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Improving Accuracy of Self-Reported Diagnoses of Rheumatoid Arthritis in the French Prospective E3N-EPIC cohort

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ABSTRACT

Objectives

The French E3N-EPIC cohort enrolled 98,995 women aged 40–65 years at inclusion since 1990 to study the main risk factors for cancer and severe chronic conditions in women. They were prospectively followed with biennially self-administered questionnaires collecting self-reported medical, environmental, and lifestyle data. Our objective was to assess the accuracy of self-reported diagnoses of rheumatoid arthritis (RA) and to devise algorithms to improve the ascertainment of RA cases in our cohort.

Methods

Women who self-reported an inflammatory rheumatic disease (IRD) were asked to provide access to their medical record, and to answer an IRD questionnaire. Medical records were independently reviewed. Positive predictive values (PPV) of self-reported RA alone, then coupled with the IRD questionnaire, and with a medication reimbursement database were then assessed. These algorithms were then applied to the whole cohort to ascertain RA cases.

Results

Of the 98,995 participants, 2692 self-reported RA. Medical records were available for a sample of 399 participants, including 305 who self-reported RA. Self-reported RA was accurate only for 42% participants. Combining self-reported diagnoses to answers to a specific IRD questionnaire or to the medication reimbursement database improved the PPV (75.6% and 90.1%, respectively). Using the devised algorithms, we could identify 964 RA cases in our cohort.

Conclusion

Accuracy of self-reported RA is poor but adding answers to a specific questionnaire or data from a medication reimbursement database performed satisfactorily to identify RA cases in our cohort. It will subsequently allow investigating many potential risk factors of RA in women.

ARTICLE SUMMARY

Strengths and limitations of this study

- Two algorithms were devised and tested to improve accuracy of self-reported diagnosis of rheumatoid arthritis in a large population-based cohort.
- A large sample of medical records was available and independently reviewed to test the devised algorithm.
- Nearly a thousand cases of rheumatoid arthritis were identified, which will subsequently allow investigating many potential risk factors of rheumatoid arthritis in this cohort.
- The control population was women who self-reported another rheumatic disease and not healthy women.
- The sample of medical records was not provided at random.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory rheumatic disease (IRD) in adults, and is a major cause of functional alteration and handicap. RA is a complex multifactorial autoimmune disease in which both genetic and environmental factors interact in the pathogenesis of the disease to trigger auto-immunity [1].

Little is known about environmental factors that may contribute to the disease, except smoking, which has been reproducibly reported as associated with an increased risk of anti-citrullinated protein autoantibody (ACPA)-positive RA, particularly in individuals carrying the HLA-DRB1-shared epitope alleles [2–6]. The role of other environmental factors has been suggested but results were rarely reproducible. Only epidemiological studies, such as case-control studies or cohort studies can appropriately address the question. The main advantage of case-control studies is that cases are easily ascertained, with detailed phenotypes and easy availability of biological data, but their main limits are a retrospective collection of environmental factors, the risk of hindsight and recall bias, and a potentially biased control population. Cohort studies offer the advantage of having a prospective collection of environmental factors before disease onset and a non-biased non-cases population. However, collected information about disease phenotypes is usually limited, and in large population-based cohorts, diagnoses are often self-reported.

The diagnosis accuracy of self-reported RA has been studied in various populations, and vary considerably, between 7 and 96% [7–15]. One of the evocated reasons is the confusion between RA and other forms of arthritis, mainly osteoarthritis (OA), the prevalence of which being higher than RA in general populations [16]. If the accuracy of self-reported diagnosis is poor, using self-reported RA alone as case definition might create an ascertainment bias, because of the high rate of false positive cases.

To overcome this lack of accuracy, some studies have used a linkage with national patient registries, primary health care records and/or hospital discharge databases usually based on International Classification of Diseases (ICD) codes [17–21]. However, such registries are not always available, and these methods can also lack specificity [22]. Other studies have ascertained self-reported RA with a medical record review [23,24]. However, in large cohorts, medical record screening is time-consuming, expensive, and subject to difficulties in obtaining patients' consents and medical charts [12]. These difficulties underscore the need for increasing accuracy of RA case definition based on self-reported and/or other available information.

Our primary objective was to evaluate the accuracy of self-reported diagnoses of RA in a French population-based cohort and to determine if the use of additional information obtained from a dedicated questionnaire and from a medication reimbursement database could improve their accuracy. A secondary objective was to use the devised algorithms to identify RA cases in this large cohort for subsequent epidemiological studies.

MATERIAL AND METHODS

The E3N-EPIC cohort study

The E3N cohort study (*Etude Epidémiologique auprès des femmes de la Mutuelle générale de l'Education Nationale*) is a French prospective cohort study including 98,995 women living in France and covered by a national health insurance scheme primarily involving teachers [25]. This study is also the French component of the European Prospective Investigation into Cancer and Nutrition (EPIC). It was initiated in France in 1990 to study the main risk factors for cancer and severe chronic conditions in women. Participants ages were 40 to 65 at inclusion. After the baseline questionnaire (Q1), participants were biennially mailed questionnaires (Q2 to Q12) to update their health-related information and newly diagnosed diseases. The last questionnaire to date (Q12) was sent in 2018, but corresponding data are not yet available. Besides, a drug-reimbursement claims database has been available since 2004 for all cohort women from their medical insurance records (*Mutuelle Générale de l'Éducation Nationale* [MGEN]). The average follow-up rate per questionnaire has been 83% and, overall, the total proportion of patients lost to follow-up since 1990 was < 3% in 2014. All women gave written informed consent, and approvals were obtained from the French National Commission for Data Protection and Individual Freedom (327346-V14) and the French Advisory Committee on Information Processing in Material Research in the Field of Health (13.794).

Participants

In three follow-up questionnaires (Q9, Q10, and Q11, sent in 2007, 2011, and 2014, respectively), study participants self-reported a diagnosis of IRD (RA and/or spondyloarthritis [SpA]) by answering the following questions: "Do you have RA?" (yes/no) at Q9, Q10, and Q11, and "Do you have ankylosing spondylitis" (yes/no) at Q10 and Q11, together with the date of IRD diagnosis. In addition, women were asked at each questionnaire from baseline if they had been hospitalized since the last questionnaire, and if so, they had to specify the

reasons for those admissions. All women who self-reported RA or SpA in questionnaires and/or in hospitalization reasons were eligible to participate in the validation study, those who self-reported SpA serving as a control population.

IRD questionnaire design

A specific IRD questionnaire was designed to ascertain diagnoses of RA and SpA (S1 Appendix*)*. The questionnaire was adapted from a telephone questionnaire designed by Guillemin *et al*, with reference to the signs, symptoms, and epidemiological criteria for RA (American College of Rheumatology 1987) [26,27]. Since Guillemin's questionnaire was not designed to be sent by mail, we adapted it with the help of a patients' association (*Association Française des Polyarthrites et rhumatismes inflammatoires chroniques* [AFPric]). In this IRD questionnaire, women had the possibility to confirm or retract their self-reported diagnosis (S1 Appendix, Q0, Q1). We included additional questions: if a physician confirmed the diagnosis (only a general practitioner, a rheumatologist, and/or an internist), date of diagnosis, date of first symptoms, presence of ACPA, and current and past treatments.

All eligible women were sent this specific IRD questionnaire with an information letter and were asked to send back the questionnaire and their medical chart comprising all relevant medical documents in relation with their rheumatic condition, including medical reports, laboratory findings, hand and foot radiographs, and results of rheumatoid factors (RF) and anti-citrullinated protein antibodies (ACPA) testing, when available. A first mailing was sent on June 2017, and a reminder was sent in December 2017 to those who did not answer the first one.

RA ascertainment algorithm from IRD questionnaire

Based on data from the IRD questionnaire, a decision algorithm aimed at improving the accuracy of self-reported RA was devised by a consensus of rheumatologists (RS, XM, and ED). We considered as RA cases women who confirmed having RA in the IRD specific questionnaire, and self-reported at least one of the following: 1) RA diagnosis confirmed by a rheumatologist and/or another physician (internal medicine specialist or general practitioner) 2) taking or having taken any of the RA conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) or biologic DMARDs (listed in S1 Appendix, Question 34), 3) having positive RF or ACPA, or 4) at least 4 of the seven 1987-ACR criteria (listed in S1 Appendix, Questions 8,9,11,14–18).

RA ascertainment algorithm from medication reimbursement database

The MGEN medication reimbursement database included, for all E3N participants, all medications delivered by community-based pharmacies since 2004. Thus, medications only delivered by hospital pharmacies (*ie* intravenous infusions), and medications used before 2004 were not available.

Using this medication reimbursement database, we devised a second algorithm: women were considered as RA cases if they self-reported having RA, and had had reimbursements for any medication considered to be used in the treatment of RA: conventional synthetic or biologic DMARD among methotrexate, leflunomide, any sub-cutaneous tumor necrosis factor alpha (TNF-α) inhibitor, and sub-cutaneous abatacept or tocilizumab. Oral steroids, being widely used for other reasons, were not considered specific enough to be included in this definition. This algorithm had been previously used to ascertain RA cases in our cohort [28].

RA cases ascertainment: medical chart review

Medical records were obtained from the IRD questionnaire mailing for a subset of women and included medical reports from hospitalization and/or from outpatient medical visits, laboratory findings and/or bone X-rays. They were independently reviewed by 2 trained rheumatologists (YN and RS), blinded to the self-reported diagnoses and confirmed cases or not according to the RA diagnosis algorithm. Classification was based on reviewer's expertise, and not on strict American college of rheumatology (ACR) 1987 criteria or ACR/European League against Rheumatism (EULAR) 2010 criteria [27,29], and was used as the reference to assess the accuracy of self-reported diagnosis of RA alone and associated with additional information from a specific IRD questionnaire and from a medication reimbursement database. If the provided medical data were enough to confirm a diagnosis, reviewers classified women as RA, or not RA (including alternate diagnoses, such as OA, SpA, or other). Disagreements between the 2 reviewers were resolved by consensus. If diagnosis could not be ascertained by medical chart review, cases were considered as uncertain and were not used for determining the accuracy of the algorithms.

Identification of RA cases in the E3N cohort

Since, we expected that the accuracy of self-reported RA diagnoses alone would not be sufficient, we used the devised algorithms to identify RA cases in our cohort (including women who did not provide their medical records). For women who answered the IRD questionnaire, we used the algorithm based on this questionnaire, and for those who self-

reported RA in Q9, Q10, and/or Q11 but did not answer the specific IRD questionnaire, were deceased or lost to follow-up, we subsequently used the algorithm based on the medication reimbursement database. Women with available medical record who were identified as RA cases by these algorithms were reassessed as non-cases if their diagnosis was invalidated by medical chart review (false positive cases).

Statistical analysis

To assess the accuracy of self-reported diagnosis alone, and the two algorithms based on the IRD questionnaire and/or the medication reimbursement database, we used the classification based on medical chart review as the gold standard. Thus, this assessment was performed on the subset of participants with an available medical chart and for whom its review allowed to classify them as case or non-case. The level of agreement between each algorithm and the chart review diagnoses was assessed by the kappa statistic with 95% confidence intervals. Positive predictive value (PPV) and negative predictive value (NPV), sensitivity and specificity of each algorithm were calculated.

Finally, a descriptive analysis of demographic characteristics was performed on all women enrolled in the E3N study, on women who self-reported RA, on those who self-reported RA and provided their medical charts, on chart-reviewed confirmed RA, and on RA cases identified by combining self-report to the IRD questionnaire and/or the medication reimbursement database. All analyses were carried out using the SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

IRD case identification

Among the 98,995 participants, 3,230 women self-reported RA and/or SpA and were eligible to participate in the validation study: 2,692 self-reported RA, 637 self-reported SpA, and 109 women self-reported both RA and SpA. Demographic characteristics of the whole cohort, and of women who self-reported RA is described in Table 1.

Table 1. Baseline characteristics of the study population

	All women	Self-reported RA	Self-reported RA with available medical records	Confirmed RA after chart review	Identified RA with devised algorithms
N	**(N=98,995)**	**(N=2,692)**	**(N=305)**	**(N=129)**	**(N=964)**
Age at Q1 (years)	49.4 (6.7)	51.1 (6.7)	49.6 (5.6)	48.5 (5.2)	50.2 (6.3)
Year of birth					
< 1930	7,808 (7.9)	278 (10.3)	13 (4.3)	2 (1.6)	59 (6.1)
[1930–1940]	31,529 (31.9)	1,114 (41.4)	112 (36.7)	37 (28.7)	380 (39.4)
[1940–1950]	56,647 (57.2)	1,247 (46.3)	177 (58.0)	88 (68.1)	509 (52.8)
≥ 1950	3,011 (3.0)	53 (2.0)	3 (1.0)	2 (1.6)	16 (1.7)
Body mass index at Q1 (kg/m²)	22.6 (3.2)	23.2 (3.4)	23.0 (2.9)	22.9 (2.9)	23.0 (3.4)
Smoking status					
Not available	945 (1.0)	17 (0.6)	0 (0)	0 (0)	7 (0.7)
Current smoker	14,755 (14.8)	420 (15.6)	40 (13.1)	16 (12.4)	158 (16.4)
Non smoker	53,130 (53.7)	1,465 (54.4)	176 (57.7)	75 (58.1)	504 (52.3)
Former smoker	30,165 (30.5)	790 (29.4)	89 (29.2)	38 (29.5)	295 (30.6)
Passive smoking in childhood	12,854 (13.0)	398 (14.8)	48 (15.7)	19 (14.7)	158 (16.4)
Educational level					
Not available	4,277 (4.3)	136 (5.1)	14 (4.6)	5 (3.9)	55 (5.7)
<High School	16,185 (16.4)	597 (22.2)	61 (19.9)	19 (14.7)	186 (19.3)
Up to 2 years after high school	44,986 (45.4)	1,186 (44.1)	131 (43.0)	57 (44.2)	432 (44.8)
≥3 years after high school	33,547 (33.9)	773 (28.6)	99 (32.5)	48 (37.2)	291 (30.2)
Socio-professional category					
Not available	15,800 (16.0)	337 (12.5)	25 (8.2)	11 (8.5)	106 (11.0)
Teacher	62,013 (62.6)	1,632 (60.6)	198 (64.9)	86 (66.7)	609 (63.2)
Higher managerial and professional occupations	2,499 (2.5)	83 (3.1)	9 (3.0)	3 (2.3)	28 (2.8)
Intermediate occupations	15,340 (15.5)	495 (18.4)	58 (19.0)	27 (20.9)	179 (18.6)
Unemployed	2,602 (2.6)	106 (3.9)	10 (3.3)	1 (0.8)	28 (2.8)
Other	741 (0.8)	39 (1.5)	5 (1.6)	1 (0.8)	14 (1.5)
Deprivation index	-0.3 (1.0)	-0.2 (1.0)	-0.1 (1.0)	-0.2 (0.9)	-0.3 (1.1)

Results are presented as n (%) for categorical variables and mean (STD) for continuous variables. RA: rheumatoid arthritis.

RA cases ascertainment: medical chart review

Mailings were sent to 2,924 of the eligible women (306 women could not be contacted because of death or withdrawn consent), with a recall letter for those who failed to answer. The specific IRD questionnaire was sent back by 2,182 eligible women (74.6%), including 1,833 women who self-reported RA (84%). Medical charts were sent by 594 women (20.3%). Among them, 195 (32.8%) could not be classified because of insufficient provided medical data and were therefore excluded from the performance study. Thus, 399 women provided sufficient medical data to ascertain their diagnosis. Among them, 129 (32.3%) were classified as RA cases, 60 (15.0%) as SpA cases, and 210 (52.6%) as having another diagnosis (*ie* osteoarthritis or other diagnosis). All 399 women completed the IRD questionnaire and had available medication reimbursement data on the MGEN database. The accuracy of the different diagnosis algorithms has been assessed on this subset of 399 women. Among the 399 women, 305 had self-declared RA. The demographic characteristics of these 305 women are described in Table 1.

Determination of accuracy of self-reported diagnosis and validation algorithms

Accuracy of the validation algorithms compared to medical chart review is described in Table 2. Of the 305 women who self-reported RA with an available medical chart, only 125 (41 %) were confirmed by chart review, leading to a PPV and specificity of self-report of 41 and 33%, respectively. Concordance between self-reported RA alone and medical chart review was low (kappa statistic=0.2).

Table 2. Agreement between self-reported rheumatic disease and medical chart review

Self-reported diagnosis	n	Available medical chart, n	Confirmed cases, n	Agreement between self-report and medical chart review n (%)
RA	2692	305	129	125 (41)
RA only	2583	290	129	122 (42)
SpA	637	90	60	48 (53)
SpA only	528	75	60	42 (56)
RA and SpA	109	15	0	0 (0)
Total	3230	399		

RA: rheumatoid arthritis; SpA: spondylarthritis.

The addition of the IRD questionnaire dramatically improved PPV and specificity (Table 3). When combining self-reported RA with the IRD questionnaire algorithm (any of the 4 definitions), PPV was 72%, sensitivity 94% and specificity 83%, with a kappa statistic of 0.7. The combination associated with the best performances (highest PPV, sensitivity and specificity) was self-reported RA plus use of any specific RA medication; the one with the lowest specificity was self-reported RA plus confirmation by a rheumatologist of another physician. The combinations of self-reported RA with the use of RA medication and the ACR criteria were specific but had the lowest sensitivities. Alternate diagnoses for the false positive cases detected by this algorithm are reported in Table 4.

Using medication reimbursement data from the MGEN database also improved PPV and sensitivities of self-report alone (Table 3). If women self-reported RA and had at least one reimbursement of any RA specific medication, PPV was 90%, sensitivity 71%, specificity 87%, and kappa coefficient 0.7. With this algorithm, 10 women were detected by the medication reimbursement database but did not have RA (false positive cases, Table 4). All of them had received methotrexate. Also, 38 women were not detected by this algorithm but had RA (false negative): 21 received methotrexate before 2004, thus before the onset of the MGEN reimbursement database, 5 received intravenous biologic DMARDs not available in the database, and 27 received treatments which were not specific enough of RA (Table 5).

Combining self-report to both IRD questionnaire and medication reimbursement database improved PPV (98%) but considerably lowered sensitivity (67%), with no amelioration of the kappa value (Table 3).

Table 3. Agreement between self-report of RA alone, combined to the IRD questionnaire and to the medication reimbursement database with chart review

	Chart review (gold standard)			Positive Predictive Value, %	Negative Predictive Value, %	Sensitivity, %	Specificity, %	Kappa Coefficient (95% CI)
	Yes	No	Total					
Self-report of RA								
Yes	125	180	305	41.0	95.7	96.9	33.3	0.22 (0.17-0.28)
No	4	90	94					
Total	129	270	399					
Self-report of RA + IRD questionnaire								
1. Confirmation by a rheumatologist or an internal medicine specialist								
Yes	120	43	166	72.3	96.1	93	83	0.71 (0.65-078)
No	9	224	233					
Total	129	270	399					
2. RA medication								
Yes	118	11	129	91.5	95.9	91.5	95.9	0.87 (0.82-0.93)
No	11	259	270					
Total	129	270	399					
3. Positive RF and/or ACPA								
Yes	72	3	75	96.0	82.4	55.8	98.9	0.61 (0.53-0.70)
No	57	267	324					
Total	129	270	399					
4. ACR criteria								
Yes	63	7	70	90.0	79.9	48.8	97.4	0.52 (0.43-0.61)
No	66	263	329					
Total	129	270	399					
Any of these 4 definition								
Yes	121	47	168	72.0	96.5	93.8	82.6	0.71 (0.64-0.78)
No	8	223	231					
Total	129	270	399					
Self-report of RA + medication reimbursement database								
Yes	91	10	101	90.1	87.3	70.5	87.3	0.71 (0.63-0.78)
No	38	260	298					
Total	129	270	399					
Self-report of RA + IRD questionnaire + medication reimbursement database								
Yes	86	2	88	97.7	86.2	66.7	99.3	0.72 (0.64-0.79)
No	43	268	311					
Total	129	270	399					

RA: rheumatoid arthritis; IRD: inflammatory rheumatic disease; CI: confidence interval.

Table 4. Alternate diagnoses for false positive cases detected by the algorithms

	Alternate diagnosis
False positive cases detected by self-report + IRD questionnaire, N=39	Osteoarthritis (n=24) Scapulohumeral periarthritis (n=5) Polymyalgia rheumatica (n=3) Primary Sjögren's syndrome (n=3) Systemic lupus erythematosus (n=2) Osteoporosis (n=1) Lumbar sciatic (n=1)
False positive cases detected by self-report + reimbursement database, N=10	Psoriatic arthritis (n=7) Systemic lupus erythematosus (n=2) Osteoarthritis associated with inflammatory bowel disease (n=1)

IRD: inflammatory rheumatic disease

Table 5. RA treatment of the 38 false negative RA cases not detected by the reimbursement database

Treatment	N
Methotrexate*	21
Glucocorticoids alone	8
Hydroxychloroquine	14
Sulfasalazine	5
Infliximab	4
Rituximab	1

*Women received methotrexate before 2004, before the onset of the medication database

Identification of RA cases in the E3N cohort

Finally, we used both algorithms to identify RA cases in our cohort. Among the 1,833 women who answered the IRD questionnaire and self-declared RA, 904 RA cases (49.3%) were confirmed by the algorithm based on the IRD questionnaire (self-reported RA and any of the 4 definitions). Among them we excluded the 47 (5.2%) false positive cases (based on medical chart review) and 34 (3.8%) RA cases without diagnosis date, thus not allowing to know whether they were incident or prevalent. Finally, 823 (44.9%) RA cases were identified by this algorithm. The second algorithm based on the MGEN reimbursement database was used on the 859 remaining eligible women who self-reported RA but did not answer the questionnaire, and identified 141 (16,4%) RA cases. Overall, 964 RA cases were detected by one of the two algorithms, including 698 incident cases and 266 prevalent cases, during a mean follow-up of 25.2 years (S2 Appendix). Demographical characteristics of the identified RA cases is shown in Table 1.

DISCUSSION

In this large prospective cohort of French adult women, we examined the accuracy of self-reported diagnoses of RA and provided interesting information regarding the way to validate these diagnoses. As expected, in our study, the accuracy of self-reported diagnoses of RA was poor. But combining self-report to a specific IRD questionnaire providing addition self-reported data and/or to a medication reimbursement database, dramatically improved accuracy of RA diagnoses, with high sensitivity, specificity and PPV. Using these algorithms, we could detect nearly one thousand RA cases in this cohort.

The accuracy of self-reported RA diagnoses has previously been evaluated in other cohorts [7–9,12,13,15,23,24]. Reliability, sensitivity, and specificity of self-reported RA varied widely, depending on how the question was phrased, and on the confirmation method (diagnostic registries, chart review, use of ACR criteria, and/or clinical evaluation). When compared to chart review, PPV varies between 7 and 35% [8,9,15,24,30]. In the Nurses' Health Study [23], Karlson *et al* only confirmed 7% of the original self-reported RA, by reviewing the medical charts to look if women fulfilled the ACR criteria. In our cohort, self-reported diagnoses of RA were accurate for ~ 40% of the cases. Comparison with other studies, mainly involving English language questionnaires, might be difficult. Indeed, our higher rate of accurate diagnoses could be partially explained by language differences, RA and osteoarthritis being phonetically close in English, but not in French.

Nevertheless, this accuracy was not sufficient. Thus, to improve the accuracy of RA diagnosis, we used self-reported data from an IRD questionnaire, derived from a validated questionnaire designed to validate RA and SpA cases by phone interviews in a population of patients of 10 French university hospital rheumatology units [26]. We adapted it with the help of a patients' association that reviewed the wording and phrasing to make it clearly understandable to general population subjects, and we added questions about the presence or absence of RF and/or ACPA and on RA medication. Using this questionnaire, self-report of RA combined to a self-reported use of RA medication had the excellent accuracy, with both high sensitivity and specificity. Although very specific, and useful for further disease phenotyping, a self-report of positive RF and/or ACPA resulted in a low sensitivity and using this definition might miss RA cases. Using the ACR criteria in the IRD questionnaire resulted in a low sensitivity, because those criteria were not designed to be used in self-reported questionnaires, nevertheless they were highly specific. Our results demonstrate that the use of a limited list of items, particularly focusing on specific medications, in a dedicated questionnaire could improve drastically self-report accuracy.

We also assessed the performance of the algorithm using the medication reimbursement database. This method had been used to identify RA cases in the first study on RA in the E3N cohort study [28]. As expected, the algorithm has an excellent specificity and PPV, but underestimates the number of RA cases. Indeed, the database included all medications delivered by community-based pharmacies since 2004 and we only considered methotrexate, leflunomide, sub-cutaneous TNF-α inhibitors, and sub-cutaneous abatacept or tocilizumab; therefore we could not detect RA cases treated before 2004 and no longer treated with those drugs, those only treated by intravenous biologics delivered by hospital pharmacies only, and those with other treatments (e.g. hydroxychloroquine). Thus, if an exhaustive medication reimbursement database was available, using this algorithm could probably lead to both high specificities and high sensitivities.

Using both algorithms, we detected nearly one thousand RA cases, mainly incident cases. Although, there might be some false positive RA cases among them, given difficulties to ascertain RA cases in large epidemiologic studies, and the accuracy of the used algorithms to limit their number, this rate might be small.

We acknowledge some limitations to the present study. First, it was not designed to estimate the number of unreported RA cases in our cohort. Our population of non-cases were women who did not self-report RA but self-reported another IRD, which could bias our results. Ideally, we would have analyzed medical records from women who did not report any IRD to determine the proportion of cases missed. Thus, NPVs are reported but should be interpreted with caution. However, our main problematic here was not to miss cases but to ascertain those we detected. Nevertheless, for future epidemiologic study, having some RA cases in our control group might be a possibility, but the number of these cases is likely to be small, and, given the large number of non-cases in our cohort, the risk of bias induced by the false negative cases is negligible.

Another limit could be the representativeness of the sample of women who provided their medical records, sent on a voluntary basis, thus not at random, but it is unlikely that it would have biased our findings, this sample being similar to the rest of the women.

To conclude, our study highlights the poor accuracy of self-reported RA diagnoses, even among educated women. We demonstrated that this accuracy could be improved using medication reimbursement data and/or other self-reported data from a specific questionnaire. It appears that obtaining data on RA specific treatments either from patients themselves or from health insurance database is one of the best option. Even much less sensitive, obtaining

confirmation of ACPA or RF positivity from patients was also highly specific, and offer the advantage of giving a key phenotypic characteristic, particularly important when studying RA risk factors. These algorithms can be used in large population-based cohort, sparing the difficulties of obtaining complete medical charts, and the time and cost of medical chart review. Our results could serve as an example for other teams that aim at ascertaining RA cases in large epidemiological studies. Also, the validation of almost 1.000 RA cases in our cohort will serve as a basis to future epidemiological studies, since the design and the long follow-up of participants of our cohort will be used to investigate many potential RA risk factors.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript. YN, CS, ED, XM, MCB and RS were responsible for conception and design. YN, GG, MCB and RS were responsible for collection of data and analysis. All authors were responsible for the interpretation of data. YN and RS wrote the first version of the manuscript. All authors critically revised and approved the final version of the manuscript.

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ETHICAL APPROVAL INFORMATION

This study was approved by the French authorities ("Comité Consultatif sur le Traitement de l'information en matière de Recherche dans le domaine de la Santé" and "Commission Nationale de l'Informatique et des Libertés"). An informed consent was obtained from all patients.

COMPETING INTERESTS

None of the authors declared any competing interest in link with the present study

DATA SHARING

Data are available on demand by emailing the corresponding author.

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S1 Appendix. Specific IRD questionnaire, adapted from Guillemin et al. [25].

Subjects are asked to answer "yes" or "no" to the following questions:

Q0. Do you confirm having one of these rheumatic disorders?

Q1. Which was your rheumatic disease?

- ☐ Rheumatoid arthritis?
- ☐ Spondyloarthritis / axial spondyloarthritis and/or peripheral spondyloarthritis (formerly called ankylosing spondyloarthritis)?
- ☐ Psoriatic arthritis?
- ☐ Other: please precise

Q2. Was this diagnosis confirmed by a physician? If "yes", which one?

- ☐ Rheumatologist
- ☐ General practitioner
- ☐ Internist
- ☐ Other

Q3. What was the date of diagnosis?

Q4. What was the date of first symptoms?

Q5. Do you have full reimbursement for health care for this disease (*ALD – Affection longue durée)?*

Concerning your joint pain:

Q6. Are you at present experiencing, or have you in the past experienced, pains in your joints more than 2 weeks in a row (hands, wrists, feet, shoulder, elbows, knees)?

Q7. Are your joints swollen or have they been in the past?

Q8. Are or were your joints symmetrically affected, that is to say about the same on each side? (both hands, or both feet for example)

Q9. Are or were your hands affected?

Q10. Are or were your lower limbs affected (that is to say, your groin, your hip joint, your knees, your ankles, or your feet)?

Q11. Are or were more than three joints affected?

Q12. Has the pain lasted or did it last more than six weeks?

Q13. Have you ever been woken up by joint pain?

Q14. Are or were your joints stiff in the morning?

If Yes: For about how many minutes?

- ☐ < 30 minutes

- ☐ 30 minutes to 1 hour
- ☐ > 1 hour

Q15. Have you or have you had nodules under the skin on your elbows or hands?

Q16. Have you had the rheumatoid factor test, sometimes called the latex test or the Waaler-Rose test? If “yes”: Do you know if it was positive?

Q17. Have you had the anti CCP test, sometimes called ACPA test? If “yes”: Do you know if it was positive?

Q18. Have you had anti-fillagrin antibody test or anti-keratin antibody test? If “yes”: Do you know if it was positive?

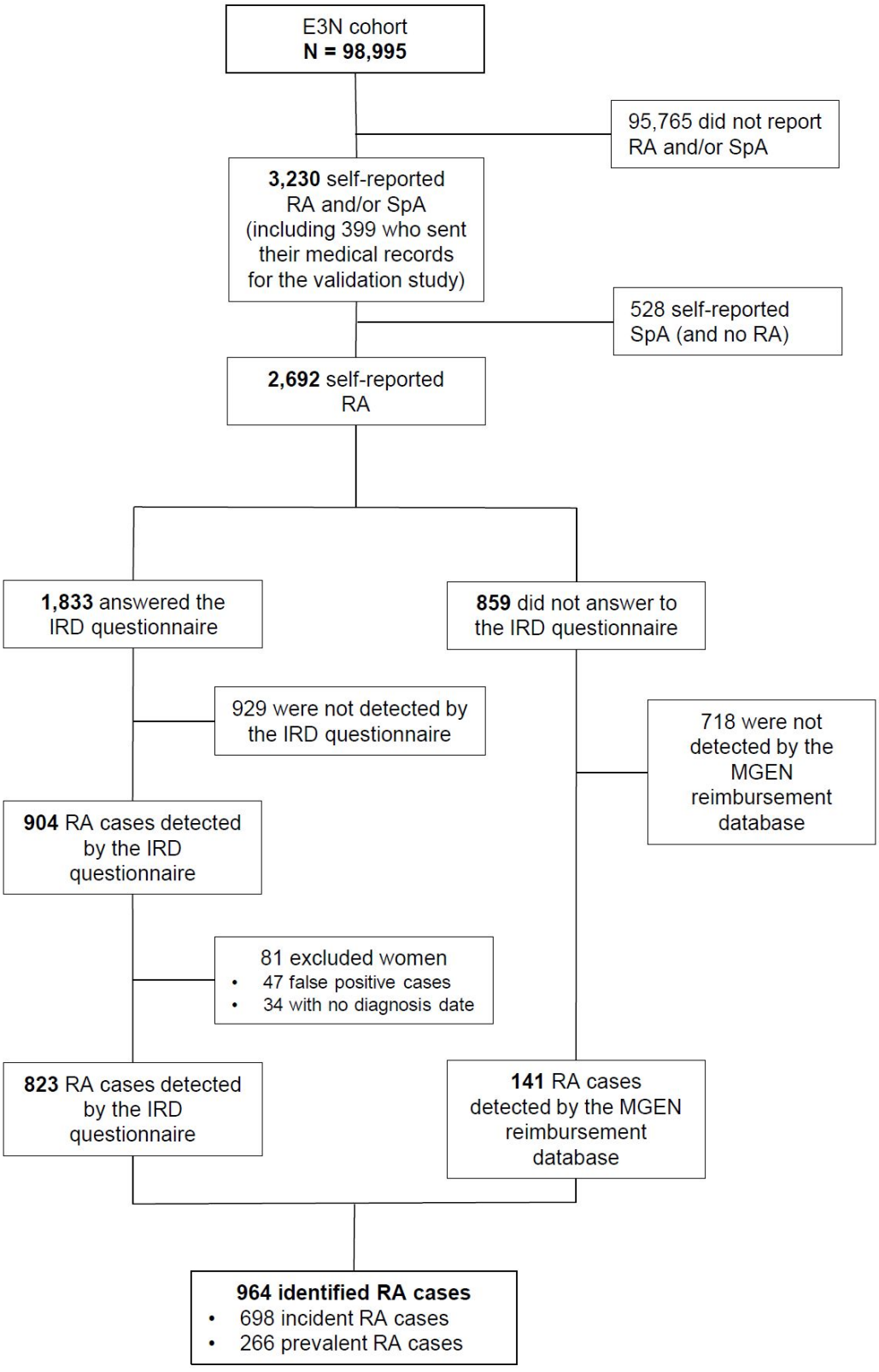
Q19. Have you had x ray examinations of your hands and wrists?

[Q20 to Q33: specific questions for axial spondyloarthritis and/or psoriatic rheumatism]

Q34. Among the following treatment, which one(s) do or did you receive for your disease?

- ☐ methotrexate (Novatrex®, Imeth®, Metoject®)
- ☐ leflunomide (Arava®)
- ☐ sulfasalazine (Salazopyrine®)
- ☐ hydroxychloroquine (Plaquenil®)
- ☐ azathioprine (Imurel®)
- ☐ gold salts, aurothiopropanolsulfonate (Allochrysine®, Auranofin®)
- ☐ ciclosporine (Neoral®)
- ☐ D-penicillamine (Trolovol®)
- ☐ tiopronine (Acadione®)
- ☐ Anakinra (Kineret®)
- ☐ infliximab (Remicade®, Inflectra®, Remsima®)
- ☐ etanercept (Enbrel®, Benepali®)
- ☐ adalimumab (Humira®)
- ☐ certolizumab (Cimzia®)
- ☐ golimumab (Simponi®)
- ☐ abatacept (Orencia®)
- ☐ tocilizumab (Roactemra®)
- ☐ rituximab (Mabthera)

S2 Appendix. Flow chart of the identification of RA cases in the E3N cohort.



E3N: "Etude Epidémiologique auprès des femmes de la Mutuelle générale de l'Education Nationale"; RA: rheumatoid arthritis; SpA: spondylarthritis; IRD: inflammatory rheumatic disease; MGEN: "Mutuelle Générale de l'Education Nationale".

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Improving Accuracy of Self-Reported Diagnoses of Rheumatoid Arthritis in the French Prospective E3N-EPIC cohort: A Validation Study

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Improving Accuracy of Self-Reported Diagnoses of Rheumatoid Arthritis in the French Prospective E3N-EPIC cohort: A Validation Study

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ABSTRACT

Objectives

The French E3N-EPIC cohort enrolled 98,995 women aged 40–65 years at inclusion since 1990 to study the main risk factors for cancer and severe chronic conditions in women. They were prospectively followed with biennially self-administered questionnaires collecting self-reported medical, environmental, and lifestyle data. Our objective was to assess the accuracy of self-reported diagnoses of rheumatoid arthritis (RA) and to devise algorithms to improve the ascertainment of RA cases in our cohort.

Design

A validation study.

Participants

Women who self-reported an inflammatory rheumatic disease (IRD) were asked to provide access to their medical record, and to answer an IRD questionnaire. Medical records were independently reviewed.

Primary and secondary outcome measures

Positive predictive values (PPV) of self-reported RA alone, then coupled with the IRD questionnaire, and with a medication reimbursement database were assessed. These algorithms were then applied to the whole cohort to ascertain RA cases.

Results

Of the 98,995 participants, 2692 self-reported RA. Medical records were available for a sample of 399 participants, including 305 who self-reported RA. Self-reported RA was accurate only for 42% participants. Combining self-reported diagnoses to answers to a specific IRD questionnaire or to the medication reimbursement database improved the PPV (75.6% and 90.1%, respectively). Using the devised algorithms, we could identify 964 RA cases in our cohort.

Conclusion

Accuracy of self-reported RA is poor but adding answers to a specific questionnaire or data from a medication reimbursement database performed satisfactorily to identify RA cases in our cohort. It will subsequently allow investigating many potential risk factors of RA in women.

ARTICLE SUMMARY

Strengths and limitations of this study

- Two algorithms were devised and tested to improve accuracy of self-reported diagnosis of rheumatoid arthritis in a large population-based cohort.
- A large sample of medical records was available and independently reviewed to test the devised algorithm.
- Nearly a thousand cases of rheumatoid arthritis were identified, which will subsequently allow investigating many potential risk factors of rheumatoid arthritis in this cohort.
- The control population was women who self-reported another rheumatic disease and not healthy women.
- The sample of medical records was not provided at random.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory rheumatic disease (IRD) in adults, and is a major cause of functional alteration and handicap. RA is a complex multifactorial autoimmune disease in which both genetic and environmental factors interact in the pathogenesis of the disease to trigger auto-immunity.[1]

Little is known about environmental factors that may contribute to the disease, except smoking, which has been reproducibly reported as associated with an increased risk of anti-citrullinated protein autoantibody (ACPA)-positive RA, particularly in individuals carrying the HLA-DRB1-shared epitope alleles.[2–6] The role of other environmental factors has been suggested but results were rarely reproducible. Only epidemiological studies, such as case-control studies or cohort studies can appropriately address the question. The main advantage of case-control studies is that cases are easily ascertained, with detailed phenotypes and easy availability of biological data, but their main limits are a retrospective collection of environmental factors, the risk of hindsight and recall bias, and a potentially biased control population. Cohort studies offer the advantage of having a prospective collection of environmental factors before disease onset and a non-biased non-cases population. However, collected information about disease phenotypes is usually limited, and in large population-based cohorts, diagnoses are often self-reported.

The diagnostic accuracy of self-reported RA has been studied in various populations, and varies considerably, between 7 and 96%.[7–15] One of the evocated reasons is the confusion between RA and other forms of arthritis, mainly osteoarthritis (OA), the prevalence of which being higher than RA in general populations.[16] If the accuracy of self-reported diagnosis is poor, using self-reported RA alone as case definition might create an ascertainment bias, because of the high rate of false positive cases.

To overcome this lack of accuracy, some studies have used a linkage with national patient registries, primary health care records and/or hospital discharge databases usually based on International Classification of Diseases (ICD) codes.[17–21] However, such registries are not always available, and these methods can also lack specificity.[22] Other studies have ascertained self-reported RA through linkage with a medical record review, or even with clinical examination of all suspected cases.[23–25] However, in large cohorts, medical record screening is time-consuming, expensive, and subject to difficulties in obtaining patients' consents and medical charts.[12] These difficulties underscore the need for increasing accuracy of RA case definition based on self-reported and/or other available information.

Our primary objective was to evaluate the accuracy of self-reported diagnoses of RA in a French population-based cohort and to determine if the use of additional information obtained from a dedicated questionnaire and from a medication reimbursement database could improve their accuracy. A secondary objective was to use the devised algorithms to identify RA cases in this large cohort for subsequent epidemiological studies.

MATERIAL AND METHODS

The E3N-EPIC cohort study

The E3N cohort study (*Etude Epidémiologique auprès des femmes de la Mutuelle générale de l'Education Nationale*) is a French prospective cohort study including 98,995 women living in France and covered by a national health insurance scheme primarily involving teachers.[26] This study is also the French component of the European Prospective Investigation into Cancer and Nutrition (EPIC). It was initiated in France in 1990 to study the main risk factors for cancer and severe chronic conditions in women. Participants ages were 40 to 65 at inclusion. After the baseline questionnaire (Q1), participants were biennially mailed questionnaires (Q2 to Q12) to update their health-related information and newly diagnosed diseases. The last questionnaire to date (Q12) was sent in 2018, but corresponding data are not yet available. In addition, a drug-reimbursement claims database has been available since 2004 for all cohort women from their medical insurance records (*Mutuelle Générale de l'Éducation Nationale* [MGEN]). The average follow-up rate per questionnaire has been 83% and, overall, the total proportion of patients lost to follow-up since 1990 was < 3% in 2014. All women gave written informed consent, and approvals were obtained from the French National Commission for Data Protection and Individual Freedom (327346-V14) and the French Advisory Committee on Information Processing in Material Research in the Field of Health (13.794).

Participants

In three follow-up questionnaires (Q9, Q10, and Q11, sent in 2007, 2011, and 2014, respectively), study participants self-reported a diagnosis of IRD (RA and/or spondyloarthritis [SpA]) by answering the following questions: "Do you have RA?" (yes/no) at Q9, Q10, and Q11, and "Do you have ankylosing spondylitis" (yes/no) at Q10 and Q11, together with the date of IRD diagnosis. In addition, women were asked at each questionnaire from baseline if they had been hospitalized since the last questionnaire, and if so, they had to specify the reasons for those admissions. All women who self-reported RA or SpA in questionnaires and/or in

hospitalization reasons were eligible to participate in the validation study, those who self-reported SpA serving as a control population.

IRD questionnaire design

A specific IRD questionnaire was designed to ascertain diagnoses of RA and SpA (online supplementary appendix 1*)*. The questionnaire was adapted from a telephone questionnaire designed by Guillemin *et al*, with reference to the signs, symptoms, and epidemiological criteria for RA (American College of Rheumatology 1987).[27,28] In this IRD questionnaire, women had the possibility to confirm or retract their self-reported diagnosis (online supplementary appendix 1, Q0, Q1). We included additional questions: if a physician confirmed the diagnosis (only a general practitioner, a rheumatologist, and/or an internist), date of diagnosis, date of first symptoms, presence of ACPA, and current and past treatments.

All eligible women were sent this specific IRD questionnaire with an information letter and were asked to send back the questionnaire and their medical chart comprising all relevant medical documents in relation with their rheumatic condition, including medical reports, laboratory findings, hand and foot radiographs, and results of rheumatoid factors (RF) and anti-citrullinated protein antibodies (ACPA) testing, when available. A first mailing was sent on June 2017, and a reminder was sent in December 2017 to those who did not answer the first one.

RA ascertainment algorithm from IRD questionnaire

Based on data from the IRD questionnaire, a decision algorithm aimed at improving the accuracy of self-reported RA was devised by a consensus of rheumatologists (RS, XM, and ED). We considered as RA cases women who confirmed having RA in the IRD specific questionnaire, and self-reported at least one of the following: 1) RA diagnosis confirmed by a rheumatologist and/or another physician (internal medicine specialist or general practitioner) 2) taking or having taken any of the RA conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) or biologic DMARDs (listed in online supplementary appendix 1, Question 34), 3) having positive RF or ACPA, or 4) at least 4 of the seven 1987-ACR criteria (listed in online supplementary appendix 1, Questions 8,9,11,14–18).

RA ascertainment algorithm from medication reimbursement database

The MGEN medication reimbursement database included, for all E3N participants, all medications delivered by community-based pharmacies since 2004. Thus, medications only

delivered by hospital pharmacies (*ie* intravenous infusions), and medications used before 2004 were not available.

Using this medication reimbursement database, we devised a second algorithm: women were considered as RA cases if they self-reported having RA, and had had reimbursements for any conventional synthetic or biologic DMARD used in the treatment of RA, including methotrexate, leflunomide, any sub-cutaneous tumor necrosis factor alpha (TNF-α) inhibitor, and sub-cutaneous abatacept or tocilizumab. Oral steroids, being widely used for other reasons, were not considered specific enough to be included in this definition. This algorithm had been previously used to ascertain RA cases in our cohort.[29] All algorithms are reported in detail in online supplementary table S1.

RA cases ascertainment: medical chart review

Medical records were obtained from the IRD questionnaire mailing for a subset of women and included medical reports from hospitalization and/or from outpatient medical visits, laboratory findings and/or bone X-rays. They were independently reviewed by 2 trained rheumatologists (YN and RS), blinded to the self-reported diagnoses and confirmed cases or not according to the RA identification algorithm. Classification was based on reviewer's expertise, and not on strict American college of rheumatology (ACR) 1987 criteria or ACR/European League against Rheumatism (EULAR) 2010 criteria,[28,30] and was used as the reference to assess the accuracy of self-reported diagnosis of RA alone and associated with additional information from the specific IRD questionnaire and from the medication reimbursement database. If the provided medical data were enough to confirm a diagnosis, reviewers classified women as RA, or not RA (including alternate diagnoses, such as OA, SpA, or other). Disagreements between the 2 reviewers were resolved by consensus. If diagnosis could not be ascertained by medical chart review, cases were considered as uncertain and were not used to determine the accuracy of the algorithms.

Identification of RA cases in the E3N cohort

Since, we expected that the accuracy of self-reported RA diagnoses alone would not be sufficient, we used the devised algorithms to identify RA cases in our cohort (including women who did not provide their medical records). For women who answered the IRD questionnaire, we used the algorithm based on this questionnaire, and for those who self-reported RA in Q9, Q10, and/or Q11 but did not answer the specific IRD questionnaire, were deceased or lost to follow-up, we subsequently used the algorithm based on the medication reimbursement

database. Women with available medical record who were identified as RA cases by these algorithms were reassessed as non-cases if their diagnosis was invalidated by medical chart review (false positive cases).

Statistical analysis

To assess the accuracy of self-reported diagnosis alone, and the two algorithms based on the IRD questionnaire and/or the medication reimbursement database, we used the classification based on medical chart review as the reference standard. Thus, this assessment was performed on the subset of participants with an available medical chart and for whom its review allowed to classify them as case or non-case. The level of agreement between each algorithm and the chart review diagnoses was assessed by the kappa statistic with 95% confidence intervals. Positive predictive value (PPV) and negative predictive value (NPV), sensitivity and specificity of each algorithm were calculated.

Finally, a descriptive analysis of demographic characteristics was performed on all women enrolled in the E3N study, on women who self-reported RA, on those who self-reported RA and provided their medical charts, on chart-reviewed confirmed RA, and on RA cases identified by combining self-report to the IRD questionnaire and/or the medication reimbursement database. All analyses were carried out using the SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Patient and Public Involvement

Patients and/or the public were involved in this validation study. Our validation study relied on a self-completed patient questionnaire adapted from a previous questionnaire not designed to be sent by mail. We modified the questionnaire for this purpose and added some questions on X-rays, and on ACPA and RF testing. To make sure that the revised questionnaire could be clearly understandable by patients, a patients' association (Association Française des Polyarthrites et rhumatismes inflammatoires chroniques [AFPric]) helped us to review the contents and wording of the questionnaire. The findings from this study will be shared with E3N participants through the next newsletter.

RESULTS

IRD case identification

Among the 98,995 participants, 3,230 women self-reported RA and/or SpA and were eligible to participate in the validation study: 2,692 self-reported RA, 637 self-reported SpA, and 109 women self-reported both RA and SpA. Demographic characteristics of the whole cohort, and of women who self-reported RA is described in Table 1.

Table 1. Baseline characteristics of the study population

	All women	Self-reported RA	Self-reported RA with available medical records	Confirmed RA after chart review	Identified RA with devised algorithms
N	**(N=98,995)**	**(N=2,692)**	**(N=305)**	**(N=129)**	**(N=964)**
Age at Q1 (years)	49.4 (6.7)	51.1 (6.7)	49.6 (5.6)	48.5 (5.2)	50.2 (6.3)
Year of birth					
< 1930	7,808 (7.9)	278 (10.3)	13 (4.3)	2 (1.6)	59 (6.1)
[1930–1940]	31,529 (31.9)	1,114 (41.4)	112 (36.7)	37 (28.7)	380 (39.4)
[1940–1950]	56,647 (57.2)	1,247 (46.3)	177 (58.0)	88 (68.1)	509 (52.8)
≥ 1950	3,011 (3.0)	53 (2.0)	3 (1.0)	2 (1.6)	16 (1.7)
Body mass index at Q1 (kg/m²)	22.6 (3.2)	23.2 (3.4)	23.0 (2.9)	22.9 (2.9)	23.0 (3.4)
Smoking status					
Not available	945 (1.0)	17 (0.6)	0 (0)	0 (0)	7 (0.7)
Current smoker	14,755 (14.8)	420 (15.6)	40 (13.1)	16 (12.4)	158 (16.4)
Non smoker	53,130 (53.7)	1,465 (54.4)	176 (57.7)	75 (58.1)	504 (52.3)
Former smoker	30,165 (30.5)	790 (29.4)	89 (29.2)	38 (29.5)	295 (30.6)
Passive smoking in childhood	12,854 (13.0)	398 (14.8)	48 (15.7)	19 (14.7)	158 (16.4)
Education level					
Not available	4,277 (4.3)	136 (5.1)	14 (4.6)	5 (3.9)	55 (5.7)
<High School	16,185 (16.4)	597 (22.2)	61 (19.9)	19 (14.7)	186 (19.3)
Up to 2 years after high school	44,986 (45.4)	1,186 (44.1)	131 (43.0)	57 (44.2)	432 (44.8)
≥3 years after high school	33,547 (33.9)	773 (28.6)	99 (32.5)	48 (37.2)	291 (30.2)
Socio-professional category					
Not available	15,800 (16.0)	337 (12.5)	25 (8.2)	11 (8.5)	106 (11.0)
Teacher	62,013 (62.6)	1,632 (60.6)	198 (64.9)	86 (66.7)	609 (63.2)
Higher managerial and professional occupations	2,499 (2.5)	83 (3.1)	9 (3.0)	3 (2.3)	28 (2.8)
Intermediate occupations	15,340 (15.5)	495 (18.4)	58 (19.0)	27 (20.9)	179 (18.6)
Unemployed	2,602 (2.6)	106 (3.9)	10 (3.3)	1 (0.8)	28 (2.8)
Other	741 (0.8)	39 (1.5)	5 (1.6)	1 (0.8)	14 (1.5)
Deprivation index	-0.3 (1.0)	-0.2 (1.0)	-0.1 (1.0)	-0.2 (0.9)	-0.3 (1.1)

Results are presented as n (%) for categorical variables and mean (SD) for continuous variables. RA: rheumatoid arthritis.

RA cases ascertainment: medical chart review

Mailings were sent to 2,924 of the eligible women (306 women could not be contacted because of death or withdrawn consent), with a recall letter for those who failed to answer. The specific IRD questionnaire was sent back by 2,182 eligible women (74.6%), including 1,833 women who self-reported RA (84%). Medical charts were sent by 594 women (20.3%). Among them, 195 (32.8%) could not be classified because of insufficient provided medical data and were therefore excluded from the performance study. Thus, 399 women provided sufficient medical data to ascertain their diagnosis. Among them, 129 (32.3%) were classified as RA cases, 60 (15.0%) as SpA cases, and 210 (52.6%) as having another diagnosis (*ie* osteoarthritis or other diagnosis). All 399 women completed the IRD questionnaire and had available medication reimbursement data on the MGEN database. The accuracy of the different diagnosis algorithms has been assessed on this subset of 399 women. Among the 399 women, 305 had self-declared RA. The demographic characteristics of these 305 women are described in Table 1.

Determination of accuracy of self-reported diagnosis and validation algorithms

Accuracy of the validation algorithms compared to medical chart review is described in Table 2. Of the 305 women who self-reported RA with an available medical chart, only 125 (41 %) were confirmed by chart review, leading to a PPV and specificity of self-report of 41 and 33%, respectively. Concordance between self-reported RA alone and medical chart review was low (kappa statistic=0.2).

Table 2. Agreement between self-reported rheumatic disease and medical chart review

Self-reported diagnosis	n	Available medical chart, n	Confirmed cases, n	Agreement between self-report and medical chart review n (%)
RA	2692	305	129	125 (40.9)
RA only	2583	290	129	122 (42.1)
SpA	637	90	60	48 (53.3)
SpA only	528	75	60	42 (56.0)
RA and SpA	109	15	0	0 (0.0)
Total	3230	399		

RA: rheumatoid arthritis; SpA: spondylarthritis.

The addition of the IRD questionnaire dramatically improved PPV and specificity (Table 3). When combining self-reported RA with the IRD questionnaire algorithm (any of the 4 definitions), PPV was 72%, sensitivity 94% and specificity 83%, with a kappa statistic of 0.7. The combination associated with the best performances (highest PPV, sensitivity and specificity) was self-reported RA plus use of any specific RA medication; the one with the lowest specificity was self-reported RA plus confirmation by a rheumatologist of another physician. The combinations of self-reported RA with positive RF and/or ACPA or with the ACR criteria were specific but had the lowest sensitivities. Alternate diagnoses for the false positive cases detected by this algorithm are reported in Table 4.

Using medication reimbursement data from the MGEN database also improved PPV and sensitivities of self-report alone (Table 3). If women self-reported RA and had at least one reimbursement of any RA specific medication, PPV was 90%, sensitivity 71%, specificity 87%, and kappa coefficient 0.7. With this algorithm, 10 women were detected by the medication reimbursement database but did not have RA (false positive cases, Table 4). All of them had received methotrexate. Also, 38 women were not detected by this algorithm but had RA (false negative): 21 received methotrexate before 2004, thus before the onset of the MGEN reimbursement database, 5 received intravenous biologic DMARDs not available in the database, and 27 received treatments which were not specific enough of RA (online supplementary table S2).

Combining self-report to both IRD questionnaire and medication reimbursement database improved PPV (98%) but considerably lowered sensitivity (67%), with no amelioration of the kappa value (Table 3).

Table 3. Agreement between self-report of RA alone, combined to the IRD questionnaire and to the medication reimbursement database with chart review

	Chart review (reference standard)			Positive Predictive Value, %	Negative Predictive Value, %	Sensitivity, %	Specificity, %	Kappa Coefficient (95% CI)
	Yes	No	Total					
Self-report of RA								
Yes	125	180	305	41.0	95.7	96.9	33.3	0.22 (0.17–0.28)
No	4	90	94					
Total	129	270	399					
Self-report of RA + IRD questionnaire								
1. Confirmation by a rheumatologist or an internal medicine specialist								
Yes	120	43	166	72.3	96.1	93	83	0.71 (0.65–078)
No	9	224	233					
Total	129	270	399					
2. RA medication								
Yes	118	11	129	91.5	95.9	91.5	95.9	0.87 (0.82–0.93)
No	11	259	270					
Total	129	270	399					
3. Positive RF and/or ACPA								
Yes	72	3	75	96.0	82.4	55.8	98.9	0.61 (0.53–0.70)
No	57	267	324					
Total	129	270	399					
4. ACR criteria								
Yes	63	7	70	90.0	79.9	48.8	97.4	0.52 (0.43–0.61)
No	66	263	329					
Total	129	270	399					
Any of these 4 definitions								
Yes	121	47	168	72.0	96.5	93.8	82.6	0.71 (0.64–0.78)
No	8	223	231					
Total	129	270	399					
Self-report of RA + medication reimbursement database								
Yes	91	10	101	90.1	87.3	70.5	87.3	0.71 (0.63–0.78)
No	38	260	298					
Total	129	270	399					
Self-report of RA + IRD questionnaire + medication reimbursement database								
Yes	86	2	88	97.7	86.2	66.7	99.3	0.72 (0.64–0.79)
No	43	268	311					
Total	129	270	399					

RA: rheumatoid arthritis; IRD: inflammatory rheumatic disease; CI: confidence interval.

Table 4. Alternate diagnoses for false positive cases detected by the algorithms

	Alternate diagnosis
False positive cases detected by self-report + IRD questionnaire, N=39	Osteoarthritis (n=24) Scapulohumeral periarthritis (n=5) Polymyalgia rheumatica (n=3) Primary Sjögren's syndrome (n=3) Systemic lupus erythematosus (n=2) Osteoporosis (n=1) Lumbar sciatic (n=1)
False positive cases detected by self-report + reimbursement database, N=10	Psoriatic arthritis (n=7) Systemic lupus erythematosus (n=2) Osteoarthritis associated with inflammatory bowel disease (n=1)

IRD: inflammatory rheumatic disease

Identification of RA cases in the E3N cohort

Finally, we used both algorithms to identify RA cases in our cohort. Among the 1,833 women who answered the IRD questionnaire and self-declared RA, 904 RA cases (49.3%) were confirmed by the algorithm based on the IRD questionnaire (self-reported RA and any of the 4 definitions). Among them we excluded the 47 (5.2%) false positive cases (based on medical chart review) and 34 (3.8%) RA cases without diagnosis date, thus not allowing to know whether they were incident or prevalent. Finally, 823 (44.9%) RA cases were identified by this algorithm. The second algorithm based on the MGEN reimbursement database was used on the 859 remaining eligible women who self-reported RA but did not answer the questionnaire, and identified 141 (16,4%) RA cases. Overall, 964 RA cases were detected by one of the two algorithms, including 698 incident cases and 266 prevalent cases, during a mean follow-up of 25.2 years (Figure 1). In addition, 65.1% of our identified cases have been identified by at least two methods, and 16.4% and 21% have even been validated by three or four methods, respectively (online supplementary table S3). Demographical characteristics of the identified RA cases are shown in Table 1.

DISCUSSION

In this large prospective cohort of French adult women, we examined the accuracy of self-reported diagnoses of RA and provided interesting information regarding the way to validate these diagnoses. As expected, in our study, the accuracy of self-reported diagnoses of RA was poor. But, combining self-report to a specific IRD questionnaire providing addition self-reported data and/or to a medication reimbursement database, dramatically improved accuracy of RA diagnoses, with high sensitivity, specificity and PPV. Using these algorithms, we could detect nearly one thousand RA cases in this cohort.

The accuracy of self-reported RA diagnoses has previously been evaluated in other cohorts.[7–9,12,13,15,23,24] Reliability, sensitivity, and specificity of self-reported RA varied widely, depending on how the question was phrased, and on the confirmation method (diagnostic registries, chart review, use of ACR criteria, and/or clinical evaluation). When compared to chart review, PPV varies between 7 and 35%.[8,9,15,24,31] In the Nurses' Health Study,[23] Karlson *et al* only confirmed 7% of the original self-reported RA, by reviewing the medical charts to look if women fulfilled the ACR criteria. In our cohort, self-reported diagnoses of RA were accurate for ~ 40% of the cases. Comparison with other studies, mainly involving English language questionnaires, might be difficult. Indeed, our higher rate of accurate diagnoses could be partially explained by language differences, RA and osteoarthritis being phonetically close in English, but not in French.

Nevertheless, this accuracy was not sufficient. Thus, to improve the accuracy of RA diagnosis, we used self-reported data from an IRD questionnaire, derived from a validated questionnaire designed to validate RA and SpA cases by phone interviews in a population of patients of 10 French university hospital rheumatology units.[27] We adapted it with the help of a patients' association that reviewed the wording and phrasing to make it clearly understandable to general population subjects, and we added questions about the presence or absence of RF and/or ACPA and on RA medication. Using this questionnaire, self-report of RA combined to a self-reported use of RA medication had the excellent accuracy, with both high sensitivity and specificity. Although very specific, and useful for further disease phenotyping, a self-report of positive RF and/or ACPA resulted in a low sensitivity and using this definition might miss RA cases. Using the ACR criteria in the IRD questionnaire resulted in a low sensitivity, because those criteria were not designed to be used in self-reported questionnaires, nevertheless they were highly specific. Our results demonstrate that the use of a limited list of items, particularly focusing on specific medications, in a dedicated questionnaire could drastically improve self-report accuracy.

We also assessed the performance of the algorithm using the medication reimbursement database. This method had been used to identify RA cases in the first study on RA in the E3N cohort study.[29] As expected, the algorithm has an excellent specificity and PPV, but underestimates the number of RA cases. Indeed, the database included all medications delivered by community-based pharmacies since 2004 and we only considered methotrexate, leflunomide, sub-cutaneous TNF-α inhibitors, and sub-cutaneous abatacept or tocilizumab; therefore we could not detect RA cases treated before 2004 and no longer treated with those drugs, those only treated by intravenous biologics delivered by hospital pharmacies only, and those with other treatments (e.g. hydroxychloroquine). Thus, if an exhaustive medication reimbursement database was available, using this algorithm could probably lead to both high specificities and high sensitivities.

Using both algorithms, we detected nearly one thousand RA cases, mainly incident cases. Since a proper evaluation with the reference standard (ie medical chart review) was not available for all women, there might be some false positive RA cases among them. But given the number of methods used to limit their number and their accuracy, this rate might be small.

We acknowledge some limitations to the present study. First, it was not designed to estimate the number of unreported RA cases in our cohort. Our population of non-cases were women who did not self-report RA but self-reported another IRD, which could bias our results. Ideally, we would have analysed medical records from women who did not report any IRD to determine the proportion of cases missed. Thus, reported sensitivities and NPVs but should be interpreted with caution. However, our main concern was to avoid false positive cases ie to ascertain detected cases, rather than to avoid missing a few cases. Therefore, there may be a few undetected RA cases in the control group, but the number of these cases is likely to be small, and, given the large number of non-cases in our cohort, the risk of bias induced by the false negative cases is negligible. Also, our validation study relies on an additional questionnaire. Answers to this questionnaire were not obtained for all women, which might have created a response bias. However, such bias was limited by using the medication reimbursement database for women who did not answer to the IRD questionnaire.

Another limitation could be the representativeness of the sample of women who provided their medical records, sent on a voluntary basis, thus not at random. This could have introduced a selection bias toward more severe disease, inflating the accuracy. However, medical chart review confirmed the diagnosis of RA in only 41% of them, showing that both cases and non-cases provided medical chart. Also, women who provided their medical charts

did not differ from other women who self-reported IRD in terms of age or education level, which may limit the bias.

Finally, the algorithms we devised to improve accuracy of self-reported RA diagnoses could prove useful to validate RA diagnoses in other population-based cohorts. However, they could be difficult to transpose from the French care setting to another one; thus, all data potentially available for validation (medication database, national patient registries, primary care records and/or hospital discharge databases) must be considered.

CONCLUSIONS

To conclude, our study highlights the poor accuracy of self-reported RA diagnoses, even among educated women. We demonstrated that this accuracy could be improved using medication reimbursement data and/or other self-reported data from a specific questionnaire. Even if ascertaining RA diagnoses with a complete medical chart review might probably be one of the best option, it appears that obtaining other information, particularly on RA specific treatment, either from the patients themselves or from health insurance databases can be a reasonably good alternative, sparing the difficulties of obtaining complete medical charts, and the time and cost of medical chart review. Even much less sensitive, obtaining confirmation of ACPA or RF positivity from patients was also highly specific, and offer the advantage of giving a key phenotypic characteristic, particularly important when studying RA risk factors. Our results could help other teams that aim at ascertaining RA cases in large epidemiological studies. Also, the validation of almost 1.000 RA cases in our cohort will serve as a basis to future epidemiological studies, since the design and the long follow-up of participants of our cohort will be used to investigate many potential RA risk factors.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript. YN, CS, ED, XM, MCB and RS were responsible for conception and design. YN, GG, MCB and RS were responsible for collection of data and analysis. All authors were responsible for the interpretation of data. YN and RS wrote the first version of the manuscript. All authors critically revised and approved the final version of the manuscript.

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ETHICAL APPROVAL INFORMATION

This study was approved by the French authorities ("Comité Consultatif sur le Traitement de l'information en matière de Recherche dans le domaine de la Santé" and "Commission Nationale de l'Informatique et des Libertés"). An informed consent was obtained from all patients.

COMPETING INTERESTS

None of the authors declared any competing interest in link with the present study

DATA SHARING

Data are available on demand by emailing the corresponding author.

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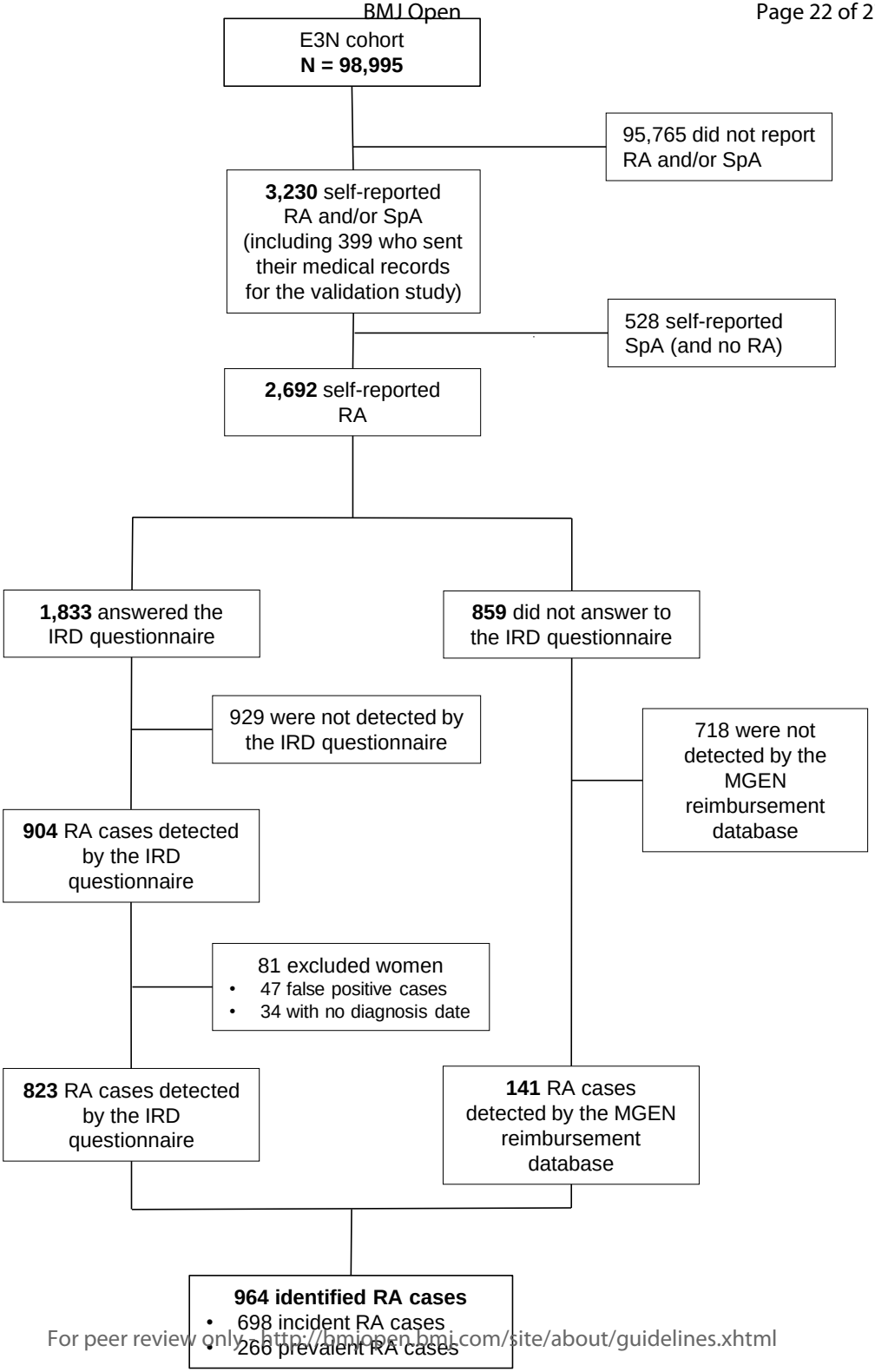
FIGURE LEGENDS

Figure 1. Flow chart of the identification of RA cases in the E3N cohort.

E3N: "Etude Epidémiologique auprès des femmes de la Mutuelle générale de l'Education Nationale"; RA: rheumatoid arthritis; SpA: spondylarthritis; IRD: inflammatory rheumatic disease; MGEN: "Mutuelle Générale de l'Education Nationale".



Appendix S1. Specific IRD questionnaire, adapted from Guillemin et al. [25].

Subjects are asked to answer "yes" or "no" to the following questions:

Q0. Do you confirm having one of these rheumatic disorders?

Q1. Which was your rheumatic disease?

- ☐ Rheumatoid arthritis?
- ☐ Spondyloarthritis / axial spondyloarthritis and/or peripheral spondyloarthritis (formerly called ankylosing spondyloarthritis)?
- ☐ Psoriatic arthritis?
- ☐ Other: please precise

Q2. Was this diagnosis confirmed by a physician? If "yes", which one?

- ☐ Rheumatologist
- ☐ General practitioner
- ☐ Internist
- ☐ Other

Q3. What was the date of diagnosis?

Q4. What was the date of first symptoms?

Q5. Do you have full reimbursement for health care for this disease (*ALD – Affection longue durée)?*

Concerning your joint pain:

Q6. Are you at present experiencing, or have you in the past experienced, pains in your joints more than 2 weeks in a row (hands, wrists, feet, shoulder, elbows, knees)?

Q7. Are your joints swollen or have they been in the past?

Q8. Are or were your joints symmetrically affected, that is to say about the same on each side? (both hands, or both feet for example)

Q9. Are or were your hands affected?

Q10. Are or were your lower limbs affected (that is to say, your groin, your hip joint, your knees, your ankles, or your feet)?

Q11. Are or were more than three joints affected?

Q12. Has the pain lasted or did it last more than six weeks?

Q13. Have you ever been woken up by joint pain?

Q14. Are or were your joints stiff in the morning?

If Yes: For about how many minutes?

- ☐ < 30 minutes
- ☐ 30 minutes to 1 hour
- ☐ > 1 hour

Q15. Have you or have you had nodules under the skin on your elbows or hands?

Q16. Have you had the rheumatoid factor test, sometimes called the latex test or the Waaler-Rose test? If "yes": Do you know if it was positive?

Q17. Have you had the anti CCP test, sometimes called ACPA test? If "yes": Do you know if it was positive?

Q18. Have you had anti-fillagrin antibody test or anti-keratin antibody test? If "yes": Do you know if it was positive?

Q19. Have you had x ray examinations of your hands and wrists?

[Q20 to Q33: specific questions for axial spondyloarthritis and/or psoriatic rheumatism]

Q34. Among the following treatment, which one(s) do or did you receive for your disease?

- ☐ methotrexate (Novatrex®, Imeth®, Metoject®)
- ☐ leflunomide (Arava®)
- ☐ sulfasalazine (Salazopyrine®)
- ☐ hydroxychloroquine (Plaquenil®)
- ☐ azathioprine (Imurel®)
- ☐ gold salts, aurothiopropanolsulfonate (Allochrysine®, Auranofin®)
- ☐ ciclosporine (Neoral®)
- ☐ D-penicillamine (Trolovol®)
- ☐ tiopronine (Acadione®)
- ☐ Anakinra (Kineret®)
- ☐ infliximab (Remicade®, Inflectra®, Remsima®)
- ☐ etanercept (Enbrel®, Benepali®)
- ☐ adalimumab (Humira®)
- ☐ certolizumab (Cimzia®)
- ☐ golimumab (Simponi®)
- ☐ abatacept (Orencia®)
- ☐ tocilizumab (Roactemra®)
- ☐ rituximab (Mabthera)

Table S1. Used algorithms to identify of rheumatoid arthritis cases in the E3N-EPIC cohort

Identification algorithm
Algorithm 1: using the IRD questionnaire Self-report of RA (Q1) + at least one of the following criteria: 1. diagnosis confirmed by a rheumatologist of physician (Q2) 2. current or past use of csDMARDs and/or bDMARDs (Q34) 3. positive RF and/or ACPA and/or anti-fillagrin and/or anti-keratin antibody (Q16, Q17 and Q18) 4. sum of the following questions ≥ 4 (1 point per positive answer at each question) o Symmetrically affected joints (Q8) o Affected hands (Q9) o More than three joints affected (Q11) o Stiff joints in the morning > 1 hour (Q14) o Nodules under the skin on elbows or hands (Q15) o Positive RF, or ACPA, or anti-fillagrin antibody or anti-keratin antibody (Q16, Q17, or Q18).
Algorithm 2: using the drug reimbursement database Self-report of RA in the three follow-up questionnaires (2007, 2011, 2014) + at least one reimbursement of csDMARDs and/or bDMARDs among methotrexate, leflunomide, all sub-cutaneous TNF-α inhibitors, sub-cutaneous abatacept and sub-cutaneous tocilizumab

IRD: inflammatory rheumatic diseases; RA: rheumatoid arthritis; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; bDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; TNF-α: tumor necrosis factor alpha.

Table S2. RA treatment of the 38 false negative RA cases not detected by the reimbursement database

Treatment	N
Methotrexate*	21
Glucocorticoids alone	8
Hydroxychloroquine	14
Sulfasalazine	5
Infliximab	4
Rituximab	1

*Women received methotrexate before 2004, before the onset of the medication database

Table S3. Number of fulfilled criteria for the 964 identified RA cases

Number of methods	Validation method				n (%)	Total n (%)
	Rheumatologist and/or physician	Treatment¶	Antibodies	ACR criteria		
4	■	■	■	■	202 (21.0)	202 (21.0)
3	■	■	■		81 (8.4)	158 (16.4)
	■	■		■	61 (6.3)	
	■		■	■	14 (1.5)	
		■	■	■	2 (0.2)	
2			■	■	1 (0.1)	268 (27.8)
		■	■		1 (0.1)	
	■	■			222 (23.0)	
	■		■		12 (1.2)	
	■			■	32 (3.3)	
1				■	1 (0.1)	336 (34.9)
			■		1 (0.1)	
		■			141 (14.6)	
	■				193 (20.0)	
N (%)	828 (85.9)	699 (72.5)	314 (32.6)	313 (32.5)	964	

¶ Treatments have been collected through validation questionnaire and/or by the drug reimbursement database.