Cohort Profile

Cohort Profile: The Epidemiology of Chronic Diseases and Multimorbidity. The EpiChron Cohort Study

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Why was the cohort set up?

Greater life expectancy in Europe over the past few decades has been translated into an increasing burden of chronic diseases that accumulate as the population ages, whereas acute infectious diseases have been progressively pushed into the background. The incidence of conditions such as hypertension, obesity and asthma has increased dramatically worldwide, and cancer, diabetes and respiratory and cardiovascular diseases are responsible for almost 70% of global deaths.1 Concurrently, the prevalence of multimorbidity (as of people affected by more than one chronic disorder) is also increasing and appears as the most common chronic condition at present.2 Multimorbidity affects almost 3 in 4 individuals aged 65 years and older,3 although it represents a problem not only for the elderly but also for adult and even young populations,4 at whom prevention strategies should aim.

People affected by multimorbidity often experience fragmentation of care, greater and inadequate use of health services5 and polypharmacy,6 which in turn may increase the risk of low adherence and adverse drug reactions.7,8 All of this leads to individuals’ quality of life deterioration9 and higher risk of mortality.10 Besides, handling patients with multimorbidity represents a daily challenge for physicians and health systems.11,12

Research on ageing and chronicity has been established as a priority in the European health policy agenda,13 leading to the creation of the European Innovation Partnership
on Active and Healthy Ageing (EIP on AHA) and the Joint Actions on Chronic Diseases CHRODIS and CHRODIS+: two initiatives of the European Commission in which multimorbidity is tackled. However, many knowledge gaps on the aetiology, epidemiology and risk factors of multimorbidity remain to be filled, which hinders the implementation of effective evidence-based interventions.

The European General Practice Research Network (EGPRN) recently highlighted the importance of measuring the impact of multimorbidity on health outcomes and health service use, and prospective cohort studies were proposed as the most appropriate study design since they enable study of multimorbidity over time in ‘real-life’ conditions. Population cohorts based on large clinical-administrative databases have shown a high potential for research in health and health services, and are among the preferred options for this kind of investigation.

In line with this, in 2005 the EpiChron Research Group on Chronic Diseases began to study chronic diseases and multimorbidity through data stored in the computerized medical records of patients living in Aragon, a region of north-eastern Spain. The relevance of the results obtained with cross-sectional data encouraged the group to set up a regional population cohort of 1.25 million inhabitants, named the EpiChron Cohort Study, which was favourably evaluated by the Clinical Research Ethics Committee of Aragon (CEICA). Baseline data collection was finalized in December 2010 and follow-up is expected to extend until 2020. Both cross-sectional and longitudinal studies on multimorbidity and comorbidity of major index chronic diseases, as well as pharmaco-epidemiological studies, are the main expected outputs of this project. A longitudinal approach is essential to identify causal relationships among risk factors, diseases and drugs, development of chronic diseases and multimorbidity, and the incidence of adverse health outcomes.

Finally, data sharing and scaling-up of knowledge to different settings and/or countries are also key points of this project. Cross-national comparisons may be useful to increase the validity of results, and to identify social and structural inequalities that may explain differences in the incidence and evolution of chronic diseases and their impact on society. One first step toward the integration and harmonization of large health-related databases such as the EpiChron Cohort was recently taken within the framework of the EIP on AHA, with the final goal to create a structure capable of supporting multi-country health care research projects.

Who is in the cohort?

The EpiChron Cohort includes all inhabitants in the north-eastern Spanish region of Aragon, registered as users of the public health system (1 253 292 individuals on 1 January 2011, approximately 98% of the total number of inhabitants in the region). It is a dynamic open cohort, so that new users are continuously included throughout the study period. All data contained in the cohort are pseudonymized.

How often have they been followed up?

The follow-up of cohort participants is initially intended to last for a period of 10 years, from 2011 to 2020, by means of annual waves of data extraction on 1 January each year. At present, six waves of data extraction have been conducted, and information from 1 January 2011 to 31 December 2015 is available for research. The reasons for early termination of follow-up are death of the individual or withdrawal from the regional public health system. The possibility of extending the follow-up period will be considered in 2020, according to the findings obtained during the initial study period and available funding.

What has been measured?

The EpiChron Cohort links the information contained in clinical-administrative databases from different care settings at the individual level (e.g. patient index database, primary, specialist, hospital and emergency care, and pharmacy billing databases).

The variables collected in the cohort study can be classified as patient general data and demographic, clinical and health outcomes, health care services use and pharmaceutical data. These variables derive from patients’ routine contacts with the regional health system, and subsequently undergo depuration and quality control processes using computational algorithms. Raw data are also subject to statistical treatment leading to the creation of new variables related to specific research questions (e.g. number of hospital readmissions in a given period of time, number of visits to different care settings). The creation of additional variables requires a clinical perspective and research consensus (e.g. presence and type of multimorbidity and/or polypharmacy, level of adherence to treatment, immigrant status etc.). Moreover, original diagnoses are re-coded according to the Expanded Diagnosis Clusters (EDCs) using the Johns Hopkins ACG® System which groups together diseases that describe similar or related conditions and is internationally used to define multimorbidity, together with the list of 114 chronic EDCs developed by Salisbury. Thus, the EpiChron Cohort is not a mere integration of clinical-administrative databases, but is also a population cohort specifically formed to serve as a basis for research on the clinical epidemiology of chronic diseases with a temporal horizon of 10 years. The
most relevant baseline characteristics of the EpiChron Cohort are summarized in Table 2. A ranking of the most prevalent chronic conditions by sex and age is presented in Table 3.

The integration of large numbers of multi-source data enables information collection and analysis which would be otherwise impossible, for example: (i) patients with a specific index chronic condition; (ii) patterns of diseases and their relation with health services use and negative health outcomes such as mortality, adverse drug reactions, hospital admissions for ambulatory care sensitive conditions, and/or readmissions in a given period of time; (iii) drug prescription profiles; and (iv) adherence to medical plans. The study population will depend on the aim of each study, ranging from the general population to more specific groups of individuals such as older adults, multimorbid patients or hospitalized patients. We also study the epidemiology of chronic diseases and multimorbidity in the immigrant population, defined according to country of birth, nationality and length of stay in the host country.22,23

The EpiChron Cohort has already been used to study the comorbidity of major index chronic diseases such as diabetes,24 chronic respiratory diseases (submitted manuscript) and dementia,25 and studies on breast cancer and heart failure are ongoing. The systematic association among diseases (i.e. multimorbidity patterns) and among drugs (i.e. polypharmacy patterns) has also been investigated.26,27 Studies on the pharmaco-epidemiology of drugs for chronic conditions such as agomelatine and cilostazol have also been conducted28 focusing on the identification of adverse drug reactions, lack of effectiveness and adherence problems. The use of new oral antidiabetic drugs is planned to be studied in the near future. The level of adherence to pharmacological treatments for specific chronic diseases and drug families has also been measured.29

### Table 1. Original variables available in the EpiChron Cohort for each individual and in each data extraction wave according to type of variable and data source

| Type of variable | Data source          | Variables measured                                                                 |
|------------------|----------------------|-------------------------------------------------------------------------------------|
| Sociodemographic data | Patient Index Database | Patient ID, sex, birthday, nationality/country of birth, registration date, city/zip code, type of user, administrative health area, death or withdrawal from the regional health service |
|                  | Primary care         | Patient ID, centre ID, General practitioner ID                                     |
|                  | Specialist care      | Patient ID, centre ID, source of referral                                          |
|                  | Hospital care        | Patient ID, hospital ID, sex, birthday                                              |
|                  | Emergency room       | Patient ID, support date, duration of first evaluation, service                     |
|                  | Pharmaceutical billing | Patient ID                                                                         |
| Patient General Data (DGP) | Primary care         | Height, weight, drinking and smoking habits                                         |
| Clinical and health outcomes data | Primary care | Diagnoses\(^a\) (opening and closing date of the care episode), clinical parameters (date and value), diagnostic tests (date and type of test), adverse drug reactions (start and ending date, drug, route of administration, dose, adverse reaction, hospital admission, outcome) |
|                  | Hospital             | Diagnoses\(^b\), procedures, treatments, exitus (death), Diagnoses Related Groups (DRG) |
|                  | Emergency room       | Reason for visit, diagnoses\(^b\), diagnostic tests                                |
| Health care services use data | Primary care | Visits (date and type of visit, specialty), referrals (date of referral and specialty) |
|                  | Specialist care      | Date of visit, first/subsequent visit, medical specialty                           |
|                  | Hospital care        | Date of admission, type of admission, date of discharge, reasons for discharge, service of discharge, days in intensive care, length of stay, readmissions, hospital transfer, surgical and diagnostic procedures |
|                  | Emergency room       | Date of discharge, type of discharge                                               |
| Pharmaceutical data | Emergency room       | ATC\(^c\) code, dosage, number of packages, prescription date                      |
|                  | Pharmaceutical billing | Prescription date, billing date, ATC\(^c\) code, national drug code, number of packages, price, prescribing health care service |

\(^a\)Using the International Classification of Primary Care, 1st edition (ICPC).
\(^b\)Using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).
\(^c\)Using the Anatomical, Therapeutic, Chemical (ATC) classification system.
Table 2. Demographic, clinical, pharmaceutical and health service use baseline characteristics of the EpiChron Cohort population by sex and age (years) group in 2011

| Demographic data | Men | Women | Total |
|------------------|-----|-------|-------|
| Population (n, %) | 77 391 (12.5) | 260 915 (42.0) | 620 661 (49.5) |
| Mean age (SD) | 7.8 (3.7) | 53.6 (5.7) | 42.7 (22.1) |
| Urban area (n, %) | 46 346 (59.9) | 99 132 (59.3) | 367 228 (59.2) |
| Immigrant (n, %) | 11 040 (14.3) | 14 163 (8.5) | 30 203 (12.9) |

| Clinical data | Men | Women | Total |
|----------------|-----|-------|-------|
| Number of chronic diseases types (mean, SD) | 0.6 (0.0) | 1.4 (0.0) | 0.6 (0.0) |
| Population with multimorbidity (n, %) | 10 033 (13.0) | 87 066 (53.1) | 269 808 (42.7) |
| Population (n, %) with: | | | |
| 0 diseases | 44 401 (57.4) | 22 192 (28.7) | 24 875 (36.4) |
| 1 disease | 22 957 (29.7) | 11 739 (15.5) | 12 478 (18.3) |
| 2 diseases | 7 977 (9.8) | 6 433 (8.6) | 14 410 (21.4) |
| 3 diseases | 1932 (2.5) | 1932 (2.5) | 3864 (5.7) |
| 4 diseases | 124 (0.16) | 124 (0.16) | 248 (0.37) |
| 5 diseases | | | |
| Number of purchased drug types (mean, SD) | 2.5 (0.0) | 2.8 (0.0) | 2.6 (0.0) |
| Population (n, %) who purchased: | | | |
| 0 drugs | 22 192 (28.7) | 11 193 (14.5) | 33 385 (50.6) |
| 1 drug | 22 192 (28.7) | 11 193 (14.5) | 33 385 (50.6) |
| 2 drugs | 7935 (12.5) | 24 011 (9.2) | 31 946 (47.6) |
| 3 drugs | 7 977 (9.8) | 13 573 (8.1) | 21 540 (32.0) |
| 4 drugs | 14 444 (18.7) | 27 879 (19.7) | 42 323 (64.0) |
| 5-9 drugs | | | |
| ≥ 10 drugs | 1319 (1.7) | 1319 (1.7) | 2638 (3.9) |
| Health services use | | | |
| Primary care (n, %) | 67 114 (86.7) | 17 142 (24.5) | 238 256 (36.4) |
| Visits to primary care (mean, SD) | 8.5 (0.0) | 127 517 (76.3) | 471 479 (76.0) |
| Visits to GP (mean, SD) | 8.5 (0.0) | 127 517 (76.3) | 471 479 (76.0) |
| Specialist care (n, %) | 32 133 (41.5) | 12 478 (18.3) | 44 611 (66.1) |
| Visits to specialist care (mean, SD) | 3.1 (0.0) | 127 517 (76.3) | 471 479 (76.0) |

(continued)
What has it found? Key findings and publications

A number of findings and publications have arisen from the EpiChron Cohort Study. One of the most important findings is the strong relationship between multimorbidity and the occurrence of adverse drug events. This is particularly evident when multiple medications are prescribed, requiring intervention by different specialists. The existence of non-random associations among chronic diseases has been identified in primary care patients, resulting in clinically meaningful multimorbidity patterns. Observations have also been made for specific multimorbidity patterns in hospitalized geriatric patients, such as the induced-dependency and falls patterns, which may facilitate the early detection of patients with high vulnerability to stressors.

A cross-national comparison with patients from The Netherlands offered initial clues for the potential universal validity of the EpiChron findings. The comparison showed similarities for several multimorbidity patterns, suggesting a commonality in the epidemiology of chronic diseases across different contexts. The use of latent variable mixture modelling (i.e., longitudinal latent class growth analysis and growth mixture models) is one possible methodological approach to identify distinctive developmental trajectories, calibrating the probability of single individuals following such trajectories. Predictive modelling techniques will be employed to predict adverse health outcomes in multimorbid patients, depending on demographics, disease stages, and health outcomes. The longitudinal analyses will enable confirmation of cause-effect relationships or provide further insights into the complex interplay of multimorbidity over time and their relation with health trajectories and health outcomes.

All studies to date have been performed from a cross-sectional point of view, offering a picture of the situation at a given time point. These studies have been useful to describe and characterize the epidemiology of chronic diseases and multimorbidity in the population and to hypothesize potential causal associations among risk factors. However, future studies will focus on the longitudinal analysis of these associations, providing a more comprehensive understanding of the factors influencing multimorbidity over time and their relation with health outcomes.

Table 2. Continued

|                  | Men (mean, SD) | Women (mean, SD) | Total (mean, SD) |
|------------------|----------------|------------------|-----------------|
| Hospital admissions | 1.20 (0.02)     | 1.22 (0.01)    | 1.36 (0.00)     |
|                   | 1.34 (0.01)     | 1.46 (0.01)    | 1.36 (0.00)     |
|                   | 1.29 (0.06)     | 1.18 (0.01)    | 1.34 (0.01)     |
|                   | 1.30 (0.01)     | 1.30 (0.01)    | 1.34 (0.01)     |
|                   | 1.27 (0.00)     | 1.31 (0.00)    |                 |
| Days/hospitalization | 2.7 (0.1)        | 5.0 (0.1)       | 6.7 (0.0)       |
|                   | 6.0 (0.1)        | 8.4 (0.1)       | 6.7 (0.0)       |
|                   | 3.0 (0.1)        | 3.7 (0.0)       | 5.5 (0.1)       |
|                   | 6.0 (0.0)        | 6.3 (0.0)       |                 |
| Emergency room (n, %) | 12 732 (16.5) | 40 013 (15.3) | 24 283 (14.5) |
|                   | 24 283 (14.5)   | 104 281 (16.8) |                 |
|                   | 10 639 (14.6)   | 41 812 (17.1)  |                 |
|                   | 25 724 (15.7)   | 114 245 (18.1) |                 |
|                   | 36 070 (24.0)   | 218 526 (17.4) |                 |
| Visits to emergency room (mean, SD) | 1.54 (0.01) | 1.44 (0.01) | 1.53 (0.00) |
|                   | 1.50 (0.01)     | 1.71 (0.01)    | 1.53 (0.00)     |
|                   | 1.55 (0.01)     | 1.58 (0.01)    | 1.61 (0.01)     |
|                   | 1.49 (0.01)     | 1.57 (0.00)    | 1.55 (0.00)     |

aStandard deviation.
bVersus rural area.
cVersus native.
dOnly diseases considered as chronic by Salisbury et al.11 were taken into account.
eConsidered as at least one chronic condition according to the criteria established by Salisbury et al.11
fData refer to different drugs at the third level of the Anatomical, Therapeutic, Chemical (ATC) classification system.
gData regarding n and % refer to the population that has visited the corresponding service at least once during the study period in relation to the total population in each age group. Data regarding mean and SD have been calculated taking only into account the population that has visited each health service at least once.
hIncludes all primary care services, including consultations and home visits, and excluding visits to the nurse.
iGeneral practitioner (including consultations and home visits, and excluding visits to the nurse).
jNot applicable (boys and girls aged 0 to 14 are not seen by the GP, but by their paediatrician).
elaboration of clinical practice guidelines if further evidenced in other contexts.

We have further demonstrated the existence of non-random associations among prescribed drugs, giving rise to the so-called polypharmacy patterns \(^{27}\) (Table 4). These patterns affect a significant proportion of the population and are sound from both pharmacological and clinical points of view, although future longitudinal studies are needed to confirm some of the proposed causal associations.

The nature and impact of comorbidities in patients with a given chronic disease such as obesity, diabetes, dementia or hypertension, has also been investigated. The coexistence of mental comorbidity in patients with type 2 diabetes has been

| Age group | Men | Women |
|-----------|-----|-------|
| 0–14 years | | |
| Dermatitis and eczema | 18.1 | Dermatitis and eczema | 19.4 |
| Asthma | 9.8 | Asthma | 6.7 |
| Behaviour problems | 6.5 | Blindness | 4.9 |
| Blindness | 4.1 | Behaviour problems | 4.0 |
| Congenital anomalies of limbs, hands and feet | 3.1 | Congenital anomalies of limbs, hands, and feet | 2.7 |
| Developmental disorder | 2.3 | Kyphoscoliosis | 2.0 |
| Attention-deficit disorder | 2.1 | Other endocrine disorders | 1.8 |
| Kyphoscoliosis | 1.5 | Disease of hair and hair follicles | 1.4 |
| Obesity | 1.3 | Obesity | 1.3 |
| Deafness, hearing loss | 1.2 | Developmental disorder | 1.3 |
| 15–44 years | Disorders of lipid metabolism | 6.5 |
| Dermatitis and eczema | 5.0 | Varicose veins of lower extremities | 6.3 |
| Asthma | 3.7 | Hypothyroidism | 5.1 |
| Obesity | 2.8 | Depression | 5.1 |
| Low back pain | 2.8 | Disease of hair and hair follicles | 4.5 |
| Depression | 2.2 | Asthma | 4.4 |
| Hypertension | 2.2 | Obesity | 4.0 |
| Disease of hair and hair follicles | 1.8 | Disorders of lipid metabolism | 3.6 |
| Substance use | 1.7 | Low back pain | 3.5 |
| Blindness | 1.6 | Anxiety, neuroses | 3.3 |
| 45–64 years | Disorders of lipid metabolism | 27.1 |
| Hypertension | 22.1 | Hypertension | 18.5 |
| Diabetes | 8.6 | Varicose veins of lower extremities | 16.1 |
| Obesity | 7.0 | Depression | 13.5 |
| Arthropathy | 6.0 | Hypothyroidism | 12.2 |
| Dermatitis and eczema | 6.0 | Arthropathy | 11.6 |
| Depression | 4.9 | Osteoporosis | 9.4 |
| Low back pain | 4.4 | Obesity | 9.2 |
| Deafness, hearing loss | 3.8 | Dermatitis and eczema | 7.3 |
| Ischaemic heart disease (including AMI) | 3.7 | Low back pain | 5.2 |
| ≥ 65 years | Hypertension | 52.8 |
| Disorders of lipid metabolism | 33.2 | Disorders of lipid metabolism | 37.3 |
| Prostatic hypertrophy | 20.9 | Arthropathy | 32.1 |
| Diabetes | 20.9 | Varicose veins of lower extremities | 25.2 |
| Arthropathy | 20.1 | Osteoporosis | 23.0 |
| Cataract, aphakia | 14.4 | Depression | 17.8 |
| Emphysema, chronic bronchitis, COPD | 12.7 | Diabetes | 17.2 |
| Ischaemic heart disease (including AMI) | 12.7 | Cataract, aphakia | 17.1 |
| Cardiac arrhythmia | 9.5 | Obesity | 13.4 |
| Obesity | 9.4 | Hypothyroidism | 12.7 |

COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction.

\(^{27}\)Expanded Diagnostic Clusters; only those considered as chronic by Salisbury et al.\(^ {11}\) were taken into account.
shown to increase the number of unplanned hospital admissions, and discordant comorbidities have an important effect on specialist care use. The two most frequent comorbidities in patients with dementia were hypertension and diabetes, although factor analysis showed that other comorbidities such as Parkinson’s disease, congestive heart failure and cerebrovascular disease were significantly associated with the index condition. These findings highlight that the analysis of comorbidities for an index disease must not be exclusively based on prevalence rates, but rather on methodologies that allow for the discovery of non-random associations among diseases. Mental comorbidities also affect the levels of adherence to antihypertensive treatment in patients with hypertension, underscoring the need for patient- rather than disease-centred care.

Regarding the pharmaco-epidemiology of drugs for specific chronic conditions, a collaborative study conducted in several European countries to characterize new users of cilostazol, a drug to improve walking distances in patients with intermittent claudication, showed that most users were elderly patients with a high prevalence of comorbidity, high concurrent use of interacting drugs and high discontinuation rates in the first 3 months of treatment.

The effect of immigrant status on health and health services use has also been investigated. The length of stay of immigrants in the host country plays a decisive role on their morbidity burden, observing a worsening of the health status with longer stays in the host country. The global use of health care services has been shown to be lower for immigrants than for nationals, which may be explained by the healthy migrant effect or by possible inequalities in health care provision. Immigrants’ pharmaceutical use has also been studied and compared with that in a Norwegian setting, and the similarities found between the two countries highlights the need to consider specific immigrant-related features when providing health care to this group of the population.

What are the main strengths and weaknesses?

The main strength of the EpiChron Cohort lies in the fact that it is a population cohort that represents almost the
entire population of Aragon (1.25 million individuals approximately), which is also representative of the Spanish population in terms of age, sex and immigration. Data are continuously subject to quality control procedures that involve data collection, request, extraction and processing to improve their reliability, validity, quality and appropriateness for research. Specific data processing carried out in the cohort is described in detail in Annex I, available as Supplementary data at IJE online. Furthermore, although the 10-year follow-up might not be enough for studying the aetiology and prognosis of some chronic diseases, it should be sufficient to study mid- and long-term trends over time and to unravel cause-effect relationships regarding multimorbidity and specific chronic conditions.

Among the main weaknesses of the study, it is worth highlighting that the cohort draws on information from administrative databases and electronic health records which have not been primarily designed for research purposes, but for health care management. Consequently, some errors or missingness may occur during registration by health professionals, although they are continuously trained in diagnosis coding and use of data collection software. Some potential variables such as lifestyle factors are not systematically gathered for all individuals, and others such as socioeconomic and educational indicators are not registered at all. However, socioeconomic status could be indirectly known through the pharmaceutical co-payment range established by the Spanish National Health System according to legal order from 20 April 2012 (Official State Gazette number 98 from 24 April 2012). Furthermore, an effort is currently being made to link other socioeconomic proxy variables (e.g. deprivation index according to census section of participants). Finally, data from private health care use are not included, although they only represent less than 2% of the total health care use in Aragon.

Can I get hold of the data? Where can I find out more?

Data contained in the EpiChron Cohort are not expected to be freely available on a public server for the moment. However, requests for collaborative work regarding complementary data analyses, cross-national comparisons or new methodological approaches to the study of chronic diseases and multimorbidity are welcome. Data sharing and integration of cohorts available in this area are key points of the EpiChron Cohort Study. Please contact the Principal Investigator (Alexandra Prados-Torres) by e-mail [sprados.iacs@aragon.es] for further information.

Cohort profile in a nutshell

- EpiChron is a health register-based population cohort study investigating the clinical epidemiology, inappropriate health service use and health outcomes associated with chronic diseases and multimorbidity.
- The cohort includes all inhabitants of the Spanish north-eastern region of Aragon and registered as users of the public health system (i.e. 1 253 292 individuals of all ages) on 1 January 2011.
- The follow-up of cohort participants is expected to last until 2020 by means of annual waves of data extraction.
- The dataset integrates sociodemographic and clinical characteristics, health services use, drug prescriptions, and health outcomes (e.g. complications, mortality, adverse drug reactions) information obtained from clinical-administrative databases.
- The EpiChron Cohort is not available online, although potential collaborators are encouraged to contact the Principal Investigator by e-mail [sprados.iacs@aragon.es] for further information. Data sharing, integration of cohorts and scaling-up of knowledge in chronic diseases and multimorbidity are key points of the project.

Supplementary Data

Supplementary data are available at IJE online.

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