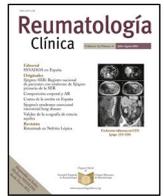




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Original Article

Prevalence of Rheumatic Diseases in Adult Population in Spain (EPISER 2016 Study): Aims and Methodology[☆]



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ABSTRACT

Aims: To describe the methodology of the EPISER 2016 (study of the prevalence of rheumatic diseases in adult population in Spain), as well its strengths and limitations. The aim of this study is to estimate the prevalence of rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), osteoarthritis (knee, hip, hands, and cervical and lumbar spine), fibromyalgia, gout and clinical osteoporotic fracture.

Material and method: Population-based, multicenter, cross-sectional study, with the participation of 45 municipalities in the 17 Spanish autonomous communities. The reference population will consist of adults aged 20 years and over residing in Spain. A computer-assisted telephone interview (CATI) system will be used for data collection. Diagnostic suspicions and diagnoses received by the participants will be studied by rheumatologists in the referral hospitals in the selected municipalities. Statistical analysis: the prevalence of the rheumatic diseases will be calculated using estimators and their 95% confidence intervals. Weights will be calculated in each of the sampling stages in accordance with the probability of selection. The distribution of the population in Spain will be obtained from the Spanish Statistics Institute.

Conclusions: Sociodemographic and lifestyle changes over the last 16 years justify EPISER 2016. This study will provide current data about the prevalences of RA, AS, PsA, SLE, SS, osteoarthritis, fibromyalgia, gout and clinical osteoporotic fracture. The results will allow comparisons with studies from other countries and EPISER 2000.

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Prevalencia de enfermedades reumáticas en población adulta en España (estudio EPISER 2016). Objetivos y metodología

RESUMEN

Palabras clave:

Epidemiología

Metodología

Prevalencia

Artritis reumatoide

Espondilitis anquilosante

Artritis psoriásica

Gota

Lupus eritematoso sistémico

Artrosis

Fibromialgia

Síndrome de Sjögren

Fractura osteoporótica

Objetivos: Describir la metodología del estudio de prevalencia de las enfermedades reumáticas en la población adulta en España, EPISER 2016, así como sus fortalezas y limitaciones. El objetivo del proyecto es estimar la prevalencia de artritis reumatoide (AR), artropatía psoriásica (APs), espondilitis anquilosante (EA), lupus eritematoso sistémico (LES), síndrome de Sjögren (SS), artrosis (de rodilla, cadera, manos, columna cervical y lumbar), fibromialgia, gota y fractura osteoporótica clínica.

Material y método: Estudio transversal multicéntrico de base poblacional en el que participan 45 municipios de las 17 comunidades autónomas. La población de referencia está compuesta por adultos de 20 o más años residentes en España. La recogida de información se llevará a cabo mediante encuesta telefónica empleando el sistema Computer Assisted Telephone Interview (CATI). Las sospechas diagnósticas y los diagnósticos autorreferidos serán estudiados por reumatólogos del hospital de referencia de los municipios seleccionados. Análisis estadístico: se calcularán las prevalencias de enfermedades reumáticas mediante estimadores y sus IC del 95%. Se calcularán factores de ponderación en función de la probabilidad de selección en cada una de las etapas del muestreo. Se tendrá en cuenta la distribución de la población en España según datos del Instituto Nacional de Estadística.

Conclusiones: Los cambios sociodemográficos y en hábitos de vida durante los últimos 16 años justifican la realización de EPISER 2016. El estudio ofrecerá datos actualizados de prevalencia en AR, EA, APs, LES, SS, artrosis, fibromialgia, gota y fractura osteoporótica clínica. Los resultados permitirán comparar los datos con estudios de otros países y con el EPISER 2000.

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Introduction

Musculoskeletal disorders are one of the major disease burdens on a worldwide basis.¹ According to the data of the European Health Interview Survey conducted in Spain in 2014, chronic low back pain and osteoarthritis are among the 5 conditions that the population over the age of 14 years complain of with the highest frequency.² Musculoskeletal diseases have a significant impact on the quality of life and functional capacity of those affected, as well as a substantial economic impact.^{3–8}

Until EPISER 2000, the epidemiological data on rheumatic diseases in Spain were insufficient and there were considerable methodological differences.^{9,10} EPISER 2000 enabled us to estimate the prevalence of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), low back pain, osteoarthritis in hands and knees, fibromyalgia and osteoporosis in the Spanish adult population.^{11–13}

Sociodemographic changes and those affecting health habits that have taken place in the last 16 years in our country justify

a new edition of the EPISER study, due to the influence that some of them may have had in the prevalence of rheumatic diseases.^{14–16} Sociodemographic changes can be summarized in an increase in the proportion of individuals over the age of 64 years and an increase in the foreign population, according to data from the Spanish Statistical Office (SSO).¹⁷ With respect to lifestyle, there has been an increase in the incidence of obesity and individuals who are overweight,^{2,18} and changes related to tobacco use: in men it has decreased in all age groups, whereas in women it has decreased in the group aged 15–34 years, but has increased in the group aged 35–64.¹⁹

The main objective of EPISER 2016 is to estimate the prevalence in the Spanish adult population of RA, SLE, osteoarthritis of the knees and hands, and fibromyalgia, diseases studied in EPISER 2000. Moreover, EPISER 2016 includes as an objective the determination of the prevalence of diseases that were not studied in EPISER 2000, specifically, ankylosing spondylitis (AS), psoriatic arthritis (PsA), Sjögren's syndrome (SS), osteoarthritis of the hip,

cervical and lumbar spine, gout and clinical osteoporotic fracture. As a secondary objective, we proposed to estimate the frequency in the last year and due to osteoarticular problems, with which the Spanish adult population consulted with a physician and received medication during at least one month.

The results of EPISER 2016 will enable us to: 1) determine the prevalence of rheumatic diseases that had not been studied until now (AS, PsA, osteoarthritis of the hip, cervical and lumbar spine, and gout); 2) determine the current prevalence of previously studied rheumatic diseases (RA, SLE, osteoarthritis of the knees and hands and fibromyalgia), enabling us to draw up hypotheses on the potential sociodemographic factors or health habits that can explain the possible changes in the prevalence of these diseases over the last 16 years; and 3) provide relevant information to health administrators and funders, that enables them to measure the importance in terms of social and health care aspects of rheumatic diseases, helping them to predict the budgetary impact generated by new drugs that reach the market for the treatment of some of these disorders.

In this report, we describe the design and methodology of EPISER 2016, as well as its strengths and limitations.

Methods

General Design

Population-based cross-sectional descriptive study.

Reference Population and Study Subjects

General adult population of 20 years or more living in Spain.

The participants in the study were men and women of 20 years or more, whose usual residence was one of the municipalities participating in the study, with capacity to comprehend and communicate with the interviewers, and who gave their consent to participate.

Sample

We designed a random sample of individuals of different ages that was stratified and was studied by groups. The sampling strategy was as follows:

1. Stratification in terms of the rural/urban nature of the municipalities, in accordance with the rural/urban ratio existing in Spain (75% of the population resides in urban municipalities). We randomly selected those Spanish autonomous communities in which we would study a rural municipality and in others an urban municipality. We considered urban municipalities to be those with at least a population of more than 10,000 inhabitants, in accordance with the data of the registry of 2015.^{20,21}
2. Stratification according to autonomous communities. For this, we randomly selected a municipality in the communities with less than 4 million inhabitants and 2 municipalities in the communities of more than 4 million (Andalusia, Catalonia, Community of Madrid and the Valencian Community). The researchers in the study were rheumatologists of the referral hospital of the selected municipalities.
3. We selected 2 reserve municipalities in each autonomous community. We searched for municipalities with a referral hospital that was different from that initially selected, considering that the change could be that no rheumatologist of the referral hospital of the selected municipality agreed to participate in the study.
4. In each participating municipality, we realized a random selection of individuals stratified by age and by sex in accordance with

the distribution of the Spanish population. The same numbers of individuals were recruited in each municipality.

To facilitate the recruitment of participants, we excluded municipalities with less than 1000 inhabitants. For this same reason, for rural areas, we decided to select 5 or 6 municipalities, rather than just one. To do this, first we randomly selected one municipality among all the rural towns in the corresponding autonomous community and, then, we randomly selected rural municipalities in the catchment area of the referral hospital first selected. The municipalities thus selected were considered to be only one for recruitment.

Sample Size

Assuming a Poisson distribution, a sample of 4000 individuals would permit a 95% confidence interval of 0.30–0.77 around a prevalence of 0.5% (expected prevalence in RA) and of 0.14–0.54 around a prevalence of 0.3% (expected prevalence in PsA). If we take into account a percentage of dropouts of 20%, it would be necessary to have a sample of 5000 individuals.

Recruitment

Before initiating the fieldwork, we issued information on the study in the selected municipalities, in the attempt to adapt the strategy of dissemination to each of them (by means of local announcements, informative posters in health centers and the rheumatology department of the referral hospital, etc.).

In each locality, we telephoned the participating individuals, to carry out the questionnaire to screen for the diseases to be studied (Annex 1). In the urban municipalities, the calls are focused on the populations of more than 10,000 inhabitants.

The calls are made to home telephones randomly selected in the municipalities included. To obtain the telephone numbers, we employ public sources. Initially, we interview any individual who lived at the contacted home and his or her consent to participate. As we began completing the quotas in terms of age and sex, in successive calls, we will request the participation of individuals in the strata that had not been completed, to finally reach the total sample of 5000 participants.

Both for the random selection of the telephone numbers in each locality and for the initial screening interviews, we will engage the participation of an external company dedicated to sociological studies with experience in the health area and with a call center service (Ipsos España). For this, they will employ a computer-assisted telephone interview (CATI), that enables them to randomly select the telephone numbers and make the calls through a software program. It controls the quotas (of sex and age) via an online system, which is continuously updated with the information of the interviews carried out. Each of the 4 interviewers assigned to the project works with a computer, the screen of which shows the exact text that should be read to the interviewee. This system of contacts and appointments makes it possible to program postponements, so that a registry can be recovered when the interviewee is not at home or requests that the questionnaire be carried out at some other time.

Prior to the initiation of the study, we compared the number of home telephones in each municipality with the number of homes, according to data from the latest population census. In those cases in which there were important differences, the change of municipality was assessed.

During recruitment, there is an intermediate analysis to determine the proportion of smokers in the sample. If in this analysis there is a significant difference with respect to the proportion of smokers in Spain (according to data available in the European

Table 1
Diseases Studied in EPISER 2000 and EPISER 2016. Criteria Employed in the Confirmation of the Suspected Diagnosis.

Disease	EPISER 2000 criteria	EPISER 2016 criteria
RA	1987 ACR criteria modified depending on the populations	1987 ACR criteria modified according to populations 2019 ACR/EULAR criteria
PsA		CASPAR criteria
AS		Modified New York criteria
SLE	1982 ACR criteria	1982 ACR criteria 2012 SLICC criteria
SS		International criteria for the classification of Sjögren's syndrome (European-American consensus)
Osteoarthritis of the knee	Clinical ACR criteria	Clinico-radiologic criteria and clinical criteria, both issued by the ACR
Osteoarthritis of the hands	Clinical ACR criteria	Clinical ACR criteria
Osteoarthritis of the hip		Clinico-radiologic criteria issued by the ACR
Osteoarthritis of the cervical spine		Clinico-radiologic criteria defined by the scientific committee for the EPISER project
Osteoarthritis of the lumbar spine		Clinico-radiologic criteria defined by the scientific committee for the EPISER project
Fibromyalgia	Criteria based on ACR 1990	Criteria based on ACR 1990
Gout		Criteria from the 2015 ACR/EULAR

ACR, American College of Rheumatology; AS, ankylosing spondylitis; CASPAR, Classification Criteria for Psoriatic Arthritis; EULAR, European League Against Rheumatism; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics; SS, Sjögren's syndrome.

Health Interview Survey conducted in Spain in 2014),² this variable will be taken into account in the recruitment, so that said difference will not exist in the final sample. This same strategy will be followed with the, ratio between those born in Spain and those born in other countries, taking as a reference the statistic of the continuous registry available on the SSO website.²⁰

Screening of the Diseases to Be Studied and Confirmation of the Positive Result of the Screening

If in the interview of the call center to an individual, the latter mentions having been diagnosed with any of the diseases in the study, he or she will be asked in which center and who was the attending specialist. Depending on the response, there could be 2 possibilities:

- If the individual was diagnosed in the referral hospital of the municipality, the consent of the patient will be requested so that the rheumatologists who participate as researchers in said hospital can confirm the diagnosis in the clinical history.
- If the individual was attended to in a center that is not the referral hospital of the municipality, the patient will be asked to give his or her permission so that the rheumatologist involved in the investigation in the referral hospital of the municipality contact with said physician to confirm the diagnosis. If this was not possible, the investigating rheumatologist would contact with the patient to ask for a copy of the clinical record in which the diagnosis is confirmed.

Individuals who have not been diagnosed, but have a positive result in screening for any of the diseases being studied on the basis of the associated symptoms, will be telephoned once again to assess the suspicion by means of a second more specific questionnaire (Annex 1). This second telephone interview will be carried out by the investigating rheumatologist from the referral hospital of the municipality.

Those individuals in which there remains the suspicion that they have a rheumatic disease after the second call, will be asked to visit the investigating rheumatologist of the referral hospital to complete the process of diagnostic confirmation (physical examination and ancillary tests), in accordance with the diagnostic classification criteria of the suspected disease (Table 1). In the case of osteoarthritis of the cervical and lumbar spine, due to the lack of validated criteria to be utilized in the study, they were established by the project's scientific committee, taking into account clinical

and radiological aspects, and where they were performed. In order to enable the comparison with EPISER 2000, for the conditions included in said project, the criteria utilized in that study will again be employed.

The fieldwork will be coordinated in such a way that the time elapsed between the interview of the call center and the call from the rheumatologist was 45 days or less.

Being lost to follow-up will be considered in those cases in which the individual completes the interview of the call center and the rheumatologist cannot confirm or rule out the suspected diseases.

Validation of the Screening Questionnaire

For the definition of the questionnaire, that employed in EPISER 2000 will be utilized, together with a nonsystematic review of the literature.^{22–29} To define its extension and the wording of the questions, we took into account the fact that it would be applied by telephone on the part of personnel that had no relation to health care. The questions were reached by consensus by the principal investigator (PI) and the scientific committee.

Prior to initiating the fieldwork, we held a session for training in the administration of the questionnaire for the interviewers, imparted by methodologists of the Spanish Society of Rheumatology (SER) and the project's PI.

The administration, comprehension and acceptance of the questionnaire was evaluated by means of a pilot study of 40 telephone interviews supervised by personnel of the SER, made to men and women of different age groups and educational levels. Thus, it was possible to make corrections and clarifications prior to initiating the sampling. The mean duration was 10–15 min, which was considered acceptable for a telephone questionnaire.

Likewise, we did a study of the negative predictive value of the screening questionnaire. For this, we randomly selected 200 individuals (10 from each municipality) with a negative result in the screening. They will be telephoned by the investigating rheumatologist in their area for the purpose of confirming the negative findings. If it is impossible to rule out a positive result on the basis of the telephone call, the individual will be given an appointment for examination and the pertinent ancillary tests depending on the suspected disorder.

Statistical Analysis

The main objective of this study is to estimate the prevalence of rheumatic diseases. For this, we will calculate estimators and

their confidence intervals. Having proposed a complex design, adjustments will be calculated in each of the sampling stages in accordance with the probability of selection. We will take into account the distribution of the Spanish population according to data from the SSO, with the objective of achieving the greatest representativeness. In the analysis, we will utilize specific svy commands for complex sampling from the statistical package Stata v13.1 (StataCorp, College Station, Texas, United States).

Quality Control and Monitoring

While the call center is carrying out interviews, supervisors from that company can access the interviews taking place at that time (through audio and the monitor) to confirm that they are being administered correctly. Likewise, there will be a session in which the study methodologists will listen to the surveys in real-time without knowing who is the interviewer, to subsequently organize a meeting to deal with possible ways to improve the administration of the questionnaire; in this case, there will be another session to confirm that these points have been incorporated.

The research unit of the SER will monitor the database obtained by the call center with the information collected in the telephone calls. Special attention will be given to the search for relevant variables not complied with or inconsistencies in the responses.

The rheumatologists participating in the study have been instructed about the study procedure. They will contact the study coordinators and methodologists in the case of doubts or problems.

All of the information gathered by the rheumatologists will be included in an on-line data collection notebook designed for this study. It will be monitored on-line by the SER research unit to confirm that diagnostic criteria of the corresponding disease have been collected and that there are no inconsistencies or relevant missing values, especially in those cases in which the investigator rules out the suspicion and decides not to meet the individual, despite a positive result in accordance with the criteria defined by the scientific committee.

Ethical Aspects

This study will be developed in accordance with the protocol and the standards of good clinical practice, as described in the harmonized tripartite guideline of the International Conference on Harmonisation (ICH).³⁰

The investigator will insure that the study is performed in total conformity with the principles established in the Declaration of Helsinki referring to medical research in humans.

Verbal informed consent will be requested of all the individuals in the first telephone contact. In accordance with the constitutional law on the protection of personal data, the individuals will be informed about the reason for the telephone call and the study, what their participation would consist of and the management of their personal data; they will also be informed that, if they decide to participate, they will be free to interrupt their participation in the study at any time. The participants will need to give their approval and their approval will be taped. There will be no cuts in the recording, which will be complete, and the identity of the persons who give their consent must be made clear. In addition, they will previously be told of the recording before taping begins.

Moreover, we will request written informed consent from those who come to the research center to undergo a physical examination and ancillary tests.

The Spanish Foundation of Rheumatology (FER) will be responsible for the files that contain the general data acquired in the study. Thus, a contract for this purpose has been signed with Ipsos España. Prior to data collection, the FER sent the file to the Data Protection

Agency. It will be incorporated and it has been integrated into a high level in the security document of that entity.

The study was approved by the research ethics committees of the participating centers.

Discussion

EPISER 2016 is the second study on the prevalence of rheumatic diseases conducted in a random sample that was representative of the adult population in Spain. The time elapsed since the performance of EPISER 2000 and the sociodemographic changes and those affecting lifestyle that have taken place since then justify carrying out this new project.

Aside from the diseases included in EPISER 2000, in EPISER 2016, we have added the study of the prevalence of PsA, AS, SS, osteoarthritis (of the hip and of the cervical and lumbar spine) and gout. In 2000, we included osteoporosis and, on this occasion, we will estimate the prevalence of clinical osteoporotic fracture and the distribution of the risk of osteoporotic fracture. As in EPISER 2000, we will include the population of 20 years or more. Thus, the comparability of the results of the two studies will be greater.

The need for a large sample size and the participation of centers of different health care levels in highly diverse geographic areas presents a series of methodological and organizational difficulties, which we have attempted to resolve in the design described in the present article.

The study includes municipalities from all of the Spanish autonomous communities. Thus, we expect geographic representativeness of the sample, minimizing the possible influence of risk factors or protectors against the conditions studied that can be distributed in a differential manner depending on the regions and affect the prevalence.

In studies of the prevalence of rheumatic diseases in the general population conducted until now in other countries, distinct strategies have been employed for the initial screening. In Portugal, Greece, Turkey and Mexico the decision was made to have face-to-face surveys.^{22,31–33} In Italy and Greece, questionnaires were sent by conventional mail.^{34,35} Whereas in France, Serbia and Lithuania, the questionnaires were carried out by telephone.^{36–40}

In EPISER 2000, the screening process and diagnostic confirmation were performed face-to-face, and thus the rheumatologists received all of the participants in the study. On this occasion, screening for disease was done using a telephone questionnaire, as it made it possible to achieve a large sample dispersion with a lower cost and took less time.⁴¹ This has allowed an increase in the sample size, and it is expected that there will be greater precision in the estimations.

Because of its feasibility, it was decided to utilize home telephones since, having selected specific municipalities, we had no access to a database with cellphone numbers corresponding to each of the participating municipalities. The fact of contacting only through home phones could introduce selection bias. In accordance with the data of the study by García-Contente et al.,⁴² individuals with access only to a cellphone were usually manual workers, with a lower educational level, born in a country outside of Spain and were smokers. Of these variables, tobacco use constitutes a known risk factor for some of the disorders being studied.^{43–45} Thus, it was decided to do an intermediate analysis to determine the proportion of smokers in the sample and the ratio of those born in Spain and those born outside of Spain (for the possible influence of the prevalence in some of these diseases of factors associated with the place of origin, such as the ethnic group). Moreover, in the selection of municipalities, we took into account the proportion of available home phones with respect to the number of homes in the municipality. If, during the fieldwork, we found that it was impos-

sible to complete the sampling in accordance with the defined representativeness criteria, we would assess the utilization of the cellphone databases, always maintaining the priority of sources of public access.

To evaluate the representativeness of the final sample, we will compare the baseline characteristics with those of the general Spanish population, in accordance with the SSO. Lastly, in the statistical analysis, we will make an adjustment to take into account the different selection probabilities.

Prior to initiating the telephone calls, we carried out a pilot study of the initial screening questionnaire. This enabled us to include clarifications and modifications to better the application on the part of the interviewers, as well as comprehension and acceptance on the part of the interviewees.

In the design of the questionnaire, in the case of the employee of the call center, priority was given to sensitivity, whereas in the utilization by the rheumatologists we intended to increase the specificity, in the attempt to maintain sensitivity. Due to questions related to the feasibility of the study, these validity parameters concerning questionnaires have not been studied prior to its administration. However, in the case of the employee of the call center, a study will be performed with regard to the negative predictive value in a subsample of 200 interviewees with a negative result who were randomly selected.

In the case of the questionnaire utilized by the rheumatologists, if the suspicion according to the criteria defined by the scientific committee is not maintained, the researchers can also receive the patient if for the content of the call they consider it necessary to rule out the diagnosis. Likewise, if the suspicion is maintained in accordance with the criteria defined by the scientific committee, the researchers should justify the motive in the case of ruling it out and deciding not to call the individual; each of these cases will be assessed individually in the monitoring of the study.

To insure the homogeneity and specificity of the diagnosis, the criteria to employ in the confirmation of the cases detected in the study have been specifically defined. Those diagnosed prior to the initiation of EPISER 2016 will not be given new appointments for confirmation. However, in the training sessions for investigators and in the study materials, we have stressed the necessity of not accepting diagnoses that have not been clearly identified and which can be doubtful.

In conclusion, with this study, we update the estimation of the prevalence of rheumatic diseases in the Spanish adult population. They are interesting for both health care professionals, and for administrators and funders of the health care system. Moreover, even with the limitations derived from methodological differences, comparisons can be made with the values obtained in EPISER 2000, which makes it possible to formulate hypotheses concerning the influence of the factors causing these diseases.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects

mentioned in the article. The corresponding author is in possession of this document.

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Conflicts of Interest

The authors declare they have no conflicts of interest in relation to the EPISER 2016 study.

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Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.reumae.2018.10.004](https://doi.org/10.1016/j.reumae.2018.10.004).

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