patients in northeastern Poland." Mult Scler Relat Disord **41**: 102051.

BACKGROUND: To determine and compare comorbidity levels in the multiple sclerosis (MS) population in Poland using a matched cohort from the general population. METHODS: We compared our database (standardized medical histories and medical records) from a MS center at the Department of Neurology, Medical University of Bialystok, Poland) with local National Health Fund (NHF) data (all patients presenting to healthcare facilities with a diagnosis of MS (ICD 10: G35)). We identified 1299 MS cases from the NHF data and 952,434 age and geographically matched controls. We estimated the prevalence of depression, sleep disorders, epilepsy, hypertension, hyperlipidemia, diabetes, atherosclerosis, lung infections, thyroid disease, discopathy, and urinary tract infections in the MS population versus matched controls. RESULTS: In all, 815 cases of MS (67.6% women and 32.4% men) were registered with the MS center. According to the patients' medical records (with ICD 10 coding), the most common comorbidities were hypertension (4.3%) and thyroid diseases (3.3%). In addition, in standardized medical histories comorbidities were reported by MS patients: depression/depressed mood in 37.6% of patients (67% of whom had sought treatment), pain in 69.6% patients, urinary incontinence in 39.2% patients (44.9% of whom were treated), memory-related problems and fatigue in 39.2% and 70.8% patients, respectively. In the local NHF data, the most common comorbidities were hypertension (8%), diseases that cause back pain [ICD 10:M50-54 (4.3%),G54-55 (3%), M47-48 (5.4%)], urinary tract infection (3.5%), depression (2.4%), hyperlipidemia (2%), and diabetes (2%). All comorbidities except depression and sleep disorders were more common in the matched controls than in the MS population. Diabetes and hyperlipidemia in the MS population were more common in men than women. Most patients (89%) were not treated with disease-modifying therapies. CONCLUSION: The most common comorbidity in the MS population is hypertension. The MS population has an increased prevalence of depression versus the matched controls. MS patients-especially men and older individuals-are at increased risk of developing vascular diseases.

Karampampa, K., Gyllensten, H., Yang, F., et al. (2020). "Healthcare, Sickness Absence, and Disability Pension Cost Trajectories in the First 5 Years After Diagnosis with Multiple Sclerosis: A Prospective Register-Based Cohort Study in Sweden." Pharmacoecon Open **4**(1): 91-103.

OBJECTIVES: The aim was to longitudinally explore the healthcare, sickness absence (SA), and disability pension (DP) cost trajectories among newly diagnosed people with multiple sclerosis (MS), and investigate whether trajectories differ by year of MS diagnosis, sociodemographics, and multi-morbidity. METHODS: People with MS in Sweden, aged 25-60 years and with a new MS diagnosis in the years 2006, 2007, 2008, or 2009 (four different cohorts) were identified in nationwide registers and followed prospectively for 5 years, determining the annual, per patient, direct (inpatient and specialised outpatient healthcare, co-payments, and dispensed drugs) and indirect (SA and DP) costs. Descriptive statistics and group-based trajectories were computed. RESULTS: In total, 3272 people with new MS were identified. In all cohorts, direct costs increased the year after diagnosis and thereafter declined (e.g. from euro8261 to euro9128, and to euro7953, 5 years after diagnosis, for the 2006 cohort). SA costs continuously decreased over 5 years, while DP costs increased (e.g. from euro9795 to euro2778 vs. from euro7277 to euro15,989, respectively, for the 2006 cohort). When pooling all cohorts, four trajectories of direct and indirect costs were identified. A total of 32.1% of people with MS had high direct and indirect costs, which first increased and then decreased; the contrary was seen for trajectories with low direct and indirect costs. CONCLUSIONS: There is heterogeneity in the development of MS costs over time after diagnosis; decreasing cost trajectories could be associated with the use of innovative MS therapies, slowing disease progression over time.

Kawachi, I., Okamoto, S., Sakamoto, M., et al. (2019). "Recent transition of medical cost and relapse rate of multiple sclerosis in Japan based on analysis of a health insurance claims database." BMC Neurol **19**(1): 324.

BACKGROUND: In this study, we aimed to understand the trends in total and itemized medical expenses, especially of disease-modifying therapy (DMT), for multiple sclerosis (MS) in Japan through an analysis of health insurance claims data. METHODS: We analyzed a database containing health insurance claims data from hospitals that have adopted the Diagnosis Procedure Combination/Per-Diem Payment System in Japan. According to an algorithm based on diagnosis codes, data for all patients diagnosed with MS from April 2008 to July 2016 were extracted. Medical costs, rate of each medical treatment, and rate of relapses were analyzed by calendar-year. Medical costs in the month of relapse were compared with average medical costs per month of all MS patients by a cross-sectional analysis. RESULTS: Four thousand three hundred seventy-four MS patients were identified in the database. Total medical cost per patient per month (PPPM) increased from ¥87,640 (US$787.7 or €723.0 as of May 2017) to ¥102,846 (US$924.4 or €848.4) during the study period. This increment was mainly attributed to the growth in cost of outpatient DMT prescriptions, which increased from ¥23,039 (US$207.1 or €190.1) to ¥51,351 (US$461.5 or €423.6). In contrast, the rate of hospitalizations and relapses PPPM decreased during the study period (from 0.053 to 0.030, and 0.032 to 0.019, respectively). Medical costs in the month of relapse (¥424,661, US$3816.8 or €3503.1) were 3.57 times higher than the average monthly costs for all MS patients (¥119,021, US$1069.8 or €981.8), with the majority comprising hospitalization cost. CONCLUSION: Concomitant with the increased usage of DMT, the total medical cost for treating MS is increasing in Japan. However, rates of relapse and hospitalization have shown a decreasing trend. Although this study does not show the direct causality between DMT and reduction of relapse rates/fewer hospitalizations among MS patients, a reduction in hospital costs has been revealed concomitantly with the increasing prevalence of DMT.

Kobelt, G., Thompson, A., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe." Mult Scler **23**(8): 1123-1136.

BACKGROUND: The current focus in multiple sclerosis (MS) is on early diagnosis and drug intervention, with a view to modifying disease progression. Consequently, healthcare costs have shifted from inpatient care and rehabilitation to outpatient care. OBJECTIVES: This European burden of illness study provides data that can be combined with other evidence to assess whether management approaches provide value to society. METHODS: A cross-sectional study was conducted in 16 countries. Patients reported on their disease, health-related quality of life (HRQoL) and resource consumption. Descriptive analyses were performed by disease severity. Costs are reported from a societal perspective in 2015€ PPP (adjusted for purchasing power parity). RESULTS: The 16,808 participants had a mean age of

51.5 years, and 52% had relapsing-remitting multiple sclerosis (RRMS). Work capacity declined from 82% to 8%, and utility declined from normal population values to less than zero with advancing disease. Mean costs were 22,800€ PPP in mild, 37,100€ PPP in moderate and 57,500€ PPP in severe disease; healthcare accounted for 68%, 47% and 26%, respectively. Fatigue and cognitive difficulties were reported by 95% and 71% of participants, respectively; both had a significant independent effect on utility. CONCLUSION: Costs and utility were highly correlated with disease severity, but resource consumption was heavily influenced by healthcare systems organisation and availability of services.

Kotsopoulos, N., Connolly, M. P., Dort, T., et al. (2020). "The fiscal consequences of public health investments in disease-modifying therapies for the treatment of multiple sclerosis in Sweden." J Med Econ: 1-7.

Background and aims: The economic consequences of multiple sclerosis (MS) are broader than those observed within the health system. The progressive nature suggests that people will not be able to live a normal productive life and will gradually require public benefits to maintain living standards. This study investigates the public economic impact of MS and how investments in disease-modifying therapies (DMTs) influence the lifetime costs to government attributed to changes in lifetime tax revenue and disability benefits based on improved health status linked to delayed disease progression.Methods: Disease progression rates from previous MS Markov cohort models were applied to interferon beta-1a, peginterferon beta-1a, dimethyl fumarate, and natalizumab using a public economic framework. The established relationship between expanded disability status scale and work-force participation, annual earnings, and disability rates for each DMT were applied. Subsequently, we assessed the effect of DMTs on discounted governmental costs consisting of health service costs, social insurance and disability costs, and changes in lifetime tax revenues.Results: Fiscal benefits attributed to informal care and community services savings for interferon beta-1a, peginterferon beta-1a, dimethyl fumarate, and natalizumab were SEK340,387, SEK486,837, SEK257,330, and SEK958,852 compared to placebo, respectively. Tax revenue gains linked to changes in lifetime productivity for interferon beta-1a, peginterferon beta-1a, dimethyl fumarate, and natalizumab were estimated to be SEK27,474, SEK39,659, SEK21,661, and SEK75,809, with combined fiscal benefits of cost savings and tax revenue increases of SEK410,039, SEK596,592, SEK326,939, and SEK1,208,023, respectively.Conclusion: The analysis described here illustrates the broader public economic benefits for government attributed to changes in disease status. The lifetime social insurance transfer costs were highest in non-treated patients, and lower social insurance costs were demonstrated with DMTs. These findings suggest that focusing cost-effectiveness analysis only on health costs will likely underestimate the value of DMTs.

Koziarska, D., Krol, J., Nocon, D., et al. (2018). "Prevalence and factors leading to unemployment in MS (multiple sclerosis) patients undergoing immunomodulatory treatment in Poland." PLoS One **13**(4): e0194117.

Multiple Sclerosis (MS) is the most common, primary neurogenic cause of disability among young adults. We investigated demographic and clinical factors associated with unemployment on the example of 150 MS patients receiving immunomodulatory treatment in Poland. This study was based on clinical evaluation and collection of self-reported questionnaires, with an attention to self-motivation, severe fatigue and moderate disability. Patients who were unemployed (40% of all patients) had a mean disease duration of almost 5 years. Older (p<0.001), less educated (p = 0.007) and more severely disabled patients (p<0,001) were most likely to be unemployed. Moderate disability (OR = 11.089 95% CI: 4.11-34.201, p<0,001), severe fatigue (OR = 2.625 95% CI: 1.02-6.901, p = 0,046) and lower level of self-motivation (KNS) (OR = 0.947, 95% CI: 0.896-0.006, p = 0.042) were independently associated with unemployment.

Li, P., Hu, T., Yu, X., et al. (2018). "Impact of Cost-Sharing Increases on Continuity of Specialty Drug Use: A Quasi-Experimental Study." Health Serv Res **53 Suppl 1**(Suppl Suppl 1): 2735-2757.

OBJECTIVE: To examine the impact of cost-sharing increases on continuity of specialty drug use in Medicare beneficiaries with multiple sclerosis (MS) or rheumatoid arthritis (RA). DATA SOURCES/STUDY SETTING: Five percent Medicare claims data (2007-2010). STUDY DESIGN: Quasi-experimental study examining changes in specialty drug use among a group of Medicare Part D beneficiaries without low-income subsidies (non-LIS) as they transitioned from a 5 percent cost-sharing preperiod to a ≥25 percent cost-sharing postperiod, as compared to changes among a disease-matched contemporaneous control group of patients eligible for full low-income subsidies (LIS), who faced minor cost sharing (≤$6.30 copayment) in both the pre- and postperiods. DATA COLLECTION/EXTRACTION METHODS: Key variables were extracted from Medicare data. PRINCIPAL FINDINGS: Relative to the LIS group, the non-LIS group had a greater increase in incidence of 30-day continuous gaps in any Part D treatment from the lower cost-sharing period to the higher cost-sharing period (MS, absolute increase = 10.1 percent, OR = 1.61, 95% CI 1.19-2.17; RA, absolute increase = 21.9 percent, OR = 2.75, 95% CI 2.15-3.51). The increase in Part D treatment gaps was not offset by increased Part B specialty drug use. CONCLUSIONS: Cost-sharing increases due to specialty tier-level cost sharing were associated with interruptions in MS and RA specialty drug treatments.

Lo, J., Chan, L. et Flynn, S. (2020). "A Systematic Review of the Incidence, Prevalence, Costs, and Activity and Work Limitations of Amputation, Osteoarthritis, Rheumatoid Arthritis, Back Pain, Multiple Sclerosis, Spinal Cord Injury, Stroke, and Traumatic Brain Injury in the United States: A 2019 Update." Arch Phys Med Rehabil.

OBJECTIVES: To present recent evidence on the prevalence, incidence, costs, activity limitations, and work limitations of common conditions requiring rehabilitation. DATA SOURCES: Medline (PubMed), SCOPUS, Web of Science, and the gray literature were searched for relevant articles about amputation, osteoarthritis, rheumatoid arthritis, back pain, multiple sclerosis, spinal cord injury, stroke, and traumatic brain injury. STUDY SELECTION: Relevant articles (N=106) were included. DATA EXTRACTION: Two investigators independently reviewed articles and selected relevant articles for inclusion. Quality grading was performed using the Methodological Evaluation of Observational Research Checklist and Newcastle-Ottawa Quality Assessment Form. DATA SYNTHESIS: The prevalence of back pain in the past 3 months was 33.9% among community-dwelling adults, and patients with back pain contribute $365 billion in all-cause medical costs. Osteoarthritis is the next most prevalent condition (approximately 10.4%), and patients with this condition contribute $460 billion in all-cause medical costs. These 2 conditions are the most prevalent and costly (medically) of the illnesses explored in this study. Stroke follows these conditions in both prevalence (2.5%-3.7%) and medical costs ($28 billion). Other conditions may have a lower prevalence but are associated with relatively higher per capita effects. CONCLUSIONS: Consistent with previous findings, back pain and osteoarthritis are the most prevalent conditions with high aggregate medical costs. By contrast, other conditions have a lower prevalence or cost but relatively higher per capita costs and effects on activity and work. The data are extremely heterogeneous, which makes anything beyond broad comparisons challenging. Additional information is needed to determine the relative impact of each condition.

Magyari, M. et Sorensen, P. S. (2019). "The changing course of multiple sclerosis: rising incidence, change in geographic distribution, disease course, and prognosis." Curr Opin Neurol **32**(3): 320-326.

> PURPOSE OF REVIEW: This review provides a brief update of new research findings on the changing epidemiology, disease course, and prognosis of multiple sclerosis (MS). RECENT FINDINGS: Evidence not only continues to support the female predominance in incidence and prevalence of the disease but also supports an increase in incidence of MS in geographic areas that were previously considered to be low incidence for the disease. SUMMARY: An increased interest in population-based registries and databases will provide more valid epidemiological measures and observational studies conducted in well-defined study populations. Such studies are crucial for an accurate description of both changing prognosis of MS and differential characteristics of the various MS phenotypes.

Malinowski, K. P., Kawalec, P. P. et Mocko, P. (2016). "Indirect costs of absenteeism due to rheumatoid arthritis, psoriasis, multiple sclerosis, insulin-dependent diabetes mellitus, and ulcerative colitis in 2012: a study based on real-life data from the Social Insurance Institution in Poland." Expert Rev Pharmacoecon Outcomes Res **16**(2): 295-303.

> INTRODUCTION: The aim of this study is to assess the indirect costs of six major autoimmune diseases including seropositive rheumatoid arthritis, other types of rheumatoid arthritis, psoriasis, multiple sclerosis, Type 1 diabetes, and ulcerative colitis. METHODS: Relevant data for 2012 on sick leave and short- and long-term work disabilities were obtained from the Social Insurance Institution in Poland. Indirect costs were estimated using the human capital approach based on gross domestic product per capita, gross value added per worker, and gross income per worker in Poland in 2012 and expressed in euro. RESULTS: We recorded data on the total number of 45,500 patients. The total indirect costs were EUR 146,862,569; 353,683,508; and 108,154,271, calculated using gross domestic product, gross value added, and gross income, respectively. CONCLUSIONS: Considering only data on absenteeism collected by the Social Insurance Institution in Poland, we can conclude that the selected autoimmune diseases are associated with great indirect costs.

Moccia, M., Tajani, A., Acampora, R., et al. (2019). "Healthcare resource utilization and costs for multiple sclerosis management in the Campania region of Italy: Comparison between centre-based and local service healthcare delivery." PLoS One **14**(9): e0222012.

> BACKGROUND: Multiple sclerosis (MS) requires multidisciplinary management. We evaluated differences in healthcare resource utilization and costs between Federico II and Vanvitelli MS Centres of Naples (Italy), representative of centralised (i.e., MS Care Unit) and local service-based models of multidisciplinary care, respectively. METHODS: We included MS patients continuously seen at the same local healthcare services and MS Centre (Federico II = 187; Vanvitelli = 90) from 2015 to 2017. Healthcare resources for MS treatment and management were collected and costs were calculated. Adherence was estimated as the rate of medication possession ratio (MPR) during 3-years of follow-up. Mixed-effect linear regression models were used to estimate differences in all outcomes between Federico II and Vanvitelli. RESULTS: Patients at Federico II had more consultations within the MS centre (p<0.001), blood tests (p<0.001), and psychological/cognitive evaluations (p = 0.040). Patients at Vanvitelli had more consultations at local services (p<0.001). Adherence was not-significantly lower at Vanvitelli (p = 0.060), compared with Federico II. Costs for MS treatment and management were 10.6% lower at Vanvitelli (12417.08±8448.32EUR) (95%CI = -19.0/-2.7%;p = 0.007), compared with Federico II (15318.57±10919.59EUR). DISCUSSION: Healthcare services were more complete (and expensive) at the Federico II centralised MS Care Unit, compared with the Vanvitelli local service-based organizational model. Future

research should evaluate whether better integration between MS Centres and local services can lead to improved MS management and lower costs.

Murley, C., Karampampa, K., Alexanderson, K., et al. (2020). "Diagnosis-specific sickness absence and disability pension before and after multiple sclerosis diagnosis: An 8-year nationwide longitudinal cohort study with matched references." Mult Scler Relat Disord **42**: 102077.

BACKGROUND: Multiple sclerosis (MS) typically onsets when of working age and may reduce work capacity. Previous studies have examined the risk of sickness absence (SA) and disability pension (DP) among MS patients, however, limited knowledge is available on whether MS patients have an excess risk for SA/DP when compared with the general population in Sweden. Moreover, no information exists on the actual diagnoses for SA and DP among MS patients and whether the patterns of SA/DP diagnoses differs to those without MS. We aimed to explore diagnosis-specific SA and DP among working-aged MS patients both before and after MS diagnosis, in comparison to the levels and distributions of SA and DP diagnoses of a matched reference group and analyze the risk of diagnosis-specific DP. MATERIALS AND METHODS: Longitudinal Swedish register data of the 2567 MS patients diagnosed with MS in 2009-2012 when aged 25-59 and 10,268 population-based matched references (matched on sex, age, educational level, type of living area, and country of birth) were analysed regarding annual diagnosis-specific SA and DP in the four years before and four years after MS diagnosis. Annual differences in the mean numbers of SA and/or DP net days were calculated with 95% confidence intervals (CI). Hazard ratios (HR) with 95% CI from Cox proportional hazard models were used to compare risks for new all-cause and diagnosis-specific DP after MS diagnosis among the MS patients and references. RESULTS: The mean SA/DP net days/year increased among MS patients over follow-up, due to both MS and other diagnoses. During follow-up, around 50% of MS patients had some SA/DP compared to 20% of references. The mean days of SA/DP among the MS patients compared to references increased from 10.3 more days (95% CI: 6.6-14.2) four years prior to MS diagnosis to 68.9 days (62.8-75.1) 4 years after MS diagnosis. Although most new DP among MS patients were due to MS, 15% were not. The adjusted HR for all-cause DP was 23.1 (18.1-29.5). MS patients also had higher risks of new DP due to all diagnoses except MS (HR 3.4; 2.4-4.8), musculoskeletal (HR 2.6; 1.1-6.0) and mental (HR 2.0; 1.1-3.6) diagnoses compared with references. CONCLUSION: MS patients had higher levels of SA/DP days/year than the references, already 4 years before the MS diagnosis, and increasingly so thereafter. The excess of SA/DP prior to MS diagnosis could be related to MS onset. However, the excess of SA/DP days were not all due to MS diagnoses, even after being diagnosed with MS. MS patients had a higher risk of having a new DP after being diagnosed with MS in total, but also for diagnoses other than MS.

Ochi, H. (2020). "[Epidemiology of Multiple Sclerosis: Is Multiple Sclerosis on the Rise?]." Brain Nerve **72**(5): 467-484.

Multiple sclerosis (MS) is a worldwide disease with an uneven geographic distribution. There has been a sharp increase in MS prevalence over time almost throughout the world, including Japan. The reasons for the increase in the prevalence of MS are unknown. However, evidence suggests that genetic and environmental factors and their interaction contribute to the etiology of MS. Therefore, the increase in prevalence can be attributed in part to a greater exposure to certain environmental risk factors in genetically susceptible individuals and also to increased survival rates and improved assessment. To clarify whether the increase in MS prevalence reflects a real increase in disease frequency, it is essential to assess temporal and geographical differences in MS incidence and to compair incidence in different ethnic populations. However, epidemiological data on incidence are limited, and there are marked geographical disparities in available data, most of which were obtained from studies in Europe and North America. In addition, there are marked variabilities in methodology, objectives, and study periods. Further epidemiological studies with appropriate standardization are needed to determine whether the risk of MS has changed over time.

Ohlmeier, C., Gothe, H., Haas, J., et al. (2020). "Epidemiology, characteristics and treatment of patients with relapsing remitting multiple sclerosis and incidence of high disease activity: Real world evidence based on German claims data." PLoS One **15**(5): e0231846.

BACKGROUND: Multiple Sclerosis (MS) is a chronic inflammatory, immune mediated disease of the central nervous system, with Relapsing Remitting MS (RRMS) being the most common type. Within the last years, the status of high disease activity (HDA) has become increasingly important for clinical decisions. Nevertheless, little is known about the incidence, the characteristics, and the current treatment of patients with RRMS and HDA in Germany. Therefore, this study aims to estimate the incidence of HDA in a German RRMS patient population, to characterize this population and to describe current drug treatment routines and further healthcare utilization of these patients. METHODS: A claims data analyses has been conducted, using a sample of the InGef Research Database that comprises data of approximately four million insured persons from around 70 German statutory health insurances (SHI). The study was conducted in a retrospective cohort design, including the years 2012-2016. Identification of RRMS population based on ICD-10 code (ICD-10-GM: G35.1). For identification of HDA, criteria from other studies as well as expert opinions have been used. Information on incidence, characteristics and current treatment of patients with RRMS and HDA was considered. RESULTS: The overall HDA incidence within the RRMS population was 8.5% for 2016. It was highest for the age group of 0-19 years (29.4% women, 33.3% men) and lowest for the age group of ≥ 50 years (4.3% women, 5.6% men). Mean age of patients with RRMS and incident HDA was 38.4 years (SD: 11.8) and women accounted for 67.8%. Analyses of drug utilization showed that 82.4% received at least one disease-modifying drug (DMD) in 2016. A percentage of 49.8% of patients received drugs for relapse therapy. A share of 55% of RRMS patients with HDA had at least one hospitalization with a mean length of stay of 13.9 days (SD: 18.3 days) in 2016. The average number of outpatient physician contacts was 28.1 (SD: 14.0). CONCLUSIONS: This study based on representative Germany-wide claims data from the SHI showed a high incidence of HDA especially within the young RRMS population. Future research should consider HDA as an important criterion for the quality of care for MS patients.

Oreja-Guevara, C., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for Spain." Mult Scler **23**(2_suppl): 166-178.

INTRODUCTION: In order to estimate the value of interventions in multiple sclerosis (MS) where lifetime costs and outcomes cannot be observed, outcome data have to be combined with costs. This requires that cost data be regularly updated. OBJECTIVES AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting data on resource consumption, work capacity, health-related quality of life (HRQoL) and prevalent symptoms for patients with MS. Descriptive analyses are presented by level of severity, from the societal perspective, in EUR 2015. RESULTS: A total of 462 patients (mean age 43 years) participated in Spain; 96% were below retirement age and of these, 45% were employed. Employment was related to disability, and MS affected productivity at work for 72% of those working. Overall, 92% and 64% of patients experienced fatigue and cognitive difficulties as a problem, respectively. Mean utility and total annual costs were estimated at 0.772 and euro20,600 at Expanded Disability Status Scale (EDSS) 0-3, 0.486 and euro48,500 at EDSS 4-

6.5 and 0.182 and euro68,700 at EDSS 7-9, respectively. The mean cost of a relapse was euro2050. CONCLUSION: This study illustrates the burden of MS on Spanish patients and provides current data that are important for development of health policies.

Palmer, A. J., Colman, S., O'Leary, B., et al. (2013). "The economic impact of multiple sclerosis in Australia in 2010." Mult Scler **19**(12): 1640-1646.

BACKGROUND: Multiple sclerosis (MS) has a major impact on health and is a substantial burden on patients and society. We estimated the annual costs of MS in Australia from individual and societal perspectives using data from the Australian MS Longitudinal Study (AMSLS) and prevalence figures from 2010. METHODS: Direct and indirect costs were estimated from a subsample of 712 AMSLS subjects who completed baseline and follow-up economic impact surveys. All costs are in 2010 Australian dollars (AUD). RESULTS: Annual costs per person with MS were AUD48,945 (95% CI: 45,138 to 52,752). Total costs were AUD1.042 (0.9707 to 1.1227) billion based on a prevalence of 21,283. The largest component was indirect costs due to loss of productivity (48%). Costs increased with increasing disability: AUD36,369, AUD58,890 and AUD65,305 per patient per year for mild, moderate and severe disability, respectively. Total costs of MS to Australian society have increased 58% between 2005 and 2010. CONCLUSIONS: This study confirms that MS imposes a substantial burden on Australian society, particularly impacting on productivity. The burden increases with worsening disability associated with the disease. Investment in interventions that slow progression, as well as resources, services and environments that assist people with MS to retain employment, is supported.

Paz-Zulueta, M., Parás-Bravo, P., Cantarero-Prieto, D., et al. (2020). "A literature review of cost-of-illness studies on the economic burden of multiple sclerosis." Mult Scler Relat Disord **43**: 102162.

BACKGROUND: Multiple sclerosis has both high healthcare and social impacts. OBJECTIVE: The purpose of this article is to analyse the available literature describing the economic burden of multiple sclerosis and to compare costs among studies examining main cost drivers. METHODS: A literature search on studies published in English on cost-of-illness of multiple sclerosis included in this review using PubMed, the Cochrane Library, SCOPUS and Web of Science includes a retrospective horizon and it describes direct and indirect costs in patients categorized into severity groups. RESULTS: Several papers were obtained from the database search (n=37). Additionally, results from "hand searching" were also included, where a wider horizon was considered. Cost estimates were compared among studies that used a societal perspective on costs, time-period studied, and year of price level used. The estimated total annual cost per patient in Europe is on average 40,300€ (n=20). In addition, differences by geographic areas and severity groups are also considered. All in all, the higher the severity, the higher the associated costs. CONCLUSIONS: This systematic review provides one clear finding: multiple sclerosis places a huge economic burden on healthcare models and societies due to productivity losses and caregiver burden. Moreover, costs of drugs were main cost determinants for less severe cases of multiple sclerosis and informal care and production losses for the most severe cases of multiple sclerosis.

Pentek, M., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for Hungary." Mult Scler **23**(2_suppl): 91-103.

INTRODUCTION: To estimate the value of interventions in multiple sclerosis (MS) - where lifetime costs and outcomes cannot be observed - outcome data have to be combined with costs. This requires that cost data be regularly updated. OBJECTIVES AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting data on resource consumption, work capacity, health-related quality of life (HRQoL) and prevalent symptoms for patients with MS. Descriptive analyses are presented by level of disability, from the societal perspective, in HUF 2015. RESULTS: A total of 521 patients (mean age 47 years) participated; 85% were below retirement age, and of these, 47% were employed. Employment was related to disability and MS affected productivity at work for 82% of those working. Overall, 94% and 66% of patients experienced fatigue and cognitive difficulties as a problem, respectively. The mean utility and annual costs were 0.691 and 3,432,000HUF at Expanded Disability Status Scale (EDSS) 0-3, 0.491 and 5,262,000HUF at EDSS 4-6.5 and 0.076 and 6,235,000HUF at EDSS 7-9, respectively. The average cost of a relapse was estimated at 240,500HUF. CONCLUSION: This study illustrates the burden of MS on Hungarian patients and provides current data that are important for the development of health policies.

Rajagopalan, K., Brook, R. A., Beren, I. A., et al. (2011). "Comparing costs and absences for multiple sclerosis among US employees: pre- and post-treatment initiation." Curr Med Res Opin **27**(1): 179-188.

BACKGROUND: Limited data exist on the effects of Disease Modifying Treatments (DMTs) on direct and indirect costs among employees treated for Multiple Sclerosis (MS). The objective was to compare costs and absences among employees treated with DMTs (e.g., interferons [IFNs]: IFN-beta1a-IM = Avonex = 'A', IFN-beta1b = Betaseron = 'B', IFN-beta1a-SC = Rebif = 'R', or glatiramer acetate = Copaxone = 'C') for MS pre and post therapy initiation. METHODS: A healthcare claims database of US employees (2001-2008) was used to identify patients with two or more DMT prescriptions or one DMT prescription with a MS diagnosis (ICD-9 = 340.X) who were continuously employed and with health plan coverage 6 months pre and post DMT initialization. Outcome measures included: direct costs; indirect costs and absences associated with sick leave (SL) and short-term disability (STD); and medical costs and utilization by place of service (POS). All costs are inflation-adjusted to 2010 US$. Between- and within-group outcomes were compared using Student's t-tests for continuous and chi-square tests for discrete variables and considered significant when P </= 0.05. RESULTS: Overall, 153 eligible employees were identified: 'A' = 68, 'B' = 22, 'R' = 21, 'C' = 42; 76 employees had SL eligibility; 89 had STD eligibility; and 97 employees had POS indicators. Following treatment initiation, healthcare costs decreased significantly for 'A' users (-53.8%, -$3084) and 'B' users (-67.1%, -$4103), while SL costs only decreased significantly for 'A' users (-60.5%, -$704); changes in SL absence days for 'A' and 'B' users were significantly lower than for 'C' users (both P < 0.05). In the POS sample, total medical costs significantly decreased for 'A' (-$3643), 'B' (-$3470), and 'C' (-$3762), while 'R' increased ($2093) non-significantly. Only 'A' users had significant proportion-of-care reductions (Emergency Department, Outpatient Hospital, and 'Other' locations). CONCLUSION: Among MS employees treated with DMTs in the real-world, 'A' and 'B' users had significantly greater reductions in SL costs post therapy initiation compared with 'C' and 'R'. Only 'A' users showed a significant reduction in SL absence days, while the other cohorts reported increases. LIMITATIONS: Small sample sizes may limit the interpretability of these results.

Rasmussen, P. V., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for Denmark." Mult Scler **23**(2_suppl): 53-64.

BACKGROUND: To estimate the value of treatments in multiple sclerosis (MS) - where lifetime costs and outcomes cannot be observed - outcome data have to be combined with cost data. This, in turn, requires that cost data be regularly updated. OBJECTIVES AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting current data on resource consumption, work capacity, health-related quality of life (HRQoL) and prevalent symptoms for patients with MS. Descriptive analyses are presented

> by level of severity, from the societal perspective, in 2015 Danish Kronor (DKK). RESULTS: A total of 830 patients (mean age of 54 years) participated; 78% were below retirement age and of these, 43% were employed. Employment was related to disease severity, and MS was felt to affect productivity at work by 73% of patients, most often through fatigue. Overall, 95% and 65% of patients felt that fatigue and cognition, respectively, were a problem. Mean utility and costs were 0.770 and 196,900DKK at Expanded Disability Status Scale (EDSS) 0-3, 0.619 and 287,300DKK at EDSS 4-6.5, and 0.302 and 533,250DKK at EDSS 7-9. The average cost of a relapse was estimated at 19,000DKK. CONCLUSION: This study illustrates the burden of MS on Danish patients and provides current data that are important for the development of health policies.

Rieckmann, P., Centonze, D., Elovaara, I., et al. (2018). "Unmet needs, burden of treatment, and patient engagement in multiple sclerosis: A combined perspective from the MS in the 21st Century Steering Group." Mult Scler Relat Disord **19**: 153-160.

> BACKGROUND: Patient engagement is vital in multiple sclerosis (MS) in order to optimise outcomes for patients, society and healthcare systems. It is essential to involve all stakeholders in potential solutions, working in a multidisciplinary way to ensure that people with MS (PwMS) are included in shared decision-making and disease management. To start this process, a collaborative, open environment between PwMS and healthcare professionals (HCPs) is required so that similarities and disparities in the perception of key areas in patient care and unmet needs can be identified. With this patient-centred approach in mind, in 2016 the MS in the 21st Century Steering Group formed a unique collaboration to include PwMS in the Steering Group to provide a platform for the patient voice. METHODS: The MS in the 21st Century initiative set out to foster engagement through a series of open-forum joint workshops. The aims of these workshops were: to identify similarities and disparities in the perception and prioritisation in three key areas (unmet needs, the treatment burden in MS, and factors that impact patient engagement), and to provide practical advice on how the gaps in perception and understanding in these key areas could be bridged. RESULTS: Combined practical advice and direction are provided here as eight actions: 1. Improve communication to raise the quality of HCP-patient interaction and optimise the limited time available for consultations. 2. Heighten the awareness of 'hidden' disease symptoms and how these can be managed. 3. Improve the dialogue surrounding the benefit versus risk issues of therapies to help patients become fully informed and active participants in their healthcare decisions. 4. Provide accurate, lucid information in an easily accessible format from reliable sources. 5. Encourage HCPs and multidisciplinary teams to acquire and share new knowledge and information among their teams and with PwMS. 6. Foster greater understanding and awareness of challenges faced by PwMS and HCPs in treating MS. 7. Collaborate to develop local education, communication and patient-engagement initiatives. 8. Motivate PwMS to become advocates for self-management in MS care. CONCLUSION: Our study of PwMS and HCPs in the MS in the 21st Century initiative has highlighted eight practical actions. These actions identify how differences and gaps in unmet needs, treatment burden, and patient engagement between PwMS and HCPs can be bridged to improve MS disease management. Of particular interest now are patient-centred educational resources that can be used during time-limited consultations to enhance understanding of disease and improve communication. Actively bridging these gaps in a joint approach enables PwMS to take part in shared decision-making; with improved communication and reliable information, patients can make informed decisions with their HCPs, as part of their own personalised disease management.

Roxburgh, R. H., Seaman, S. R., Masterman, T., et al. (2005). "Multiple Sclerosis Severity Score: using disability and disease duration to rate disease severity." Neurology **64**(7): 1144-1151.

BACKGROUND: There is no consensus method for determining progression of disability in patients with multiple sclerosis (MS) when each patient has had only a single assessment in the course of the disease. METHODS: Using data from two large longitudinal databases, the authors tested whether cross-sectional disability assessments are representative of disease severity as a whole. An algorithm, the Multiple Sclerosis Severity Score (MSSS), which relates scores on the Expanded Disability Status Scale (EDSS) to the distribution of disability in patients with comparable disease durations, was devised and then applied to a collection of 9,892 patients from 11 countries to create the Global MSSS. In order to compare different methods of detecting such effects the authors simulated the effects of a genetic factor on disability. RESULTS: Cross-sectional EDSS measurements made after the first year were representative of overall disease severity. The MSSS was more powerful than the other methods the authors tested for detecting different rates of disease progression. CONCLUSION: The Multiple Sclerosis Severity Score (MSSS) is a powerful method for comparing disease progression using single assessment data. The Global MSSS can be used as a reference table for future disability comparisons. While useful for comparing groups of patients, disease fluctuation precludes its use as a predictor of future disability in an individual.

Ruutiainen, J., Viita, A. M., Hahl, J., et al. (2016). "Burden of illness in multiple sclerosis (DEFENSE) study: the costs and quality-of-life of Finnish patients with multiple sclerosis." J Med Econ **19**(1): 21-33.

OBJECTIVE: Although multiple sclerosis (MS) is one of the most common causes of non-traumatic disability among young adults, no published data on its economic and health-related quality-of-life (HRQoL) burden is available from Finland. The DEFENSE study aimed to estimate the costs and HRQoL of patients with MS (PwMS) in Finland and explore how these variables are influenced by disease severity and relapses. METHODS: Overall, 553 PwMS registered with the Finnish Neuro Society, a national patient association in Finland, completed a self-administered questionnaire capturing information on demographics, disease characteristics and severity (Expanded Disease Severity Scale [EDSS]), relapses, resource consumption and HRQoL. RESULTS: The PwMS had a mean EDSS score of 4.0. Overall, 44.1% had relapsing-remitting form of the disease (RRMS). The mean age was 53.8 years and 55.7% had retired prematurely due to MS. Disease-modifying therapies (DMTs) were used by 42.7% of the study population, and 21.5% across all disease types and severities had experienced relapses during the previous year. The mean total annual cost of MS was €46,994, which increased with advancing disease from €10,835 (EDSS score = 0) to €109,901 (EDSS score = 8-9). The mean utility was 0.644. HRQoL decreased with increasing disease severity. Relapses imposed an additional utility decrement among the PwMS with RRMS and EDSS ≤5 and had a trend-like effect on total costs. LIMITATIONS: The cross-sectional setting did not allow assessment of the significance of relapses in early MS or the use of DMTs on the prognosis of the disease. CONCLUSION: The study confirms previous findings from other countries regarding a significant disease burden associated with MS and provides, for the first time, published numerical estimates from Finland. Treatments that slow disease progression and help PwMS retain employment for a longer duration have the highest potential to reduce the disease burden associated with MS.

Sa, M. J., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for Portugal." Mult Scler **23**(2_suppl): 143-154.

BACKGROUND: In order to assess the value of management strategies in multiple sclerosis (MS), outcome data have to be combined with cost data. This, in turn, requires that cost data be regularly updated. OBJECTIVE AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting current data on resource consumption, work capacity and health-related quality of life (HRQoL). Descriptive analyses are presented by level of severity; costs are estimated in the societal perspective, in EUR 2015. RESULTS: A total of 535 patients (mean age 48.5 years) participated; 92% were below retirement age and of these, 43% were employed. Employment was related to disease severity, and MS was felt to affect productivity at work by 72% of patients, most often through fatigue. Overall, 98% and 74% of patients felt that fatigue and cognition were a problem. Mean utility and costs were 0.756 and euro16,500 at the Expanded Disability Status Scale (EDSS) 0-3, 0.572 and euro28,700 at EDSS 4-6.5 and 0.206 and euro34,400 at EDSS 7-9. The average cost of a relapse was estimated at euro2930. CONCLUSION: This study illustrates the burden of MS on Portuguese patients and provides current data that are important for the development of health policies.

Selmaj, K., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for Poland." Mult Scler **23**(2_suppl): 130-142.

BACKGROUND: In order to estimate the value of interventions in multiple sclerosis (MS) - where lifetime costs and outcomes cannot be observed - outcome data have to be combined with costs. This requires that cost data be regularly updated. OBJECTIVE AND METHODS: This study is part of a cross-sectional retrospective study in 16 European countries collecting current data on resource consumption, work capacity, health-related quality of life (HRQoL) and prevalent symptoms for patients with MS. Descriptive analyses are presented by level of severity, from the societal perspective, in 2015 Polish Zloty (PLN). RESULTS: A total of 411 MS patients (mean age = 40 years) participated in Poland; 94% were below retirement age, and of these, 59% were employed. Employment was related to disability, and MS affected productivity for 85% of those working. Overall, 97% and 71% of patients experienced fatigue and cognition as important problems, respectively. Mean utility and total annual costs were 0.686 and 48,700 PLN at Expanded Disability Status Scale (EDSS) 0-3, 0.521 and 59,200 PLN at EDSS 4-6.5 and 0.208 and 81,600 PLN at EDSS 7-9, respectively. The average cost of a relapse was 3,900 PLN. CONCLUSION: This study illustrates the burden of MS on Polish patients and provides current data that are important for developing health policies.

Sicras-Mainar, A., Ruíz-Beato, E., Navarro-Artieda, R., et al. (2017). "Impact on healthcare resource utilization of multiple sclerosis in Spain." BMC Health Serv Res **17**(1): 854.

BACKGROUND: Multiple sclerosis (MS) is a chronic disease with a high socioeconomic impact. The aim of this study was to assess healthcare resources utilization and costs in a sample of patients with MS. METHODS: A retrospective, cohort study was conducted using electronic medical records from 19 primary care centres in Asturias and Catalonia, Spain. Adult patients diagnosed with MS were distributed into two groups according to the Expanded Disability Status Scale (EDSS) score: 0-3.5 (no-moderate disability) and 4-9.5 (severe disability). Healthcare (direct cost) and non-healthcare costs (work productivity losses) were analysed. An analysis of covariance (ANCOVA) was used for correction, $p < 0.05$. A multiple regression model was performed to obtain the variables associated with costs. RESULTS: A total of 222 patients were analyzed; mean (SD) age: 45.5 (12.5) years, 64.4% female, and 62.2% presented a diagnosis of relapsing-remitting MS. Median EDSS score was 2.5, with 68.5% of the patients with no to moderate disability. The mean annual cost per MS patient was €25,103. For no-moderate and severe disability, the ANCOVA-adjusted mean annual cost was €23,157 and €29,242, respectively ($p = 0.013$). Direct costs and MS disease-modifying therapy accounted for 39.4% and 31.7% of the total costs, respectively. The total costs were associated with number of relapses ($\beta = 0.135$, $p = 0.001$), time since diagnosis ($\beta = 0.281$, p = 0.023), and age (β = 0.198, p = 0.037). CONCLUSIONS: Multiple sclerosis imposes a substantial economic burden on the Spanish National Health System, patients and society as a whole. Costs significantly correlated with disease progression.

Stenager, E. (2019). "A global perspective on the burden of multiple sclerosis." Lancet Neurol **18**(3): 227-228.

Svendsen, B., Grytten, N., Bø, L., et al. (2018). "The economic impact of multiple sclerosis to the patients and their families in Norway." Eur J Health Econ **19**(9): 1243-1257.

BACKGROUND: Multiple sclerosis (MS) imposes high economic costs on society, but the patients and their families have to bear some of these costs. OBJECTIVE: We aimed to estimate the magnitude of these economic costs in Norway. METHOD: We collected data through a postal questionnaire survey targeting 922 MS patients in Hordaland County, western Norway, in 2013-2014; 546 agreed to participate and were included. The questionnaire included clinical and demographic characteristics, volume and cost of MS-related resource use, work participation, income, government financial support, and disability status. RESULTS: The mean annual total economic costs for the patients and their families were €11,603. Indirect costs accounted for 66% and were lower for women than for men. The direct costs were nearly identical for men and women. The costs increased up to Expanded Disability Status Scale score 6 except for steps between 3 and 4 where it remained nearly constant. The costs reduced from EDSS 6 to 8, and increased from 8 to 9. Lifetime costs ranged from €24,897 to €70,021 for patients with late disease onset and slow progression, and between €441,934 and €574,860 for patients with early onset and rapid progression. CONCLUSION: The economic costs of MS impose a heavy burden on the patients and their families. Supplementing the information on the cost of MS to society, our finding should be included as background information in decisions on reimbursing and allocating public resources for the well-being of MS patients and their families.

Thompson, A., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for the United Kingdom." Mult Scler **23**(2_suppl): 204-216.

INTRODUCTION: In order to estimate the value of interventions in multiple sclerosis (MS) - where lifetime costs and outcomes cannot be observed - outcome data have to be combined with costs. This requires that cost data be regularly updated. OBJECTIVES AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting data on resource consumption and work capacity, health-related quality of life (HRQoL) and prevalent symptoms for patients with MS. Descriptive analyses are presented by level of disability, from the societal perspective, in EUR (2015). RESULTS: A total of 779 patients (mean age = 57 years) participated; 72% were below retirement age and of these, 36% were employed. Employment was related to disease severity, and MS affected productivity at work for 84% of patients. Overall, 96% and 72% of the patients experienced fatigue and cognition as a problem. Mean utility and annual costs were 0.735 and 11,400GBP at Expanded Disability Status Scale (EDSS) = 0-3, 0.534 and 22,700GBP at EDSS = 4-6.5, and 0.135 and 36,500GBP at EDSS = 7-9. The mean cost of a relapse was estimated at 790GBP. CONCLUSION: This study illustrates the burden of MS on UK patients and provides current data on MS that are important for development of health policies.

Tinghog, P., Bjorkenstam, C., Carstensen, J., et al. (2014). "Co-morbidities increase the risk of disability pension among MS patients: a population-based nationwide cohort study." BMC Neurol **14**: 117.

BACKGROUND: Multiple sclerosis (MS) is a chronic and often disabling disease. In 2005, 62% of the MS patients in Sweden aged 16-65 years were on disability pension. The objective of this study is to investigate whether the presence of common co-morbidities increase MS patients' risk for disability pension. METHODS: This population-based cohort study included 4 519 MS patients and 4 972 174 non-MS patients who in 2005 were aged 17-64 years, lived in Sweden, and were not on disability pension. Patients with MS were identified in the nationwide in- and outpatient registers, while four different registers were used to construct three sets of measures of musculoskeletal, mental, and cardiovascular disorders. Time-dependent proportional hazard models with a five-year follow up were performed, adjusting for socio-demographic factors. RESULTS: All studied disorders were elevated among MS patients, regardless of type of measure used. MS patients with mental disorders had a higher risk for disability pension than MS patients with no such co-morbidities. Moreover, mental disorders had a synergistic influence on MS patients' risk for disability pension. These findings were also confirmed when conducting sensitivity analyses. Musculoskeletal disorders appeared to increase MS patients' risk for disability pension. The results with regard to musculoskeletal disorders' synergistic influence on disability pension were however inconclusive. Cardiovascular co-morbidity had no significant influence on MS-patients' risk for disability pension. CONCLUSIONS: Co-morbidities, especially mental disorders, significantly contribute to MS patients' risk of disability pension, a finding of relevance for MS management and treatment.

Tinghog, P., Hillert, J., Kjeldgard, L., et al. (2013). "High prevalence of sickness absence and disability pension among multiple sclerosis patients: a nationwide population-based study." Mult Scler **19**(14): 1923-1930.

INTRODUCTION: Although multiple sclerosis (MS) often implies substantial disability, there is little knowledge about sick leave and disability pension among MS patients. OBJECTIVES: The purpose of this study was to estimate the prevalence rates of sick leave and disability pension among MS patients and to explore how socio-demographics are associated with such rates. METHODS: The register data of all people who lived in Sweden in 2005 and were 16-64 years old was used to identify 9721 MS patients and matched controls. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated and effect modifications were evaluated with Wald X(2) tests. RESULTS: In 2005, 61.7% of the MS patients were on partial or full disability pension compared to 14.2% among the controls. Of the others, 36.8% had >/= 1 sick-leave spell for >14 days during that year. Socio-demographics were similarly associated with sick leave and disability pension among MS patients and controls, with the noteworthy exceptions that female gender and immigration status were less potent risk factors in the MS population (p<0.05). CONCLUSION: In spite of widespread access to modern health care including disease-modifying drugs, the majority of MS patients of working ages were on a disability pension. Strategies enabling MS patients to retain their footing in the labour market are needed.

Uitdehaag, B., Kobelt, G., Berg, J., et al. (2017). "New insights into the burden and costs of multiple sclerosis in Europe: Results for the Netherlands." Mult Scler **23**(2_suppl): 117-129.

INTRODUCTION: To estimate the value of interventions in multiple sclerosis (MS) - where lifetime costs and outcomes cannot be observed - outcome data have to be combined with costs. This requires that cost data be regularly updated. OBJECTIVES AND METHODS: This study is part of a cross-sectional retrospective study in 16 countries collecting data on resource consumption and work capacity, health-related quality of life (HRQoL) and prevalent symptoms for patients with MS. Descriptive analyses are presented by level of severity, from the societal perspective, in EUR 2015. RESULTS: A total of 382 patients (mean age: 54 years) participated in the Netherlands; 81% were below retirement age and of these, 31% were employed. Employment was inversely related to disease severity, and MS affected productivity at work for 82% of patients. Overall, 96% and 73% of patients experienced fatigue and cognitive difficulties, respectively, as a problem. Mean utility and annual costs were 0.744 and euro23,100 at Expanded Disability Status Scale (EDSS) 0-3, 0.595 and euro32,300 at EDSS 4-6.5, and 0.297 and euro50,500 at EDSS 7-9. The mean cost of a relapse was estimated at euro3000. CONCLUSION: This study provides current data on MS in the Netherlands that are important for the development of health policies and to estimate the value of current and future treatments.

Wang, Y., Tian, F., Fitzgerald, K. C., et al. (2020). "Socioeconomic status and race are correlated with affective symptoms in multiple sclerosis." Mult Scler Relat Disord **41**: 102010.

OBJECTIVE: Investigate the relationship between socioeconomic status (SES) and race with self-reported fatigue, depression, and anxiety levels in multiple sclerosis (MS). METHODS: Cross-sectional review of the MS Partners Advancing Technology and Health Solutions (MS PATHS) database for adults with MS in the United States. We evaluated race and socioeconomic status (available markers: insurance, employment status, or level of education) as predictors of fatigue, depression, and anxiety sub-scores of the Neuro-QoL (Quality of life in neurological disorders), with particular interest between Caucasians/whites (CA) and African Americans/blacks (AA). Multivariate linear regression models included as covariates age, sex, disability status, smoking status, body mass index, and disease-modifying therapy. RESULTS: 7,430 individuals were included; compared to CA, AA tended to be younger, more female-predominant, and had a higher level of disability. AA had completed slightly less education, had a higher level of Medicaid coverage or uninsured status, and had higher rates of unemployed or disabled status. In the univariate model, markers of lower SES, by whichever definition we used, correlated with worse affective symptoms. In the multivariate model stratified by race, CA showed similar trends. In contrast, in AA, only lower SES by employment status was correlated with worse affective symptoms. In both CA and AA, moderate and severe level of disability correlated with worse affective symptoms. CONCLUSION: SES and race may influence affective symptoms reported by individuals with MS. The reasons for the correlation are likely multifactorial. Longitudinal studies should strive to identify factors associated with risk of affective symptoms in MS that may be modifiable.

Yan, K., Balijepalli, C., Desai, K., et al. (2020). "Epidemiology of pediatric multiple sclerosis: A systematic literature review and meta-analysis." Mult Scler Relat Disord **44**: 102260.

BACKGROUND: Multiple sclerosis (MS) is a debilitating immune disease leading to demyelination, neurodegeneration, and chronic inflammation of the central nervous system. Pediatric MS is a rare form of the disease and effects approximately 2-10% of individuals with MS. Diagnostic criteria and therapies are continuously evolving, thus it is imperative to further understand the epidemiology and subsequently global and regional disease burden of pediatric MS. Our objective was to conduct a systematic literature review and meta-analysis to assess the incidence and prevalence of pediatric MS globally. Subgroup analyses were also conducted by region and diagnostic criteria used to ascertain cases. METHODS: A systematic literature review was conducted using searches run in EMBASE and MEDLINE. A hand search was also conducted, and the bibliographies of any relevant articles were reviewed for any studies potentially not captured by the databases. A random effects model was used to combine epidemiological estimates across studies. Subgroup analyses by region and diagnostic criteria were performed in instances when three or more studies were available for analyses. RESULTS: A total of 2,965 publications were identified, of which 187 were

> eligible for full-text screening. A total of 21 full-text articles met the eligibility criteria and were included for data extraction, with 18 studies included for meta-analysis. Regional epidemiologic estimates were obtained for North America, Europe, Middle East, and Asia. Country specific data was available for Canada, United States, Germany, Iceland, Netherlands, Sardinia, Slovenia, UAE/Abu Dhabi, Iran, Israel, Jordan, Kuwait, Tunisia, Taiwan, and Japan. Thirteen studies representing 12 countries reported incidence of pediatric MS. Overall incidence ranged from 0.05 to 2.85 and pooled global incidence was calculated to be 0.87 (95% CI: 0.35-1.40) per 100,000 individuals annually. Ten studies representing 10 countries reported on the prevalence of pediatric MS. Overall prevalence ranged from 0.69 to 26.92 per 100,000 individuals and pooled global prevalence was calculated to be 8.11 (95% CI: 2.28-13.93) per 100,000 people. CONCLUSION: To our knowledge, this is the first meta-analysis conducted to provide pooled estimates of incidence and prevalence estimates of pediatric MS globally. In general, incidence estimates were similar across regions; however, prevalence was found to be more variable. Noticeable gaps in evidence include a lack of pediatric MS estimates from other large regions of the world such as Africa, South America, Russia, and Australia. Moreover, there is a need for more population-based studies using the most up to date diagnostic criteria.

Zhang, T., Tremlett, H., Zhu, F., et al. (2018). "Effects of physical comorbidities on disability progression in multiple sclerosis." Neurology **90**(5): e419-e427.

> OBJECTIVE: To examine the association between physical comorbidities and disability progression in multiple sclerosis (MS). METHODS: We conducted a retrospective cohort study using linked health administrative and clinical databases in 2 Canadian provinces. Participants included adults with incident MS between 1990 and 2010 who entered the cohort at their MS symptom onset date. Comorbidity status was identified with validated algorithms for health administrative data and was measured during the 1 year before study entry and throughout the study period. The outcome was the Expanded Disability Status Scale (EDSS) score as recorded at each clinic visit. We used generalized estimating equations to examine the association between physical comorbidities and EDSS scores over time, adjusting for sex, age, cohort entry year, use of disease-modifying drugs, disease course, and socioeconomic status. Meta-analyses were used to estimate overall effects across the 2 provinces. RESULTS: We identified 3,166 individuals with incident MS. Physical comorbidity was associated with disability; with each additional comorbidity, there was a mean increase in the EDSS score of 0.18 (95% confidence interval [CI] 0.09-0.28). Among specific comorbidities, the presence of ischemic heart disease (IHD) or epilepsy was associated with higher EDSS scores (IHD 0.31, 95% CI 0.01-0.61; epilepsy 0.68, 95% CI 0.11-1.26). CONCLUSIONS: Physical comorbidities are associated with an apparent increase in MS disability progression. Appropriate management of comorbidities needs to be determined to optimize outcomes.

Impact de la maladie sur la situation professionnelle et sur l’emploi

ÉTUDES FRANÇAISES

Abbas, D., Gehanno, J. F., Caillard, J. F., et al. (2008). "Caractéristiques des personnes atteintes d’une sclérose en plaques selon la situation professionnelle." Annales de Réadaptation et de Médecine Physique **51**(5): 386-393.
http://www.sciencedirect.com/science/article/S0168605408000664

> Objectifs Décrire l'état de santé et la situation professionnelle d'une population de patients atteints de sclérose en plaques en âge de travailler et comparaison d'un groupe de sujets qui travaillent (groupe T1) à un groupe de sujets qui ne travaillent pas (groupe T2). Matériels et méthode C'est une étude descriptive. Des données démographiques, médicales et professionnelles ont été recueillies par questionnaires à l'issue d'une consultation spécialisée de neurologie. Une analyse statistique descriptive et comparative a été réalisée. Résultats Soixante-seize patients ont été inclus dans l'étude : 54 travaillent (groupe T1), 22 ne travaillent plus (groupe T2). Le taux d'emploi était de 71 %, avec une durée moyenne d'évolution de la maladie de neuf ans au moment de l'étude. Le groupe T2 avait un niveau scolaire plus faible (p=0,02), comportait davantage de formes progressives (p=0,0001), d'atteintes motrices (p=0,01), cérébelleuses (p=0,02) ou cognitives (p=0,03) avec un retentissement fonctionnel (score EDSS) plus important (p=0,0001). En considérant le dernier poste de travail occupé dans les deux groupes, les personnes du groupe T1 étaient employées plus souvent dans des grandes entreprises (p=0,03), ou dans le secteur public (p=0,003), la reconnaissance de la qualité de travailleur handicapé (ex. Commission technique d'orientation et de reclassement professionnel [Cotorep]) était moins fréquente (p=0,03). C'est aussi dans ce groupe que le travail demandait le moins de force physique (p=0,05), le moins de précision manuelle (p=0,05), avec le moins de problème d'accès (p=0,03). Conclusion Cette étude montre les différences qui existent dans cette population en fonction de la situation professionnelle. Elle souligne l'importance des variables cliniques et démographiques comme déterminants des différences de statut professionnel. Elle montre sans surprise que c'est dans le groupe sans activité professionnelle que le handicap au travail est reconnu le plus important. Les facteurs liés aux contraintes induites par le travail ressortent peu car les items du questionnaire ne sont pas suffisamment adaptés.

Cambier-Langrand, E., Leroyer, A., Zéphir, H., et al. (2016). "Impact socioprofessionnel précoce de la sclérose en plaques : une étude prospective d'une série de 24 patients." Archives des Maladies Professionnelles et de l'Environnement **77**(2): 165-178.
http://www.sciencedirect.com/science/article/pii/S1775878515003379

> Objectif Étudier l'impact précoce de la sclérose en plaques (SEP) sur la situation socioprofessionnelle de patients actifs au moment du diagnostic et rechercher les facteurs pronostiques du maintien ou non en emploi parmi des données sociodémographiques, cliniques et socioprofessionnelles. Méthode Suivi prospectif d'une série de patients atteints d'une SEP évoluant depuis moins de cinq ans, ou ayant présenté un syndrome cliniquement isolé au cours des cinq dernières années. Les patients ont été inclus à T1 et revus environ 2ans plus tard, à T2. Lors des consultations de suivi réalisées à T1 et à T2, des données sociodémographiques, cliniques et socioprofessionnelles ont été recueillies. L'évaluation de la fatigue a été réalisée par la version française de la Fatigue Impact Scale (EMIF-SEP), de la qualité de vie par le Medical Outcome Study Short-Form 36 (SF-36), de la capacité de travail par le Work Ability Index (WAI) et celle des performances cognitives par la batterie courte d'évaluation des fonctions cognitives destinée aux patients souffrant de SEP (BCcogSEP). Le test exact de Fisher et le test de Kruskal-Wallis ont été utilisés pour étudier les facteurs pronostiques à T1 du devenir socioprofessionnel à T2. Résultat Le devenir de 24 des 41 patients inclus a pu être étudié. La durée médiane d'évolution de la maladie était de 16,5 mois à l'inclusion. La SEP a été à l'origine de modifications socioprofessionnelles chez 10 (42 %) des patients revus à T2. Les scores EDSS (p=0,04), EMIF-SEP (p=0,05), physique du SF-36 (p=0,04) et WAI (p=0,04) altérés à T1 ont été identifiés comme facteurs pronostiques de la perte d'activité professionnelle précoce. Le score WAI (p=0,02) altéré et le score déficitaire à la BCcogSEP (p=0,05) à T1 ont été identifiés comme facteurs pronostiques de modifications socioprofessionnelles précoces. Discussion et conclusion Notre étude souligne l'intérêt d'évaluer le degré de handicap physique, les performances cognitives, le retentissement de

la fatigue, la perception de l’état de santé physique et la capacité de travail chez les patients nouvellement diagnostiqués, afin de pouvoir agir précocement en vue de leur maintien en emploi.

Colinet, S. (2018). "Associations d'usagers et sclérose en plaques : impact du néolibéralisme en France sur les trajectoires de vie des patients." Sante Publique **30**(1): 25-33.

[BDSP. Notice produite par EHESP DR0x9IHJ. Diffusion soumise à autorisation]. Introduction : La sclérose en plaques est une maladie neurologique qui entraîne une limitation des performances corporelles. Ses impacts sur la vie sociale et professionnelle des personnes atteintes sont majeurs car, les symptômes restant souvent invisibles, les incapacités du malade suscitent l'incompréhension dans une société marquée par le dogme néolibéral de la performance. L'engagement associatif constitue alors fréquemment pour les malades un support à leur trajectoire. Objectif : L'objectif de cette recherche était d'identifier comment se manifestent les principes du néolibéralisme dans les discours des sujets atteints de sclérose en plaques, de comprendre les effets induits par l'intégration du néolibéralisme, et de préciser le rôle joué par l'engagement associatif dans les trajectoires de vie. Méthodes : Il s'agissait d'une étude qualitative : 30 entretiens individuels et quatre entretiens collectifs ont été réalisés avec des patients, ainsi que 23 observations de réunions et de groupes de réflexion d'associations de patients. Dix personnes rencontrées en entretien ont par ailleurs rédigé un mini-journal ayant pour objet une restitution quotidienne de leur action associative. Les données ont été analysées thématiquement, indépendamment dans un premier temps, de manière croisée ensuite. Le Logiciel AtlasTi a été utilisé. Résultats : L'association constitue sous deux formes, pratique et idéologique, une illustration de la résistance au néolibéralisme, notamment au travers des prises de responsabilités individuelles et collectives. Toutefois, elle recrée dans une certaine mesure des espaces de performance. Conclusion : Sur le plan pratique, cette recherche vient réaffirmer la nécessité de créer des activités collectives pour accompagner les sujets atteints de maladie chronique.

Créange, A. et Labauge, P. (2009). "Handicap social des formes précoces de sclérose en plaques." Rev Neurol (Paris) **165**: S167-S172.
http://www.sciencedirect.com/science/article/pii/S0035378709721307

Résumé La sclérose en plaques (SEP) est la maladie source cause de handicap du sujet jeune la plus fréquente dans les pays industrialisés. En raison de l’âge jeune des patients, du caractère chronique et récidivant, des atteintes multifocales, de l’évolution vers une forme progressive dans la moitié des cas, la SEP a des conséquences individuelles, familiales et socioprofessionnelles sources d’un handicap social fréquent, y compris au début de la maladie. A la phase précoce, le handicap est essentiellement social avec perte de revenus et perte d’emploi dans la moitié des cas, incidence familiale majeure, avec une fréquence estimée de divorce ou séparation de 10 %, et une nécessité d’aides quotidiennes dans 12 % des cas. Multiple sclerosis is the most frequent cause of handicap in young adults. Because of the young age of patients, the chronic relapsing course, the multifocal consequences of lesions, and the frequent progressive chronic course, multiple sclerosis has multiple consequences including individuals, familial, social and professional, that induces, in the early stage, a wide social handicap overflowing consequences of the neurological deficit. Since the onset of the disease, social events are very frequent: jobless and decrease of salaries (50% of the cases), divorce (10%), daily help (12%).

Daveluy, W. (2014). "Pathologies neuro-dégénératives : evaluation des capacites et maintien dans l’emploi." Archives des Maladies Professionnelles et de l'Environnement(75): 511–542.

L'appréciation des capacités et de l'aptitude au travail dans le cadre d'une pathologie neurodégénérative est une situation relativement peu fréquente dans le quotidien d'un professionnel de santé au travail. Cette évaluation est rendue complexe, d'une part car elle concerne une intrication de troubles moteurs, sensoriels, cognitifs, comportementaux et psychologiques comme dans la sclérose en plaques (SEP) et la maladie de Parkinson, et des troubles peu visibles et de mesure peu aisée pour le médecin du travail comme dans la démence de type Alzheimer, avec des troubles essentiellement cognitifs et comportementaux. D'autre part, la problématique de l'adéquation des capacités à l'activité professionnelle se posera régulièrement, au fil de l'évolution de la pathologie, avec la nécessité d'évaluations et de remises en question régulières et de fréquence ajustable, afin de pouvoir définir les éventuelles restrictions, appréhender les possibilités de maintien dans l'emploi et préconiser les aménagements nécessaires et adaptations des modalités du poste.

Fantoni-Quinton, S., Kwiatkowski, A., Vermersch, P., et al. (2016). "Impact of multiple sclerosis on employment and use of job-retention strategies: The situation in France in 2015." J Rehabil Med **48**(6): 535-540.

OBJECTIVE: The main objective of this survey of persons with multiple sclerosis was to describe their employment situation. Secondary objectives were to ascertain when and how multiple sclerosis symptoms first impact employment per se and what strategies persons with multiple sclerosis use to cope with their employment problems. METHODS: A retrospective survey was conducted to collect data from persons with multiple sclerosis aged 18 years and over, using a computer-assisted web tool. RESULTS: A total of 941 respondents were working at the time of multiple sclerosis diagnosis or had worked subsequently. Median time since diagnosis was 10 years. Multiple sclerosis had an impact on employment for 74.3% of respondents. The overall employment rate at the time of the survey was 68.1%; 27.2% had discontinued their occupational activity for a multiple sclerosis-related reason. Median time from diagnosis to multiple sclerosis-related cessation of occupational activity was 24.0 years (95% confidence interval (CI) 21.7-26.3 years). Respondents were poorly aware of available tools designed to assist them in retaining employment. CONCLUSION: This study highlights the importance of early intervention by the occupational medicine physician in order to favour job retention and use of available tools by all workers with MS and not only those with a recognized status as a disabled worker.

Guilleux, A., Regaert, C., Espagnacq, M., et al. (2020). "Le parcours professionnel des patients atteints de sclérose en plaques à partir des données de la base nationale Hygie." Revue d'Épidémiologie et de Santé Publique **68**: S65.
http://www.sciencedirect.com/science/article/pii/S0398762020303023

Contexte La sclérose en plaques (SEP) est une affection neurologique qui débute souvent entre 20 ans et 40 ans, touche deux à trois femmes pour un homme et réduit l'espérance de vie de 6–7 ans. En France, elle touche 100 000 personnes, dont 80 % de 20–64 ans. Cette maladie chronique est handicapante et a donc des implications sur la vie professionnelle. Or, peu d'études sont disponibles pour mesurer ces effets, aucune sur un échantillon aléatoire représentatif. L'objectif de notre étude est de quantifier l'impact de la SEP sur le parcours professionnel à court et moyen termes. Méthode L'étude s'appuie sur les données de la base Hygie qui sont issues d'un appariement de données de la Caisse nationale d'assurance vieillesse et de la Caisse nationale de l'assurance maladie, se rapportant exclusivement au secteur privé. Cet échantillon aléatoire est constitué de bénéficiaires ayant cotisé au moins une fois au régime général de retraite. La SEP a été identifiée par la déclaration en affection longue durée (ALD). Cette déclaration constitue notre date index autour de laquelle 5 événements d'intérêt binaires annuels ont été comparés : emploi stable, emploi instable, chômage, inactivité, maladie. Résultats Au total, 1401 individus ayant une ALD SEP entre 1983 et 2013 et avec une carrière exploitable ont été identifiés, parmi eux 70,4 % étaient des femmes. La moyenne d'âge au moment de la reconnaissance en ALD était de 38,9 ans (±9,8). La durée de suivi professionnel était en moyenne de 29,4 ans (±10,8). L'analyse de la sous-population disposant d'au moins 5 ans de carrière avant et après la reconnaissance en ALD (n=772) a montré que le taux d'emploi stable était de 65,8 % dans les cinq ans avant la reconnaissance contre 46,8 % dans les 5 ans suivant la déclaration de l'ALD (p<0,0001). À l'inverse, les taux d'inactivité et de chômage augmentaient, passant de 18,3 % à 37,4 % (p<0,0001) et de 3,4 % à 4,7 % (p<0,005), respectivement. Sur la même période, le nombre de personnes ayant au moins un épisode de maladie passait de 8,5 % à 20,2 % (p<0,0001). Conclusion Cette étude confirme l'effet pénalisant de la SEP sur le parcours professionnel. L'apport d'un groupe contrôle (sans ALD) ainsi que l'analyse selon différentes caractéristiques que sont le sexe et l'âge des malades, et leur niveau de salaire à leur entrée sur le marché du travail permettra d'enrichir cette analyse préliminaire.

Hoffmann, J. (2016). Le maintien dans l'emploi des patients atteints de sclérose en plaques. Nancy Université de Lorraine, Faculté de Médecine. Université de Nancy. Ecole de Santé Publique. (E.S.P.). Vandoeuvre lès Nancy. FRA. **Thèse : Doctorat en médecine.:** 83.

Cette thése a pour objectif de décrire les caractéristiques socioprofessionnelles des patients atteints de sclérose en p laques (SEP) et les actions de maintien dans l'emploi menées au cour de leur carrière. L'analyse a été réalisée à partir d'une étude épidémiologique descriptive. 41 patients hospitalisés dans l'unité d'Hôpital de Jour du service de Neurologie du CHRU de Nancy ont été inclus entre mai et août 2016. Ces patients ont répondu à un auto-questionnaire portant sur leurs caractéristiques socioprofessionnelles et sur leur maladie. Le taux d'emploi observé était de 48,8 %, majoritairement sur des emplois à temps plein, pour une durée médiane d'évolution de la maladie de 10 ans. Cette publication confirme l'association statistique entre la perte d'emploi et le faible niveau d'étude et les emplois physiques. En ce qui concerne les mesures de maintien dans l'emploi, est observé un taux élevé de patients Reconnus en Qualité de Travailleur Handicapé (RQTH) et un taux de 30 % d'aménagements de poste, reclassement ou reconversion professionnelle. 67 % des patients ayant bénéficié d'un aménagement de leur poste sont employés. 69 % des patients interrogés ont informé le médecin du travail du diagnostic de SEP. L'étude souligne également le rôle majeur du médecin du travail dans la mise en place d'aménagements de poste étant donné que 92 % des patients dont le poste a été aménagé ont faire part de leur maladie au médecin du travail. L'identification précoce des patients souffrant de SEP à risque de désinsertion professionnelle est la clé de voûte des actions de maintien dans l'emploi efficaces. Ainsi, un entretien entre le salarié et le médecin du travail rapidement après l'annonce du diagnostic, un rapprochement entre le médecin du travail et le neurologue et une information précoce des patients sur les outils concourant au maintien dans l'emploi sont autant de pistes à explorer pour favoriser le maintien dans l'emploi des patients atteints de SEP.

Ongagna, J. C., Passadori, A., Pinelli, J., et al. (2015). "Difficultés ressenties au travail par les patients atteints de sclérose en plaques." Rev Neurol (Paris) **171**(11): 782-786.
http://www.sciencedirect.com/science/article/pii/S0035378715007912

Introduction La sclérose en plaques (SEP) est une maladie du système nerveux central qui affecte le jeune adulte à une période où il se lance dans la vie active. Le retentissement de la maladie sur la vie professionnelle est souvent majeur. L'objectif de cette enquête était de recenser les problèmes que rencontrent les personnes atteintes de sclérose en plaques dans le cadre de leur travail. Méthodes Il s'agit d'une enquête régionale réalisée en 2010 par des praticiens neurologues et de médecine physique et de réadaptation (MPR) d'Alsace sur une période de 4 mois. Résultats Deux cent sept patients SEP en âges de travailler ont répondu à cette enquête. Le taux d'emploi était de 67,6 %. Parmi les difficultés exprimées par les patients, la fatigabilité physique et intellectuelle apparaissent comme les principales difficultés ressenties au travail. Discussion Les problèmes de fatigabilité mis en avant par les patients sont des éléments pouvant présager d'une perte d'emploi, et qui nécessite la mise en place de manière précoce de mesures de sauvegarde, en favorisant une prise en charge pluridisciplinaire. Aim Multiple sclerosis (MS) is a disease of the central nervous system that affects young adults at a time when they launch into the workforce. The disease often has a great impact on working life. The objective of this survey was to identify the problems faced by people with multiple sclerosis in the context of their work. Methods To describe the difficulties experienced at work by patients with multiple sclerosis, we carried out in 2010 a regional survey including neurology and functional rehabilitation centers. Results Two hundred and seven MS patients of working age responded to the survey. The employment rate was 67.6%. Among difficulties expressed by patients, physical and mental fatigue appeared as the issues affecting work. For 41% of respondents, preventive measures at work could help maintain or resume employment. Conclusion Problems of fatigability put forward by MS patients are elements that can predict a loss of employment.

ÉTUDES INTERNATIONALES

Abdullah, E. J., Badr, H. E. et Manee, F. (2018). "MS People's Performance and Satisfaction With Daily Occupations: Implications for Occupational Therapy." OTJR (Thorofare N J) **38**(1): 28-37.

People with multiple sclerosis (MS) face difficulties in performing daily occupations. The objectives of this study were to assess the performance of and level of satisfaction with daily occupations among people with MS, and to explore factors associated with their performance and satisfaction. A cross-sectional study was conducted among 200 MS individuals. The Arabic version of Satisfaction With Daily Occupations (SDO) scale was used. Mann-Whitney U, Kruskal-Wallis, Chi-square tests, and binary logistic regression were used for data analysis. SDO performance and satisfaction median scores were 10/14 and 51/70, respectively. Multivariate analysis revealed that unemployment and cognitive symptoms were associated with poor occupational performance. Furthermore, unemployment, being married, visual problems, and low endurance were significant correlates of poor satisfaction with performing daily occupations. Social and clinical factors contributed to dissatisfaction with the poor performance of daily occupations among people with MS. Intervention studies are needed to investigate the role of occupational therapy in improving the performance of daily occupations in people with MS.

Anens, E., Zetterberg, L., Urell, C., et al. (2017). "Self-reported physical activity correlates in Swedish adults with multiple sclerosis: a cross-sectional study." BMC Neurol **17**(1): 204.

BACKGROUND: The benefits of physical activity in persons with Multiple Sclerosis (MS) are considerable. Knowledge about factors that correlate to physical activity is helpful in order to develop successful strategies to increase physical activity in persons with MS. Previous studies have focused on correlates to physical activity in MS, however falls self-efficacy, social support and enjoyment of physical activity are not much studied, as well as if the correlates differ with regard to disease severity. The aim of the study was to examine associations between physical activity and age, gender, employment, having children living at home, education, disease type, disease severity, fatigue, self-efficacy for physical activity,

falls self-efficacy, social support and enjoyment of physical activity in a sample of persons with MS and in subgroups with regard to disease severity. METHODS: This is a cross-sectional survey study including Swedish community living adults with MS, 287 persons, response rate 58.2%. The survey included standardized self-reported scales measuring physical activity, disease severity, fatigue, self-efficacy for physical activity, falls self-efficacy, and social support. Physical activity was measured by the Physical Activity Disability Survey - Revised. RESULTS: Multiple regression analyzes showed that 59% (F(6,3) = 64.9, p = 0.000) of the variation in physical activity was explained by having less severe disease (beta = -0.30), being employed (beta = 0.26), having high falls self-efficacy (beta = 0.20), having high self-efficacy for physical activity (beta = 0.17), and enjoying physical activity (beta = 0.11). In persons with moderate/severe MS, self-efficacy for physical activity explained physical activity. CONCLUSIONS: Consistent with previous research in persons with MS in other countries this study shows that disease severity, employment and self-efficacy for physical activity are important for physical activity. Additional important factors were falls self-efficacy and enjoyment. More research is needed to confirm this and the subgroup differences.

Antao, L., Shaw, L., Ollson, K., et al. (2013). "Chronic pain in episodic illness and its influence on work occupations: a scoping review." Work **44**(1): 11-36.

OBJECTIVES: The aim of this review was to understand and synthesize the realm of knowledge on intermittent work capacity (IWC) about strategies to support work sustainability. Specifically, this review focused on literature that examined productive work with individuals who have chronic pain due to Fibromyalgia, Breast Cancer, Multiple Sclerosis, and Human Immunodeficiency Virus. METHODS: A scoping review of research conducted across 10 databases. Nature of the knowledge base on return to work barriers and strategies and future recommended strategies needed to support persons with IWC in maintaining work participation were charted and thematically analyzed and organized into micro, meso and macro categories. RESULTS: Majority of the knowledge base reflects factors impeding and facilitating employment or re-employment at the micro level. At the micro level, self advocacy was a strategy that persons with IWC used to maintain employment and navigate stigmatizing work environments to meet their needs. At the meso level education and knowledge sharing with employers to increase awareness was underscored; at the macro level introduction of new policies was recommended. CONCLUSIONS: These findings suggest the need for future greater examination of the dialectical relationships across micro, meso and macro level strategies to overcome work disparities for persons with IWC.

Baughman, B. C., Basso, M. R., Sinclair, R. R., et al. (2015). "Staying on the job: The relationship between work performance and cognition in individuals diagnosed with multiple sclerosis." J Clin Exp Neuropsychol **37**(6): 630-640.

People with multiple sclerosis (MS) are apt to become unemployed as the disease progresses, and most research implies that this is due to diminishing mobility. Some studies have shown that presence of cognitive impairment also predicts employment status. Yet, no studies have examined how neuropsychological factors predict vocational performance among individuals with MS who remain employed. We assessed employer- and self-rated work performance, mobility status, and neuropsychological function in a sample of 44 individuals diagnosed with MS. Results suggest that cognitive impairment is common in these employed individuals, despite largely intact mobility status. Moreover, a significant interaction emerged, such that cognitively impaired individuals' work performance was rated more poorly by supervisors. In contrast, self-ratings of work performance were higher in cognitively impaired than in unimpaired participants. These novel findings suggest that

cognitive impairment may influence work performance, even in patients whose physical disability status is relatively intact.

Beier, M., Hartoonian, N., D'Orio, V. L., et al. (2019). "Relationship of perceived stress and employment status in individuals with multiple sclerosis." Work **62**(2): 243-249.

BACKGROUND: Many individuals with multiple sclerosis (MS) are unemployed relatively soon after diagnosis. There is a paucity of research on the relationship between psychological distress and employment status in persons with MS. OBJECTIVE: To explore the relative distress of employed versus unemployed individuals with MS. METHODS: Secondary cross-sectional analysis of a mailed survey. Variables were categorized by demographics (age, gender, education, marital status), disease (EDSS, MS symptom duration, fatigue, MS-type), and psychosocial factors (depression, anxiety, perceived stress, self-reported general cognitive concerns, self-reported executive dysfunction). Univariate logistic regression analysis was used to identify variables significantly associated with employment status. All significant variables were then included in a multivariate model to identify the most salient correlates. RESULTS: Univariate analyses identified 10 variables that were significantly associated with employment status: age, education, EDSS, MS symptom duration, MS-type, depression symptoms, perceived stress, fatigue, and self-reported cognitive symptoms. The multivariate model yielded four demographic and disease-related variables and one emotional distress variable (older age, moderate disability [EDSS], longer symptom duration, MS-type, higher perceived stress) as significant. CONCLUSIONS: After adjusting for disease variables, demographics, and significant psychosocial factors, perceived stress remained associated with employment status, such that greater perceived stress was associated with being unemployed.

Benedict, R. H., Rodgers, J. D., Emmert, N., et al. (2014). "Negative work events and accommodations in employed multiple sclerosis patients." Mult Scler **20**(1): 116-119.

Work disability is common in multiple sclerosis (MS) and cognitive disorder discriminates disabled from employed patients. Our goal was to develop and validate an online vocational status monitoring tool measuring negative work events and use of accommodations. We enrolled 52 employed patients completing an online survey and a clinical examination including tests of motor function, cognitive abilities, and depression. The survey recorded a wide range of reported work problems. Regression models predicting negative work events, and use of accommodations, retained measures of ambulation, cognition, and depression. These data provide preliminary support for the validity of online vocational monitoring in MS.

Bishop, M., Frain, M., Rumrill, P., et al. (2009). "The relationship of self-management and disease modifying therapy use to employment status among adults with multiple sclerosis ." Journal of Vocational Rehabilitation **231**(2): 119-128.

People with multiple sclerosis (MS) may face numerous barriers to employment retention. Comprehensively understanding these barriers is important for implementing effective vocational rehabilitation interventions. Although several demographic and MS-related variables have consistently been found to be related to employment status, self-management and adherence to treatment have infrequently been evaluated in this context. This article explores the relationships between employment status and the use of disease-modifying therapy and self-management among a community-based sample of adults with MS using both bivariate and multivariate analyses. Group comparisons between employed and unemployed adults with MS suggested that both self-management and DMT use are significantly related to employment. In a stepwise binary logistic regression analysis, age, duration in years diagnosed with MS, and scores on a multi-dimensional MS self-management scale were positively related to employment. The results are discussed in terms of their implications for rehabilitation intervention.

Bjorkenstam, C., Alexanderson, K., Wiberg, M., et al. (2015). "Heterogeneity of sickness absence and disability pension trajectories among individuals with MS." Mult Scler J Exp Transl Clin **1**: 2055217315595638.

BACKGROUND: The variability of progression of multiple sclerosis (MS) suggests that MS is a heterogeneous entity. OBJECTIVE: The objective of this article is to determine whether sickness absence (SA) and disability pension (DP) could be used to identify groups of patients with different progression courses. METHODS: We analyzed mean-annual net months of SA/DP, five years prior to MS diagnosis, until the year of diagnosis, and five years after for 3543 individuals diagnosed 2003-2006, by modeling trajectory subgroups. RESULTS: Five different groups were identified, revealing substantial heterogeneity among MS patients. Before diagnosis, 74% had a flat trajectory, while the remaining had a sharply increasing degree of SA/DP. After diagnosis, 95% had a flat or marginally increasing trajectory, although at various SA/disability pension (DP) levels, whereas a small group of 5% had decreasing SA/DP. A majority had few or no SA/DP months throughout the 11-year study period. Higher age and a lower educational level were associated with an unfavorable trajectory (p values <0.01). CONCLUSIONS: There's a considerable heterogeneity of MS progression in terms of SA/DP. Compared with other measures of disability, sickness-absence and disability pension offer a continuous variable that can be assigned to every individual for each time period without missing data. To what extent the SA/DP measure reflects classical MS outcome-measures as well as how correlated it is with co-morbidities and working-conditions needs to be investigated further.

Boe Lunde, H. M., Telstad, W., Grytten, N., et al. (2014). "Employment among patients with multiple sclerosis-a population study." PLoS One **9**(7): e103317.

OBJECTIVE: To investigate demographic and clinical factors associated with employment in MS. METHODS: The study included 213 (89.9%) of all MS patients in Sogn and Fjordane County, Western Norway at December 31st 2010. The patients underwent clinical evaluation, structured interviews and completed self-reported questionnaires. Demographic and clinical factors were compared between patients being employed versus patients being unemployed and according to disease course of MS. Logistic regression analysis was used to identify factors independently associated with current employment. RESULTS: After a mean disease duration of almost 19 years, 45% of the population was currently full-time or part- time employed. Patients with relapsing -remitting MS (RRMS) had higher employment rate than patients with secondary (SPMS) and primary progressive (PPMS). Higher educated MS patients with lower age at onset, shorter disease duration, less severe disability and less fatigue were most likely to be employed. CONCLUSIONS: Nearly half of all MS patients were still employed after almost two decades of having MS. Lower age at onset, shorter disease duration, higher education, less fatigue and less disability were independently associated with current employment. These key clinical and demographic factors are important to understand the reasons to work ability in MS. The findings highlight the need for environmental adjustments at the workplace to accommodate individual 's needs in order to improve working ability among MS patients.

Busche, K. D., Fisk, J. D., Murray, T. J., et al. (2003). "Short term predictors of unemployment in multiple sclerosis patients." Can J Neurol Sci **30**(2): 137-142.

BACKGROUND: Unemployment is common in people with multiple sclerosis (MS) and is associated with loss of income and impaired health related quality of life. This study determined variables associated with unemployment and risk factors for the development of unemployment in people with MS. METHODS: Ninety-six patients who were under age 65 and participated in two previous studies to measure economic costs and health related quality of life in MS were included. The baseline employment rate and variables associated with unemployment at baseline were determined. The ability of these variables to predict unemployment over the next two and a half years was then evaluated. RESULTS: At baseline 50.1% (50/96) of participants were employed. Two and a half years later only 40.6% (39/96) remained employed. This represents loss of employment for 22.0% (11/50) of those originally employed. Factors associated with unemployment at baseline included greater disability, progressive disease course, longer disease duration, and older age. Risk factors for loss of employment over the next 2.5 years included greater disability and older age. CONCLUSIONS: This study confirms the low employment rate among people with MS and confirms the association of several previously-reported factors with greater risk of unemployment. It is also the first study to confirm that some of these factors also increase the risk of future unemployment. People with MS who are over age 39 or have moderate disability and are still employed can now be identified as at risk for becoming unemployed over the next 2.5 years. They should be considered for interventions to maintain employment or to lessen the impact of unemployment.

Cadden, M. et Arnett, P. (2015). "Factors Associated with Employment Status in Individuals with Multiple Sclerosis." Int J MS Care **17**(6): 284-291.

BACKGROUND: Unemployment is common in individuals with multiple sclerosis (MS) and is associated with substantial socioeconomic burden. Several MS-related factors have been found to be associated with employment status, including fatigue, depression, cognitive problems, and motor difficulties. However, few studies have examined these factors collectively in predicting employment. The present study aimed to explore these variables together in predicting employment status in MS. METHODS: Fifty-three individuals with MS participating in a research study of cognitive, emotional, and social factors related to MS were examined. Composite scores were created using factor analysis that represented cognition, fatigue, depression, and motor function. These composite scores, along with the Expanded Disability Status Scale score, were explored as predictors of employment status (working, not working) via logistic regression. Models of mediation were also investigated. RESULTS: A model including composite scores of motor function, cognition, depression, and fatigue significantly distinguished those who are unemployed versus employed. However, only the cognitive, motor, and fatigue composite scores were found to be significantly associated with unemployment individually. RESULTS of a mediation analysis using 1000 bootstrap samples indicated that the cognitive and fatigue composite scores significantly mediated the effect of disability on work status. CONCLUSIONS: Cognitive function and fatigue mediate the effect of MS disability on employment status. Interventions targeting cognitive difficulties and fatigue in MS may be effective in helping individuals maintain employment.

Campbell, J., Rashid, W., Cercignani, M., et al. (2017). "Cognitive impairment among patients with multiple sclerosis: associations with employment and quality of life." Postgrad Med J **93**(1097): 143-147.

OBJECTIVES: To explore the relationship between cognitive impairment and conventional measures of disability in multiple sclerosis (MS), quality of life (QOL) and employment status using the brief international cognitive assessment for multiple sclerosis (BICAMS) in the routine outpatient clinic. METHODS: 62 patients with MS were assessed on the BICAMS test battery for cognitive impairment. Data were obtained on employment status and a number of questionnaires completed including fatigue severity score, multiple sclerosis neuropsychological questionnaire, hospital anxiety and depression scale, the functional assessment of multiple sclerosis (FAMS) as well as on the EuroQOL five dimension questionnaire (EQ-5D). Other assessments include the patient activation measure and unidimensional self-efficacy scale for multiple sclerosis. RESULTS: Cognitive assessment revealed 44 subjects (65%) had evidence of cognitive impairment on formal testing. In comparison with patients without evidence of cognitive impairment, cognitively impaired patients exhibited significantly higher rates of unemployment (p=0.009). The symbol digits modalities test was the most significant predictor of unemployment. Cognitive impairment was associated with lower QOL scores on the FAMS (p=0.001) and EQ-5D (p<0.001). CONCLUSIONS: BICAMS provides a sensitive and easy to administer screening test for cognitive impairment within the outpatient setting. Cognitive impairment is common in our cohort of patients with MS attending outpatients and appears to be associated with increased rates of unemployment and lower measures of QOL.

Cancelliere, C., Donovan, J., Stochkendahl, M. J., et al. (2016). "Factors affecting return to work after injury or illness: best evidence synthesis of systematic reviews." Chiropr Man Therap **24**(1): 32.

BACKGROUND: Work disability is a major personal, financial and public health burden. Predicting future work success is a major focus of research. OBJECTIVES: To identify common prognostic factors for return-to-work across different health and injury conditions and to describe their association with return-to-work outcomes. METHODS: Medline, Embase, PsychINFO, Cinahl, and Cochrane Database of Systematic Reviews and the grey literature were searched from January 1, 2004 to September 1, 2013. Systematic reviews addressing return-to-work in various conditions and injuries were selected. Eligible studies were critically appraised using the Scottish Intercollegiate Guidelines Network criteria to identify low risk of bias reviews. RESULTS: Of the 36,193 titles screened and the 94 eligible studies reviewed, 56 systematic reviews were accepted as low risk of bias. Over half of these focused on musculoskeletal disorders, which were primarily spine related (e.g., neck and low back pain). The other half of studies assessed workers with mental health or cardiovascular conditions, stroke, cancer, multiple sclerosis or other non-specified health conditions. Many factors have been assessed, but few consistently across conditions. Common factors associated with positive return-to-work outcomes were higher education and socioeconomic status, higher self-efficacy and optimistic expectations for recovery and return-to-work, lower severity of the injury/illness, return-to-work coordination, and multidisciplinary interventions that include the workplace and stakeholders. Common factors associated with negative return-to-work outcomes were older age, being female, higher pain or disability, depression, higher physical work demands, previous sick leave and unemployment, and activity limitations. CONCLUSIONS: Expectations of recovery and return-to-work, pain and disability levels, depression, workplace factors, and access to multidisciplinary resources are important modifiable factors in progressing return-to-work across health and injury conditions. Employers, healthcare providers and other stakeholders can use this information to facilitate return-to-work for injured/ill workers regardless of the specific injury or illness. Future studies should investigate novel interventions, and other factors that may be common across health conditions.

Cardone, A. (2017). "Having the conversation about work with people with multiple sclerosis: a guide for healthcare professionals." Neurodegener Dis Manag **7**(6s): 41-44.

The ability to work is important for people with multiple sclerosis (MS). However, only 37% of those with mild MS are in work. Across Europe, lost work productivity accounts for a third of the euro15 billion total annual cost of MS. Supporting people with MS into employment should be a clinical care priority in order to maximize work productivity, inclusiveness and therapeutic benefit. A guide for healthcare professionals on having conversations about work with people with MS has been developed through the 'Ready for Work' project. Work should be considered as a clinical outcome. The focus should be on what patients can do, rather than what they cannot do, at work. Effective communication is fundamental in supporting patients' return to work.

Carrieri, L., Sgaramella, T. M., Bortolon, F., et al. (2014). "Determinants of on-the-job-barriers in employed persons with multiple sclerosis: the role of disability severity and cognitive indices." Work **47**(4): 509-520.

BACKGROUND: Literature has shown that work maintenance is central in order to guarantee participation to persons with disability. Knowledge about potential sources of difficulties and obstacles is then crucial in order to prevent barriers and facilitate work maintenance and career development for persons with disabilities. OBJECTIVE: Studies analyzing on-the-job barriers among employed people with multiple sclerosis (MS) have found evidence for a role of clinical determinants. The aim of this study was to describe in more detail the role of disability severity and of cognitive indices on work barriers. PARTICIPANTS: Thirty-two employed adults with a diagnosis of MS with mild to moderate disability severity were included in the study. They were involved in the descriptive study while attending their planned care in the MS unit. METHODS: Subjects completed neurocognitive tasks, a self-report measure of executive functioning and a face-to-face semi-structured interview exploring their perception of barriers at work. RESULTS: Regression analyses showed a specific role of disability severity on perception of barriers due to physical, cognitive and interpersonal relationships; cognitive indices, on the other hand, predicted barriers ascribed to company policy (cognitive score), to accessibility (planning score) or difficulties in cognitive and task related abilities (self-rated executive functioning). CONCLUSION: These findings underline the relevance of objective tasks and self-report questionnaire, direct and indirect multi-dimensional assessment of functioning for an early intervention planning. An ecological model of career development in adults with disabilities is also supported.

Castelo-Branco, A., Landfeldt, E., Svedbom, A., et al. (2019). "Clinical course of multiple sclerosis and labour-force absenteeism: a longitudinal population-based study." Eur J Neurol **26**(4): 603-609.

BACKGROUND AND PURPOSE: Multiple sclerosis (MS) is a chronic neurological disease associated with substantial disability and morbidity. The objective of our study was to assess the long-term consequences of MS clinical course on sick leave and disability pension. METHODS: Patients with relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS) were identified through the Swedish Multiple Sclerosis Registry. We calculated the mean annual prevalence and number of sick leave and disability pension days by clinical course, age and year pre- and post-diagnosis, and compared outcomes using Welch's t-tests and ANOVA models, mixed-effects regression and survival analysis. RESULTS: The sample included 5371 patients (4568 with RRMS, 390 with SPMS and 413 with PPMS). The mean annual number of days with sick leave and disability pension ranged from 101 at 1 year after diagnosis to 164 after 11 years for patients with RRMS. Corresponding estimates for PPMS were 188 and 311 days. Higher levels of absenteeism were observed in patients with PPMS versus RRMS 7 years before diagnosis for sick leave ($P < 0.025$) and 10 years before diagnosis for disability pension ($P < 0.034$). Differences between SPMS and PPMS were minor. CONCLUSIONS: Patients with RRMS had substantially lower levels of sick leave and disability pension over time compared with their counterparts with SPMS and PPMS, whereas labour-force absenteeism was similar for patients with SPMS and PPMS. These findings contribute to the understanding of the impact of MS on socioeconomic outcomes and help inform the discussion on the clinical classification of different courses of the disease.

Chen, J., Taylor, B., Palmer, A. J., et al. (2019). "Estimating MS-related work productivity loss and factors associated with work productivity loss in a representative Australian sample of people with multiple sclerosis." Mult Scler **25**(7): 994-1004.

BACKGROUND: Little is known about the work productivity loss in multiple sclerosis (MS). OBJECTIVES: To quantify the MS-related work productivity loss and to compare factors associated with labour force participation and work productivity loss. METHODS: Participants were from the Australian MS Longitudinal Study. MS-related work productivity loss included absenteeism (time missed from work) and presenteeism (reduced productivity while working). Data were analysed using log-binomial and Cragg hurdle regression. RESULTS: Among 740 MS employees, 56% experienced any work productivity loss due to MS in the past 4 weeks. The mean total work productivity loss was 2.5 days (14.2% lost productive time), absenteeism 0.6 days (3.4%) and presenteeism 1.9 days (10.8%)), leading to AU$6767 (US$4985, EUROeuro4578) loss per person annually. Multivariable analyses showed that work productivity was determined most strongly by symptoms, particularly 'fatigue and cognitive symptoms' and 'pain and sensory symptoms', while older age, and lower education level were also predictive of not being in the labour force. CONCLUSION: MS-related presenteeism was three times higher than absenteeism, highlighting the importance of presenteeism being included in employment outcomes. The dominance of symptom severity as predictors of both work participation and productivity loss emphasises the need for improved management of symptoms.

Chen, J., Taylor, B. V., Blizzard, L., et al. (2018). "Effects of multiple sclerosis disease-modifying therapies on employment measures using patient-reported data." J Neurol Neurosurg Psychiatry **89**(11): 1200-1207.

BACKGROUND: The direct comparative evidence on treatment effects of available multiple sclerosis (MS) disease-modifying therapies (DMTs) is limited, and few studies have examined the benefits of DMTs on employment outcomes. We compared the effects of DMTs used in the previous 5 years on improving the work attendance, amount of work and work productivity of people with MS. METHODS: The Australian MS Longitudinal Study collected data from participants on DMTs usage from 2010 to 2015 and whether DMTs contributed to changes in employment outcomes. We classified 11 DMTs into three categories based on their clinical efficacy (beta-interferons and glatiramer acetate as category 1; teriflunomide and dimethyl fumarate as category 2; fingolimod, natalizumab, alemtuzumab and mitoxantrone as category 3). Each DMT used by a participant was treated as one observation and analysed by log-multinomial regression. RESULTS: Of the 874 participants included, 1384 observations were generated. Those who used category 3 (higher efficacy) DMTs were 2-3 times more likely to report improvements in amount of work, work attendance and work productivity compared with those who used category 1 (classical injectable) DMTs. Natalizumab was associated with superior beneficial effects on patient-reported employment outcomes than fingolimod (RR=1.76, 95% CI 1.02 to 3.03 for increased work attendance and RR=1.46, 95% CI 1.02 to 2.10 for increased work productivity). CONCLUSIONS: Those using the higher efficacy (category 3) DMTs, particularly fingolimod and natalizumab, reported significant increases in amount of work, work attendance and work productivity, suggesting they have important beneficial effects on work life in people with MS.

Chiu, C. Y., Chan, F., Bishop, M., et al. (2013). "State vocational rehabilitation services and employment in multiple sclerosis." Mult Scler **19**(12): 1655-1664.

BACKGROUND: Obtaining and maintaining suitable employment can be a significant challenge for people with multiple sclerosis (MS). OBJECTIVE: The objective of this article is to identify what vocational rehabilitation (VR) services helped MS clients obtain and maintain employment, after controlling for the effect of demographic covariates and disability-related government benefits. METHODS: We retrieved data from the Rehabilitation Services Administration (RSA) 911 database in the fiscal year (FY) 2009, and used VR services as predictors to predict employment outcomes of people with MS by hierarchical logistic regression. RESULTS: A total of 924 out of 1920 MS clients (48.1%) were successfully employed after receiving VR services. Logistic regression analysis results indicated that cash benefits (OR =0.51, $p < 0.001$) and public medical benefits (OR =0.76, $p < 0.01$) were negatively associated with employment outcomes, whereas counseling and guidance (OR = 1.68, $p < 0.001$), job placement assistance (OR = 2.43, $p < 0.001$), on-the-job supports (OR = 1.62, $p < 0.01$), maintenance services (OR = 1.59, $p < 0.01$), and assistive technology services (OR =2.09, $p < 0.001$) were significant predictors of positive employment outcomes. CONCLUSION: VR services were found to be associated with employment status. MS patients experiencing problems obtaining or maintaining employment should be encouraged to pursue services from state VR agencies.

Chiu, C. Y., Chan, F., Edward Sharp, S., et al. (2015). "Employment as a health promotion intervention for persons with multiple sclerosis." Work **52**(4): 749-756.

OBJECTIVE: To examine the relationship between employment status (no employment, part-time employment, and full-time employment) and functional disability, health-related quality of life, and life satisfaction of people with MS. METHODS: 157 individuals with MS completed a survey packet, including employment status, self-report disability severity, and health-related scales. A series of multivariate analysis of variance was performed to determine the differences between employment groups in health-related outcomes. RESULTS: The unemployed group had the highest levels of incapacity and social impairments among the three groups. They also had the lowest physical health-related quality of life and life satisfaction. The part-time employed group had the lowest levels of depression and higher levels of physical activity participation among the three groups of individuals with MS. CONCLUSIONS: Employment is significantly related to health-related quality of life, and as a result, it should be considered an important public health intervention for people with MS.

Chiu, C.-Y., Tansey, T. N., Chan, F., et al. (2015). "Effect of Rehabilitation Technology Services on Vocational Rehabilitation Outcomes of Individuals With Multiple Sclerosis." Rehabilitation Research Policy and Education(2): 183-192.
https://connect.springerpub.com/content/sgrrrpe/29/2/183

Objectives: To examine the effect of rehabilitation technology interventions on the employment or job retention outcomes of individuals with multiple sclerosis (MS) served by the state-federal vocational rehabilitation program using a case-control study design. Participants: Data for this study were extracted from the Rehabilitation Services Administration Case Service Report database. The sample included 8,715 individuals with MS aged between 16 and 64 years old whose cases were closed between the fiscal years of 2007 and 2011. Outcome measure: Competitive employment. Results: The classification and

> regression tree method identified 5 homogeneous subgroups ranging from high to low propensity to receive rehabilitation technology services. Specifically, individuals with MS employed at application were most likely to receive rehabilitation technology intervention. The effect of rehabilitation technology on job retention was especially strong for individuals aged 35 years or older with a college education. Conclusion: These findings suggest that rehabilitation technology is an effective service for enhancing job retention outcomes of middle-aged and older adults with MS and provide valuable information for policymakers, health care providers, rehabilitation counselors, and educators.

Chruzander, C., Tinghög, P., Ytterberg, C., et al. (2016). "Longitudinal changes in sickness absence and disability pension, and associations between disability pension and disease-specific and contextual factors and functioning, in people with multiple sclerosis." J Neurol Sci **367**: 319-325.
http://www.sciencedirect.com/science/article/pii/S0022510X16303240

> Background Even though it is well known that disability due to MS is highly associated with employment status, the long-term longitudinal perspective on sickness absence and disability pension over the MS trajectory is lacking. In addition, further knowledge of risk factors for future disability pension is needed. Objectives To explore long-term longitudinal changes in the prevalence of sickness absence and disability pension in people with MS (PwMS), as well as to explore associations between disease-specific factors, contextual factors and functioning, and the outcome of future full-time disability pension. Methods A prospective, population-based survival cohort study, with a nine year follow-up, including 114 PwMS was conducted by combining face-to-face collected data and register-based data. Results The prevalence of full-time disability pension increased from 20% to 50%, however 24% of the PwMS had no disability pension at all at end of follow-up. Sex, age, disease severity and impaired manual dexterity were associated with future full-time disability pension. Conclusions The large increase in prevalence of PwMS on full-time disability pension during the MS trajectory, calls for the development and implementation of evidence-based interventions, aiming at keeping PwMS in the work force. Modifiable factors, such as manual dexterity should be targeted in such interventions.

Clemens, L. et Langdon, D. (2018). "How does cognition relate to employment in multiple sclerosis? A systematic review." Mult Scler Relat Disord **26**: 183-191.

> BACKGROUND: Almost half of people with multiple sclerosis (MS), with low levels of physical disability, are unemployed. It is likely that the impact of "invisible" symptoms of MS, such as cognition, are involved. Evidence also suggests that cognition is a mediating factor between physical disabilities and unemployment. METHODS: A systematic review was conducted to investigate the link between objective cognitive performance and unemployment in MS. The search was carried out in September 2017 using identical search terms across three search engines: PubMed, PSYCH Info and Web of Science. Inclusion criteria included peer review, participant age range of 18 to 65, objective neuropsychological testing and self-reported employment information. RESULTS: The search returned a total of 910 articles of which 13 were considered eligible for inclusion. The eligible studies consistently found that people with MS who were unemployed, or who had more negative work-related events, performed less well on neuropsychological tests than both employed people with MS and healthy control groups. People with MS who were employed or had no changes in their work situation also performed less well than healthy controls on neuropsychological tests. Significant between group differences were seen in the following cognitive domains: information processing speed, immediate recall, delayed recall and executive function. CONCLUSION: Difficulties with employment and/or reduced work hours were associated with cognitive impairment in MS.

Concetta Incerti, C., Magistrale, G., Argento, O., et al. (2015). "Occupational stress and personality traits in multiple sclerosis: A preliminary study." Mult Scler Relat Disord **4**(4): 315-319.

> Multiple Sclerosis (MS) is a demyelinating and neurodegenerative disease of the central nervous system, causing a wide range of neurological and psychological symptoms. Impairment of ambulation and cognition in particular are associated with work difficulties and unemployment. Although many aspects of work status have been investigated in MS, there are no reports on factors that predict the development of occupational stress, prior to job loss. The aim of this preliminary study was to ascertain if personality traits predispose MS patients to occupational stress. We evaluated 26 MS patients using physical disability scales and self-report questionnaires focused on mood, fatigue, and personality [measured with the NEO Five Factor Inventory]. The primary outcome measure was the Occupational Stress Indicator [OSI]. Results showed significant positive correlations ($p<.05$) between high neuroticism, and occupational stress. Conversely, low extraversion and conscientiousness were also associated with job stress. The direction of these correlations was consistent with prior research showing that high neuroticism, and low extraversion and conscientiousness, are risk factors for MS disease severity as evidenced by brain atrophy, cognitive impairment and adaptation in MS. We are developing interventions to help patients cope with these maladaptive personality dispositions in the hope that employment may be maintained.

Cores, E. V., Vanotti, S., Burin, D. I., et al. (2014). "[Factors associated to the work situation of patients with multiple sclerosis]." Rev Neurol **58**(4): 175-183.

> INTRODUCTION: Multiple sclerosis is a demyelinating neurological disease that usually gives rise to motor, perceptive, affective and cognitive disorders in patients. These symptoms can lead the person to lose his or her job and lower the quality of life of both patients and their relatives. AIM: To review the literature on demographic, clinical, cognitive, psychiatric, occupational and social variables associated with the work situation. DEVELOPMENT: Cross-sectional and longitudinal studies have detected variables related with unemployment. Empirical research has shown how physical disability, fatigue and the progression of the disease exert a clear influence on the patient's work situation. Yet, the same degree of evidence is not true for gender, depression, age, duration of the disease and cognitive variables. Little attention has been given to work characteristics such as job discrimination, employer's attitude, labour laws, colleagues' attitudes and transport problems. CONCLUSIONS: Many of the factors that determine job loss in a patient with multiple sclerosis can be identified in time to allow them to be modified or offset. The knowledge provided by the studies mentioned above makes it possible to detect patients who are at risk of losing their job so that interventions can be carried out with the aim of preventing such a situation from occurring. More particularly, the vulnerability profile includes high physical disability and fatigue, progressive development of the disease and the presence of cognitive impairment, among others.

Coyne, K. S., Boscoe, A. N., Currie, B. M., et al. (2015). "Understanding Drivers of Employment Changes in a Multiple Sclerosis Population." Int J MS Care **17**(5): 245-252.

> BACKGROUND: Qualitative data are lacking on decision making and factors surrounding changes in employment for patients with multiple sclerosis (MS). This study aimed to increase our understanding of the key symptoms and factors leading patients with MS to leave work or reduce employment. METHODS: Adults with MS who reported leaving the workforce, reducing work hours, or changing jobs due to MS in the past 6 months were recruited from four US clinical sites. Patients participated in semistructured interviews to

discuss MS symptoms and reasons for changing employment status. All interviews were transcribed and coded for descriptive analyses. RESULTS: Twenty-seven adults (mean age = 46.3 years, mean duration of MS diagnosis = 10.9 years) with a range of occupations participated; most were white (81.5%) and female (70.4%). Physical symptoms (eg, fatigue, visual deficits) (77.8%) were the most common reasons for employment change; 40.7% of patients reported at least one cognitive symptom (eg, memory loss). Fatigue emerged as the most pervasive symptom and affected physical and mental aspects of patients' jobs. Most patients (85.2%) reported at least two symptoms as drivers for change. Some patients reported a significant negative impact of loss of employment on their mental status, family life, and financial stability. CONCLUSIONS: Fatigue was the most common symptom associated with the decision to leave work or reduce employment and can lead to a worsening of other MS symptoms. Comprehensive symptom management, especially fatigue management, may help patients preserve their employment status.

D'Hooghe M, B., De Cock, A., Benedict, R. H. B., et al. (2019). "Perceived neuropsychological impairment inversely related to self-reported health and employment in multiple sclerosis." Eur J Neurol.

BACKGROUND AND PURPOSE: Multiple sclerosis (MS) patients frequently report cognitive difficulties which impact daily functioning. The objective was to investigate the relationship between patient-reported cognitive impairment and depression, demographic and MS-related variables, and to clarify its impact on self-reported health measures and employment. METHOD: A large two-centre survey included the MS Neuropsychological Screening Questionnaire (MSNQ), the two-question screening tool for depression, vitality, health-related quality of life, the Health-Promoting Lifestyle Profile II and questions assessing social network satisfaction and employment status. RESULTS: Of the 751 respondents (median age 54 years, median Expanded Disability Status Scale 5, 66.2% female), two-thirds reported perceived neuropsychological impairment or depressive symptoms. Whilst depressive symptoms were related to higher MSNQ scores, the MSNQ poorly predicted depression. After correcting for confounders, higher MSNQ scores and depressive symptoms decreased vitality, health-related quality of life and health-promoting behaviours and increased the probability of being socially dissatisfied. In participants below retirement age, higher MSNQ and Expanded Disability Status Scale scores increased the probability of unemployment, whilst depression did not. CONCLUSION: The contribution of the MSNQ to self-reported health measures and its unique explanatory power regarding unemployment suggest that subjective cognitive complaints are connected to subtle, yet meaningful, neuropsychological dysfunction.

D'Hooghe M, B., Haentjens, P., Van Remoortel, A., et al. (2016). "Self-reported levels of education and disability progression in multiple sclerosis." Acta Neurol Scand **134**(6): 414-419.

OBJECTIVES: The purpose of our study is to investigate whether socioeconomic indicators such as education, financial concerns, employment, and living status are associated with disease progression in relapsing-onset and progressive-onset Multiple Sclerosis (MS). MATERIALS AND METHODS: We performed a cross-sectional survey among individuals with MS, registered by the Flemish MS society and included socioeconomic indicators. A Cox proportional hazard regression was performed with the time from MS onset and from birth to reach an ambulatory disability milestone corresponding to Expanded Disability Status Scale (EDSS) 6 (requiring a cane) as outcome measure, adjusted for gender, age at MS onset, and immunomodulatory treatment. RESULTS: Among the participants with relapsing-onset MS, subjects reporting education for more than 12 years had a reduced risk of reaching EDSS 6 compared to subjects reporting education for less than 12 years [HR from onset 0.68 (95%

CI 0.49-0.95); HR from birth 0.71 (95% CI 0.51-0.99)]. In progressive-onset MS, longer education was associated with an increased hazard to reach EDSS 6 [HR from onset 1.25 (95% CI 0.91-1.70); HR from birth 1.39 (95% CI 1.02-1.90)]. CONCLUSIONS: Our study shows an association of self-reported levels of education with disability progression in MS, with the highest level being protective in relapsing-onset MS.

Doesburg, D., Vennegoor, A., Uitdehaag, B. M. J., et al. (2019). "High work absence around time of diagnosis of multiple sclerosis is associated with fatigue and relapse rate." Mult Scler Relat Disord **31**: 32-37.

> BACKGROUND: Multiple sclerosis (MS) is associated with high rates of disability pension and work absence. Little is known about work absence in early MS. The objectives of this study were (1) to assess the prevalence of work absence shortly after MS diagnosis, (2) to explore health-related quality of life (HRQoL) and disease impact in relation to work absence and (3) to investigate demographic and clinical factors that may be associated with high work absence. METHODS: Patients with relapsing remitting (RRMS) or primary progressive MS (PPMS) were included shortly after MS diagnosis. We collected data on work absence due to MS in the year prior to inclusion, disability (Expanded Disability Status Scale), relapse rate, fatigue (Neurological Fatigue Index), health-related quality of life (HRQoL, 36-Item Short Form Survey) and disease impact (Multiple Sclerosis Impact Scale). For analysis, patients were divided in 2 groups: low work absence (<1 month) and high work absence (>/=1 month). Data was analyzed using backward logistic regression techniques. RESULTS: In total, 90 MS patients participated (80 RRMS, 10 PPMS, mean age=39.3 years, median disease duration since diagnosis=0.5 year). Work absence in the year prior to inclusion was reported by 66 patients (73.3%). High work absence of >/= 1 month was reported by 41 patients (45.6%). Disability, gender, age, disease duration and education did not differ between groups. Patients with high work absence reported a lower HRQoL and higher disease impact compared to patients with low work absence. Backward regression analysis showed that high work absence is associated with being single/not married, fatigue and relapses. The strongest association was found for fatigue (highest fatigue vs. lowest fatigue level: OR total group=7.8, RRMS=15.8). In RRMS patients the second-strongest association was relapse rate (>/=2 relapses in the past year vs. no relapses: OR 11.1). CONCLUSION: Prevalence of work absence is high in early MS. Patients with high work absence report a lower HRQoL and a higher disease impact. High work absence is associated with being single/not married, fatigue and relapses. Interventions aimed at fatigue and prevention of relapses may help maintain employment in early MS.

Doogan, C. et Playford, E. D. (2014). "Supporting work for people with multiple sclerosis." Mult Scler **20**(6): 646-650.

> People with multiple sclerosis experience some of the highest rates of unemployment among groups of individuals with severe and chronic disabilities. While unpredictable relapses, physical and cognitive symptoms all may play a role in job loss, it is more likely that job loss can be attributed to a complex interaction between disease-related factors and contextual factors, such as the working environment, and employer attitudes. This interaction leads to the concept of work instability, that is, the mismatch between work demands and the individual's capacity to meet these demands. Vocational rehabilitation services aim to provide people with multiple sclerosis vocational assessment, rehabilitation and support to enable them to find, regain or remain in work and access other occupational and educational opportunities. Such services consist of a multidisciplinary team with the ability to provide education around disclosure, and work-place accommodations, offer emotional support, maintain work performance, liaise with employers, and support to re-enter the workplace.

Helpful interventions include early disclosure, proper workplace accommodation, education of employers, and government-funded initiatives to support disabled employees. Future research needs to agree on methods of recording outcomes and evaluate specific vocational rehabilitation interventions.

Dorstyn, D., Roberts, R., Murphy, G., et al. (2018). "Online Resource to Promote Vocational Interests Among Job Seekers With Multiple Sclerosis: A Randomized Controlled Trial in Australia." Arch Phys Med Rehabil **99**(2): 272-280.

OBJECTIVE: To provide a preliminary evaluation of the effectiveness of an online resource for job seekers with multiple sclerosis (MS). DESIGN: Randomized controlled design. SETTING: Community-dwelling cohort. PARTICIPANTS: Adults (N = 95) with relapsing-remitting or progressive MS were randomly assigned to one of two groups. Forty-five accessed an email delivered, 7 module resource, Work and MS, over a 4 week period. Waitlist control participants (n=50) were offered the opportunity to access Work and MS 4 weeks postenrollment. MAIN OUTCOME MEASURES: Primary outcomes focused on vocational interests (My Vocational Situation Scale) and self-efficacy in job-seeking activities (Job-Procurement Self Efficacy Scale). Secondary outcomes focused on perceived workplace difficulties (Multiple Sclerosis Work Difficulties Questionnaire [MSWDQ]), optimism (Life Orientation Test - Revised), and mood (Patient Health Questionnaire-9). RESULTS: Intention-to-treat analyses revealed pre-post gains: participants who accessed Work and MS reported improved confidence in their career goals (My Vocational Situation Scale g=.55; 95% confidence interval [CI], .14-.96; P=.008) and positively reappraised potential workplace difficulties (MSWDQ g range, .42-.47; P range, .023-.042). The effect on job self-efficacy was not significant, but changed in the expected direction (g=.17; 95% CI, -.23 to .57; P=.409). Completer data revealed larger, significant effect estimates (g range, .52-.64; P range, .009-.035). CONCLUSIONS: Findings provide preliminary support for the utility of a job information resource, Work and MS, to augment existing employment services. The results also suggest the need to test employment-ready interventions in a larger study population. This might include the addition of online peer support to increase intervention compliance.

Dorstyn, D., Roberts, R., Murphy, G., et al. (2017). "Piloting an email-based resource package for job seekers with multiple sclerosis." Disabil Rehabil **39**(9): 867-873.

PURPOSE: Media-based rehabilitation provides a powerful opportunity to examine vocational behaviors in the disability sector. However, this research is preliminary at best. This paper reports pilot data. METHOD: Eighteen adults with multiple sclerosis (MS) accessed an email-delivered, resource-based package, Work and MS. Pre- and post-access vocational self-efficacy and identity (Job-Procurement Self Efficacy Scale, My Vocational Situation Scale-primary outcomes), life orientation and depressed mood (Life Orientation Test - revised and Patient Health Questionnaire-9 - secondary outcomes) were assessed. Pre- and post-change scores were examined with Wilcoxon signed ranks tests and Hedges g effect sizes with associated 95% confidence intervals. Reliable change analyses were additionally calculated to determine the clinical significance of individual change scores. RESULTS: Significant and positive effects were reported for vocational self-efficacy, identity, and optimism. Reliable change scores in one or more of these key outcomes were reported by 30% of the sample. Satisfaction with the content and delivery of the email-based intervention was also noted. CONCLUSIONS: Preliminary evidence suggests that Work and MS can help to promote vocational goals, interests and strengths among job seekers with a disability by providing a set of tools, information and linkages relating to vocational pursuits and career development. Replication with a randomized control design is indicated. Implications for Rehabilitation Research indicates a high unemployment rate among working-age adults with MS. A combination of disease-specific, psychological, programmatic and societal variables contribute to employment instability in this group. This pilot study demonstrates that an e-mail-based resource package, Work and MS, provides an innovative and feasible option for promoting consumer engagement with vocational services and, potentially, improving vocational outcomes. Work and MS has potential applicability to other disability groups.

Dorstyn, D. S., Roberts, R. M., Murphy, G., et al. (2019). "Employment and multiple sclerosis: A meta-analytic review of psychological correlates." J Health Psychol **24**(1): 38-51.

The association between employment and psychological health in adults with multiple sclerosis was examined (N = 33 studies). Standardised mean differences (Hedges' g) between those employed and those not in the workforce were calculated. Employed peers reported significantly greater quality of life and mood, cited fewer work and multiple sclerosis-related difficulties and were more likely to adopt problem-focused coping strategies, considered to be more effective in managing specific stressors. These data are consistent with the positive by-products of maintaining work with multiple sclerosis. Further research is needed to determine the longitudinal course of coping for those who remain employed.

Dunn, J. (2010). "Impact of mobility impairment on the burden of caregiving in individuals with multiple sclerosis." Expert Rev Pharmacoecon Outcomes Res **10**(4): 433-440.

Multiple sclerosis (MS) is a chronic, immune-mediated neurologic disease that typically strikes young adults during their most productive years, and is associated with a wide range of functional deficits and progressive disability. Loss of mobility is among the most disabling effects of MS, adversely affecting multiple outcomes, including independence, employment and quality of life. Relative to other common diseases, MS is associated with a disproportionately high socioeconomic burden. Informal and unpaid caregivers, such as family and friends, play a vital, sustained and often difficult role in supporting the ability of MS patients to live and function at home. However, there are few data characterizing caregiver burden in MS. This review was conducted to examine the need and impact of caregiving for patients with MS, focusing on the contribution of mobility impairment to loss of patient independence.

Findling, O., Baltisberger, M., Jung, S., et al. (2015). "Variables Related to Working Capability among Swiss Patients with Multiple Sclerosis—A Cohort Study." PLoS One **10**(4): e0121856.
https://doi.org/10.1371/journal.pone.0121856

Introduction Reduced working capability is one of the most devastating consequences of multiple sclerosis (MS). We aimed to study working capability and related variables in Swiss MS patients. Materials and Methods A cross-sectional analysis of employment status and risk factors for reduced working capability among MS patients treated at our outpatient clinic. A questionnaire was mailed to 644 MS patients and returned by 69.7%. 405 patients (66% female, mean age 44.2 years (SD±10.2), median EDSS 3.0 (SD±1.8)) were eligible for subsequent analysis. Results After a mean disease duration of 12.3 years (SD±8.25), full or part time employment was declared by 26.7% and 25.7%, respectively. Incapacity to work was reported by 27.1%. A total of 52.8% specified MS as the cause for altered working capability, whereas 20.5% cited reasons unrelated to the disorder. Even with minimal disability (EDSS<3) a significant proportion of patients (24%) reported reduced working capability. Among the MS-specific restricting factors were fatigue (47.6%), sensorimotor deficits (31.1%), impaired vision (3.3%) and pain (2.8%). Conclusion MS continues to takes its toll on the professional life of the patients early in the course. While complete incapacity becomes relevant with moderate to severe disability, many patients scale down to part-time even with minimal impairment.

Frndak, S. E., Irwin, L. N., Kordovski, V. M., et al. (2015). "Negative work events reported online precede job loss in multiple sclerosis." J Neurol Sci **357**(1-2): 209-214.

PURPOSE: Determine if a recently validated online survey of negative work events can predict future job loss among multiple sclerosis (MS) patients. METHOD: Evaluated were 284 employed individuals (63 healthy controls, 221 MS patients), every three months, using an online vocational monitoring tool. Job loss rates in MS patients were compared with the healthy controls. Survey responses from MS patients suffering job loss (n=23) were then compared to those maintaining employment. Analyses focused on the frequency of negative work events. RESULTS: While 23 (10%) of MS patients lost their job after baseline, there was no job loss among the healthy controls. Compared to stably employed patients, those suffering job loss had been diagnosed with MS later in life, were more likely to report a progressive disease course, and had greater physical disability as measured by the Patient Derived Disease Steps (PDDS). Declining patients were also more likely to report negative work events within three months of job loss (e.g., verbal criticism for errors or removal of responsibilities). Stepwise logistic regression predicting MS job loss retained the PDDS, age at diagnosis, years working for employer and reporting a negative work event. CONCLUSIONS: The results show that physical disability and patient reported risk factors for job loss can be monitored using an online survey tool. The tool can trigger clinical assessments to help prevent unemployment and assist patients in procuring disability benefits.

Ford, H. L., Wicks, C. R., Stroud, A., et al. (2019). "Psychological determinants of job retention in multiple sclerosis." Mult Scler **25**(3): 419-426.

BACKGROUND: Maintaining paid work is a key issue for people with multiple sclerosis (PwMS). Different factors, including psychological attributes, can influence job retention. Understanding their role should inform potential interventions to help PwMS retain employment. OBJECTIVES: The aim of this study was to identify the key factors which improve job retention in an employed cohort of PwMS. METHODS: This three-year longitudinal study used validated self-completed measures of physical and psychological factors at four time points over 28 months. RESULTS: Of 208 employed PwMS, just over 1 in 10 was no longer working at the end of the study. Three variables were predictive of continuing employment; low 'work instability' at baseline increased the odds of job retention by a factor of 12.76; high levels of self-efficacy by a factor of 4.66 and being less than 50 years of age increased the odds of job retention by a factor of 3.90. Path analysis demonstrated the mediating role of self-efficacy between the physical impact of MS and the level of work instability at exit. CONCLUSION: Screening for work instability and self-efficacy in a clinical setting followed by appropriate interventions to increase self-efficacy and reduce work instability could aid job retention in MS.

Forslin, M., Fink, K., Hammar, U., et al. (2018). "Predictors for Employment Status in People With Multiple Sclerosis: A 10-Year Longitudinal Observational Study." Arch Phys Med Rehabil **99**(8): 1483-1490.

OBJECTIVE: To identify predictors for employment status after 10 years in a cohort of people with multiple sclerosis (MS), with the aim to increase knowledge concerning factors present at an early stage that are important for working life and work-life balance. DESIGN: A 10-year longitudinal observational cohort study. SETTING: University hospital. PARTICIPANTS: A consecutive sample of people with MS (N=154) of working age were included at baseline, of which a total of 116 people participated in the 10-year follow-up; 27 people declined participation and 11 were deceased. INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: Baseline data on personal factors and functioning were used as independent variables. Employment status 10 years after baseline, categorized as full-time work, part-time work, and no work, was used as the dependent variable. A generalized ordinal logistic regression was used to analyze the predictive value of the independent variables. RESULTS: Predictors for full- or part-time work after 10 years were young age (P=.002), low perceived physical impact of MS (P=.02), fatigue (P=.03), full-time work (P=.001), and high frequency of social/lifestyle activities (P=.001) at baseline. Low perceived physical impact of MS (P=.02) at baseline also predicted full-time work after 10 years. CONCLUSIONS: This study underlines the complexity of working life for people with MS, and indicates that it may be valuable to give more attention to the balance between working and private life, both in clinical practice and future research, to achieve a sustainable working life over time.

Frndak, S. E., Irwin, L. N., Kordovski, V. M., et al. (2015). "Negative work events reported online precede job loss in multiple sclerosis." J Neurol Sci **357**(1): 209-214.
http://www.sciencedirect.com/science/article/pii/S0022510X15004530

Purpose Determine if a recently validated online survey of negative work events can predict future job loss among multiple sclerosis (MS) patients. Method Evaluated were 284 employed individuals (63 healthy controls, 221 MS patients), every three months, using an online vocational monitoring tool. Job loss rates in MS patients were compared with the healthy controls. Survey responses from MS patients suffering job loss (n=23) were then compared to those maintaining employment. Analyses focused on the frequency of negative work events. Results While 23 (10%) of MS patients lost their job after baseline, there was no job loss among the healthy controls. Compared to stably employed patients, those suffering job loss had been diagnosed with MS later in life, were more likely to report a progressive disease course, and had greater physical disability as measured by the Patient Derived Disease Steps (PDDS). Declining patients were also more likely to report negative work events within three months of job loss (e.g., verbal criticism for errors or removal of responsibilities). Stepwise logistic regression predicting MS job loss retained the PDDS, age at diagnosis, years working for employer and reporting a negative work event. Conclusions The results show that physical disability and patient reported risk factors for job loss can be monitored using an online survey tool. The tool can trigger clinical assessments to help prevent unemployment and assist patients in procuring disability benefits.

Frndak, S. E., Kordovski, V. M., Cookfair, D., et al. (2015). "Disclosure of disease status among employed multiple sclerosis patients: association with negative work events and accommodations." Mult Scler **21**(2): 225-234.

BACKGROUND: Unemployment is common in multiple sclerosis (MS) and detrimental to quality of life. Studies suggest disclosure of diagnosis is an adaptive strategy for patients. However, the role of cognitive deficits and psychiatric symptoms in disclosure are not well studied. OBJECTIVE: The goals of this paper were to (a) determine clinical factors most predictive of disclosure, and (b) measure the effects of disclosure on workplace problems and accommodations in employed patients. METHODS: We studied two overlapping cohorts: a cross-sectional sample (n = 143) to determine outcomes associated with disclosure, and a longitudinal sample (n = 103) compared at four time points over one year on reported problems and accommodations. A case study of six patients, disclosing during monitoring, was also included. RESULTS: Disclosure was associated with greater physical disability but not cognitive impairment. Logistic regression predicting disclosure status retained physical disability, accommodations and years of employment ($p < 0.0001$). Disclosed patients reported more work problems and accommodations over time. The case study revealed that reasons for disclosing are multifaceted, including connection to employer, decreased mobility and problems at work. CONCLUSION: Although cognitive impairment is linked to unemployment, it does not appear to inform disclosure decisions. Early disclosure may help maintain employment if followed by appropriate accommodations.

Gerhard, L., Dorstyn, D. S., Murphy, G., et al. (2020). "Neurological, physical and sociodemographic correlates of employment in multiple sclerosis: A meta-analysis." J Health Psychol **25**(1): 92-104.

Illness severity and sociodemographic characteristics of 7,053 employees with multiple sclerosis and 11,043 peers not in the workforce were compared (Hedges' g with 95% confidence interval and p values). Pooled findings from 25 studies confirmed the main role of a relapsing-remitting disease course and higher education to employment. To a lesser extent, disease duration, fatigue and pain symptoms and age also differentiated the two groups. Vocational interventions for persons with multiple sclerosis should focus on job retention, including mechanisms to accommodate and facilitate functional independence. Longitudinal data are needed to distinguish the characteristics of those who achieve and maintain competitive employment.

Giovannetti, A. M., Schiavolin, S., Brenna, G., et al. (2016). "Cognitive function alone is a poor predictor of health-related quality of life in employed patients with MS: results from a cross-sectional study." Clin Neuropsychol **30**(2): 201-215.

OBJECTIVE: Depression, anxiety, disease severity, and cognitive functions impact on the quality of life of people with MS. However, the majority of studies were not based on multivariate models and did not target employed patients. The aim of this study was to investigate predictors of HRQoL in persons with MS in the workforce considering cognitive, psychological, disease severity, and disability-related variables. METHODS: Cross-sectional study. Hierarchical block regression analyses were conducted to identify predictors of physical and mental components of HRQoL, measured with the MSQOL-54. Candidate predictors included cognitive functioning (a selection of Rao's BRB-NT), sample features (age, education, MS duration), depressive symptoms (BDI-II), anxiety (STAI-Y), disability (WHODAS 2.0), and MS severity (EDSS): those that correlated with PCS and MCS with p < .250 and those that correlated with other predictors with coefficients >.800 were excluded from regression analyses. RESULTS: In total, 181 patients (60.8% females, mean age 39.6, median EDSS 1.5) were included. In both models, cognitive variables had a poor explicative power. The models improved significantly when psychological, as well as, disease severity and disability variables were added. R(2) of complete models was 0.732 for the physical component, 0.697 for the mental one: BDI-II, STAI-State and, some WHODAS 2.0 scales were significant predictors of HRQoL. CONCLUSIONS: Monitoring anxiety, depressive symptoms, and level of disability through self-reported questionnaires may provide useful suggestions to improve the HRQoL of persons with MS in the workforce, permitting to address possible problems in the work context and plan corrective actions.

Glad, S. B., Nyland, H., Aarseth, J. H., et al. (2011). "How long can you keep working with benign multiple sclerosis?" J Neurol Neurosurg Psychiatry **82**(1): 78-82.

OBJECTIVE: To study employment in benign multiple sclerosis (MS), the frequency of employment was analysed and the effect of early clinical and demographic factors on time to disability pension was evaluated in a population based MS cohort. The frequency of depression, cognitive function, fatigue and pain between benign and non-benign MS patients was compared, and their impact on employment in benign MS was studied. METHODS: All

188 patients alive, including 60 benign patients with onset of MS during 1976-1986 in Hordaland County, Western Norway, were interviewed and clinically examined in 2003. The Expanded Disability Status Scale (EDSS), depression (Beck Depression Inventory), cognitive function, fatigue, pain, year of disability pension, employment and type of occupation were registered. Benign MS was defined as an EDSS score </=3.0 at least 10 years after disease onset. RESULTS: After a mean disease duration of 22.2 years, 32.4% of the cohort were still employed. A relapsing-remitting course, higher educational level and light physical work were significantly associated with longer time to disability pension in the general MS population. Thirty-nine (65.0%) benign MS patients were employed, independent of light or heavy physical work. Mild depressive symptoms were markedly associated with not being employed in benign MS (OR=7.3). CONCLUSIONS: A relapsing-remitting course, higher educational level and light physical work significantly predicted longer time to disability pension in the total MS population. Among the benign MS patients, depressive symptoms, although mild, were strongly associated with not being employed.

Glanz, B. I., Degano, I. R., Rintell, D. J., et al. (2012). "Work productivity in relapsing multiple sclerosis: associations with disability, depression, fatigue, anxiety, cognition, and health-related quality of life." Value Health **15**(8): 1029-1035.

OBJECTIVES: To characterize work productivity in relapsing multiple sclerosis (MS) by using a work productivity scale and to identify associations between work productivity and disability, depression, fatigue, anxiety, cognition, and health-related quality of life. METHODS: Three hundred seventy-seven subjects with a clinically isolated syndrome or relapsing remitting MS participated in the study. Subjects underwent neurological examinations and completed patient-reported outcome and cognitive measures. Subjects also completed the Work Productivity and Activity Impairment Questionnaire: General Health to quantify absenteeism (missing work because of health problems), presenteeism (impairment while working), overall work impairment, and daily activity impairment attributable to health problems. Univariate correlations and multivariate models were used to determine the associations between each work productivity variable and clinical, patient-reported outcome, and cognitive measures. RESULTS: Seventy-six percent of subjects were employed. Fourteen percent of working subjects reported absenteeism, and 47% reported presenteeism. The mean work time lost because of absenteeism was 4%, and the mean work time lost because of presenteeism was 12%. Absenteeism was not significantly associated with disease or patient-reported outcome measures. Statistically significant correlations (0.32-0.53) were found between presenteeism and increasing disability, fatigue, depression, anxiety, and reduced quality of life. No associations were observed between presenteeism and disease duration or cognitive function. CONCLUSIONS: Subjects with clinically isolated syndrome/relapsing remitting MS reported substantial work productivity losses due to presenteesim. Presenteeism was associated with increasing fatigue, depression, anxiety, and reduced quality of life. It is possible that the early identification and treatment of fatigue and mental health symptoms may improve productivity while working and extend employment for individuals with MS.

Goverover, Y., Strober, L., Chiaravalloti, N., et al. (2015). "Factors That Moderate Activity Limitation and Participation Restriction in People With Multiple Sclerosis." Am J Occup Ther **69**(2): 6902260020p6902260021-6902260029.

We examined the variables most associated with activity limitation (i.e., cooking) and participation restriction (i.e., employment) in 72 people with multiple sclerosis (MS). Participants underwent a comprehensive neuropsychological test battery assessing memory, executive functions, visual perception, and processing speed and completed questionnaires assessing activity, participation, fatigue, and affective symptoms. Results showed that processing speed was the only variable consistently significantly related to both activity and participation. When examining specific aspects of activity and participation in isolation, employment status was significantly associated with education level, visual memory, fatigue, and processing speed. Cooking ability was associated with performance on tasks of working memory, verbal memory, and processing speed. These findings suggest that processing speed is a primary cognitive factor in MS influencing quality of both activity and participation in everyday life.

Grytten, N., Skar, A. B., Aarseth, J. H., et al. (2017). "The influence of coping styles on long-term employment in multiple sclerosis: A prospective study." Mult Scler **23**(7): 1008-1017.

> BACKGROUND: The aim was to investigate predictive values of coping styles, clinical and demographic factors on time to unemployment in patients diagnosed with multiple sclerosis (MS) during 1998-2002 in Norway. METHOD: All patients (N = 108) diagnosed with MS 1998-2002 in Hordaland and Rogaland counties, Western Norway, were invited to participate in the long-term follow-up study in 2002. Baseline recordings included disability scoring (Expanded Disability Status Scale (EDSS)), fatigue (Fatigue Severity Scale (FSS)), depression (Beck Depression Inventory (BDI)), and questionnaire assessing coping (the Dispositional Coping Styles Scale (COPE)). Logistic regression analysis was used to identify factors associated with unemployed at baseline, and Cox regression analysis to identify factors at baseline associated with time to unemployment during follow-up. RESULTS: In all, 41 (44%) were employed at baseline. After 13 years follow-up in 2015, mean disease duration of 22 years, 16 (17%) were still employed. Median time from baseline to unemployment was 6 years (+/-5). Older age at diagnosis, female gender, and depression were associated with patients being unemployed at baseline. Female gender, long disease duration, and denial as avoidant coping strategy at baseline predicted shorter time to unemployment. CONCLUSION: Avoidant coping style, female gender, and longer disease duration were associated with shorter time to unemployment. These factors should be considered when advising patients on MS and future employment.

Gyllensten, H., Wiberg, M., Alexanderson, K., et al. (2016). "How does work disability of patients with MS develop before and after diagnosis? A nationwide cohort study with a reference group." BMJ Open **6**(11): e012731.

> OBJECTIVES: We compared work disability of patients with multiple sclerosis (MS) from 5 years before with 5 years after diagnosis, with that of matched controls, and analysed whether progression in work disability among patients with MS was associated with sociodemography. DESIGN: Population-based cohort study. SETTING: The adult Swedish general population. PARTICIPANTS: Residents aged 24-57 diagnosed with MS (n=3685) in 2003-2006 and 18 425 matched controls without MS. PRIMARY AND SECONDARY OUTCOME MEASURES: Annual net days of sickness absence (SA) and disability pension (DP), used as a proxy for work disability, followed from 5 years before to 5 years after diagnosis (ie, T-5-T+5). For patients with MS, regression was used to identify sociodemographic factors related to progression in work disability. RESULTS: Work disability of patients with MS increased gradually between T-5 and T-1 (mean: 46-82 days) followed by a sharp increase (T+1, 142 days), after which only a marginal increase was observed (T+5, 149 days). The matched controls had less work disability, slightly increasing during the period to a maximum of approximately 40 days. Men with MS had a sharper increase in work disability before diagnosis. High educational level was associated with less progression in work disability before and around diagnosis. CONCLUSIONS: Patients with MS had more work disability days

also 5 years before diagnosis. Several sociodemographic variables were associated with the absolute level and the progression in SA and DP.

Hategeka, C., Traboulsee, A. L., McMullen, K., et al. (2019). "Association of Unemployment and Informal Care with Stigma in Multiple Sclerosis: Evidence from the Survey on Living with Neurological Conditions in Canada." Int J MS Care **21**(5): 214-225.

Background: Multiple sclerosis (MS) typically affects young adults during their primary productive years. We assessed the magnitude of, and factors associated with, employment status and informal care in people with MS in Canada. Methods: Data were compiled from the nationally representative cross-sectional Survey on Living with Neurological Conditions in Canada (SLNCC), which included adolescents and adults (age >/=15 years). Employment status was categorized as currently working or not working. The frequency of informal care that people with MS received was categorized as none, less than daily, or daily. Logistic regression analyses were undertaken to identify factors associated with employment status and informal care requirements in people with MS. Results: Of 4409 SLNCC respondents, 631 had MS, of whom 530 were included in the analysis. Of 358 respondents aged 18 to 65 years, 47.8% were not working because of MS; 44.0% reported receiving informal care, with more than half requiring daily care. For caregivers' employment, 15.5% reduced work and 8.2% stopped working because of caregiving. Greater feelings of stigmatization were associated with not working (adjusted odds ratio, 7.42 [95% CI, 2.59-21.28]) and greater informal care (adjusted odds ratio, 3.83 [95% CI, 1.84-7.96]), adjusting for sex, age, education, health-related quality of life, time since MS diagnosis, and comorbidity. Conclusions: People who feel stigmatized because of their MS are more likely to be unemployed and to require more informal care. Further research is needed to understand the temporal nature of the association between stigma and employment, productivity loss, and informal care.

Honan, C. A., Brown, R. F. et Batchelor, J. (2015). "Perceived cognitive difficulties and cognitive test performance as predictors of employment outcomes in people with multiple sclerosis." J Int Neuropsychol Soc **21**(2): 156-168.

Perceived cognitive difficulties and cognitive impairment are important determinants of employment in people with multiple sclerosis (pwMS). However, it is not clear how they are related to adverse work outcomes and whether the relationship is influenced by depressive symptoms. Thus, this study examined perceived and actual general cognitive and prospective memory function, and cognitive appraisal accuracy, in relation to adverse work outcomes. The possible mediating and/or moderating role of depression was also examined. A cross-sectional community-based sample of 111 participants (33 males, 78 females) completed the Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ), Beck Depression Inventory - Fast Screen (BDI-FS), and questions related to their current or past employment. They then underwent cognitive testing using the Screening Examination for Cognitive Impairment, Auditory Consonant Trigrams test, Zoo Map Test, and Cambridge Prospective Memory Test. Perceived general cognitive and prospective memory difficulties in the workplace and performance on the respective cognitive tests were found to predict unemployment and reduced work hours since MS diagnosis due to MS. Depression was also related to reduced work hours, but it did not explain the relationship between perceived cognitive difficulties and the work outcomes. Nor was it related to cognitive test performance. The results highlight a need to address the perceptions of cognitive difficulties together with cognitive impairment and levels of depression in vocational rehabilitation programs in pwMS.

Honarmand, K., Akbar, N., Kou, N., et al. (2011). "Predicting employment status in multiple sclerosis patients: the utility of the MS functional composite." J Neurol **258**(2): 244-249.

As many as two-thirds of multiple sclerosis (MS) patients are unable to retain employment. Neurological and cognitive status are known to be significant predictors of unemployment, but the relationship between the two is unclear. Furthermore, the association between employment status and depression, anxiety, and personality has not been adequately explored in MS patients. This study examined the demographic, neurological, neuropsychological, and personality factors associated with unemployment in MS. We also sought to determine the utility of the Multiple Sclerosis Functional Composite (MSFC), a measure of MS-related disability incorporating physical and cognitive measures, in predicting employment status. A consecutive sample of 106 MS patients (61.3% unemployed) completed the Brief Repeatable Battery of Neuropsychological Tests (BRBN), Hospital Anxiety and Depression Scale (HADS), and NEO Five-Factor Personality Inventory. The MSFC emerged as the most robust predictor of employment status in MS patients, exceeding the predictive value of the EDSS. Together with NEO "Agreeableness" and HADS Depression subscore, the MSFC accounted for 49.8% of the variance in employment status. Unemployment was also associated with a progressive disease course, longer disease duration, and being female. While Global Cognitive Impairment did not differentiate between groups, unemployed patients scored significantly lower on three of five BRBN indices: Symbol Digit Modality Test, Paced Auditory Serial Addition Test, and Word List Generation. The findings highlight the utility of the MSFC as a predictor of unemployment in MS. Furthermore, a strong association was found between unemployment and the personality construct "Agreeableness", and severity of depression.

Incerti, C. C., Argento, O., Magistrale, G., et al. (2017). "Adverse working events in patients with multiple sclerosis." Neurol Sci **38**(2): 349-352.

Multiple sclerosis (MS) and working status have recently arisen great interest. Fatigue, physical disability, cognition, and psychological disturbances have been linked to unemployment, as well to accidents during daily activities. The aim of our study was to determine frequency of different types of accidents at workplace (AWE) and possible clinical differences among employed (MSe) and unemployed (MSu) MS patients. Sixty MS patients (31 employed, 29 unemployed) and twenty healthy control subjects were recruited. All employed participants were requested to complete an ad-hoc questionnaire to collect AWE and related risks occurring at workplace in the past 2 months. Physical, cognitive, mood, and fatigue evaluations were also assessed. Illness and bumps along with risk of bumps and near falls resulted the most frequent AWE and risks occurring in MSe. Interestingly, those AWE were mostly observed among subjects with anxiety, depression, and cognitive fatigue rather than depending on severity of physical impairment. Moreover, psychological aspects, like anxiety and anger, seemed to play a crucial role in determining AWE. This study provides data on AWE occurrence and suggests possible mechanisms underlying negative events at workplace in MS. This might be important for planning strategies of AWE prevention in MS patients.

Jacobsen, C., Zivadinov, R., Myhr, K. M., et al. (2020). "Brain atrophy and employment in multiple sclerosis patients: a 10-year follow-up study." Mult Scler J Exp Transl Clin **6**(1): 2055217320902481.

Background: Multiple sclerosis is often associated with unemployment. The contribution of grey matter atrophy to unemployment is unclear. Objectives: To identify magnetic resonance imaging biomarkers of grey matter and clinical symptoms associated with unemployment in multiple sclerosis patients. Methods: Demographic, clinical data and 1.5 T magnetic resonance imaging scans were collected in 81 patients at the time of inclusion and after 5 and 10 years. Global and tissue-specific volumes were calculated at each time point.

Statistical analysis was performed using a mixed linear model. Results: At baseline 31 (38%) of the patients were unemployed, at 5-year follow-up 44 (59%) and at 10-year follow-up 34 (81%) were unemployed. The unemployed patients had significantly lower subcortical deep grey matter volume (P < 0.001), specifically thalamus, pallidus, putamen and hippocampal volumes, and cortical volume (P = 0.011); and significantly greater T1 (P < 0.001)/T2 (P < 0.001) lesion volume than the employed patient group at baseline. Subcortical deep grey matter volumes, and to a lesser degree cortical volume, were significantly associated with unemployment throughout the follow-up. Conclusion: We found significantly greater atrophy of subcortical deep grey matter and cortical volume at baseline and during follow-up in the unemployed patient group. Atrophy of subcortical deep grey matter showed a stronger association to unemployment than atrophy of cortical volume during the follow-up.

Johnson, K. L., Bamer, A. et Fraser, R. T. (2009). "Disease and Demographic Characteristics Associated with Unemployment Among Working-Age Adults with Multiple Sclerosis." Int J MS Care **11**(3): 137-143.

Previous studies of employment in people with multiple sclerosis (MS) have been inconsistent in identifying associated factors, and few have examined the role of secondary health conditions. The goal of this study was to examine the association of these health conditions, including pain, fatigue, depression, sleep problems, anxiety, and incontinence, with employment status in individuals with MS. Data were collected using a cross-sectional self-report survey of 1271 people with MS, of whom 1124 were between the ages of 18 and 65 years and provided employment information. Self-report of employment status was used as an outcome variable for multivariate logistic regression. In total, 40.4% (n = 454) of surveyed individuals were employed half-time or more. Variables significantly associated with unemployment in the multivariate model were severity of disease (as measured by Expanded Disability Status Scale score), difficulties in thinking, female sex, increased age, and increased duration of MS. The symptoms of fatigue, pain, depression, and anxiety were not significantly associated with employment status in this sample. The combined impact of cognitive changes and overall severity of mobility impairment significantly influenced employment status in this community sample. Future longitudinal studies are needed to better elucidate the circumstances surrounding changes in employment status and identify points at which vocational rehabilitation interventions might be most effective.

Jones, E., Pike, J., Marshall, T., et al. (2016). "Quantifying the relationship between increased disability and health care resource utilization, quality of life, work productivity, health care costs in patients with multiple sclerosis in the US." BMC Health Serv Res **16**: 294.

BACKGROUND: Multiple sclerosis (MS) is a chronic progressive condition affecting the central nervous system. Progression of MS results in increased level of disability and most patients will eventually experience some degree of functional impairment and impaired mobility. Costs and burdens escalate as MS disability increases. However, there is a lack of recent data on the impact of MS disability on the cost and burden among patients in the US. METHODS: Data for this study were drawn from a real world, cross-sectional survey undertaken between 2013 and 2014. Neurologists completed detailed patient report forms (PRF) for the most recent consulting patients with MS (age >18 years). Patient's perceptions of their diagnosis and health-related quality of life (HRQoL) were collected through a patient self-completion questionnaire (PSC). Regression analysis was used to evaluate the relationship between disability (determined by latest Expanded Disability Status Scale [EDSS] score) and current relapse and health care resource utilization, health care costs, HRQoL and work productivity. RESULTS: PRF data were collected for 715 patients (335 also completed a PSC). Patients with higher disability scores (EDSS 3-5 and >5 vs <3 points) and current relapse (vs

> no current relapse) reported significantly greater health resource utilization for physician visits ($p < 0.05$) and hospitalizations ($p < 0.05$) in the preceding 12 months. In addition, they had poorer HRQoL ($p < 0.05$), were significantly more likely to be unemployed ($p < 0.05$) and to have had to stop working due to MS ($p < 0.05$). They also incurred significantly higher health care related costs, including costs for physician consultations, hospitalizations and therapy ($p < 0.05$). The total costs of care were $51,825, $57,889 and $67,116 for EDSS < 3, EDSS 3-5 and EDSS > 5 groups, respectively; $51,692 and $58,648 for non-relapse and relapse groups, respectively. CONCLUSIONS: For MS patients in the US, health resource utilization and healthcare care costs increase with progression of disability. As the disability worsens, patients also exhibit diminished HRQoL and lower work productivity. There is a need for treatments that slow down or delay disability progression among MS patients.

Jongen, P. J., Wesnes, K., van Geel, B., et al. (2014). "Relationship between working hours and power of attention, memory, fatigue, depression and self-efficacy one year after diagnosis of clinically isolated syndrome and relapsing remitting multiple sclerosis." PLoS One **9**(5): e96444.

> The role of cognitive domain dysfunction with respect to vocational changes in persons with Clinically Isolated Syndrome (CIS) and early Relapsing Remitting Multiple Sclerosis (eRRMS) is insufficiently known. We investigated thirty-three patients--14 CIS, 19 eRRMS -, mean (standard deviation [SD]) time since diagnosis 13.5 (4.8) months and mean (SD) Expanded Disability Status Scale (EDSS) score 1.3 (1.1). Patients were assessed on the CDR System, a set of automated tests of cognitive function, which yielded scores for Power of Attention (ms), Continuity of Attention (#), Working Memory (SI), Episodic Memory (#) and Speed of Memory (ms). Work-related items and the confounding variables fatigue, depression, disease impact and self-efficacy, were assessed by self-report questionnaires. Patients had poorer Power of Attention compared to normative data (1187 [161.5] vs. 1070 [98.6]; $P<0.0001$) and slower Speed of Memory (4043 [830.6]) vs. 2937 [586.1]; $P<0.0001$). Power of Attention (Pearson $r = -0.42$; $P<0.04$), Working Memory ($r = 0.42$; $P<0.04$) and depression $r = -0.41$; $P<0.05$) correlated with number of days worked per week. Fatigue ($r = -0.56$; $P<0.005$), self-efficacy ($r = 0.56$; $P<0.005$) and disease impact ($r = -0.46$; $P<0.05$) correlated with number of hours worked per week. Persons who wished to work less had poorer Power of Attention (1247 vs. 1116 ms; $P<0.02$), those who wished to change job had poorer Episodic Memory (1.35 vs. 1.57; $p<0.03$). People who reduced working hours within 12 months after diagnosis had higher fatigue and disease impact, and lower self-efficacy. The findings of this pilot study indicate that one year after the diagnosis of CIS and RRMS Power of Attention and Speed of Memory are reduced, that Power of Attention and Memory are associated with a capability of working less hours, and that fatigue, depression and disease impact may negatively, and self-efficacy positively affect working hours.

Joustra, M. L., Janssens, K. A., Bultmann, U., et al. (2015). "Functional limitations in functional somatic syndromes and well-defined medical diseases. Results from the general population cohort LifeLines." J Psychosom Res **79**(2): 94-99.

> OBJECTIVE: Functional somatic syndromes (FSS), defined as physical syndromes without known underlying organic pathology, are sometimes regarded as less serious conditions than well-defined medical diseases (MD). The aims of this study were to evaluate functional limitations in FSS, and to compare the results to MD patients with the same core symptoms. METHODS: This study was performed in 89,585 participants (age: 44.4+/-12.4 years, 58.5% female) of the general-population cohort LifeLines. Quality of Life (QoL) and work participation were examined as indicators of functional limitations. QoL was assessed with two summary scales of the RAND-36: the physical component summary (PCS) and the mental component summary (MCS). Work participation was assessed with a self-reported

questionnaire. QoL and work participation were compared between FSS and MD patients, using Chi-squared tests and ANCOVA-analyses, adjusted for age, sex, educational level, and mental disorders. RESULTS: Of the participants, 11.0% (n=9861) reported a FSS, and 2.7% (n=2395) reported a MD. Total QoL, PCS and MCS were significantly lower in all separate FSS and MD compared to controls (P</=.001). Clinically relevant differences in QoL were found between chronic fatigue syndrome and multiple sclerosis patients, and between fibromyalgia syndrome and rheumatoid arthritis patients. Compared to controls, FSS and MD patients reported a comparably reduced working percentage, increased sick absence, early retirement due to health-related reasons, and disability percentage (P</=.001). CONCLUSION: Functional limitations in FSS patients are common, and as severe as those in patients with MD when looking at QoL and work participation, emphasizing that FSS are serious health conditions.

Julian, L. F., Vella, L. et Vollmer, T. (2008). "Employment in multiple sclerosis: Exiting and re-entering the work force." J Neurol **255**(9): 1354-1360.

Multiple sclerosis (MS) is associated with significant economic burden and high rates of unemployment. This investigation evaluated patient and disease characteristics associated with work loss and work initiation using the NARCOMS patient registry. Patient and disease characteristics associated with transitions to unemployment or employment were evaluated cross-sectionally and prospectively over the course of two assessment periods (mean interval of 1.56 ± 0.93 years). Eligible participants included 8,867 patients for the cross-sectional component, and 8,122 for longitudinal analyses. At Time 1 and Time 2 56–58 % of MS patients were not employed. At Time 1, unemployed participants more likely to have a progressive disease course, had a longer symptom duration, greater levels of disability as measured by the PDDS, and greater functional limitations across all domains of the performance scales ($p < 0.0001$ for all). At Time 2, increasing MS symptoms in the past 6 months increased the odds of becoming unemployed. In addition, specific problems in mobility, hand function, fatigue, and cognitive performance domains were associated with increased odds of becoming unemployed. Less severe problems in similar areas, including mobility, hand function, and cognitive functioning were also predictive of work initiation among patients not employed. MS is associated with high rates of unemployment. Specific physical and mental health limitations confer risk of employment cessation over time, as well as the likelihood of employment initiation. This study has implications for rehabilitation interventions to target specific MS related limitations that place patients at greatest risk for work status changes.

Kadrnozkova, L., Vaneckova, M., Sobisek, L., et al. (2018). "Combining clinical and magnetic resonance imaging markers enhances prediction of 12-year employment status in multiple sclerosis patients." J Neurol Sci **388**: 87-93.

BACKGROUND: Multiple sclerosis (MS) is frequently diagnosed in the most productive years of adulthood and is often associated with worsening employment status. However, reliable predictors of employment status change are lacking. OBJECTIVE: To identify early clinical and brain magnetic resonance imaging (MRI) markers of employment status worsening in MS patients at 12-year follow-up. METHODS: A total of 145 patients with early relapsing-remitting MS from the original Avonex-Steroids-Azathioprine (ASA) study were included in this prospective, longitudinal, observational cohort study. Cox models were conducted to identify MRI and clinical predictors (at baseline and during the first 12months) of worsening employment status (patients either (1) working full-time or part-time with no limitations due to MS and retaining this status during the course of the study, or (2) patients working full-time or part-time with no limitations due to MS and switching to being unemployed or working part-time due to MS). RESULTS: In univariate analysis, brain parenchymal fraction, T1 and T2 lesion volume were the best MRI predictors of worsening employment status over the 12-year follow-up period. MS duration at baseline (hazard ratio (HR)=1.10, 95% confidence interval (CI) 1.03-1.18; p=0.040) was the only significant clinical predictor. Having one extra milliliter of T1 lesion volume was associated with a 53% greater risk of worsening employment status (HR=1.53, 95% CI 1.16-2.02; p=0.018). A brain parenchymal fraction decrease of 1% increased the risk of worsening employment status by 22% (HR=0.78, 95% CI 0.65-0.95; p=0.034). CONCLUSION: Brain atrophy and lesion load were significant predictors of worsening employment status in MS patients. Using a combination of clinical and MRI markers may improve the early prediction of an employment status change over long-term follow-up.

Kantor, D., Bright, J. R. et Burtchell, J. (2018). "Perspectives from the Patient and the Healthcare Professional in Multiple Sclerosis: Social Media and Patient Education." Neurol Ther **7**(1): 23-36.

A diagnosis of multiple sclerosis (MS) is life-altering. Because the course of MS is heterogeneous, patients may face uncertainty in terms of long-term physical and cognitive challenges, potential loss of employment, and the risk of social isolation. Patients often turn to the Internet and social media for information about MS and its management, and to seek out fellow patients and support groups. Here, we examine the use of social media and the Internet among patients with MS, considering its impact on patient education. We consider the access that these conduits provide not only to other patients with MS but also to a wealth of disease-related information online. These themes are further illustrated with first-hand experiences of the patient author and her physician. We also explore the impact of the Internet and social media on the education and support of patients with MS from the healthcare professional's (HCP's) perspective, including opportunities for HCPs to promote disease education among their patients, and the advantages that arise from patients being better informed about their disease. The rise of the Internet and social media has changed the patient experience, helping patients to support each other, to educate themselves proactively about their condition, and to participate more actively in decisions relating to disease management than perhaps was the case historically. Funding Novartis Pharmaceuticals Corporation.

Karampampa, K., Gyllensten, H., Yang, F., et al. (2019). "Healthcare, Sickness Absence, and Disability Pension Cost Trajectories in the First 5 Years After Diagnosis with Multiple Sclerosis: A Prospective Register-Based Cohort Study in Sweden." Pharmacoecon Open **4**(1):91-103.
https://link.springer.com/article/10.1007/s41669-019-0150-3

OBJECTIVES: The aim was to longitudinally explore the healthcare, sickness absence (SA), and disability pension (DP) cost trajectories among newly diagnosed people with multiple sclerosis (MS), and investigate whether trajectories differ by year of MS diagnosis, sociodemographics, and multi-morbidity. METHODS: People with MS in Sweden, aged 25-60 years and with a new MS diagnosis in the years 2006, 2007, 2008, or 2009 (four different cohorts) were identified in nationwide registers and followed prospectively for 5 years, determining the annual, per patient, direct (inpatient and specialised outpatient healthcare, co-payments, and dispensed drugs) and indirect (SA and DP) costs. Descriptive statistics and group-based trajectories were computed. RESULTS: In total, 3272 people with new MS were identified. In all cohorts, direct costs increased the year after diagnosis and thereafter declined (e.g. from euro8261 to euro9128, and to euro7953, 5 years after diagnosis, for the 2006 cohort). SA costs continuously decreased over 5 years, while DP costs increased (e.g. from euro9795 to euro2778 vs. from euro7277 to euro15,989, respectively, for the 2006 cohort). When pooling all cohorts, four trajectories of direct and indirect costs were

> identified. A total of 32.1% of people with MS had high direct and indirect costs, which first increased and then decreased; the contrary was seen for trajectories with low direct and indirect costs. CONCLUSIONS: There is heterogeneity in the development of MS costs over time after diagnosis; decreasing cost trajectories could be associated with the use of innovative MS therapies, slowing disease progression over time.

Kavaliunas, A., Danylaite Karrenbauer, V., Gyllensten, H., et al. (2019). "Cognitive function is a major determinant of income among multiple sclerosis patients in Sweden acting independently from physical disability." Mult Scler **25**(1): 104-112.

> BACKGROUND: In multiple sclerosis (MS), various aspects of cognitive function can be detrimentally affected, thus patients' employment and social functioning is commonly impacted. OBJECTIVE: To analyse income among MS patients in relation to cognitive function, assessed with the Symbol Digit Modalities Test (SDMT). METHODS: A cross-sectional study including 2080 MS patients was conducted linking national register-based data. Descriptive statistics and a two-part model were used to estimate differences in earnings and social benefits. RESULTS: MS patients in the highest SDMT score quartile earned more than twice annually compared to patients in the lowest quartile, whereas patients in the lowest quartile received three times more income through social benefits. The difference in earnings and benefits across the SDMT performance quartiles remained statistically significant after adjusting for various clinical and socio-demographic variables, including physical disability. The corrected prevalence ratios for MS patients in the highest quartile for having income from earnings and benefits were 1.40 (95% confidence interval (CI): 1.29-1.49) and 0.81 (95% CI: 0.71-0.90), respectively, when compared to the patients in the lowest quartile. CONCLUSION: Cognitive function affects the financial situation of MS patients negatively and independently of physical disability. This warrants cognitive testing as a routine measure in health care services for MS patients.

Kavaliunas, A., Tinghog, P., Friberg, E., et al. (2019). "Cognitive function predicts work disability among multiple sclerosis patients." Mult Scler J Exp Transl Clin **5**(1): 2055217318822134.

> Background: In multiple sclerosis various aspects of cognitive function can be detrimentally affected. More than that, patients employment and social functioning is likely to be impacted. Objective: To determine whether work disability among multiple sclerosis patients could be predicted by the symbol digit modalities test. Methods: A register-based cohort study was conducted. Individual data on work disability, operationalised as annual net days of sickness absence and/or disability pension were retrieved at baseline, when the symbol digit modalities test was performed, after one-year and 3-year follow-up for 903 multiple sclerosis patients. The incidence rate ratios for work disability were calculated with general estimating equations using a negative binomial distribution and were adjusted for gender, age, educational level, family composition, type of living area and physical disability. Results: After one year of follow-up, the patients in the lowest symbol digit modalities test quartile were estimated to have a 73% higher rate of work disability when compared to the patients in the highest symbol digit modalities test quartile (incidence rate ratio 1.73, 95% confidence interval 1.422.10). This estimate after 3-year follow-up was similar (incidence rate ratio 1.68, 95% confidence interval 1.402.02). Conclusion: Cognitive function is to a high extent associated with multiple sclerosis patients' future work disability, even after adjusting for other factors.

Kavaliunas, A., Wiberg, M., Tinghog, P., et al. (2015). "Earnings and Financial Compensation from Social Security Systems Correlate Strongly with Disability for Multiple Sclerosis Patients." PLoS One **10**(12): e0145435.

BACKGROUND: Multiple sclerosis (MS) patients earn lower incomes and receive higher benefits. However, there is limited knowledge of how this is correlated with their disability. OBJECTIVE: To elucidate sources and levels of income among MS patients with different disability, assessed with the Expanded Disability Status Scale. METHODS: A total of 7929 MS patients aged 21-64 years and living in Sweden in 2010 were identified for this cross-sectional study. Descriptive statistics, logistic and truncated linear regression models were used to estimate differences between MS patients regarding earnings, disability pension, sickness absence, disability allowance, unemployment compensation, and social assistance. RESULTS: The average level of earnings was ten times lower and the average level of health-related benefits was four times higher when comparing MS patients with severe and mild disability. MS patients with severe disability had on average SEK 166,931 less annual income from earnings and SEK 54,534 more income from benefits compared to those with mild disability. The combined average income for MS patients was 35% lower when comparing patients in the same groups. The adjusted risk ratio for having earnings among MS patients with severe disability compared to the patients with mild disability was 0.33 (95% CI 0.29-0.39), while the risk ratio for having benefits was 1.93 (95% CI 1.90-1.94). CONCLUSIONS: Disease progression affects the financial situation of MS patients considerably. Correlations between higher disability and patient income were observed, suggesting that earnings and benefits could be used as measures of MS progression and proxies of disability.

Kern, S., Kuhn, M. et Ziemssen, T. (2013). "[Chronically ill and unemployed? A review on vocational status in multiple sclerosis]." Fortschr Neurol Psychiatr **81**(2): 95-103.

BACKGROUND: Multiple sclerosis (MS) is one of the most common neurological disorders in young adults. It is characterised by a chronic progressive course with far reaching implications on the patient's private and professional life. Based on the current literature, employment status is analysed in relation to disease-specific, therapeutic, psychosocial, and socioeconomic factors. A special emphasis is placed on the vocational status of MS patients in Germany. RESULTS: According national and international studies, around 40 % of all MS patients are currently unemployed. Main reasons for early retirement are disease-specific factors such as impaired mobility, disability in the upper extremities, fatigue, and cognitive impairment. According to the German Multiple Sclerosis Registry (GMSR), these symptoms are still insufficiently treated. In patients with minor motoric impairment (EDSS </= 3.0), depressive symptoms seem to have a major impact on employment status. Disease progression, older age at diagnosis, and hard physical work are negative predictors in terms of employment situation. The lack of flexible working hours, the inability to have flexible resting times at work, a lack of understanding from colleagues and employers as well as the personal attitude were main non-disease-specific reasons for early retirement. CONCLUSIONS: The current knowledge on the vocational status in MS is mainly based on international studies (e. g., Scandinavia, England, USA, Australia, MSIF Survey). For Germany, only the GMSR supports significant information on the employment status of MS patients. According to the GMSR, ataxia, fatigue and cognitive dysfunction are still insufficiently treated - a situation that is at least partly due to insufficient treatment options. Comprehensive studies that focus on a broad range of possible influencing factors on vocational status of German MS patients are currently lacking.

Khan, F., Ng, L. et Turner-Stokes, L. (2009). "Effectiveness of vocational rehabilitation intervention on the return to work and employment of persons with multiple sclerosis." Cochrane Database Syst Rev(1): Cd007256.

BACKGROUND: Multiple sclerosis is a neurological disease that frequently affects adults of working age, resulting in a range of physical, cognitive and psychosocial deficits that impact on workforce participation. Although, the literature supports vocational rehabilitation (VR) approaches in persons with multiple sclerosis (pwMS), the evidence for its effectiveness is yet to be established. OBJECTIVES: To evaluate the effectiveness of VR programs compared to alternative programs or care as usual on return to work, workability and employment in pwMS; to evaluate the cost effectiveness of these programs. SEARCH STRATEGY: Electronic searches included: Cochrane Central Register of Controlled Trials "CENTRAL" 2008 issue 3, MEDLINE (PubMed) (1966- 2008), EMBASE (1988- 2008), CINAHL (1982- 2008), PEDro (1990-2008), the Cochrane Rehabilitation and Related Therapies Field trials Register and the National Health Service National Research Register. SELECTION CRITERIA: Randomized and controlled clinical trials, including before - after controlled trials, that compare VR rehabilitation with alternative intervention such as standard or a lesser form of intervention or waitlist controls. DATA COLLECTION AND ANALYSIS: Two reviewers selected trials and rated their methodological quality independently. A 'best evidence' synthesis was performed, based on methodological quality. Trials were grouped in terms of type and setting of VR programs. MAIN RESULTS: Two trials (one RCT and one CCT) (total 80 participants) met the review criteria. Both trials scored poorly on the methodological quality assessment. There was 'insufficient evidence' for VR programs for (a)'competitive employment', in altering rates of job retention, changes in employment, improvement in rates of re-entry into the labour force; (b) for altering 'work ability' by improving participants' confidence in the accommodation request process, or employability maturity or job seeking activity. No evidence could be assimilated for changes in proportions of persons in supported employment or on disability pensions, nor for cost-effectiveness. AUTHORS' CONCLUSIONS: There was inconclusive evidence to support VR for pwMS. However, the review highlights some of the challenges in providing VR for pwMS. Clinicians need to be aware of vocational issues, and to understand and manage barriers for maintaining employment. Proactive and timely VR programs should incorporate practical solutions to deal with work disability, workplace accommodation and educate employers, and the wider community. Liaison with policy makers is imperative for government initiatives that encourage work focused VR programs. Future research in VR should focus on improving methodological and scientific rigour of clinical trials; on the development of appropriate and valid outcome measures; and on cost effectiveness of VR programs.

Kirk-Brown, A. K. et Van Dijk, P. A. (2014). "An empowerment model of workplace support following disclosure, for people with MS." Mult Scler **20**(12): 1624-1632.

BACKGROUND: Vocational interventions aimed at increasing job retention for people with multiple sclerosis (MS) are reliant upon a partnership with a supportive work environment. A better understanding of the types of psychosocial support that are most conducive to retaining employees' sense of work-efficacy will enhance the success of interventions aimed at reducing workplace barriers to job maintenance. OBJECTIVE: The objective of this study is to identify the types of psychosocial support that people with MS require post-disclosure, in order to maintain their employment status. In particular, we examined the roles of psychological safety and work-efficacy. METHODS: We interviewed 40 employees with MS either individually (n = 25) or within three focus groups (n = 15). These interviews were audio-taped and the content analysed, using an inductive thematic approach. RESULTS: Themes to emerge in organisational responses to disclosure were: a focus on ability (leading to enhanced perceptions of psychological safety and higher work-efficacy) and on disability (leading to diminished psychological safety and reduced perceptions of work-efficacy). CONCLUSION: Organisational responses to disclosure demonstrating trust and inclusive decision making, and focussing on employee abilities, enhance perceptions of psychological safety at work. This increases the likelihood that employees with MS will retain their sense of work-efficacy and reduce their intentions to leave.

Kirk-Brown, A. K., Van Dijk, P. A., Simmons, R. D., et al. (2014). "Disclosure of diagnosis of multiple sclerosis in the workplace positively affects employment status and job tenure." Mult Scler **20**(7): 871-876.

BACKGROUND: For many employees with multiple sclerosis (MS), disclosure of their diagnosis at work is seen as a high-risk strategy that might lead to diminished perceptions of their capabilities by supervisors and colleagues, if not outright discrimination. The consequence of this mistrust surrounding the disclosure process is that employees with MS may leave it until too late to effectively manage symptoms at work. OBJECTIVE: The objective of this paper is to statistically evaluate the relationship between disclosure of diagnosis at work and maintenance of employment. METHODS: Three annual, large-sample self-report surveys of MS patients prospectively examined the relationship between disclosure of diagnosis at work and employment status. A total of 1438 people responded to all three surveys. Of employed persons in 2010 (n = 946), 673 also responded to the 2012 survey. Of these 673 respondents 564 were still employed. RESULTS: People who had disclosed their MS status to an employer were more likely to remain in employment in Year 3. The effect of disclosure in predicting employment status remained after controlling for age, gender, hours worked and level of disability. CONCLUSION: This study provides the first empirical support for the positive role of disclosure in maintaining employment status, measured both as job retention and tenure in current employment.

Kobelt, G., Langdon, D. et Jonsson, L. (2019). "The effect of self-assessed fatigue and subjective cognitive impairment on work capacity: The case of multiple sclerosis." Mult Scler **25**(5): 740-749.

OBJECTIVES:: The impact of physical disability in multiple sclerosis on employment is well documented but the effect of neurological symptoms has been less well studied. We investigated the independent effect of self-reported fatigue and cognitive difficulties on work. METHODS:: In a large European cost of illness survey, self-reported fatigue, subjective cognitive impairment (SCI), and productivity at work were assessed with visual analogue scales (VAS 0-10). The analysis controlled for country, age, age at diagnosis, gender, education, and physical disability. RESULTS:: A total of 13,796 patients were of working age and 6,598 were working. Physical disability had a powerful impact on the probability of working, as did education. The probability of working was reduced by 8.7% and 4.4% for each point increase on the VAS for SCI and fatigue, respectively ($p < 0.0001$). Regular work hours decreased linearly with increasing severity of fatigue and cognitive problems, while sick leave during the 3 months preceding the assessment increased. Finally, the severity of both symptoms was associated with the level at which productivity at work was affected ($p < 0.0001$). CONCLUSION:: Our results confirm the independent contribution of self-reported fatigue and SCI on work capacity and highlight the importance of assessment in clinical practice.

Korchounov, A., Tabatadze, T., Spivak, D., et al. (2014). "MS related employment and disease modifying treatment in the German working population: 1994-2009." NeuroRehabilitation.

BACKGROUND: Relapses in MS may affect the acquisition and maintenance of employment due to associated neurological deficits. Several disease modifying drugs (DMD) like interferons or glatiramer reduce the frequency of relapses and decrease their severity in MS. OBJECTIVE: To investigate the influence of DMD on employment prevalence and employment rate with relapsing remitting Multiple Sclerosis (RR-MS) in the German working population from 1994 to 2009. METHODS: Database assessment of working patients with MS and German labour market statistic database. RESULTS: Four DMD have been introduced in Germany for the treatment of RR-MS during the observation time: Interferon beta-1b (Betaferon) was approved 1996 whereas interferon beta-1a has been available in intramuscular formulation since 1997 (Avonex) and subcutaneous formulation since 1998 (Rebif). The non-interferon glatiramer (Copaxone) was introduced in 2001. Both general employment and employment with MS have increased during this period. The employment increase with RR-MS was higher than in general population only after the availability of all four DMD during the time period 2002-2009 (p = 0.008). The overall mean employment prevalence of RR-MS subjects was 0.82 +/- 0.03 among 1,000 workers. The annual prescription volume of all DMD rose every year since their introduction until the end of our observation of about 10% annually. Employment increases among RR-MS patients highly correlated with the time frame of DMD availability (correlation rate 0.88, p < 0.0001). The employment rate with DMD was higher than without treatment (p < 0.0001). CONCLUSION: The introduction of DMD may have positively influenced the employment with MS.

Kordovski, V. M., Frndak, S. E., Fisher, C. S., et al. (2015). "Identifying employed multiple sclerosis patients at-risk for job loss: When do negative work events pose a threat?" Mult Scler Relat Disord **4**(5): 409-413.

BACKGROUND: Physical disability and cognitive impairment are significant predictors of unemployment in multiple sclerosis (MS). However, little is known about the frequency of work problems in employed patients, in comparison to employed healthy persons. OBJECTIVE: Use an online monitoring tool to compare the frequency of negative work events in MS patients and healthy controls, and determine a threshold at which the frequency of work problems is clinically meaningful. METHODS: The sample comprised 138 MS patients and 62 healthy controls. All reported on recent negative work events and accommodations using an online survey. The clinical test battery measured depression, motor and cognitive function. Statistical tests compared the frequency of work problems in MS patients and healthy controls. Clinical neuro-performance scales were then assessed in at-risk patients with many work problems, versus those with no work problems. RESULTS: As a group, employed MS patients exhibited deficits in motor ability, verbal memory, and processing speed and were more likely than controls to report negative work events and accommodations. At-risk patients, that is, those reporting more than one negative work event, had more pronounced motor and cognitive deficits than their relatively stable counterparts. CONCLUSION: The data show that employed MS patients report more negative work events and accommodations than employed healthy persons. Those patients deemed at risk for job loss have more cognitive and motor impairment, suggesting the need for cognitive training and specific accommodation strategies in the work place.

Koziarska, D., Krol, J., Nocon, D., et al. (2018). "Prevalence and factors leading to unemployment in MS (multiple sclerosis) patients undergoing immunomodulatory treatment in Poland." PLoS One **13**(4): e0194117.

Multiple Sclerosis (MS) is the most common, primary neurogenic cause of disability among young adults. We investigated demographic and clinical factors associated with unemployment on the example of 150 MS patients receiving immunomodulatory treatment in Poland. This study was based on clinical evaluation and collection of self-reported questionnaires, with an attention to self-motivation, severe fatigue and moderate disability. Patients who were unemployed (40% of all patients) had a mean disease duration of almost 5 years. Older (p<0.001), less educated (p = 0.007) and more severely disabled patients (p<0,001) were most likely to be unemployed. Moderate disability (OR = 11.089 95% CI: 4.11-

34.201, p<0,001), severe fatigue (OR = 2.625 95% CI: 1.02-6.901, p = 0,046) and lower level of self-motivation (KNS) (OR = 0.947, 95% CI: 0.896-0.006, p = 0.042) were independently associated with unemployment.

Krause, I., Kern, S., Horntrich, A., et al. (2013). "Employment status in multiple sclerosis: impact of disease-specific and non-disease-specific factors." Mult Scler **19**(13): 1792-1799.

BACKGROUND: Multiple sclerosis (MS) is associated with high rates of early retirement (ER). OBJECTIVES: A German cohort of MS patients and healthy control subjects (HCs) were compared cross-sectionally to investigate disease- and non-disease-specific factors that are associated with employment status (ES) in MS and to identify predictors of ES in MS. METHODS: A total of 39 ER MS patients, 48 employed MS patients, and 37 HCs completed a brief neuropsychological battery and questionnaires related to depressive symptoms, fatigue, health-related quality of life (HrQoL) and health locus of control (HLC). Neurological disability was assessed by the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC). RESULTS: ER compared with employed MS patients scored significantly higher in neurological disability, depressive symptoms and fatigue and significantly lower in cognitive functioning and HrQoL. Further, both groups differed with regard to age, education, disease course and duration but not in HLC. Neurological disability, age and fatigue were identified as significant predictors of ES in MS. CONCLUSIONS: ES in MS was associated with demographic aspects, neurological and cognitive status, depressive symptoms, fatigue and HrQoL but was not associated with HLC. Findings confirm neurological disability, age and fatigue as independent predictors of ES in MS.

Krause, J. S., Dismuke-Greer, C. E., Jarnecke, M., et al. (2019). "Employment and Gainful Earnings Among Those With Multiple Sclerosis." Arch Phys Med Rehabil **100**(5): 931-937.e931.

OBJECTIVE: To identify demographic, educational, and disease-related characteristics associated with the odds of employment and earnings among participants with multiple sclerosis (MS). DESIGN: Cross-sectional using self-report assessment obtained by mail or online. SETTING: Medical university in the southeastern United States. PARTICIPANTS: Participants with MS (N=1059) were enrolled from a specialty hospital in the southeastern United States. All were adults younger than 65 years at the time of assessment. INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: Current employment status and earnings. RESULTS: MS factors were highly related to employment, yet not as strongly to conditional earnings. Those with no symptoms reported 6.25 greater odds of employment than those with severe current symptoms. Compared with those with progressive MS, those with relapsing or remitting had greater odds of employment (odds ratio [OR]=2.24). Participants with no perceived cognitive impairment had 1.83 greater odds of employment than those with moderate to severe perceived cognitive impairment. Those with <10 years since MS diagnosis had 2.74 greater odds of employment compared with those with >20 years since diagnosis. An absence of problematic fatigue was highly related to the probability of employment (OR=5.01) and higher conditional earnings ($14,454), whereas the remaining MS variables were unrelated to conditional earnings. For non-MS variables, education was highly related to employment status and conditional earnings, because those with a postgraduate degree had 2.87 greater odds of employment and $44,346 greater conditional earnings than those with no more than a high school certificate. Non-Hispanic whites had 2.22 greater odds of employment and $16,118 greater conditional earnings than non-Hispanic blacks, and men reported $30,730 more in conditional earnings than women. CONCLUSIONS: MS indicators were significantly associated with employment status including time since diagnosis, fatigue, symptom severity, and presence of cognitive impairment.

> However, among those who were employed, conditional earnings were less highly related to these factors and more highly related to educational attainment.

Krause, J. S., Dismuke-Greer, C. E., Reed, K. S., et al. (2019). "Employment and job benefits among those with spinal cord dysfunction: A comparison of people with spinal cord injury and multiple sclerosis." Arch Phys Med Rehabil.

> OBJECTIVE: (1) Identify the proportion of participants with spinal cord dysfunction (SCD) reporting each of 10 job benefits and compare the proportions between participants with spinal cord injury (SCI) and multiple sclerosis (MS), and (2) examine if diagnostic criteria, demographics, education level, and functional limitations are associated with the number of job benefits received. DESIGN: Econometric modeling of cross-sectional data using a 2-step data analytic model of employment and job benefits. SETTING: Medical university in the Southeastern United States (US). PARTICIPANTS: Participants were identified from the Southeastern US. After eliminating those 65 and older, there were 2624 adult participants with SCD; 1234 had MS and 1390 had SCI. INTERVENTIONS: N/A MAIN OUTCOME MEASURES: Current employment status; number of benefits received and specific benefits received. RESULTS: A greater proportion of MS participants received benefits, with significant differences observed on all but 1 type of benefit. Among those who were employed, a greater number of benefits was associated with having MS, greater education, younger age, married or in an unmarried couple, and not having functional restrictions with cognition, doing errands or shopping alone in the community, and walking. CONCLUSIONS: Employed participants with MS were more likely to receive job benefits, indicative of a higher quality of employment, compared to participants with SCI. Employment without benefits is a form of underemployment which disproportionately affects individuals with many of the same characteristics that initially lead to disparities in probability of gainful employment.

Krokavcova, M., Nagyova, I., Rosenberger, J., et al. (2012). "Employment status and perceived health status in younger and older people with multiple sclerosis." Int J Rehabil Res **35**(1): 40-47.

> This study explores how employment is associated with perceived physical and mental health status in people with multiple sclerosis (MS) adjusted for sociodemographic and clinical variables stratified by age. The sample consisted of 184 MS patients divided into a younger (<45 years) and an older (>/=45 years) age group. Respondents underwent an interview, a neurological examination on disability [Expanded Disability Status Scale (EDSS)], and completed the Short Form-36 Health Survey. Of the respondents (mean age 40.5+/-6.2 years), 43.5% were employed. Significant differences between younger and older patients were found in employment, EDSS, disease duration, and five Short Form-36 Health Survey dimensions. Block-step multiple regression explained 32.4% of the variance in physical health and 14.5% in mental health in the younger group. Being employed was significantly related to good physical health, whereas EDSS diminished the effect of being employed on physical health. The most important variable for mental health was employment status in the younger group. For the older age group, 19.1% of the variance in physical health and 14.0% of the variance in mental health was explained by the studied variables. Male gender and a lower EDSS were significant explanatory variables of better physical health. Male gender significantly explained mental health in the older age group. In conclusion, employment status was an explanatory variable for physical health and mental health in the younger patients. EDSS played a significant role in physical health for all patients. A vocational rehabilitation program could prevent eventual nonemployment and improve health outcomes in older MS people.

Krokavcova, M., Nagyova, I., Van Dijk, J. P., et al. (2010). "Self-rated health and employment status in patients with multiple sclerosis." Disabil Rehabil **32**(21): 1742-1748.

> PURPOSE: The aim is to explore the association between self-rated health and employment status in patients with multiple sclerosis (MS) when controlling for age, gender, functional disability, disease duration, anxiety and depression. METHOD: One hundred eighty-four people with MS completed a sociodemographic questionnaire that included questions on employment status, the first item of the Short Form-36 Health Survey and the Hospital Anxiety and Depression Scale. Functional disability was assessed using the Expanded Disability Status Scale. The probability of good self-rated health in employed persons was investigated using stepwise logistic regression analyses. RESULTS: Patients with MS who reported good self-rated health were 2.46 times more likely to be employed (95% confidence interval [CI]: 1.08-5.59). Patients without anxiety were 2.64 times more likely to be employed (95%CI: 1.23-5.67). Patients with higher EDSS scores were 0.49 times less likely to be employed (95%CI: 0.33-0.70). Age, gender, disease duration and the presence of depression did not show an increased chance of patient employment. CONCLUSIONS: Patients with MS with good self-rated health are more likely to be employed, even after adjusting for age, gender, education, functional disability, disease duration, depression and anxiety. Dependent on the findings of longitudinal studies unravelling the relevant causal pahways, self-rated health might be used as a quick and cheap prognostic marker, which could warn about the possible loss of employment, or changes in functional disability.

Kwiatkowski, A., Marissal, J. P., Pouyfaucon, M., et al. (2014). "Social participation in patients with multiple sclerosis: correlations between disability and economic burden." BMC Neurol **14**: 115.

> BACKGROUND: Economic costs related to treatment of multiple sclerosis (MS) must be justified by health state, quality of life (QOL) and social participation improvement. This study aims to describe correlations between social participation, economic costs, utility and MS-specific QOL in a sample of patients with MS (pwMS). METHODS: We interviewed 42 pwMS receiving natalizumab and collected clinical data, direct medical costs, productivity loss, utility (EQ5D-VAS), MS-specific QOL (SEP-59), social participation with the Impact on Participation and Autonomy questionnaire (IPA). We performed descriptive and correlation analyses. RESULTS: 41 pwMS, with a mean Expanded Disability Status Scale (EDSS) score of 4.0, completed questionnaires. Mean annual global cost per patient was 68448 +/-33374 Euros and increased with EDSS (r = 0.644), utility (r = -0.456) and IPA (r = 0.519-0.671) worsening. Mean utility was 0.52 +/- 0.28. Correlations between IPA and QOL (EQ5D-VAS or SEP-59) were observed (r = -0.53 to -0.78). Association between QOL and EDSS was smaller (EQ5D-VAS) or absent. Productivity losses were poorly correlated to EDSS (r = 0.375). CONCLUSION: Moderate to strong correlations of social participation with clinical status (EDSS), QOL, utility and economic costs encourage exploring better these links in larger cohorts. The stronger correlation between social participation and QOL than between EDSS and QOL needs to be confirmed.

Landfeldt, E., Castelo-Branco, A., Svedbom, A., et al. (2016). "Sick leave and disability pension before and after diagnosis of multiple sclerosis." Mult Scler **22**(14): 1859-1866.

> BACKGROUND: Multiple sclerosis (MS) is associated with considerable morbidity and serious disability, but little is known of the long-term impact of the disease on work ability. OBJECTIVES: To assess sick leave (short-term absence) and disability pension (long-term absence) before and after diagnosis of MS. METHODS: Patients with MS in Sweden were identified in a nationwide disease-specific register and matched with general population controls. Sick leave and disability pension were measured before and after index (i.e. the MS

diagnosis date). RESULTS: The final sample comprised 6092 patients and 60,345 controls (mean age 39 years; 70% female). The mean annual prevalence of sick leave ranged from 12% the first year after index to 23% after 11 years among patients and from 13% to 13% among controls. Corresponding estimates for disability pension were 12% and 55% for patients and 7% and 9% for controls. Significant differences in sick leave were observed up to 15 years before index and 3 years for disability pension. CONCLUSION: Patients with MS in Sweden have elevated levels of sick leave and disability pension up to 15 years before disease diagnosis. Our results highlight the burden of disease on affected patients and society and underscore the substantial unmet medical need.

Landfeldt, E., Castelo-Branco, A., Svedbom, A., et al. (2018). "The long-term impact of early treatment of multiple sclerosis on the risk of disability pension." J Neurol **265**(3): 701-707.

OBJECTIVE: The objective of this retrospective, observational study was to estimate the long-term impact of early treatment of multiple sclerosis (MS) on the risk of disability pension. METHODS: Our cohort comprised patients with MS in Sweden, identified in a nationwide disease-specific register (the Swedish Multiple Sclerosis Registry), who started treatment with a disease-modifying drug (DMD) between January 1, 2002, and December 31, 2012. We analyzed the association between time from onset of MS to treatment initiation and full-time disability pension using survival analysis. RESULTS: Our sample comprised 2477 patients. Unadjusted Kaplan-Meier failure functions showed that patients who started treatment within six months after onset had a lower risk of disability pension across follow-up compared with patients initiating therapy after 12 months. Outcomes from the univariate Cox proportional hazards model showed that time from onset to treatment initiation (in years) was significantly associated with disability pension (HR 1.03, $p < 0.001$). Outcomes from the multivariable Cox proportional hazards model showed that patients who started treatment within 6 months after onset had, on average, a 36% lower risk (HR 0.74, $p = 0.010$) of full-time disability pension during follow-up compared with patients starting treatment after 18 months when controlling for age, sex, marital status, university education, and prevalent comorbidities. CONCLUSIONS: We show that early treatment with DMDs of MS is associated with a significantly reduced risk of disability pension. Our findings highlight the potential long-term benefits of early treatment of MS and should be helpful to inform ongoing discussion on the optimum medical management of the disease.

Landfeldt, E., Castelo-Branco, A., Svedbom, A., et al. (2018). "Personal Income Before and After Diagnosis of Multiple Sclerosis." Value Health **21**(5): 590-595.

BACKGROUND: Multiple sclerosis (MS) is associated with serious morbidity and labor force absenteeism, but little is known of the long-term impact of the disease on personal income. OBJECTIVES: To assess long-term consequences of MS on personal salary and disposable income. METHODS: Patients with MS in Sweden were identified in a nationwide, disease-specific register and matched with general population controls. We assessed mean annual personal gross salary and disposable income each year before and after index (i.e., the MS diagnosis date) using data from national registers. RESULTS: The final sample consisted of 5,472 patients and 54,195 controls (mean age 39 years; 70% females). There was no significant difference in gross salary between patients and controls in any year within the pre-index period. In contrast, on average during follow-up post diagnosis, patients with MS had euro5,130 less gross salary per year compared with controls, ranging from a loss of euro2,430 the first year to euro9,010 after 11 years. Within 10 years after index, 45% of patients had at least one record of zero gross salary, compared with 32% for controls. Mean annual disposable income was comparable between patients and controls across follow-up, with significant differences only at years 9 and 10 post-index. CONCLUSIONS: We show that many patients with MS in Sweden lose their ability to support for themselves financially but still have a relatively high disposable income because of social transfers. Our findings underscore the detrimental impact of MS on affected patients and the considerable economic burden of disease to society.

Lehmann, A. I., Rodgers, S., Kamm, C. P., et al. (2020). "Factors associated with employment and expected work retention among persons with multiple sclerosis: findings of a cross-sectional citizen science study." J Neurol **267**(10): 3069-3082.

BACKGROUND: Multiple sclerosis (MS) notably affects adults of working age. For persons with MS (PwMS), being employed enhances their quality of life and it may be regarded as an indicator of overall functioning. Thus, ensuring work participation in PwMS is of general public health interest. OBJECTIVE: To examine relevant socio-demographic, MS-, health- and work-related factors, including psychosocial working conditions, associated with currently working PwMS in Switzerland and their expected work retention. METHODS: Using cross-sectional data of PwMS in the Swiss MS Registry (n = 541, median age = 48 [IQR 40;55]), multivariable logistic regression models were computed. First, currently working PwMS were characterised in comparison with those not currently working. Second, expected work retention, operationalized as subjective judgement "likely to work in the same job in 2 years", was examined within the group of currently working PwMS. RESULTS: The factors age (OR 0.96, 95% CI 0.92-0.99), sex (OR 0.28, 95% CI 0.13-0.60), highest achieved job position (OR 1.21, 95% CI 1.01-1.46), health-related quality of life (HRQoL) (OR 1.02, 95% CI 1.01-1.04) and the number of MS symptoms (OR 0.90, 95% CI 0.82-0.98) were associated with currently working PwMS. Moreover, HRQoL (OR 1.07, 95% CI 1.04-1.10) and psychosocial working conditions, such as job resources (e.g. autonomy, control or social support) (OR 2.83, 95% CI 1.50-5.33) and job demands (e.g. workload, time pressure) (OR 0.41, 95% CI 0.18-0.90) were important factors for expected work retention among this group. CONCLUSIONS: Resourceful psychosocial working conditions are crucial for PwMS to maintain employment. Employers could contribute to work retention among PwMS by creating a work environment with resourceful psychosocial working conditions and providing, for instance, social support.

Leniger, T., Heiker, M. et Ghadimi, A. (2019). "[The multiple sclerosis functional composite correlates with the sociomedical recommendation of earning capacity of rehabilitants with Multiple Sclerosis]." Fortschr Neurol Psychiatr.

BACKGROUND: The multiple sclerosis functional composite (MSFC) measures various MS-related impairments consisting of three subtests for mobility, motor hand function, and cognitive function. In medical rehabilitation, the MSFC may be a helpful instrument for the sociomedical recommendation of earning capacity (RoEC) at the end of rehabilitation. The aim of the study was to correlate the MSFC with the RoEC and to review the RoEC validity by the return to work (RTW) six months after discharge. METHODS: In a retrospective unicenter longitudinal study, the MSFC of 84 rehabilitants of working age was determined at the beginning (t0) and end (t1) of inpatient rehabilitation. The MSFC (total score and subtests) was correlated with the RoEC (positive >/= 3h per day; negative <3h per day). Six months after discharge, the RTW (positive >/= 3h per day; negative <3h per day) was assessed. RESULTS: Seventy of the 84 rehabilitants (83 %) received a positive RoEC. They showed no differences in epidemiological, MS or rehabilitation-specific characteristics as compared to the 14 rehabilitants with negative RoEC. Rehabilitants with positive RoEC as compared to those with negative RoEC showed significantly higher scores in the MSFC total score (z-Score: +0.11 vs. -0.55, p < 0.001) and subtests cognition (PASAT-3: 42.3 points vs. 27.7 points; p < 0.001) and mobility (T24FW: 5.1 sec vs. 6.7 sec; p = 0.002). Whereas the motor hand function was without significant difference (NHPT: 23.4 sec vs. 26.5 sec; p = 0.064). Both groups changed for better in the total score and subtests over time (t0, t1), but without significance. The RTW after six months were determined in 31 of the 84 rehabilitants (37 %); 90 % of these rehabilitants judged their RoEC as applicable. A positive RoEC correlated significantly with a positive RTW (r = 0.411; p = 0.022). However, a correlation between MSFC (t1) (total score, subtests) and RTW after six months could not be observed. CONCLUSION: On function level, the MSFC (total score >/= 0) correlates significantly with a positive RoEC at discharge whose validity was shown by correlation with the RTW six months after discharge. The subtests cognition and mobility were decisive. In medical rehabilitation of MS, determining the MSFC can be helpful for developing a valid recommendation for participation in the form of a RoEC.

Leslie, M., Kinyanjui, B., Bishop, M., et al. (2015). "Patterns in workplace accommodations for people with multiple sclerosis to overcome cognitive and other disease-related limitations." NeuroRehabilitation **37**(3): 425-436.

BACKGROUND: Cognitive symptoms and other functional limitations associated with multiple sclerosis (MS) have a significant negative impact on employment status. Work accommodations positively impact the ability of a person with MS to obtain and retain employment, however, current understanding of the role of accommodations in the careers of adults with MS is limited. OBJECTIVE: To analyze the percentage of American workers with MS who utilize workplace accommodations as per Title I of the ADA, the types of accommodations most frequently required, and differences in disease variables, job-related factors, and quality of life between workers using and not using work accommodations. METHODS: Data from 746 employed adult members of the National MS Society surveyed about career concerns were analyzed. Descriptive and inferential statistics were used as appropriate to address the research questions. RESULTS: Approximately 25% reported having requested accommodations, and 87.7% reported receiving the requested accommodation. Participants with progressive MS, cognitive impairment, higher number of MS symptoms and greater symptom severity were more likely to use work accommodations. Participants with accommodations reported poorer job match and career optimism than those using no accommodations. CONCLUSION: This large-scale analysis addresses several outstanding questions concerning work accommodations among workers with MS. Cognitive symptoms and disease severity are strongly associated with need for accommodations, however accommodations do not appear to promote job satisfaction or longevity. The accommodation request process and the impact of accommodations on employment retention remain important research foci.

Li, J., Fitzgerald, S. M., Bishop, M., et al. (2015). "Disease-related and functional predictors of employment status among adults with multiple sclerosis." Work **52**(4): 789-797.

BACKGROUND: Due to the extent and complexity of its physical, cognitive, and psychological accompaniments, multiple sclerosis has tremendously negative effects on employment outcomes for adults with the disease. OBJECTIVE: This article extends the current understanding of the relationship between disease-related and functional factors and employment status among adults with multiple sclerosis. METHODS: Findings are reported in terms of descriptive statistics and logistic regression. The logistic regression analysis was completed to determine the extent to which disease-related and functional predictors contributed to the overall prediction model for the employment status of adults with MS. RESULTS: The combined variables explained approximately 33% of the variance in employment status. In addition to three items of the Psychological subscale and 12 items of the Physical subscale, one of the items from the Cognitive Functioning Scale contributed to the prediction of employment status. CONCLUSIONS: The findings emphasize the importance of including physical, psychological, and cognitive functioning variables when predicting employment status among adults with multiple sclerosis.

Lorefice, L., Fenu, G., Frau, J., et al. (2018). "The impact of visible and invisible symptoms on employment status, work and social functioning in Multiple Sclerosis." Work **60**(2): 263-270.

BACKGROUND: Frequently diagnosed in young adulthood, multiple sclerosis (MS) and several MS-related factors can influence patients' unemployment status and negatively affect work productivity and daily functioning. OBJECTIVE: We examined MS patients' employment status and evaluated clinical features influencing it. Furthermore, we investigated patients' burdens due to visible and invisible MS symptoms through their worsening daily functioning. METHODS: The study included outpatients affected by MS according to the 2010 McDonald criteria. The co-occurrence of invisible symptoms (fatigue, depression and apathy) was stated using validated, self-administered tools: Fatigue Severity Scale (FSS); Beck Depression Inventory-Second Edition (BDI-II); Apathy Evaluation Scale (AES). Impairment in daily functioning due to MS was assessed using the Work and Social Adjustment Scale (WSAS). Descriptive statistics, hierarchical regression analyses, Pearson's correlation, and the t-test were conducted. RESULTS: Of the 123 participants, 52 (42.3%) were unemployed. Results showed employment to be positively associated with higher education levels (p 0.01); female gender (p 0.03) and higher disability (p 0.02) showed negative associations with employment. No associations were found between employment and fatigue or clinically relevant depressive and apathetic symptoms. High correlations were found between WSAS score and Expanded Disability Status Scale score (r = 565, p < 0.001), BDI-II score (r = 588, p < 0.001), and FSS score (r = 545, p < 0.001). CONCLUSION: Our study revealed physical disability's significance in determining MS patients' unemployment. Alternatively, invisible MS symptoms negatively affected principally patients' social lives. Therefore, programs should be designed to improve MS patients' work integration and daily activities.

Macaron, G., Baldassari, L. E., Nakamura, K., et al. (2020). "Cognitive processing speed in multiple sclerosis clinical practice: association with patient-reported outcomes, employment and magnetic resonance imaging metrics." Eur J Neurol.

BACKGROUND AND PURPOSE: To analyze the relationship between cognitive processing speed, patient-reported outcome measures (PROMs), employment and magnetic resonance imaging (MRI) metrics in a large multiple sclerosis cohort. METHODS: Cross-sectional clinical data, PROMs, employment and MRI studies within 90 days of completion of the Processing Speed Test (PST), a technology-enabled adaptation of the Symbol Digit Modalities Test, were collected. MRI was analyzed using semi-automated methods. Correlations of PST score with PROMs and MRI metrics were examined using Spearman's rho. Wilcoxon rank sum testing compared MRI metrics across PST score quartiles and linear regression models identified predictors of PST performance. Effects of employment and depression were also investigated. RESULTS: In 721 patients (mean age 47.6 +/- 11.4 years), PST scores were significantly correlated with all MRI metrics, including cord atrophy and deep gray matter volumes. Linear regression demonstrated self-reported physical disability, cognitive function, fatigue and social domains (adjusted R(2) = 0.44, P < 0.001) as the strongest clinical predictors of PST score, whereas that of MRI variables included T2 lesion volume, whole-brain fraction and cord atrophy (adjusted R(2) = 0.42, P < 0.001). An inclusive model identified T2 lesion volume, whole-brain fraction, self-reported upper extremity function, cognition and social participation as the strongest predictors of PST score (adjusted R(2) = 0.51, P < 0.001). There was significant effect modification by depression on the relationship between self-reported cognition and PST performance. Employment status was associated with PST scores independent of age and physical disability. CONCLUSION: The PST score correlates with PROMs, MRI measures of focal and diffuse brain injury, and employment. The PST score is a feasible and meaningful measure for routine multiple sclerosis care.

Maltby, V. E., Lea, R. A., Ribbons, K., et al. (2020). "Comparison of BICAMS and ARCS for assessment of cognition in multiple sclerosis and predictive value of employment status." Mult Scler Relat Disord **41**: 102037.

BACKGROUND: Cognitive impairment is common in multiple sclerosis (MS) but not adequately monitored by Expanded Disability Status Scale assessment. The Audio Recorded Cognitive Screen (ARCS) and Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) are easy-to-use tools to assess cognitive function in clinical practice. OBJECTIVE: To compare the sensitivity of ARCS to BICAMS and their relative predictive value for employment status. METHODS: MS patients and healthy controls were assessed using the ARCS and the BICAMS consecutively. Receiver Operating Characteristic (ROC) curve analyses were used to compare the two tests. A step-wise, logistic regression analysis was used to identify the cognitive test(s) that best predicted employment status and quality of life. RESULTS: Total ARCS, memory and attention domain scores were moderately correlated with all BICAMS tests (r=0.3-0.5; P</=0.05). Total ARCS predicts cognitive impairment with good sensitivity and specificity relative to the BICAMS tests (AUC = 0.8; P=0.00045). Total ARCS detects higher levels of impairment than BICAMS in MS patients (44% versus 21%). The memory domain of the ARCS and the BVMT-R were the best predictors of employment status (OR = 1.12 and 1.14, P < 0.05). CONCLUSION: BICAMS and ARCS have comparable sensitivity for cognitive impairment in MS. Memory assessment from either tests is the best predictor of employment status; however, the BICAMS is a better predictor of work productivity.

Marck, C. H., Aitken, Z., Simpson, S., Jr., et al. (2020). "Predictors of Change in Employment Status and Associations with Quality of Life: A Prospective International Study of People with Multiple Sclerosis." J Occup Rehabil **30**(1): 105-114.

Purpose This prospective international study aimed to assess the changes in employment, and predictors thereof, and associated change in mental health quality of life in people with multiple sclerosis (MS). Methods People with MS were recruited online through social media, forums and newsletters to complete an online English-language survey in 2012 and again in 2015, to assess changes in employment and clinical characteristics. Results 1276 people with MS of working age were included of whom 35.9% were employed full time, 25.6% part-time, 3.1% were unemployed and seeking employment, 19.7% were retired due to disability and 15.7% were not in the labour force. Part/full time employment decreased from 61.4 to 57.1% of the sample 2.5 years later, and 25.5% experienced some change in employment status. Lower level of education and higher level of disability at baseline predicted loss of employment at follow-up. 62.0% of the sample indicated that MS impacted on employment over their lifetime, associated with a lower level of education and progressive MS at time of diagnosis. Retiring due to disability was predictive of a decreased mental health related QOL score. Conclusion Employment status was negatively impacted by MS for most participants. We showed for the first time that employment loss was prospectively associated with poorer mental health related quality of life. Employment support including vocational services, reasonable flexibility in the workplace, and legal protection against discrimination should be widely available to assist people with MS, especially for those with progressive onset MS, higher disability and lower levels of education who are at higher risk of employment loss.

Mateen, B. A., Doogan, C., Hayward, K., et al. (2017). "Systematic Review of Health-Related Work Outcome Measures and Quality Criteria-Based Evaluations of Their Psychometric Properties." Arch Phys Med Rehabil **98**(3): 534-560.

> OBJECTIVE: To examine the state of psychometric validation in the health-related work outcome literature. DATA SOURCES: We searched PubMed, PubMed Central, CINAHL, Embase (plus Embase Classic), and PsycINFO from inception to January 2016 using the following search terms: stroke, multiple sclerosis, epilepsy, spinal cord injury, brain injury, musculoskeletal disease, work, absenteeism, presenteeism, occupation, employment, job, outcome measure, assessment, work capacity evaluation, scale, and questionnaire. STUDY SELECTION: From the 22,676 retrieved abstracts, 597 outcome measures were identified. Inclusion was based on content analysis. There were 95 health-related work outcome measures retained; of these, 2 were treated as outliers and therefore are discussed separately. All 6 authors individually organized the 93 remaining scales based on their content. DATA EXTRACTION: A follow-up search using the same sources, and time period, with the name of the outcome measures and the terms psychometric, reliability, validity, and responsiveness, identified 263 unique classical test theory psychometric property datasets for the 93 tools. An assessment criterion for psychometric properties was applied to each article, and where consensus was not achieved, the rating delivered by most of the assessors was reported. DATA SYNTHESIS: Of the articles reported, 18 reporting psychometric data were not accessible and therefore could not be assessed. There were 39 that scored <20% of the maximum achievable score, 106 scored between 20% and 40%, 82 scored between 40% and 60%, 15 scored between 60% and 80%, and only 1 scored >80%. The 3 outcome measures associated with the highest scoring datasets were the Sheehan Disability Scale, the Fear Avoidance Beliefs Questionnaire, and the assessment of the Subjective Handicap of Epilepsy. Finally, only 2 psychometric validation datasets reported the complete set of baseline psychometric properties. CONCLUSIONS: This systematic review highlights the current limitations of the health-related work outcome measure literature, including the limited number of robust tools available.

Maurino, J., Martinez-Gines, M. L., Garcia-Dominguez, J. M., et al. (2020). "Workplace difficulties, health-related quality of life, and perception of stigma from the perspective of patients with Multiple Sclerosis." Mult Scler Relat Disord **41**: 102046.

> INTRODUCTION: In Multiple Sclerosis (MS), withdrawal from employment is a critical problem. This study explores relationships between disease characteristics, work difficulties, health-related quality of life, depression, and stigma and how these factors affect employment status. METHODS: A multicenter, non-interventional, cross-sectional study was conducted in adults with relapsing-remitting MS (RRMS) and primary progressive MS (PPMS). Patient-reported questionnaires included: 23-item Multiple Sclerosis Work Difficulties Questionnaire, 29-item Multiple Sclerosis Impact Scale, Stigma Scale for Chronic Illness, and Beck Depression Inventory-Fast Screen. RESULTS: A total of 199 individuals (mean age = 43.9 +/- 10.5 years, 60.8% female, 86.4% with RRMS) participated in the study. Mean time from diagnosis was 9.6 +/- 7.2 years and median Expanded Disability Status Scale score was 2.0 (interquartile range: 1.0-3.5). Employment rate was 47.2% (n = 94). Mean physical and psychological MSIS-29 impact sub-scores were 40.38 +/- 17.1 and 20.24 +/- 7.8, respectively. Forty patients (19.9%) had at least one SSCI-8 item with a score of 4 or 5, suggesting the presence of stigma often or always. Eighty-one patients (40.7%) were depressed and 25 (12.6%) had moderate-to-severe depression. Work difficulties were higher in those with worse functional status, a diagnosis of PPMS, and lower educational levels. Employed participants had lower perceptions of stigma and depressive symptoms than those not employed. Higher perceptions of stigma were also strongly linked to higher physical and

psychological impact on health-related quality of life and greater work difficulties. Depressive symptoms were also strongly related to work-related problems. CONCLUSIONS: Work difficulties, stigma and poor quality of life are common in MS patients, even in a population with low physical disability. Evaluation of these dimensions in clinical practice would allow the development of targeted rehabilitation and specific work plans for MS employers.

McDonald, E. A. et Simmons, R. (2010). "23. Longitudinal employment change in multiple sclerosis and the importance of symptom management." Journal of Clinical Neuroscience **17**(12): 1617. http://www.sciencedirect.com/science/article/pii/S0967586810005114

McFadden, E., Horton, M. C., Ford, H. L., et al. (2012). "Screening for the risk of job loss in multiple sclerosis (MS): development of an MS-specific Work Instability Scale (MS-WIS)." Mult Scler **18**(6): 862-870.

BACKGROUND: Multiple sclerosis (MS) mainly presents amongst those of working age. Depending upon the type of MS, many people embark upon a long period of managing their day-to-day work-related needs in the face of intermittent and sometimes persistent disabling symptoms. The objective of this study was to explore the concept of work instability (WI) following the onset of MS and develop a Work Instability Scale (WIS) specific to this population. METHOD: WI amongst those with MS in work was explored through qualitative interviews which were then used to generate items for a WIS. Rasch analysis was used to refine the scaling properties of the MS-WIS, which was then validated against expert vocational assessment by occupational health physiotherapists and ergonomists. RESULTS: The resulting measure is a 22-item, self-administered scale which can be scored in three bands indicating low, medium and high risk of WI (job retention) problems. The scale meets modern psychometric requirements for measurement, indicated by adequate fit to the Rasch model with absence of local dependency and differential item functioning (DIF) by age, gender and hours worked. CONCLUSIONS: The scale presents an opportunity in routine clinical practice to take positive action to reduce sickness absence and prevent job loss.

McKay, K. A., Manouchehrinia, A., Berrigan, L., et al. (2019). "Long-term Cognitive Outcomes in Patients With Pediatric-Onset vs Adult-Onset Multiple Sclerosis." JAMA Neurol. **7**6(9):1028-103. https://pubmed.ncbi.nlm.nih.gov/31206130/

Importance: Cognitive impairment in multiple sclerosis (MS) can lead to reduced quality of life, social functioning, and employment. Few studies have investigated cognitive outcomes among patients with pediatric-onset MS (POMS) over the long term. Objective: To compare long-term information-processing efficiency between patients with POMS and adult-onset MS (AOMS). Design, Setting, and Participants: This population-based longitudinal cohort study accessed the Swedish MS Registry (SMSreg), which collates information from all 64 neurology clinics in Sweden. Registered cases with definite MS in the SMSreg with an onset before April 15, 2018, and at least 2 Symbol Digit Modalities Test (SDMT) scores recorded were included. Only persons aged 18 to 55 years and with duration of disease of less than 30 years at the time of SDMT administration were included, to ensure comparable ranges between patients with POMS and AOMS. Of 8247 persons with an SDMT recorded in the SMSreg, 5704 met inclusion criteria, 300 (5.3%) of whom had POMS. Data were collected from April 1, 2006, through April 15, 2018 and analyzed from April through August 2018. Exposures: Pediatric-onset MS (onset <18 years of age) vs AOMS (onset >/=18 years of age). Main Outcomes and Measures: Information-processing efficiency measured every 6 or 12 months by the SDMT. Linear mixed-effects models were used to compare all available SDMT scores between patients with POMS and those with AOMS. Persons with cognitive impairment (ever vs never) were identified using regression-based norms and compared

between POMS and AOMS groups using logistic regression. Results: Of the 5704 participants, 4015 were female (70.4%), and 5569 had a relapsing-onset disease course (97.6%). Most participants were exposed to a disease-modifying therapy (DMT) during follow-up (98.8%). Median age at baseline for the POMS group was 25.6 years (interquartile range, 21.0-31.7 years) and for the AOMS group, 38.3 years (interquartile range, 31.4-45.2 years). A total of 46429 unique SDMT scores were analyzed. After adjustment for sex, age, disease duration, disease course, total number of SDMTs completed, oral or visual SDMT form, and DMT exposure, the SDMT score for patients with POMS was significantly lower than that of patients with AOMS (beta coefficient, -3.59 [95% CI, -5.56 to -1.54]). The SDMT score for patients with POMS declined faster than that of patients with AOMS (beta coefficient, -0.30 [95% CI, -0.42 tp -0.17]). The odds of cognitive impairment were also significantly elevated in the POMS group (odds ratio, 1.44; 95% CI, 1.06-1.98). Conclusions and Relevance: In adulthood, patients with POMS demonstrated a more rapid reduction in information-processing efficiency over time and were more likely to experience cognitive impairment than patients with AOMS, independent of age or disease duration. Further investigation is required to understand the mechanisms by which early MS onset influences cognitive outcomes.

Meide, H. V., Gorp, D. V., van der Hiele, K., et al. (2018). ""Always looking for a new balance": toward an understanding of what it takes to continue working while being diagnosed with relapsing-remitting multiple sclerosis." Disabil Rehabil **40**(21): 2545-2552.

BACKGROUND: The aim of this study was to gain insight into the meaning of work in the everyday lives of people with relapsing-remitting multiple sclerosis, and the barriers and facilitators to staying in work. METHODS: Nineteen employed adults diagnosed with relapsing-remitting multiple sclerosis participated in narrative interviews. All interviews were transcribed and coded for thematic analysis. RESULTS: For people with relapsing-remitting multiple sclerosis, continuing to work was a precarious balancing act. Five themes influenced this balance: becoming familiar with the disease, adjusting expectations, having an understanding and realistic line manager, seeing work as meaningful life activity and strategic considerations. CONCLUSIONS: People receiving a diagnosis of relapsing-remitting multiple sclerosis have to refamiliarize themselves with their own body in a meaningful way to be able to continue their work. Rehabilitation professionals can support them herein by taking into account not merely functional capabilities but also identity aspects of the body. Medication that stabilizes symptoms supports making the necessary adjustments. A trusting relationship with the line manager is vital for this adaptation process. Additionally, a match between being adequately challenged by work, while still having the capacity to meet those work demands, is needed, as is long-term financial stability. Implications for rehabilitation Rehabilitation professionals can support employees with relapsing-remitting multiple sclerosis by taking into account not merely functional capabilities but also identity aspects of the body. A trusting relationship with the line manager, including a timely disclosure of the diagnosis, is vital for people with relapsing-remitting multiple sclerosis to remain at work. For people with relapsing-remitting multiple sclerosis, there is a delicate balance between being adequately challenged by work while still having the capacity to meet work demands.

Messmer Uccelli, M., Specchia, C., Battaglia, M. A., et al. (2009). "Factors that influence the employment status of people with multiple sclerosis: a multi-national study." J Neurol **256**(12): 1989-1996.

Paid employment is valuable for society and for the individual. A diagnosis of a chronic illness such as multiple sclerosis (MS) can influence a person's employment status. Previous studies have reported that demographic and disease-related aspects can predict whether a person with MS will leave their job. The aim of the study was to assess the factors that people with MS believe to contribute to their employment status and to determine whether any of these differentiate people with MS who are employed from those who are not employed. A multinational questionnaire assessed aspects related to employment that facilitate or hinder job maintenance. Data was collected in 18 European countries. A total of 1,141 questionnaires were completed. Of those responding, 694 (61%) subjects were employed and 477 (39%) were unemployed. The items that significantly differentiated the groups were related to MS symptoms, workplace environment and financial considerations. While MS influences employment status for many people who face difficult symptoms, aspects like a flexible work schedule and financial security are important and perhaps key to promoting job maintenance among people with MS.

Moberg, J. Y., Laursen, B., Koch-Henriksen, N., et al. (2017). "Employment, disability pension and income for children with parental multiple sclerosis." Mult Scler **23**(8): 1148-1156.

BACKGROUND: Little is known about the consequences of parental multiple sclerosis (MS) on offspring's socioeconomic circumstances. OBJECTIVE: To investigate employment, disability pension and income in offspring of parents with MS compared with matched reference persons in a nationwide register-based cohort study. METHODS: All Danish-born persons with onset of MS during 1950-1986 were retrieved from the Danish Multiple Sclerosis Registry. Their offspring were identified using the Civil Registration System. One random offspring from each sibship was matched by sex and year of birth with eight random reference persons. RESULTS: We included 2456 MS offspring and 19,648 reference persons. At age 30, employment was lower among MS offspring than reference children (odds ratio (OR): 0.89; 95% confidence interval (CI): 0.84-0.95; p = 0.0003), and they more often received disability pension (OR: 1.31; 95% CI: 1.15-1.50; p < 0.0001) at ages 30 and 40 but not at age 50. Although the mean income was not significantly lower for the MS offspring cohort, most of them attained an annual personal income below 250,000 DKK (Danish krone), that is, ~33,650 EUR (OR: 0.91; 95% CI: 0.84-0.99; p = 0.04). CONCLUSION: Having had a parent with MS may affect employment and increase the risk of disability pension and low income in adult life.

Moore, P., Harding, K. E., Clarkson, H., et al. (2013). "Demographic and clinical factors associated with changes in employment in multiple sclerosis." Mult Scler **19**(12): 1647-1654.

OBJECTIVE: The objective of this paper is to investigate demographic and disease factors associated with changes in employment role and status in multiple sclerosis (MS). METHODS: Questionnaires on current symptoms, employment status and factors associated with changes in employment were sent to a community sample of 566 MS patients. RESULTS: A total of 221 completed questionnaires were analysed. Of 169 employed at diagnosis, 43.3% had left employment at a mean of 11.9 years after disease onset. Of those still employed, 55% had changed their role or working hours to accommodate symptoms relating to their disease. These patients reported greater fatigue (p = 0.001), pain (p = 0.033) and memory problems (p = 0.038) than those whose employment had remained unaffected. Multinomial logistic regression revealed the factors most strongly predictive of employment status were disability level, years of education, disease duration and fatigue (p = 0.032). CONCLUSIONS: Despite changes to public perceptions and legislative protection over the last 20 years, high rates of MS patients still leave the workforce prematurely, reduce working hours or change employment roles. These data have significant implications when considering social and economic impacts of MS, support the value of employment metrics as long-term outcome measures, and demonstrate the need to improve employment requirements and flexibility of working practices in individuals with MS.

Morrison, J. D. et Stuifbergen, A. K. (2016). "Predictors of Fatigue Impact in Persons With Long-Standing Multiple Sclerosis." J Neurosci Nurs **48**(3): 143-150.

> BACKGROUND: Fatigue is a common experience among persons diagnosed with multiple sclerosis (MS). Fatigue negatively influences quality of life, interferes with activities of daily living, and impairs the ability to maintain gainful employment. Mechanisms underlying the pathophysiologic determinants of fatigue in MS are poorly understood, and effective treatments to manage fatigue present a challenge. Although the use of pharmacologic therapies is recommended to treat symptomatic fatigue, undertreatment of fatigue is common. Better long-term management and symptomatic relief may be provided by the use of nonpharmacologic treatments such as increased physical activity, energy conservation, and cognitive behavioral therapy. METHODS: The purpose of this study was to explore the physical, cognitive, and psychosocial dimensions of fatigue impact among persons with long-standing MS-defined here as having been diagnosed with MS for 17 years or more. A sample of 331 participants with MS completed surveys measuring fatigue impact, MS-related functional limitation, depressive symptoms, barriers to health promotion, personal resources, and health promoting behaviors. RESULTS: MS-related functional limitation and depressive symptoms were the strongest predictors of fatigue impact. MS-related functional limitation explained the greatest amount of variance in models predicting physical and psychosocial fatigue impact, whereas depressive symptoms explained the most variance in models predicting total and cognitive fatigue impact. Barriers to health promotion explained the least amount of variance among the models. Personal resources and health promoting behaviors were not significant predictors of fatigue impact in this study. CONCLUSION: Interventions aimed at reducing MS-related functional limitations, depressive symptoms, and barriers to health promotion may have beneficial influences on fatigue impact, whereas actions designed to promote personal resource adequacy as well as engagement in health promoting behaviors may not translate into improvements in fatigue impact in persons with MS.

Morrow, S. A., Drake, A., Zivadinov, R., et al. (2010). "Predicting loss of employment over three years in multiple sclerosis: clinically meaningful cognitive decline." Clin Neuropsychol **24**(7): 1131-1145.

> Cognitive dysfunction is common in multiple sclerosis (MS), yet the magnitude of change on objective neuropsychological (NP) tests that is clinically meaningful is unclear. We endeavored to determine NP markers of the transition from employment to work disability in MS, as indicated by degree of decline on individual tests. Participants were 97 employed MS patients followed over 41.3 +/- 17.6 months with a NP battery covering six domains of cognitive function. Deterioration at follow-up was designated as documented and paid disability benefits (conservative definition) or a reduction in hours/work responsibilities (liberal definition). Using the conservative definition, 28.9% reported deteriorated employment status and for the liberal definition, 45.4%. The Symbol Digit Modalities Test (SDMT) and California Verbal Learning Test, Total Learning (CVLT2-TL) measures distinguished employed and disabled patients at follow-up. Controlling for demographic and MS characteristics, the odds ratio of a deterioration based on a change of 2.0 on the CVLT2-TL was 3.7 (95% CI 1.2-11.4 and SDMT by 4.0 was 4.2 (95% CI 1.2-14.8), accounting for 86.7% of the area under the ROC curve. We conclude that decline on NP testing over time is predictive of deterioration in vocational status, establishing a magnitude of decline on NP tests that is clinically meaningful.

Morse, C. L., Schultheis, M. T., McKeever, J. D., et al. (2013). "Multitasking in multiple sclerosis: can it inform vocational functioning?" Arch Phys Med Rehabil **94**(12): 2509-2514.

OBJECTIVE: To examine associations between multitasking ability defined by performance on a complex task integrating multiple cognitive domains and vocational functioning in multiple sclerosis (MS). DESIGN: Survey data collection. SETTING: Laboratory with referrals from an outpatient clinic. PARTICIPANTS: Community-dwelling individuals with MS (N=30) referred between October 2011 and June 2012. INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: The modified Six Elements Test (SET) to measure multitasking ability, Fatigue Severity Scale to measure fatigue, several neuropsychological measures of executive functioning, and vocational status. RESULTS: Among the sample, 60% of individuals have reduced their work hours because of MS symptoms (cutback employment group) and 40% had maintained their work hours. Among both groups, SET performance was significantly associated with performance on several measures of neuropsychological functioning. Individuals in the cutback employment group demonstrated significantly worse overall performance on the SET (P=.041). Logistic regression was used to evaluate associations between SET performance and vocational status, while accounting for neuropsychological performance and fatigue. The overall model was significant (chi(2)3=8.65, P=.032), with fatigue [Exp(B)=.83, P=.01] and multitasking ability [Exp(B)=.60, P=.043] retained as significant predictors. CONCLUSIONS: Multitasking ability may play an important role in performance at work for individuals with MS. Given that multitasking was associated with vocational functioning, future efforts should assess the usefulness of incorporating multitasking ability into rehabilitation planning.

Murley, C., Friberg, E., Hillert, J., et al. (2019). "Validation of multiple sclerosis diagnoses in the Swedish National Patient Register." Eur J Epidemiol **34**(12): 1161-1169.

Population-based registers are widely used in epidemiological studies. We aimed to estimate the validity of multiple sclerosis (MS) diagnoses registered in the Swedish National Patient Register (NPR) by two sequential register-based case-definition algorithms. Prevalent MS patients aged 16-64 years were identified from the in- and specialised out-patient NPR in 2001-2013, using International Classification of Diseases code G35. These identified MS diagnoses were validated through two sequential register-based case-definition algorithms, as the 'gold-standard' reference, by linking individual-level data longitudinally to other nationwide registers. The primary algorithm first sought to corroborate the MS diagnoses with MS-specific information in other nationwide registers. The exploratory secondary algorithm identified individuals with MS-related information in other registers and those who were unable to be followed sufficiently. Through multi-register linkage, we estimated the number of confirmed and uncertain individuals with an MS diagnosis recorded in the NPR. A total of 19,781 individuals (mean age at first visit 45.2 years; 69.5% women) had at least one MS diagnosis recorded in the NPR during 2001-2013. Using the two case-definition algorithms, 92.5% (n = 18,291) of the MS diagnoses recorded in the NPR were confirmed, while 7.5% (n = 1490) remained uncertain. Our findings indicate that a very high percentage of patients coded with an MS diagnosis in the Swedish NPR actually have MS, and supports the use of the NPR as a viable source to identify individuals with an MS diagnosis for population-based research. This exploratory methods paper suggests an alternative novel method to verify individuals' diagnoses in register-based settings.

Murley, C., Mogard, O., Wiberg, M., et al. (2018). "Trajectories of disposable income among people of working ages diagnosed with multiple sclerosis: a nationwide register-based cohort study in Sweden 7 years before to 4 years after diagnosis with a population-based reference group." BMJ Open **8**(5): e020392.

OBJECTIVES: To describe how disposable income (DI) and three main components changed, and analyse whether DI development differed from working-aged people with multiple sclerosis (MS) to a reference group from 7 years before to 4 years after diagnosis in Sweden. DESIGN: Population-based cohort study, 12-year follow-up (7 years before to 4 years after diagnosis). SETTING: Swedish working-age population with microdata linked from two nationwide registers. PARTICIPANTS: Residents diagnosed with MS in 2009 aged 25-59 years (n=785), and references without MS (n=7847) randomly selected with stratified matching (sex, age, education and country of birth). PRIMARY AND SECONDARY OUTCOME MEASURES: DI was defined as the annual after tax sum of incomes (earnings and benefits) to measure individual economic welfare. Three main components of DI were analysed as annual sums: earnings, sickness absence benefits and disability pension benefits. RESULTS: We found no differences in mean annual DI between people with and without MS by independent t-tests (p values between 0.15 and 0.96). Differences were found for all studied components of DI from diagnosis year by independent t-tests, for example, in the final study year (2013): earnings (-64 867 Swedish Krona (SEK); 95% CI-79 203 to -50 528); sickness absence benefits (13 330 SEK; 95% CI 10 042 to 16 500); and disability pension benefits (21 360 SEK; 95% CI 17 380 to 25 350). A generalised estimating equation evaluated DI trajectory development between people with and without MS to find both trajectories developed in parallel, both before (-4039 SEK; 95% CI -10 536 to 2458) and after (-781 SEK; 95% CI -6988 to 5360) diagnosis. CONCLUSIONS: The key finding of parallel DI trajectory development between working-aged MS and references suggests minimal economic impact within the first 4 years of diagnosis. The Swedish welfare system was responsive to the observed reductions in earnings around MS diagnosis through balancing DI with morbidity-related benefits. Future decreases in economic welfare may be experienced as the disease progresses, although thorough investigation with future studies of modern cohorts are required.

Murley, C., Yang, F., Gyllensten, H., et al. (2018). "Disposable income trajectories of working-aged individuals with diagnosed multiple sclerosis." Acta Neurol Scand **138**(6): 490-499.

OBJECTIVES: The economic situation of individuals diagnosed with multiple sclerosis (MS) is under studied, with the levels and sources of incomes suggested to vary with socio-demographics. We aimed to describe the diversity of disposable income (DI) trajectories among working-aged individuals with incident MS, and investigate the associations of socio-demographic characteristics with identified trajectories. MATERIALS & METHODS: A population-based cohort study of all 1528 individuals first diagnosed with MS in 2008-2009 when aged 25-59, with data linked from three nationwide Swedish registers. DI was defined as net earnings plus net income from benefits. Trajectories of mean annual DI from 7 years prior to 4 years after diagnosis were identified by group-based trajectory modelling. An individual's group membership was determined by individual model-fit estimates from a multinomial logit function. Chi-squared tests and multinomial logistic regressions estimated the associations between trajectory membership and socio-demographic (sex, age, education, birth country, type of living area and family situation) and work disability (sickness absence and disability pension) characteristics. RESULTS: Seven distinct DI trajectories were identified: two consistently low (50.7% of individuals); four increasing (39.0%); and one decreasing (10.3%). Socio-demographic and work disability characteristics were associated with trajectories; the increasing trajectories had older age-profiles and higher proportions of men, while university education was less common in the consistently low trajectories. CONCLUSIONS: We identified high diversity in DI development within the cohort around MS diagnosis. Socio-demographic and work disability characteristics differed between the trajectories. This broader information of the economic situation is important to convey to patients.

Nicholas, J. A., Electricwala, B., Lee, L. K., et al. (2019). "Burden of relapsing-remitting multiple sclerosis on workers in the US: a cross-sectional analysis of survey data." BMC Neurol **19**(1): 258.

> BACKGROUND: Multiple sclerosis (MS) is prevalent among working age individuals (20-60 years), leading to high burden on work productivity. Few data are available about the absenteeism and presenteeism in employed individuals with MS in comparison to non-MS personnel. This study aimed to quantify the burden of illness of employed US adults with relapsing-remitting multiple sclerosis (RRMS) and examine burden by levels of work impairment. METHODS: A retrospective cross-sectional analysis was conducted using patient-reported responses from the US National Health and Wellness Survey (NHWS). Data from NHWS 2015-2016 were analyzed from 196 employed RRMS respondents who were matched 1:4 to employed respondents without MS based on demographic and general health characteristics. Demographic and general health characteristics for employed RRMS individuals were analyzed by levels of work impairment (none, 1-30%; 31-68%; 69-100%). Work productivity (absenteeism, presenteeism, and work impairment), decrements in health-related quality of life (HRQoL) (short form-36, EQ-5D), and healthcare resource utilization (HCRU) were compared to determine the burden of RRMS. RESULTS: After propensity score matching, the levels of absenteeism and presenteeism were 2 and 1.8 times higher in the employed RRMS population than the employed non-MS population, respectively ($P < 0.001$ for both). HRQoL was significantly lower in employed respondents with RRMS than those without MS ($P < 0.001$ for all). Employed respondents with RRMS had significantly more HCRU over 6 months compared to those without MS ($P < 0.001$). Furthermore, among employed RRMS respondents, greater levels of impairment were associated with increasing disease severity, greater healthcare resource use, fatigue, and cognitive impairment and inversely associated with mental and physical HRQoL ($P < 0.0001$ for all). CONCLUSIONS: Among employed individuals, respondents with RRMS had lower, work productivity, HRQoL, and higher HCRU as compared with those without MS. Given the large impact RRMS has on work impairment, a need exists to manage individuals on therapies that improve HRQoL, reduce symptoms, and improve their ability to perform in the workforce.

Pack, T. G., Szirony, G. M., Kushner, J. D., et al. (2014). "Quality of life and employment in persons with multiple sclerosis." Work **49**(2): 281-287.

> BACKGROUND: Work is salient to life, is central to well-being, and is a means by which individuals define themselves. Disabilities such as Multiple Sclerosis (MS), however, can confound the interaction between person and work. OBJECTIVE: In the current study, in an effort to examine the effects of type of employment upon quality of life (QOL), employment was divided into three categories (full-time employment, part-time employment, and unemployment). METHOD: Comparisons were then made between QOL ratings and the three categories. Although studies of QOL and MS are appearing more frequently in the literature, few studies have addressed this issue. RESULTS: A priori comparisons and Analysis of Variance resulted in the finding that persons with MS who were employed tended to rate their levels of QOL nearly one third of a standard deviation higher than their unemployed counterparts. CONCLUSION: Results of the study emphasize the need for the provision of quality vocational services to persons with MS. Issues such as quality vocational services, timeliness, and the importance of continued work are discussed.

Pearson, J. F., Alla, S., Clarke, G., et al. (2017). "Multiple Sclerosis impact on employment and income in New Zealand." Acta Neurol Scand **136**(3): 223-232.

BACKGROUND AND OBJECTIVES: We investigated the demographic, social and clinical characteristics associated with employment status and income for people with multiple sclerosis (MS) in New Zealand (NZ). METHODS: The NZ National MS Prevalence study included all persons resident in NZ on census day 2006 diagnosed with MS (96.7% coverage). Factors associated with employment and income status among the working age population (25-64 years) were identified by linear regression. RESULTS: Over 90% of working age people with MS (n=1727) had a work history, but 54% were not working. Work loss occurred early in the disease course, and at low disability (P<.001). Advancing age, progressive disease, longer disease duration, higher disability levels, partner loss and lower education were associated with work loss (P<.001). Working age people with MS had lower income than the NZ population (P<.0001). Higher qualifications yielded no additional income for MS females and about half the additional income for MS males (P<.0001). CONCLUSIONS: MS profoundly reduces employment and income early in the disease course, and at low levels of disability, however, unemployment is not entirely accounted for by clinical, social and demographic factors. These findings suggest social supports should be explored early in the disease course to reduce loss of income and unemployment for people with MS.

Persechino, B., Fontana, L., Buresti, G., et al. (2019). "Improving the job-retention strategies in multiple sclerosis workers: the role of occupational physicians." Ind Health **57**(1): 52-69.

Several studies evaluated whether a person with multiple sclerosis is employed or not and investigated the main symptoms that hinder the job performance. However, despite occupational physicians are fundamental in managing disabled subjects, there is a serious lack of data regarding their role in improving employability of these workers. In this regard, we assessed occupational physicians' professional activity and training/updating needs in order to identify and develop management tools, operative procedures and training programs helpful to support and implement adequate job-retention strategies. Four hundred three Italian occupational physicians compiled a self-administered questionnaire to evaluate individual demographics, health surveillance system, fitness for work and training needs. Our findings confirmed the suitability to adopt environmental adjustments at workplace (particularly referring to the ergonomics of workstation, the typology of occupational risk factors and the working time) to accommodate individual's needs in order to improve working ability among multiple sclerosis workers. Moreover, training events discussing operational guidelines and standardized instruments and/or methodologies to adequately manage the disable workers should be fostered. Therefore, in this regard, occupational physicians could play a key role but they need more high-quality training especially concerning the different tools that are currently available to assess the work issues in multiple sclerosis patients.

Pfleger, C. C., Flachs, E. M. et Koch-Henriksen, N. (2010). "Social consequences of multiple sclerosis (1): early pension and temporary unemployment--a historical prospective cohort study." Mult Scler **16**(1): 121-126.

Multiple sclerosis affects young and middle-aged people and often leads to physical and cognitive handicaps. There is a need for detailed knowledge of the social consequences of the disease. We aim here to describe the course of the working life and career of multiple sclerosis patients at the time of onset and thereafter, in terms of probability of early pension and income development. All 2538 patients with multiple sclerosis in Denmark with disease onset between 1980 and 1989, identified through the Danish MS-Registry, were included in this study. Twenty matched control persons per patient were randomly drawn from the civil registration system. Information on economic status was retrieved from Statistics Denmark. A survival analysis technique was used with onset as the starting point. We found that the probability of remaining without early pension was at 5 years 70% for patients and 97% for controls, and at 20 years 22% for patients and 86% for controls. Due to lower rates for early pension, gross income with time was lower in patients than controls. We conclude that multiple sclerosis seriously affects the economic life of multiple sclerosis patients, even within a few years of onset.

Pompeii, L. A., Moon, S. D. et McCrory, D. C. (2005). "Measures of physical and cognitive function and work status among individuals with multiple sclerosis: a review of the literature." J Occup Rehabil **15**(1): 69-84.

> The purpose of this review was to critically evaluate the multiple sclerosis (MS) literature that has examined physical and cognitive function in relation to ability to work. Although numerous factors may be considered when determining work ability, physical and/or cognitive functional limitations associated with MS are presumably the primary determinants of work capacity. An exhaustive search of the literature produced 20 research articles that described 18 studies. Findings from these studies support that limitations in physical or cognitive function can hinder one's ability to work; however, ability to work could not be based solely on these measures of function. Work ability among individuals extended beyond measures of impairment to include level of education, job characteristics, and disease symptoms such as fatigue. In summary, measures of physical and cognitive function can guide physicians when clinically evaluating an individual with MS, but are poor indicators for precluding an individual from working.

Ponzio, M., Brichetto, G., Zaratin, P., et al. (2015). "Workers with disability: the case of multiple sclerosis." Neurol Sci **36**(10): 1835-1841.

> The impact of the multiple sclerosis (MS) on the individual's ability to work is important especially because the onset of the disease occurs mainly between 20 and 30 years of age. This study evaluated different factors associated with job maintenance using a questionnaire that defined what factors are considered obstacle or help in work management. A cross-sectional study of people with MS was carried out in Italy. A total of 1016 individuals with MS were enrolled in the study. Our results showed that negative item related to job maintenance as 'attitudes of other in the workplace' was associated with a lower likelihood of being employed (OR 0.65, 95% CI 0.57-0.76), while 'your attitudes toward work' (OR 1.37, 95% CI 1.19-1.59), 'attitudes of other in the workplace' (OR 1.41, 95% CI 1.17-1.69) and 'personal considerations' (OR 1.54, 95% CI 1.23-1.93), positive items related to job maintenance, were associated with a higher likelihood of being employed. In addition, a poor quality of life and severity disease as well same demographic characteristics (i.e. to be resident in South Italy or in the Islands, living in own original family, have lower educational level) inhibited significantly the job maintenance together with a heavy job and a fixed-term contract. In conclusion, a complex set of variables contribute to the barriers faced by PwMS who are employed suggesting that different stakeholders may play an important role in difficult management of the work for people with MS.

Purmonen, T., Hakkarainen, T., Tervomaa, M., et al. (2020). "Impact of multiple sclerosis phenotypes on burden of disease in Finland." J Med Econ **23**(2): 156-165.

> Aims: The aim of this study was to quantify how multiple sclerosis (MS) phenotypes differ from each other in respect of costs and quality-of-life.Materials and methods: The study is based on survey data from Finnish patients with MS (n = 553). The information contained disease type, disease severity according to self-reported Expanded Disease Severity Scale (EDSS), healthcare resource use, and medication use. In addition, information related to

employment and early retirement was collected. EQ-5D-VAS and Multiple Sclerosis Impact Scale-29 (MSIS-29) instruments were used to collect quality-of-life data, and Fatigue Severity Scale (FSS) instrument for evaluating fatigue. Patients were stratified based on their disease type (relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS)) and disease severity. The data were primarily analyzed using summary statistics.Results: SPMS had the highest annual total cost (71,177euro) followed by PPMS (51,082euro) and RRMS (36,492euro). Early retirement covered the greatest share of costs in RRMS (39%) and SPMS (43%). In PPMS, early retirement and professional care were the two most equally important cost drivers, contributing together 56% of the total costs. Direct healthcare costs were responsible for 33%, 19%, and 18% of total costs in RRMS, SPMS, and PPMS. The mean EDSS in RRMS, SPMS, and PPMS were 2.5, 5.5, and 5.9, respectively. Differences in the quality-of-life were observed with both disease specific (MSIS-29) and generic (EQ-5D-VAS) instruments. The mean utility value from EQ-5D among patients with RRMS, SPMS, and PPMS was 0.76, 0.52, and 0.49, respectively. In addition, patients with SPMS and PPMS were more likely to report fatigue than patients with RRMS.Conclusions: MS phenotype has an impact on costs and quality-of-life of the patients. Early retirement seems to be one of the most important contributors to MS-related costs.

Raggi, A., Covelli, V., Schiavolin, S., et al. (2016). "Work-related problems in multiple sclerosis: a literature review on its associates and determinants." Disabil Rehabil **38**(10): 936-944.

PURPOSE: To explore which variables are associated to or determinants of work-related difficulties or unemployment in persons with multiple sclerosis (MS). METHOD: Papers published between 1993 and February 2015 were included. Quality was judged as poor, acceptable, good or excellent. Determinants were extracted from prospective and retrospective data, associated variables from cross-sectional data; variables were grouped by similarity. Evidence was judged as strong if there were at least two good studies reporting the same results; limited if there was only one good and some acceptable studies. RESULTS: Forty-two papers were selected, for a total of 31,192 patients (75% females). Work-related difficulties were referred as unemployment, lower amount of worked hours or job cessation. Strong evidence of impact over work-related difficulties was found for a core set of variables, i.e., expanded disability status scale, MS duration, patients' age, fatigue and walking problems. Little evidence exists on the impact of contextual factors. DISCUSSION: Most of the variables identified as associated to or determinants of work-related difficulties can be treated through rehabilitative interventions. It is important that future research addresses not only unemployment issues in MS, but also the amount and severity of problems affecting work-related tasks relying on specific assessment instruments. IMPLICATIONS FOR REHABILITATION: Multiple sclerosis (MS) affects young persons of working age and limitation in work activities is part of MS-related disability, but they are not consistently addressed in MS research: EDSS, MS duration, patients' age, fatigue, walking problems, cognitive and neuropsychological impairments were the factors most commonly found as associated to or determinant of difficulties with work. Evidence exists that rehabilitation interventions are effective for fatigue, cognitive impairment, mobility and walking difficulties. However, research did not address the impact of rehabilitation programmes on vocational outcomes. Rehabilitation researchers should include MS-specific assessment instruments for work-related difficulties to standardised clinical protocols, so that the benefits of rehabilitation on persons' ability to work can be demonstrated directly: in this way, cost-benefit balance analyses can be added to the evaluation of treatment effectiveness.

Rajagopalan, K., Brook, R. A., Beren, I. A., et al. (2011). "Comparing costs and absences for multiple sclerosis among US employees: pre- and post-treatment initiation." Curr Med Res Opin **27**(1): 179-188.

BACKGROUND: Limited data exist on the effects of Disease Modifying Treatments (DMTs) on direct and indirect costs among employees treated for Multiple Sclerosis (MS). The objective was to compare costs and absences among employees treated with DMTs (e.g., interferons [IFNs]: IFN-beta1a-IM = Avonex = 'A', IFN-beta1b = Betaseron = 'B', IFN-beta1a-SC = Rebif = 'R', or glatiramer acetate = Copaxone = 'C') for MS pre and post therapy initiation. METHODS: A healthcare claims database of US employees (2001-2008) was used to identify patients with two or more DMT prescriptions or one DMT prescription with a MS diagnosis (ICD-9 = 340.X) who were continuously employed and with health plan coverage 6 months pre and post DMT initialization. Outcome measures included: direct costs; indirect costs and absences associated with sick leave (SL) and short-term disability (STD); and medical costs and utilization by place of service (POS). All costs are inflation-adjusted to 2010 US$. Between- and within-group outcomes were compared using Student's t-tests for continuous and chi-square tests for discrete variables and considered significant when P </= 0.05. RESULTS: Overall, 153 eligible employees were identified: 'A' = 68, 'B' = 22, 'R' = 21, 'C' = 42; 76 employees had SL eligibility; 89 had STD eligibility; and 97 employees had POS indicators. Following treatment initiation, healthcare costs decreased significantly for 'A' users (-53.8%, -$3084) and 'B' users (-67.1%, -$4103), while SL costs only decreased significantly for 'A' users (-60.5%, -$704); changes in SL absence days for 'A' and 'B' users were significantly lower than for 'C' users (both P < 0.05). In the POS sample, total medical costs significantly decreased for 'A' (-$3643), 'B' (-$3470), and 'C' (-$3762), while 'R' increased ($2093) non-significantly. Only 'A' users had significant proportion-of-care reductions (Emergency Department, Outpatient Hospital, and 'Other' locations). CONCLUSION: Among MS employees treated with DMTs in the real-world, 'A' and 'B' users had significantly greater reductions in SL costs post therapy initiation compared with 'C' and 'R'. Only 'A' users showed a significant reduction in SL absence days, while the other cohorts reported increases. LIMITATIONS: Small sample sizes may limit the interpretability of these results.

Roessler, R. T., Rumrill, P. D. et Timblin, R. (2017). "Focus group perspectives on high-priority employment barriers facing Americans with multiple sclerosis." Journal of Vocational Rehabilitation **47**(2): 223-233.

BACKGROUND:People with multiple sclerosis (MS) are known to face a multitude of challenges as they attempt to re-initiate or maintain their careers following onset of the disease. OBJECTIVE:Less is known, however, about the subjective experiences of people with MS regarding employment barriers. METHODS:Using the results of a larger national survey of the employment concerns of people with MS that was conducted in 2014–2015 as a basis for data collection, this qualitative study involved six focus groups comprising 20 people with MS and 27 MS service providers. RESULTS:Focus group participants offered subjective perspectives on and suggestions for addressing employment barriers that represented four major themes: understanding the provisions of the Affordable Care Act, on-the-job accommodations and the Americans with Disabilities Act, reassignment as a job retention strategy, and disclosure of disability. CONCLUSION:Findings are discussed within the context of existing literature.

Roessler, R. T., Turner, R. C., Robertson, J. L., et al. (2005). "Gender and Perceived Illness Severity:Differential Indicators of Employment Concerns for Adults with Multiple Sclerosis?" Rehabilitation Counseling Bulletin **48**(2): 66-74.
https://journals.sagepub.com/doi/abs/10.1177/00343552050480020101

Although research has indicated a link between gender and perceived illness severity and the employment status of people with multiple sclerosis (MS), it has not addressed questions regarding the relationship between those variables and specific types of employment concerns. In this study, a sample of 1,310 adults with MS replied to a mail survey eliciting their concerns regarding employment services and policies. Regardless of perceived severity and gender, adults with MS were dissatisfied with many important employment services and policies. Findings also indicated gender and severity interactions, which are discussed in terms of implications for rehabilitation interventions.

Rogan, E. (2014). "Activities of the European multiple sclerosis platform." Eur Neurol **72 Suppl 1**: 43-46.

BACKGROUND: The European Multiple Sclerosis Platform (EMSP) is an umbrella organization for national multiple sclerosis (MS) patients' associations in 34 European countries. Its focus is to improve the quality of life (QoL) of individuals with MS and inform society about the challenges of living with this chronic and debilitating disease. SUMMARY: The EMSP, which is comprised of 39 MS societies across Europe, represents the interests of more than 600,000 individuals with MS and another 1.5 million persons affected by the disease, including family and caregivers. The organization works to achieve high quality, equitable treatment and support for persons with MS throughout Europe, as reflected in its main activities and projects. These include: the European Code of Good Practice in MS; a European MS register (EUReMS); a MS Barometer to assess QoL; the MS Nurse PROfessional curriculum to provide standards for MS nurse training; a photographic exhibition entitled Under Pressure; the Believe and Achieve project which focuses on employment for young people with MS; and collaboration in World MS Day, an international MS awareness day. Key Messages: The activities and projects of the EMSP are geared towards making a difference in the lives of individuals with MS in Europe and their wider support networks, including physicians, neurologists, nurses and carers.

Ruet, A., Deloire, M., Hamel, D., et al. (2013). "Cognitive impairment, health-related quality of life and vocational status at early stages of multiple sclerosis: a 7-year longitudinal study." J Neurol **260**(3): 776-784.

The association between cognitive impairment, health-related quality of life (HRQoL) and vocational status has been studied in recent years in cross-sectional studies in multiple sclerosis (MS), but longitudinal data are still lacking. This study assesses this association in a sample of 65 newly diagnosed MS patients followed longitudinally. Each patient underwent a standardised clinical assessment, cognitive tests and the HRQoL SEP-59 questionnaire six months after the MS diagnosis (baseline) and seven years later (y7).Vocational status was also established at baseline and at y7 in MS patients. The HRQoL at baseline was severely reduced in MS patients compared with healthy subjects. The independent predictors for HRQoL composite scores at y7 were the baseline depression score and the memory Z-score. Accordingly, 81.5 % of MS patients worked at baseline and only 54.4 % worked at y7. Among the MS patients who did not work at y7, 72.7 % of them were cognitively impaired, while 27.3 % were unimpaired at baseline. The vocational status at y7 was significantly associated with the baseline IPS Z-score, EDSS and age. Vocational status at y7 and its change over 7 years was significantly associated with cognitive deterioration. IPS or memory dysfunction in the early stages of MS is correlated with a decreased level in health perception, independent of fatigue, depression and physical disability. Cognitive impairment at the diagnosis of MS increases the risk of changing vocational status in MS patients seven years later.

Rumrill, P. D., Roessler, R. T., Li, J., et al. (2015). "The employment concerns of Americans with multiple sclerosis: Perspectives from a national sample." Work **52**(4): 735-748.

BACKGROUND: The recent rehabilitation literature does not include a thorough assessment of the employment concerns of people with MS. OBJECTIVE: This article presents descriptive findings from a national survey of the employment concerns of Americans with multiple sclerosis (MS; N = 1,924), representing nine chapters of the National Multiple Sclerosis Society. METHODS: Respondents were asked to evaluate 38 employment concerns items on two dimensions, importance and satisfaction, for the purpose of identifying strengths and weaknesses in the employment policies and practices affecting the labor force participation of people with MS. RESULTS: Results revealed a total of 32 employment strengths and six employment weaknesses. CONCLUSIONS: In spite of a jobless rate of more than 60 percent, people with MS were satisfied with the majority of employment concerns. Implications of these findings for rehabilitation policy and service delivery are examined.

Sabanagic-Hajric, S. et Alajbegovic, A. (2015). "Impacts of education level and employment status on health-related quality of life in multiple sclerosis patients." Med Glas (Zenica) **12**(1): 61-67.

AIM: To evaluate the impacts of education level and employment status on health-related quality of life (HRQoL) in multiple sclerosis patients. METHODS: This study included 100 multiple sclerosis patients treated at the Department of Neurology, Clinical Center of the University of Sarajevo. Inclusion criteria were the Expanded Disability Status Scale (EDSS) score between 1.0 and 6.5, age between 18 and 65 years, stable disease on enrollment. Quality of life (QoL) was evaluated by the Multiple Sclerosis Quality of Life-54 questionnaire (MSQoL-54). Mann-Whitney and Kruskal-Wallis test were used for comparisons. Linear regression analyses were performed to evaluate prediction value of educational level and employment status in predicting MSQOL-54 physical and mental composite scores. RESULTS: Full employment status had positive impact on physical health (54.85 vs. 37.90; p les than 0.001) and mental health (59.55 vs. 45.90; p les than 0.001) composite scores. Employment status retained its independent predictability for both physical (r(2)=0.105) and mental (r(2)=0.076) composite scores in linear regression analysis. Patients with college degree had slightly higher median value of physical (49.36 vs. 45.30) and mental health composite score (66.74 vs. 55.62) comparing to others, without statistically significant difference. CONCLUSION: Employment proved to be an important factor in predicting quality of life in multiple sclerosis patients. Higher education level may determine better QOL but without significant predictive value. Sustained employment and development of vocational rehabilitation programs for MS patients living in the country with high unemployment level is an important factor in improving both physical and mental health outcomes in MS patients.

Salter, A., Stahmann, A., Ellenberger, D., et al. (2020). "Data harmonization for collaborative research among MS registries: A case study in employment." Mult Scler: 1352458520910499.

OBJECTIVE: To assess the feasibility of collaboration and retrospective data harmonization among three multiple sclerosis (MS) registries by investigating employment status. METHODS: We used the Maelstrom guidelines to facilitate retrospective harmonization of data from three MS registries, including the NARCOMS (North American Research Committee on MS) Registry, German MS Register (GMSR), and United Kingdom MS (UK-MS) Register. A protocol was developed based on the guidelines, and summary-level data were used to combine results. Employment status and a limited set of factors associated with employment (age, sex, education, and disability level) were harmonized. A meta-analytic approach was used to pool estimates using a weighted average of logistic regression estimates and their variances in a random effects model. RESULTS: Employment status, age, sex, education, and disability were mapped. The overall employment rate was 57% (11,143 employed out of 19,562 persons with MS) with the GMSR having the highest proportion of participants employed (66.2%), followed by the UK-MS (55.2%) and NARCOMS (43.0%) registries. As disability level increased, the odds of not being employed increased. CONCLUSION: Harmonization across registries was feasible. The Maelstrom guidelines provide a valuable roadmap for conducting high-quality harmonization projects. The pooling of data sources has the potential to be an important mechanism for conducting research in MS.

Salter, A., Thomas, N., Tyry, T., et al. (2017). "Employment and absenteeism in working-age persons with multiple sclerosis." J Med Econ **20**(5): 493-502.

AIMS: To better understand the impact of the clinical course of multiple sclerosis (MS) and disability on employment, absenteeism, and related factors. MATERIALS AND METHODS: This study included respondents to the North American Research Committee on Multiple Sclerosis Registry spring 2015 update survey who were US or Canadian residents, aged 18-65 years and reported having relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), or primary progressive MS (PPMS). The RRMS and SPMS participants were combined to form the relapsing-onset MS (RMS) group and compared with the PPMS group regarding employment status, absenteeism, and disability. Multivariable logistic regression was used to examine the relationship between employment-related outcomes and factors that may affect these relationships. RESULTS: Of the 8004 survey respondents, 5887 (73.6%) were 18-65 years of age. The PPMS group (n = 344) had a higher proportion of males and older mean age at the time of the survey and at time of diagnosis than the RMS group (n = 4829). Female sex, age, age at diagnosis, cognitive and hand function impairment, fatigue, higher disability levels, >/=3 comorbidities, and a diagnosis of PPMS were associated with not working. After adjustment for disability, the employed PPMS sub-group reported similar levels of absenteeism to the employed RMS sub-group. LIMITATIONS: Limitations of the study include self-report of information and the possibility that participants may not fully represent the working-age MS population. CONCLUSIONS: In MS, employment status and absenteeism are negatively affected by disability, cognitive impairment, and fatigue. These findings underscore the need for therapies that prevent disability progression and other symptoms that negatively affect productivity in persons with MS to enable them to persist in the workforce.

Sander, L., Kugler, J. et Elsner, B. (2020). "[The influence of multiple sclerosis-related symptoms on health-related quality of life]." Fortschr Neurol Psychiatr.

BACKGROUND: Multiple sclerosis (MS) is a chronic disease that is associated with a variety of MS-specific symptoms. Many of these symptoms have a negative impact on health-related quality of life (HRQoL). Until now it is unclear which MS-specific symptoms have the highest impact on the HRQoL. METHODOLOGY: The study is based on the data of a member survey of the German MS Society (DMSG) in 2015 (n = 424). Considering socio-demographic variables and general medical variables, the influence of MS-specific symptoms on HRQoL was examined. The HRQoL was collected using the Multiple Sclerosis Quality of Life-54 (MSQOL-54) instrument. In a pretest, all influencing variables were tested for a significant mean difference (p = 0.05), or a mean correlation (Pearson's r >/= 0.3). Subsequently, the influence of the variables identified in the pretest on the HRQoL was investigated by multiple linear regression analysis. RESULTS: We calculated a mean physical health composite score (PHCS) of 48.3 (sd = 17.7) and a mean mental health composite score (MHCS) of 56.0 (sd = 20.1). The most fundamental factors influencing HRQoL were the MS-specific symptoms of depression, pain and cognitive impairment. MS-related symptoms with a mobility context showed declining PHCS. Speech disorder and dizziness were associated with a decreasing MHCS. Employment status was the only socio-economic factor that significantly affected HRQoL in multiple regression. The general medical factors showed no significant influence on HRQoL. CONCLUSION: MS-specific symptoms have a major impact on the HRQoL of people with MS. Our study show that especially the so-called 'hidden symptoms' such as the symptoms of depression, pain and cognitive impairment have a significant influence on the HRQoL. Greater attention should be paid to these in the care of people with MS.

Schiavolin, S., Leonardi, M., Giovannetti, A. M., et al. (2013). "Factors related to difficulties with employment in patients with multiple sclerosis: a review of 2002-2011 literature." Int J Rehabil Res **36**(2): 105-111.

We assess the knowledge available on the difficulties experienced by multiple sclerosis (MS) patients in work-related activities. A literature review was carried out using the keywords 'multiple sclerosis' and 'employment' or 'work' through PubMed and EMBASE. Papers reporting patient-derived data on difficulties at work as primary or secondary outcome measures and published in the period 2002-December 2011 were searched. A total of 26 papers were selected, for a total of 32 507 patients (mean age 46.2 years; 42.1% with relapsing-remitting MS). Most papers reported observational studies or cross-sectional surveys focused on health-related quality of life and MS costs. Symptoms more frequently addressed are fatigue, mobility and cognitive impairments. Limited research has been carried out on the working environment. We found a relatively small number of papers published in the last 10 years on the difficulties that patients with MS can experience at work, and this kind of information always appeared as a secondary outcome. In general, it is possible to affirm that MS has a strong impact on patients' employment status, as the mean unemployment rate was 59%. Research on factors promoting maintenance of remunerative employment is required.

Shahrbanian, S., Auais, M., Duquette, P., et al. (2013). "Does pain in individuals with multiple sclerosis affect employment? A systematic review and meta-analysis." Pain Res Manag **18**(5): e94-e100.

BACKGROUND: Individuals with multiple sclerosis (MS) experience some of the highest unemployment rates among all groups of chronic illnesses. Pain has been found to be a common reason for sick leave or early retirement in healthy populations or other groups with chronic illness; however, there is little awareness regarding the effect of pain on the work status of individuals with MS. OBJECTIVES: To estimate the extent to which individuals with pain differ in employment status compared with those without pain among MS patients. METHODS: An extensive systematic review of the scientific literature was performed within the framework of the Cochrane Collaboration to identify studies focusing on the effect of pain on employment in individuals with MS. The following databases were searched: PubMed, EMBASE, PsychInfo, Web of Science, MD Consult and Elsevier, and Science Direct. The methodological quality of studies was assessed using the McMaster Critical Review Form. RESULTS: Ten articles met the inclusion criteria and were included in the systematic review. Of these studies, five that exhibited clinical, methodological and statistical homogeneity were included in the meta-analysis. The between-groups (pain + versus pain -) pooled random OR of being employed was 0.7 (strong), and was significantly different from unity (95% CI 0.5 to 0.9; P=0.001). CONCLUSIONS: The results of the present study indicated that individuals with MS who experience pain were significantly more likely to report a decreased employment rate than individuals with MS who were pain free.

Simmons, R. D., Tribe, K. L. et McDonald, E. A. (2010). "Living with multiple sclerosis: longitudinal changes in employment and the importance of symptom management." J Neurol **257**(6): 926-936.

People with multiple sclerosis (MS) tend to have lower participation in paid employment compared to those with other chronic diseases. In two large-sample, self-report surveys of MS patients performed 4 years apart, employment rates were measured both cross-sectionally and longitudinally. The reasons for employment loss and perceived risk of future employment loss were also assessed. A total of 1,135 patients responded to the first survey, 1,329 to the second, and 667 to both. Longitudinal loss of employment was 5.4% over the 4 years 2003-2007, a period of relative national economic prosperity. By 2007, 56% of MS patients had lost employment due to MS and 64% were not in the paid labour force. Regression analysis indicated that men were more likely than women to leave their employment because of their MS, and older people were more likely than younger ones to do so. Level of occupational skill using Australian Bureau of Statistics categorisation was not predictive of maintaining or losing employment. The main reasons reported by people with MS for their loss of employment involved the ineffective management of symptoms of MS in the workplace, rather than workplace-related factors including insufficient flexibility of employment conditions or being asked to leave or sacked. The most frequently listed symptoms relating to employment loss, and perceived risk of losing current employment, were fatigue, mobility-related symptoms, arm and hand difficulties, and cognitive deficits. These findings imply that many employees with MS are leaving their planning for effective symptom management, and for appropriate accommodations in the workplace, until such planning is too late to be effective. The potential advantages of early, supported disclosure of diagnosis to employers before MS symptoms become a problem are discussed.

Steinemann, N., Kuhle, J., Calabrese, P., et al. (2018). "The Swiss Multiple Sclerosis Registry (SMSR): study protocol of a participatory, nationwide registry to promote epidemiological and patient-centered MS research." BMC Neurol **18**(1): 111.

BACKGROUND: Multiple sclerosis (MS) is one of the most frequently observed neurological conditions in Switzerland, but data sources for country-wide epidemiological trend monitoring are lacking. Moreover, while clinical and laboratory MS research are generally well established, there is a gap in patient-centered MS research to inform care management, or treatment decisions and policy making not only in Switzerland but worldwide. METHODS: In light of these research gaps, the Swiss Multiple Sclerosis Society initiated and funded the Swiss Multiple Sclerosis Registry (SMSR) an open-ended, longitudinal and prospective, nationwide, patient-centered study. The SMSR recruits adult persons with a suspected or confirmed MS diagnosis who reside or receive care in Switzerland. The SMSR has established a governance structure with clear rules and guidelines. It follows a citizen-science approach with direct involvement of persons with MS (PwMS), who contribute actively to registry development, operations, and research. Main scientific goals entail the study of MS epidemiology in Switzerland, health care access and provision, as well as life circumstances and wellbeing of persons with MS. The innovative study design ("layer model") offers several participation options with different time commitments. Data collection is by means of regular surveys and medical record abstraction. Survey participation is offered in different modes (web, paper & pencil) and in the three main national languages (German, French, Italian). Participants also receive regular data feedbacks for personal use and self-monitoring, contextualized in the whole population of study participants. Data feedbacks are also used to solicit data corrections of key variables from participants. DISCUSSION: The SMSR combines the advantages of traditional and novel research methods in medical research and has recruited over 1600 PwMS in its first year. The future-oriented design and technology will enable a response not only to future technological innovations and research trends, but also to challenges in health care provision for MS. TRIAL

REGISTRATION: ClinicalTrials.gov NCT02980640 ; December 6, 2016; retrospectively registered.

Smith, M. M. et Arnett, P. A. (2005). "Factors related to employment status changes in individuals with multiple sclerosis." Mult Scler **11**(5): 602-609.

In a sample of 50 individuals with multiple sclerosis (MS), participants able to work full-time ('W'), those who reduced their hours ('CB') and those who were unemployed ('NW') were compared on demographic and disease variables and symptoms that the participants identified as being responsible for their work status change. The NW group had significantly greater physical disability than the other two groups and significantly more fatigue than the W group. The CB group had significantly more years of education and higher occupational prestige ratings than the NW group. The W group reported significantly greater mood disturbance compared with the NW group. Employment status was unrelated to age, gender, full scale IQ estimate, disease duration, diagnosis duration or cognitive functioning. Ninety per cent of the CB group reported that fatigue was a primary symptom responsible for their work status change, whereas 86% of the NW group reported that broad physical/neurological symptoms were responsible for their change in work status.

Strober, L., Chiaravalloti, N., Moore, N., et al. (2014). "Unemployment in multiple sclerosis (MS): utility of the MS Functional Composite and cognitive testing." Mult Scler **20**(1): 112-115.

Unemployment is a significant concern among individuals with multiple sclerosis (MS). Determinations regarding ability to work are highly dependent on measurement tools used by neurologists and allied professionals. However, little is known of the usefulness of these tools when determining issues pertaining to employment status. The purpose of the present investigation was to examine the utility of the Multiple Sclerosis Functional Composite (MSFC) and a brief cognitive test battery when examining employment status in MS. Seventy-seven individuals with MS completed the MSFC and a brief cognitive test battery. On the MSFC, unemployed individuals demonstrated worse upper extremity functioning. There was no difference on the Paced Auditory Serial Addition Task (PASAT), the sole cognitive measure of the MSFC. On cognitive testing, unemployed individuals performed worse on measures of memory, information processing speed, and executive functioning. Through logistic regression analysis, the Symbol Digit Modalities Test (SDMT) was found to be the sole predictor of employment status among the significant disease, MSFC and cognitive variables. Consistent with previous findings, logistic regression found the SDMT to be a significant predictor of employment status. Given the lack of significant group differences on the PASAT, continued consideration of replacing the PASAT with the SDMT in the MSFC appears warranted.

Strober, L. B. et Arnett, P. A. (2016). "Unemployment among women with multiple sclerosis: the role of coping and perceived stress and support in the workplace." Psychol Health Med **21**(4): 496-504.

Unemployment is high among individuals with multiple sclerosis (MS). Certain disease variables and demographics have been found to distinguish employed and unemployed individuals. However, these variables only account for 14-20% of the variance. Other factors, such as coping, perceived stress and social support, in the workforce have been proposed, but not yet fully examined. The purpose of the present investigation was to examine the role of known factors associated with unemployment in MS, as well as coping and perceived work stress and social support. Sixty-eight women with MS were asked about their employment status and reasons for leaving. They completed a comprehensive assessment including measures of cognition, disease symptoms, psychological functioning, coping and stress. Consistent with previous findings, certain disease and demographic variables were associated with being unemployed. In particular, women who left work due to their MS were found to be older, had a longer disease duration and progressive course, reported greater disability and fatigue, and performed worse on a cognitive measure. However, we also found that coping style distinguished those who were employed from those who left work due to their MS. In particular, those who left work reported utilizing maladaptive coping mechanisms such as behavioral disengagement and substance use. With regard to perceived work stress and support, individuals who were employed reported that job security and fellow co-workers were more of an uplift than a hassle in their lives, suggesting some benefit in employment. These findings suggest that further consideration be given to role of coping and perception of the benefit of employment among individuals with MS when making recommendations regarding work decisions.

Strober, L. B. et Callanan, R. M. (2019). "Unemployment in multiple sclerosis across the ages: How factors of unemployment differ among the decades of life." J Health Psychol: 1359105319876340.

Rates of unemployment in multiple sclerosis are high. Certain disease, psychological, and person-specific factors contribute to these high rates. The present study examined these factors and associated risk of unemployment by age. Participants (n = 221) completed an online survey on employment. Participants were broken down by decade of life. Several factors predicted whether someone felt as if they needed to leave the workforce. However, the extent to which these factors contributed to unemployment risk varied by age. Interventions aimed at maintaining employment should address these factors and take into consideration one's stage of life, disease, and career.

Strober, L. B., Chiaravalloti, N. et DeLuca, J. (2018). "Should I stay or should I go? A prospective investigation examining individual factors impacting employment status among individuals with multiple sclerosis (MS)." Work **59**(1): 39-47.

BACKGROUND: Rates of unemployment among individuals with multiple sclerosis (MS) are as high as 80%. While several factors for such high rates of unemployment have been identified, they do not account for the majority of the variance. OBJECTIVE: This study examines person-specific factors such as personality and coping, which may better account for individuals leaving the workforce. METHOD: Forty individuals with MS (20 considering reducing work hours or leaving the workforce and 20 remaining employed) were matched on age, gender, education, disease duration, and disease course, and administered a comprehensive survey of factors purported to be related to employment status. RESULTS: Based on multiple, logistic regression analyses certain disease factors and person-specific factors differentiate those who are considering leaving work or reducing work hours and those staying employed. In particular, those expressing the need to reduce work hours or leaving the workforce reported more fatigue, anxiety, depression, and use of behavioral disengagement as a means of coping. In contrast, those staying employed reported greater levels of extraversion, self-efficacy, and use of humor as a means of coping. Together, fatigue, use of humor, and use of behavioral disengagement as a means of coping were the most significant factors, accounting for 44% of the variance. CONCLUSIONS: Findings suggest that greater consideration be given to these factors and that interventions tailored to address these factors may assist individuals with MS staying employed and/or making appropriate accommodations.

Strober, L. B., Christodoulou, C., Benedict, R. H., et al. (2012). "Unemployment in multiple sclerosis: the contribution of personality and disease." Mult Scler **18**(5): 647-653.

BACKGROUND: Multiple sclerosis (MS) is the leading cause of neurological disability among young and middle-aged adults. One of the most devastating consequences of MS in this relatively young population group is unemployment. Although certain demographic and disease factors have been associated with employment, few studies have examined the contribution of person-specific factors, such as personality. OBJECTIVE: The goal of this study was to determine the extent to which personality, demographics, and clinical measures contribute to unemployment in MS. METHOD: A total of 101 individuals with MS who were enrolled in a clinical trial on cognition underwent a brief neuropsychological battery and completed questionnaires related to vocation, mood, fatigue, and personality. Neurological impairment was measured with the Expanded Disability Status Scale (EDSS). RESULTS: Employment status was related with disease duration, MS subtype, level of neurological impairment, fatigue, performance on measures assessing information processing speed (Symbol Digit Modalities Test (SDMT)), learning and memory (Selective Reminding Test), and the personality characteristic of persistence. Based on a forward logistic regression analysis, EDSS, SDMT, and persistence were the strongest predictors of employment status. CONCLUSIONS: These findings underscore the importance of personality on outcomes in MS and point to the need for more clinical attention and research in this area.

Sweetland, J., Howse, E. et Playford, E. D. (2012). "A systematic review of research undertaken in vocational rehabilitation for people with multiple sclerosis." Disabil Rehabil **34**(24): 2031-2038.

OBJECTIVE: The National Service Framework (NSF) for Long-Term Neurological Conditions (LTNC) highlights the need for vocational rehabilitation (VR) services in quality requirement 6. As a part of a review of this requirement, an extensive literature review was undertaken to identify, review and report on all relevant research undertaken in the area of employment for people with multiple sclerosis (MS). DATA SOURCES: A systematic review of the English language literature for studies under the headings: multiple sclerosis and employment, unemployment, vocational rehabilitation, occupational health, job and work adjustment. The following databases were systematically searched AMED (1985 to Feb 2010), CINAHL (1982 to Feb 2010), PsycINFO (1806 to Feb 2010), EMBASE (1974 to Feb 2010), Medline (1950 to Feb 2010) and PubMed (1950 to Feb 2010). DATA EXTRACTION AND STUDY SELECTION: Four hundred and sixty-two papers were identified. This number was reduced removing the duplicates, non-English, not reporting research, not primarily about MS and not primarily about work which left 89 papers reviewed. CONCLUSION: The body of evidence reviewed gives clear indicators as to what the barriers to working with MS are and what is required for a VR service to meet the often complex needs of people with MS. Further research is needed to identify the efficacy of different models of VR, and their cost-effectiveness, and particularly for means of identifying and measuring the effectiveness of interventions that support work retention.

Tauhid, S., Chu, R., Sasane, R., et al. (2015). "Brain MRI lesions and atrophy are associated with employment status in patients with multiple sclerosis." J Neurol **262**(11): 2425-2432.

Multiple sclerosis (MS) commonly affects occupational function. We investigated the link between brain MRI and employment status. Patients with MS (n = 100) completed a Work Productivity and Activity Impairment (WPAI) (general health version) survey measuring employment status, absenteeism, presenteeism, and overall work and daily activity impairment. Patients "working for pay" were considered employed; "temporarily not working but looking for work," "not working or looking for work due to age," and "not working or looking for work due to disability" were considered not employed. Brain MRI T1 hypointense (T1LV) and T2 hyperintense (T2LV) lesion volumes were quantified. To assess lesional destructive capability, we calculated each subject's ratio of T1LV to T2LV (T1/T2).

> Normalized brain parenchymal volume (BPV) assessed brain atrophy. The mean (SD) age was 45.5 (9.7) years; disease duration was 12.1 (8.1) years; 75 % were women, 76 % were relapsing-remitting, and 76 % were employed. T1LV, T1/T2, Expanded Disability Status Scale (EDSS) scores, and activity impairment were lower and BPV was higher in the employed vs. not employed group (Wilcoxon tests, $p < 0.05$). Age, disease duration, MS clinical subtype, and T2LV did not differ between groups ($p > 0.05$). In multivariable logistic regression modeling, adjusting for age, sex, and disease duration, higher T1LV predicted a lower chance of employment ($p < 0.05$). Pearson correlations showed that EDSS was associated with activity impairment ($p < 0.05$). Disease duration, age, and MRI measures were not correlated with activity impairment or other WPAI outcomes ($p > 0.05$). We report a link between brain atrophy and lesions, particularly lesions with destructive potential, to MS employment status.

Tinghog, P., Hillert, J., Kjeldgard, L., et al. (2013). "High prevalence of sickness absence and disability pension among multiple sclerosis patients: a nationwide population-based study." Mult Scler **19**(14): 1923-1930.

> INTRODUCTION: Although multiple sclerosis (MS) often implies substantial disability, there is little knowledge about sick leave and disability pension among MS patients. OBJECTIVES: The purpose of this study was to estimate the prevalence rates of sick leave and disability pension among MS patients and to explore how socio-demographics are associated with such rates. METHODS: The register data of all people who lived in Sweden in 2005 and were 16-64 years old was used to identify 9721 MS patients and matched controls. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated and effect modifications were evaluated with Wald X(2) tests. RESULTS: In 2005, 61.7% of the MS patients were on partial or full disability pension compared to 14.2% among the controls. Of the others, 36.8% had >/= 1 sick-leave spell for >14 days during that year. Socio-demographics were similarly associated with sick leave and disability pension among MS patients and controls, with the noteworthy exceptions that female gender and immigration status were less potent risk factors in the MS population ($p<0.05$). CONCLUSION: In spite of widespread access to modern health care including disease-modifying drugs, the majority of MS patients of working ages were on a disability pension. Strategies enabling MS patients to retain their footing in the labour market are needed.

Van der Hiele, K., Middelkoop, H. A., Ruimschotel, R., et al. (2014). "A pilot study on factors involved with work participation in the early stages of multiple sclerosis." PLoS One **9**(8): e105673.

> BACKGROUND: Up to 30% of recently diagnosed MS patients lose their jobs in the first four years after diagnosis. Taking into account the personal and socio-economic importance of sustaining employment, it is of the utmost importance to examine factors involved with work participation. OBJECTIVE: To investigate differences in self-reported functioning in recently diagnosed MS patients with and without a paid job. METHODS: Self-reports of physical and cognitive functioning, depression, anxiety and fatigue were gathered from 44 relapsing-remitting MS patients diagnosed within 3 years. RESULTS: Patients with a paid job (57%) reported better physical functioning ($p<0.001$), better memory functioning ($p = 0.01$) and a lower physical impact of fatigue ($p = 0.018$) than patients without a paid job. Physical functioning was the main predictor of employment status in a logistic regression model. In those with a paid job better memory functioning ($r = 0.54$, $p = 0.005$) and a lower social impact of fatigue ($r = -0.46$, $p = 0.029$) correlated with an increased number of working hours. CONCLUSION: Better physical functioning is the primary factor involved with increased work participation in early MS. Better self-reported memory functioning and less social

fatigue were associated with increased working hours. These findings highlight the importance of battling these symptoms in the early stages of MS.

van der Hiele, K., van Gorp, D., Ruimschotel, R., et al. (2015). "Work Participation and Executive Abilities in Patients with Relapsing-Remitting Multiple Sclerosis." PLoS One **10**(6): e0129228.

The majority of patients with Multiple Sclerosis (MS) are unable to retain employment within 10 years from disease onset. Executive abilities, such as planning, working memory, attention, problem solving, inhibition and mental flexibility may have a direct impact on the ability to maintain a job. This study investigated differences in subjective and objective executive abilities between relapsing-remitting MS patients with and without a paid job. We included 55 relapsing-remitting MS patients from a community-based sample (47 females; mean age: 47 years; 36% employed). Patients underwent neurological, cognitive and psychological assessments at their homes, including an extensive executive test battery. We found that unemployed patients had a longer disease duration (t(53)=2.76, p=0.008) and reported more organising and planning problems (chi2(1)=6.3, p=0.012), higher distractibility (Kendall's tau-b= -0.24, p=0.03) and more cognitive fatigue (U=205.0, p=0.028, r=-0.30) than employed patients. Unemployed patients completed slightly less categories on the Wisconsin Card Sorting Test (U=243.5, p=0.042, r=-0.28). Possible influential factors such as age, educational level, physical functioning, depression and anxiety did not differ between groups. In conclusion, while relapsing-remitting MS patients without a paid job reported more executive problems and cognitive fatigue than patients with a paid job, little differences were found in objective executive abilities. Further research is needed to examine possible causal relations.

van der Hiele, K., van Gorp, D. A., Heerings, M. A., et al. (2015). "The MS@Work study: a 3-year prospective observational study on factors involved with work participation in patients with relapsing-remitting Multiple Sclerosis." BMC Neurol **15**: 134.

BACKGROUND: Multiple Sclerosis (MS) is the most common cause of neurological disability in young and middle-aged adults. At this stage in life most people are in the midst of their working career. The majority of MS patients are unable to retain employment within 10 years from disease onset. Leading up to unemployment, many may experience a reduction in hours or work responsibilities and increased time missed from work. The MS@Work study examines various factors that may influence work participation in relapsing-remitting MS patients, including disease-related factors, the working environment and personal factors. METHODS/DESIGN: The MS@Work study is a multicenter, 3-year prospective observational study on work participation in patients with relapsing-remitting MS. We aim to include 350 patients through 15-18 MS outpatient clinics in the Netherlands. Eligible participants are 18 years and older, and either currently employed or within three years since their last employment. At baseline and after 1, 2 and 3 years, the participants are asked to complete online questionnaires (including questions on work participation, work problems and accommodations, cognitive and physical ability, anxiety, depression, psychosocial stress, quality of life, fatigue, empathy, personality traits and coping strategies) and undergo cognitive and neurological examinations. After six months, patients are requested to only complete online questionnaires. Patient perspectives on maintaining and improving work participation and reasons to stop working are gathered through semi-structured interviews in a sub-group of patients. DISCUSSION: Prospective studies with long-term follow-up on work participation in MS are rare, or take into account a limited number of factors. The MS@Work study provides a 3-year follow-up on various factors that may influence work participation in patients with relapsing-remitting MS. We aim to identify factors that relate to job loss and to provide information about preventative measures for physicians, psychologists and other professionals working in the field of occupational health.

Van Dijk, P. A., Kirk-Brown, A. K., Taylor, B., et al. (2017). "Closing the gap: Longitudinal changes in employment for Australians with multiple sclerosis." Mult Scler **23**(10): 1415-1423.

BACKGROUND AND OBJECTIVES: Previous studies have documented far lower employment participation rates for people with multiple sclerosis (PwMS) compared to the general population. In a large national sample of PwMS, we examined employment status, longitudinal changes in employment and the provision of modifications to work role/environment from 2010 to 2013. METHODS: Employment data were collected through the Australian MS Longitudinal Study from 2010 to 2013, with 1260 people responding to all four surveys. Employment rates were compared with the Australian general population. The survey included questions on the provision of modifications to employees' work role and work environment. RESULTS: Employment (full- and part-time) increased from 48.8% in 2010 to 57.8% in 2013, mainly due to increases in male full-time employment. The employment gap between PwMS and the general population fell from 14.3% in 2010 to 3.5% in 2013. Male employment rates, however, remain significantly lower than the general population. The majority of PwMS who required adjustments to either their work role or environment received them. CONCLUSION: The gap in employment between PwMS and the general population has substantially reduced from 2010 to 2013, with organisations responding positively to requests for work role/environment adjustments.

van Egmond, E., van Gorp, D., Honan, C., et al. (2019). "A Dutch validation study of the Multiple Sclerosis Work Difficulties Questionnaire in relapsing remitting multiple sclerosis." Disabil Rehabil: 1-10.

Purpose: The current study aimed to evaluate the psychometric properties of the Dutch version of the Multiple Sclerosis Work Difficulties Questionnaire-23 (MSWDQ-23).Methods: Two hundred and thirty-nine employed persons with multiple sclerosis (MS) and 59 healthy controls completed the MSWDQ-23. To verify the factor structure, a confirmatory factor analysis was conducted. To assess construct validity, the MSWDQ-23 scores were correlated to measures of physical disability, fatigue, cognitive and neuropsychiatric problems, depression, health-related quality of life, and work-related variables. MSWDQ-23 scores were compared within different age groups, gender, education levels, and job types. Predictive validity was assessed using a logistic regression analysis to predict a deterioration in employment status after one year based on MSWDQ-23 scores.Results: The internal consistency of the MSWDQ-23 was acceptable (alpha = 0.913, 95% CI = 0.897-0.928) and the results indicated a fair fit. The MSWDQ-23 showed acceptable construct validity, confirming 94% of the hypotheses. The total scale and the psychological/cognitive subscale were able to predict a deterioration in employment status after one year (chi(2)(1)=18.164, p < 0.001).Conclusions: The Dutch version of the MSWDQ-23 is a valid and internally consistent instrument to measure self-reported work difficulties in persons with MS.Implications for rehabilitationThe Dutch version of the 23-item Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ-23) is a reliable and valid tool to measure self-reported work difficulties in people with multiple sclerosis (MS).More psychological and cognitive work difficulties are predictive of a deteriorated employment status after one year.The MSWDQ-23 is a helpful tool for researchers and (occupational) health professionals to identify current work difficulties in persons with MS and identify persons at risk for a deterioration in employment one year later.

van Gorp, D. A. M., van der Hiele, K., Heerings, M. A. P., et al. (2019). "Cognitive functioning as a predictor of employment status in relapsing-remitting multiple sclerosis: a 2-year longitudinal study." Neurol Sci **40**(12): 2555-2564.

> BACKGROUND: Cognitive functioning has been linked to employment outcomes in multiple sclerosis (MS) in cross-sectional studies. Longitudinal studies are however lacking and previous studies did not extensively examine executive functioning. OBJECTIVES: We examined whether baseline cognitive functioning predicts a change in employment status after 2 years, while taking into account mood, fatigue and disability level. METHODS: A total of 124 patients with relapsing-remitting MS (pwMS) and 60 healthy controls were included. They underwent neurological and neuropsychological examinations and completed online questionnaires. PwMS were divided into a stable and deteriorated employment status group (SES and DES), based on employment status 2 years after baseline. We first examined baseline differences between the SES and DES groups in cognitive functioning, mood, fatigue and disability level. A logistic regression analysis was performed, with change in employment status (SES/DES) as dependent variable. RESULTS: The DES group included 22% pwMS. Group differences were found in complex attention, executive functioning, self-reported cognitive functioning, fatigue and physical disability. More physical disability (OR = 1.90, p = 0.01) and lower executive functioning (OR = 0.30, p = 0.03) were retained as independent predictors of DES (R(2) = 0.22, p </= 0.001). CONCLUSIONS: Baseline physical disability and executive functioning, but none of the other variables, moderately predicted a deterioration in employment status 2 years later. TRIAL REGISTRATION: This observational study is registered under NL43098.008.12: 'Voorspellers van arbeidsparticipatie bij mensen met relapsing-remitting Multiple Sclerose'. This study is registered at the Dutch CCMO register (https://www.toetsingonline.nl).

van Gorp, D. A. M., van der Klink, J. J. L., Abma, F. I., et al. (2018). "The capability set for work - correlates of sustainable employability in workers with multiple sclerosis." Health Qual Life Outcomes **16**(1): 113.

> BACKGROUND: The aim of this study was to examine whether work capabilities differ between workers with Multiple Sclerosis (MS) and workers from the general population. The second aim was to investigate whether the capability set was related to work and health outcomes. METHODS: A total of 163 workers with MS from the MS@Work study and 163 workers from the general population were matched for gender, age, educational level and working hours. All participants completed online questionnaires on demographics, health and work functioning. The Capability Set for Work Questionnaire was used to explore whether a set of seven work values is considered valuable (A), is enabled in the work context (B), and can be achieved by the individual (C). When all three criteria are met a work value can be considered part of the individual's 'capability set'. RESULTS: Group differences and relationships with work and health outcomes were examined. Despite lower physical work functioning (U = 4250, p = 0.001), lower work ability (U = 10591, p = 0.006) and worse self-reported health (U = 9091, p </= 0.001) workers with MS had a larger capability set (U = 9649, p </= 0.001) than the general population. In workers with MS, a larger capability set was associated with better flexible work functioning (r = 0.30), work ability (r = 0.25), self-rated health (r = 0.25); and with less absenteeism (r = - 0.26), presenteeism (r = - 0.31), cognitive/neuropsychiatric impairment (r = - 0.35), depression (r = - 0.43), anxiety (r = - 0.31) and fatigue (r = - 0.34). CONCLUSIONS: Workers with MS have a larger capability set than workers from the general population. In workers with MS a larger capability set was associated with better work and health outcomes. TRIAL REGISTRATION: This observational study is registered under NL43098.008.12: 'Voorspellers van arbeidsparticipatie bij mensen met relapsing-remitting Multiple Sclerose'. The study is registered at the Dutch CCMO

register (https://www.toetsingonline.nl). This study is approved by the METC Brabant, 12 February 2014. First participants are enrolled 1(st) of March 2014.

Vijayasingham, L. (2018). "Work right to right work: An automythology of chronic illness and work." Chronic Illn **14**(1): 42-53.

Objectives Chronic illness is known to disrupt and redirect the usual course of work trajectories. This article aims to portray the longitudinal course of negotiating work after multiple sclerosis. Methods Using therapy and personal journals to reconstruct memories and experience, an autoethnography is produced and narrated within Campbell's "Hero's Journey" automythology framework. Results The narrative highlights the intrasubjectivity of illness meaning-the changing internal meaning-making and external behavior and decision-making dynamics. The journey of being inhibited to "Work Right", to "Looking for the Right" and ultimately, finding "Right Work" is charted; portrayed as a bittersweet maneuver to achieve work-illness equilibrium. Discussion This journey traverses a spectrum of negative coping-the exhibition of deviant work behaviors, disengagement and depression; to recalibration and renewal; culminating in living the "new normal", and finding moral and meaningful work engagements. Life trajectories with chronic illness are often skewed and redirected; but longitudinal narratives of normalization and coping also highlight the pursuits to secure and maintain a life of meaning and value.

Vijayasingham, L., Jogulu, U. et Allotey, P. (2017). "Work Change in Multiple Sclerosis as Motivated by the Pursuit of Illness-Work-Life Balance: A Qualitative Study." Mult Scler Int **2017**: 8010912.

Individuals with multiple sclerosis have a tendency to make early decisions for work change, even in reversible, episodic, or mild disease stages. To better understand how a multiple sclerosis (MS) diagnosis influences perceptions of work and motivations for work changes, we conducted a hermeneutic phenomenology study to explore the work lives of ten individuals with MS in Malaysia. The interpretive analysis and cumulative narratives depict an overarching change in their concept of ideal work and life aspirations and how participants make preemptive work changes to manage illness-work-life futures in subjectively meaningful ways. Discussions on their integrated pursuit of finding dynamic and subjective illness-work-life balance include reconciling the problem of hard work and stress on disease activity and progress, making positive lifestyle changes as health management behaviour, and the motivational influence of their own life and family roles: the consideration of their spouses, parents, and children. At an action level, work change was seen as moral and necessary for the management of illness futures. Our findings contribute insights on how individual perceptions and holistic life management decisions contribute to on-going and disrupted work trajectories, which can inform practice and policy on early interventions to support continued employment.

Vijayasingham, L., Jogulu, U. et Allotey, P. (2020). "Chronic illness and sustainable careers: How individuals with multiple sclerosis negotiate work transitions in a middle-income country." Soc Sci Med **245**: 112699.

Reports of work change and transitions are common amongst individuals with chronic illnesses such as multiple sclerosis (MS). However, there is little research on the lived experience of these work transitions. The scarcity of this research is particularly evident within low-and-middle-income countries, where protection laws and resources such as anti-discrimination laws and reasonable work modifications may not exist or be well enforced. In this paper, we explore how and why individuals with MS seek and achieve work transitions in the structural context of Malaysia. We interviewed ten working individuals with MS (July-december 2015) using a joint hermeneutic phenomenology and constructivist grounded theory approach. Using a broad conceptual lens of 'sustainable careers', we examine their careers as a series of experiences, decisions, and events, paying attention to the influences of context, time, their personal levels of agency and sense of meaning. Participants described work transitions as early as within the first year of diagnosis, that were prompted by voluntary, involuntary and semi-voluntary reasons. Key aspects of the process of seeking new roles included an exploration of alternative roles and paths, and then acquiring, trialing/adapting and remaining engaged in their new roles. Participants identified the perception and experience of 'being unemployable', based on how their diagnosis and short-term symptoms were responded to by employers. Nevertheless, participants used various strategies and career resources to obtain and maintain meaningful work roles. However, success in obtaining or maintaining new roles were not equally achieved. This research draws attention to the cumulative economic disadvantage of a chronic illness diagnosis, even at milder and episodic stages. Furthermore, it reiterates the need for cohesive structural protection in low-and-middle-income countries to facilitate a more equal ability to remain economically resilient and capable of engaging in meaningful long-term careers when living with a chronic illness.

Vijayasingham, L. et Mairami, F. F. (2018). "Employment of patients with multiple sclerosis: the influence of psychosocial-structural coping and context." Degener Neurol Neuromuscul Dis **8**: 15-24.

Patients with multiple sclerosis tend to report higher levels of work difficulties and negative outcomes, such as voluntary and involuntary work termination and reduced work participation. In this article, we discuss the complex interactions of disease, personal coping strategies, and social and structural factors that contribute to their work experiences and outcomes. An overview of the coping strategies and actions that leverage personal and context-level factors and dynamics is also provided to support the overall goal of continued work in patients with MS.

Wiberg, M., Friberg, E., Stenbeck, M., et al. (2015). "Sources and level of income among individuals with multiple sclerosis compared to the general population: A nationwide population-based study." Mult Scler **21**(13): 1730-1741.

INTRODUCTION: Multiple sclerosis (MS) is associated with reduced work capacity, but there is limited knowledge about MS patients' sources of income. OBJECTIVES: The purpose of this study was to elucidate MS patients' earnings and social benefits compared to those of the general population. METHODS: From nationwide registers of all residents in Sweden aged 21-64 years in 2010 (n=5,291,764), those with an MS diagnosis (n=13,979) were compared to a propensity score matched reference group (n=69,895). Descriptive statistics and regression models were used to estimate the percentage difference between the MS patients and the matched references regarding the following annual incomes: earnings, disability pension, sickness absence, disability allowance, unemployment compensation and social assistance. RESULTS: Both MS patients and the matched references received most of their income from earnings followed by disability pension and sickness absence. MS patients that were diagnosed in 2010 had 15% lower earnings than the matched references, while MS patients diagnosed before 2005 had 38% lower earnings. Corresponding figures regarding summed social benefits were 33% and 130% higher for MS patients, respectively. CONCLUSION: The results indicate that MS patients are overrepresented, in relative and absolute terms, regarding health-related benefits and have lower levels of earnings. However, the redistributing welfare systems appear to financially compensate the MS patients considerably.

Wiberg, M., Murley, C., Tinghog, P., et al. (2019). "Earnings among people with multiple sclerosis compared to references, in total and by educational level and type of occupation: a population-based cohort study at different points in time." BMJ Open **9**(7): e024836.

> OBJECTIVES: To investigate earnings among people with multiple sclerosis (PwMS) before and after MS diagnosis compared with people without MS, and if identified differences were associated with educational levels and types of occupations. Furthermore, to assess the proportions on sickness absence (SA) and disability pension (DP) in both groups. DESIGN: Population-based longitudinal cohort study, 10 years before until 5 years after MS diagnosis. SETTING: Working-age population using microdata linked from nationwide Swedish registers. PARTICIPANTS: Residents in Sweden in 2004 aged 30-54 years with MS diagnosed in 2003-2006 (n=2553), and references without MS (n=7584) randomly selected by stratified matching. OUTCOME MEASURES: Quartiles of earnings were calculated for each study year prior to and following the MS diagnosis. Mean earnings, by educational level and type of occupation, before and after diagnosis were compared using t-tests. Tobit regressions investigated the associations of earnings with individual characteristics. The proportions on SA and/or DP, by educational level and type of occupation, for the diagnosis year and 5 years later were compared. RESULTS: Differences in earnings between PwMS and references were observed beginning 1 year before diagnosis, and increased thereafter. PwMS had lower mean earnings for the diagnosis year (difference=SEK 28 000, p<0.05), and 5 years after diagnosis, this difference had more than doubled (p<0.05). These differences remained after including educational level and type of occupation. Overall, the earnings of PwMS with university education and/or more qualified occupations were most like their reference peers. The proportions on SA and DP were higher among PwMS than the references. CONCLUSIONS: The results suggest that the PwMS' earnings are lower than the references' beginning shortly before MS diagnosis, with this gap increasing thereafter. Besides SA and DP, the results indicate that educational level and type of occupation are influential determinants of the large heterogeneity of PwMS' earnings.

Wicks, C. R., Ward, K., Stroud, A., et al. (2016). "Multiple sclerosis and employment: Associations of psychological factors and work instability." J Rehabil Med **48**(9): 799-805.

> BACKGROUND: People with multiple sclerosis often stop working earlier than expected. Psychological factors may have an impact on job retention. Investigation may inform interventions to help people stay in work. OBJECTIVE: To investigate the associations between psychological factors and work instability in people with multiple sclerosis. METHODS: A multi-method, 2-phased study. Focus groups were held to identify key themes. Questionnaire packs using validated scales of the key themes were completed at baseline and at 8-month follow-up. RESULTS: Four key psychological themes emerged. Out of 208 study subjects 57.2% reported medium/high risk of job loss, with marginal changes at 8 months. Some psychological variables fluctuated significantly, e.g. depression fell from 24.6% to 14.5%. Work instability and anxiety and depression were strongly correlated (chi2 p < 0.001). Those with probable depression at baseline had 7.1 times increased odds of medium/high work instability, and baseline depression levels also predicted later work instability (Hosmer-Lemeshow test 0.899; Nagelkerke R Square 0.579). CONCLUSION: Psychological factors fluctuated over the 8-month follow-up period. Some psychological variables, including anxiety and depression, were significantly associated with, and predictive of, work instability. Longitudinal analysis should further identify how these psychological attributes impact on work instability and potential job loss in the longer term.

Wickstrom, A., Dahle, C., Vrethem, M., et al. (2014). "Reduced sick leave in multiple sclerosis after one year of natalizumab treatment. A prospective ad hoc analysis of the TYNERGY trial." Mult Scler **20**(8): 1095-1101.

> BACKGROUND: In a retrospective study, we have previously shown that work ability was improved after the initiation of natalizumab treatment in relapsing-remitting multiple sclerosis (RRMS). In another prospective trial (TYNERGY) the effect on MS-related fatigue was evaluated after 12 months of treatment with natalizumab. A comprehensive Capacity for Work Questionnaire (CWQ) was used to collect data regarding number of working hours and sickness absence. The predefined intention-to-treat analysis regarding work ability did not, however, show significant results. OBJECTIVES: The objective of this paper is to assess the amount of sick leave in RRMS before and after one year of natalizumab treatment and correlate it to fatigue and walking ability. METHODS: This is a post-hoc analysis of the complete data from the CWQ used in the TYNERGY trial. RESULTS: MS patients receiving sickness benefit before start of treatment reduced their sickness benefit by an absolute change of 33% after one year of natalizumab treatment. Younger age and improvement of walking ability correlated significantly with reduction of sick leave. CONCLUSIONS: This ad-hoc analysis of prospectively collected data supported our previous retrospective study and thus indicates a positive relationship between natalizumab treatment and improvement in work ability.

Wickstrom, A., Nystrom, J. et Svenningsson, A. (2013). "Improved ability to work after one year of natalizumab treatment in multiple sclerosis. Analysis of disease-specific and work-related factors that influence the effect of treatment." Mult Scler **19**(5): 622-630.

> BACKGROUND: Multiple sclerosis (MS) constitutes one of the major diseases that leads to neurological impairment and as a consequence also reduces ability to work. OBJECTIVES: The purpose of this study was to analyze possible effects on work ability resulting from highly active anti-inflammatory treatment in MS. METHODS: We analyzed the effects of introducing an anti-inflammatory treatment, natalizumab, in MS, on factors related to work ability. This was done through a comprehensive questionnaire distributed to all patients in Sweden starting on natalizumab treatment between June 2007 and May 2008, identified via the Swedish National MS registry. RESULTS: MS patients who were receiving sickness benefit and were treated with natalizumab approximately doubled their working ability in relation to their total employment rate. We also documented a significant improvement of their ability to cope with work-related requirements after one year of natalizumab treatment, an improvement which was independent of the previous level of employment. Predictors of a positive effect on work ability were short disease duration, younger age and lower Expanded Disability Status Scale (EDSS) grade at treatment onset. CONCLUSIONS: Our data support the notion that early inflammatory control in MS is essential to preserve a healthy state in MS that counteracts the negative consequences of the disease both at a personal and at a societal level.

Wickstrom, A., Sundstrom, P., Wickstrom, L., et al. (2015). "Improved working ability in a contemporary MS population compared with a historic non-treated MS population in the same geographic area of Sweden." Mult Scler J Exp Transl Clin **1**: 2055217315608203.

> BACKGROUND: Multiple sclerosis (MS) often causes a reduced ability to work. Improved disease control as well as adjustment of working conditions may improve work ability in MS. OBJECTIVES: The objective of this article is to compare the degree of sickness absence in two MS populations that either have or have not received disease-modifying drug (DMD) treatments or active work-promoting measures. METHODS: We investigated the occurrence

of sickness absence in MS patients living in Vasterbotten County, Sweden, in 2013, in which the majority of MS patients receive DMD treatment. The result was compared with a previous survey in the same area during a period when no DMD was available and no work-promoting measures for MS patients were practiced. RESULTS: The proportion of MS patients active in the labor market or studying increased from 38% to 70% in the contemporary compared with the historic population (p < 0.001). The proportion of MS patients with a full-time disability pension decreased from 27% to 12% (p < 0.001). There was a significant decrease of sickness absence in several individual EDSS grades. CONCLUSIONS: Our data indicate that treatment with DMDs combined with active work-promoting measures lead to improved work ability in MS.

Yorkston, K. M., Johnson, K., Klasner, E. R., et al. (2003). "Getting the work done: a qualitative study of individuals with multiple sclerosis." Disabil Rehabil **25**(8): 369-379.

THE PROBLEM: Work can be defined as an activity performed to accomplish something in the presence of obstacles that may make accomplishing the goal difficult. For individuals with MS, work is not only limited by physical impairments but also by factors such as fatigue and cognitive changes PURPOSE: The aim of this study is to examine the experiences of individuals with mild to moderate MS as they carry out everyday work activities both inside and outside the home. METHOD: Eleven women and three men were recruited from the community to participate in a series of semi-structured interviews. Using qualitative research methodology that examined the experiences of the participants, two major themes and seven subthemes emerged. RESULTS: The first theme, Defining the work, included Priorities: seeing what's important; Plans: learning about resources and requirements; and PERSPECTIVES: fixing it yourself. The second theme, Changing how things get done, includes Precipitating factors; Awareness; Constructing the strategies; and Evaluating the strategies. CONCLUSIONS: Individuals with MS develop strategies and utilize resources in order to get the work done. Comparisons are made between existing intervention theories or programmes and the experiences described by participants in this study.