

# BMJ Open Co-prescription patterns of cardiovascular preventive treatments: a cross-sectional study in the Aragon worker' health study (Spain)

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## ABSTRACT

**Objectives** To identify cardiovascular disease (CVD) preventive treatments combinations, among them and with other drugs, and to determine their prevalence in a cohort of Spanish workers.

**Design** Cross-sectional study.

**Setting** Aragon Workers' Health Study (AWHS) cohort in Spain.

**Participants** 5577 workers belonging to AWHS cohort. From these subjects, we selected those that had, at least, three prescriptions of the same therapeutic subgroup in 2014 (n=4605).

**Primary and secondary outcome measures** Drug consumption was obtained from the Aragon Pharmaceutical Consumption Registry (Farmasalud). In order to know treatment utilisation, prevalence analyses were conducted. Frequent item set mining techniques were applied to identify drugs co-prescription patterns. All the results were stratified by sex and age.

**Results** 42.3% of men and 18.8% of women in the cohort received, at least, three prescriptions of a CVD preventive treatment in 2014. The most prescribed CVD treatment were antihypertensives (men: 28.2%, women 9.2%). The most frequent association observed among CVD preventive treatment was agents acting on the renin-angiotensin system and lipid-lowering drugs (5.1% of treated subjects). Co-prescription increased with age, especially after 50 years old, both in frequency and number of associations, and was higher in men. Regarding the association between CVD preventive treatments and other drugs, the most frequent pattern observed was lipid-lowering drugs and drugs used for acid related disorders (4.2% of treated subjects).

**Conclusions** There is an important number of co-prescription patterns that involve CVD preventive treatments. These patterns increase with age and are more frequent in men. Mining techniques are a useful tool to identify pharmacological patterns that are not evident in the individual clinical practice, in order to improve drug prescription appropriateness.

## INTRODUCTION

Despite a decline in recent decades, cardiovascular disease (CVD) remains the leading cause of premature death in Europe. The

## Strengths and limitations of this study

- The use of data mining techniques is useful to detect co-prescription patterns that are not evident in the individual clinical practice.
- Farmasalud database provides information on prescriptions issued via the Spanish National Health System, but no information on prescriptions issued via the private sector. Also, information on clinical characteristics or the reasons to start treatment are not available.
- Data pertain to prescriptions dispensed. So, it is not possible to know whether or not the patients used the medication.

downward trend in CVD mortality is evident in Spain, which has comparatively lower mortality rates than neighbouring countries.<sup>1</sup>

The population ageing, the increase of diagnoses or changes in lifestyles, among others, have resulted in a progressive increase in the prescription of drugs such as antihypertensives and lipid-lowering agents.<sup>2</sup> In Spain, the consumption of lipid-lowering drugs increased by 442% between 2000 and 2012, from 18.9 DID (daily defined doses/1000 inhabitants/day) to 102.6 DID.<sup>3</sup> An increase in the consumption of antihypertensive drugs, from 165.5 DID in 2000 to 299.0 DID in 2012, has also been described.<sup>4</sup> Finally, although not as acute as the aforementioned patterns, the prescription of anti-diabetic drugs increased during the period 2000 to 2014.<sup>5</sup> In this context, drug utilisation studies constitute a useful tool to determine the frequency of use and prescribing patterns of drugs for CVD prevention in different populations.

CVD preventive treatments are usually prescribed in combination: for example, in secondary prevention the co-prescription of aspirin, multiple blood pressure lowering

drugs and a statin could lead to substantial CVD risk reductions.<sup>6</sup> Nonetheless, there are some risks associated with polypharmacy. For instance, the prescription of multiple drugs in the context of cardiovascular disease has been linked to a lower treatment compliance<sup>7</sup> and a highest frequency of adverse effects.<sup>8</sup> So, in patients with CVD it is recommended to check and eliminate inappropriate drugs according to the patient's needs.<sup>9</sup> A deeper knowledge of drug utilisation and drug co-prescription is crucial to further evaluation of CVD treatments' effectiveness in real conditions and appropriateness. The use of new tools, such as data mining methods,<sup>10</sup> allows us to describe efficiently treatment's co-prescriptions.

The aim of this study was to apply frequent item set mining, a well-known data mining technique, to determine the prevalence of use of drugs for the prevention of CVD (antidiabetics, antihypertensives, lipid-lowering drugs, anticoagulants and antiplatelet agents) by sex and age in a cohort of Spanish workers and to identify CVD preventive treatments co-prescriptions. This data mining technique will allow us to quantify the prevalence and co-prescriptions patterns in a fast and efficient manner.

## METHOD

### Design and information sources

The Aragon Workers' Health Study (AWHS) is a prospective longitudinal study based on annual examinations of a cohort of factory workers at General Motors Spain, located in Figueruelas (Zaragoza). The study began in 2009 and enrolment of participants ended in December 2012. The information collected is derived from annual medical examinations of the workers, additional questionnaires on lifestyle and cardiovascular risk factors, analysis of biological samples and imaging tests for the diagnosis of subclinical atherosclerosis. Exclusion criteria include a history of CVD or the presence of clinical conditions that limit survival to less than 3 years. This study was approved by the Aragon Committee for Ethics and Clinical Research. All participants agreed to participate and provided written informed consent. Further information on the AWHS is cited in the bibliography.<sup>11</sup> Baseline characteristics of the cohort are shown in [table 1](#).

Using data obtained from the AWHS cohort, we designed a study to examine the prevalence of preventive treatment of CVD in 2014. Information on drug consumption was obtained from the Aragon Pharmaceutical Consumption Registry (Farmasalud). This database contains information on drugs dispensed by pharmacies for prescriptions issued via the Aragon Health System, but does not record over-the-counter drugs or prescriptions from private healthcare providers or hospitals. However, it should be noted that the overwhelming majority of the Spanish population is covered by the public health system. Also, these drugs are mainly for outpatient use. The following information was obtained from the Farmasalud database: patient code, sex, date of birth, month in which the drug was dispensed, Anatomical Therapeutic

**Table 1** Aragon workers' health study baseline characteristics

	Men (n=5048)	Women (n=351)
	Mean (SD) or N (%)	Mean (SD) or N (%)
Age, y	49.3 (8.7)	40.8 (11.6)
BMI (kg/m <sup>2</sup> )	27.7 (3.6)	24.4 (3.8)
Systolic BP (mm Hg)	127.0 (14.7)	111.4 (13.2)
Diastolic BP (mm Hg)	83.8 (10.1)	76.4 (9.5)
Total cholesterol (mg/dL)	212.4 (37.6)	204.3 (39.9)
HDL-C (mg/dL)	52.4 (11.0)	66.5 (14.2)
Triglycerides (mg/dL)	148.8 (106.1)	89.7 (75.5)
Glucose (mg/dL)	98.3 (19.6)	91.2 (16.3)
Smoking habits		
Never	1796 (35.8)	146 (41.8)
Former	1359 (27.1)	46 (13.2)
Current	1862 (37.1)	157 (45.0)

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BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol.

Chemical Classification System (ATC) code, as defined by the WHO,<sup>12</sup> the number of defined daily doses and the number of packages dispensed. Data was collected for the following ATC codes (second level, therapeutic subgroup): A10 (antidiabetics), B01 (antithrombotics), C02 (antihypertensives – antiadrenergic agents), C03 (diuretics), C07 (beta blocking agents), C08 (calcium channel blockers), C09 (agents acting on the renin-angiotensin system) and C10 (lipid-lowering drugs). Also, data from the rest of therapeutic subgroups was included, in order to explore the patterns of prescription. These data on drug prescribing were combined with anonymised data collected from the AWHS cohort.

### Public involvement

Patients were not involved in the participation nor in the design of this study.

### Analyses

To determine the prevalence of preventive treatment for CVD, we obtained prescription rates per 100 inhabitants and corresponding 95% CI. Due to the low number of female participants, corresponding 95% CI values were calculated using the exact method. For each of the ATC groups considered, rates were calculated as the number of individuals per 100 workers who received at least three prescriptions of the same therapeutic subgroup for 2014. We consider that three prescriptions of the same therapeutic subgroup within a year are indicative of a regular use. A descriptive analysis was performed for each cardiovascular preventive treatment therapeutic subgroup. These analyses were also conducted for other therapeutic subgroups, according their frequency of prescription.

**Table 2** Rates per 100 workers with at least three prescriptions of the same therapeutic subgroup of preventive treatments for cardiovascular disease. Results stratified by sex and age, 2014

		<=49	50 to 54	55–to 59	>59	Total
ANTIDIABETICS	Men	1.1 (0.5 to 1.7)	4.4 (3.2 to 5.6)	8.6 (7.3 to 9.9)	12.2 (10.3 to 14.2)	6.7 (6.0 to 7.4)
	Women	0.00	1.4 (0.0 to 7.4)	0.00	0.00	–
ANTIHYPERTENSIVES	Men	6.4 (5.0 to 7.7)	28.2 (25.6 to 30.9)	33.4 (31.2 to 35.5)	44.9 (42.0 to 47.9)	28.2 (27.0 to 29.5)
	Women	2.0 (0.6 to 5.0)	17.8 (9.8 to 28.5)	18.8 (10.1 to 30.5)	16.7 (5.6 to 34.7)	9.2 (6.5 to 12.7)
LIPID-LOWERING DRUGS	Men	6.8 (5.4 to 8.2)	22.4 (19.9 to 24.9)	30.3 (28.2 to 32.5)	36.9 (34.0 to 39.8)	24.4 (23.3 to 25.6)
	Women	1.5 (0.3 to 4.3)	11.0 (4.9 to 20.5)	25.0 (15.0 to 37.4)	33.3 (17.3 to 52.8)	10.1 (7.2 to 13.6)
ANTITHROMBOTICS	Men	0.7 (0.3 to 1.2)	5.7 (4.3 to 7.0)	9.9 (8.5 to 11.3)	12.1 (10.2 to 14.1)	7.3 (6.6 to 8.0)
	Women	0.00	6.9 (2.3 to 15.3)	1.6 (0.0 to 8.4)	3.3 (0.1 to 17.2)	1.9 (0.8 to 3.9)
GLOBAL	Men	12.4 (10.6 to 14.2)	41.8 (38.9 to 44.7)	51.2 (48.9 to 53.5)	62.2 (59.3 to 65.1)	42.3 (40.9 to 43.6)
	Women	4.0 (1.7 to 7.7)	28.8 (18.8 to 40.6)	42.2 (29.9 to 55.2)	43.3 (25.5 to 62.6)	18.8 (14.9 to 23.1)

CI calculation in men: approximate method; women: exact method.

Data were further analysed after stratification for age and sex.

To analyse treatment's co-prescriptions and their frequency, we used the frequent item set mining technique. Frequent item set mining is used to discover sets of attributes or *items* shared among a large number of subjects or *transactions* in a given database<sup>13</sup>. The formal definition of the frequent item set mining technique is as follows. We are given a set  $B = \{i_1, \dots, i_n\}$  of *items* (the item base) and a database  $T = \{t_1, \dots, t_m\}$  of *transactions*. The term *item set* refers to any subset of the item base  $B$ . The *cover*  $K_T(I) = \{k \in \{1, \dots, m\} \mid I \in t_k\}$  of an item set  $I \subseteq B$  indicates the transactions it is contained in. The support  $s_T(I)$  is the number of these transactions,  $s_T(I) = |K_T(I)|$ . Given a user-specified *minimum support*  $s_{min} \in \mathbb{N}$ , an item set  $I$  is called *frequent* (in  $T$ ) iff  $s_T(I) \geq s_{min}$ . The goal of frequent item set mining is to find all item sets  $I \subseteq B$  that are frequent in the database  $T$ . In our study, the *item base*  $B$  is the set of all the drugs used in the cohort. Each transaction  $t_i$  is the item set that contains the drugs prescribed to the patient  $i$  of the cohort more than three times in the year of study. The frequent item sets considered are those with a support at least 1% of the cohort population analysed.

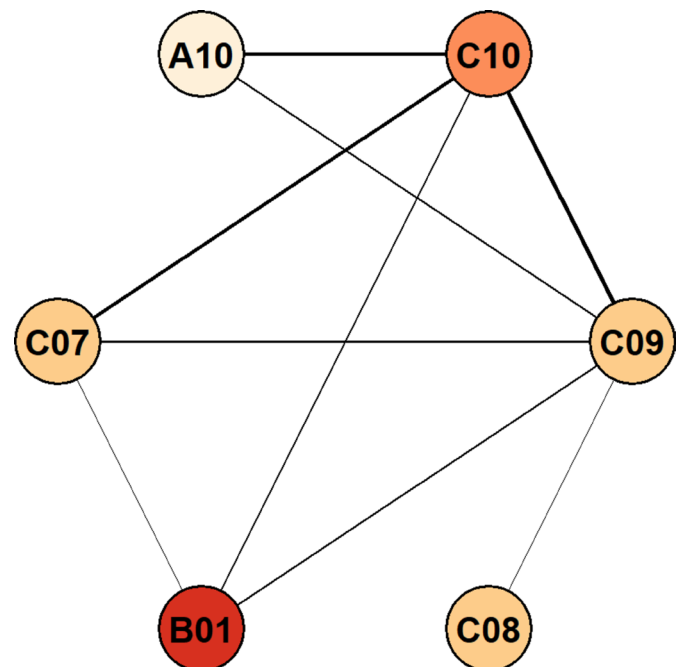
We used the Eclat algorithm (Equivalence CLASS Transformation) proposed by Zaki.<sup>14</sup> Eclat algorithm uses a depth-first search for discovering frequent item sets. The analyses were performed using Python and R languages. The frequent item sets of cardinality two are depicted using a graph, where each node represents a drug, each edge connects two drugs present in a frequent item set and the edge width represents the support of the frequent item set (thicker edges indicate item sets with higher support). Frequent item sets with larger cardinality are described in the text.

## RESULTS

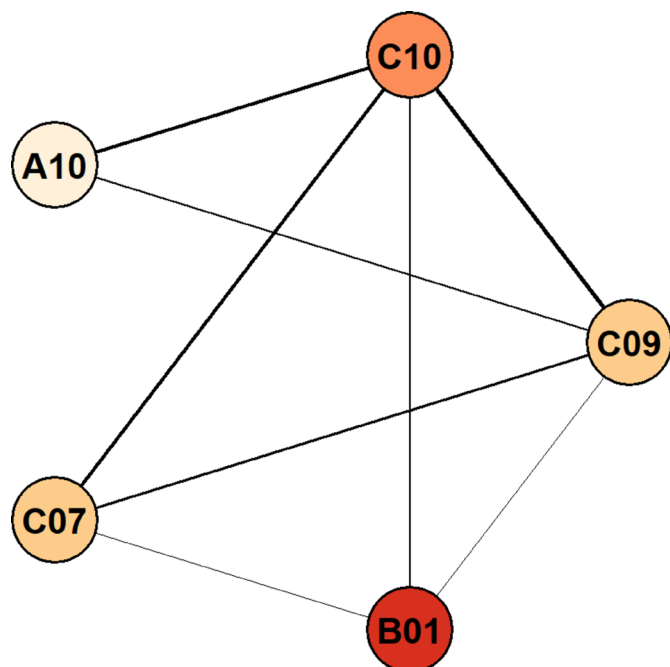
A total of 5577 workers belonging to AWHs cohort were included in the study. From these workers, we selected

those that had, at least, three prescriptions of the same therapeutic subgroup in 2014 ( $n=4605$ ). Of these, 4307 were men (93.5%) and 298 women. In the year analysed, 21.9% were less than 50 years of age and 22.0% were 60 years or older.

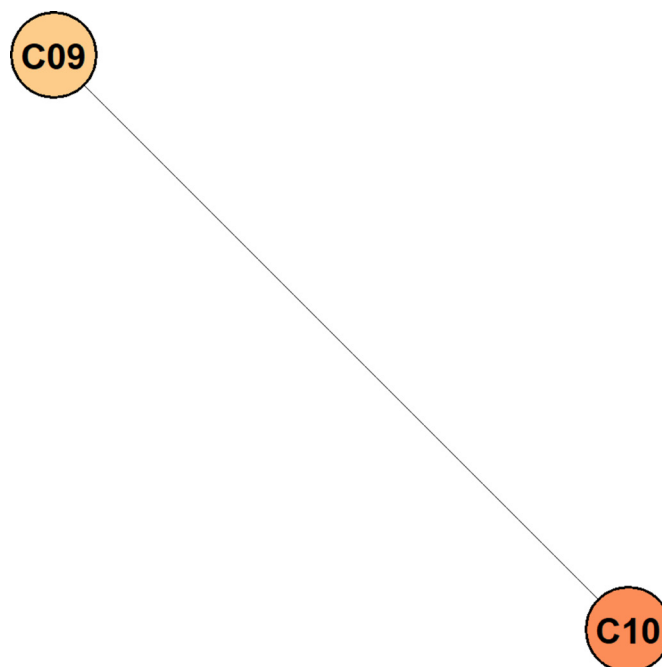
As shown in table 2, 42.3% of men (95% CI 40.9 to 43.6) and 18.8% of women (95% CI 14.9 to 23.1) received at least three prescriptions for a drug for CVD prevention in 2014. The drugs prescribed most frequently to men were antihypertensives (28.2%; 95% CI 27.0 to 29.5), followed by lipid-lowering drugs (24.4%; 95% CI 23.3 to 25.6). In



**Figure 1** Combinations of cardiovascular disease preventive drugs. AWHs population, 2014. Thicker lines express a higher frequency of association. A10: antidiabetics, B01: antithrombotics, C07: beta blocking agents, C08: calcium channel blockers, C09: agents acting on the renin-angiotensin system, C10: lipid-lowering drugs. AWHs, Aragon Workers' Health Study.



**Figure 2** Combinations of cardiovascular disease preventive drugs in men. AWHs population, 2014. Thicker lines express a higher frequency of association. A10: antidiabetics, B01: antithrombotics, C07: beta blocking agents, C09: agents acting on the renin-angiotensin system, C10: lipid-lowering drugs. AWHs, Aragon Workers' Health Study.



**Figure 3** Combinations of cardiovascular disease preventive drugs in women. AWHs population, 2014. Thicker lines express a higher frequency of association. A10: antidiabetics, B01: antithrombotics, C07: beta blocking agents, C09: agents acting on the renin-angiotensin system, C10: lipid-lowering drugs. AWHs, Aragon Workers' Health Study.

women, the most commonly prescribed preventive treatments for CVD were lipid-lowering drugs (10.1%; 95% CI 7.2 to 13.6), followed by antihypertensives (9.2%; 95% CI 6.5 to 12.7). For men, 7.3% had at least three prescriptions for an antithrombotic drug filled in 2014 and 6.7% for antidiabetic drugs. For women, 1.9% had at least three prescriptions for an antithrombotic drug and there was no dispensation of antidiabetics. The rate of dispensation raised with age, with the highest prescription rate change between <50 and 50 to 54 years old group. The highest dispensation rates were found for the group of workers of over 59 years of age (men: 62.2%; 95% CI 59.3 to 65.1, women: 43.3%; 95% CI 25.5 to 62.6). The largest differences between age groups were observed for antihypertensives in men and for lipid-lowering drugs in women.

Figure 1 shows the combinations of CVD preventive drugs for the AWHs population that had, at least, three prescriptions in 2014. The most frequent association was found between drugs acting on the renin-angiotensin system (C09) and lipid modifying agents (C10) (5.1% of the subjects). Other combinations, like beta blocking agents (C07)-lipid modifying agents (C10), antidiabetics (A10)-lipid modifying agents (C10), beta blocking agents (C07)-drugs acting on the renin-angiotensin system (C09) or antithrombotics (B01)-lipid modifying agents (C10) were prescribed with lower frequency (2.4%, 2.3%, 2.1% and 2.0%, respectively). Combinations of more than three CVD preventive drugs were also found. So, co-prescription of beta blocking agents (C07)-drugs acting on the renin-angiotensin system (C09)-lipid modifying

agents (C10) was observed in 1.1% of the subjects. The same percentage was found for the association of antidiabetics (A10)-lipid modifying agents (C10)-drugs acting on the renin-angiotensin system (C09).

When analyses were stratified by sex, the most frequent associations of CVD preventive drugs in men (figure 2) were drugs acting on the renin-angiotensin system (C09)-lipid modifying agents (C10) (5.3%), beta blocking agents (C07)-lipid modifying agents (C10) (2.6%) and antidiabetics (A10)-lipid modifying agents (C10) (2.4%). In women (figure 3), the only combination found was between drugs acting on the renin-angiotensin system (C09)-lipid modifying agents (C10), but its frequency was very low (1.7% of women in 2014).

The number of drugs associated increased with age. In the group from 50 to 54 years old, 4.5% of the subjects received the combination drugs acting on the renin-angiotensin system (C09)-lipid modifying agents (C10). In the group of 55 to 59 years old, this combination was found in the 5.5% of the cases and, in the group of age >59, in 9.5% of the subjects. Other co-treatments in this group of age were beta blocking agents (C07)-lipid modifying agents (C10) (4.6%), antidiabetics (A10)-lipid modifying agents (C10) (4.2%) and antidiabetics (A10)-drugs acting on the renin-angiotensin system (C09) (4.2%). The youngest group (<50 years old) had no combinations that represented, at least, 1% of the population analysed. (online supplementary material 1).

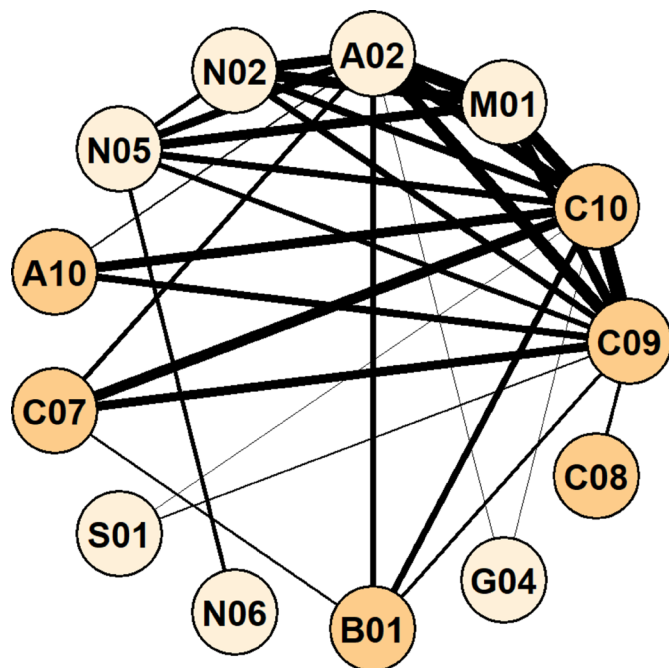
Other drugs were also found in the cohort, as can be seen in table 3. The highest prescription was observed in

**Table 3** Rates per 100 workers with at least three prescriptions of the same therapeutic subgroup of other treatments. Results stratified by sex and age, 2014

		<=49	50–to 54	55–to 59	>59	Total
ACID RELATED DISORDERS	Men	4.8 (3.6 to 5.9)	14.0 (11.9 to 16.0)	20.2 (18.3 to 22.0)	26.1 (23.5 to 28.7)	16.4 (15.4 to 17.4)
	Women	1.5 (0.3 to 4.3)	11.0 (4.9 to 20.5)	15.6 (7.8 to 26.9)	20.0 (7.7 to 38.6)	7.3 (4.9 to 10.5)
ANTI-INFLAMMATORY AND ANTIRHEUMATIC	Men	7.3 (5.9 to 8.8)	14.5 (12.5 to 16.6)	17.1 (15.4 to 18.8)	22.7 (20.2 to 25.2)	15.4 (14.4 to 16.4)
	Women	9.0 (5.4 to 13.8)	11.0 (4.9 to 20.5)	23.4 (13.8 to 35.7)	13.3 (3.8 to 30.8)	12.2 (9.1 to 16.0)
ANALGESICS	Men	3.5 (2.5 to 4.6)	8.0 (6.4 to 9.6)	8.9 (7.6 to 10.3)	13.9 (11.8 to 15.9)	8.5 (7.7 to 9.2)
	Women	4.0 (1.7 to 7.7)	15.1 (7.8 to 25.4)	9.4 (3.5 to 19.3)	16.7 (5.6 to 34.7)	8.2 (5.6 to 11.4)
PSYCHOLEPTICS	Men	4.5 (3.4 to 5.7)	8.7 (7.0 to 10.4)	9.4 (8.1 to 10.8)	10.7 (8.9 to 12.6)	8.4 (7.6 to 9.1)
	Women	3.5 (1.4 to 7.0)	16.4 (8.8 to 27.0)	20.3 (11.3 to 32.2)	16.7 (5.6 to 34.7)	10.1 (7.2 to 13.6)

CI calculation in men: approximate method; women: exact method.

the group >59 years of age and for drugs used for acid related disorders (A02) (men: 26.1%, 95% CI 23.5 to 28.7; women: 20.0%, 95% CI 7.7 to 38.6), followed by anti-inflammatory and antirheumatic products (M01) (men: 22.7%, 95% CI 20.2 to 25.2; women: 13.3%, 95% CI 3.8–30.8). The combinations between CVD preventive drugs and other treatments can be observed in [figure 4](#). This figure shows that CVD preventive treatments were frequently prescribed with drugs used for acid related



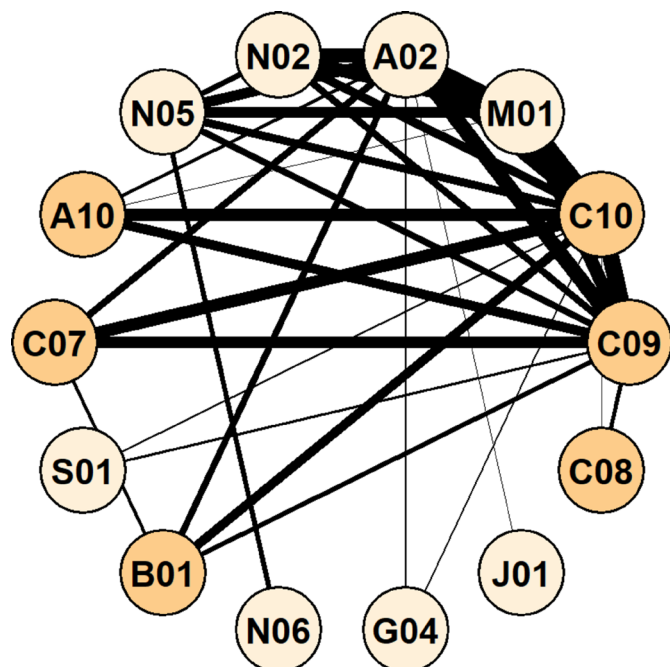
**Figure 4** Combinations between cardiovascular disease preventive drugs and other treatments. AWHs population, 2014. Thicker lines express a higher frequency of association. A02: drugs used for acid related disorders, A10: antidiabetics, B01: antithrombotics, C07: beta blocking agents, C08: calcium channel blockers, C09: agents acting on the renin-angiotensin system, C10: lipid-lowering drugs, G04: urological drugs, M01: anti-inflammatory and antirheumatic products, N02: analgesics, N05: psycholeptics, N06: psychoanaleptics, S01: ophthalmological drugs. AWHs, Aragon Workers' Health Study.

disorders (A02), anti-inflammatory and antirheumatic products (M01), analgesics (N02) and psycholeptics (N05). The highest combination rates belong to drugs used for acid related disorders (A02) - lipid modifying agents (C10) (4.2% of the subjects), drugs used for acid related disorders (A02) - drugs acting on the renin-angiotensin system (C09) (3.4%) and anti-inflammatory and antirheumatic products (M01) - lipid modifying agents (C10) (3.3%). The most frequent combination of three drugs was the association between drugs used for acid related disorders (A02) - drugs acting on the renin-angiotensin system (C09) - lipid modifying agents (C10), which was observed in 1.6% of the subjects. In men ([figure 5](#)) the same combinations were observed. In women ([figure 6](#)), the most frequent association with a CVD preventive treatment was observed between drugs acting on the renin-angiotensin system (C09) - anti-inflammatory and antirheumatic products (M01) (1.3%).

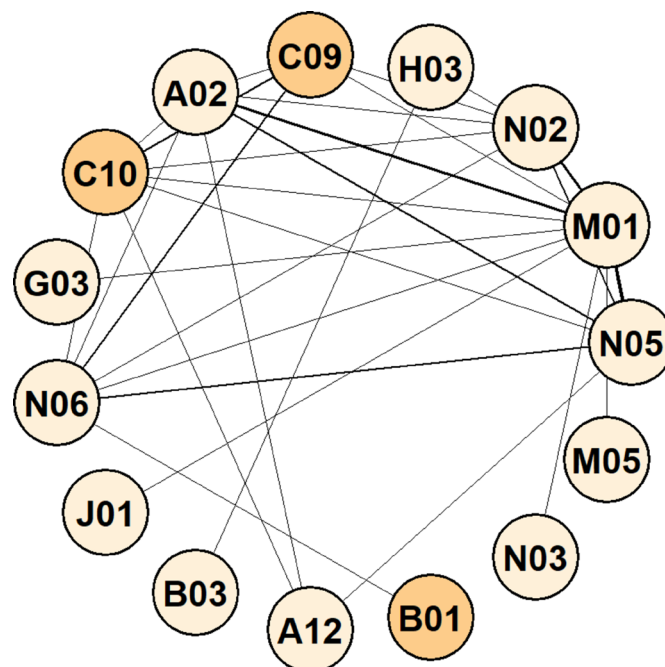
When differences by groups of age were analysed (online supplementary material 2) the highest frequency of association was shown in people >59 years old. In this group of age, the most frequent association found was between drugs used for acid related disorders (A02) - lipid modifying agents (C10) (7.8%). Other co-prescriptions with CVD preventive treatments were anti-inflammatory and antirheumatic products (M01) - lipid modifying agents (C10) (5.9%), drugs used for acid related disorders (A02) - drugs acting on the renin-angiotensin system (C09) (6.0%) and anti-inflammatory and antirheumatic products (M01) - drugs acting on the renin-angiotensin system (C09) (5.6%). Also, 3.7% of the people of this group received the combination of drugs used for acid related disorders (A02) - drugs acting on the renin-angiotensin system (C09) - lipid modifying agents (C10).

## DISCUSSION

Frequent item set mining has shown to be a useful technique in order to identify co-prescription patterns. In our prescriptions database, which includes 86 different drugs, frequent item set mining took seconds to explore all



**Figure 5** Combinations between cardiovascular disease preventive drugs and other treatments in men. AWHs population, 2014. Thicker lines express a higher frequency of association. A02: drugs used for acid related disorders, A10: antidiabetics, A12: mineral supplements, B01: antithrombotics, B03: antianaemic preparations, C07: beta blocking agents, C08: calcium channel blockers, C09: agents acting on the renin-angiotensin system, C10: lipid-lowering drugs, G03: sex hormones and modulators of the genital system, G04: urological drugs, H03: thyroid therapy, J01: antibacterials for systemic use, M01: anti-inflammatory and antirheumatic products, N02: analgesics, N03: antiepileptics, N05: psycholeptics, N06: psychoanalectics, S01: ophthalmological drugs. AWHs, Aragon Workers' Health Study.



**Figure 6** Combinations between cardiovascular disease preventive drugs and other treatments in women. AWHs population, 2014. Thicker lines express a higher frequency of association. A02: drugs used for acid related disorders, A10: antidiabetics, A12: mineral supplements, B01: antithrombotics, B03: antianaemic preparations, C07: beta blocking agents, C08: calcium channel blockers, C09: agents acting on the renin-angiotensin system, C10: lipid-lowering drugs, G03: sex hormones and modulators of the genital system, G04: urological drugs, H03: thyroid therapy, J01: antibacterials for systemic use, M01: anti-inflammatory and antirheumatic products, N02: analgesics, N03: antiepileptics, N05: psycholeptics, N06: psychoanalectics, S01: ophthalmological drugs. AWHs, Aragon Workers' Health Study.

possible co-prescription patterns. This exploration would have been extremely time-consuming using traditional descriptive methods.

The prescription of CVD preventive drugs in the cohort was frequent. The most commonly prescribed drugs were antihypertensives, followed by lipid-lowering drugs. These findings are in line with those of previous studies<sup>3 4</sup> in which antihypertensives and statins accounted for over 50% of prescribed preventive treatments for CVD.<sup>2</sup> Although few women were included in the AWHs cohort, we found that the rate of prescription was significantly higher in men than in women for all the therapeutic subgroups analysed. Sex differences in the prescribing of drugs for CVD prevention is a controversial issue<sup>15</sup> and previous studies have described a sex bias in the prescription of primary and secondary CVD preventive drugs, showing higher prescription rates for men. This bias is maintained over time<sup>16</sup> and is especially evident in the prescribing of drugs for dyslipidaemia.<sup>17 18</sup> In Spain, Sánchez *et al.*<sup>19</sup> reported a higher frequency of prescribing of CVD drugs in men than in women, and an inverse pattern in patients of over 70 years. A study

performed in the autonomous community of Valencia<sup>20</sup> reported no sex differences in the prescribing of drugs for the cardiovascular system. Some authors have emphasised the need to improve prescribing for women, and have proposed strategies including greater inclusion of women in clinical trials to gather further information and facilitate the adaptation of clinical practice guidelines.<sup>18</sup> In our study, the low number of women included, which may have led to errors in the estimates obtained, and sex differences in baseline risk factors<sup>21</sup> could, at least partially, account for the observed results.

The frequency of co-prescription patterns was high. Co-prescription increased with age, and the highest increase has been observed after the age of 50. There is a high number of drug associations in people  $\geq 60$  years old. These associations involve drugs acting on the renin-angiotensin system, lipid modifying agents, drugs for acid related disorders, anti-inflammatory and antirheumatic products, analgesics, beta blocking drugs and antidiabetics. The association observed in this study among CVD preventive treatments has already been described in literature. Calderón-Larrañaga *et al.*<sup>22</sup> analysed systematic

associations in drug prescription in general population. The authors described the existence of a 'cardiovascular pattern' in people from 45 to 64 years old. This pattern is similar to the most frequent combination found in the cohort (lipid modifying agents, drugs acting on renin-angiotensin system, beta blocking drugs, antidiabetics and antithrombotics). It is important to highlight that, some of these drugs, are already combinations of different treatments. This is especially noteworthy in the case of drugs acting on the renin-angiotensin system, where two or three different drugs can be prescribed together. As it has been previously described,<sup>23</sup> there are many negative consequences associated with polypharmacy, like medication non-adherence, an increased risk of adverse drug events and greater healthcare costs. Some authors suggest<sup>8</sup> that the existence of cardiovascular polypharmacy could be associated with subsequent development of acute kidney injury and other negative clinical outcomes. In this sense, patient-centred care and shared decision-making, could be effective ways of limiting drugs associated morbidity and promoting patient's satisfaction.<sup>24</sup>

Regarding the association between CVD preventive treatments and other drugs, co-prescription between antithrombotics and drugs for acid related disorders could be explained by the adverse gastric effects of anti-thrombotics.<sup>25</sup> Also, these drugs co-prescription show the possibility of the existence of other associated treatments. So, there are probably other patterns of prescription that have not been shown due to our inclusion criteria, but that should be taken into account in order to manage polypharmacy. We have also found a high frequency of association between drugs used for acid related disorders and antihypertensives and lipid modifying agents. This combination would only be justified in case of gastric or duodenal ulcer, where the benefits outweigh the risks, especially in short time treatments.<sup>26</sup> The association that involve anti-inflammatory and antirheumatic products and analgesics, would be associated within a 'pain pattern',<sup>22</sup> which also explains their association with drugs used for acid related disorders, due to their adverse effects. ATC group N05, which includes antipsychotics and anxiolytics, was also associated with CVD preventive treatments. These drugs, used for non-specific anxiety disorders, are used frequently across all ages.<sup>27</sup>

Some of the described patterns could lead to safety problems. This is the case of the associations including non-steroidal anti-inflammatory drugs (NSAIDs). Some of their risks are gastrointestinal bleeding, hypertension and a higher risk of cardiovascular events.<sup>28</sup> Previous studies have observed a high NSAIDs utilisation in patients with chronic illnesses that could contraindicate their use.<sup>22 29</sup> There is also a safety problem in the association between ACE inhibitors/angiotensin receptor antagonists, diuretics and NSAIDs. This association, known as the 'triple whammy', may impair renal function.<sup>30</sup> So, prior evaluation should be conducted in order to avoid these treatments in people with high risk of adverse effects. Regarding proton pump inhibitors, which are the A02

drug most commonly used to prevent NSAID-induced gastropathy in Spain, its use should be limited to patients with gastrointestinal risk factors after the age of 60.<sup>25</sup> In our study, 1.4% people aged >59 years presented the association antithrombotic - anti-inflammatory and anti-rheumatic products, with no drugs used for acid related disorders associated. This result shows a low appropriateness according to clinical recommendations.

Some limitations of the present study should be noted. First, the Farmasalud database only records prescriptions issued via the Spanish National Health System. Although there is no information on private sector, we consider that the number of prescriptions excluded from the present study is unlikely to be significant, since 99% of the Spanish population is covered by the National Health System. It should also be borne in mind that these data pertain solely to prescriptions dispensed; it is thus not possible to know whether or not the patients used the medication, or whether they did so in accordance with the recommendations. Regular treatment was defined as those cases with, at least, three dispensations of the same therapeutic subgroup in the same year. So, in this study, co-prescription means that drugs have been prescribed in the same year. Taking into consideration that CVD preventive treatments are used in a chronic way, CVD drugs combination should coincide in time. Nonetheless, co-prescription with some drugs used for acute illnesses, as anti-inflammatory and antirheumatic products, should be interpreted cautiously. Also, the 'three prescription criteria' used could lead to inappropriately consider as treated individuals who received several prescriptions of a drug but did not take it in a persistent manner. For instance, if a patient presents three different prescriptions of a particular drug/subgroup and they are separated in time, could be incorrectly considered as user of this drug/subgroup. Further analyses are therefore needed to explore if co-prescribed treatments are continuous and coexisting over time. Farmasalud provides information on a limited number of variables pertaining to the study participants and their treatment. Information on clinical characteristics or the reasons to start treatment, among others, was not available. This lack of information limits the interpretation of results and the clinical appropriateness of treatments. Finally, the cohort characteristics could compromise the external validity of the study. The low number of women and the age range of the population is due to the occupational characteristics of the cohort (workers of a car factory). This fact could limit the generalisation of results to those men in the same group of age. On the other hand, strengths of the present study include the type of data analysed, and specifically the population coverage offered by individual-level data, as well as the use of new techniques of analysis, in order to detect association patterns in a friendly way.

As Hand stated,<sup>31</sup> data mining is useful to find unsuspected relationships and to summarise the data in novel ways that are both understandable and useful for clinical practice. So, the goal of data mining is to gain a deep

understanding of our datasets. Regarding frequent item set mining techniques, they were initially used to discover customers' sales patterns among items purchased. In the last years these methods have been applied in biomedical research to discover relationships among symptoms, health conditions and diseases.<sup>10</sup> The present work demonstrates frequent item set mining applicability in drug utilisation studies, as it provides useful insight about treatment patterns in an efficient manner.

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## REFERENCES

- García González JM. Contributions of cardiovascular mortality to Spanish life expectancy from 1980 to 2009. *Rev Esp Cardiol* 2013;66:848–53.
- Sanfélix-Gimeno G, Peiró S, Librero J, et al. Grupo IUM-SNS. [Population analysis by area of health of changes in consumption, price and expenditure of cardiovascular drugs in eight autonomous communities, Spain, 2005]. *Rev Esp Salud Publica* 2010;84:389–407.
- Informe de utilización de medicamentos U/HLP/ V1/17012014. *Utilización de medicamentos hipolipemiantes en España durante el periodo 2000-2012*. Madrid: Agencia Española de Medicamentos y Productos Sanitarios, 2014. (accessed April 2018).
- Greciano V, Macías Saint-Gerons D, González-Bermejo D, et al. Use of Antihypertensive Drugs in Spain: National Trends From 2000 to 2012. *Rev Esp Cardiol* 2015;68:899–903.
- Informe de utilización de medicamentos U/AN/V1/03092015. *Utilización de medicamentos antidiabéticos en España durante el periodo 2000-2014*. Madrid: Agencia Española de Medicamentos y Productos Sanitarios, 2014.
- Yusuf S, Attaran A, Bosch J, et al. Working Group on the Summit on Combination Therapy for CVD. Combination pharmacotherapy to prevent cardiovascular disease: present status and challenges. *Eur Heart J* 2014;35:353–64.
- Rottlaender D, Scherner M, Schneider T, et al. [Polypharmacy, compliance and non-prescription medication in patients with cardiovascular disease in Germany]. *Dtsch Med Wochenschr* 2007;132:139–44.
- Chao CT, Tsai HB, Wu CY, et al. Cumulative Cardiovascular Polypharmacy Is Associated With the Risk of Acute Kidney Injury in Elderly Patients. *Medicine* 2015;94:e1251.
- Volpe M, Chin D, Paneni F. The challenge of polypharmacy in cardiovascular medicine. *Fundam Clin Pharmacol* 2010;24:9–17.
- Yoo I, Alafairet P, Marinov M, et al. Data mining in healthcare and biomedicine: a survey of the literature. *J Med Syst* 2012;36:2431–48.
- Casasnovas JA, Alcaide V, Civeira F, et al. Aragon workers' health study—design and cohort description. *BMC Cardiovasc Disord* 2012;12:45.
- ATCC/DDD Index 2018. WHO collaborating Centre for Drug Statistics Methodology. [http://www.whocc.no/atc\\_ddd\\_index/](http://www.whocc.no/atc_ddd_index/) (accessed Feb 2018).
- Borgelt C. Frequent item set mining. *Wiley Interdisciplinary Reviews: Data Mining and Knowledge Discovery* 2012;2:437–56.
- Zaki MJ. Scalable algorithms for association mining. *IEEE Trans Knowl Data Eng* 2000;12:372–90.
- Mosca L. Sex, statins, and statistics. *Lancet* 2015;385:1368–9.
- Koopman C, Vaartjes I, Heintjes EM, et al. Persisting gender differences and attenuating age differences in cardiovascular drug use for prevention and treatment of coronary heart disease, 1998–2010. *Eur Heart J* 2013;34:3198–205.
- Driscoll A, Beauchamp A, Lyubomirsky G, et al. Suboptimal management of cardiovascular risk factors in coronary heart disease patients in primary care occurs particularly in women. *Intern Med J* 2011;41:730–6.
- Manteuffel M, Williams S, Chen W, et al. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. *J Womens Health* 2014;23:112–9.
- Sánchez DP, Guillén JJ, Torres AM, et al. [Analysis of medications dispensed to control the main cardiovascular risks in the Murcia Region: are there gender differences?]. *Aten Primaria* 2014;46:147–55.
- Sanfélix J, Palop V, Pereiró I, et al. Gender influence in the quantity of drugs used in primary care. *Gac Sanit* 2008;22:11–19.
- Catalán-Ramos A, Verdú JM, Grau M, et al. @GPC-ICS Group. Population prevalence and control of cardiovascular risk factors: what electronic medical records tell us. *Aten Primaria* 2014;46:15–24.
- Calderón-Larrañaga A, Gimeno-Feliu LA, González-Rubio F, et al. Polypharmacy patterns: unravelling systematic associations between prescribed medications. *PLoS One* 2013;8:e84967.
- Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf* 2014;13:57–65.
- Wenger NK, Doherty CL, Gurwitz JH, et al. Optimization of drug prescription and medication management in older adults with cardiovascular disease. *Drugs Aging* 2017;34:803–10.
- Warlé-van Herwaarden MF, Koffeman AR, Valkhoff VE, et al. Time-trends in the prescribing of gastroprotective agents to primary care patients initiating low-dose aspirin or non-steroidal anti-inflammatory drugs: a population-based cohort study. *Br J Clin Pharmacol* 2015;80:589–98.
- Groc B. Inhibidores de la bomba de protones: no son “protectores”, son fármacos [Internet]. Fundació Institut Català de Farmacologia. Universitat Autònoma de Barcelona. 2016:1–4 <https://ddd.uab.cat/record/86197>.
- Violán C, Foguet-Boreu Q, Roso-Llorach A, et al. Patrones de multimorbilidad en adultos jóvenes en Cataluña: un análisis de clústeres. *Atención Primaria* 2016;48:479–92.
- de Abajo FJ, Gil MJ, García Poza P, et al. Risk of nonfatal acute myocardial infarction associated with non-steroidal antiinflammatory drugs, non-narcotic analgesics and other drugs used in osteoarthritis: a nested case-control study. *Pharmacoepidemiol Drug Saf* 2014;23:1128–38.
- Adams RJ, Appleton SL, Gill TK, et al. Cause for concern in the use of non-steroidal anti-inflammatory medications in the community—a population-based study. *BMC Fam Pract* 2011;12:70.
- Lapi F, Azoulay L, Yin H, et al. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *BMJ* 2013;346:e8525.
- Hand DJ. Principles of data mining. *Drug Saf* 2007;30:621–2.