

Searching for a prodrome for rheumatoid arthritis in the primary care record

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1 **Searching for a prodrome for rheumatoid arthritis in the primary care record: A case-control study**
2 **in the Clinical Practice Research Datalink**

3

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18 **ABSTRACT**

19 **Background**

20 Rheumatoid arthritis (RA) has articular and non-articular manifestations. Early, intensive treatment
21 has substantial benefit for both. This requires patients be identified as soon as symptoms develop.

22 **Objectives**

23 To determine whether selected signs and symptoms can be identified in the primary care records of
24 patients prior to a formal diagnosis of RA being made and, if so, how early they can be identified.

25 **Methods**

26 A case-control study was constructed within the UK Clinical Practice Research Datalink (CPRD). 3577
27 individuals with 'definite' RA, were matched to 14287 individuals without inflammatory arthritis. An
28 index date was established (i.e. date general practitioner (GP) first appeared to suspect RA). Rates of
29 consultation and consultations for suspected early RA symptoms were compared in cases and
30 controls in the two years prior to the index date using conditional logistic regression, adjusted for
31 number of consultations.

32 **Results**

33 The mean (standard deviation) age of participants was 58.8 (14.5) years and 66.8% were female.
34 Rates of any consultation were significantly higher in RA cases than in controls for at least two years
35 prior to the index date. Cases were more likely to have a pre-diagnosis coded consultation for joint,
36 and particularly hand symptoms (aOR 11.44 (9.60, 13.63)), morning stiffness (8.10 (3.54, 18.5)),
37 carpal tunnel syndrome (4.57 (3.54, 5.88)) and other non-articular features.

38 **Conclusions**

39 In patients who develop RA, GP consultation rates are higher for at least two years prior to the first
40 recorded suspicion of RA. This study highlights symptoms that should raise a GP's index of suspicion
41 for RA.

42

43 **KEY WORDS:** Rheumatoid arthritis; Diagnosis; Primary care

44 **INTRODUCTION**

45 Rheumatoid arthritis (RA) causes joint pain, stiffness and damage and can lead to excess morbidity
46 and mortality. It has a prevalence in the UK of around 0.67% [1]. It is known that early, intensive
47 treatment can increase the likelihood of remission and reduce long term joint damage and
48 comorbidities [2,3].

49 Delay in making a diagnosis of RA, and therefore in treating it, can occur at a number of points in the
50 patient journey [3-6]; first in the patient recognising their symptoms and seeking help from primary
51 care, second in the primary care physician recognising the potential for a diagnosis of RA and making
52 a referral to a rheumatology specialist, and third in seeing a rheumatologist and starting appropriate
53 treatment. Work has been ongoing to understand the causes of patient delay [7-12], which has
54 comprised in-depth studies of the symptoms reported by patients prior to their diagnosis of RA [13-
55 16]. These symptoms have included problems with joints, fatigue, weakness [13], muscle cramps,
56 psychological distress, and loss of motor control [14].

57 Primary care delay continues to be a significant contributor to overall diagnostic delay for people
58 with RA [17]. This could be because GPs are not aware of the need to refer quickly [18], or because
59 they find it difficult to identify 'red flag' symptoms, for example because of co-existing
60 musculoskeletal conditions [19,20]. We hypothesised that we would be able to identify signs and
61 symptoms in the coded part of the medical record that increase the likelihood of a future RA
62 diagnosis, increasing GPs awareness and facilitating a more rapid referral.

63 We present a case-control study to assess the association of clinical features reported by patients in
64 the earliest phases of RA with future diagnosis of the condition using the UK Clinical Practice
65 Research Datalink (CPRD).

66

67 **MATERIALS AND METHODS**

68 **Data source: the Clinical Practice Research Datalink**

69 The CPRD is an anonymised source of routinely collected primary care health records covering
70 approximately 6.9% of the UK's population. It is broadly representative of this population in terms of
71 age, sex and ethnicity [21]. The data exist in coded form and include details of symptoms, diagnoses
72 and prescriptions. Clinical data are assigned Read codes (the hierarchical clinical coding system
73 currently used in UK primary care) by the GP. Data are collected for clinical purposes and so it can be
74 assumed that anything the GP considers relevant might be coded, regardless of whether any clinical
75 action was required as a result. The coding of data has been shown to be accurate for a range of
76 conditions [22]. The CPRD assigns an 'up-to-standard' date for when a practice has a high enough
77 quality of coding to be used for research. We use only up-to-standard data in this study.

78

79 **Definition of rheumatoid arthritis**

80 Previous work in the General Practice Research Database (predecessor to CPRD) developed an
81 algorithm to identify individuals with RA [23]. The algorithm combines Read codes for RA with
82 prescription information and potential alternative diagnoses to create a case definition that is
83 specific, but not overly sensitive. It has been updated to allow for the inclusion of new Read codes
84 and the use of biological disease modifying anti-rheumatic drugs (DMARD) [24].

85

86 **Analysis sample**

87 All individuals with a first Read code for RA in the CPRD between 2007 and 2012 were identified and
88 the algorithm to define RA was applied [24]. Those who met this specific definition of RA were then
89 matched to four individuals of the same sex and from the same practice who were born in the same
90 3-year time interval who did not have a Read code for any inflammatory arthropathy up until the
91 time of the case's first RA code, in order to form a case-control study.

92

93 **The index date: first indication of RA in the records**

94 The date at which the first RA Read code was recorded may not accurately reflect the date at which
95 the GP first suspected RA in the patient [25,26], as he/she may wait until diagnosis is confirmed by a
96 specialist before entering this diagnostic code. As a proxy for the date of first clinical suspicion of RA,
97 an index date was defined. Based on previous work in the CPRD [27,28], this index date was taken to
98 be the earliest of the first RA code, or other code from the Read code subchapter N04 (rheumatoid
99 arthritis and other inflammatory arthropathy), the date of the first prescription of a DMARD or first
100 referral to rheumatology in the three years preceding the first RA Read code (Figure 1).

101

102 **Early signs and symptoms**

103 Signs and symptoms that may precede a diagnosis of RA were identified from the literature [13-16]
104 and consultation with experts. Whilst some of the signs/symptoms described in the literature were
105 not possible to define within the medical record (e.g. muscle burning as one would feel after
106 exercise), other signs/symptoms were clearly defined syndromes and conditions that could be
107 specified and studied in more detail (e.g. carpal tunnel syndrome, shoulder pain).

108 The final set of the signs/symptoms included is given in Tables 2 (articular) and 3 (non-articular). Lists
109 of Read codes to define each sign/symptom, the concepts they represent and the process to achieve
110 the lists are available at [29].

111 Where a sign/symptom was not recorded, it was assumed that the individual did not experience it,
112 rather than data being missing.

113

114 **Statistical analyses**

115 Rates of consultation

116 A consultation was defined as a day on which a Read coded contact with the practice was made.

117 Where there were multiple contacts/Read codes on the same day, only one was included in the

118 consultation rate analysis. Monthly rates of consultations in the 2-year period before the index date

119 were estimated and compared in cases and controls using incidence rate ratios with 95% confidence
120 intervals (CI).

121

122 Signs and symptoms associated with RA

123 We investigated signs/symptoms in the 2-year period prior to the index date. Cumulative time
124 periods were defined at 1, 6, 12 and 24 months prior to the index date. Each period included
125 previous periods (Figure 1). Additionally, we considered the period 12 to 24 months before the index
126 date to allow comparison with the period 0 to 12 months before the index date. In these analyses all
127 Read coded contacts were considered, even when multiple codes were entered on the same date.

128

129 Conditional logistic regression was used to assess the association between signs/symptoms and case
130 control (RA) status, allowing for the matched design in each of the time periods described above.

131 Results are presented as unadjusted odds ratios and then adjusted for the rate of consultations (as
132 defined above) in the period in question. All values are presented as odds ratios (OR) with 95% CI.

133

134 Data management and analyses were conducted in Stata 14.2 [30].

135

136 Approval for this study was granted by the Independent Scientific Advisory Committee of the CPRD
137 (reference 13_126).

138

139 **RESULTS**

140 **Sample**

141 Between 2007 and 2012, 4161 people were identified with a first Read code for RA. Of these, 3577
142 met the criteria for RA using the algorithm described above [24] and were matched to 14287
143 controls (Table 1). The mean (standard deviation) age of the both cases and controls was 58.8 (14.5)

144 years and 66.8% were female (Table 1). Current and previous smoking were more common in cases
145 than controls.

146

147 **Numbers of consultations**

148 For two years prior to the index date, the overall consultation rate was significantly higher in each
149 month in cases than in controls (Figure 2) (incidence rate ratio 1.22 (1.21, 1.22)). This increase
150 became more pronounced in the 6 months before the index date and in the final month before,
151 cases consulted at 2.68 (95% CI 2.61, 2.76) times the rate of controls (mean: 2.39 consultations per
152 person).

153

154 **Signs and symptoms preceding a diagnosis of RA**

155 **Articular symptoms**

156 All articular signs/symptoms were associated with a future diagnosis of RA in all time periods in both
157 unadjusted and adjusted analyses, with the exception of jaw pain which was not significantly
158 associated with RA following adjustment for the number of consultations in the 0 to 1-month period
159 (Table 2). In the 0 to 1-month period, joint symptoms (adjusted OR (95% CI), 14.82 (12.48, 17.60)),
160 and specifically hand problems (61.07 (31.58, 118.10)), were strongly associated with the
161 development of RA. Palindromic rheumatism occurred only in cases in the 12 months preceding the
162 index date. The strength of all associations was lessened by adjustment for the number of
163 consultations (except for jaw pain in the 0 to 6-month period) and associations were generally
164 stronger for consultations closer to the index date.

165

166 **Non-articular symptoms**

167 In the 0 to 1-month period there were four non-articular signs/symptoms that had large (odds
168 ratio \geq 6) unadjusted associations with development of RA (morning stiffness, muscle pain: 13.83
169 (5.11, 37.42) and carpal tunnel syndrome: 2.96 (1.38, 6.34)). All remained strongly and significantly

170 associated after adjustment (Table 3). Morning stiffness was recorded in 14 cases (0.39%), but not in
171 any controls, hence an estimate of the strength of association could not be made. Unintentional
172 weight loss was not significantly associated with RA in the month before the index date, but was in
173 all other time periods (except adjusted analysis in 12 to 24-month period (Supplementary tables)). In
174 all time periods, there was a significant unadjusted association between fatigue and development of
175 RA, but this association was attenuated and not significant after adjustment for number of
176 consultations. No association was seen with sleep problems or flu-like illness (Table 3).
177 Psychological problems were significantly associated with a higher odds of RA in all unadjusted
178 analyses (except 0 to 24 months before the index date, where association was positive, but not
179 significant), but significantly associated with a decreased odds of RA after adjustment.

180

181 Comparison of consultation 0-12 and 12-24 months before the index date

182 Comparison of the associations of signs/symptoms during the periods 0 to 12-months and 12 to 24-
183 months before the index date suggested that signs/symptoms grouped together (Supplementary
184 tables). A similar pattern of association was seen in both time periods for fatigue, altered sensations,
185 postnatal occurrence of RA, weakness, psychological problems and carpal tunnel syndrome. There
186 was no unadjusted association between sleep and RA in either time period and only after
187 adjustment in the 12 to 24-month period for falling. Flu-like symptoms were associated with RA in
188 the 12 to 24-month period (adjusted analyses only (1.46 (1.04, 2.07)), but not closer to the index
189 date. All articular signs/symptoms and the remaining non-articular signs/symptoms were more
190 strongly associated with RA in the 0 to 12-month period than in the 12 to 24-month period. This was
191 particularly noticeable for hand symptoms (aOR 0 to 12-months: 23.75 (18.49, 30.51); 12 to 24-
192 months: 2.70 (2.05, 3.56)), morning stiffness (0 to 12-months: 9.72 (3.84, 24.60); 12 to 24-months:
193 0.93 (0.08, 10.64)) and muscle pain (0 to 12-months: 3.15 (2.22, 4.47); 12 to 24-months: 1.22 (0.75,
194 1.97)).

195

196 **DISCUSSION**

197 The rate of consultations increases rapidly in the period before the index date in those with RA
198 compared to controls, and key signs and symptoms are recorded at a higher rate before an RA
199 diagnosis. In the final month before the index date, these include all joint symptoms, but particularly
200 those involving the hand, and the non-articular symptoms morning stiffness, muscle pain and carpal
201 tunnel syndrome. In longer periods before the index date, there is also an increase in the recording
202 of other features such as unintentional weight loss. Other symptoms reported by patients in
203 previous studies (e.g. fatigue, cramping, poor sleep) [13-16], showed less clear associations.

204

205 The strengths of our study include the large sample size and use of a validated definition of RA [24].
206 Whilst it could be argued that the definition had good specificity at the expense of sensitivity, the
207 exclusion of controls with any record of inflammatory arthropathy should reassure that there was no
208 contamination of the control group with potential cases. The data for this study were taken from a
209 high quality database containing a representative sample of individuals in UK primary care. As such,
210 the results should be generalizable to other primary care settings. Despite its strengths, this study
211 also has some weaknesses. First, multiple statistical testing, which could result in false positive
212 associations. Second, we do not know the thought processes of the GPs who coded the
213 consultations and how this might have affected our findings. This question cannot be answered in
214 routinely collected data, but would require in-depth interviews with GPs as to their views and clinical
215 practice. This in itself may prove difficult, as an individual GP will see a new case of RA only rarely
216 and may not be able to report what action they would take [20].

217

218 We adjusted our findings for the total number of consultations (days with ≥ 1 Read coded
219 consultation) in order to adjust for ascertainment/surveillance bias, whereby the presence of the
220 patient in the surgery makes it easier for the GP to identify and code signs/symptoms. This
221 adjustment for number of consultations attenuated the association of a number of signs/symptoms

222 (physical functioning, cramps, weakness and restless legs) with RA. This may suggest that these
223 signs/symptoms are more common in those with RA, but are only recorded in those who attend
224 more frequently. A similar process may explain the change in direction of association with
225 psychological problems when adjusting for number of consultations: people with coded
226 psychological problems consult more frequently and it may be that controls receive psychological
227 codes, but RA cases receive codes for physical symptoms because these take priority for the GP.
228 Due to small numbers, non-significant associations in the final month before the index date should
229 be interpreted with caution, as they may well represent a type II statistical error, especially where
230 the signs/symptom was associated with RA in longer time periods and the absolute estimate of the
231 size of association is similar across time periods (e.g. unintentional weight loss). However, it could be
232 that these symptoms are simply more common at an earlier stage in the pre-clinical picture of RA
233 and become less commonly reported or over-shadowed by other symptoms in the final weeks
234 before the GP suspects RA.

235

236 Previous literature has described the symptoms patients report before a diagnosis of RA [13-16], and
237 there is a feeling among rheumatologists that they know what symptoms they expect to see in early
238 RA. However, to our knowledge this is the first paper to consider whether these signs and symptoms
239 occur in the primary care record, whether they are more common in those who later received a
240 diagnosis of RA than in those who do not and how long before RA is suspected by the GP these signs
241 and symptoms are present.

242

243 Within this study, classical features of RA such as hand pain and stiffness were more frequently
244 coded within the primary care record, and were seen more frequently up to 2 years before the index
245 date. However, musculoskeletal symptoms in regions not traditionally associated with early RA (e.g.
246 neck and shoulder pain) were also reported more frequently by patients who eventually developed
247 RA. Joint symptoms, particularly in the hands, and other well-recognised non-articular features

248 should raise the index of suspicion of RA in patient presenting in primary care, particularly when
249 accompanied by a general increase in patient contact with the primary care. However, GPs should
250 also be aware that these features have low specificity and only a small proportion of patients with
251 these symptoms will go on to receive a diagnosis of RA. For example, whilst we have confirmed that
252 people with RA are more likely to have hand symptoms, an RA outcome is seen in only a minority of
253 patients that have hand symptoms recorded in primary care. Further studies will be needed to
254 investigate what other symptoms/signs increase the likelihood of an RA diagnosis.

255 Other early symptoms reported by patients such as falls and sleep problems did not show any
256 association with RA. This may represent a true lack of association, or it may be that either patients
257 did not report these symptoms to the GP or that GPs did not code them, especially if they did not fit
258 with the GP's concept of what is important.

259 The association of flu-like symptoms with RA only in the 12 to 24-month period may suggest that
260 rather than being part of an RA prodrome, flu-like symptoms may be a marker of an insult on the
261 immune system that reflects the phase of immune tolerance breakage [31].

262

263 The next steps should be to identify groups of symptoms that constitute a prodrome of RA and at
264 the same time educate GPs as to the key symptoms that may indicate RA prior to the cardinal
265 symptoms of morning stiffness and hand symptoms that they already appear to recognise, although
266 further work is needed to refine the specificity of these common symptoms.

267 In the future, it may be possible to create automated electronic alerts for the GP within the records
268 system that highlight the risk for an individual patient when certain codes are entered. This already
269 happens for example to alert the GP to the possibility of sepsis.

270

271 What our study was not able to do was to identify new signs or symptoms from the record that may
272 occur at a higher rate in those who go on to receive an RA diagnosis than in those who do not; to do

273 so would have required an alternative methodological approach to identify patterns in consultation
274 that were not defined by code lists (e.g. 32]).

275

276 **CONCLUSION**

277 We have provided definitive evidence of the presence of some key features of early RA in the
278 primary care medical record prior to the GP appearing to recognise the condition. Primary care
279 professionals should be aware of the range of articular and non-articular features, specifically hand
280 symptoms, muscle pain, carpal tunnel syndrome and unintentional weight loss, accompanied by an
281 increased rate of consultation, as potentially forming a prodromal syndrome for RA. Increased
282 awareness of these symptoms combined with education on the need for early referral could
283 facilitate earlier treatment of RA, increasing the likelihood of remission and reducing long term joint
284 damage and comorbidities.

285

286 **CONFLICT OF INTERESTS**

287 KR reports personal fees from BMS, personal fees from Abbvie, grants from Pfizer, personal fees
288 from Pfizer, personal fees from UCB, outside the submitted work. The other authors report no
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290

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301

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406 **Figure Legends**

407 Figure 1 Schematic representation of data set

408 Figure 2 Consultation rates (per person year) in cases and controls prior to index date