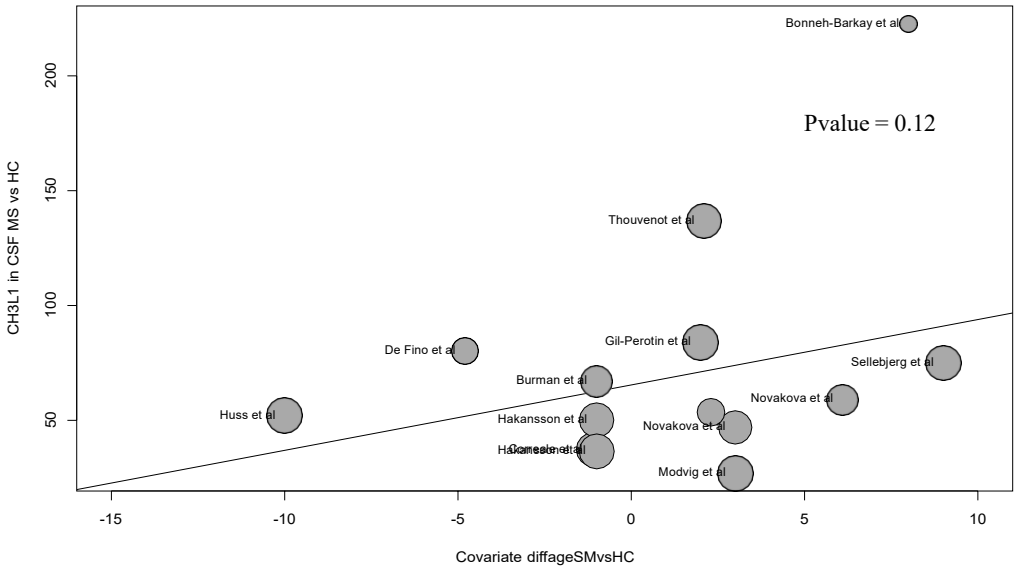
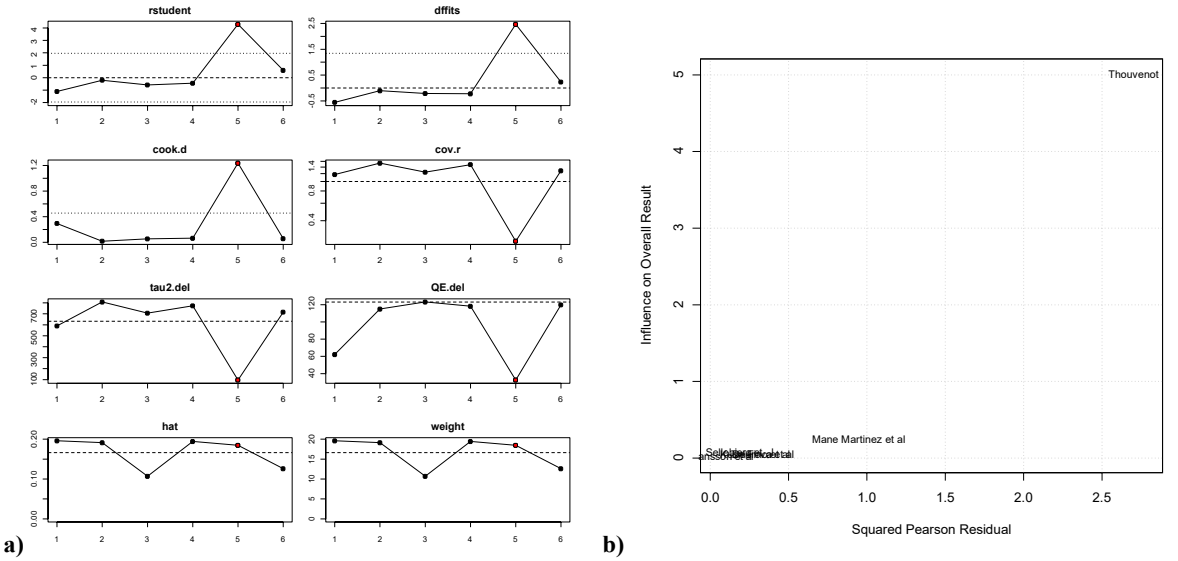
eFig.1 Results of meta-regression. Effects of age on the effect size of the comparisons of patients with MS and healthy controls. *On the X-Axis, covariate represents the mean difference of the age in Multiple Sclerosis patients vs Healthy controls, for all the studies. On the Y-Axis, standardized mean differences (SMD) of CSF levels of CHI3L1 are reported for all the studies. The size of the circles corresponds to the weight of the studies.*

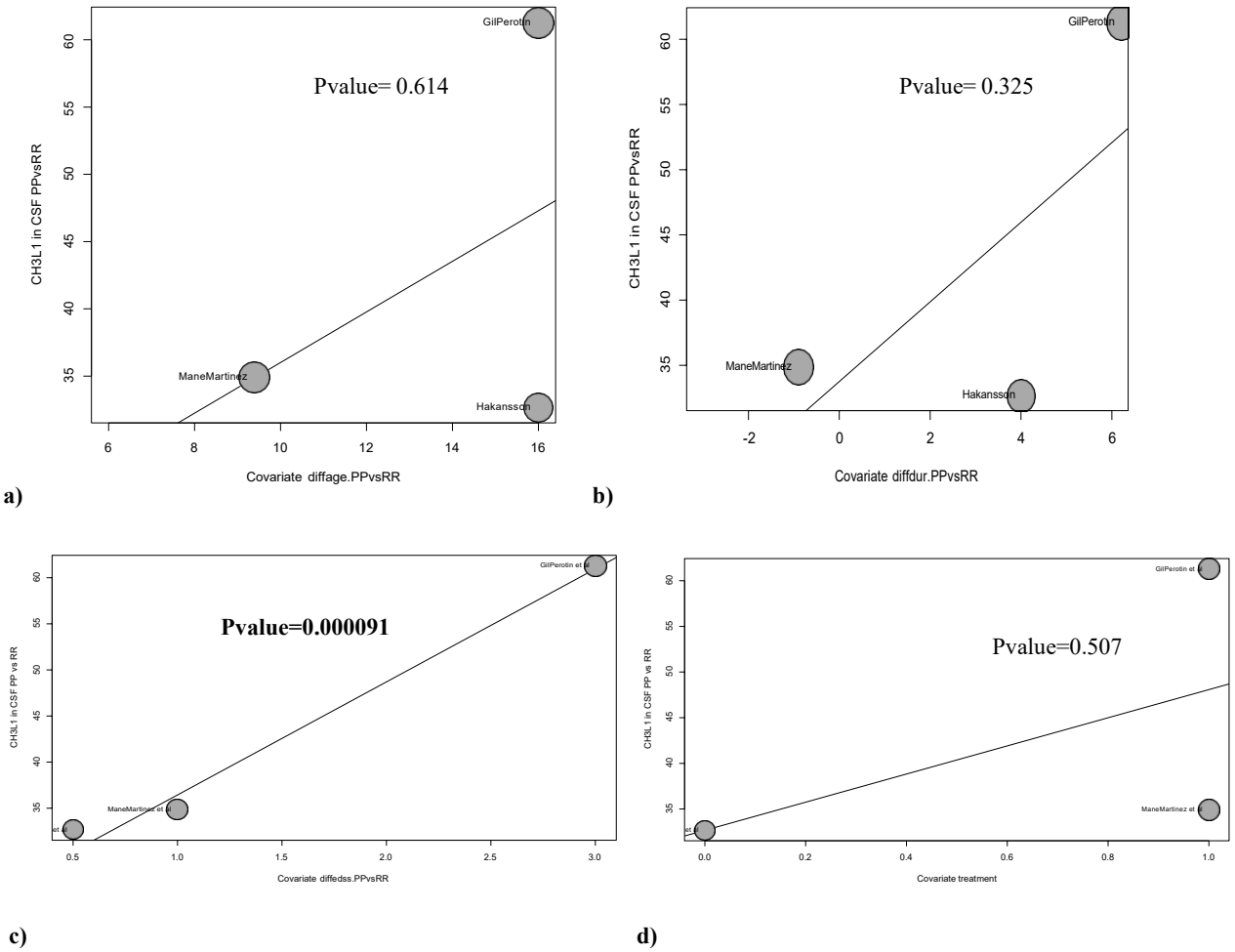


Abbreviations: diffage: mean difference of the age; SM: Multiple Sclerosis; HC: healthy controls;

eFig.2 a) plots showing results of the influence analysis of the studies used to evaluate the effect size of the comparisons of patients with MS and CIS. *For each plot, in the X-axis the studies included in the matanalysis are reported (1= Manè-Martinez et al., 2016; 2=Hakansson et al., 2016; 3=De Fino et al., 2019; 4=Sellebjerg et al., 2019; 5=Thouvenot et al., 2019; 6=Kusnierovà et al., 2020). On Y-axis, values of the following results are estimated: externally standardized residuals (rstudent), DFFITS values, Cook's distances (cook.d), covariance ratios (cov.r), leave-one-out estimates of the amount of heterogeneity (tau2.del), leave-one-out values of the test statistics for heterogeneity (QE.del), hat values and weights of the study. The red dots represent the outlier studies suggested to be excluded in the sensitivity analysis* **b)** Baujat plot of the studies used to evaluate the effect size of the comparisons of patients with MS and CIS. *The plot shows the contribution of each study to the overall Q-test statistic for heterogeneity (defined as Squared Pearson Residual) on the X-axis, versus the influence of each study on Y-axis.*



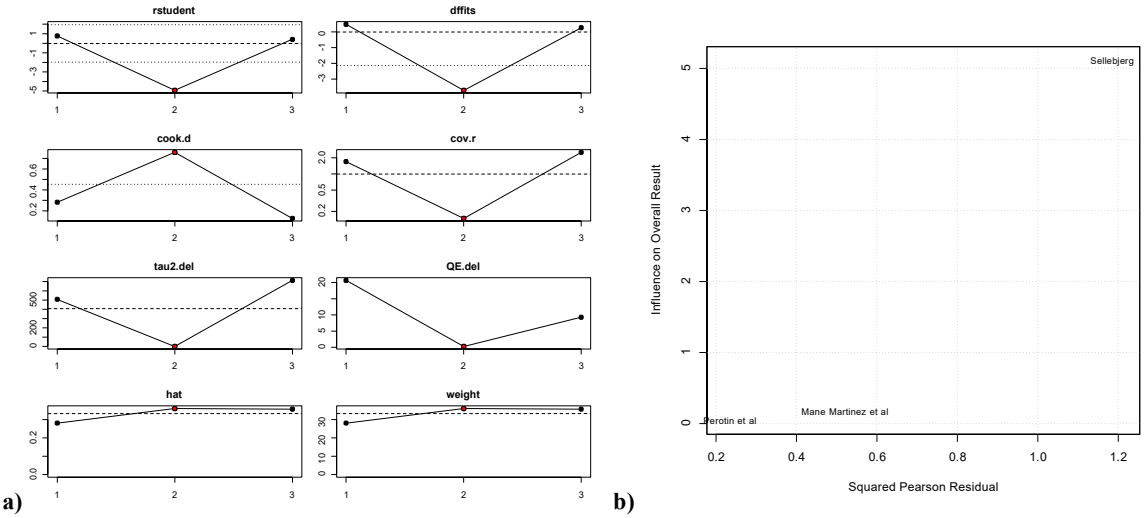
eFig.3 Results of meta-regression. Effects of **a)** age *(on the X-Axis, covariate represents the mean difference of the age between relapsing-remitting and primary-progressive MS. Data are expressed in years)* **b)** disease duration *(on the X-Axis, covariate represents the mean difference of disease duration between relapsing-remitting and primary-progressive MS. Data are expressed in years)* **c)** EDSS score *(on the X-Axis, covariate represents the mean difference in the EDSS between relapsing-remitting and primary-progressive MS)* **d)** previous disease-modifying treatment *(on the X-Axis, covariate represents the presence/absence of previous treatment). On the Y-Axis, standardized mean differences (SMD) of CSF levels of CHI3L1 in RRMS vs PPMS are reported for all the studies. The size of the circles corresponds to the weight of the studies.*



Abbreviations: diffage: mean difference of the age; diffdur: mean difference of disease duration; diffedss: mean difference of EDSS score; PP: Primary-Progressive Multiple Sclerosis; RR: Relapsing-Remitting Multiple Sclerosis;

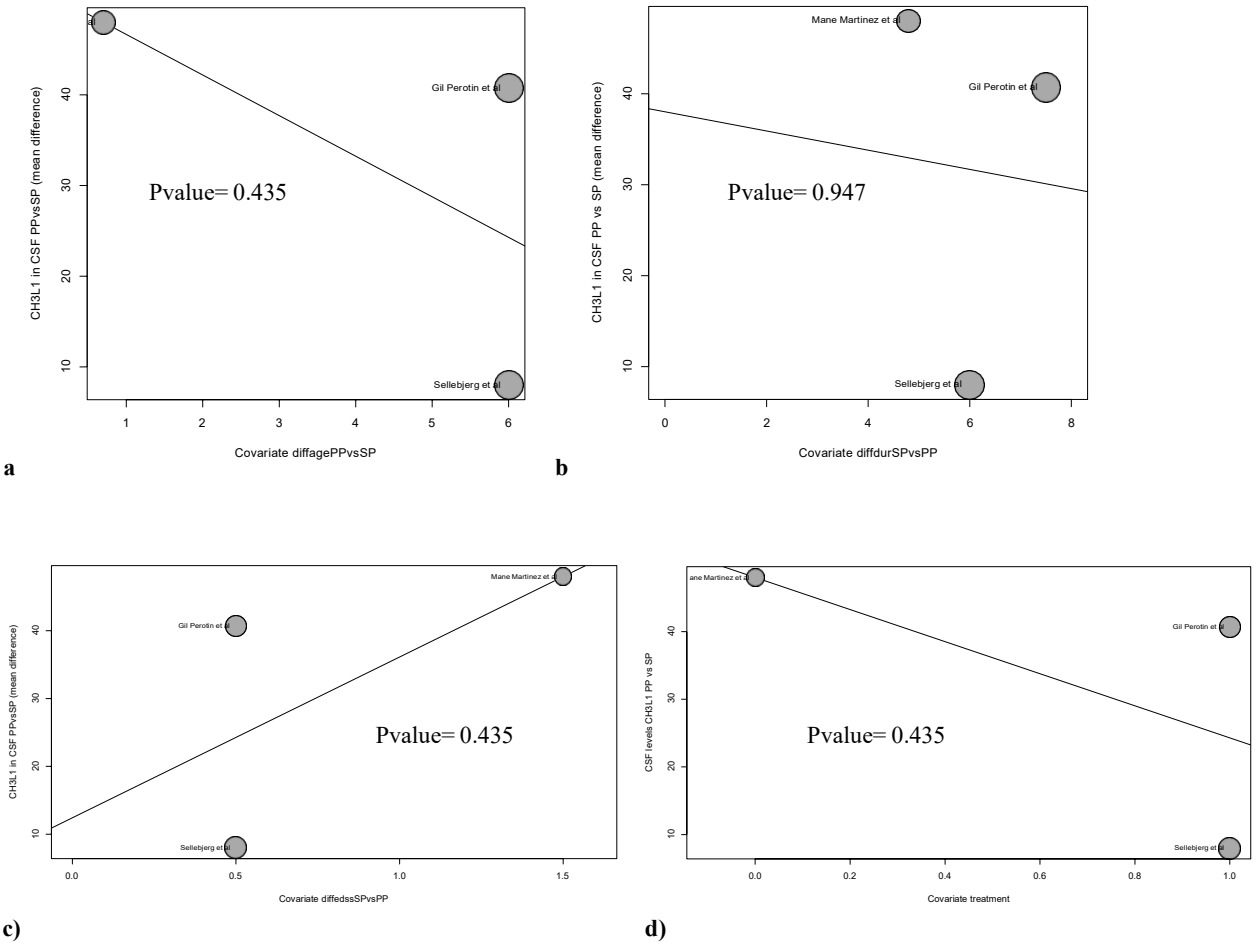
eFig.4 a) plots showing results of the influence analysis of the studies used to evaluate the effect size of the comparisons of patients with PPMS and SPMS. *For each plot, in the X-axis the studies included in the matanalysis are reported (1= Manè-Martinez et al., 2016; 2=Sellebjerg et al., 2017; 3=Gil-Perotin et al., 2019). On Y-axis, values of the following results are estimated: externally standardized residuals (rstudent), DFFITS values, Cook's distances (cook.d), covariance ratios (cov.r), leave-one-out estimates of the amount of heterogeneity (tau2.del), leave-one-out values of the test statistics for heterogeneity (QE.del), hat values and weights*

of the study. The red dots represent the outlier studies suggested to be excluded in the sensitivity analysis **b)** Baujat plot of the studies used to evaluate the effect size of the comparisons of patients with PPMS and SPMS. *The plot shows the contribution of each study to the overall Q-test statistic for heterogeneity (defined as Squared Pearson Residual) on the X-axis, versus the influence of each study on Y-axis.*



a) **b)**

eFig.5 Results of meta-regression. Effects of **a)** age *(on the X-Axis, covariate represents the mean difference of the age between primary-progressive and secondary-progressive MS. Data are expressed in years)*; **b)** disease duration *(on the X-Axis, covariate represents the mean difference of disease duration between primary-progressive and secondary-progressive MS. Data are expressed in years)*; **c)** EDSS score *(on the X-Axis, covariate represents the mean difference in the EDSS primary-progressive and secondary-progressive MS)*; **d)** previous disease-modifying treatment *(on the X-Axis, covariate represents the presence/absence of previous treatment). On the Y-Axis, standardized mean differences (SMD) of CSF levels of CHI3L1 in PPMS vs SPMS are reported for all the studies. The size of the circles corresponds to the weight of the studies.*



a **b**

c) **d)**

Abbreviations: diffage: mean difference of the age; diffdur: mean difference of disease duration; diffedss: mean difference of EDSS score; PP: Primary-Progressive Multiple Sclerosis; SP: Secondary-Progressive Multiple Sclerosis;