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ABSTRACT

Background: Little is known about the association between the socioeconomic status (SES) and disability risk of patients with Multiple Sclerosis (MS).

Objective: The aim of this study was to assess the influence of low SES, otherwise known as socioeconomic deprivation, on the disability risk of MS patients.

Methods: 4498 patients with a relapsing MS disease onset between 1982 and 2017 were included from the databases of three MS expert centres (Caen, Rouen, Lille) of the French Observatory for MS (OFSEP). Sociodemographic and clinical data of 3641 patients were used for the analysis. The EDI (European Deprivation Index), an ecological and composite indicator was used to assess the level of socioeconomic deprivation. Comparisons of time to reach EDSS 4 and EDSS 6, chosen as disability milestones, according to EDI quintiles were performed by Kaplan-Meier analysis. Cox proportional hazard models were also conducted to assess the risk according to EDI quintiles with adjustment to sex, MS type and age at disease onset.

Results: In the study population (n=3641), most patients were women (71.9%; n =2664). The mean age at disease onset was 32.2 years (SD =9.7). 1684 (46%) patients reached EDSS 4 and 1005 (28%) reached EDSS 6. The risk of reaching EDSS 4 and EDSS 6 in more socioeconomically deprived patients (EDI Q5) was independently higher than in the less socioeconomically deprived patients (EDI Q1) (HR=1.37 95%CI [1.15-1.64]) to reach EDSS 4 and (HR=1.42 95%CI [1.13-1.75]) to reach EDSS 6.

Conclusions: In this study, socioeconomic deprivation was significantly associated to the disability risk in MS patients. Better knowledge of socioeconomic disparities in MS may help adapt care to settings and improve the quality of care given to patients in the future.

1 INTRODUCTION

Socioeconomic status (SES) is closely linked to modifiable risk factors, including the geographical, social and educational environment which impact a patients' health (Chen and Miller, 2013). SES has a profound influence on the access to healthcare and has been associated with the incidence and course of disability, including mortality, in the general population of many chronic diseases such as diabetes, cancer, kidney disease and infectious and cardiovascular diseases (Pérez-Hernández et al., 2019; Wändell et al., 2016; Zghebi et al., 2017).

In Multiple Sclerosis (MS), low SES, otherwise known as socioeconomic deprivation, has shown to be a risk factor of MS in large cohorts of MS patients (Bjørnevik and al., 2016; Briggs and al., 2014; Nielsen and al., 2013). Moreover, some studies have shown a relationship between ethnicity and disability which have beenconnected to low SES. For example, first-and second-generation North African immigrants to France reached Expanded Disability Status Scale (EDSS) 4 and 6 sooner than patients of European descent (Sidhom and al., 2017). Additionally, a study conducted in the US that used the North American Research Committee on Multiple Sclerosis (NARCOMS) data, highlighted that African Americans had a greater risk of disability than Caucasians Americans, and failure to perform adjustment for the SES would overestimate the association with disability by up to 25% (Marrie and al., 2006). Immigration has also been a well-known factor of socioeconomic vulnerability, and SES may play a role in this process (Nazroo, 2003).

The association of SES with the risk of disability has only been investigated in a few studies, to date. Besides lifestyle factors, such as smoking and comorbidities, some studies have shown the effect of SES on the progression of disability (Briggs et al., 2019; Harding et al., 2019). Therefore, SES may impact the disability risk in MS patients, in addition to factors such as age at MS onset, early relapses and time to progression (Manouchehrinia and al., 2017; Scalfari and al., 2013).

The objective of this study was to investigate whether a low SES estimated by the European Deprivation Index (EDI) (Pornet et al., 2012), a relevant proxy used to assess the level of socioeconomic deprivation, was associated with the disability risk in a large cohort of MS patients.

2 MATERIAL AND METHODS

2.1 Study population

The French MS Observatory (OFSEP) comprises of 23 centres, each of which use the European Database for Multiple Sclerosis (EDMUS) (Cotton and al., 2015). Data were extracted from three of these centres in the Hauts-de-France (Lille) and Normandy regions (Caen, Rouen). Patients over 15 years of age with an RRMS onset (RR and SP types), diagnosed according to the Poser and McDonald 2001, and the 2005 criteria between January1st, 1982 and January 1st, 2017 were used in this study (N=4498) **(Figure 1).**

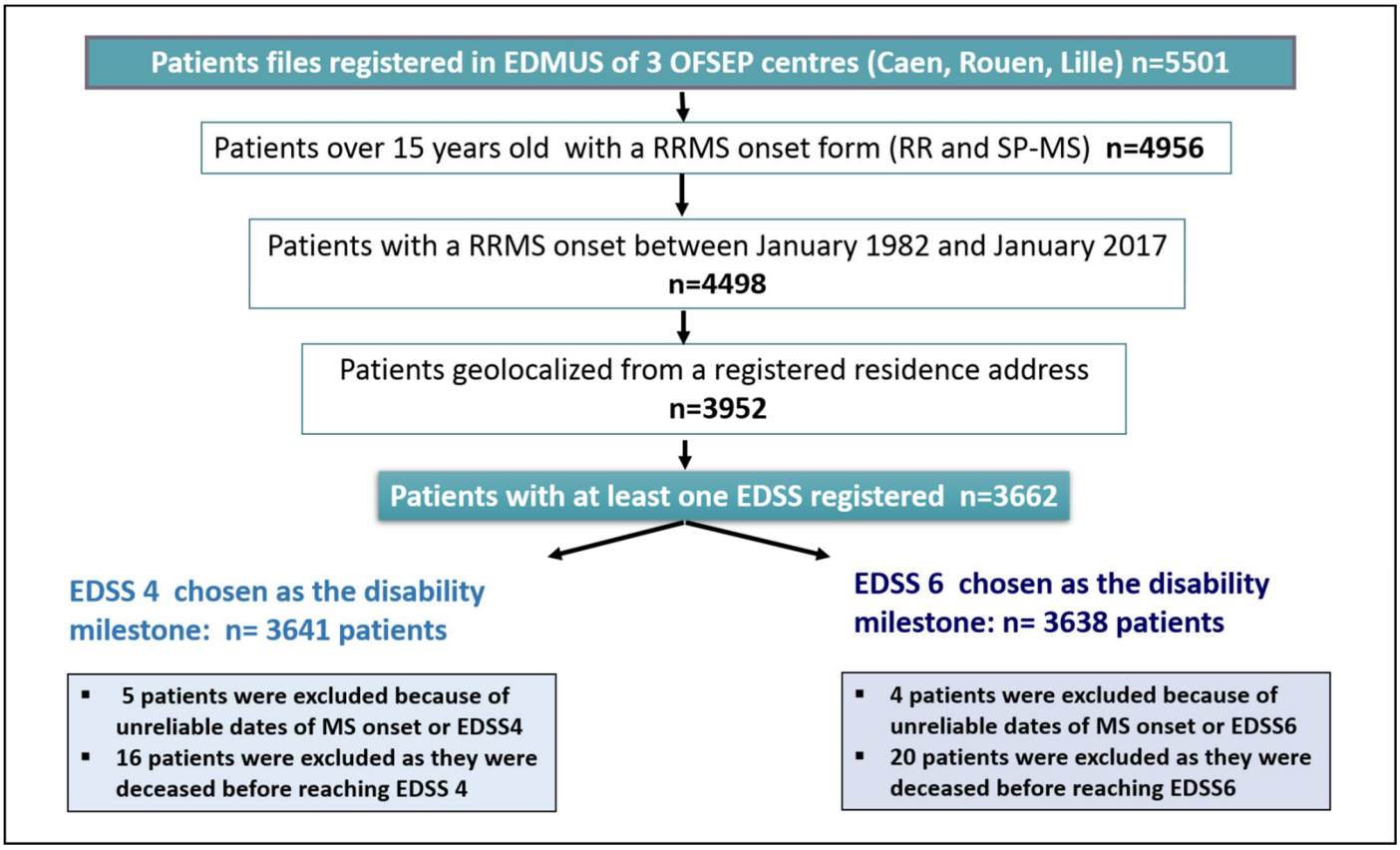


Figure 1: Flow chart of the study population extracted from the EDMUS of three OFSEP centres in Caen, Rouen and Lille in France to investigate whether socioeconomic status was associated with the disability risk of multiple sclerosis patients from January 1982 to January 2017
DMT: Disease-Modifying Treatment; EDSS: Expanded Disability Status Scale; MS: Multiple Sclerosis
OFSEP: French Observatory for MS; RR: Relapsing-remitting; SP: Secondary Progressive

For each centre, data collection in the EDMUS database and its use for clinical and epidemiological research were approved by the French National Ethics Committee, *Commission Nationale de l'Informatique et des Libertés:* CNIL-N° 1024268 (Caen), CNIL-N° 1634682 (Rouen), CNIL-N° 1177070 (Lille).

2.2 Socioeconomic status assessment

The socioeconomic indicator was based on each patient's place of residence geolocated according to the Geographic Information System (GIS ARCGIS 10.2®) version and assigned to an "*Ilot Regroupé pour l'Information Statistique"* (IRIS) which is the smallest French geographic unit for which census data are available. The EDI in France was used to attribute a socioeconomic deprivation score to the IRIS (Pornet and al., 2012). The EDI is a composite indicator based on the concept of relative poverty calculated from 10 weighted variables referring to both objective and subjective poverty. Variables were chosen from the EU-SILC 2011 (European Statistics on Income and Living Conditions) survey on poverty and were matched with the national census survey (Arora et al., 2015). The EDI, as a categorical variable, was used for the purpose of comparison with other studies. EDIs were distributed into quintiles calculated according to its national distribution. An EDI used as the SES indicator at neighbourhood level was attributed to 3952 patients.

2.3 Disability milestone assessment

In this study, two disability milestones were used: EDSS 4 and EDSS 6. The main variable was defined as the delay (in years) between MS onset and the date at which EDSS 4 and EDSS 6 were reached**.** If the first EDSS recorded was equal to 4 (n=248; 6.8%) or 6 (n=209 5.7%), the delay was considered equal to half a day. If the first EDSS entered was greater than 4 or 6 then the delay was right-censored. If the date of EDSS 4 (n=346) or of EDSS 6 (n=123) was not recorded, then the median date was calculated between the previous and next date of recorded EDSS value and date. The event of interest for the analysis was to reach EDSS 4 or EDSS 6. For patients who never reached EDSS 4 or EDSS 6, the delay was censored on the date of the last EDSS recorded. Four case types were used to assess the censoring of milestones (**Figure 2**).

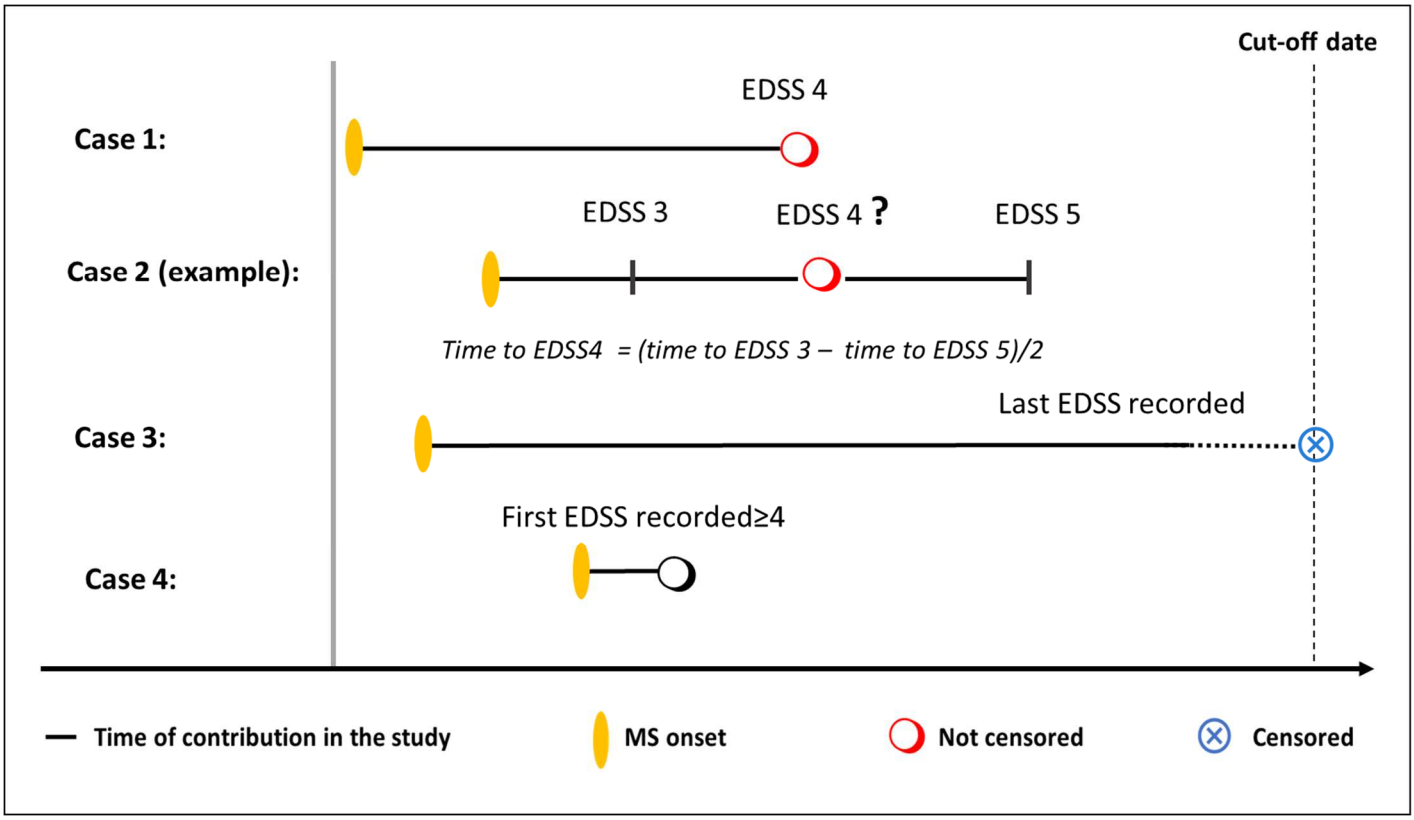


Figure 2: Disability milestone assessment strategy used to determine the censoring of the EDSS 4 milestone and EDSS 6 milestone, as the event of interest.
EDSS: Expanded Disability Status Scale; MS: Multiple Sclerosis

2.4 Statistical analysis

The end of inclusion date was set to ensure the completeness of the data. The cut-off date was set at the end of June 2017. Due to incoherent dates of events (EDSS 4 or EDSS6 attainment) or to death before the event the number of patients excluded from the study populations were slightly different between analysis with EDSS 4 and EDSS 6 (**Figure 1**).

The Kaplan-Meier (KM) estimator was used to obtain a graphical representation of the different categorical variables: sex, MS types, age at disease onset, number of relapses in the first two years, number of Disease-Modifying Treatments (DMT), and EDI quintiles. For each stratified univariate KM, a log-rank test was performed to detect any differences between the population groups in the probability of reaching EDSS 4 and reaching EDSS 6 in the KM analysis.

A series of adjusted multivariate Cox proportional hazard models were performed with the attainment of EDSS 4 as a dependent variable and EDI quintiles as independent variables. The following covariates were used as other independent adjustment variables: sex , age at disease-onset, MS-form at cut-off date on 31

June 2017, the number of relapses in the first two years of disease-onset and the number of DMT initiated before reaching EDSS 4 or EDSS 6 by default at the date of the last recorded EDSS.

Two sensitivity analyses were performed, one on 3295 patients with recorded dates of EDSS 4 and the other on 3515 patients with recorded dates of EDSS 6 **(see supplementary material 1)**.

Two different subgroup analyses were also performed, with the same multivariate Cox model, with the first limited to the analysis to RRMS patients at the cut-off date and the second to patients who were treated with a DMT.

All statistical analyses were performed using SAS version 9.4 and STATA IC/SE 14. A p-value ≤0,05 was considered significant.

3 RESULTS

The characteristics of the study population according to EDSS 4 (n=3641) or EDSS 6 (n=3638), including median delays to reach them, are summarised in **Table 1**.

3.1 Influence of socioeconomic deprivation on time to reach EDSS 4

The median time to reach EDSS 4 was 2.79 years less for patients in quintile 5 than for those in quintile 1 **(Table 1 and Figure 3).** The hazard ratio for reaching EDSS 4 gradually increased according to the level of socioeconomic deprivation (p-trend < 0.0001): quintile 2 (HR=0.93 95% CI [0.77-1.13]), quintile 3 (HR=1.11 95% CI [0.93-1.33]), quintile 4 (HR=1.15 95% CI [0.97-1.13]), and quintile 5 (HR=1.37 95% CI [1.17-1.60]).

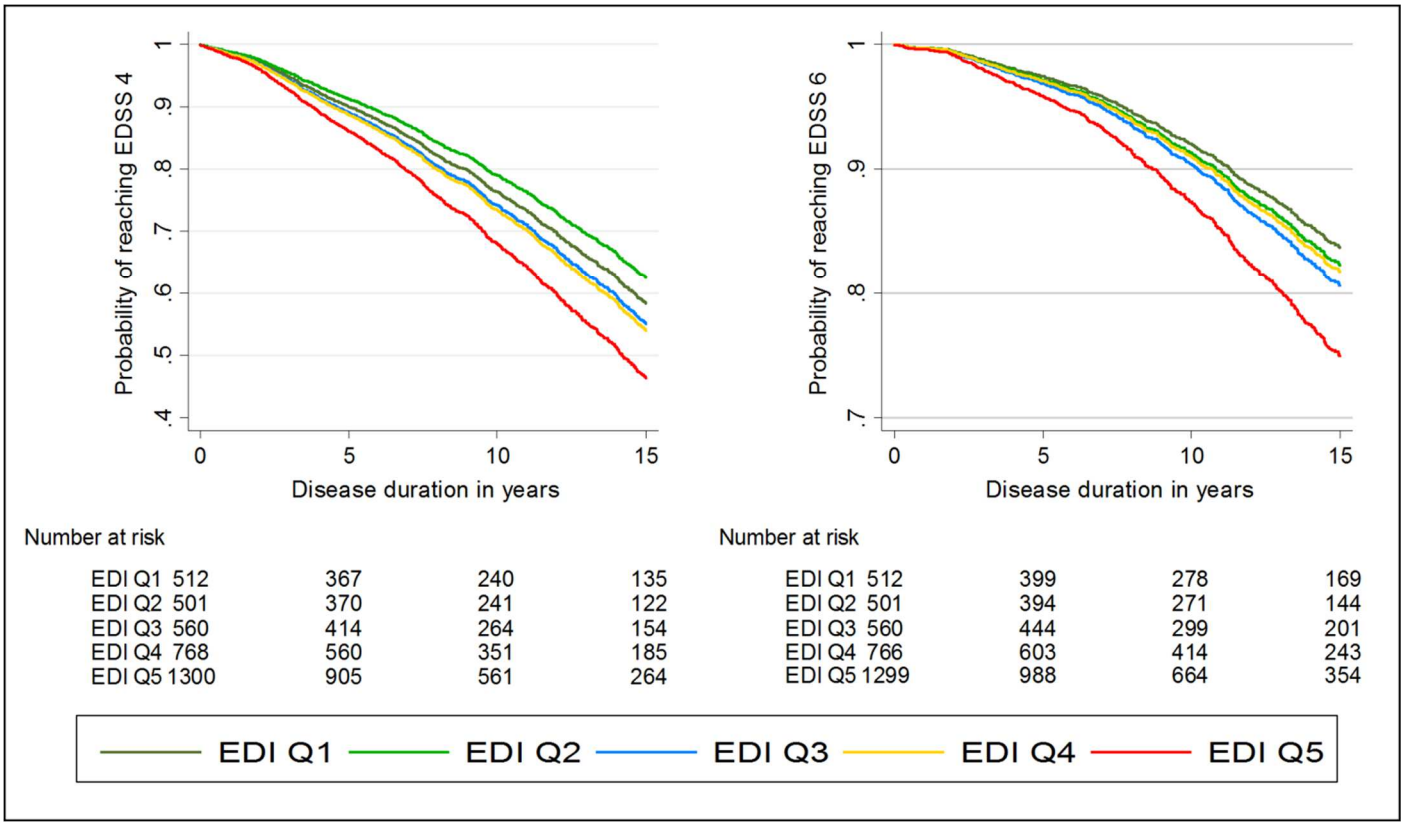


Figure 3: Influence of socioeconomic deprivation on disability risk in MS patients. Adjusted multivariate Cox proportional estimates for risk of reaching EDSS 4 (left part) and EDSS 6 (right part). EDI quintiles used as level of deprivation.
EDSS: Expanded Disability Status Scale; EDI: European Deprivation Index

In multivariate analyses with adjustment for sex, MS types, age at MS onset, and the number of relapses in the first two years of the disease, a continuous trend was observed from the lowest to highest EDI with respect to the association with the risk of reaching EDSS 4 (p-trend<0.001). Higher EDI scores, i.e. those in quintiles 4 and 5, were significantly associated with a higher risk of reaching EDSS 4 compared to those in quintile 1 with EDI-Q4 HR=1.20 95% CI [1.01-1.42] and EDI-Q5 HR=1.44 95% CI [1.23-1.68]. After additional adjustment for the number of DMT, the risk of reaching EDSS 4 increased significantly and gradually with the level of socioeconomic deprivation, from a low (quintiles 1 and 2), to moderate (quintiles 3 and 4) HR=1.19 95% CI [1.00-1.40] to high level of socioeconomic deprivation (quintile 5) HR=1.40 95% CI [1.20-1.64] **(Table 2 and Figure 3).**

Considering only RR-MS patients independently from the adjustment for the other covariates, a continuous trend was observed from the lowest to highest quintile, with respect to the association to the risk

of reaching EDSS 4 (p-trend<0.001). The highest EDI score (quintile 5) was significantly associated with a higher risk of reaching EDSS 4 compared to the lowest level of deprivation, HR=1.44 95% CI [1.17-1.77].

When performing the same multivariate Cox model with the subgroup of patients who were treated with at least one DMT, a similar continuous trend was found from the lowest to highest quintile.

The risk of reaching EDSS 4 in more socioeconomically deprived patients (EDI Q5) was significantly higher than for the least socioeconomically deprived patients (EDI Q1) (HR=1.37 95%CI [1.15-1.64]).

3.2 Influence of socioeconomic deprivation on delay to reach EDSS 6

Compared to the quintile 1 patients, the median time to reach EDSS 6 was 1.5 years less for quintile 5 patients **(Table 1).** The hazard ratio for reaching EDSS 6 was also significantly higher (HR=1.32 95% CI [1.09-1.61]).

When sex , MS type and age at MS onset, the number of relapses in the first two years of the disease were used as covariates in the multivariate analysis, the highest EDI scores, i.e. those in quintile 5 were significantly associated with a higher risk of reaching EDSS 6 compare to quintile 1, EDI-quintile 5 HR=1.39 95% CI [1.14-1.70]. When an additional adjustment for the number of DMT was performed, the association between EDI-quintile 5 and disability risk was similar **(Table 2)**.

When SP-MS patients were excluded from the multivariate analysis, the highest EDI scores, i.e. those in quintile 5, remained significantly associated with a higher risk of reaching EDSS 6 than patients in quintile 1: HR=1.41 95% CI [1.03-1.93].

In the subgroup of patients who were treated with at least one DMT, the most socioeconomically deprived patients had a significantly higher risk of reaching EDSS 6 than patients in quintile 1: EDI quintile 5 HR=1.42 95% CI [1.13-1.75].

4 DISCUSSION

Socioeconomic deprivation was strongly associated with the increased risk of disability in MS patients at different stages of the disease. Socioeconomic deprivation was independently associated with the disability risk in regard to reaching EDSS 4 and EDSS 6, which are key disability milestones. The highest level of social deprivation was significantly associated with a higher disability risk after the adjustment of other main factors that contribute to disability.

More than 3600 MS patients from the three OFSEP centres in two different regions in France were included. The three MS reference centres operate in a moderate-to-high incidence area for MS. The same guidelines for data acquisition and management were applied in all cities to ensure quality and relevance of the OFSEP (Vukusic and al., 2018). This MS population is representative of the French MS population **(see supplementary material 2)**.

To date, the influence of SES has received little attention among the numerous predisposing factors of MS severity. D'hooghe and al. (D'hooghe and al., 2016) demonstrated an association between SES, rated by self-reported level of education and progression of disability in a Belgian MS cohort, which was consistent and complementary to our findings. The study showed, having more than 12 years of education was a protective factor for reaching EDSS 6 in patients with a relapsing-remitting onset. However, the study may have suffered from a selection bias due to a 57 % non-response rate, and a higher rate of responses coming from patients who had received more education may have occurred. A study based on more representative data from British Columbia (CA) in Canada and the United Kingdom (UK), demonstrated that lower neighbourhood-level SES was associated with a higher risk of disability progression (Harding et al., 2019). These authors were, according to our knowledge, the first to use population base data for investigating the relation between SES and disability risk. In France, socioeconomic inequalities have been shown to be greater compared to other Western European countries (Mackenbach and al., 2008). Even though future international studies are required for an accurate comparison, existing results suggest that social inequalities are more prominent in France.

There were some strengths in this study. The first was that two disability milestones were assessed in a large population that demonstrated the influence of socioeconomic deprivation at different stages of disability. Secondly, the EDI which is an ecological and composite proxy of SES avoids selection bias and includes the effect of the socioeconomic environment that an individual indicator cannot provide (Ribet and al., 2007). The EDI may be a reliable indicator to use in this kind of study for different chronic diseases and many European countries (Guillaume and al., 2016).

The relation between SES and disability risk cannot be explained simply and is probably the consequence of complex interactions between biological mechanisms, lifestyles and the healthcare system. An adverse SES at an early age seems to facilitate biological pathways that lead to a pro-inflammatory profile persisting at adult age (Keita et al., 2014; Miller et al., 2009; Pietras and Goodman, 2013). This may be the case in MS as a low SES has been shown to be a risk factor for MS in large population and/or cohort studies (Briggs and al., 2014; Nielsen and al., 2013; Bjørnevik and al., 2016).

Amongst factors that depended directly or indirectly on SES, some were more pertinent in MS. In many chronic diseases, diagnostic delay has been shown to be longer for the less socioeconomically privileged. Extended delays to presentation and/or diagnosis seemed to be associated with a poorer outcome in many conditions. Time from referral to neurology consultation in MS may be very long for various reasons that have not been clearly identified (Kelly and al., 2011).

Diagnostic delay has also been known to increase if obesity, smoking, or physical or mental comorbidities are present (Marrie and al., 2009), since SES is associated with more comorbidities. The time between symptom onset and diagnosis may have been delayed by patients and/or physician mistakenly attributing MS symptoms to pre-existing diseases.

In the general population, lower SES was linked to a higher disability risk (Minkler and al., 2006) and multiple comorbidities. In a study based on the large MS population registry NARCOMS, low SES was associated with an increased probability of any physical comorbidities (Marrie and al., 2008). As comorbidities were not recorded in this study database, it was not taken as an adjustment criterion. Communication between doctors and patients may have been another major aspect of care quality,

especially in chronic diseases where a long-term follow-up is required. A low SES generally linked with a low level of education may have made it difficult for some patients to understand health-related information and conditioned their participation in treatment decisions (Willems and al., 2005). Moreover, patients with a low SES were thought to have poorer attendance at medical appointments, to be less involved in their medical follow-up (Minden and al., 2008) and to have less constructive dialogue with physicians than patients with higher SES (Chiovetti, 2006). This may have contributed to differences in disease outcomes and partly explain the higher risk of early disability in more socioeconomically deprived patients.

Socioeconomic disparities in access to treatment of MS patients were demonstrated in two previous studies. One found that being from a socioeconomically deprived area significantly reduced the probability of receiving a DMT prescription (Owens and al., 2013) and another demonstrated that SES in RR-MS patients influenced access to a second-line DMT (Calocer and al., 2018). The second studies results did not subsequently differ when they were adjusted for the number of DMT in the analysis, and the access to DMT could not account entirely for the association between low SES and a disability risk.

Clinically, MS is a two-stage disease, defined in the first stage by focal inflammation and in the second by neurodegeneration and diffuse inflammation that lead to the progressive phase (Leray and al., 2010). The influence of DMT on decreasing the disability risk was significant for reaching EDSS 4 but not for EDSS 6. This finding was consistent with previous studies showing that DMT reduces the risk of reaching EDSS 3 and to a lesser extent the risk of reaching EDSS 6, if patient were treated before EDSS 3 (Cocco and al., 2015).

The beneficial effect of treatment on disability risk in treated patients with a DMT is probably due to two reasons. First, the time of DMT exposure was not taken into account and therefore, a short DMT followed by a period with no treatment was considered as receiving DMT. Secondly, having more than one treatment may have led to a better response to breakthrough disease.

There were a few limitations to this study. As time to progression was somewhat uncertain and subject to the evolution of various criteria over time (Lorscheider and al., 2016), the clinical phase at the cut-off date was used and not for the one at the date of the event. However, the association found between SES and

disability risk was ensured to be the same when analysis was conducted only on RRMS patients. To deal with the missing information about EDSS values and dates, an approximation of the median time was made, so as to consider the evolution of disability as a constant, which was not like the natural course of MS that has a non-linear progression. The proportion of patients with this missing information was similar in all quintiles, so the consequences on the outcomes of this imputation may be neglected. To ensure the credibility of the results, two sensitivity analyses were performed in which patients with unknown dates of EDSS 4 or EDSS 6 were removed. The pattern of the association was very similar **(see supplementary material 1)**.

Expressing SES with the EDI, which includes aggregated data at a small population level, may have led to an ecological bias (Greenland and Morgenstern, 1989). Considering the proximal social environment of a place of residence is a pragmatic solution used in numerous countries. Since the 1990s, many deprivation indices (e.g. Townsend, Carstairs, IMD, Quebec Index of Material and Social Deprivation and EDI) linked to small areas and based on aggregated data have shown their validity, reliability, and responsiveness for use in public health research. Moreover, besides the effect of the individual characteristics of SES, the effect of neighbourhood, i.e. contextual effect, has been highlighted in numerous studies (Diez Roux, 2016). Therefore, ecological indicators capture a part of the socioeconomic environment.

Information on the address of residence was initially extracted at the time when data on patients were first registered in the population-based database. As the residential history was not saved in the database, the SES may have changed over time. It may be worth to perform studies in the future to consider the residential history and disease course of MS patient during a long-term period.

In conclusion, this study showed that socioeconomic deprivation contributed to disability risk in MS patients. The mechanism linking socioeconomic deprivation and disability risk in MS should be further investigated by focusing on access to care, as well as, patients' health behaviours. Physicians working in MS expert centres and care networks should take the present findings into account when treating low SES patients, in order to adapt their care.

REFERENCES

Arora, V.S., Karanikolos, M., Clair, A., Reeves, A., Stuckler, D., McKee, M., 2015. Data Resource Profile: The European Union Statistics on Income and Living Conditions (EU-SILC). Int. J. Epidemiol. 44, 451–461. https://doi.org/10.1093/ije/dyv069

Bjørnevik, K., Riise, T., Benjaminsen, E., Celius, E.G., Dahl, O.P., Kampman, M.T., Løken-Amsrud, K.I., Midgard, R., Myhr, K.-M., Torkildsen, Ø., Vatne, A., Grytten, N., 2016. Level of education and multiple sclerosis risk over a 50-year period: Registry-based sibling study. Mult. Scler. J. 22, 104–111. https://doi.org/10.1177/1352458516646863

Briggs, F.B.S., Acuña, B.S., Shen, L., Bellesis, K.H., Ramsay, P.P., Quach, H., Bernstein, A., Schaefer, C., Barcellos, L.F., 2014. Adverse socioeconomic position during the life course is associated with multiple sclerosis. J. Epidemiol. Community Health 68, 622–629. https://doi.org/10.1136/jech-2013-203184

Briggs, F.B.S., Thompson, N.R., Conway, D.S., 2019. Prognostic factors of disability in relapsing remitting multiple sclerosis. Mult. Scler. Relat. Disord. 30, 9–16. https://doi.org/10.1016/j.msard.2019.01.045

Calocer, F., Dejardin, O., Droulon, K., Launoy, G., Defer, G., 2018. Socio-economic status influences access to second-line disease modifying treatment in Relapsing Remitting Multiple Sclerosis patients. PLOS ONE 13, e0191646. https://doi.org/10.1371/journal.pone.0191646

Chen, E., Miller, G.E., 2013. Socioeconomic status and health: mediating and moderating factors. Annu. Rev. Clin. Psychol. 9, 723–749. https://doi.org/10.1146/annurev-clinpsy-050212-185634

Chiovetti, A., 2006. Bridging the gap between health literacy and patient education for people with multiple sclerosis. J. Neurosci. Nurs. J. Am. Assoc. Neurosci. Nurses 38, 374–378.

Cocco, E., Sardu, C., Spinicci, G., Musu, L., Massa, R., Frau, J., Lorefice, L., Fenu, G., Coghe, G., Massole, S., Maioli, M.A., Piras, R., Melis, M., Porcu, G., Mamusa, E., Carboni, N., Contu, P., Marrosu, M.G., 2015. Influence of treatments in multiple sclerosis disability: A cohort study. Mult. Scler. J. 21, 433–441. https://doi.org/10.1177/1352458514546788

Cotton, F., Kremer, S., Hannoun, S., Vukusic, S., Dousset, V., Imaging Working Group of the Observatoire Français de la Sclérose en Plaques, 2015. OFSEP, a nationwide cohort of people with multiple sclerosis: Consensus minimal MRI protocol. J. Neuroradiol. J. Neuroradiol. 42, 133–140. https://doi.org/10.1016/j.neurad.2014.12.001

D'hooghe, M.B., Haentjens, P., Van Remoortel, A., De Keyser, J., Nagels, G., 2016. Self-reported levels of education and disability progression in multiple sclerosis. Acta Neurol. Scand. 134, 414–419. https://doi.org/10.1111/ane.12555

Diez Roux, A.V., 2016. Neighborhoods and Health: What Do We Know? What Should We Do? Am. J. Public Health 106, 430–431. https://doi.org/10.2105/AJPH.2016.303064

Greenland, S., Morgenstern, H., 1989. Ecological Bias, Confounding, and Effect Modification. Int. J. Epidemiol. 18, 269–274. https://doi.org/10.1093/ije/18.1.269

Guillaume, E., Pornet, C., Dejardin, O., Launay, L., Lillini, R., Vercelli, M., Marí-Dell'Olmo, M., Fernández Fontelo, A., Borrell, C., Ribeiro, A.I., Pina, M.F. de, Mayer, A., Delpierre, C., Rachet, B., Launoy, G., 2016. Development of a cross-cultural deprivation index in five European countries. J. Epidemiol. Community Health 70, 493–499. https://doi.org/10.1136/jech-2015-205729

Harding, K.E., Wardle, M., Carruthers, R., Robertson, N., Zhu, F., Kingwell, E., Tremlett, H., 2019. Socioeconomic status and disability progression in multiple sclerosis: A multinational study. Neurology 92, 1–10. https://doi.org/10.1212/WNL.0000000000007190

Keita, A.D., Judd, S.E., Howard, V.J., Carson, A.P., Ard, J.D., Fernandez, J.R., 2014. Associations of neighborhood area level deprivation with the metabolic syndrome and inflammation among middle- and older- age adults. BMC Public Health 14, 13–19. https://doi.org/10.1186/1471-2458-14-1319

Kelly, S.B., Chaila, E., Kinsella, K., Duggan, M., McGuigan, C., Tubridy, N., Hutchinson, M., 2011. Multiple sclerosis, from referral to confirmed diagnosis: an audit of clinical practice. Mult. Scler. J. 17, 1017–1021. https://doi.org/10.1177/1352458511403643

Leray, E., Yaouanq, J., Le Page, E., Coustans, M., Laplaud, D., Oger, J., Edan, G., 2010. Evidence for a two-stage disability progression in multiple sclerosis. Brain 133, 1900–1913. https://doi.org/10.1093/brain/awq076

Lorscheider, J., Buzzard, K., Jokubaitis, V., Spelman, T., Havrdova, E., Horakova, D., Trojano, M., Izquierdo, G., Girard, M., Duquette, P., Prat, A., Lugaresi, A., Grand'Maison, F., Grammond, P., Hupperts, R., Alroughani, R., Sola,

P., Boz, C., Pucci, E., Lechner-Scott, J., Bergamaschi, R., Oreja-Guevara, C., Iuliano, G., Van Pesch, V., Granella, F., Ramo-Tello, C., Spitaleri, D., Petersen, T., Slee, M., Verheul, F., Ampapa, R., Amato, M.P., McCombe, P., Vucic, S., Sánchez Menoyo, J.L., Cristiano, E., Barnett, M.H., Hodgkinson, S., Olascoaga, J., Saladino, M.L., Gray, O., Shaw, C., Moore, F., Butzkueven, H., Kalincik, T., MSBase Study Group, 2016. Defining secondary progressive multiple sclerosis. Brain J. Neurol. 139, 2395–2405. https://doi.org/10.1093/brain/aww173

Mackenbach, J.P., Stirbu, I., Roskam, A.J., Schaap, M.M., Menvielle, G., Leinsalu, M., Kunst, A.E., Health, E.U.W.G. on S.I. in, 2008. Socioeconomic inequalities in health in 22 European countries. N Engl J Med 358, 2468–81. https://doi.org/10.1056/NEJMsa0707519

Manouchehrinia, A., Westerlind, H., Kingwell, E., Zhu, F., Carruthers, R., Ramanujam, R., Ban, M., Glaser, A., Sawcer, S., Tremlett, H., 2017. Age related multiple sclerosis severity score: Disability ranked by age. Mult. Scler. J. 23, 1938–1946.

Marrie, R.A., Cutter, G., Tyry, T., Vollmer, T., Campagnolo, D., 2006. Does multiple sclerosis-associated disability differ between races? Neurology 66, 1235–1240. https://doi.org/10.1212/01.wnl.0000208505.81912.82

Marrie, R.A., Horwitz, R., Cutter, G., Tyry, T., Campagnolo, D., Vollmer, T., 2009. Comorbidity delays diagnosis and increases disability at diagnosis in MS. Neurology 72, 117–124. https://doi.org/10.1212/01.wnl.0000333252.78173.5f

Marrie, R.A., Horwitz, R., Cutter, G., Tyry, T., Campagnolo, D., Vollmer, T., 2008. Comorbidity, socioeconomic status and multiple sclerosis. Mult. Scler. 14, 1091–1098. https://doi.org/10.1177/1352458508092263

Miller, G.E., Chen, E., Fok, A.K., Walker, H., Lim, A., Nicholls, E.F., Cole, S., Kobor, M.S., 2009. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc. Natl. Acad. Sci. U. S. A. 106, 14716. https://doi.org/10.1073/pnas.0902971106

Minden, S.L., Hoaglin, D.C., Hadden, L., Frankel, D., Robbins, T., Perloff, J., 2008. Access to and utilization of neurologists by people with multiple sclerosis. Neurology 70, 1141–1149. https://doi.org/10.1212/01.wnl.0000306411.46934.ef

Minkler, M., Fuller-Thomson, E., Guralnik, J.M., 2006. Gradient of Disability across the Socioeconomic Spectrum in the United States. N. Engl. J. Med. 355, 695–703. https://doi.org/10.1056/NEJMsa044316

Nazroo, J.Y., 2003. The structuring of ethnic inequalities in health: economic position, racial discrimination, and racism. Am. J. Public Health 93, 277–284. https://doi.org/10.2105/ajph.93.2.277

Nielsen, N.M., Jørgensen, K.T., Bager, P., Stenager, E., Pedersen, B.V., Hjalgrim, H., Koch-Henriksen, N., Frisch, M., 2013. Socioeconomic Factors in Childhood and the Risk of Multiple Sclerosis. Am. J. Epidemiol. 177, 1289–1295. https://doi.org/10.1093/aje/kws350

Owens, T., Evangelou, N., Whynes, D.K., 2013. Rationing and deprivation: disease-modifying therapies for multiple sclerosis in the United Kingdom. Eur J Health Econ 14, 315–21. https://doi.org/10.1007/s10198-012-0378-7

Pérez-Hernández, B., Rubio-Valverde, J.R., Nusselder, W.J., Mackenbach, J.P., 2019. Socioeconomic inequalities in disability in Europe: contribution of behavioral, work-related and living conditions. Eur. J. Public Health 29, 640–647. https://doi.org/10.1093/eurpub/ckz009

Pietras, S.A., Goodman, E., 2013. Socioeconomic status gradients in inflammation in adolescence. Psychosom. Med. 75, 442–448. https://doi.org/10.1097/PSY.0b013e31828b871a

Pornet, C., Delpierre, C., Dejardin, O., Grosclaude, P., Launay, L., Guittet, L., Lang, T., Launoy, G., 2012. Construction of an adaptable European transnational ecological deprivation index: the French version. J. Epidemiol. Community Health 66, 982–989. https://doi.org/10.1136/jech-2011-200311

Ribet, C., Melchior, M., Lang, T., Zins, M., Goldberg, M., Leclerc, A., 2007. [Characterisation and measurement of social position in epidemiologic studies]. Rev. Epidemiol. Sante Publique 55, 285–295. https://doi.org/10.1016/j.respe.2007.04.001

Scalfari, A., Neuhaus, A., Daumer, M., Deluca, G.C., Muraro, P.A., Ebers, G.C., 2013. Early relapses, onset of progression, and late outcome in multiple sclerosis. JAMA Neurol. 70, 214–222. https://doi.org/10.1001/jamaneurol.2013.599

Sidhom, Y., Maillart, E., Tezenas du Montcel, S., Kacem, I., Lubetzki, C., Gouider, R., Papeix, C., 2017. Fast multiple sclerosis progression in North Africans: Both genetics and environment matter. Neurology 88, 1218–1225. https://doi.org/10.1212/WNL.0000000000003762

Vukusic, S., Casey, R., Rollot, F., Brochet, B., Pelletier, J., Laplaud, D.-A., De Sèze, J., Cotton, F., Moreau, T., Stankoff, B., Fontaine, B., Guillemin, F., Debouverie, M., Clanet, M., 2018. Observatoire Français de la Sclérose en Plaques (OFSEP): A unique multimodal nationwide MS registry in France. Mult. Scler. Houndmills Basingstoke Engl. 1–5. https://doi.org/10.1177/1352458518815602

Wändell, P., Carlsson, A.C., Gasevic, D., Sundquist, J., Sundquist, K., 2016. Neighbourhood socio-economic status and all-cause mortality in adults with atrial fibrillation: a cohort study of patients treated in primary care in Sweden. Int. J. Cardiol. 202, 776. https://doi.org/10.1016/j.ijcard.2015.09.027

Willems, S., De Maesschalck, S., Deveugele, M., Derese, A., De Maeseneer, J., 2005. Socio-economic status of the patient and doctor–patient communication: does it make a difference? Patient Educ. Couns. 56, 139–146. https://doi.org/10.1016/j.pec.2004.02.011

Zghebi, S.S., Steinke, D.T., Carr, M.J., Rutter, M.K., Emsley, R.A., Ashcroft, D.M., 2017. Examining trends in type 2 diabetes incidence, prevalence and mortality in the UK between 2004 and 2014. Diabetes Obes. Metab. 19, 1537–1545. https://doi.org/10.1111/dom.12964

Table 1 : Characteristics of patients diagnosed with MS from 1982 to 2016. (a) Kaplan-Meier analysis estimates median delay to reach EDSS 4 and to reach EDSS 6. (b) Log rank test used to calculate significance.

	EDSS 4 as disability milestone					EDSS 6 as disability milestone				
Factors	**Number of MS patients**	**EDSS 4 not reached**	**EDSS 4 reached**	**Median delay (years)**	**p-value (LR test)**	**Number of MS patients**	**EDSS 6 not reached**	**EDSS 6 reached**	**Median delay (years)**	**p-value (LR test)**
Sex					0.0049					0.0004
Females	2623(72%)	1430	1193	15.61[14.99-16.41]		2619(72%)	1926	693	22.32[21.39-23.1]	
Males	1018(28%)	527	491	14.4[13.35-15.58]		1019(28%)	707	312	20.31[19.34-21.47]	
MS types					<0.0001					<0.0001
RR	2889(79%)	1943	946	18.48[17.86-19.65]		2888(79%)	2509	379	29.96[27.42-.]	
SP	752(21%)	14	738	11.26[10.65-11.98]		750(21%)	124	626	14.65[13.95-15.53]	
Age at disease onset					<0.0001					<0.0001
[15-25[	957(26%)	579	378	18.18[17.25-19.92]		957(26%)	738	219	25.06[23.45-26.28]	
[25-35[	1359(37%)	760	599	16.72[15.32-17.64]		1356(37%)	1014	342	22.96[21.76-24.38]	
[35-45[	921(25%)	432	489	13.02[12.09-14.07]		921(25%)	623	298	19.17[18.17-20.31]	
[45-55[	352(10%)	166	186	10.02[9.01-12.04]		352(10%)	227	125	15.49[13.82-17.18]	
>55	52(1%)	20	32	6.75[4.08-15.74]		52(1%)	31	21	18.13[8-20.78]	
Number of relapses in the first 2 years of the disease					<0.0001					
1 relapse	1823(50%)	994	829	17.51[17.01-18.22]		1822(50%)	1309	513	22.86[22.04-24.33]	<0.0001
2 relapses	984(27%)	542	442	14.24[12.99-15.26]		983(27%)	738	245	20.82[19.18-22.12]	
>2 relapses	834(23%)	421	413	11.67[10.6-12.86]		833(23%)	586	247	19.17[17.32-21.32]	
Number of DMT					< 0.0001					
None	743(20%)	374	369	13.38[12.36-14.96]		588(16%)	423	165	19.79[18.01-21.25]	0.0016
1 DMT	1253(34%)	661	592	14[12.99-14.65]		1099(30%)	821	278	21.28[19.97-22.73]	
>1 DMT	1645(45%)	922	723	17.24[16.45-17.86]		1951(54%)	1389	562	22.48[21.53-23.45]	
Level of socioeconomic deprivation										
EDI-Q1	512(14%)	292	220	16.28[15.01-18.4]	< 0.0001	512(14%)	378	134	22.49[20.78-24.84]	0.0025
EDI-Q2	501(14%)	306	195	17.86[16.45-19.26]		501(14%)	374	127	22.61[19.99-25.31]	
EDI-Q3	560(15%)	297	263	16.46[14.63-17.39]		560(15%)	404	156	22.73[19.88-25.06]	
EDI-Q4	768(21%)	412	356	15.34[14.31-16.91]		766(21%)	568	198	22.04[20.87-24.42]	
EDI-Q5	1300(36%)	650	650	13.62[12.85-14.59]		1299(36%)	909	390	20.96[20.06-21.61]	

DMT: Disease-Modifying Treatment; EDSS: Expanded Disability Status Scale; LR: Log-rank test; EDI: European Deprivation Index; RR: Relapsing-remitting; SP: Secondary Progressive

Table 2: Association between socioeconomic deprivation and the risks of reaching EDSS 4 and EDSS 6 in

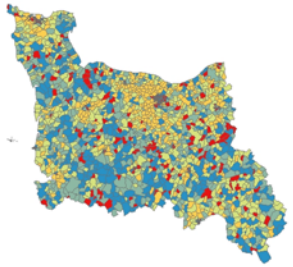
	Risk to reach EDSS 4		Risk to reach EDSS 6	
Factors	**HR CI95%**	**p-value (LR test)**	**HR CI95%**	**p-value (LR test)**
Sex		0.0101		0.0049
Females	1 (Reference)		1 (Reference)	
Males	1.15[1.03-1.28]		1.22[1.06-1.39]	
MS types		<0.0001		<0.0001
RR	1 (Reference)		1 (Reference)	
SP	2.19[1.99-2.42]		4.04[3.54-4.6]	
Age at disease onset		<0.0001		<0.0001
[15-25[	1 (Reference)		1 (Reference)	
[25-35[	1.18[1.03-1.34]		1.13[0.95-1.34]	
[35-45[	1.55[1.35-1.78]		1.44[1.2-1.72]	
[45-55[	2.39[2.00-2.87]		2.64[2.1-3.31]	
>55	2.71[1.87-3.93]		3.27[2.05-5.22]	
Number of relapses in the 2 first years of the disease		<0.0001		<0.0001
1 relapse	1 (Reference)		1 (Reference)	
2 relapses	1.66[1.48-1.87]		1.44[1.23-1.68]	
>2 relapses	2.45[2.17-2.78]		2.02[1.72-2.36]	
Number of DMT		<0.0001		0.4697
None	1 (Reference)		1 (Reference)	
1 DMT	0.96[0.84-1.1]		0.96[0.78-1.17]	
>1 DMT	0.73[0.64-0.83]		0.9[0.75-1.08]	
Level of socioeconomic deprivation		<0.0001		0.0008
EDI-Q1	1 (Reference)		1 (Reference)	
EDI-Q2	0.89[0.74-1.09]		0.99[0.78-1.26]	
EDI-Q3	1.19[1.00-1.43]		1.11[0.88-1.39]	
EDI-Q4	1.19[1.00-1.4]		1.07[0.86-1.33]	
EDI-Q5	1.4[1.20-1.64]		1.38[1.13-1.69]	

MS patients. Adjusted multivariate hazard ratios

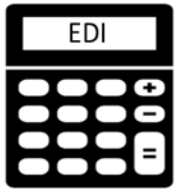
DMT: Disease-Modifying Treatment; EDSS: Expanded Disability Status Scale; LR: Log-rank test; EDI: European Deprivation Index; RR: Relapsing-remitting; SP: Secondary Progressive; HR: Hazard Ratio, CI: Confidence Interval

Patients files registered in 3 EDMUS databases (CAEN, ROUEN, LILLE) n=5501

Patients geolocated from an registered residence address n=3952

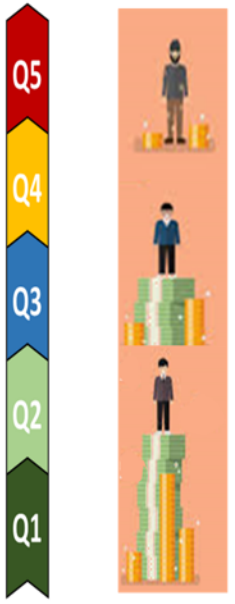


For each IRIS an EDI score can be associated.



EDI score can be distributed into **quintiles** ⇒ deprivation gradient

Most deprived



Less deprived

EDI ATTRIBUTION

IRIS: Smallest geographical unit with socio-economic homogeneity