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1 **Association Between Diseases and Symptoms Diagnosed in Primary Care**
2 **and the Subsequent Specific Risk of Multiple Sclerosis**

3
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50 **Objective:**

51 Previous studies have reported a possible prodrome in multiple sclerosis (MS) defined by non-
52 specific symptoms including mood disorder or genito-urinary symptoms and increased health
53 care use detected several years before diagnosis.

54 This study aimed to evaluate agnostically the associations between diseases and symptoms
55 diagnosed in primary care and the risk of multiple sclerosis (MS) relative to controls and two
56 other autoimmune inflammatory diseases with similar population characteristics, namely lupus
57 and Crohn's disease.

58 **Methods:**

59 A case-control study was conducted using electronic health records from the Health
60 Improvement Network database in the UK and France. We agnostically assessed the
61 associations between 113 diseases and symptoms in the five years before and after diagnosis in
62 patients with subsequent diagnosis of MS. Individuals with a diagnosis of MS were compared
63 to individuals without MS, and individuals with two other auto-immune diseases, Crohn's
64 disease and lupus.

65 **Results:**

66 The study population consisted of patients with MS (n= 20,174), patients without MS
67 (n=54,790), patients with Crohn's disease (n=30,477) or patients with lupus (n=7,337). Twelve
68 ICD-10 codes were significantly positively associated with the risk of MS compared to controls
69 without MS. After considering ICD-10 codes suggestive of neurological symptoms as the first
70 diagnosis of MS, five ICD-10 codes remained significantly associated with MS: depression
71 (UK OR 1.22 [95%CI 1.11-1.34]), sexual dysfunction (1.47 [1.11-1.95]), constipation (1.5
72 [1.27-1.78]), cystitis (1.21 [1.05-1.39]), and urinary tract infections of unspecified site (1.38
73 [1.18-1.61]). However, none of these conditions was selectively associated with MS in
74 comparisons with both lupus and Crohn's disease. All five ICD-10 codes identified were still
75 associated with MS during the five years after diagnosis.

76 **Conclusion:**

77 We identified 5 health conditions associated with subsequent MS diagnosis, which may be
78 considered not only prodromal but also early-stage symptoms. However, these health
79 conditions overlap with prodrome of two other autoimmune diseases, hence lacking specificity
80 to MS.

81

82 **Introduction**

83

84 A mismatch between clinical symptoms and visible brain lesions on magnetic resonance
85 imaging (MRI), the so-called clinico-radiological paradox, has been known for decades in
86 multiple sclerosis (MS).¹ While this phenomenon has been linked to the heterogeneity of MS
87 clinical outcomes, it could also explain why certain subtle, non-specific symptoms were
88 identified prior to the neurological diagnosis and described as MS prodrome. Moreover, recent
89 studies suggest that patients with MS display increased serum neurofilament biomarkers before
90 the onset of typical MS symptoms.^{2,3} Prodromal health conditions would not be sufficiently
91 pronounced to warrant diagnosis, but they might indicate the start of the neuroinflammatory
92 process, similar to preclinical pathophysiological mechanisms occurring before clinical onset
93 in other neurological diseases.^{4,5} The recognition of a prodromal period would help to gain
94 knowledge on the consequences of the appearance and accumulation of MS lesions but also on
95 the temporality of MS pathophysiological processes. Although it is unlikely that the description
96 of a prodrome in MS might lead to specific intervention in the general population, it could be
97 important to identify such period in populations with a high risk of developing MS due to
98 familial history or in the case of radiologically isolated syndrome (RIS). A recent study from
99 the RISC consortium has found a 51% cumulative probability of a first clinical event at 10 years
100 in patients with RIS.⁶ For those at highest risk of a first clinical event, identifying prodromal

101 health conditions within these 10 years might lead to potential earlier therapeutic intervention.
102 This assumption would be relevant only if MS prodrome would be rather specific to MS, and
103 not similar to other auto-immune conditions.

104 Previous studies have reported pre-diagnostic features, such as depression, fatigue, sleep
105 disorders or urinary infections, associated with MS and occurring up to 10 years before
106 diagnosis.⁷⁻⁹ However, most studies on MS prodrome have focused on either hypothesis-driven
107 searches for non-specific symptoms,^{8,9} or major disease categories.⁷ It is also important to
108 compare the early presentation of MS with other inflammatory diseases and to determine which
109 of the pre-diagnosis features are specific to MS. There is also a need for further analyses of
110 differences in the clinical presentation of MS prodrome by age,¹⁰ sex,⁹⁻¹¹ and year of diagnosis¹²
111 in order to improve our understanding of the prodrome onset.

112 We set up and analyzed two nested case-control studies based on data from two large primary
113 care databases in the UK and France, extracted from The Health Improvement Network (THIN)
114 database. We sought to confirm the previously reported associations⁷⁻⁹ between pre-diagnosis
115 features and the subsequent diagnosis of MS, to assess whether combining these pre-diagnosis
116 features could provide a greater ability to discriminate between patients with subsequent MS
117 and patients without MS, and to compare presentations before and after diagnosis. We also
118 aimed to compare MS cohort with control cohorts of patients with other autoimmune diseases
119 — lupus and Crohn's disease — to determine whether the features identified were specific to
120 MS or common to several autoimmune diseases. Lupus and Crohn's disease were selected
121 because both have female predominance, affect young adults,¹³ and both present pre-clinical
122 non-specific signs and symptoms. In lupus, increased pre-diagnosis healthcare use has been
123 reported,¹⁴ notably childhood-onset lupus cases had higher frequency of pre-diagnosis
124 psychiatric conditions compared to matched controls.¹⁵ In Crohn's disease, an association
125 between pre-diagnosis depression and incident Crohn's disease was reported.¹⁶ Although these

126 diseases have distinct phenotypes and involve different target organs, there is an overlap of
127 environmental risk factors for disease occurrence or exacerbation such as stress and smoking.¹⁷⁻
128 ²⁰ Hence, to determine which health conditions are specific to MS prodrome, we compared MS
129 to both a systemic (lupus) and an organ-specific (Crohn's disease) auto-immune disease.

130

131 **Methods**

132 *Study design and participants*

133 We used The Health Improvement Network (THIN) database,²¹ a large standardized European
134 database of fully anonymized and non-extrapolated electronic medical records collected from
135 physicians by the company GERS SAS²¹ and coded according to the International Classification
136 of Diseases, 10th revision (ICD10). The THIN database complies with all current European
137 data protection laws (General Data Protection Regulation) and adheres to the Observational
138 Medical Outcomes Partnership model.²¹ Details on data collection are specified in the method
139 section of supplementary materials. We considered data recorded from Jan 1, 1996, to March
140 28, 2022 in the UK and from Jan 1, 1998, to March 28, 2022 in France.

141 In both countries, we defined a cohort of cases with incident MS and respectively three other
142 control cohorts: i) individuals without incident MS; ii) patients with incident lupus; iii) patients
143 with incident Crohn's disease. Patients with MS were required to have a record of the ICD-10
144 code G35, lupus the ICD-10 code M32, and Crohn's disease the ICD-10 code K50. The amount
145 of co-occurrence between these diseases in our database did not warrant the exclusion of
146 individuals with more than one auto-immune disease. We first compared the MS cohort to
147 controls without MS in primary and sensitivity analyses and used all significant findings for
148 further analyses in which we compared the MS cohort to lupus and Crohn's disease cohorts. In
149 the primary analysis, index date was defined as the earliest date of at least one of the following
150 conditions: i) G35 code; ii) other ICD-10 codes related to a demyelinating event (e.g myelitis

151 or optic neuritis, complete list in **eTable 1**). Age at MS onset was defined as age at the index
152 date. As exact diagnosis date may be difficult to firmly determine in primary care setting, we
153 also ran a sensitivity analysis, in which we shifted the index date further back, to the earliest
154 ICD-10 code indicating neurological symptoms (e.g. paresthesia, dizziness) which could be
155 interpreted retrospectively as MS clinical onset.¹² For this purpose, we used the ICD-10 codes
156 listed in **eTable 2**.

157

158 For each country, we randomly selected three controls without MS for each MS case, matched
159 in terms of age at index date, sex and year at index date. A symptom was considered to be
160 present if either the corresponding ICD-10 code or the prescription of a symptom-specific drug
161 was recorded (**eTable 3** and **eTable 4**). Only individuals with available data at least two years
162 before the index date in the case and control cohorts were included, as shown in the flowchart
163 in **eFigure 1, 2**. For the sensitivity analysis, we applied the same shift in index date to each
164 matched control. We also defined a cohort of patients with MS and individuals without MS
165 with at least 5 years of data before diagnosis to ensure balanced available data between the two
166 groups.

167

168 *Exposure extraction on the basis of ICD10 classification*

169 We defined past exposure to the health conditions considered, based on the ICD-10 codes
170 provided directly in both the French and UK databases. The validity of significant diagnoses in
171 THIN is high.²²⁻²⁴ More specifically for MS, a previous study using one ICD-10 code G35 to
172 define MS reported similar incidence and prevalence findings to a General Practice Research
173 (GPRD) study.^{25,26} This previous study also had similar results to an internal validation study
174 of MS identification in the GPRD which reported high accuracy.^{26,27} We used the first three
175 characters of the code, defining disease category. In this exploratory approach, we assessed the

176 association between MS and each of the health conditions defined by ICD-10 codes with a
177 relative frequency of more than 0.5% in both MS and control cohorts and in both countries.

178

179 *Standard protocol approvals, registrations, and patients consent*

180 Approval was sorted before carrying out this study (and for the use of datasets). The study was
181 a retrospective analysis of secondary anonymised patient data only. For the UK database, data
182 is only available to researchers carrying out approved medical research. Ethical approval was
183 granted by the NHS South-East Multicentre Research Ethics Committee in 2003 (ref:
184 03/01/073) for establishment of the THIN database, and it was updated in 2011. A further
185 update and approval was granted in 2020 by the NHS South Central, Oxford C Research Ethics
186 Committee (Ref: 20/SC/0011). For the French Database, several audits were conducted by
187 CNIL (Commission Nationale de l'Informatique et des Libertés, the French authority
188 responsible for the protection of personal data). Data are available from the GERS SAS for
189 researchers who meet the criteria for access to confidential data. Researchers willing to replicate
190 the results should address a request to the Cegedim company (info@the-health-improvement-
191 network.co.uk). The study was approved by the THIN Scientific Research Committee (SRC)
192 on 4th Feb 2022 (SRC reference 21-016). There was no need for written informed consent from
193 participants. No photographs, videos, or other information of recognizable persons is used in
194 this article. Authorization for disclosure was therefore not necessary.

195

196 **Statistical analysis**

197 We used logistic regression to analyse the association between each health condition
198 corresponding to a specific ICD10 code and the diagnosis of MS. We quantified the association
199 by calculating odds ratios (ORs) and 95% CIs for exposure to a particular health condition
200 within five years of the index date. *P* values were corrected for multiple comparisons with the

201 Bonferroni method, with an alpha risk of 5%. Values of $p < 0.0004$ in two-tailed tests were
202 considered significant ($p = 0.05$ with Bonferroni correction for 113 potential exposures). As the
203 exclusion of some patients with MS and controls without MS (**eFigure 1** and **eFigure 2**) led to
204 a break in the matching, all analyses were adjusted for sex (dichotomous variable), age at
205 diagnosis (continuous variable), year at diagnosis (continuous variable), and the duration of
206 follow-up (continuous variable). For the comparison between MS and other autoimmune
207 diseases, we performed a logistic regression analysis controlled for age at index date, sex, and
208 duration of follow-up.

209 We studied post-diagnosis presentation, using a Cox regression model with MS as the exposure
210 of interest, considering the given health condition as the outcome and the time to the event or
211 the time to last visit or data extraction as the time variable. To compare pre and post-diagnosis
212 presentation, we restricted the cohorts of patients with incident MS and no MS to patients with
213 at least two years of data before and after the index date.

214 We stratified our analyses before and after MS diagnosis on sex, age at diagnosis, and year at
215 diagnosis. To stratify on age at diagnosis, we split the data into three cohorts of equal size, using
216 the 33rd and 66th percentiles for age at diagnosis as cutoff points. To stratify on year at diagnosis,
217 we used the year 2010 and 2017 since new MS diagnostic criteria were defined in 2010²⁸ and
218 2017.²⁹ These criteria have been shown to facilitate earlier diagnosis and to increase sensitivity
219 of MS diagnosis.^{30,31}

220 In investigations of temporal associations, we also used the significant findings from the
221 comparison of the MS cohort to individuals without MS, with the exception of one condition,
222 to chart the single-year prevalence of the prescription of symptom-specific drugs for each of
223 the 15 years before and after MS diagnosis. We also investigated healthcare use, based on the
224 mean number of GP visits per year. To handle patients who were not followed during the entire
225 30 years period, the prevalence was computed based on the exact number of patients at risk for

226 each specific year. We also included analyses on specific subsets of patients who were followed
227 for at least x number of years (where x can be 15, 10, or 5) before and after diagnosis.
228 Finally, we conducted the analyses in each country, and we also pooled the data by combining
229 individual patient records from the two countries, adding country as covariate to account for
230 heterogeneity between countries (referred as pooled analyses). Indeed, data homogeneity is
231 partly guaranteed by shared data collection process and OMOP data format between countries,
232 but heterogeneity remains in the type of population and healthcare settings in each country.
233 Pooling individual patient records allowed to increase statistical power, and presenting results
234 in separate countries allowed to examine the consistency of findings in different settings.

235

236 **Results**

237 *Demographic information*

238 In this analysis, from French and British health records, we included respectively 4,366 and
239 15,808 patients with MS, 12,531 and 42,226 individuals without a diagnosis of MS, 2,041 and
240 5,296 patients diagnosed with lupus, and 9,605 and 20,872 patients diagnosed with Crohn's
241 disease. Age and sex distribution of MS cohort, and the three control cohorts of patients with
242 other autoimmune diseases or individuals without MS are presented in **Table 1**.

243 Median age at MS diagnosis was 46 years (37–57 years) in the UK and 44 years (34–54 years)
244 in France, with an age at first MS symptoms of 44 years (34–54 years) in the UK and 42 years
245 (32–52 years) in France. For patients diagnosed after 2017, age at first MS symptoms decreased
246 to 39 years (30–50 years) in the UK and 40 years (30–51 years) in France. More follow-up data
247 were available from the UK sample, with 9 person-years of data available before the index date
248 in the full analytical cohort versus only 6 person-years on average for the French sample.
249 Median number of visits per year was also higher in the UK than in France.

250 Female predominance was observed in MS, lupus, and Crohn's disease cohorts.

251 Lupus cohort contained slightly older patients and included more women than MS cohort,
252 whereas Crohn's disease cohort contained younger patients, with fewer women than MS cohort.
253 Co-occurrence between MS and lupus and MS and Crohn's disease was respectively 6 (0.13%)
254 and 15 (0.34%) in France and 89 (0.56%) and 28 (0.18%) in the UK, which did not warrant
255 further consideration.

256

257 *Primary analysis*

258 Overall, 113 health conditions were considered in the French and UK databases (**eTable 5**). We
259 identified 12 health conditions as significantly positively associated with a diagnosis of MS
260 when recorded in the five years before MS diagnosis, in both countries (**eTable 6**). Only one of
261 these conditions was a neurologic disorder: epilepsy and recurrent seizures. Two psychiatric
262 disorders, depression and sexual dysfunction (not caused by organic disorder or disease) were
263 more frequently recorded in patients with MS than in controls without MS. The other associated
264 health conditions were related to disorders of the vestibular system, functional intestinal
265 disorders (principally constipation), limb pain, cystitis, disorders of the urinary system
266 (principally urinary tract infection), skin paresthesia, dizziness and giddiness, headache, and
267 malaise and fatigue. Skin paresthesia, dizziness and giddiness, and disorders of vestibular
268 function may be interpreted as MS symptoms that were not recognized as such by the GP.

269

270 *Sensitivity analysis*

271 Only major depressive disorder, sexual dysfunction, constipation, cystitis, and urinary tract
272 infection of unspecified site remained significantly more frequent in patients with MS than in
273 controls without MS in the sensitivity analysis (**Figure 1, eTable 6**). Overall, 91.2% of the
274 patients diagnosed with functional intestinal disorders (ICD-10 code K59) in the UK and 92.4%
275 of those diagnosed with such disorders in France had constipation (ICD-10 code K59.0).

276 Similarly, 98.8% of the patients diagnosed with disorders of the urinary system (ICD-10 code
277 N39) in the UK and 97.9% of those diagnosed with such disorders in France had urinary tract
278 of unspecified site infection (ICD-10 code N39.0). In the following, the ICD-10 codes K59 and
279 N39 will be regarded respectively as constipation and urinary tract infection of unspecified site.
280 When restricting the analysis to patients with at least five years of history before the index date,
281 all health conditions remained significantly positively associated in the UK and in the pooled
282 analysis; however, sexual dysfunction, cystitis, and urinary tract infection (site not specified)
283 were not significantly associated in the French cohort, most likely due to a lack of statistical
284 power (**eTable 7**). Summary statistics for this cohort are presented (**eTable 8**). Characteristics
285 of the cohorts are similar to those of the original cohorts with at least two years of retrospective
286 data.

287

288 *Pre and post-diagnosis analysis*

289 To facilitate the pre and post diagnosis comparison, we restricted our cohorts to patients with
290 at least two years of data before and after diagnosis. Characteristics of the cohorts are similar
291 to those of the original cohorts with at least two years of retrospective data (**eTable 9**). All
292 health conditions considered to be associated with MS diagnosis in the pre-diagnosis analysis
293 were also associated with MS diagnosis in the post-diagnosis analysis in both France and UK
294 cohorts (**Table 2** in pooled analysis, and **eTable 10 and 11** for UK and France respectively).
295 Moreover, in the UK and in the pooled analysis (**Table 2** and **eTable 10**), ORs for all conditions
296 were significantly higher in the post-diagnosis period compared to the pre-diagnosis period.

297

298 *Combination of pre-diagnosis health conditions*

299 Combining observed pre-diagnosis features significantly increased the ability to discriminate
300 MS cases and controls without MS for men (pooled OR 2.46, 2.05–2.95 for at least two

301 features), whereas no effect was observed for women or in subgroups stratified by age at onset
302 (**Table 3**).

303

304 *Comparison with other autoimmune diseases*

305 Depression, sexual dysfunction, cystitis and urinary tract infection (site not specified) were
306 found to be more frequent among people subsequently diagnosed with MS than in Crohn's
307 disease patients, in the pooled analysis of data from France and the UK (**Figure 2** in pooled
308 analysis, and **eFigure 3** for UK and France). However, no health condition was found to be
309 significantly associated with MS in comparisons with lupus patients. Constipation was found
310 to be significantly positively associated with Crohn's disease in comparison to MS.

311

312 *Longitudinal analysis*

313 We found that the difference in the prevalence of antidepressant use between MS and controls
314 without MS was much more pronounced after than before MS diagnosis. Indeed, the period
315 prevalence increased from 14% and 10% for MS patients and controls without MS,
316 respectively, in the five years before diagnosis to 37% and 19%, respectively, in the five years
317 after MS diagnosis, with the number of MS patients using antidepressants increasing by 20%
318 during the year of MS diagnosis (**Figure 3** for the pooled analysis, **eFigure 4** and **eFigure 5** for
319 the UK and French cohort respectively). Increase in antidepressant prescriptions was less
320 pronounced at the time of diagnosis for patients with lupus or Crohn's disease. For MS, lupus
321 and Crohn's disease, there was a rise of number of GP visits after the diagnosis, with a peak
322 with the first two years post-diagnosis of these auto-immune conditions. Concordant temporal
323 trends of prescriptions and GP visits were observed in cohorts with data in the entire time
324 periods (**eFigure 6** and **eFigure 7**).

325

326 *Stratification by age at diagnosis, sex, and year of diagnosis*

327 The ORs for pre-diagnosis autonomic symptoms (functional intestinal disorders, cystitis, and
328 urinary tract infection of unspecified site) increased with increasing age at diagnosis, though
329 not reaching significance, whereas those for depression and sexual dysfunction did not vary
330 with age. Overall, ORs for pre-diagnosis presentations were higher in men than women,
331 especially for urinary tract infection (women: OR 1.29, 1.12–1.48; men: OR 2.16, 1.50–3.10).
332 Finally, pre-diagnosis depression and constipation decreased with more recent year of
333 diagnosis, though not reaching significance (**Table 2**).

334

335

336 **Discussion**

337

338 We used two large independent primary care databases to explore pre-diagnosis health
339 conditions associated with MS. To our knowledge, this is the first transnational data-driven
340 study of the pre and post-diagnosis presentations of MS.

341 Median age at first diagnosis was 39 and 40 in the UK and France in the sensitivity analysis
342 after 2017. This is slightly higher than the reported mean age at diagnosis of 37.6 years in a
343 previous study¹², but considerably lower than the reported 43 years and 47 years in other
344 previous studies.^{32,33} These previous studies were based on administrative claims data. In a
345 smaller clinical cohort linked to administrative data, mean age at symptom onset (as recalled
346 by the patient during a neurologist visit) was 36.5 years suggesting that the first clinical
347 manifestations of the disease might not have been recorded in our study and other previous
348 studies.³²

349 In the primary analysis, we identified a group of symptoms recorded by GPs during the five-
350 year period leading up to MS diagnosis. However, some of these symptoms suggested that the

351 patient had already experienced a relapse or onset of MS and, therefore, that the diagnosis of
352 MS recorded in the database was later than the actual onset of MS.¹² In the sensitivity analysis
353 using the earliest symptom suggestive of MS as the index date, five conditions were
354 significantly associated with a subsequent diagnosis of MS and were considered putative pre-
355 diagnosis features. Our findings confirmed the reported pre-diagnosis associations for
356 autonomic symptoms (intestinal function disorders, cystitis, and urinary tract infections)^{8,9,32,34}
357 and depression.^{7,8,32,34} Symptoms of sexual dysfunction have been recognized to occur at or
358 after the onset of MS symptoms or MS diagnosis;³⁵⁻³⁷ however, to our knowledge, no other
359 study has ever reported a health condition related to sexual dysfunction as a pre-diagnosis
360 feature of MS. Sexual dysfunctions reported were coded as a psychological disorder not caused
361 by a disease. It remains unclear whether this health condition results from the patient's
362 experience of the prodrome — in which case, the psychological nature of the sexual dysfunction
363 would be confirmed — or whether it is caused by an ongoing disease, such as medullary MS
364 lesions, if the patient reports no motor or sensory symptoms. Other health conditions identified
365 in prodrome studies in the primary care context, such as anxiety, fatigue, anemia, and sleep
366 disorders,^{8,34,38} were not significantly associated with MS diagnosis in our sensitivity study.
367 This study is original as it investigates the possibility of an MS prodrome in two large countries,
368 and it may have eliminated several spurious correlations.

369 In our study, ORs for depression were higher in France compared to the UK, this difference
370 could be attributed to the difference in healthcare system or difference in the type of
371 remuneration (capitation based for the UK versus fee-for-service based for France).

372 A previous study reported a positive association between pre-diagnosis depression and the
373 incidence of inflammatory bowel disease, MS, and rheumatoid arthritis separately, which could
374 suggest similarities in the pre-diagnosis presentations (potentially due to shared risk factors or
375 etiology) of auto-immune diseases.³⁹ In our study, none of the observed associations was

376 selectively associated with MS in comparison with lupus, whereas urinary tract infection,
377 cystitis, sexual dysfunction, and major depressive disorder were found to be selectively
378 associated with MS in a comparison with Crohn's disease. However, these associations were
379 weak, suggesting that urinary tract infections, sexual dysfunction, and major depressive
380 disorder may not be specific to MS. The finding that depression is specifically associated with
381 MS in comparison to Crohn's disease contradicts a previous study which found no association.¹²
382 The other observed conditions were not tested in other studies. A previous review reported that
383 studies of the preclinical phase of lupus are complicated by the fact that lupus cannot be
384 diagnosed until sufficient clinical manifestations have occurred, potentially accounting for the
385 lack of difference between the prodromal features of MS and lupus.⁴⁰

386 Several previous studies have investigated whether pre-diagnosis presentations of MS vary with
387 age and sex.⁹⁻¹¹ One study reported higher rates of pre-diagnosis anemia in men than in women,
388 whereas sex had no effect on the rates of pre-diagnosis fatigue and pain.⁹ Our findings are
389 consistent with a previous study suggesting that males had more exacerbated pre-diagnosis
390 presentations, namely higher healthcare use and genito-urinary prescriptions (ATC level 1
391 classification).¹⁰ Another study observed that musculoskeletal diseases were more frequent for
392 women and reproductive system diseases more frequent for males.¹¹ However, these studies
393 used large disease categories (several groups of ICD-10 codes) or prescription categories (ATC
394 level 1) which did not allow us to properly compare with our findings. In our study, an effect
395 of sex was also observed when combining the observed pre-diagnosis features. Concerning the
396 effect of age, previous findings observed a stronger effect of MS on overall healthcare in the 5
397 years prior to the first demyelinating event for older vs. younger adults.¹⁰ In our work, we only
398 found that autonomic symptoms increased with age, though not reaching significance. Overall,
399 diversity in the presentation of pre-diagnosis conditions was observed for males and females,

400 and across age groups which suggests that these variables should be used to investigate pre-
401 clinical manifestations in MS.

402 The associations were weaker for diagnoses established after 2010, but this difference was not
403 statistically significant due to the small sample size. The updated diagnostic criteria have
404 probably decreased time to diagnosis, as shown by the four-year decrease in the UK and the
405 two-year decrease in France for age at MS diagnosis since 2010.

406 It remains unclear whether the identified pre-clinical conditions are risk factors for MS, or
407 nonspecific early MS symptoms. Moreover, due to the frequency of these symptoms in the
408 general population and the non-specificity regarding prodrome form other auto-immune
409 diseases, we should not expect that the identification of a prodrome will dramatically change
410 clinical care, at least in the general population. We found that disclosure of MS diagnosis and
411 evolution had a strong impact on all these associations. In large EHR databases, some time may
412 elapse between disclosure of the diagnosis and the first record for a few patients. Given the
413 large increase in antidepressant use at and after MS diagnosis, also reported in a previous
414 study,³⁹ we cannot rule out the possibility that the observed association with depression can be
415 explained by a few patients for whom the first record of MS appears several years after the first
416 true diagnosis. Caution is therefore required in interpretation and it would probably be hasty to
417 conclude that use of these observed prodromal associations would help to improve early
418 diagnosis of MS.

419 Our study has several strengths. It is a fully agnostic study of the MS prodrome, based on data
420 from two large databases in two different countries. This should ensure that the results are
421 highly generalizable. This study also includes a comparison with the period after MS
422 diagnosis, and a stratification for age, sex, and year of diagnosis, in line with the
423 recommendations of previous studies.⁴¹ However, like most studies based on primary care
424 databases, it is also subject to several limitations. First, no data for potential confounding

425 factors, such as education level, ethnicity, socioeconomic status, body-mass index, or genetic
426 information, were available. Second, UK THIN database contains slightly fewer people aged
427 under 25 years,²¹ possibly explaining that age at diagnosis is a bit higher than what we could
428 expect from other epidemiological studies. Third, controls were also selected from primary
429 care databases, therefore the control cohort did not include individuals who never consulted a
430 general practitioner.

431 **Conclusion**

432

433 We performed a modern large-scale data-driven survey of a potential prodrome of MS in the
434 primary care setting. Our findings confirm that several pre-diagnostic features of MS can be
435 observed in large-scale electronic health record data. We also show that the prodromal
436 presentation depends on sex and that all pre-diagnosis health conditions associated with MS
437 were recorded more frequently in the [0-5] years after MS diagnosis compared to the [0-5] years
438 before MS diagnosis. Future studies are required to determine whether the detection of these
439 health conditions can help to decrease age at diagnosis of MS, although our results suggest that
440 they are probably not sufficiently specific to define an MS prodrome.

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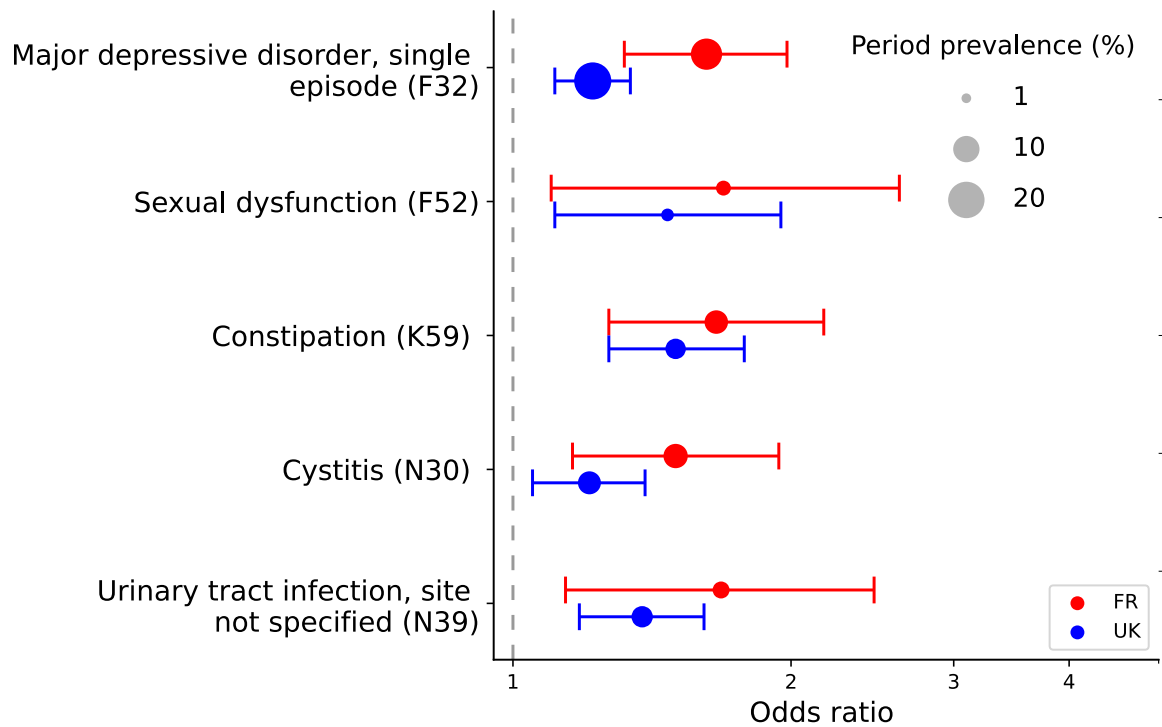
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	Size, n	Sex (female)	Age at diagnosis	Age at first symptom of MS	Person-years of data available before diagnosis	Number of visits per year before diagnosis
UK						
MS						
Whole cohort	15808	70.5%	46 (37 - 57)	44 (34 - 54)	9 (5 - 13)	6 (2 - 7)
Year of MS diagnosis						
<2010	10108	70.9%	48 (38 - 58)	46 (37 - 56)	7 (5 - 10)	6 (2 - 7)
[2010,2017]	4319	69.9%	44 (35-54)	41 (31 - 51)	13 (8 - 18)	6 (2 - 7)
>2017	1381	69.1%	44 (34 - 55)	39 (30 - 50)	17 (9 - 23)	5 (2 - 7)
Lupus	5296	88.2%	48 (36 - 61)		9 (5 - 14)	8 (3 - 10)
Crohn's disease	20872	54.5%	42 (27 - 59)		7 (4 - 12)	6 (2 - 8)
No MS	42226	70.2%	46 (36 - 56)		7 (4 - 12)	5 (2 - 6)
France						
MS						
Whole cohort	4366	70.2%	44 (34 - 54)	42 (32 - 52)	6 (3 - 10)	4 (2 - 6)
Year of MS diagnosis						
<2010	1890	69.8%	45 (35 - 55)	44 (34 - 55)	4 (3 - 6)	5 (2 - 7)
[2010,2017]	1708	70.4%	43 (34 - 52)	41 (32 - 50)	8 (4 - 11)	4 (2 - 5)
>2017	768	71.0%	43 (32 - 54)	40 (30 - 51)	10 (5 - 15)	3 (1 - 5)
Lupus	2041	81.5%	47 (36 - 60)		7 (4 - 10)	5 (2 - 7)
Crohn's disease	9605	55.9%	40 (27 - 55)		7 (4 - 11)	4 (1 - 5)
No MS	12564	70.2%	43 (33 - 53)		4 (3 - 7)	3 (1 - 4)

453 **Table 1. Characteristics of patients with MS, Crohn's disease, or lupus, and controls.** The data are

454 shown as percentage or median (IQR).



455

456 **Figure 1. ORs for significant associations in the sensitivity analysis for five years before**
 457 **the index date.** Only significant associations both in the French and UK cohorts are shown,
 458 with red and blue dots, respectively. The size of the dot is proportional to the period prevalence.
 459 The period prevalence is defined as the number of diagnoses or symptoms observed over the
 460 period divided by the number of patients at risk during the period. Bars correspond to 95% CIs
 461 after correction for multiple comparison.

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	Sex			Age at onset			Year of diagnosis		
	Whole cohort (No. MS : 15454 No. no MS : 26253)	Women (No. MS : 10966 No. no MS : 18821)	Men (No. MS : 4488 No. no MS : 7442)	<40 (No. MS : 5151 No. no MS : 7079)	[40,53] (No. MS : 5152 No. D no MS : 9620)	>53 (No. MS : 5151 No. no MS : 9253)	<2010 (No. MS : 10283 No. no MS : 18964)	[2010,2017] (No. MS : 4417 No. no MS : 6419)	>2017 (No. MS : 754 No. no MS : 732)
Before diagnosis									
F32 : Major depressive disorder, single episode	1.34 (1.24 - 1.45)*	1.31 (1.20 - 1.43)*	1.48 (1.26 - 1.74)*	1.34 (1.16 - 1.55)*	1.36 (1.20 - 1.53)*	1.32 (1.15 - 1.51)*	1.40 (1.27 - 1.53)*	1.26 (1.10 - 1.46)*	0.90 (0.63 - 1.29)
F52 : Sexual dysfunction	1.63 (1.31 - 2.03)*	1.60 (1.05 - 2.42)*	1.61 (1.24 - 2.09)*	1.85 (1.07 - 3.18)*	1.91 (1.35 - 2.70)*	1.42 (1.01 - 1.98)*	1.69 (1.29 - 2.22)*	1.59 (1.07 - 2.34)*	.*
K59 : Constipation	1.89 (1.63 - 2.18)*	1.73 (1.47 - 2.04)*	2.55 (1.87 - 3.48)*	1.48 (1.12 - 1.96)*	1.99 (1.53 - 2.59)*	2.16 (1.73 - 2.70)*	2.05 (1.67 - 2.50)*	1.70 (1.35 - 2.14)*	1.17 (0.70 - 1.96)
N30 : Cystitis	1.39 (1.23 - 1.57)*	1.32 (1.16 - 1.49)*	2.78 (1.83 - 4.21)*	1.18 (0.95 - 1.47)	1.25 (1.02 - 1.54)*	1.72 (1.41 - 2.10)*	1.47 (1.26 - 1.71)*	1.20 (0.97 - 1.48)	1.24 (0.77 - 2.00)
N39 : Urinary tract infection, site not specified	1.38 (1.21 - 1.57)*	1.29 (1.12 - 1.48)*	2.16 (1.50 - 3.12)*	1.15 (0.89 - 1.47)	1.28 (1.02 - 1.61)*	1.65 (1.35 - 2.03)*	1.50 (1.29 - 2.22)*	1.09 (0.83 - 1.42)	1.32 (0.64 - 2.74)
After diagnosis									
F32 : Major depressive disorder, single episode	1.96 (1.83 - 2.11)*	1.84 (1.69 - 1.99)**	2.42 (2.09 - 2.80)*	2.12 (1.88 - 2.39)*	1.98 (1.75 - 2.23)*	1.91 (1.67 - 2.20)*	1.97 (1.81 - 2.14)*	2.0 (1.73 - 2.32)*	1.68 (1.09 - 2.61)*
F52 : Sexual dysfunction	2.84 (2.43 - 3.31)*	1.96 (1.41 - 2.73)*	3.13 (2.62 - 3.73)*	4.64 (3.34 - 6.44)*	3.98 (3.06 - 5.18)*	1.43 (1.10 - 1.85)*	2.94 (2.46 - 3.52)*	2.56 (1.87 - 3.49)*	.*
K59 : Constipation	3.36 (3.07 - 3.68)*	3.08 (2.77 - 3.42)*	4.29 (3.57 - 5.16)*	3.14 (2.62 - 3.76)*	4.14 (3.52 - 4.86)*	3.17 (2.75 - 3.65)*	3.57 (3.19 - 4.00)*	2.82 (2.40 - 3.32)*	2.65 (1.62 - 4.32)*
N30 : Cystitis	2.49 (2.29 - 2.72)*	2.2 (2.01 - 2.41)*	6.02 (4.58 - 7.93)*	2.14 (1.82 - 2.51)*	2.6 (2.24 - 3.02)*	2.84 (2.46 - 3.28)*	2.67 (2.40 - 2.96)*	2.07 (1.76 - 2.45)*	1.91 (1.23 - 2.96)*
N39 : Urinary tract infection, site not specified	2.69 (2.43 - 2.98)*	2.49 (2.23 - 2.78)*	3.92 (3.03 - 5.07)*	2.3 (1.90 - 2.79)*	2.76 (2.31 - 3.30)*	2.94 (2.50 - 3.44)*	2.77 (2.47 - 3.11)*	2.48 (1.98 - 3.11)*	3.23 (1.48 - 7.08)*

Table 2. ORs for all health conditions individually associated with MS in the sensitivity analysis during the five years before and five years after the occurrence of the first symptoms. Individuals with MS are compared with controls without MS. We used the whole sensitivity cohort, sex-based cohorts, age-at-onset cohorts, and year-at-diagnosis cohorts. Results are shown for the pooled data between France and UK cohorts Results from the UK and French cohorts are shown in **eTable 10** and **11** respectively.

.* cannot be calculated because too few presentations were recorded.

* for ORs associated with corrected p-values below 0.05 or initial p-value below 0.05/5. p-value are adjusted for multiple comparisons using the Bonferroni method.

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	Whole cohort (No. MS : 20174 No. no MS : 54790)	Sex			Age at onset	
		Women (No. MS : 14210 No. no MS : 38463)	Men (No. MS : 5964 No. no MS : 16309)	<40 (No. MS : 6724 No. no MS : 18263)	[40,53] (No. MS : 6724 No. no MS : 18263)	>53 (No. MS : 6726 No. no MS : 182635)
Before diagnosis						
At least one feature	1.41 (1.35 - 1.47)** (MS : 30.87 Control : 22.5)	1.32 (1.26 - 1.39)** (MS : 33.72 Control : 25.82)	1.7 (1.57 - 1.85)** (MS : 24.07 Control : 14.83)	1.3 (1.21 - 1.40)** (MS : 28.41 Control : 21.37)	1.41 (1.31 - 1.51)** (MS : 32.07 Control : 23.35)	1.48 (1.37 - 1.58)* (MS : 32.1 Control : 23.12)
At least two features	1.47 (1.36 - 1.59)** (MS : 7.16 Control : 4.52)	1.31 (1.20 - 1.43)* (MS : 8.05 Control : 5.64)	2.46 (2.05 - 2.95)** (MS : 5.02 Control : 1.95)	1.27 (1.10 - 1.47)* (MS : 5.83 Control : 4.08)	1.46 (1.28 - 1.67)** (MS : 7.14 Control : 4.52)	1.63 (1.44 - 1.84) (MS : 8.49 Control : 5.05)
At least three features	1.63 (1.37 - 1.93)** (MS : 1.46 Control : 0.8)	1.4 (1.16 - 1.68)** (MS : 1.67 Control : 1.05)	4.07 (2.53 - 6.55)** (MS : 0.95 Control : 0.22)	1.35 (0.94 - 1.94) (MS : 0.93 Control : 0.59)	1.49 (1.11 - 2.0)* (MS : 1.39 Control : 0.82)	1.94 (1.51 - 2.51)** (MS : 2.06 Control : 0.99)

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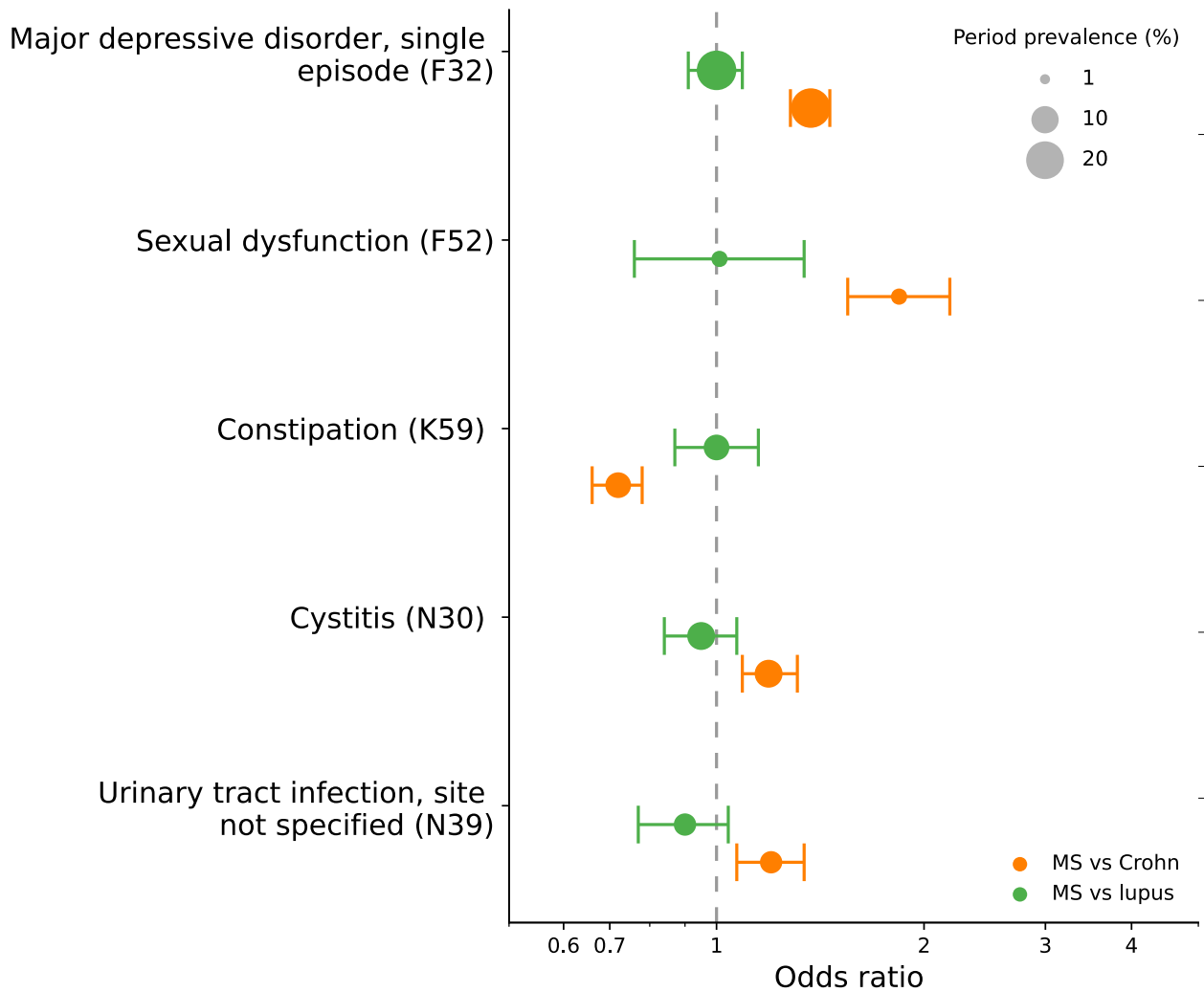
476 **Table 3. ORs and prevalence in MS and non-MS cohorts (OR (95% CI) (MS :**
477 **frequency, Control : frequency)) for combinations of at least one, two, or three health**
478 **problems individually associated with MS in the sensitivity analysis during the five years**
479 **before the occurrence of the first symptoms.** Individuals with MS are compared with
480 controls without MS. We used the whole sensitivity cohort, sex-based cohorts, and age-at-
481 onset cohorts. Results are shown for the pooled data between France and UK cohorts.

482 * for ORs associated with corrected p-values below 0.05 or initial p-value below 0.05/113. p-
483 value are adjusted for multiple comparisons using the Bonferroni method.

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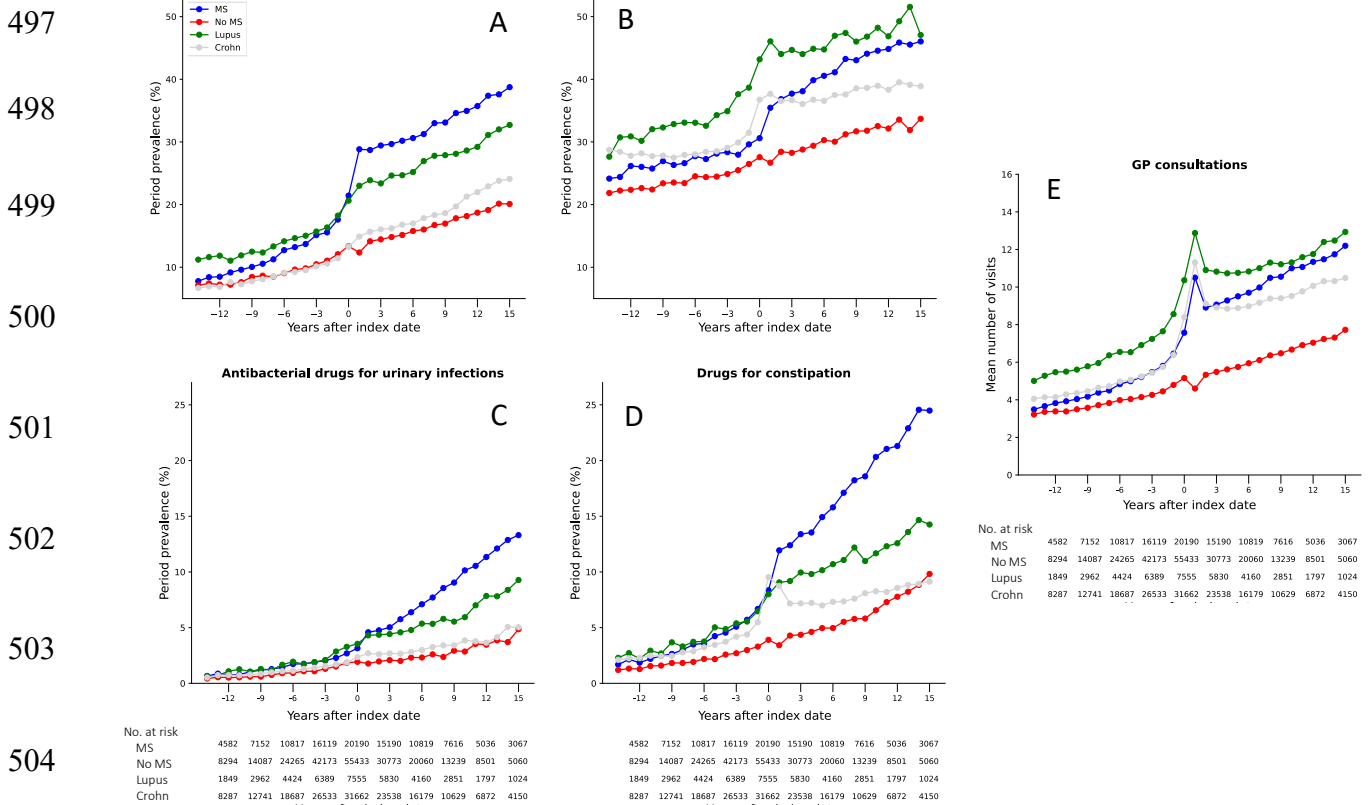
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488 **Figure 2. ORs for significant associations in the sensitivity analysis for five years before**
 489 **the index date in comparison to other auto-immune diseases.** Patients with MS are
 490 compared to patients with lupus and Crohn's disease in pooled data from the French and UK
 491 cohorts. OR > 1 indicates a higher association in MS cohort compared to Crohn's disease or
 492 lupus cohort. The size of the dot is proportional to the period prevalence. The period
 493 prevalence is defined as the number of diagnoses or symptoms observed over the period
 494 divided by the number of patients at risk during the period. Results from the French and UK
 495 cohorts individually are shown in **eFigure 3**.

496



505 **Figure 3. Period prevalence (%) of prescriptions associated with depression (A), urinary**
 506 **tract infections (B), bacterial infections (C), and constipation (D), and mean number of**
 507 **visits to the physician per year (E) in the pooled UK and France cohort. For a given**
 508 **prescription, the period prevalence is defined as the number of prescriptions observed over the**
 509 **period divided by the number of patients at risk during the period. Results from the French**
 510 **and UK cohorts individually are shown in eFigure 4 and 5.**

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648 **Contributors** OG, TN, CL and SD conceived and designed the study. LG extracted the data.

649 LG and OG ensured data quality and OG, TN, CL and SD analysed the data. OG and TN

650 generated the figures. OG, LG, BL, CL and SD interpreted the results and contributed to the

651 writing of the final version of the manuscript. All authors agreed with the results and

652 conclusions and approved the final draft.

653

654 **Competing interest** CL has received consulting or travel fees from Biogen, Novartis, Roche,
655 Sanofi, Teva and Merck Serono, none related to the present work. LG and BL are full time
656 employees of Cegedim.

657

658 **Data sharing statement** The data used in the preparation of the article are available from the
659 Cegedim company upon reasonable request (info@the-health-improvement-network.co.uk).

660

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662 program in neurodegenerative diseases (JPND) ANR-21-JPW2-0002-01 (LeMeReND) and
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667 Sappa of Alex Edelman and Associates.

668

669 **Ethics committee approval** Approval was sorted before carrying out this study (and for the
670 use of datasets). The study was a retrospective analysis of secondary anonymised patient data
671 only. For the UK database, data is only available to researchers carrying out approved medical
672 research. Ethical approval was granted by the NHS South-East Multicentre Research Ethics
673 Committee in 2003 (ref: 03/01/073) for establishment of the THIN database, and it was
674 updated in 2011. A further update and approval was granted in 2020 by the NHS South
675 Central, Oxford C Research Ethics Committee (Ref: 20/SC/0011). For the French Database,
676 several audits were conducted by CNIL (Commission Nationale de l'Informatique et des
677 Libertés, the French authority responsible for the protection of personal data). Data are

678 available from the GERS SAS for researchers who meet the criteria for access to confidential
679 data. Researchers willing to replicate the results should address a request to the Cegedim
680 company (info@the-health-improvement-network.co.uk). The study was approved by the
681 THIN Scientific Research Committee (SRC) on 4th Feb 2022 (SRC reference 21-016).

682 **Patient and Public involvement** We plan to disseminate the results of our research to the
683 public and relevant patient community through the current publication and its related press
684 release as well as presentations at scientific conferences.

685

686 The lead authors (CL, SD) affirm that this manuscript is an honest, accurate, and transparent
687 account of the study being reported; that no important aspects of the study have been omitted;
688 and that any discrepancies from the study as planned (and, if relevant, registered) have been
689 explained.

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Supplementary materials

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743 infections (B), bacterial infections (C), and constipation (D), and mean number of visits to the
744 physician per year (E) in the pooled cohort, 5 years before diagnosis up to 10 years after
745 diagnosis

746 **Supplementary method:** Details on data collection in THIN database

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748 French data were collected from a pool of 2500 general practitioners (GP),¹ and were
749 representative of the French population in terms of age, sex, and area of residence.² UK data
750 were collected from 400 general practices covering about 6% of the UK population, selected
751 for the THIN quality data-recording scheme with Vision practice management software.³
752 Several studies have already reported that the electronically coded diagnoses in this database
753 are representative of the UK general practice population in terms of demographics and type of
754 consultation.⁴ For each patient, diagnosis corresponding to each visit, prescriptions made by
755 the GP, and all other diagnoses associated with these prescriptions were available. Data for
756 education level and social status were not provided, to preserve anonymity.

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773 **eTable 1. Health conditions suggestive of a demyelinating claim**

Encephalitis, myelitis, encephalomyelitis (G04, G05)

Sequelae of inflammatory diseases of central nervous system (G09)

Demyelinating diseases of the CNS (G36, G37)

Retrobulbar neuritis and other disorders of the optic nerve and the visual pathways (H46, H47, H48)

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776 ***eTable 2. Health conditions suggestive of a MS relapse and positively associated with a future diagnosis of***
777 ***MS either in the French or British database.***

Paresthesia of skin (R20)

Tetany (R29)

Dizziness and giddiness (R42)

Abnormal and involuntary movement (R25)

Carpal tunnel syndrome (G56)

Disorders of vestibular function (H81)

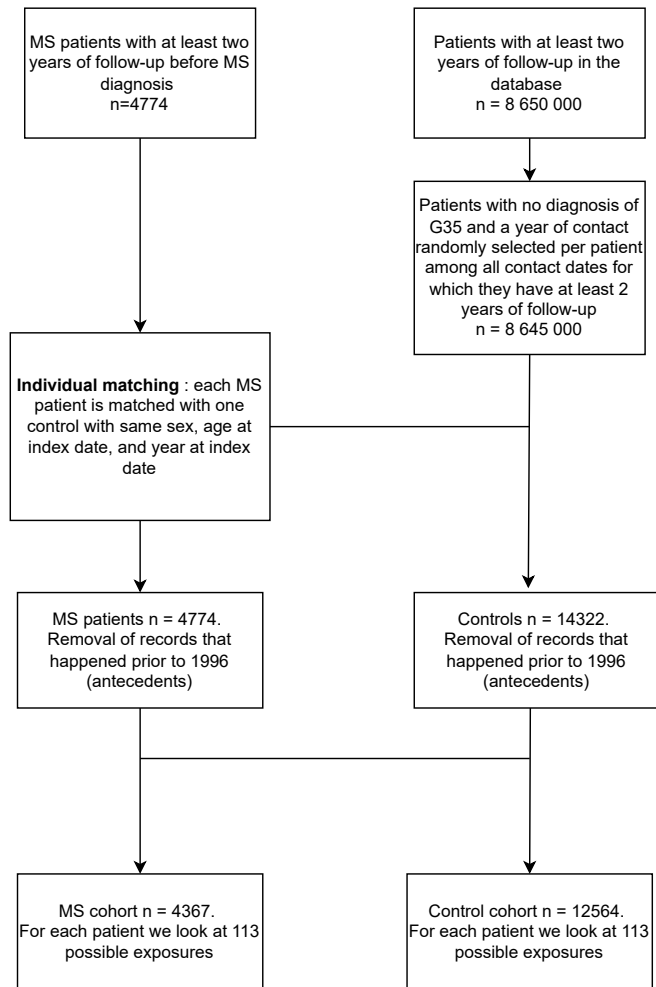
Visual disturbances (H53)

Contracture of muscle (M62)

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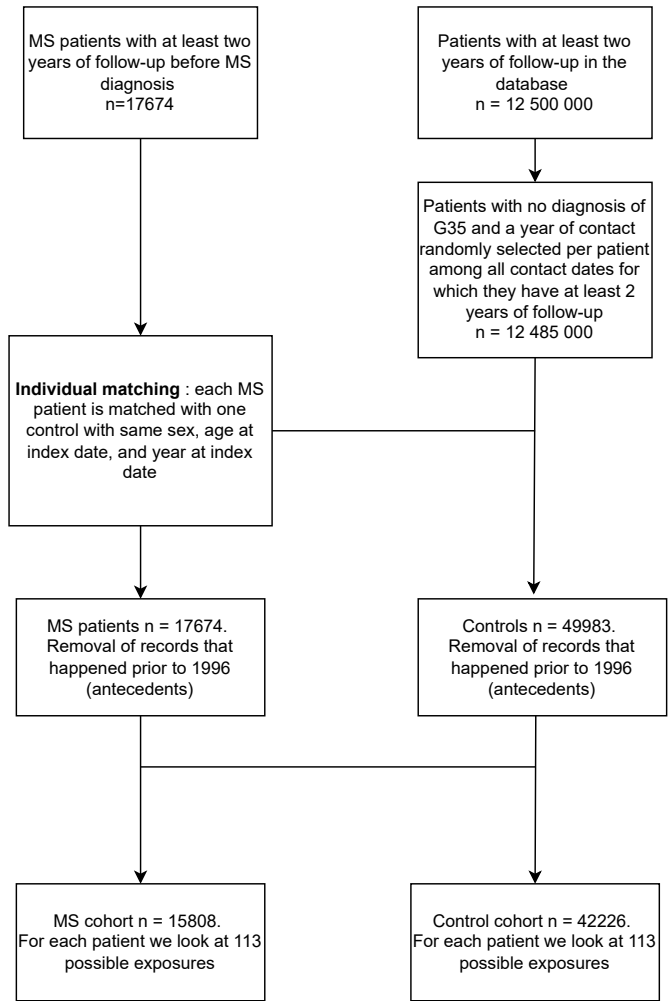
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eFigure 7. Patient selection flowchart for the French study. Note: the index date for controls is taken as the last contact date recorded during the year of contact selected randomly



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eFigure 8. Patient selection flowchart for the UK study. Note: the index date for controls is taken as the last contact date recorded during the year of contact selected randomly

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eTable 3. Proportion (%) of patients with at least one record of the conditions tested in the control populations in France and the UK at 5 years before the diagnosis. The 113 ICD10 codes that were recorded with a relative frequency of more than 0.5 % in both countries were considered.

	FR Controls (UK) n=42266	UK Controls (FR) n=12564
B00 : Herpesviral [herpes simplex] infections	3.36	2.02
B02 : Zoster	1.73	0.84
B07 : Viral warts	3.11	0.73
B34 : Viral infection of unspecified site	2.12	2.08
B35 : Dermatophytosis	5.5	2.39
B37 : Candidiasis	5.54	2.63
D50 : Iron deficiency anemia	1.89	1.09
D64 : Other anemias	0.73	0.97
E03 : Other hypothyroidism	4.51	2.39
E11 : Type 2 diabetes mellitus	3.77	2.45
E14 : Other diabetes	1.71	0.76
E66 : Overweight and obesity	1.48	1.88
E78 : Disorders of lipoprotein metabolism and other lipidemias	9.02	6.51
F10 : Alcohol related disorders	1.19	0.59
F32 : Major depressive disorder, single episode	19.65	10.75
F40 : Phobic anxiety disorders	0.88	1.19
F41 : Other anxiety disorders	8.43	10.27
F43 : Reaction to severe stress	1.49	3.3
F52 : Sexual dysfunction	1.54	1.96
G40 : Epilepsy and recurrent seizures	0.86	0.57
G43 : Migraine	4.7	4.9
G47 : Sleep disorders	1.92	6.47
G56 : Carpal tunnel syndrome	1.45	1.13
H00 : Hordeolum and chalazion	1.59	0.85
H10 : Conjunctivitis	6.02	4.21
H60 : Otitis externa	4.53	1.89
H61 : Other disorders of external ear	3.11	0.93
H66 : Suppurative and unspecified otitis media	2.2	5.1
H81 : Disorders of vestibular function	1.32	1.47
H92 : Otagia and effusion of ear	2.51	3.01
H93 : Other disorders of ear	1.03	1.05
I10 : Essential (primary) hypertension	13.7	10.51
I20 : Angina pectoris	1.14	0.58
I80 : Phlebitis and thrombophlebitis	1.09	0.71
I83 : Varicose veins of lower extremities	1.97	1.14
I84 : Hemorrhoids	6.62	3.37
J00 : Acute nasopharyngitis [common cold]	2.71	24.56
J01 : Acute sinusitis	5.7	9.52

J02 : Acute pharyngitis	6.52	17.18
J04 : Acute laryngitis and tracheitis	1.8	11.36
J11 : Influenza due to unidentified influenza virus	2.97	11.58
J20 : Acute bronchitis	2.54	9.62
J30 : Vasomotor and allergic rhinitis	5.0	2.71
J31 : Chronic rhinitis, nasopharyngitis and pharyngitis	1.17	2.16
J32 : Chronic sinusitis	0.69	0.82
J34 : Other and unspecified disorders of nose and nasal sinuses	1.17	2.11
J40 : Bronchitis	0.6	3.53
J45 : Asthma	7.99	5.07
K04 : Diseases of pulp and periapical tissues	1.06	1.03
K12 : Stomatitis and related lesions	0.98	0.9
K21 : Gastro-esophageal reflux disease	2.76	4.86
K29 : Gastritis and duodenitis	1.66	3.42
K30 : Functional dyspepsia	3.72	1.1
K44 : Diaphragmatic hernia	1.24	5.91
K58 : Irritable bowel syndrome	3.42	4.25
K59 : Functional intestinal disorders	4.37	5.22
K62 : Other diseases of anus and rectum	2.44	0.9
K80 : Cholelithiasis	0.89	0.85
L02 : Cutaneous abscess, furuncle and carbuncle	2.21	1.55
L03 : Cellulitis and acute lymphangitis	3.43	0.89
L21 : Seborrheic dermatitis	1.44	0.6
L29 : Pruritus	2.43	3.17
L30 : Other and unspecified dermatitis	4.74	4.8
L40 : Psoriasis	2.07	1.13
L50 : Urticaria	1.69	1.0
L65 : Other nonscarring hair loss	0.98	1.05
L70 : Acne	3.51	1.6
L98 : Other disorders of skin and subcutaneous tissue	4.61	0.94
M10 : Gout	1.11	0.53
M13 : Other arthritis	1.16	0.89
M19 : Other and unspecified osteoarthritis	3.09	3.77
M25 : Pain in joint	8.05	8.63
M47 : Spondylosis	1.3	1.82
M51 : Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders	0.84	0.93
M53 : Cervicobrachial syndrome	0.73	2.82
M54 : Dorsalgia	15.5	24.57
M62 : Contracture of muscle	0.63	2.09
M75 : Shoulder lesions	2.53	5.6
M77 : Other enthesopathies	3.31	6.11
M79 : Pain in limb, foot / Myalgia	14.24	8.77
M81 : Osteoporosis without current pathological fracture	0.96	0.98

N30 : Cystitis	6.99	6.81
N39 : Urinary tract infection, site not specified	5.36	2.77
N64 : Other disorders of breast	2.72	0.9
N76 : Other inflammation of vagina and vulva	1.25	1.17
N91 : Absent, scanty and rare menstruation	2.23	1.44
N92 : Excessive, frequent and irregular menstruation	7.58	1.72
N94 : Pain and other conditions associated with female genital organs and menstrual cycle	2.33	1.52
N95 : Menopausal and other perimenopausal disorders	4.91	3.13
R05 : Cough	0.83	16.59
R06 : Abnormalities of breathing	1.36	1.93
R07 : Pain in throat and chest	2.0	3.92
R10 : Abdominal and pelvic pain	4.93	12.45
R20 : Paresthesia of skin	0.86	0.82
R21 : Rash and other nonspecific skin eruption	2.35	1.13
R25 : Abnormal involuntary movements	1.25	1.33
R42 : Dizziness and giddiness	3.95	3.31
R51 : Headache	2.0	7.23
R52 : Pain, unspecified	0.99	4.52
R53 : Malaise and fatigue	1.64	12.53
R55 : Syncope and collapse	0.94	0.85
R59 : Enlarged lymph nodes	0.65	1.54
R60 : Edema, not elsewhere classified	0.92	1.32
R63 : Abnormal weight loss or gain	0.68	1.32
S83 : Dislocation and sprain of joints and ligaments of knee	0.78	0.87
S93 : Dislocation and sprain of joints and ligaments at ankle; foot and toe level	1.32	2.39
T14 : Injury of unspecified body region	3.55	8.27
T78 : Adverse effects, not elsewhere classified	1.56	8.34
Z01 : Encounter for other special examination without complaint, suspected or reported diagnosis	0.6	1.63
Z02 : Encounter for administrative examination	3.61	11.89
Z13 : Encounter for screening for other diseases and disorders	0.75	2.09
Z30 : Encounter for contraceptive management	14.1	8.36
Z76 : Persons encountering health services in other circumstances	1.5	10.29

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eTable 4. Prescriptions linked to diagnoses in the French database. Prescriptions are deemed as linked when they were given to more than 80 different people, and given in more than one out of three times for a particular diagnosis/symptom

ATC codes	ICD-10 codes
Ispaghula (psylla seeds) (A06AC01)	Other functional intestinal disorders (K59)
Macrogol (A06AD15)	Other functional intestinal disorders (K59)
Macrogol, combinations (A06AD65)	Other functional intestinal disorders (K59)
Enema combinations (A06AG20)	Other functional intestinal disorders (K59)
Carbon dioxide producing drugs (A06AX02)	Other functional intestinal disorders (K59)
Amphotericin B (A07AA07)	Candidiasis (B37)
Insulin glargine (A10AE04)	Type 2 diabetes mellitus (E11)
Metformin (A10BA02)	Type 2 diabetes mellitus (E11)
Gliclazide (A10BB09)	Type 2 diabetes mellitus (E11)
Glimepiride (A10BB12)	Type 2 diabetes mellitus (E11)
Metformin and sitagliptin (A10BD07)	Type 2 diabetes mellitus (E11)
Sitagliptin (A10BH01)	Type 2 diabetes mellitus (E11)
Repaglinide (A10BX02)	Type 2 diabetes mellitus (E11)
Vitamins, other combinations (A11JC)	Other nonscarring hair loss (L65)
Tranexamic acid (B02AA02)	Excessive, frequent and irregular menstruation (N92)
Hydrochlorothiazide (C03AA03)	Essential (primary) hypertension (I10)
Indapamide (C03BA11)	Essential (primary) hypertension (I10)
Spironolactone (C03DA01)	Essential (primary) hypertension (I10)
Other agents for treatment of hemorrhoids and anal fissures for topical use in ATC (C05AX)	Hemorrhoids (I84)
Other preparations, combinations (C05AX03)	Hemorrhoids (I84)
Rutoside, combinations (C05CA51)	Other disorders of veins (I87)
Atenolol (C07AB03)	Essential (primary) hypertension (I10)
Acebutolol (C07AB04)	Essential (primary) hypertension (I10)
Bisoprolol (C07AB07)	Essential (primary) hypertension (I10)
Celiprolol (C07AB08)	Essential (primary) hypertension (I10)
Nebivolol (C07AB12)	Essential (primary) hypertension (I10)
Amlodipine (C08CA01)	Essential (primary) hypertension (I10)
Nicardipine (C08CA04)	Essential (primary) hypertension (I10)
Lercanidipine (C08CA13)	Essential (primary) hypertension (I10)
Perindopril (C09AA04)	Essential (primary) hypertension (I10)
Ramipril (C09AA05)	Essential (primary) hypertension (I10)
Perindopril and diuretics (C09BA04)	Essential (primary) hypertension (I10)
Losartan (C09CA01)	Essential (primary) hypertension (I10)
Valsartan (C09CA03)	Essential (primary) hypertension (I10)
Irbesartan (C09CA04)	Essential (primary) hypertension (I10)
Candesartan (C09CA06)	Essential (primary) hypertension (I10)
Telmisartan (C09CA07)	Essential (primary) hypertension (I10)
Olmесartan medoxomil (C09CA08)	Essential (primary) hypertension (I10)
Losartan and diuretics (C09DA01)	Essential (primary) hypertension (I10)

Valsartan and diuretics (C09DA03)	Essential (primary) hypertension (I10)
Irbesartan and diuretics (C09DA04)	Essential (primary) hypertension (I10)
Valsartan and amlodipine (C09DB01)	Essential (primary) hypertension (I10)
Simvastatin (C10AA01)	Disorders of lipoprotein metabolism and other lipidemias (E78)
Pravastatin (C10AA03)	Disorders of lipoprotein metabolism and other lipidemias (E78)
Fluvastatin (C10AA04)	Disorders of lipoprotein metabolism and other lipidemias (E78)
Atorvastatin (C10AA05)	Disorders of lipoprotein metabolism and other lipidemias (E78)
Rosuvastatin (C10AA07)	Disorders of lipoprotein metabolism and other lipidemias (E78)
Fenofibrate (C10AB05)	Disorders of lipoprotein metabolism and other lipidemias (E78)
Ezetimibe (C10AX09)	Disorders of lipoprotein metabolism and other lipidemias (E78)
Amorolfine (D01AE16)	Dermatophytosis (B35)
Terbinafine (D01BA02)	Dermatophytosis (B35)
Calcipotriol, combinations (D05AX52)	Psoriasis (L40)
Aciclovir (D06BB03)	Herpesviral [herpes simplex] infections (B00)
Metronidazole (D06BX01)	Rosacea (L71)
Benzoyl peroxide (D10AE01)	Acne (L70)
Erythromycin (D10AF02)	Acne (L70)
Wart and anti-corn preparations (D11AF)	Viral warts (B07)
Other gynecologicals in ATC (G02CX)	Menopausal and other perimenopausal disorders (N95)
Levonorgestrel and ethinylestradiol (G03AA07)	Encounter for contraceptive management (Z30)
Desogestrel and ethinylestradiol (G03AA09)	Encounter for contraceptive management (Z30)
Gestodene and ethinylestradiol (G03AA10)	Encounter for contraceptive management (Z30)
Drospirenone and ethinylestradiol (G03AA12)	Encounter for contraceptive management (Z30)
Levonorgestrel and ethinylestradiol (G03AB03)	Encounter for contraceptive management (Z30)
Levonorgestrel (G03AC03)	Encounter for contraceptive management (Z30)
Desogestrel (G03AC09)	Encounter for contraceptive management (Z30)
Estradiol (G03CA03)	Menopausal and other perimenopausal disorders (N95)
Cyproterone and estrogen (G03HB01)	Encounter for contraceptive management (Z30)
Tadalafil (G04BE08)	Sexual dysfunction not caused by organic disorder or disease (F52)
Tamsulosin (G04CA02)	Benign prostatic hyperplasia (N40)
Levothyroxine sodium (H03AA01)	Other hypothyroidism (E03)
Pivmecillinam (J01CA08)	Cystitis (N30)
Phenoxymethylpenicillin (J01CE02)	Acute pharyngitis (J02)
Norfloxacin (J01MA06)	Cystitis (N30)
Moxifloxacin (J01MA14)	Acute sinusitis (J01)
Nitrofurantoin (J01XE01)	Cystitis (N30)
Fosfomycin (J01XX01)	Cystitis (N30)
Aciclovir (J05AB01)	Herpesviral [herpes simplex] infections (B00)
Oseltamivir (J05AH02)	Influenza due to unidentified influenza virus (J11)
Pneumococcus, purified polysaccharides antigen (J07AL01)	Need for immunization against other single infectious diseases (Z26)
Tetanus toxoid (J07AM01)	Need for immunization against other single infectious diseases (Z26)
Typhoid, purified polysaccharide antigen (J07AP03)	Need for immunization against other single infectious diseases (Z26)
Hepatitis B, purified antigen (J07BC01)	Need for immunization against other single infectious diseases (Z26)

Hepatitis A, inactivated, whole virus (J07BC02)	Need for immunization against other single infectious diseases (Z26)
Measles, combinations with mumps and rubella, live attenuated (J07BD52)	Need for immunization against other single infectious diseases (Z26)
Papillomavirus (human types 6, 11, 16, 18) (J07BM01)	Need for immunization against other single infectious diseases (Z26)
Diphtheria-poliomyelitis-tetanus (J07CA01)	Need for immunization against other single infectious diseases (Z26)
Diphtheria-pertussis-poliomyelitis-tetanus (J07CA02)	Need for immunization against other single infectious diseases (Z26)
Meloxicam (M01AC06)	Dorsalgia (M54)
Methocarbamol (M03BA03)	Dorsalgia (M54)
Colchicine (M04AC01)	Gout (M10)
Risedronic acid (M05BA07)	Osteoporosis without current pathological fracture (M81)
Sumatriptan (N02CC01)	Migraine (G43)
Naratriptan (N02CC02)	Migraine (G43)
Zolmitriptan (N02CC03)	Migraine (G43)
Almotriptan (N02CC05)	Migraine (G43)
Eletriptan (N02CC06)	Migraine (G43)
Frovatriptan (N02CC07)	Migraine (G43)
Loprazolam (N05CD11)	Sleep disorders (G47)
Fluoxetine (N06AB03)	Major depressive disorder, single episode (F32)
Citalopram (N06AB04)	Major depressive disorder, single episode (F32)
Paroxetine (N06AB05)	Major depressive disorder, single episode (F32)
Sertraline (N06AB06)	Major depressive disorder, single episode (F32)
Escitalopram (N06AB10)	Major depressive disorder, single episode (F32)
Mianserin (N06AX03)	Major depressive disorder, single episode (F32)
Mirtazapine (N06AX11)	Major depressive disorder, single episode (F32)
Venlafaxine (N06AX16)	Major depressive disorder, single episode (F32)
Duloxetine (N06AX21)	Major depressive disorder, single episode (F32)
Varenicline (N07BA03)	Nicotine dependence (F17)
Bethahistine (N07CA01)	Dizziness and giddiness (R42)
Proguanil, combinations (P01BB51)	Persons encountering health services for other counseling and medical advice, not elsewhere classified (Z71)
Ivermectin (P02CF01)	Scabies (B86)
Benzyl benzoate (P03AX01)	Scabies (B86)
Dexamethasone, combinations (R01AD53)	Acute nasopharyngitis [common cold] (J00)
Other nasal preparation combinations in ATC (R01AX30)	Acute nasopharyngitis [common cold] (J00)
Pseudoephedrine (R01BA02)	Acute nasopharyngitis [common cold] (J00)
Fusafungine (R02AB03)	Acute nasopharyngitis [common cold] (J00)
Terbutaline (R03AC03)	Asthma (J45)
Formoterol (R03AC13)	Asthma (J45)
Salmeterol and fluticasone (R03AK06)	Asthma (J45)
Montelukast (R03DC03)	Asthma (J45)
OTHER COLD PREPARATIONS in ATC (R05X)	Acute nasopharyngitis [common cold] (J00)
Tobramycin (S01AA12)	Conjunctivitis (H10)
Fusidic acid (S01AA13)	Conjunctivitis (H10)
Azithromycin (S01AA26)	Conjunctivitis (H10)
Sodium borate (S01AX07)	Conjunctivitis (H10)

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Indifferent preparations, otologicals (S02DC)

Other disorders of external ear (H61)

802 **eTable 5. ORs for all health conditions in over 0.5% of patients and controls individually associated with a**
803 **future symptom specific of MS at 5 years before the index date. In the primary analysis, we used the first**
804 **recorded demyelinating event as the index date, while in the sensitivity analysis, we used the first symptom**
805 **suggestive of MS as the index date. * cannot be calculated because too few presentations were recorded (health**
806 **conditions defined by ICD-10 codes with a relative frequency of less than 0.5). ORs and p-value are adjusted for**
807 **multiple comparisons using the Bonferroni method. P-values greater to 1 are clipped to 1.**

	Primary analysis				Sensitivity analysis			
	OR (Adjusted 95% CI)	FR Adjusted p value	OR (Adjusted 95% CI)	UK Adjusted p value	OR (Adjusted 95% CI)	FR Adjusted p value	OR (Adjusted 95% CI)	UK Adjusted p value
B00 : Herpesviral [herpes simplex] infections	1.36 (0.89 - 2.08)	1	1.02 (0.84 - 1.24)	1	1.06 (0.66 - 1.73)	1	1.0 (0.80 - 1.24)	1
B02 : Zoster	2.59 (1.49 - 4.51)	<0.0001	0.93 (0.70 - 1.23)	1	1.32 (0.66 - 2.64)	1	0.85 (0.62 - 1.16)	1
B07 : Viral warts	1.51 (0.76 - 2.98)	1	0.74 (0.59 - 0.93)	0.0001	1.13 (0.52 - 2.46)	1	0.82 (0.65 - 1.03)	0.159
B34 : Viral infection of unspecified site	1.4 (0.92 - 2.13)	0.38	1.0 (0.77 - 1.28)	1	1.4 (0.89 - 2.20)	0.731	0.96 (0.73 - 1.25)	1
B35 : Dermatophytosis	1.5 (1.03 - 2.20)	0.009	0.89 (0.76 - 1.05)	1	1.29 (0.84 - 1.98)	1	0.88 (0.74 - 1.05)	1
B37 : Candidiasis	1.58 (1.10 - 2.27)	0.0003	0.88 (0.74 - 1.03)	0.397	1.35 (0.89 - 2.04)	0.958	0.82 (0.69 - 0.98)	0.006
D50 : Iron deficiency anemia	1.82 (1.07 - 3.10)	0.004	0.8 (0.60 - 1.06)	0.537	1.71 (0.97 - 3.03)	0.059	0.73 (0.53 - 1.00)	0.03
D64 : Other anemias	1.3 (0.70 - 2.42)	1	1.04 (0.69 - 1.59)	1	1.02 (0.49 - 2.11)	1	1.0 (0.63 - 1.58)	1
E03 : Other hypothyroidism	1.35 (0.90 - 2.00)	0.771	1.0 (0.84 - 1.19)	1	1.28 (0.82 - 1.99)	1	1.01 (0.84 - 1.21)	1
E11 : Type 2 diabetes mellitus	1.56 (1.07 - 2.28)	0.001	0.76 (0.62 - 0.93)	<0.0001	1.27 (0.82 - 1.96)	1	0.78 (0.62 - 0.97)	0.003
E14 : Other diabetes	0.9 (0.41 - 1.98)	1	0.85 (0.63 - 1.14)	1	0.76 (0.31 - 1.87)	1	0.89 (0.65 - 1.22)	1
E66 : Overweight and obesity	1.25 (0.79 - 1.99)	1	0.73 (0.53 - 1.03)	0.076	1.26 (0.78 - 2.04)	1	0.66 (0.46 - 0.96)	0.005
E78 : Disorders of lipoprotein metabolism and other lipidemias	1.27 (0.99 - 1.64)	0.053	0.85 (0.75 - 0.97)	0.0003	1.07 (0.81 - 1.42)	1	0.8 (0.69 - 0.92)	<0.0001
F10 : Alcohol related disorders	1.38 (0.63 - 3.05)	1	0.55 (0.36 - 0.84)	<0.0001	*	*	0.51 (0.32 - 0.81)	<0.0001
F32 : Major depressive disorder, single episode	1.84 (1.52 - 2.21)	<0.0001	1.24 (1.14 - 1.36)	<0.0001	1.62 (1.32 - 1.98)	<0.0001	1.22 (1.11 - 1.34)	<0.0001
F40 : Phobic anxiety disorders	1.84 (1.09 - 3.09)	0.001	0.87 (0.58 - 1.31)	1	1.56 (0.92 - 2.66)	0.233	0.73 (0.45 - 1.16)	1
F41 : Other anxiety disorders	1.57 (1.29 - 1.91)	<0.0001	0.85 (0.74 - 0.98)	0.001	1.4 (1.13 - 1.73)	<0.0001	0.78 (0.67 - 0.91)	<0.0001
F43 : Reaction to severe stress	1.69 (1.23 - 2.32)	<0.0001	0.83 (0.60 - 1.15)	1	1.47 (1.05 - 2.07)	0.003	0.8 (0.58 - 1.12)	1
F52 : Sexual dysfunction	1.92 (1.29 - 2.86)	<0.0001	1.54 (1.19 - 1.99)	<0.0001	1.69 (1.10 - 2.62)	0.0008	1.47 (1.11 - 1.95)	<0.0001
G40 : Epilepsy and recurrent seizures	2.54 (1.30 - 4.97)	<0.0001	1.43 (1.00 - 2.04)	0.021	*	*	1.46 (1.00 - 2.12)	0.022
G43 : Migraine	1.55 (1.18 - 2.03)	<0.0001	1.12 (0.95 - 1.32)	1	1.21 (0.89 - 1.65)	1	1.07 (0.89 - 1.28)	1
G47 : Sleep disorders	1.64 (1.30 - 2.08)	<0.0001	1.07 (0.82 - 1.39)	1	1.36 (1.04 - 1.78)	0.002	1.01 (0.76 - 1.34)	1
G56 : Carpal tunnel syndrome	2.64 (1.64 - 4.22)	<0.0001	1.26 (0.95 - 1.67)	0.304	*	*	*	*
H00 : Hordeolum and chalazion	2.53 (1.47 - 4.36)	<0.0001	0.92 (0.68 - 1.23)	1	2.08 (1.12 - 3.83)	0.001	0.91 (0.66 - 1.26)	1
H10 : Conjunctivitis	1.42 (1.05 - 1.91)	0.002	0.85 (0.73 - 1.00)	0.026	1.28 (0.93 - 1.77)	0.514	0.82 (0.70 - 0.98)	0.003
H60 : Otitis externa	1.45 (0.94 - 2.24)	0.184	0.85 (0.71 - 1.02)	0.146	1.49 (0.93 - 2.37)	0.195	0.76 (0.62 - 0.93)	<0.0001
H61 : Other disorders of external ear	1.58 (0.87 - 2.85)	0.576	1.0 (0.81 - 1.23)	1	1.28 (0.66 - 2.50)	1	0.94 (0.75 - 1.17)	1
H66 : Suppurative and unspecified otitis media	1.45 (1.11 - 1.91)	<0.0001	0.87 (0.68 - 1.13)	1	1.32 (0.98 - 1.76)	0.054	0.93 (0.71 - 1.22)	1
H81 : Disorders of vestibular function	2.22 (1.44 - 3.43)	<0.0001	1.49 (1.13 - 1.97)	<0.0001	*	*	*	*
H92 : Otalgia and effusion of ear	1.59 (1.13 - 2.23)	<0.0001	0.9 (0.71 - 1.14)	1	1.5 (1.03 - 2.18)	0.007	0.8 (0.62 - 1.04)	0.24
H93 : Other disorders of ear, not elsewhere classified	1.38 (0.77 - 2.46)	1	1.02 (0.71 - 1.45)	1	0.87 (0.42 - 1.82)	1	0.78 (0.51 - 1.20)	1
I10 : Essential (primary) hypertension	1.28 (1.05 - 1.57)	0.0006	0.79 (0.70 - 0.88)	<0.0001	1.09 (0.87 - 1.37)	23.439	0.78 (0.69 - 0.88)	<0.0001
I20 : Angina pectoris	1.15 (0.49 - 2.70)	1	0.86 (0.60 - 1.24)	1	0.98 (0.38 - 2.52)	1	0.78 (0.53 - 1.16)	1
I80 : Phlebitis and thrombophlebitis	1.65 (0.84 - 3.24)	0.817	0.93 (0.65 - 1.33)	1	1.31 (0.57 - 3.01)	1	0.92 (0.62 - 1.35)	1

I83 : Varicose veins of lower extremities	1.47 (0.84 - 2.55)	1	0.67 (0.50 - 0.91)	<0.0001	1.32 (0.72 - 2.41)	1	0.68 (0.49 - 0.93)	0.0006
I84 : Hemorrhoids	1.46 (1.05 - 2.04)	0.002	0.82 (0.70 - 0.96)	0.0002	1.28 (0.89 - 1.83)	1	0.81 (0.68 - 0.95)	0.0001
J00 : Acute nasopharyngitis [common cold]	1.4 (1.20 - 1.62)	<0.0001	1.02 (0.82 - 1.27)	1	1.3 (1.12 - 1.52)	<0.0001	0.97 (0.77 - 1.23)	1
J01 : Acute sinusitis	1.48 (1.20 - 1.82)	<0.0001	0.91 (0.78 - 1.07)	1	1.39 (1.11 - 1.72)	<0.0001	0.91 (0.77 - 1.08)	1
J02 : Acute pharyngitis	1.35 (1.14 - 1.59)	<0.0001	0.83 (0.71 - 0.96)	0.0004	1.32 (1.11 - 1.57)	<0.0001	0.81 (0.69 - 0.96)	0.0004
J04 : Acute laryngitis and tracheitis	1.36 (1.12 - 1.65)	<0.0001	0.94 (0.71 - 1.24)	1	1.3 (1.05 - 1.59)	0.0003	0.93 (0.69 - 1.25)	1
J11 : Influenza due to unidentified influenza virus	1.31 (1.08 - 1.60)	<0.0001	0.87 (0.70 - 1.09)	1	1.25 (1.02 - 1.54)	0.005	0.86 (0.68 - 1.09)	1
J20 : Acute bronchitis	1.46 (1.19 - 1.80)	<0.0001	0.84 (0.65 - 1.07)	1	1.41 (1.14 - 1.75)	<0.0001	0.74 (0.56 - 0.97)	0.003
J30 : Vasomotor and allergic rhinitis	1.42 (0.98 - 2.06)	0.048	0.7 (0.58 - 0.85)	<0.0001	1.39 (0.93 - 2.08)	0.288	0.72 (0.59 - 0.88)	<0.0001
J31 : Chronic rhinitis, nasopharyngitis and pharyngitis	1.44 (0.96 - 2.18)	0.123	0.94 (0.67 - 1.33)	1	1.3 (0.85 - 2.00)	1	0.75 (0.51 - 1.11)	0.97
J32 : Chronic sinusitis	1.45 (0.75 - 2.82)	1	0.77 (0.47 - 1.24)	1	1.25 (0.62 - 2.53)	1	*	*
J34 : Other and unspecified disorders of nose and nasal sinuses	1.11 (0.71 - 1.73)	1	0.81 (0.57 - 1.17)	1	1.08 (0.66 - 1.75)	1	0.81 (0.55 - 1.18)	1
J40 : Bronchitis, not specified as acute or chronic	1.51 (1.10 - 2.07)	0.0001	1.18 (0.75 - 1.85)	1	1.37 (0.96 - 1.96)	0.126	1.18 (0.75 - 1.85)	1
J45 : Asthma	1.38 (1.05 - 1.83)	0.001	0.81 (0.70 - 0.93)	<0.0001	1.28 (0.95 - 1.73)	0.266	0.83 (0.72 - 0.97)	0.0007
K04 : Diseases of pulp and periapical tissues	1.6 (0.91 - 2.80)	0.275	0.88 (0.61 - 1.28)	1	1.47 (0.79 - 2.76)	1	0.8 (0.54 - 1.20)	1
K12 : Stomatitis and related lesions	1.11 (0.56 - 2.18)	1	0.77 (0.51 - 1.14)	1	1.03 (0.50 - 2.12)	1	0.76 (0.50 - 1.17)	1
K21 : Gastro-esophageal reflux disease	1.26 (0.94 - 1.68)	0.48	0.74 (0.58 - 0.94)	0.0005	1.1 (0.80 - 1.52)	1	0.7 (0.53 - 0.92)	<0.0001
K29 : Gastritis and duodenitis	1.54 (1.11 - 2.12)	<0.0001	0.75 (0.55 - 1.02)	0.081	1.26 (0.88 - 1.79)	1	0.67 (0.47 - 0.95)	0.003
K30 : Functional dyspepsia	1.23 (0.68 - 2.23)	1	0.77 (0.63 - 0.95)	0.0005	0.9 (0.44 - 1.82)	1	0.72 (0.58 - 0.91)	<0.0001
K44 : Diaphragmatic hernia	1.42 (1.10 - 1.83)	<0.0001	0.67 (0.46 - 0.98)	0.011	1.31 (1.00 - 1.72)	0.027	0.67 (0.45 - 1.01)	0.042
K58 : Irritable bowel syndrome	1.43 (1.06 - 1.93)	0.0007	0.82 (0.66 - 1.01)	0.068	1.42 (1.04 - 1.94)	0.003	0.82 (0.65 - 1.03)	0.189
K59 : Functional intestinal disorders	1.9 (1.47 - 2.44)	<0.0001	1.58 (1.35 - 1.84)	<0.0001	1.66 (1.27 - 2.17)	<0.0001	1.5 (1.27 - 1.78)	<0.0001
K62 : Other diseases of anus and rectum	0.86 (0.68 - 1.10)	1	0.86 (0.68 - 1.10)	1	1.11 (0.53 - 2.33)	1	0.77 (0.58 - 1.01)	0.05
K80 : Cholelithiasis	1.35 (0.69 - 2.63)	1	0.81 (0.54 - 1.22)	1	1.33 (0.67 - 2.66)	1	0.74 (0.47 - 1.19)	1
L02 : Cutaneous abscess, furuncle and carbuncle	1.5 (0.93 - 2.40)	0.201	0.84 (0.65 - 1.09)	1	1.37 (0.80 - 2.34)	1	0.82 (0.62 - 1.09)	1
L03 : Cellulitis and acute lymphangitis	1.78 (0.99 - 3.20)	0.036	1.01 (0.83 - 1.23)	1	1.57 (0.82 - 3.03)	1	0.92 (0.74 - 1.15)	1
L21 : Seborrheic dermatitis	1.67 (0.81 - 3.45)	1	0.86 (0.63 - 1.19)	1	*	*	0.88 (0.63 - 1.24)	1
L29 : Pruritus	1.3 (0.91 - 1.85)	0.865	0.99 (0.78 - 1.25)	1	1.16 (0.79 - 1.71)	1	0.85 (0.65 - 1.11)	1
L30 : Other and unspecified dermatitis	1.43 (1.08 - 1.89)	0.0002	1.0 (0.84 - 1.18)	1	1.37 (1.01 - 1.87)	0.016	1.0 (0.84 - 1.20)	1
L40 : Psoriasis	1.97 (1.18 - 3.27)	<0.0001	0.92 (0.71 - 1.20)	1	1.44 (0.80 - 2.61)	1	0.91 (0.69 - 1.20)	1
L50 : Urticaria	1.83 (1.05 - 3.18)	0.006	0.83 (0.61 - 1.12)	1	1.84 (1.02 - 3.30)	0.014	0.71 (0.51 - 1.00)	0.031
L65 : Other nonscarring hair loss	1.84 (1.07 - 3.16)	0.003	0.68 (0.45 - 1.04)	0.089	1.92 (1.06 - 3.49)	0.006	0.72 (0.46 - 1.12)	0.871
L70 : Acne	1.86 (1.20 - 2.89)	<0.0001	0.79 (0.64 - 0.98)	0.006	1.72 (1.08 - 2.75)	0.002	0.77 (0.61 - 0.96)	0.001
L98 : Other disorders of skin and subcutaneous tissue, not elsewhere classified	1.38 (0.74 - 2.57)	1	0.75 (0.62 - 0.91)	<0.0001	1.45 (0.73 - 2.90)	1	0.7 (0.57 - 0.86)	<0.0001
M10 : Gout	1.11 (0.45 - 2.73)	1	0.53 (0.34 - 0.81)	<0.0001	*	*	0.53 (0.33 - 0.85)	<0.0001
M13 : Other arthritis	1.26 (0.65 - 2.43)	1	0.75 (0.52 - 1.10)	0.768	1.11 (0.52 - 2.33)	1	0.69 (0.45 - 1.04)	0.106
M19 : Other and unspecified osteoarthritis	1.2 (0.86 - 1.67)	1	0.73 (0.58 - 0.92)	<0.0001	1.02 (0.70 - 1.48)	1	0.68 (0.52 - 0.87)	<0.0001
M25 : Pain in joint	1.5 (1.21 - 1.86)	<0.0001	0.97 (0.85 - 1.11)	1	1.39 (1.10 - 1.75)	<0.0001	0.91 (0.79 - 1.05)	1
M47 : Spondylosis	1.51 (0.97 - 2.34)	0.067	1.2 (0.89 - 1.62)	1	1.24 (0.76 - 2.00)	1	1.09 (0.78 - 1.52)	1
M51 : Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders	1.48 (0.82 - 2.69)	1	1.13 (0.77 - 1.66)	1	1.23 (0.60 - 2.52)	1	1.0 (0.65 - 1.53)	1

M53 : Cervicobrachial syndrome	1.85 (1.32 - 2.57)	<0.0001	1.15 (0.77 - 1.73)	1	1.47 (1.01 - 2.16)	0.019	1.01 (0.65 - 1.57)	1
M54 : Dorsalgia	1.56 (1.35 - 1.80)	<0.0001	1.0 (0.90 - 1.10)	1	0.98 (0.62 - 1.61)	<0.0001	0.9 (0.81 - 1.01)	0.057
M62 : Contracture of muscle	2.09 (1.44 - 3.02)	<0.0001	0.89 (0.70 - 1.55)	1	*	*	*	*
M75 : Shoulder lesions	1.28 (0.98 - 1.68)	0.065	1.12	1	1.11 (0.82 - 1.51)	1	0.78 (0.60 - 1.03)	0.106
M77 : Other enthesopathies	1.38 (1.07 - 1.77)	0.0003	0.77 (0.62 - 0.96)	0.0009	1.11 (0.84 - 1.48)	1	0.74 (0.58 - 0.94)	0.0003
M79 : Pain in limb, foot / Myalgia	1.72 (1.40 - 2.11)	<0.0001	1.1 (1.00 - 1.22)	0.057	1.46 (1.16 - 1.83)	<0.0001	0.96 (0.86 - 1.07)	1
M81 : Osteoporosis without current pathological fracture	1.35 (0.73 - 2.48)	1	1.07 (0.74 - 1.53)	1	1.21 (0.61 - 2.39)	1	1.0 (0.67 - 1.49)	1
N30 : Cystitis	1.68 (1.34 - 2.12)	<0.0001	1.22 (1.07 - 1.39)	<0.0001	1.5 (1.16 - 1.94)	<0.0001	1.21 (1.05 - 1.39)	0.0001
N39 : Urinary tract infection, site not specified	1.79 (1.27 - 2.51)	<0.0001	1.47 (1.27 - 1.70)	<0.0001	1.68 (1.14 - 2.46)	<0.0001	1.38 (1.18 - 1.61)	<0.0001
N64 : Other disorders of breast	2.15 (1.24 - 3.74)	<0.0001	0.88 (0.70 - 1.11)	1	1.48 (0.78 - 2.79)	1	0.77 (0.60 - 1.00)	0.033
N76 : Other inflammation of vagina and vulva	1.57 (0.92 - 2.69)	0.233	0.86 (0.61 - 1.21)	1	1.38 (0.75 - 2.53)	1	0.83 (0.58 - 1.19)	1
N91 : Absent, scanty and rare menstruation	1.62 (0.99 - 2.63)	0.03	0.85 (0.65 - 1.10)	1	1.22 (0.70 - 2.13)	1	0.87 (0.66 - 1.15)	1
N92 : Excessive, frequent and irregular menstruation	1.7 (1.10 - 2.62)	0.0005	0.85 (0.73 - 0.98)	0.002	1.45 (0.91 - 2.33)	0.447	0.86 (0.73 - 1.00)	0.018
N94 : Pain and other conditions associated with female genital organs and menstrual cycle	1.54 (0.96 - 2.48)	0.084	0.99 (0.78 - 1.27)	1	1.56 (0.95 - 2.56)	0.113	0.99 (0.77 - 1.27)	1
N95 : Menopausal and other perimenopausal disorders	1.18 (0.82 - 1.70)	1	0.92 (0.77 - 1.09)	1	1.0 (0.66 - 1.51)	1	0.88 (0.73 - 1.07)	1
R05 : Cough	1.24 (1.04 - 1.47)	0.0005	1.04 (0.71 - 1.55)	1	1.2 (1.01 - 1.44)	0.014	0.96 (0.62 - 1.47)	1
R06 : Abnormalities of breathing	1.39 (0.90 - 2.15)	0.61	0.79 (0.56 - 1.11)	1	1.33 (0.82 - 2.17)	1	0.7 (0.48 - 1.02)	0.061
R07 : Pain in throat and chest	1.32 (0.97 - 1.81)	0.115	0.82 (0.63 - 1.08)	1	1.2 (0.84 - 1.70)	1	0.71 (0.52 - 0.96)	0.003
R10 : Abdominal and pelvic pain	1.28 (1.06 - 1.55)	0.0001	0.88 (0.74 - 1.05)	1	1.18 (0.97 - 1.45)	0.285	0.84 (0.70 - 1.01)	0.077
R20 : Paresthesia of skin	14.81 (9.74 - 22.52)	<0.0001	9.45 (7.42 - 12.04)	<0.0001	*	*	*	*
R21 : Rash and other nonspecific skin eruption	1.4 (0.80 - 2.45)	1	1.04 (0.82 - 1.31)	1	1.02 (0.51 - 2.05)	1	0.93 (0.72 - 1.20)	1
R25 : Abnormal involuntary movements	1.47 (0.89 - 2.45)	0.654	2.32 (1.80 - 2.99)	<0.0001	1.21 (0.66 - 2.19)	1	*	*
R42 : Dizziness and giddiness	2.57 (1.93 - 3.41)	<0.0001	2.08 (1.78 - 2.41)	<0.0001	*	*	*	*
R51 : Headache	1.48 (1.18 - 1.87)	<0.0001	1.28 (1.01 - 1.62)	0.019	1.17 (0.90 - 1.51)	1	1.14 (0.88 - 1.48)	1
R52 : Pain, unspecified	1.66 (1.26 - 2.18)	<0.0001	0.96 (0.67 - 1.39)	1	1.32 (0.96 - 1.82)	0.172	0.83 (0.55 - 1.25)	1
R53 : Malaise and fatigue	1.76 (1.47 - 2.10)	<0.0001	1.45 (1.13 - 1.87)	<0.0001	1.55 (1.28 - 1.88)	<0.0001	1.21 (0.92 - 1.59)	1
R55 : Syncope and collapse	2.01 (1.13 - 3.58)	0.0007	1.07 (0.74 - 1.55)	1	1.33 (0.70 - 2.54)	1	0.93 (0.62 - 1.41)	1
R59 : Enlarged lymph nodes	1.76 (1.12 - 2.78)	0.0004	0.86 (0.54 - 1.39)	1	1.68 (1.04 - 2.69)	0.006	*	*
R60 : Edema, not elsewhere classified	1.47 (0.88 - 2.47)	0.702	0.99 (0.68 - 1.44)	1	1.36 (0.75 - 2.44)	1	0.79 (0.51 - 1.22)	1
R63 : Abnormal weight loss or gain	1.7 (1.04 - 2.78)	0.007	1.03 (0.67 - 1.59)	1	1.55 (0.88 - 2.70)	0.502	0.81 (0.49 - 1.33)	1
S83 : Dislocation and sprain of joints and ligaments of knee	1.51 (0.81 - 2.80)	1	0.7 (0.44 - 1.12)	0.717	1.27 (0.63 - 2.54)	1	*	*
S93 : Dislocation and sprain of joints and ligaments at ankle, foot and toe level	1.69 (1.17 - 2.45)	<0.0001	1.06 (0.78 - 1.45)	1	1.41 (0.94 - 2.10)	0.204	0.97 (0.69 - 1.36)	1
T14 : Injury of unspecified body region	1.66 (1.34 - 2.05)	<0.0001	0.93 (0.76 - 1.14)	1	1.34 (1.06 - 1.69)	0.0003	0.87 (0.70 - 1.08)	1
T78 : Adverse effects, not elsewhere classified	1.28 (1.02 - 1.61)	0.005	0.92 (0.68 - 1.25)	1	1.24 (0.97 - 1.57)	0.149	0.92 (0.67 - 1.28)	1
Z01 : Encounter for other special examination without complaint, suspected or reported diagnosis	1.16 (0.71 - 1.91)	1	1.11 (0.70 - 1.74)	1	0.75 (0.39 - 1.44)	1	*	*
Z02 : Encounter for administrative examination	1.37 (1.13 - 1.65)	<0.0001	1.24 (1.04 - 1.48)	0.0009	1.2 (0.98 - 1.48)	0.106	1.03 (0.84 - 1.27)	1
Z13 : Encounter for screening for other diseases and disorders	1.04 (0.66 - 1.65)	1	0.65 (0.41 - 1.05)	0.128	1.04 (0.64 - 1.70)	1	*	*
Z30 : Encounter for contraceptive management	1.35 (1.08 - 1.68)	<0.0001	0.98 (0.89 - 1.09)	1	1.4 (1.11 - 1.76)	<0.0001	1.06 (0.96 - 1.18)	1
Z76 : Persons encountering health services	1.22 (0.99 - 1.50)	0.065	0.81 (0.59 - 1.11)	1	1.12 (0.89 - 1.40)	1	0.84 (0.59 - 1.20)	1

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810 **eTable 6. ORs for all health conditions individually associated with a future diagnosis of MS for the five-year**
811 **period leading up to the index date. In the primary analysis, we used the first recorded G35 code or**
812 **demyelinating event as the index date, whereas, in the sensitivity analysis, we used the first recorded G35, or**
813 **demyelinating event or first symptom suggestive of MS as the index date. . . * cannot be calculated because the**
814 **health condition is used to define the index date in the sensitivity analysis. . . * cannot be calculated because too**
815 **few presentations were recorded (health conditions defined by ICD-10 codes with a relative frequency of less**
816 **than 0.5%). ORs and p-value are adjusted for multiple comparisons using the Bonferroni method. P-values**
817 **greater to 1 are clipped to 1.**

	Primary analysis						Sensitivity analysis					
	FR			UK			FR			UK		
	No. (%) [MS:controls]	OR (Adjusted 95% CI)	Adjusted p value	No. (%) [MS:controls]	OR (Adjusted 95% CI)	Adjusted p value	No. (%) [MS:controls]	OR (Adjusted 95% CI)	Adjusted p value	No. (%) [MS:controls]	OR (Adjusted 95% CI)	Adjusted p value
F32 : Major depressive disorder, single episode	789 (18.1): 1350 (10.8)	1.84 (1.52 - 2.21)	<0.0001	3801 (24.0): 8297 (19.6)	1.24 (1.14 - 1.36)	<0.0001	630 (14.4): 1139 (9.1)	1.62 (1.32 - 1.98)	<0.0001	3295 (20.8): 7030 (16.6)	1.22 (1.11 - 1.34)	<0.0001
F52 : Sexual dysfunction	154 (3.6): 246 (2.0)	1.92 (1.29 - 2.86)	<0.0001	388 (2.5): 650 (1.5)	1.54 (1.19 - 1.99)	<0.0001	123 (2.8): 209 (1.7)	1.69 (1.10 - 2.62)	0.0008	305 (1.9): 515 (1.2)	1.47 (1.11 - 1.95)	<0.0001
G40 : Epilepsy and recurrent seizures	61 (1.4): 71 (0.6)	2.54 (1.30 - 4.97)	<0.0001	188 (1.2): 363 (0.9)	1.43 (1.00 - 2.04)	0.021	..*	..*	..*	167 (1.1): 308 (0.7)	1.46 (1.00 - 2.12)	0.022
H81 : Disorders of vestibular function	144 (3.3): 184 (1.5)	2.22 (1.44 - 3.43)	<0.0001	330 (2.1): 557 (1.3)	1.49 (1.13 - 1.97)	<0.0001	* *	* *	*	* *	*	*
K59 : Functional intestinal disorders	406 (9.3): 655 (5.2)	1.9 (1.47 - 2.44)	<0.0001	1171 (7.4): 1845 (4.4)	1.58 (1.35 - 1.84)	<0.0001	340 (7.8): 591 (4.7)	1.66 (1.27 - 2.17)	<0.0001	904 (5.7): 1427 (3.4)	1.5 (1.27 - 1.78)	<0.0001
N30 : Cystitis	478 (11.0): 855 (6.8)	1.68 (1.34 - 2.12)	<0.0001	1422 (9.0): 2951 (7.0)	1.22 (1.07 - 1.39)	<0.0001	367 (8.4): 687 (5.5)	1.5 (1.16 - 1.94)	<0.0001	1176 (7.4): 2385 (5.6)	1.21 (1.05 - 1.39)	0.0001
N39 : Urinary tract infection, site not specified	217 (5.0): 348 (2.8)	1.79 (1.27 - 2.51)	<0.0001	1218 (7.7): 2263 (5.4)	1.47 (1.27 - 1.70)	<0.0001	165 (3.8): 268 (2.1)	1.68 (1.14 - 2.46)	<0.0001	997 (6.3): 1904 (4.5)	1.38 (1.18 - 1.61)	<0.0001
R20 : Paresthesia of skin	512 (11.7): 103 (0.8)	14.81 (9.74 - 22.52)	<0.0001	1220 (7.7): 363 (0.9)	9.45 (7.42 - 12.04)	<0.0001	* *	* *	*	* *	*	*
R42 : Dizziness and giddiness	372 (8.5): 415 (3.3)	2.57 (1.93 - 3.41)	<0.0001	1300 (8.2): 1667 (4.0)	2.08 (1.78 - 2.41)	<0.0001	* *	* *	*	* *	*	*
R51 : Headache	464 (10.6): 908 (7.2)	1.48 (1.18 - 1.87)	<0.0001	403 (2.6): 844 (2.0)	1.28 (1.00 - 1.62)	0.019	333 (7.6): 776 (6.2)	1.17 (0.90 - 1.51)	1	324 (2.0): 730 (1.7)	1.14 (0.88 - 1.48)	1
R53 : Malaise and fatigue	891 (20.4): 1574 (12.5)	1.76 (1.47 - 2.10)	<0.0001	376 (2.4): 692 (1.6)	1.45 (1.13 - 1.87)	<0.0001	703 (16.1): 1301 (10.4)	1.55 (1.28 - 1.88)	<0.0001	294 (1.9): 633 (1.5)	1.21 (0.92 - 1.59)	1

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820 **eTable 7. Pooled, UK, and French ORs for all health problems individually associated with MS in the**
821 **sensitivity analysis during the five years before the occurrence of the first symptoms. We used the whole**
822 **sensitivity cohort and excluded patients with less than 5 years of history before the index date in the database.**
823 *** for ORs associated with corrected p-values below 0.05 or initial p-values below 0.05/113. ORs and p-value are**
824 **adjusted for multiple comparisons using the Bonferroni method.**

	Pooled cohort (No. MS : 14932 No. no MS : 25193)		UK cohort (No. MS : 12412 No. no MS : 21736)		French cohort (No. MS : 2520 No. no MS : 3457)	
	No. (%) [MS : no MS]	OR (adjusted 95% CI)	No. (%) [MS : no MS]	OR (adjusted 95% CI)	No. (%) [MS : no MS]	OR (adjusted 95% CI)
F32 : Major depressive disorder, single episode	2956 (19.80) : 3902 (15.49)	1.30 (1.20 - 1.40)*	2574 (20.74) : 3554 (16.35)	1.29 (1.14 - 1.45)*	382 (15.16) : 349 (10.10)	1.57 (1.17 - 2.11)*
F52 : Sexual dysfunction	310 (2.08) : 343 (1.36)	1.50 (1.20 - 1.87)*	241 (1.94) : 285 (1.31)	1.43 (1.03 - 1.99)*	70 (2.78) : 59 (1.71)	1.67 (0.86 - 3.22)
K59 : Constipation	918 (6.15) : 948 (3.76)	1.59 (1.39 - 1.82)*	712 (5.74) : 767 (3.53)	1.55 (1.23 - 1.94)*	206 (8.17) : 180 (5.21)	1.62 (1.10 - 2.40)*
N30 : Cystitis	1135 (7.60) : 1517 (6.02)	1.23 (1.10 - 1.38)*	923 (7.44) : 1298 (5.97)	1.20 (1.01 - 1.43)*	212 (8.41) : 218 (6.31)	1.34 (0.92 - 1.94)
N39 : Urinary tract infection, site not specified	876 (5.87) : 1091 (4.33)	1.36 (1.19 - 1.55)*	779 (6.28) : 991 (4.56)	1.38 (1.14 - 1.66)*	97 (3.85) : 99 (2.86)	1.32 (0.77 - 2.26)

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eTable 8. Characteristics of patients with MS and individuals without MS with at least five years of data before the index date in the two cohorts. The data are shown as percentages or medians (IQR).

	Size, n	Sex (female)	Age at first symptom of MS	Person-years of data available before diagnosis	Number of visits per year before diagnosis
<i>Pooled</i>					
MS	14932	70.7%	44 (34 - 55)	8.4 (5.8 - 12.3)	4.6 (1.3 - 5.5)
No MS	25193	70.2%	46 (37 - 56)	8.5 (5.9 - 12.4)	3.8 (1.1 - 5.0)
<i>UK</i>					
MS	12412	70.7%	45 (35 - 55)	8.6 (6.0 - 12.6)	4.6 (1.3 - 5.6)
No MS	21736	70.2%	46 (36 - 56)	8.7 (6.1 - 12.7)	4.0 (1.2 - 5.2)
<i>France</i>					
MS	2520	70.7%	41 (32 - 51)	7.2 (5.1 - 10.2)	4.3 (1.3 - 5.0)
No MS	3457	70.5%	42 (33 - 53)	7.3 (5.3 - 10.3)	2.9 (0.7 - 3.9)

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eTable 9. Characteristics of patients with MS and individuals without MS with at least two years of data before and after the index date in the two cohorts. The data are shown as percentages or medians (IQR).

	Sex								Age at onset						Year of diagnosis			
	Whole cohort		Women		Men		<40		[40,53]		>53		<2010		[2010,2017]		>2017	
	MS	No MS	MS	no MS	MS	no MS	MS	no MS	MS	no MS	MS	no MS	MS	no MS	MS	no MS	MS	no MS
Pooled																		
Size, n	15454	26253	10966	18821	4488	7442	5151	7079	5152	9620	5151	9253	10283	18964	4417	6419	754	732
Sex (female)	71.3%	72.0%	100%	100%	0%	0%	73.9%	74.6%	71.8%	73.2%	68.6%	69.1%	71.8%	72.3%	69.9%	70.9%	73.1%	74.4%
Age at index date	44 (35 - 54)	45 (37 - 54)	44 (34 - 54)	45 (36 - 54)	46 (36 - 55)	46 (37 - 56)	31 (26 - 35)	31 (26 - 35)	44 (41 - 48)	44 (41 - 48)	59 (54 - 66)	60 (56 - 67)	46 (36 - 56)	46 (37 - 56)	41 (32 - 51)	43 (37 - 55)	40 (31 - 51)	41 (33 - 52)
Person-years of data available before diagnosis	6.3 (3.5 - 10.2)	6.3 (3.6 - 9.9)	6.3 (3.5 - 10.2)	6.3 (3.6 - 9.9)	6.3 (3.4 - 10.1)	6.3 (3.6 - 9.8)	5.8 (3.2 - 9.8)	5.3 (3.1 - 8.8)	6.3 (3.6 - 10.0)	6.2 (3.6 - 9.7)	6.7 (3.6 - 10.5)	6.9 (4.0 - 10.7)	5.7 (3.3 - 8.6)	5.9 (3.5 - 8.8)	8.4 (3.9 - 13.8)	8.2 (4.2 - 13.7)	9.9 (4.5 - 16.6)	8.1 (3.7 - 16.9)
Number of visits per year before diagnosis	5.3 (1.5 - 6.3)	4.1 (1.3 - 5.4)	5.5 (1.6 - 6.5)	4.4 (1.4 - 5.8)	4.7 (1.1 - 5.3)	3.5 (1.0 - 4.5)	4.6 (1.4 - 5.5)	3.7 (1.2 - 4.8)	5.1 (1.3 - 5.8)	3.7 (1.2 - 4.8)	6.2 (1.7 - 7.8)	4.9 (1.5 - 6.5)	5.3 (1.3 - 6.4)	4.0 (1.2 - 5.3)	5.2 (1.7 - 6.0)	4.3 (1.5 - 5.7)	5.2 (1.7 - 5.5)	4.9 (1.9 - 6.0)
UK																		
Size, n	12565	22751	8964	16396	3601	6365	4076	5993	4279	8318	4299	8189	8848	17087	3207	5106	510	544
Sex (female)	71.3%	72.0%	100%	100%	0%	0%	73.9%	74.6%	71.8%	73.2%	68.6%	69.1%	71.8%	72.3%	69.9%	70.9%	73.1%	74.4%
Age at index date	45 (35 - 55)	46 (37 - 55)	44 (35 - 54)	46 (36 - 55)	46 (36 - 56)	47 (38 - 56)	31 (26 - 35)	31 (26 - 35)	44 (41 - 48)	44 (41 - 48)	59 (55 - 66)	60 (56 - 67)	46 (37 - 56)	49 (40 - 58)	41 (32 - 51)	43 (34 - 52)	40 (30 - 51)	41 (33 - 52)
Person-years of data available before diagnosis	6.8 (3.9 - 10.8)	6.6 (3.8 - 10.4)	6.8 (3.9 - 10.9)	6.6 (3.8 - 10.4)	6.8 (3.9 - 10.6)	6.6 (3.8 - 10.3)	6.3 (3.5 - 10.6)	5.6 (3.2 - 9.2)	6.8 (4.1 - 10.5)	6.5 (3.8 - 10.2)	7.3 (4.2 - 11.0)	7.2 (4.3 - 11.1)	6.1 (3.8 - 9.1)	6.1 (3.6 - 9.2)	9.9 (4.8 - 15.5)	9.2 (4.6 - 14.7)	12.3 (5.7 - 18.6)	10.2 (4.4 - 17.8)
Number of visits per year before diagnosis	5.3 (1.4 - 6.3)	4.2 (1.2 - 5.5)	5.5 (1.6 - 6.6)	4.4 (1.4 - 5.8)	4.8 (1.1 - 5.3)	3.4 (0.9 - 4.4)	4.6 (1.4 - 5.5)	3.8 (1.2 - 4.9)	5.0 (1.2 - 5.8)	3.7 (1.1 - 4.8)	6.2 (1.7 - 7.9)	4.9 (1.4 - 6.6)	5.2 (1.3 - 6.3)	4.0 (1.1 - 5.3)	5.5 (1.7 - 6.4)	4.5 (1.6 - 6.0)	5.6 (1.7 - 6.0)	5.2 (1.9 - 6.3)
FR																		
Size, n	2889	3502	2002	2425	887	1077	1075	1086	873	1302	852	1064	1435	1877	1210	1313	244	189
Sex (female)	69.3%	69.2%	100%	100%	0%	0%	71.1%	70.9%	72.1%	71.9%	63.2%	63.8%	69.4%	68.4%	68.8%	69.8%	71.7%	73.5%
Age at index date	42 (33 - 52)	44 (34 - 54)	42 (33 - 51)	44 (35 - 53)	44 (34 - 55)	45 (35 - 55)	30 (24 - 32)	31 (24 - 36)	44 (41 - 48)	45 (41 - 49)	58 (54 - 66)	59 (55 - 67)	43 (34 - 55)	45 (35 - 5)	41 (32 - 50)	41 (33 - 50)	41 (31 - 51)	43 (51 - 52)
Person-years of data available before diagnosis	5.6 (3.3 - 9.2)	4.9 (3.2 - 7.6)	5.6 (3.3 - 8.9)	4.9 (3.2 - 7.6)	5.7 (3.1 - 9.6)	4.9 (3.2 - 7.6)	5.3 (3.4 - 8.7)	4.4 (3.0 - 6.8)	6.2 (3.6 - 9.7)	5.0 (3.3 - 7.7)	5.8 (3.6 - 9.2)	4.9 (3.1 - 7.6)	4.0 (2.7 - 6.0)	3.2 (2.3 - 5.1)	5.5 (2.8 - 9.4)	5.4 (3.4 - 8.8)	6.7 (3.3 - 11.9)	4.5 (2.6 - 8.8)
Number of visits per year before diagnosis	4.9 (2.1 - 6.4)	3.8 (1.5 - 5.0)	5.0 (2.2 - 6.5)	4.0 (1.6 - 5.2)	4.7 (1.8 - 5.9)	3.5 (1.5 - 4.6)	4.0 (2.0 - 5.1)	3.1 (1.4 - 4.0)	4.8 (1.9 - 6.3)	3.8 (1.5 - 4.7)	5.9 (1.9 - 7.6)	4.9 (1.9 - 6.2)	6.1 (1.9 - 7.0)	4.1 (1.5 - 5.3)	4.3 (1.5 - 5.2)	3.5 (1.3 - 4.6)	4.5 (1.6 - 4.7)	3.9 (1.8 - 4.6)

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836 **eTable 10. ORs in the UK cohort for all health conditions individually associated with MS in the sensitivity**
837 **analysis during the five years before and five years after the occurrence of the first symptoms. Individuals**
838 **with MS are compared with controls without MS. We used the whole sensitivity cohort, sex-based cohorts, age-**
839 **at-onset cohorts, and year-at-diagnosis cohorts. . * cannot be calculated because too few presentations were**
840 **recorded. * for ORs associated with corrected p-values below 0.05 or initial p-value below 0.05/5. p-value are**
841 **adjusted for multiple comparisons using the Bonferroni method.**

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	Whole cohort (MS : 12565 Control : 22751)	Sex		Age at onset			Year of diagnosis		
		Women (MS : 8964 Control : 16396)	Men (No. MS : 3601 Control : 6365)	<40 (No. MS : 4076 Control : 5993)	[40,53] (No. MS : 4279 Control : 8318)	>53 (No. MS : 4299 Control : 8189)	<2010 (No. MS : 8848 Control : 17087)	[2010,2017] (No. MS : 3207 Control : 5106)	>2017 (No. MS : 510 Control : 544)
Before diagnosis									
F32 : Major depressive disorder, single episode	1.36 (1.22 - 1.52)*	1.34 (1.18 - 1.51)*	1.49 (1.18 - 1.88)*	1.34 (1.09 - 1.64)*	1.39 (1.17 - 1.65)*	1.33 (1.10 - 1.61)*	1.39 (1.22 - 1.58)*	1.31 (1.07 - 1.62)*	1.02 (0.60 - 1.72)
F52 : Sexual dysfunction	1.65 (1.18 - 2.31)*	1.08 (0.45 - 2.60)	1.75 (1.21 - 2.54)*	1.58 (0.65 - 3.84)	1.95 (1.12 - 3.39)*	1.53 (0.94 - 2.49)	1.67 (1.10 - 2.52)*	1.61 (0.88 - 2.94)	.*
K59 : Constipation	1.87 (1.50 - 2.35)*	1.69 (1.31 - 2.18)*	2.70 (1.65 - 4.43)*	1.35 (0.85 - 2.13)	1.86 (1.23 - 2.80)*	2.30 (1.65 - 3.21)*	2.11 (1.53 - 2.91)*	1.66 (1.18 - 2.35)*	1.15 (0.53 - 2.49)
N30 : Cystitis	1.36 (1.14 - 1.63)*	1.30 (1.08 - 1.57)	2.49 (1.33 - 4.69)*	1.14 (0.82 - 1.59)	1.19 (0.87 - 1.62)	1.73 (1.30 - 2.31)*	1.44 (1.15 - 1.79)*	1.22 (0.88 - 1.68)	1.09 (0.51 - 2.34)
N39 : Urinary tract infection, site not specified	1.41 (1.18 - 1.69)*	1.31 (1.08 - 1.60)	2.27 (1.36 - 3.80)*	1.16 (0.81 - 1.64)	1.32 (0.96 - 1.81)	1.70 (1.28 - 2.26)*	1.51 (1.23 - 1.86)*	1.10 (0.74 - 1.64)	1.53 (0.46 - 5.05)
After diagnosis									
F32 : Major depressive disorder, single episode	2.0 (1.85 - 2.16)*	1.84 (1.69 - 2.02)*	2.54 (2.17 - 2.98)*	2.17 (1.91 - 2.47)*	2.05 (1.79 - 2.34)*	1.91 (1.65 - 2.22)*	1.96 (1.79 - 2.14)*	2.11 (1.79 - 2.48)*	2.11 (1.21 - 3.68)*
F52 : Sexual dysfunction	3.03 (2.56 - 3.59)*	1.62 (1.04 - 2.53)*	3.35 (2.78 - 4.03)*	5.57 (3.85 - 8.05)*	4.3 (3.20 - 5.78)*	1.45 (1.09 - 1.92)*	3.17 (2.61 - 3.86)*	2.74 (1.93 - 3.89)*	.*
K59 : Constipation	3.56 (3.22 - 3.92)*	3.2 (2.86 - 3.59)*	4.83 (3.95 - 5.90)*	3.27 (2.70 - 3.98)*	4.57 (3.83 - 5.45)*	3.34 (2.87 - 3.88)*	3.77 (3.34 - 4.25)*	3.07 (2.57 - 3.67)*	2.54 (1.47 - 4.39)*
N30 : Cystitis	2.66 (2.42 - 2.92)*	2.36 (2.13 - 2.61)*	5.9 (4.43 - 7.86)*	2.33 (1.95 - 2.79)*	2.88 (2.45 - 3.38)*	2.86 (2.46 - 3.34)*	2.76 (2.46 - 3.09)*	2.34 (1.95 - 2.81)*	2.21 (1.34 - 3.64)*
N39 : Urinary tract infection, site not specified	2.81 (2.53 - 3.13)*	2.57 (2.29 - 2.89)*	4.33 (3.30 - 5.70)*	2.35 (1.92 - 2.88)*	3.0 (2.48 - 3.63)*	3.02 (2.55 - 3.57)*	2.86 (2.54 - 3.22)*	2.74 (2.11 - 3.56)*	2.53 (1.08 - 5.91)*

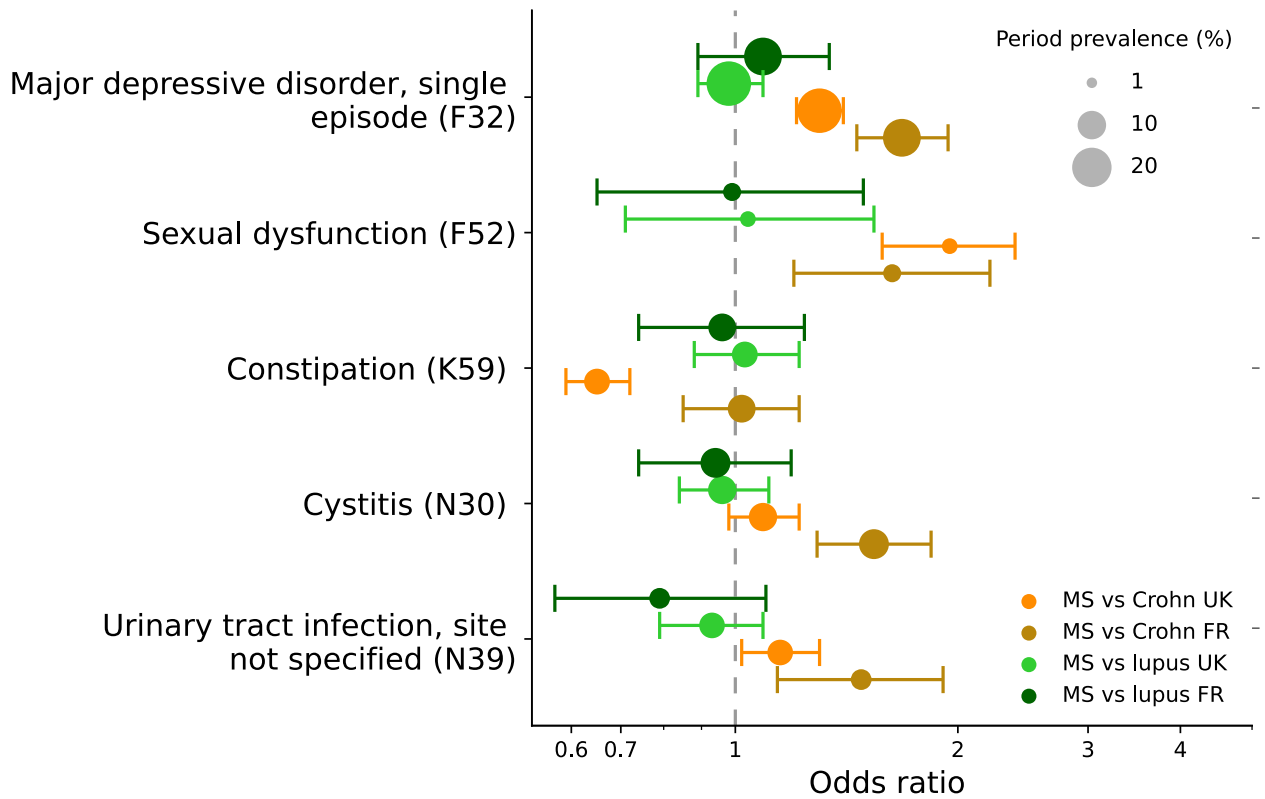
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eTable 11. ORs in the French cohort for all health conditions individually associated with MS in the sensitivity analysis during the five years before and five years after the occurrence of the first symptoms. Individuals with MS are compared with controls without MS. We used the whole sensitivity cohort, sex-based cohorts, age-at-onset cohorts, and year-at-diagnosis cohorts. * cannot be calculated because too few presentations were recorded. * for ORs associated with corrected p-values below 0.05 or initial p-value below 0.05/5. p-value are adjusted for multiple comparisons using the Bonferroni method.

	Whole cohort (MS : 2889 Control : 3502)	Sex		Age at onset			Year of diagnosis		
		Women (MS : 2002 Control : 2425)	Men (No. MS : 887 No. Control : 1077)	<40 (No. MS : 1075 No. Control : 1086)	[40,53] (No. MS : 873 No. Control : 1302)	>53 (No. MS : 852 No. Control : 1064)	<2010 (No. MS : 1435 No. Control : 1877)	[2010,2017] (No. MS : 1210 No. Control : 1313)	>2017 (No. MS : 244 No. Control : 189)
Before diagnosis									
F32 : Major depressive disorder, single episode	1.31 (1.07 - 1.62)*	1.26 (0.99 - 1.60)	1.50 (0.97 - 2.32)	1.86 (1.20 - 2.86)*	1.23 (0.90 - 1.70)	1.23 (0.84 - 1.78)	1.46 (1.11 - 1.93)*	1.31 (0.93 - 1.86)	0.86 (0.35 - 2.10)
F52 : Sexual dysfunction	1.26 (0.82 - 1.92)	1.43 (0.83 - 2.46)	1.01 (0.50 - 2.02)	1.89 (0.74 - 4.85)	1.41 (0.75 - 2.64)	0.85 (0.38 - 1.88)	1.36 (0.80 - 2.43)	1.39 (0.65 - 2.97)	.*
K59 : Constipation	1.48 (1.12 - 1.94)*	1.39 (1.01 - 1.91)*	1.78 (1.01 - 3.14)*	1.32 (0.82 - 2.13)	1.84 (1.12 - 3.00)*	1.36 (0.84 - 2.19)	1.44 (1.00 - 2.06)*	1.76 (1.08 - 2.89)*	1.39 (0.46 - 4.25)
N30 : Cystitis	1.24 (0.96 - 1.61)*	1.12 (0.85 - 1.48)	3.21 (1.35 - 7.62) *	1.12 (0.71 - 1.76)	1.24 (0.80 - 1.92)	1.42 (0.89 - 2.26)	1.44 (1.00 - 2.06)*	1.05 (0.68 - 1.60)	1.39 (0.57 - 3.39)
N39 : Urinary tract infection, site not specified	1.38 (0.92 - 2.07)	1.33 (0.86 - 2.06)	1.78 (0.62 - 5.14)	1.41 (0.68 - 2.92)	1.17 (0.59 - 2.35)	1.58 (0.79 - 3.15)	1.36 (0.94 - 1.95)	1.09 (0.59 - 2.00)	0.80 (0.23 - 2.81)
After diagnosis									
F32 : Major depressive disorder, single episode	1.85 (1.52 - 2.24)*	1.82 (1.46 - 2.27)*	1.93 (1.27 - 2.92)*	2.02 (1.43 - 2.85)*	1.64 (1.21 - 2.23)*	1.98 (1.32 - 2.98)*	1.96 (1.52 - 2.52)*	1.85 (1.32 - 2.60)*	1.06 (0.51 - 2.24)
F52 : Sexual dysfunction	1.99 (1.37 - 2.87)*	1.78 (1.08 - 2.94)*	2.26 (1.30 - 3.93)*	2.06 (1.00 - 4.27)*	2.54 (1.41 - 4.58)*	1.33 (0.69 - 2.56)	1.75 (1.12 - 2.75)*	2.12 (1.07 - 4.22)*	.*
K59 : Constipation	2.35 (1.83 - 3.00)*	2.37 (1.77 - 3.17)*	2.26 (1.43 - 3.57)*	2.62 (1.61 - 4.29)*	2.15 (1.43 - 3.23)*	2.2 (1.46 - 3.33)*	2.24 (1.61 - 3.11)*	2.27 (1.52 - 3.38)*	3.57 (1.14 - 11.18)*
N30 : Cystitis	1.69 (1.36 - 2.11)*	1.46 (1.16 - 1.83)*	.*	1.35 (0.94 - 1.92)	1.44 (0.99 - 2.10)	2.76 (1.79 - 4.26)*	1.92 (1.44 - 2.55)*	1.43 (0.99 - 2.08)	1.31 (0.50 - 3.48)
N39 : Urinary tract infection, site not specified	2.24 (1.66 - 3.01)*	2.24 (1.63 - 3.10)*	2.15 (0.99 - 4.68)	2.31 (1.30 - 4.07)*	1.77 (1.08 - 2.92)*	2.73 (1.65 - 4.53)*	2.36 (1.57 - 3.55)*	1.83 (1.17 - 2.88)*	.*

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858 **eFigure 3. ORs for significant associations in the sensitivity analysis for five years before the index date in**
 859 **comparison to other auto-immune diseases.** Patients with MS are compared to patients with lupus and Crohn's
 860 disease both in the French and UK cohorts. The size of the dot is proportional to the period prevalence. OR > 1
 861 indicates a higher association in MS cohort compared to Crohn or lupus cohort. The period prevalence is defined
 862 as the number of diagnoses or symptoms observed over the period divided by the number of patients at risk
 863 during the period.

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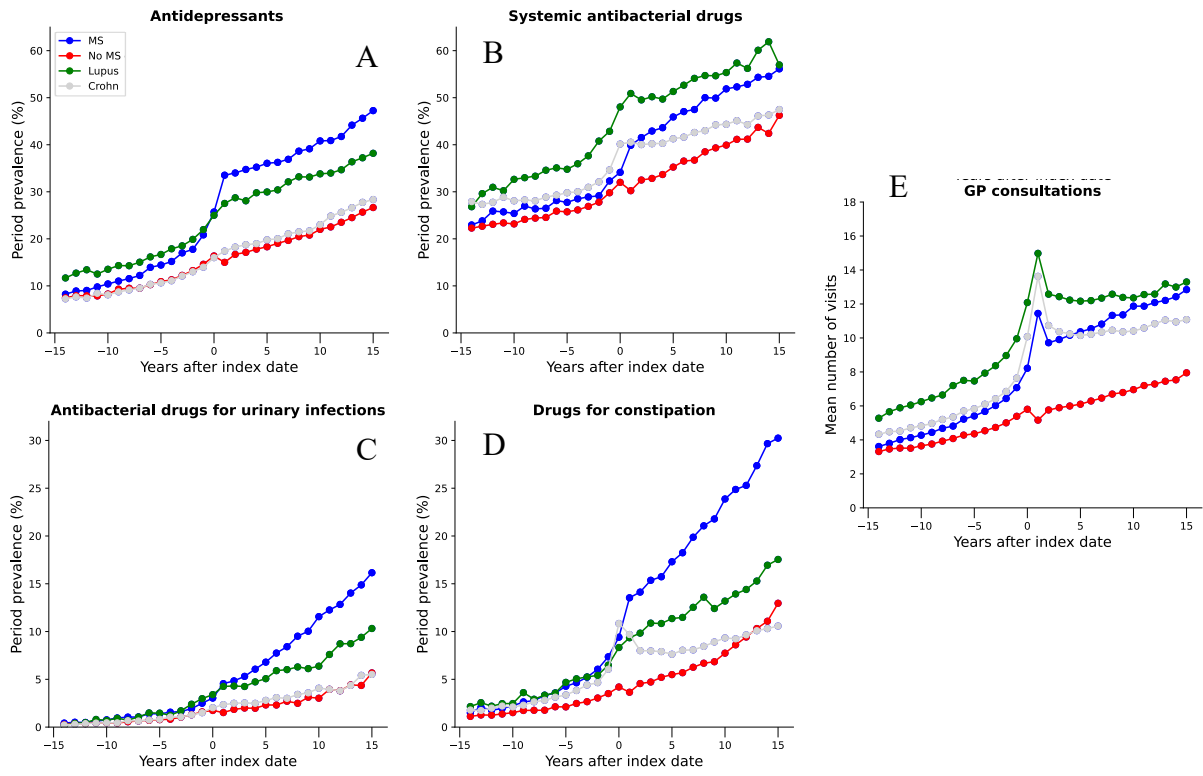
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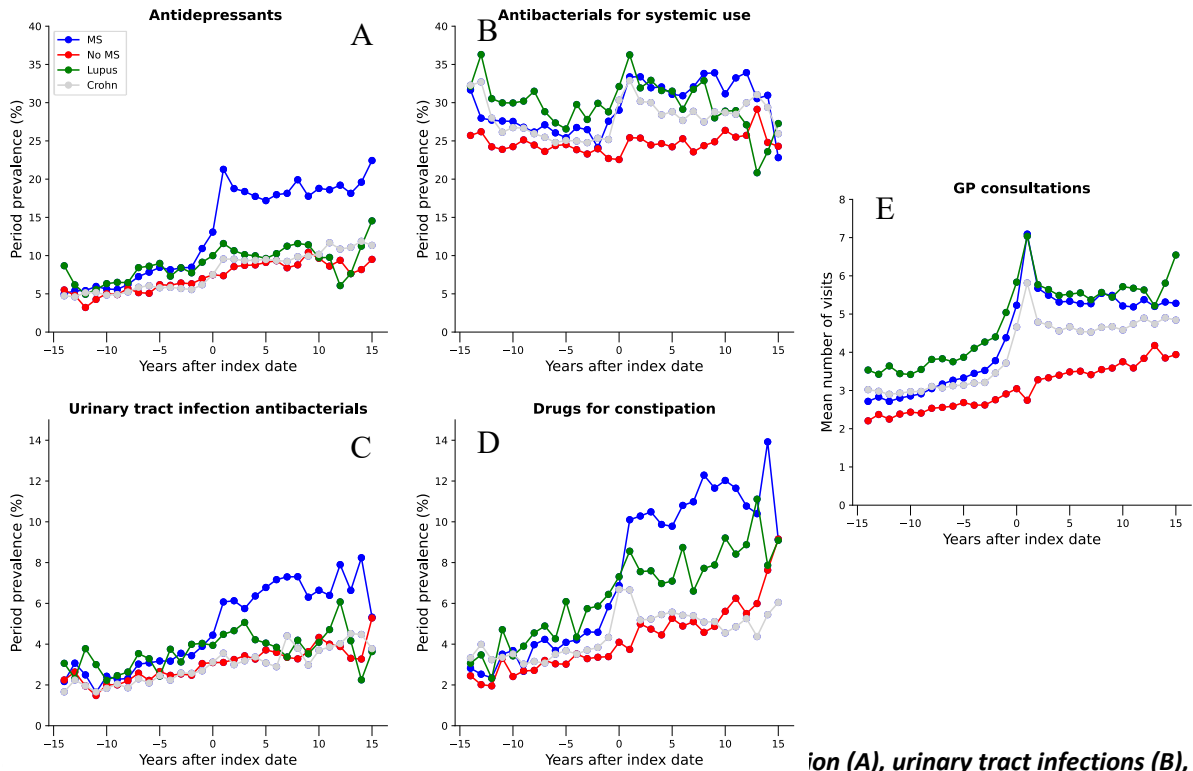
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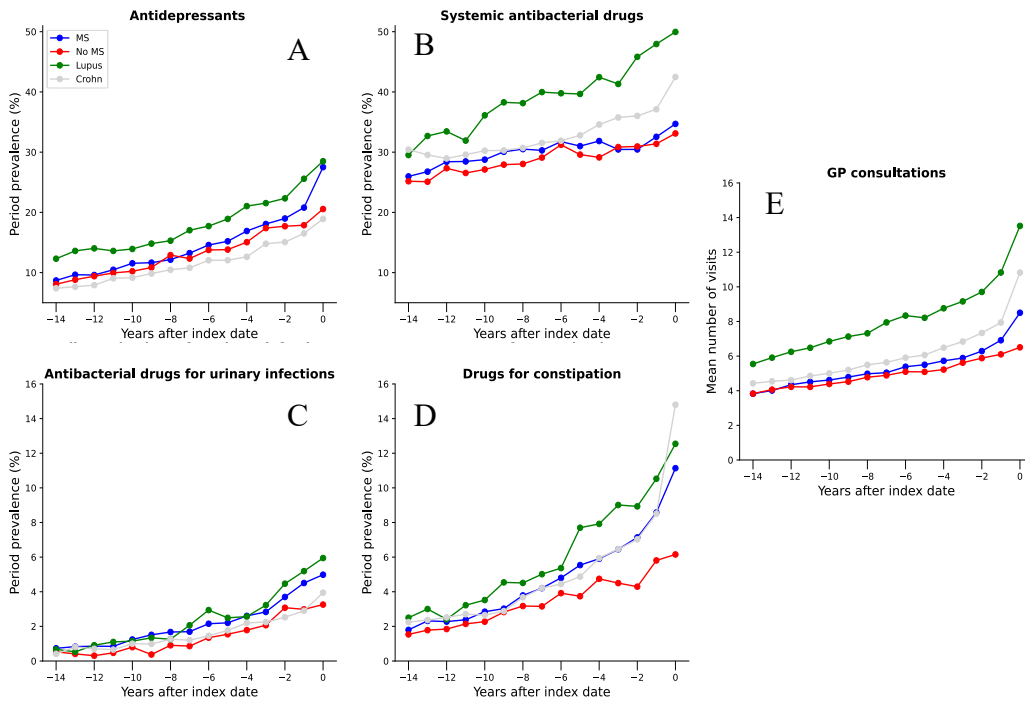
eFigure 9. Period prevalence (%) of prescriptions associated with depression (A), urinary tract infections (B), bacterial infections (C), and constipation (D), and mean number of visits to the physician per year (E) in the UK cohort. For a given prescription, the period prevalence is defined as the number of prescriptions observed over the period divided by the number of patients at risk during the period.

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ion (A), urinary tract infections (B), bacterial infections (C), and constipation (D), and mean number of visits to the physician per year (E) in the French cohort. For a given prescription, the period prevalence is defined as the number of prescriptions observed over the period divided by the number of patients at risk during the period.

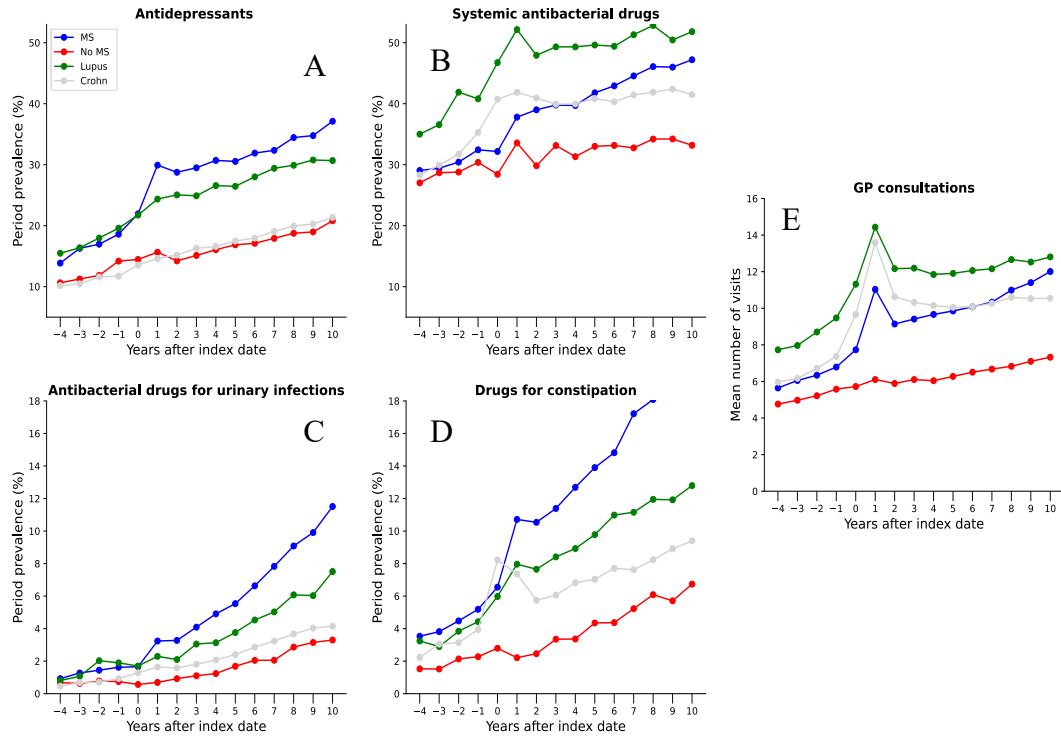
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970 **eFigure 6. Period prevalence (%) of prescriptions associated with depression (A), urinary tract infections (B),**
 971 **bacterial infections (C), and constipation (D), and mean number of visits to the physician per year (E) in the**
 972 **pooled cohort, 15 years before diagnosis. Data are from the pooled cohort with individuals having data for the**
 973 **entire 15 years before diagnosis time-window. For a given prescription, the period prevalence is defined as the**
 974 **number of prescriptions observed over the period divided by the number of patients at risk during the period.**
 975 **No. MS : 2726 (women: 1976), No. no MS : 2082 (W: 1488), No. Crohn's disease : 4849 (W: 2660), No. Lupus :**
 976 **1040 (W: 903)**

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999 **eFigure 7. Period prevalence (%) of prescriptions associated with depression (A), urinary tract infections (B),**
 1000 **bacterial infections (C), and constipation (D), and mean number of visits to the physician per year (E) in the**
 1001 **pooled cohort, 5 years before diagnosis up to 10 years after diagnosis. Data are from the pooled cohort with**
 1002 **individuals having data for the entire 5 years before diagnosis to 10 years after diagnosis time-window. For a**
 1003 **given prescription, the period prevalence is defined as the number of prescriptions observed over the period**
 1004 **divided by the number of patients at risk during the period. No. MS : 3531 (women: 2581), No. no MS : 2060 (W:**
 1005 **1579), No. Crohn's disease : 4934 (W: 2814), No. Lupus : 1380 (W:1246)**

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