International Journal of Epidemiology, 2018, 382–384e
doi: 10.1093/ije/dyx259
Advance Access Publication Date: 16 January 2018
Cohort Profile

Cohort Profile

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

A Prados-Torres,[1] B Poblador-Plou,[2] A Gimeno-Miguel,[2]* A Calderón-Larrañaga,[3] A Poncel-Falcó,[4] LA Gimeno-Feliú,[5] F González-Rubio,[6] C Laguna-Berna,[2] J Marta-Moreno,[7] M Clerencia-Sierra,[7] M Aza-Pascual-Salcedo,[8] AC Bandrés-Liso,[9] C Coscollar-Santaliestra,[5] V Pico-Soler[10] and JM Abad-Díez[11]

EpiChron Research Group on Chronic Diseases: [1]Aragon Health Sciences Institute (IACS), IIS Aragon, Miguel Servet University Hospital, Zaragoza, University of Zaragoza, Health Services Research on Chronic Patients Network (REDISSEC), Spain, JA-CHRODIS+, EU, [2]IACS, IIS Aragon, Miguel Servet University Hospital, Zaragoza, REDISSEC, Spain, [3]Aging Research Center, Karolinska Institutet, Stockholm, Sweden, REDISSEC, Spain, [4]Aragon Health Service (SALUD), REDISSEC, Spain, [5]Primary Care Health Centre (PCHC) San Pablo, Zaragoza, SALUD, University of Zaragoza, REDISSEC, Spain, [6]PCHC Delicias-Sur, Zaragoza, SALUD, REDISSEC, Spain, [7]Miguel Servet University Hospital, Zaragoza, SALUD, REDISSEC, Spain, [8]Directorate of Primary Care, SALUD, REDISSEC, Spain, [9]Aragon Health Service (SALUD), REDISSEC, Spain, [10]PCHC Torrero-La Paz, Zaragoza, SALUD, REDISSEC, Spain and [11]Aragon Health Service (SALUD), Department of Health, GRISSA Research Group, Spain

*Corresponding author. Aragon Health Sciences Institute (IACS), IIS Aragon, Miguel Servet University Hospital, Zaragoza, REDISSEC, Spain. E-mail: agimenomi.iacs@aragon.es

Editorial decision 17 November 2017; Accepted 15 December 2017

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 services[5] 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 deterioration[9] 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,[14] 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[15] since they enable study of multimorbidity over time in 'real-life' conditions.[16] 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.[17]

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.[18]

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 (Table 1). 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[19] 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.[11,20,21] 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

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	Primary care	ATC[c] code, dosage, number of packages, prescription date
	Emergency room	Number of prescriptions
	Pharmaceutical billing	Prescription date, billing date, ATC[c] code, national drug code, number of packages, price, prescribing health care service

ID, identification.
[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.

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 conducted[28] 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 2. Demographic, clinical, pharmaceutical and health service use baseline characteristics of the EpiChron Cohort population by sex and age (years) group in 2011

	Men					Women					Total
	0–14	15–44	45–64	≥ 65	Subtotal	0–14	15–44	45–64	≥ 65	Subtotal	
Demographic data											
Population (*n*, %)	77 391 (12.5)	260 915 (42.0)	167 058 (26.9)	115 297 (18.6)	620 661 (49.5)	72 940 (11.5)	245 171 (38.8)	163 959 (25.9)	150 561 (23.8)	632 631 (50.5)	1 253 292 (100)
Mean age (SD[a])	7.8 (3.7)	31.7 (8.2)	53.6 (5.7)	75.8 (7.5)	42.7 (22.1)	7.8 (3.7)	31.6 (8.2)	53.8 (5.7)	77.4 (8.1)	45.4 (23.5)	44.2 (22.8)
Urban area[b] (*n*, %)	46 346 (59.9)	160 106 (61.4)	99 132 (59.3)	61 644 (53.5)	367 228 (59.2)	43 911 (60.2)	155 773 (63.5)	105 047 (64.1)	86 613 (57.5)	391 344 (61.9)	758 572 (60.5)
Immigrant[c] (*n*, %)	11 040 (14.3)	54 219 (20.8)	14 163 (8.5)	922 (0.80)	80 344 (12.9)	10 168 (13.9)	46 100 (18.8)	11 195 (6.8)	1342 (0.89)	68 805 (10.9)	149 149 (11.9)
Clinical data											
Number of chronic diseases types[d] (mean, SD)	0.6 (0.0)	0.5 (0.0)	1.6 (0.00)	3.7 (0.0)	1.4 (0.0)	0.6 (0.0)	0.8 (0.0)	2.1 (0.0)	4.2 (0.0)	1.9 (0.0)	1.7 (0.0)
Population with multimorbidity[e] (*n*, %)	10 033 (13.0)	32 045 (12.3)	68 554 (41.0)	89 476 (77.6)	200 108 (32.2)	8057 (11.1)	49 544 (20.2)	87 066 (53.1)	125 141 (83.1)	269 808 (42.7)	469 916 (37.5)
Population (n, %) with:											
0 diseases	44 401 (57.4)	168 517 (64.6)	58 356 (34.9)	12 658 (11.0)	283 932 (45.8)	43 468 (59.6)	129 753 (52.9)	41 059 (25.0)	12 822 (8.5)	227 102 (35.9)	511 034 (40.8)
1 disease	22 957 (29.7)	60 353 (23.1)	40 148 (24.0)	13 163 (11.4)	136 621 (22.0)	21 415 (29.4)	65 874 (26.9)	35 834 (21.9)	12 598 (8.4)	135 721 (21.5)	272 342 (21.7)
2 diseases	7577 (9.8)	21 298 (8.2)	28 707 (17.2)	18 040 (15.7)	75 622 (12.2)	6178 (8.5)	29 914 (12.2)	30 807 (18.8)	19 095 (12.7)	85 994 (13.6)	161 616 (12.9)
3 diseases	1932 (2.5)	6954 (2.7)	17 764 (10.6)	18 695 (16.2)	45 345 (7.3)	1475 (2.0)	12 019 (4.9)	22 337 (13.6)	23 119 (15.4)	58 950 (9.3)	104 295 (8.3)
4 diseases	400 (0.52)	2359 (0.90)	10 302 (6.2)	16 152 (14.0)	29 213 (4.7)	302 (0.41)	4629 (1.9)	14 628 (8.9)	22 538 (15.0)	42 097 (6.7)	71 310 (5.7)
≥ 5 diseases	124 (0.16)	1434 (0.55)	11 781 (7.1)	36 589 (31.7)	49 928 (8.0)	102 (0.14)	2982 (1.2)	19 294 (11.8)	60 389 (40.1)	82 767 (13.1)	132 695 (10.6)
Drug purchase data											
Number of purchased drug types[f] (mean, SD)	2.5 (0.0)	1.7 (0.0)	3.5 (0.0)	8.1 (0.0)	3.5 (0.0)	2.4 (0.0)	2.8 (0.0)	5.1 (0.0)	9.8 (0.0)	5.0 (0.0)	4.3 (0.0)
Population (*n*, %) who purchased:											
0 drugs	22 192 (28.7)	121 696 (46.6)	49 539 (29.7)	9411 (8.2)	202 838 (32.7)	21 296 (29.2)	77 557 (31.6)	31 199 (19.0)	9926 (6.6)	139 978 (22.1)	342 816 (27.4)
1 drug	11 193 (14.5)	34 342 (13.2)	17 732 (10.6)	3734 (3.2)	67 001 (10.8)	10 770 (14.8)	30 059 (12.3)	13 097 (8.0)	2583 (1.7)	56 509 (8.9)	123 510 (9.9)
2 drugs	11 309 (14.6)	33 084 (12.7)	18 437 (11.0)	5287 (4.6)	68 117 (11.0)	10 963 (15.0)	30 704 (12.5)	14 389 (8.8)	3844 (2.6)	59 900 (9.5)	128 017 (10.2)
3 drugs	9635 (12.5)	24 011 (9.2)	16 071 (9.6)	6474 (5.6)	56 191 (9.1)	9224 (12.7)	26 403 (10.8)	14 658 (8.9)	5349 (3.6)	55 634 (8.8)	111 825 (8.9)
4 drugs	7299 (9.4)	16 674 (6.4)	13 589 (8.1)	7643 (6.6)	45 205 (7.3)	7057 (9.7)	21 262 (8.7)	13 737 (8.4)	6730 (4.5)	48 786 (7.7)	93 991 (7.5)
5–9 drugs	14 444 (18.7)	27 879 (10.7)	38 117 (22.8)	41 449 (36.0)	121 889 (19.6)	12 636 (17.3)	49 284 (20.1)	50 135 (30.6)	48 175 (32.0)	160 230 (25.3)	282 119 (22.5)
≥ 10 drugs	1319 (1.7)	3229 (1.2)	13 573 (8.1)	41 299 (35.8)	59 420 (9.6)	994 (1.4)	9902 (4.0)	26 744 (16.3)	73 954 (49.1)	111 594 (17.6)	171 014 (13.7)
Health services use[g]											
Primary care[h] (*n*, %)	67 114 (86.7)	171 424 (65.7)	127 517 (76.3)	105 424 (91.4)	471 479 (76.0)	63 307 (86.8)	191 640 (78.2)	139 906 (85.3)	139 104 (92.4)	533 957 (84.4)	1 005 436 (80.2)
Visits to primary care (mean, SD)	8.5 (0.0)	6.4 (0.0)	11.9 (0.0)	22.2 (0.1)	11.7 (0.0)	8.29 (0.0)	9.1 (0.0)	13.6 (0.0)	23.5 (0.0)	13.9 (0.0)	12.9 (0.0)
GP[i] (*n*, %)	n.a.[j]	165 610 (63.5)	122 504 (73.3)	101 005 (87.6)	419 038 (67.5)	n.a.[j]	185 938 (75.8)	135 889 (82.9)	133 971 (89.0)	483 436 (76.4)	902 474 (72.0)
Visits to GP (mean, SD)	n.a.[j]	4.9 (0.0)	8.0 (0.0)	12.2 (0.0)	7.4 (0.0)	n.a.[j]	6.4 (0.0)	9.1 (0.0)	13.0 (0.0)	8.8 (0.0)	8.2 (0.0)
Specialist care (*n*, %)	32 133 (41.5)	82 559 (31.6)	78 989 (47.3)	79 173 (68.7)	272 854 (44.0)	29 092 (39.9)	117 078 (47.8)	99 034 (60.4)	99 810 (66.3)	345 014 (54.5)	617 868 (49.3)
Visits to specialist care (mean, SD)	3.1 (0.0)	3.5 (0.0)	5.1 (0.0)	6.3 (0.0)	4.7 (0.0)	3.0 (0.0)	4.8 (0.0)	5.8 (0.0)	6.2 (0.0)	5.4 (0.0)	5.1 (0.0)
Hospital care (*n*, %)	2560 (3.3)	6257 (2.4)	10 041 (6.0)	16 321 (14.2)	35 179 (5.7)	1944 (2.7)	15 439 (6.3)	8482 (5.2)	16 482 (11.0)	42 347 (6.7)	77 526 (6.2)

(continued)

Table 2. Continued

	Men					Women					Total
	0–14	15–44	45–64	≥ 65	Subtotal	0–14	15–44	45–64	≥ 65	Subtotal	
Hospital admissions (mean, SD)	1.20 (0.02)	1.22 (0.01)	1.34 (0.01)	1.46 (0.01)	1.36 (0.00)	1.29 (0.06)	1.18 (0.01)	1.30 (0.01)	1.34 (0.01)	1.27 (0.00)	1.31 (0.00)
Days/hospitalization (mean, SD)	2.7 (0.1)	5.0 (0.1)	6.0 (0.1)	8.4 (0.1)	6.7 (0.0)	3.0 (0.1)	3.7 (0.0)	5.5 (0.1)	8.7 (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)	27 253 (23.6)	104 281 (16.8)	10 639 (14.6)	41 812 (17.1)	25 724 (15.7)	36 070 (24.0)	114 245 (18.1)	218 526 (17.4)
Visits to emergency room (mean, SD)	1.54 (0.01)	1.44 (0.01)	1.50 (0.01)	1.71 (0.01)	1.53 (0.00)	1.55 (0.01)	1.58 (0.01)	1.49 (0.01)	1.61 (0.01)	1.57 (0.00)	1.55 (0.00)

[a]Standard deviation.
[b]Versus rural area.
[c]Versus native.
[d]Only diseases considered as chronic by Salisbury *et al.*[11] were taken into account.
[e]Considered as the presence of more than one chronic condition according to the criteria established by Salisbury *et al.*[11]
[f]Data refer to different drugs at the third level of the Anatomical, Therapeutic, Chemical (ATC) classification system.
[g]Data 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.
[h]Includes all primary care services, including consultations and home visits, and also paediatrics in boys and girls aged 0 to 14 years.
[i]General practitioner (including consultations and home visits, and excluding visits to the nurse).
[j]Not applicable (boys and girls aged 0 to 14 are not seen by the GP, but by their paediatrician).

including cross-national comparisons that imply harmonization of the definition of adherence across contexts. We have also measured the use of different health services by specific population groups.[22,24]

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, diseases and health outcomes. The longitudinal analyses that we expect to carry out in the near future will enable confirmation of cause-effect relationships or prediction of trends over time. Specifically, we plan to conduct a number of studies aimed at describing trajectories of multimorbidity over time and their relation with health outcomes. 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 multimorbidity trajectories. Finally, predictive modelling techniques will be performed to predict adverse health outcomes in multimorbid patients, depending on demographic variables and the incidence of specific chronic conditions that might act as trigger for negative health outcomes, reduced life expectancy and increased mortality.

What has it found? Key findings and publications

A number of findings and publications have arisen from the EpiChron Cohort Study, also before its official start in 2011. Multimorbidity was found to be strongly related to the occurrence of adverse drug events, as far as it requires the intervention of different specialists and the prescription of multiple medications.[30] The existence of non-random associations among chronic diseases has been identified in primary care patients, resulting in clinically meaningful multimorbidity patterns[26] (Table 4), some of which are consistently described in the literature.[31] Gender differences were detected in the prevalence of these patterns among the population aged 65 years and older, probably due to a higher life expectancy and/or worse health status observed among women.[32] Specific multimorbidity patterns in hospitalized geriatric patients have also been described, such as the induced-dependency and falls patterns, which may facilitate the early detection of patients with high vulnerability to stressors.[33] Similarities for several multimorbidity patterns were found in a cross-national comparison with patients from The Netherlands,[34] which could offer initial clues for the

Table 3. Baseline prevalence of most frequent chronic diseases by sex and age group in the EpiChron Cohort population in 2011

Age group	Men		Women	
	Disease (EDC[a])	Prevalence (%)	Disease (EDC)	Prevalence (%)
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	6.7
	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	Disorders of lipid metabolism	23.7
	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[b])	3.7	Low back pain	5.2
$\geq$ 65 years	Hypertension	52.8	Hypertension	59.1
	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.
[a]Expanded Diagnostic Clusters; only those considered as chronic by Salisbury et al.[11] were taken into account.

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

Table 4. Prevalence of multimorbidity and polypharmacy patterns by age group and sex in the EpiChron Cohort. Adapted from Prados-Torres *et al.*, 2012[23] and Calderón-Larrañaga *et al.*, 2013[24]

Age	Men		Women	
15–44 years	**Multimorbidity pattern**	**Prevalence (%)**	**Multimorbidity pattern**	**Prevalence (%)**
	Cardiometabolic	0.9	Cardiometabolic	0.4
	Psychiatric-substance abuse	1.5	Mechanical-obesity-thyroidal	3.7
	Polypharmacy pattern		**Polypharmacy pattern**	
	Depression-anxiety	0.8	Depression-anxiety	0.5
	ARI	3.6	ARI	8.4
	Rhinitis-asthma	0.1		
45–64 years	**Multimorbidity pattern**		**Multimorbidity pattern**	
	Cardiometabolic	9.2	Cardiometabolic	4.1
	Mechanical-obesity-thyroidal	4.9	Mechanical-obesity-thyroidal	16.6
			Depressive	0.1
	Polypharmacy pattern		**Polypharmacy pattern**	
	Depression-anxiety	2.0	Depression-anxiety	11.9
	CV	10.9	CV	3.6
	COPD	5.2	ARI	7.4
	Pain	4.5	Menopause	0.6
≥ 65 years	**Multimorbidity pattern**		**Multimorbidity pattern**	
	Cardiometabolic	21.2	Cardiometabolic	33.3
	Mechanical-obesity-thyroidal	13.6	Mechanical-obesity-thyroidal	3.5
	Psychogeriatric	2.4	Psychogeriatric	17.3
			Depressive	0.2
	Polypharmacy pattern		**Polypharmacy pattern**	
	Depression-anxiety	0.3	Depression-anxiety	37.5
	CV	24.6	CV	8.9
	COPD	25.3	COPD	7.4

ARI, acute respiratory infection; CV, cardiovascular; COPD, chronic obstructive pulmonary disease.

shown to increase the number of unplanned hospital admissions, and discordant comorbidities have an important effect on specialist care use.[24] 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.[25] 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.[29]

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.[28]

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.[23] 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.[22] 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.[35]

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.

Funding

The EpiChron Cohort Study has been partially supported by a grant from the Institute of Health Carlos III for Strategic Actions in Health (Grant Number PI11/1126), the Program INTERREG V-A Spain-France-Andorra of the European Commission (POCTEFA) and by private funds. The funders have no role in study design, data analysis or writing of the manuscript.

Conflict of interest: None declared.

References

1. World Health Organization. *Assessing National Capacity for the Prevention and Control of Noncommunicable Diseases: Report of the 2015 Global Survey*. 2015. http://apps.who.int/iris/bitstream/10665/246223/1/9789241565363-eng.pdf?ua=1 (15 February 2017, date last accessed).
2. Pefoyo AJK, Bronskill SE, Gruneir A *et al*. The increasing burden and complexity of multimorbidity. *BMC Public Health* 2015;**15**:415.
3. Tinetti ME, Fried TR, Boyd CM. Designing health care for the most common chronic condition - multimorbidity. *JAMA* 2012; **307**:2493–94.
4. Fortin M, Bravo G, Hudon C, Vanasse A, Lapointe L. Prevalence of multimorbidity among adults seen in family practice. *Ann Fam Med* 2005;**3**:223–28.

5. van Oostrom SH, Picavet HSJ, de Bruin SR *et al*. Multimorbidity of chronic diseases and health care utilization in general practice. *BMC Fam Pract* 2014;**15**:61.
6. Marengoni A, Onder G. Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity. *BMJ* 2015; **350**:h1059.
7. Wong MC, Liu J, Zhou S *et al*. The association between multimorbidity and poor adherence with cardiovascular medications. *Int J Cardiol* 2014;**177**:477–82.
8. Tinetti ME, Bogardus ST, Agostini J V. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *N Engl J Med* 2004;**351**:2870–74.
9. Marengoni A, Angleman S, Melis R *et al*. Aging with multimorbidity: A systematic review of the literature. *Ageing Res Rev* 2011;**10**:430–39.
10. Nunes BP, Flores TR, Mielke GI, Thumé E, Facchini LA. Multimorbidity and mortality in older adults: A systematic review and meta-analysis. *Arch Gerontol Geriatr* 2016;**67**:130–4Q238.
11. Salisbury C, Johnson L, Purdy S, Valderas JM, Montgomery AA. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract* 2011;**61**:e12–e21.
12. Noël PH, Parchman ML, Williams JW *et al*. The challenges of multimorbidity from the patient perspective. *J Gen Intern Med* 2007;**22**(Suppl 3):419–24.
13. Illario M, Vollenbroek-Hutten M, Molloy DW *et al*. Active and Healthy Ageing and Independent Living. *J Aging Res* 2015; **2015**:542183.
14. Navickas R, Petric V-K, Feigl AB, Seychell M. Multimorbidity: What do we know? What should we do? *J Comorbidity* 2016;**6**: 4–11.
15. Le Reste JY, Nabbe P, Lingner H *et al*. What research agenda could be generated from the European General Practice Research Network concept of Multimorbidity in Family Practice? *BMC Fam Pract* 2015;**16**:125.
16. France EF, Wyke S, Gunn JM, Mair FS, McLean G, Mercer SW. Multimorbidity in primary care: a systematic review of prospective cohort studies. *Br J Gen Pract* 2012;**6**:e297–307.
17. Cammarota S, Bruzzese D, Catapano AL *et al*. Lower incidence of macrovascular complications in patients on insulin glargine versus those on basal human insulins: a population-based cohort study in Italy. *Nutr Metab Cardiovasc Dis* 2014;**24**:10–7.
18. Menditto E, De Gea AB, Cahir C *et al*. Scaling up health knowledge at European level requires sharing integrated data: An approach for collection of database specification. *Clin Outcomes Res* 2016;**8**:253–65.
19. Johns Hopkins University. *The Johns Hopkins ACG® System*. https://www.hopkinsacg.org/ (8 August 2017, date last accessed).
20. Brilleman SL, Gravelle H, Hollinghurst S, Purdy S, Salisbury C, Windmeijer F. Keep it simple? Predicting primary health care costs with clinical morbidity measures. *J Health Econ* 2014;**35**: 109–22.
21. Huntley AL, Johnson R, Purdy S, Valderas JM, Salisbury C. Measures of Multimorbidity and Morbidity Burden for Use in Primary Care and Community Settings: A Systematic Review and Guide. *Ann Fam Med* 2012;**10**:134–41.
22. Gimeno-Feliu LA, Calderón-Larrañaga A, Diaz E, Poblador-Plou B, Macipe-Costa R, Prados-Torres A. Global healthcare use by immigrants in Spain according to morbidity burden, area of origin, and length of stay. *BMC Public Health* 2016;**16**:450.
23. Gimeno-Feliu LA, Calderón-Larrañaga A, Diaz E, Poblador-Plou B, Macipe-Costa R, Prados-Torres A. The healthy migrant effect in primary care. *Gac Sanit* 2015;**29**:15–20.
24. Calderón-Larrañaga A, Abad-Díez JM, Gimeno-Feliu LA *et al*. Global health care use by patients with type-2 diabetes: Does the type of comorbidity matter? *Eur J Intern Med* 2015;**26**:203–10.
25. Poblador-Plou B, Calderón-Larrañaga A, Marta-Moreno J *et al*. Comorbidity of dementia: a cross-sectional study of primary care older patients. *BMC Psychiatry* 2014;**14**:84.
26. Prados-Torres A, Poblador-Plou B, Calderón-Larrañaga A *et al*. Multimorbidity patterns in primary care: interactions among chronic diseases using factor analysis. *PLoS One* 2012;**7**: e32190.
27. Calderón-Larrañaga A, Gimeno-Feliu LA, González-Rubio F *et al*. Polypharmacy patterns: Unravelling systematic associations between prescribed medications. *PLoS One* 2013;**8**: e84967.
28. Castellsague J, Perez-Gutthann S, Calingaert B *et al*. Characterization of new users of cilostazol in the United Kingdom, Spain, Sweden, and Germany. *Pharmacoepidemiol Drug Saf* 2017;**6**:615–24.
29. Calderón-Larrañaga A, Diaz E, Poblador-Plou B, Gimeno-Feliu LA, Abad-Díez JM, Prados-Torres A. Non-adherence to antihypertensive medication: The role of mental and physical comorbidity. *Int J Cardiol* 2016;**207**:310–16.
30. Calderón-Larrañaga A, Poblador-Plou B, González-Rubio F, Gimeno-Feliu LA, Abad-Díez JM, Prados-Torres A. Multimorbidity, polypharmacy, referrals, and adverse drug events: Are we doing things well? *Br J Gen Pract* 2012;**62**: 821–26.
31. Prados-Torres A, Calderón-Larrañaga A, Hancco-Saavedra J, Poblador-Plou B, Van Den Akker M. Multimorbidity patterns: A systematic review. *J Clin Epidemiol* 2014;**67**:254–66.
32. Abad-Díez JM, Calderón-Larrañaga A, Poncel-Falcó A *et al*. Age and gender differences in the prevalence and patterns of multimorbidity in the older population. *BMC Geriatr* 2014;**14**: 75.
33. Clerencia-Sierra M, Calderón-Larrañaga A, Martínez-Velilla N *et al*. Multimorbidity patterns in hospitalized older patients: Associations among chronic diseases and geriatric syndromes. *PLoS One* 2015;**10**:e0132909.
34. Poblador-Plou B, Van Den Akker M, Vos R, Calderón-Larrañaga A, Metsemakers J, Prados-Torres A. Similar multimorbidity patterns in primary care patients from two European regions: Results of a factor analysis. *PLoS One* 2014;**9**: e100375.
35. Gimeno-Feliu LA, Calderón-Larrañaga A, Prados-Torres A, Revilla-López C, Diaz E. Patterns of pharmaceutical use for immigrants to Spain and Norway: a comparative study of prescription databases in two European countries. *Int J Equity Health* 2016;**15**:32.