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Research Article

Keywords: cardiovascular diseases, public health practice, women's health, sex factors, comorbidity

Posted Date: August 27th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10391004/v1>

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Additional Declarations: No competing interests reported.

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Word count 5210.

Abstract (280 words)

Background

Emerging evidence suggests that psychosocial, autoimmune, and reproductive factors contribute substantially to cardiovascular vulnerability, yet these domains are rarely

integrated within population-based cardiovascular risk assessments. We aimed to identify sex-specific cardiovascular risk phenotypes combining traditional and non-traditional determinants and to evaluate factors associated with established CVD in women.

Methods

We conducted a population-based cross-sectional study using linked electronic health records from 138,507 adults aged 18–90 years residing in Catalonia, Spain. Sex differences in cardiovascular risk profiles were assessed using descriptive and comparative analyses. Latent cardiovascular risk phenotypes were identified through unsupervised Two-Step cluster analysis incorporating cardiometabolic, psychosocial, autoimmune, socioeconomic, and female-specific reproductive variables. Exploratory Factor analysis, multivariable logistic regression, variance inflation factors, and ROC curves were used to determine factors independently associated with established CVD among women.

Results

The study included 67,512 women (48.7%) and 70,995 men (51.3%). Five statistical cardiovascular risk phenotypes were identified: cardiometabolic, metabolic-inflammatory, psychosocial vulnerability, advanced multimorbidity, and autoimmune profiles. Women were overrepresented in psychosocial and metabolic-inflammatory phenotypes, while men predominated in the classical cardiometabolic phenotype. Among women, established CVD was independently associated with age (OR 1.07 per year; 95%CI 1.071–1.080), hypertension (OR 1.88; 95%CI 1.708–2.076), diabetes mellitus (OR 1.40; 95%CI 1.26–1.56), dyslipidaemia (OR 1.227; 95%CI 1.11–1.33), (OR 1.10 per unit; 95%CI 1.00–1.20), depression (OR 1.11; 95%CI 1.00–1.24), and multimorbidity burden (OR 1.92; 95%CI 1.84–2.00). Systemic lupus erythematosus showed particularly strong associations with CVD among younger women.

Conclusions

Women do not follow a single pathway to cardiovascular disease. Instead, cardiovascular vulnerability develops through distinct multidimensional life-course phenotypes that complement conventional risk factors. This approach may improve identification of vulnerable women and help reduce the burden of cardiovascular disease.

Keywords: cardiovascular diseases; public health practice; women's health; sex factors; comorbidity.

Background

Cardiovascular disease remains the leading cause of mortality worldwide and accounts for a substantial proportion of global morbidity. Despite decades of progress in prevention and

treatment, considerable heterogeneity persists in the distribution, determinants, and clinical manifestations of cardiovascular disease across populations.

Sex differences represent one of the most consistent and clinically relevant dimensions of cardiovascular risk [1] and growing evidence suggests that the impact of classical risk factors differs by sex [2-6] highlighting the need for sex-specific risk stratification strategies [7-10].

Beyond conventional cardiovascular risk factors, several female-specific and female-predominant risk factors have emerged as important contributors to cardiovascular disease [6]. These include reproductive factors, as well as chronic inflammatory and autoimmune conditions such as Systemic Lupus Erythematosus and Rheumatoid Arthritis [6,11]. In addition, psychosocial and gender-related determinants—including depression, perceived stress, socioeconomic disadvantage and care-giving burden—have gained increasing attention as contributors to cardiovascular risk [12-19]. These findings support a paradigm shift in cardiovascular epidemiology: cardiovascular risk does not arise from isolated factors but rather from complex constellations of biological, psychosocial and environmental determinants [20-21].

Despite growing recognition of these sex-specific cardiovascular determinants, several critical gaps remain. First, emerging domains of cardiovascular risk—such as autoimmune disease, psychosocial stress and sex-specific health factors—are rarely integrated simultaneously within large population datasets. Second, most studies evaluate risk factors using single-variable approaches, which may fail to capture how multiple determinants cluster within individuals. Third, few studies [12,13] have explored whether these determinants aggregate into distinct sex-specific risk phenotypes in real-world populations.

In this context, real-world healthcare databases provide a unique opportunity to investigate how traditional cardio-metabolic factors coexist with autoimmune,

reproductive, psychosocial, behavioural, and social determinants across the life course. We hypothesised that cardiovascular risk factors cluster into distinct sex-specific
125 multimorbidity phenotypes related to vulnerable population subgroups that remain insufficiently recognised by current cardiovascular risk prediction models. Accordingly, the aim of this study was to identify and characterise sex-specific life-course cardiovascular phenotypes using complementary multivariate statistical approaches in a large population-based cohort, with the ultimate goal of informing more personalised and equitable
130 cardiovascular prevention strategies.

Methods

The main goal was to identify sex-specific cardiovascular risk phenotypes by integrating traditional and emerging determinants in a large cohort from the general population. As secondary goals: a/ quantify prevalence differences; b/ assess association with established
135 CVD in women.

1. Study Design

A retrospective, population-based, observational cross-sectional study (period: 01/01/2025 – 30/06/2025) was conducted using routinely collected electronic clinical health records from the Terres de l'Ebre healthcare region (**Additional file 1. Terres de**
140 **l'Ebre healthcare region. Catalonia, Spain**). The hypothesis were:

1. There are sex-specific cardiovascular patterns, reflecting differences in risk profiles.
2. Integration of emerging risk domains—including psychosocial stressors, autoimmune conditions and sex-specific [6] factors—would reveal previously
145 unrecognized cardiovascular risk phenotypes within the population.

2. Study Setting

The study was carried out within the primary healthcare system of the Terres de l'Ebre region. This region has its own healthcare system, which is outlined in the Regional Health Plan 2021–2025 [22]. According to this plan, there are 178,112 people who use the healthcare services in this area (50.4% men vs 49.6% women). The region is made up of 52 municipalities with a population density of 54.5 inhabitants/km² vs 241.8/km² in Catalonia; a high ageing index: 177.6, higher than Catalonia (148.3) and Spain (118.4); and the lowest gross disposable household income per capita in Catalonia (index 77.4%). Healthcare provision is organised through 11 primary care teams managed by the Catalan Health Institute (CHI), a Govern agency. There is a main hospital, the University Hospital Verge de la Cinta, also managed by CIH. Almost all of the people (98.2%) who live there have a shared active electronic clinical record, allowing for the study of the health of the population as a whole.

3. Study Population

3.1. Reference Population: the target population includes women and men aged 18–90 years, residents of the Terres de l'Ebre healthcare region, with a digital health record available through the shared clinical history system (HC3) within the public primary care system.

Exclusion Criteria: incomplete or inaccessible records were excluded during data cleaning procedures.

3.2. Study Population: the main analytical focus was on women, comparing those with and without established cardiovascular disease.

Sample Size and Sampling Strategy

The study didn't need to figure out a specific number of people to include because it was looking at a whole population. So, every person who fit the criteria in the healthcare

registry was part of the study and no formal sample size calculation was performed. The researchers didn't leave anyone out, as long as they met the requirements.

4. Study Variables

4.1. Dependent Variables

175 The primary dependent variable was Global cardiovascular disease (CVD_1), defined as the presence of a composite cardiovascular endpoint including: *“Stroke, Ischaemic heart disease, Atrial fibrillation, Heart failure, chronic kidney disease, extra-cranial systemic embolic events, and cardiovascular death”*.

These interrelated diseases markedly reduce quality of life, with heart failure, chronic
180 kidney disease, and cardio-renal syndrome all linked to functional limitation, hospitalizations, and psychological distress. The research strongly supports viewing these conditions as a continuum requiring early detection and coordinated, interdisciplinary, and sex-informed management to reduce global burden and improve quality of life [23].

4.2. Independent Variables include both classical and emerging determinants:

- 185 1. Socio-demographic Variables: age, biological sex, educational level, migration status .
2. Socioeconomic Indicators: MEDEA deprivation index and Territorial socioeconomic index (TSI) [24] .
3. Classical clinical cardiovascular risk factors recorded in electronic health records (EHR): hypertension, diabetes mellitus / pre-diabetes, dyslipidemia, obesity, smoking status,
190 alcohol consumption, physical activity and dietary patterns.
4. Risk Scores: SCORE cardiovascular risk estimation, Barthel Index, and Pfeiffer cognitive score.
5. Multimorbidity Assessment: Adjusted Morbidity Groups (AMG) stratifying patients into 5 levels of complexity [25] .

195 6. Emerging and Sex-Specific Risk Factors: pregnancy-related complications, premature menopause, hormone replacement therapy, breast cancer treatments, polycystic ovary syndrome, endometriosis, depression and psychopharmacological use, autoimmune inflammatory diseases (rheumatoid arthritis, systemic lupus, and autoimmune thyroid diseases), and sex-based violence register.

200 5. *Data Sources and Data Collection*

Clinical data were extracted from EHD of the SAP Terres de l'Ebre region. Main sources include HC3; Hospital discharge registry (CMBD-HA) using ICD-10 coding; Regional Health Plan Terres de l'Ebre 2021–2025 [22]; Socioeconomic databases (TSI, MEDEA); Catalan Institute of Statistics (IdesCAT). All datasets will be provided in a pseudo-anonymised and encrypted format.

6. *Statistical Analysis Plan*

6.1. The baseline characteristics were summarised using frequencies and percentages for categorical variables, means and standard deviations for continuous variables, and medians and interquartile ranges for non-normally distributed variables. Comparisons between women with and without cardiovascular disease were conducted using Chi-square tests for categorical variables, Student's t-test or Mann–Whitney U test for continuous variables. Normality was assessed with the Shapiro–Wilk test.

6.2. To identify (“*which patient profiles exist?*”) latent cardiovascular risk phenotypes, an unsupervised cluster analysis was conducted using the Two-Step Cluster procedure implemented in IBM SPSS Statistics version 21.0. This analysis included traditional cardiovascular risk factors, psychosocial determinants, autoimmune conditions, and selected female-specific variables. The variables entered in the model were age, sex, body mass index, hypertension, diabetes mellitus, dyslipidemia, smoking status, alcohol use, chronic kidney disease, depression, anxiety, use of long-term psychotropic (≥ 3 months)

220 medication, hypothyroidism, hyperthyroidism, rheumatoid arthritis, systemic lupus erythematosus, anti-phospholipid syndrome, Sjogren syndrome, caregiver burden, gender-based violence, socioeconomic deprivation indicators, and female-specific reproductive factors including early menopause, gestational diabetes, high-risk pregnancy, endometriosis, polycystic ovary syndrome, hormone replacement therapy, and breast
225 cancer history. Established cardiovascular disease variables were excluded from the cluster generation process and used for post hoc characterization of the identified phenotypes.

Data preprocessing

Continuous variables were examined for normality and standardized using z-score transformation prior to clustering. Binary and categorical variables were retained in their
230 original categorical format. Variables with extremely low prevalence ($<0.1\%$) were reviewed to assess their contribution to cluster differentiation.

Missing data

Missing values were handled according to the SPSS Two-Step Cluster procedures. Whenever possible, cases with missing information in the clustering variables were
235 retained using the algorithm's likelihood-based approach to handle missing values. For continuous variables with limited missing data, median imputation was applied prior to analysis. Variables with excessive missingness ($>20\%$) were excluded from the clustering process.

Determination of the optimal number of clusters

240 The optimal number of clusters was determined automatically using the Two-Step Cluster algorithm, based on Schwarz's Bayesian Information Criterion (BIC). Various solutions with different numbers of clusters were compared by examining changes in BIC values and the ratio of distance measures between the clusters. The final selection of the cluster solution also considered clinical interpretability and epidemiological plausibility.

245 *Internal validation*

The quality of the clusters was evaluated using the silhouette measure, which assesses cohesion and separation generated by the SPSS Two-Step procedure. According to established criteria, silhouette values >0.20 indicate a fair cluster structure, while values >0.50 indicate good cluster separation. In this analysis, the five-cluster solution
250 produced a silhouette coefficient of 0.32, indicating a fair-to-good quality of the clusters.

Cluster characterization

After generating clusters, the prevalence of cardiovascular risk factors, psychosocial variables, autoimmune diseases, and female-specific determinants was calculated for each cluster. These clusters were then labeled based on their most prominent clinical
255 characteristics, resulting in the identification of five phenotypes: cardio-metabolic, psychosocial, inflammatory-autoimmune, thrombotic, and advanced multimorbidity phenotypes.

Sensitivity and stability analyses

To assess the robustness, clustering analyses were repeated by randomly splitting the
260 dataset into derivation (70%) and validation (30%) samples. The overall cluster structure and phenotype characteristics were compared across samples. Additionally, alternative cluster solutions with four and six clusters were explored, which produced similar overarching patterns but reduced clinical interpretability, supporting selection of the five-cluster model.

265 6.3. To explore the underlying construct validity and reduce the dimensionality of the collected cardiovascular risk factors among the female cohort (*“Which variables cluster together”*), an Exploratory Factor Analysis (EFA) was performed. Given the clinical nature of the variables, Principal Axis Factoring was chosen as the extraction method to identify latent dimensions based on shared variance. To achieve a simpler, more interpretable
270 structure while maintaining orthogonal independence between dimensions, a Varimax rotation with Kaiser Normalization was applied. The Factor retention and item assignment

of items were guided by eigenvalues greater than 1.0 and a minimum factor loading threshold of 0.40.

6.4. A multivariable logistic regression model was developed to identify independent
275 factors associated with cardiovascular disease in women (*“Which variables independently predict CVD?”*). Variables with $p < 0.10$ in the univariate analysis, together with clinically relevant covariates, were included in the model. Adjusted odds ratios (ORs) with 95% confidence intervals were estimated. Sequential models were fitted with progressive adjustment for age, traditional cardiovascular risk factors, and emerging female-specific
280 determinants. The dependent variable in the analysis was CVD_1. The independent variables included age, hypertension, diabetes mellitus, dyslipidemia, reproductive factors, autoimmune conditions, and psychosocial factors. Adjustment was performed for classical confounders such as age, hypertension, dyslipidemia, diabetes (HbA1c or treatment), body mass index (BMI), and smoking status. The sex-specific factors included early menopause,
285 polycystic ovary syndrome, endometriosis, gestational diabetes, and high-risk pregnancy. Autoimmune conditions examined included hypothyroidism, lupus, anti-phospholipid syndrome, rheumatoid arthritis, and Sjogren’s syndrome. Psychosocial factors encompassed depression, anxiety, psychotropic medication use, gender-based violence, and comorbidity burden as assessed by the Adjusted Morbidity Groups (AMG) index. To
290 address potential multicollinearity, the variance inflation factors (VIFs) for the included variables was examined.

6.5. A model’s performance was evaluated using the area under the ROC curve (*“Which variables best discriminate CVD?”*). This analysis focused on comparing the relative discriminatory abilities of individual factors rather than developing a clinical prediction
295 model.

7. Ethical Considerations

Ethical approval was obtained from the Jordi Gol I Gurina Ethics Committee (code 24/187-P, date: 12/02/2025), and all procedures comply with European and national data protection regulations. The study utilised anonymised, encrypted secondary
300 healthcare data; therefore, individual informed consent was not required. As a result, no formal exclusion criteria related to participant consent were applicable. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. This study is reported in accordance with the STROBE guidelines for observational studies and SAGER
305 for sex and gender equity in research. The completed cross-sectional STROBE checklist is available as **Additional file 2**.

During the preparation of this study, the authors used AI (chat.openai.com, version GPT-5.3) for language editing. However, the AI did not contribute to the study design, data collection, data analysis, interpretation of results, or the generation of scientific content.
310 All intellectual content, scientific conclusions, and final decisions regarding the manuscript were made by the authors, who reviewed and approved all text prior to submission.

Results

1. Baseline characteristics and sex-specific cardiovascular profiles

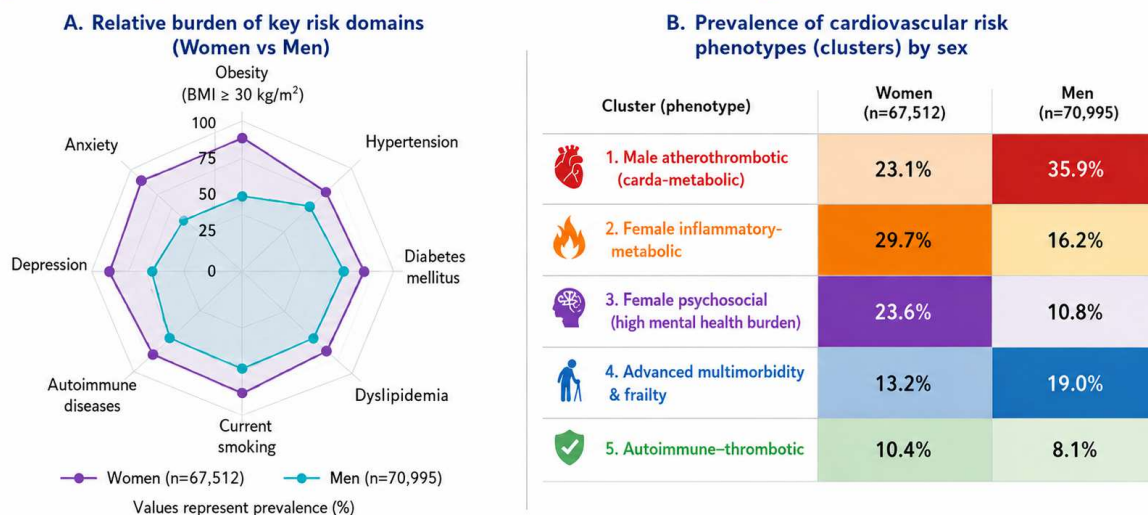
This large cohort (N = 138,507) consists of 67,512 women (48.7%) and 70,995 men (51.3%),
315 highlighting significant sex-based differences across various clinical dimensions and risk factors. Women were older than men, with average ages of 52.86 years compared to 50.59 years ($p < 0.001$). Additionally, women experienced a greater burden of functional dependence, cognitive impairment, and autoimmune diseases. Conversely, men had a higher prevalence of established cardiovascular disease, such as ischaemic heart disease,
320 heart failure, and overall CVD (**Tables 1 and 2**). However, women exhibited a more complex cardiovascular risk profile that included a combination of cardio-metabolic, reproductive, psychosocial, autoimmune, behavioural, and multimorbidity-related factors.

These findings support the existence of significant differences in cardiovascular vulnerability and support the need for further analysis to identify specific phenotypes.

Table 1. Baseline Cardiovascular Profiles: Women vs. Men

Unsupervised cluster analysis identified five distinct statistical cardiovascular phenotypes (**Figure 1**) across the study population. The largest phenotype, representing 35.9% of population, displayed a classical cardio-metabolic profile characterised by hypertension, diabetes, dyslipidemia, obesity, and chronic kidney disease; and it was predominantly observed in men. In contrast, the metabolic-inflammatory (29.7%) and psychosocial vulnerability (23.6%) phenotypes were more frequent among women. The Phenotype 4 is distinguished by the coexistence of a significant burden of multimorbidity, featuring distinct patterns of cardio-metabolic, cardiovascular, autoimmune, endocrine, and mental health conditions. Phenotype 5, the least prevalent, is characterised by autoimmune disorders, suggesting a potential immune-mediated pathway contributing to cardiovascular vulnerability. Overall, the clustering analysis revealed that cardiovascular risk factors tend to aggregate into clinically meaningful multidimensional phenotypes rather than occurring as isolated conditions.

Figure 1. Sex-specific cardiovascular risk architecture integrating traditional and non-traditional



Higher values indicate greater prevalence in each sex.

CVD: cardiovascular (ischemic heart disease, stroke, heart failure, atrial fibrillation and chronic kidney disease).

2. Identification of life-course cardiovascular phenotypes in women

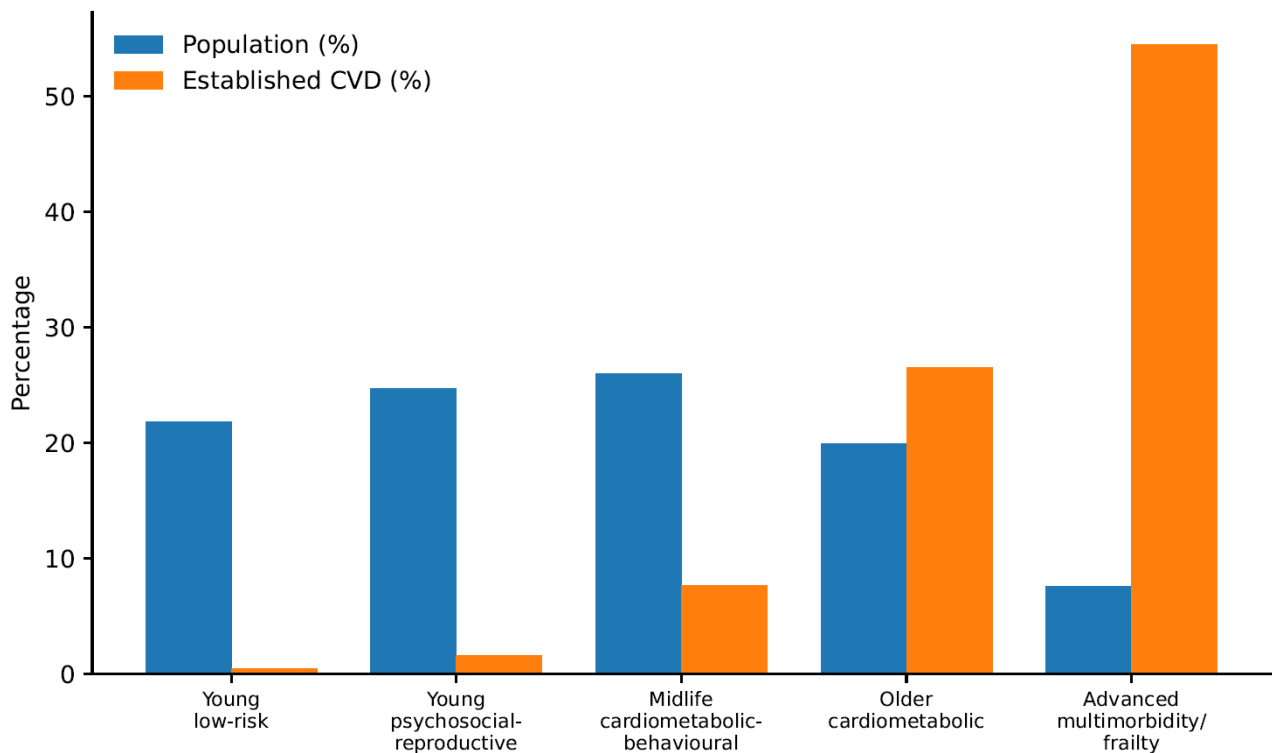
In the Exploratory Factor Analysis (**Additional file 3**), the principal axis factoring analysis with Varimax rotation successfully converged in 13 iterations, pointing out that cardiovascular risk in women is multidimensional and revealing at least five well-differentiated areas to consider based on the loading threshold (≥ 0.40): Factor 1 (Endocrine-Reproductive Risk): Polycystic Ovary Syndrome (0.921) and Early Menopause (0.919); Factor 2 (Neuropsychiatric and Psychopharmacological Load): the number of prescribed psychotropic medications (0.728) alongside a formal Depression Diagnosis (0.487); Factor 3 (Age-Related Metabolic Risk): Linked advancing chronological Age (0.544) with Dyslipidemia (0.509); Factor 4 (Systemic Comorbidity and Renal Impairment): Grouped Adjusted Morbidity Groups (GMA) (0.444) with Chronic Kidney Disease (0.440); Factor 5 (Classic Cardio-metabolic/Anthropometric Risk): comprising Body Mass Index (0.445) and Hypertension Diagnosis (0.431). Additionally, there was a secondary cross-loading for Age was noted on Factor 6 (0.424), while active smoking behaviour (*Current Smoker*) loaded independently onto Factor 8 (0.423). Conversely, distinct conditions—including Anxiety Diagnosis, Diabetes (both type 2 and gestational),

Breast Cancer, and systemic autoimmune pathologies (SLE, Sjogren, and APS)—did not show significant factor loadings in this extraction model.

360 Unsupervised multivariate analysis revealed five different life-course cardiovascular phenotypes (**Figure 2**), each characterized by a specific combination of cardio-metabolic, psychosocial, reproductive, autoimmune, behavioral, and multimorbidity-related determinants. The Midlife cardio-metabolic-behavioral phenotype was the most prevalent, accounting for 26.0% of the study population. This was followed by the Young psychosocial-reproductive (24.7%) and the Young low-risk (21.8%) phenotypes. In contrast, the Advanced multimorbidity/frailty phenotype was the least frequent, representing only 7.6% of participants. The prevalence of established CVD increased markedly across the phenotypes, rising from 0.5% in the *Young low-risk* phenotype to 54.5% in the *Advanced multimorbidity* phenotype, showing that the burden of established CVD is

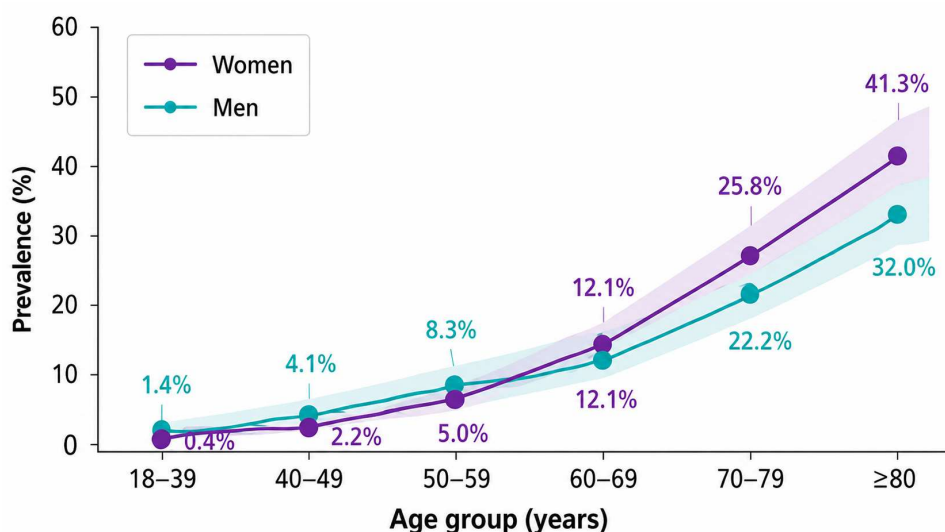
370 primarily concentrated among women with advanced multimorbidity.

Figure 2. Prevalence of cardiovascular disease across phenotypes.



375 Overall, the prevalence of CVD among women increased substantially after the age of 60 years (**Figure 3**).

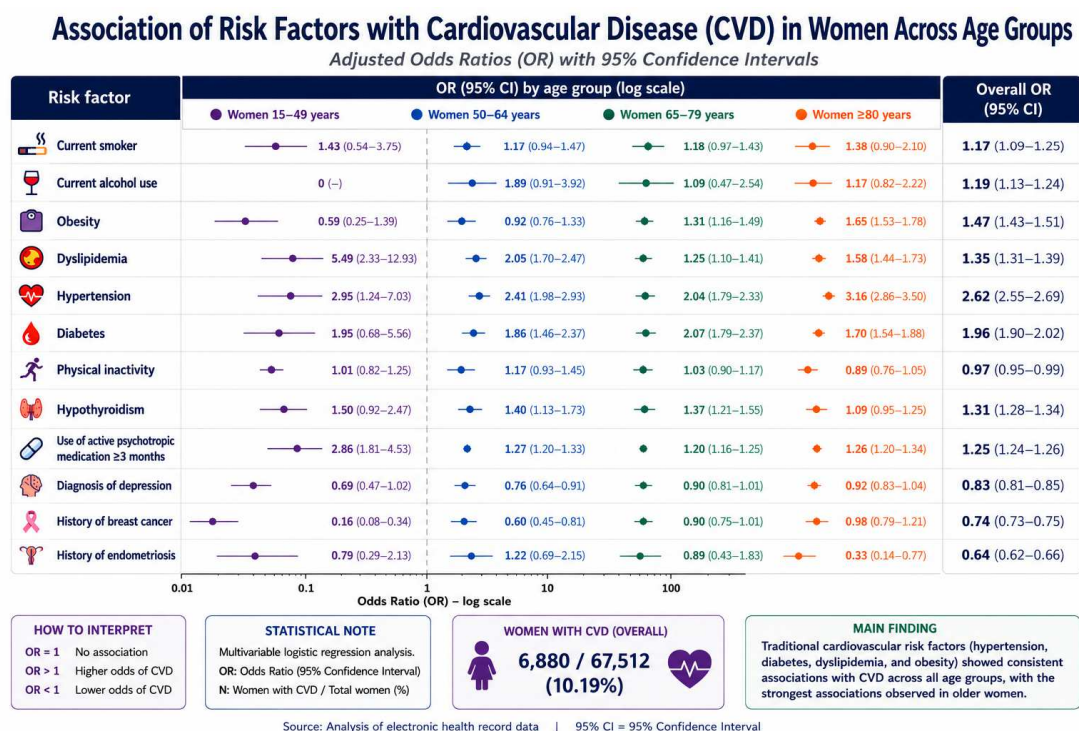
Figure 3. Cardiovascular disease prevalence across age-groups in women



The relationship between cardiovascular risk factors and CVD displayed a clear age-
 380 dependent pattern, with differences in their magnitude and relevance across different age groups (**Figure 4**). Traditional cardiovascular risk factors (hypertension, diabetes, dyslipidemia, and obesity) showed consistent associations with CVD across all age groups, with the strongest associations observed in older women. Hypertension was the most relevant predictor across all age groups, with the highest association found among women
 385 aged ≥ 80 years (OR 3.16, 95%CI 2.86–3.50). Diabetes mellitus also was associated with increased cardiovascular risk in all age categories, especially among women aged 65–79 years (OR 2.07, 95%CI 1.79–2.37). Obesity was linked to CVD (OR 1.31 CI95% 1.16–1.49) from 65 years onwards. Dyslipidemia showed a strong association with CVD, particularly among women aged 15–49 years (OR 5.49, CI95% 2.33–12.93), and this association
 390 remained significant with increasing age. The long-term use of psychotropic medication (≥ 3 months) was independently associated with an increased cardiovascular risk across all age groups, with the strongest association among women aged 15–49 years (OR 2.86, CI95%

1.81–4.53). Finally, systemic lupus erythematosus was associated with elevated cardiovascular risk, particularly among women aged 15–49 years (OR 18.67, CI95% 8.65–40.30), and remained significantly associated across all age groups.

Figure 4. Association of Risk Factors with CVD in Women across Age Groups



3. Emergent cardiovascular factors among women vs men with CVD.

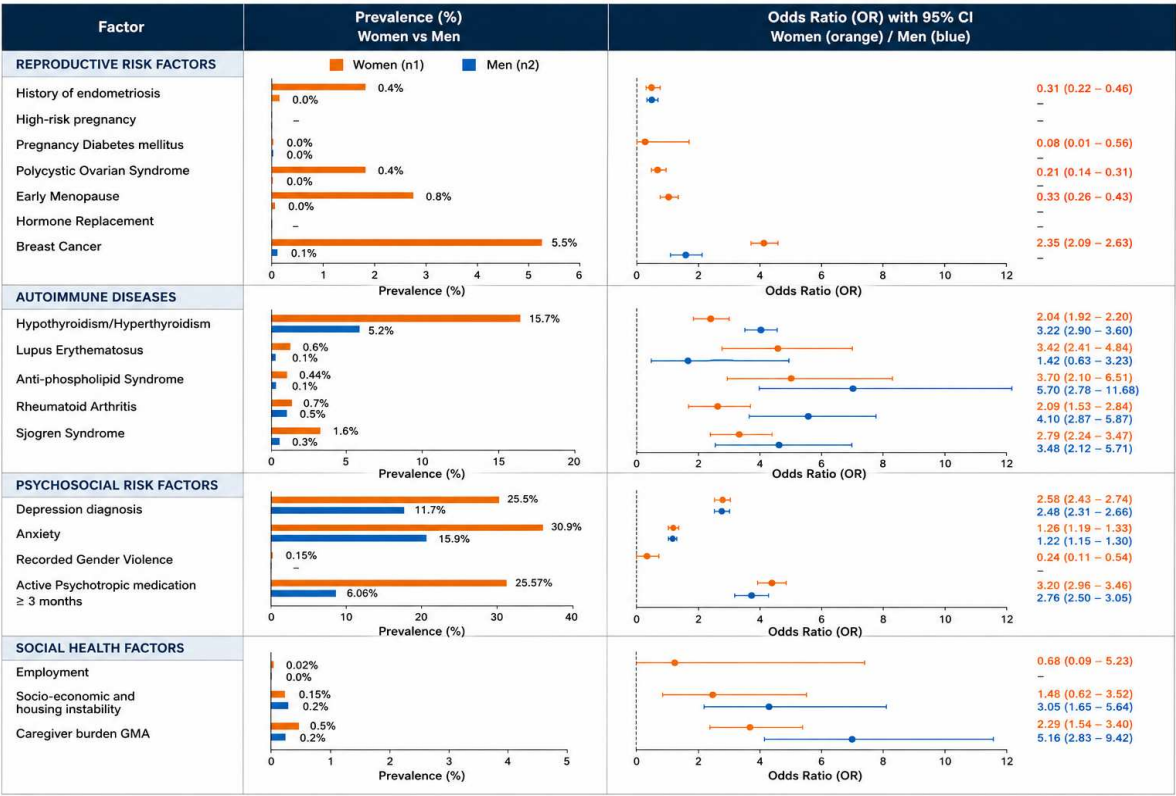
Among the reproductive risk factors assessed (Table 2), breast cancer showed the highest prevalence (2.8%) and had the strongest association with the outcome of interest (OR 2.35, 95%CI 2.09–2.63). In the category of autoimmune diseases, the prevalence of most evaluated conditions was significantly higher in women compared to men ($p < 0.001$). Similarly, rates of psychosocial risk factors were also significantly higher in women: depression diagnosis (25.5% vs. 11.7%), anxiety diagnosis (30.9% vs. 15.9%), and long-term psychotropic medication use (25.5% vs. 6.0%) compared with men ($p < 0.001$). Documented instances of gender-based violence were recorded exclusively among women.

Furthermore, socioeconomic factors and care-giving burdens also differed between sexes
 410 and were associated with significant odds ratios.

Table 2. Emerging cardiovascular risk factors in women with cardiovascular disease.

The **Figure 5** shows a sex-specific pattern: the same emerging risk domains contributed
 substantially to cardiovascular risk in both sexes, although the relative strength of some
 415 associations differed.

Figure 5. Emerging cardiovascular risk factors prevalence and OR (CI95%) in women and men with cardiovascular disease.



4. Logistic regression results: cardiovascular factors among women with CVD.

420 The multivariable logistic regression (**Table 3**) identified several independent factors associated with established CVD among women after adjustment for potential confounders. Age remained as the strongest non-modifiable determinant, with a 7% increase in the odds of CVD for each additional year of life (OR 1.07; 95%CI 1.071–1.080). Among traditional cardiovascular risk factors, hypertension showed the largest independent effect (OR 1.88;

425 95%CI 1.708–2.076), followed by diabetes mellitus (OR 1.40; 95%CI 1.263–1.559). In addition, a greater burden of multimorbidity emerged as a major contributor (OR 1.92; 95%CI 1.849–2.002), suggesting that cardiovascular vulnerability in women is closely linked to a broader context of accumulated chronic illnesses. Depression also retained an independent association after adjustment (OR 1.119; 95%CI 1.008–1.241). Finally, 430 systemic lupus erythematosus was identified as the greatest contributor ((OR 2.92; 95%CI 1.549–5.508).

Table 3. Multivariate analysis results in women with CVD

Domain/Variable	Adjusted OR (95% CI)	P value
Demographic		
Age (per year)	1.076 (1.071–1.080)	<0.001
Adjusted Morbidity Groups (AMG)	1.924 (1.849–2.002)	<0.001
Cardio-metabolic		
Hypertension	1.883 (1.708–2.076)	<0.001
Diabetes	1.403 (1.263–1.559)	<0.001
Current smoker	1.326 (1.154–1.523)	<0.001
Dyslipidemia	1.221 (1.116–1.335)	<0.001
Obesity	1.100 (1.005–1.205)	0.039
Psychosocial		
Depression	1.119 (1.008–1.241)	0.035
Autoimmune		
Systemic lupus erythematosus	2.921 (1.549–5.508)	<0.001

The highest VIFs were observed for age (5.28) and AMG (4.84) [**Additional file 4. Variance inflation factors (VIFs)**]. All other predictors had VIFs below 2.0. These findings indicate a moderate correlation between AMG and age/co-morbidity-related variables. However, there is no evidence of severe multicollinearity since none of the VIFs exceed the conventional thresholds (VIF >10)

Table 4 shows the ROC analysis and AUC evaluation for individual cardiovascular risk predictors in women with established cardiovascular disease.

Table 4. Area under the ROC curve (CI95%).

Independents CVD risk	AUC	p	CI95%
Age	0.864	< 0.001	0.858-0.870
Morbidity burden (AMG)	0.802	< 0.001	0.795-0.810
Hypertension	0.749	< 0.001	0.739-0.758
Dyslipidemia	0.678	< 0.001	0.668-0.688
Diabetes	0.616	< 0.001	0.605-0.627
Depression	0.565	< 0.001	0.554-0.575
Obesity	0.554	< 0.001	0.545-0.566

Discussion

Cardiovascular risk in women may be categorized into multidimensional life-course phenotypes that combine traditional cardio-metabolic factors with psychosocial, reproductive, autoimmune and multimorbidity-related determinants. By identifying vulnerable subgroups that are not adequately represented in conventional cardiovascular risk models, these phenotypes may help support more equitable public health strategies

450 Several key findings have emerged.. First, while traditional cardio-metabolic risk factors remain the principal determinants of established CVD, women's cardiovascular vulnerability is organized into distinct life-course phenotypes characterized by specific combinations of cardio-metabolic, psychosocial, reproductive, autoimmune, behavioral, and multimorbidity-related factors. Second, multimorbidity emerged as one of the
455 strongest correlates of established CVD, highlighting the importance of considering the cumulative burden of chronic conditions rather than isolated diseases. Finally, the convergence of exploratory factor analysis, unsupervised clustering, multivariable regression, and ROC analyses supports a multidimensional framework of cardiovascular risk in women. This framework extends beyond conventional biomedical models and
460 emphasizes the need for a life-course perspective in cardiovascular prevention (**1–6**).

Traditional cardiovascular risk factors, particularly hypertension, diabetes, dyslipidemia, obesity, and aging, remained the dominant determinants of established CVD in both women and men. These findings align with current evidence indicating that conventional cardio-metabolic risk factors continue to account for a significant proportion of
465 cardiovascular events, even as awareness of sex-specific determinants increases (**1–10**). However, these classical risk factors do not occur in isolation; they often coexist with reproductive, psychosocial, inflammatory, and multimorbidity-related conditions that shape distinct cardiovascular phenotypes throughout a woman's life. Rather than replacing traditional risk factors, these additional determinants appear to modify the context in
470 which cardiovascular risk develops and accumulates.

The inclusion of atrial fibrillation and chronic kidney disease within the composite cardiovascular outcome deserves particular consideration. Although these conditions have traditionally been viewed as co-morbidities or intermediate disease states rather than classical cardiovascular outcomes, growing evidence recognizes their central role within
475 the cardio-renal continuum and their strong association with major adverse cardiovascular events (**26,27**). From a population health perspective, incorporating these conditions

provides a broader representation of cardiovascular burden as encountered in routine clinical practice.

By using four complementary statistical methods, we got a deeper understanding of the
480 patterns and risk factors associated with CVD (**28,29**). Exploratory factor analysis identified latent dimensions underlying the observed variables, whereas unsupervised clustering revealed latent dimensions underlying the observed variables, while unsupervised clustering illustrated how these dimensions coexist within individuals, thereby defining clinically meaningful cardiovascular phenotypes. Multivariable logistic
485 regression assessed the independent associations between individual risk factors and established CVD, and ROC analyses measured their discriminatory performance. Rather than yielding discrepant findings, these statistical approaches converged towards a unified conceptual model (**Additional file 5. Statistical Approaches**). Throughout all analyses, the cardio-metabolic-aging axis consistently emerged as the primary dimension
490 of cardiovascular risk, characterized by hypertension, diabetes, dyslipidemia, obesity, and increasing age. In contrast, reproductive, psychosocial, and autoimmune determinants clustered within relatively independent domains, suggesting that cardiovascular vulnerability in women reflects multiple interacting biological and social pathways rather than a single dominant mechanism. Nevertheless, external validation in independent
495 populations remains necessary before the model can be generalized beyond similar healthcare settings.

This multidimensional architecture is particularly relevant from a sex-specific perspective. Men typically display a more homogeneous cardiovascular profile, which is largely influenced by behavioral and cardio-metabolic risk factors. In contrast, women show
500 greater heterogeneity, with cardiovascular risk distributed across several partially independent domains. The recognition of different phenotypes related to reproductive, psychosocial, autoimmune, and multimorbidity-related phenotypes supports the understanding that sex differences in CVD should be viewed as differences in the

organization of cardiovascular risk rather than simply differences in the prevalence or
505 severity of individual risk factors (**1–10**). Consequently, women may reach similar
cardiovascular outcomes through distinct trajectories that evolve throughout the life
course, reinforcing the importance of sex-sensitive approaches to cardiovascular
prevention and risk stratification (**30,31,32**).

Reproductive and endocrine factors emerged as an independent latent construct, distinct
510 from traditional cardio-metabolic determinants. This observation aligns with growing
evidence that reproductive events— such as premature menopause and polycystic ovary
syndrome—should be considered long-term markers of cardiovascular susceptibility
instead of isolated clinical conditions (**3,4,11**). Similarly, autoimmune diseases,
particularly systemic lupus erythematosus, displayed strong associations with established
515 CVD prior to adjustments. However, their independent contribution significantly
diminished after considering factors such as age, multimorbidity, and conventional
cardiovascular risk factors. Overall, these findings underscore the importance of
considering reproductive and endocrine factors, along with autoimmune diseases, when
assessing a person's risk for CVD. By taking a more comprehensive approach, healthcare
520 providers can better understand the complex relationships between these factors and CVD
and develop more effective prevention and treatment strategies (**33**).

Psychosocial disorders were substantially more common in women and clustered within
specific female phenotypes. Although depression had an independent association with
established CVD after multivariable adjustment, its effect size was considerably smaller
525 than those observed for age, multimorbidity, hypertension, or diabetes. This pattern
suggests that psychosocial conditions may function as markers of broader systemic
vulnerabilities by interacting with behavioral, metabolic, inflammatory, and healthcare-
related pathways rather than representing isolated cardiovascular risk factors. These
findings are consistent with recent evidence that emphasizes the complex and bidirectional

relationships between psychological health and cardiovascular disease, particularly in women (34).

Life-course cardiovascular phenotypes and public health implications

The life-course phenotypes identified in this study provide further insight into how cardiovascular vulnerability evolves across women's lives. Rather than representing discrete age categories, these phenotypes appear to reflect the progressive accumulation and interaction of biological, behavioral, psychosocial, reproductive, and multimorbidity-related determinants. The gradual increase in established CVD prevalence across phenotypes—from the Young low-risk group to the Advanced multimorbidity/frailty phenotype—supports the concept that cardiovascular disease develops through cumulative exposure to multiple interacting risk domains rather than through isolated cardio-metabolic abnormalities.

More than half of the women in the study who had existing heart disease also faced a complex combination of multiple health conditions, despite representing a small part of the group. This finding highlights the importance of multimorbidity as a marker of accumulated biological vulnerability and reinforces the increasing recognition of the interactions between cardiovascular, kidney and metabolic health as key factors of cardiovascular outcomes in aging populations (35,36). From a public health perspective, strategies targeting multimorbidity may therefore provide greater benefit than approaches focused exclusively on individual diseases.

Conversely, younger phenotypes were characterized by a greater contribution of reproductive, psychosocial, autoimmune, and behavioral determinants despite a relatively low prevalence of established CVD. These findings suggest that cardiovascular vulnerability may begin considerably earlier than the onset of overt clinical disease and that important opportunities for prevention exist well before women meet conventional thresholds for cardiovascular risk assessment. Similar observations have been reported in studies showing that cardiovascular risk trajectories differ substantially between women

and men throughout adult life and that young women frequently accumulate emerging metabolic and psychosocial risk factors long before cardiovascular events occur (37–41).

Our results also reinforce the importance of considering psychosocial determinants within cardiovascular prevention strategies. Anxiety, depression, chronic psychotropic treatment, and other indicators of psychosocial vulnerability were concentrated within specific female phenotypes, supporting evidence that psychological health interacts closely with cardio-metabolic and behavioral factors across the life course. Because the relationship between mental health and CVD is bidirectional, these conditions should not necessarily be interpreted as direct causal determinants of cardiovascular disease. Instead, they may identify women experiencing broader patterns of social, behavioral, and biological vulnerability that are not adequately captured by conventional cardiovascular risk models (42,43).

These observations have important implications for population-based prevention efforts. Current cardiovascular risk prediction models primarily focus on age and conventional cardio-metabolic risk factors, which may lead to an underestimation of cardiovascular vulnerability in women. This is particularly relevant for women whose risk are influenced by reproductive history, psychosocial adversity, autoimmune disorders, or progressive multimorbidity. Rather than replacing established prediction tools, integrating these multidimensional phenotypes could enhance existing approaches by facilitating earlier identification of women following different cardiovascular trajectories throughout the life course (44,45).

From a public health perspective, our findings support a shift from a disease-centered model towards a person-centered approach that integrates biological, psychological, and social determinants of health. Such an approach aligns with contemporary recommendations advocating sex-sensitive cardiovascular prevention and may contribute to reducing persistent inequalities in cardiovascular outcomes by enabling more equitable allocation of preventive interventions (6,10). Although prospective validation is required

before implementation, phenotype-based stratification could help identify vulnerable
585 subgroups that would otherwise remain undetected using conventional risk assessment
alone.

Strengths and limitations

The principal strength of this study lies in its population-based design, including a large
and representative cohort derived from routine clinical practice with near-complete
590 healthcare coverage. The availability of linked electronic health records enabled
simultaneous evaluation of conventional cardiovascular risk factors together with a broad
range of sex-specific, psychosocial, reproductive, autoimmune, socioeconomic, behavioral,
and multimorbidity-related determinants. Furthermore, the combined application of
exploratory factor analysis, unsupervised clustering, multivariable regression, and ROC
595 analysis provided complementary perspectives that strengthened the interpretation of the
observed cardiovascular phenotypes. Although the study included virtually the entire
population receiving primary healthcare within the region, the unique demographic profile
of the territory—characterized by a low population density, dispersed municipalities, and
an aging population—may limit the external validity of the findings. However, these
600 characteristics are representative of many rural and aging European regions, supporting
the relevance of the results for similar healthcare settings.

Several limitations should also be acknowledged. First, the cross-sectional design
precludes causal inference or temporal assessment of the observed associations. Second,
diagnoses were obtained from routinely collected electronic health records and may
605 therefore be subject to under-recording or misclassification. Third, confounding
unmeasured lifestyle characteristics, biomarkers, or other clinical variables cannot be
excluded. Fourth, although multicollinearity analyses indicated acceptable model stability,
partial overlap between multimorbidity measures and individual cardiovascular risk
factors may have resulted in a degree of over-adjustment. Lastly, when it comes to the link
610 between mental health disorders and cardiovascular disease, we need to be careful how we

interpret the findings, since it's possible that the relationship goes both ways, or that there are other factors involved that we're not accounting for (46).

Conclusions

Women do not follow a single pathway towards cardiovascular disease. Instead,
615 cardiovascular vulnerability is organized into distinct multidimensional life-course
phenotypes integrating cardio-metabolic, reproductive, psychosocial, autoimmune,
behavioral, and multimorbidity-related determinants. These phenotypes complement
conventional cardiovascular risk factors and provide a broader framework for
understanding sex-specific cardiovascular risk from a population health perspective.
620 Future longitudinal studies should determine whether incorporating phenotype-based
approaches into cardiovascular risk prediction improves early identification of vulnerable
women and supports more effective and equitable prevention strategies across the life
course.

List of abbreviations

625 CHI: Catalan Health Institute is the largest public health service company in Spain and is
affiliated to the Department of Health of the Generalitat de Catalunya. It is made up of
eight hospitals and about 300 primary care teams, and provides healthcare to almost six
million users, a figure that represents 75% of the total number of people with healthcare
rights in Catalonia.

630 CMBD-HA: data provided by general acute care hospitals, including inpatient admissions,
major ambulatory surgery, home hospitalization, and day hospital services.

CVD: Cardiovascular Disease.

AMG: the Adjusted Morbidity Groups is a new morbidity measurement developed and
adapted to the Spanish healthcare System. It enables the population to be classified into 6
635 morbidity groups, and in turn divided into 5 levels of complexity, along with one healthy
population group. Consequently, the population is divided into 31 mutually exclusive
categories.

HC3: is a centralized electronic medical records infrastructure used across the Catalan public healthcare network.

640 MEDEA deprivation index: is a composite socioeconomic indicator used to measure relative deprivation in small geographical areas, primarily within urban environments in Spain. It links census data to health outcomes to analyze socioeconomic inequalities and mortality patterns.

TSI: the Territorial Socioeconomic Index is a synthetic index for small geographic areas
645 that summarizes multiple socioeconomic characteristics of the population into a single value. The index combines information on employment status, educational attainment, immigration, and income for all individuals residing in each territorial unit, based on six sector-specific indicators.

Declarations

650 *Ethics approval and Consent to participate:*

Ethical approval was obtained from the Jordi Gol I Gurina Ethics Committee (code 24/187-P, date: 12/02/2025), and all procedures comply with European and national data protection regulations. The study utilised anonymised, encrypted secondary healthcare data; therefore, individual informed consent was not required. As a result, no
655 formal exclusion criteria related to participant consent were applicable. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Human Ethics and Consent to Participate declarations: not applicable

Clinical Trial number: not applicable

660 *Availability of data and materials*

The datasets generated and/or analyzed during the current study are available from the Catalan Institute Health (sensitive data) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Data are however available from the corresponding author on reasonable request and with
665 permission from Catalan Institute Health.

Competing interests: the authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This work was supported by Rovira I Virgili University (URV) and received a pre-doctoral
670 grant (File number: PREDOC_ECO-24/11 and funding code: 7Z25/024-1) within the framework of the “Public Call for the Pursuit of a Doctorate by Healthcare Professionals in the Primary Care Setting of the ICS,” issued by IDIAP Jordi Gol in collaboration with the Catalan Health Institute.

Authors’ contributions

675 APT (Anna Panisello-Tafalla) conceived the study as part of her doctoral research project, contributed to study design, data acquisition, data analysis, interpretation of findings, and drafted the manuscript. JLCE (Josep Ll. Clua-Espuny) and SRV (Silvia Reverte-Villarroya), as doctoral supervisors, contributed to the conception and methodological development of the study, supervised the research process, participated in the interpretation of results,
680 critically revised the manuscript for important intellectual content, and provided overall scientific oversight. JLN (Josep Lucas-Noll), EMS (Eulàlia Muria-Subirats), JCQ (Jordi Clua-Queralt), and ETP (Esther Torrubia-Pérez) contributed to study design, interpretation of data, and critical revision of the manuscript. All authors reviewed, revised, and approved the final version of the manuscript and agree to be accountable for all
685 aspects of the work.

Acknowledgements

The “GECA-TE project (Gender Perspective in Cardiovascular Diseases in the Terres de l’Ebre Region)” is led by the Ebrictus research group (<https://idiapjgol.org/es/grup-recerca/ebrictus/>, URL accessed on 23/june/2026), a consolidated group accredited by the
690 Agency for Management of University and Research Grants (AGAUR;

<https://agaur.gencat.cat/en/lagaur/> accessed on 20/June/2026), in collaboration with the Department of Computer Engineering and Mathematics at Universitat Rovira i Virgili (<https://www.deim.urv.cat/en/> accessed on 20/June/2026) and the Càtedra d’Innovació i Simulació en Salut de les Terres de l’Ebre <https://www.ciste.cat/> accessed on 23/June/2026). We are grateful to the clinical and administrative staff of the participating centers and the Information and Communication Technology Department (Jesus Carot-Domenech).

Authors’ information

This article forms part of the PhD programme of Anna Panisello-Tafalla at the Universitat Rovira i Virgili. Anna Panisello-Tafalla (PhD student), Josep Ll. Clua-Espuny, and Silvia Reverté-Villarroya (doctoral supervisors and senior authors) act as guarantors of the study. They accept full responsibility for the integrity of the work, had access to the data, and controlled the decision to publish. You can add information (<https://idiapjgol.org/en/grup-recerca/ebrictus/>).

The Ebrictus group is accredited by AGAUR as a consolidated group. Among the activities carried out to achieve its objectives are: 1/ To increase the knowledge of the state of population health in Terres de l’Ebre. 2/ To increase the knowledge of cerebrovascular disease, its epidemiology and prevention: the increase in the incidence of stroke due to the aging of the population (epidemiological and demographic context; new cardiovascular technology in its treatment (care context), its consequences in the form of residual disability, dependence in the ABVD and the need for care (socio-health context; and the associated direct and indirect costs (cost-effectiveness context).

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740 the Council on Clinical Cardiology and Stroke Council; Council on Basic Cardiovascular Sciences; Council on Cardiovascular and Stroke Nursing; Council on Lifelong Congenital Heart Disease and Heart Health in the Young; and Council on Peripheral Vascular Disease. Forecasting the Burden of Cardiovascular Disease and Stroke in Women in the

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Table 1. Basal cardiovascular characteristics: women vs men

	All (N)	x±sd (%)	Women (n ₁)	x±sd (%)	Men (n ₂)	x±sd (%)	p
Age	138,507	51.7±18.33	67,512	52.86±18.45	70,995	50.6±18.14	< 0.001
Obesity	15,847	26.8%	8,953	28.9%	6,534	24.4%	< 0.001
IMC	57,749	27.20±4.84	31,019	27.34±6.1	26,730	27.02±5.53	< 0.001
HTA	33,058	23.9%	15,953	23.6%	17,105	24.4%	0.043
SBP	55,759	124.86±16.01	28,832	122.61±17.24	26,922	127.27±14.2	< 0.001
DBP	55,750	76.04±11.66	28,828	75.48±12.70	26,922	76.63±10.40	<0.001
Dyslipidaemia	31,601	22.8%	16,000	23.7%	17,105	24.4%	< 0.001
Total cholesterol	88,600	192.95±41.52	48,868	198.7±39.93	39,732	185.90±42.34	< 0.001
HDL-c	78,330	54.61±14.8	42,774	59.10±14.81	35,556	49.21±12.84	< 0.001
TG	82,046	123.53±85.85	44,906	114.70±68.57	37,140	134.20±101.93	<0.001
LDL-C	76,922	114.81±35.65	42,271	118.13±34.48	34,657	110.77±36.62	< 0.001
Diabetes	13,426	9.7%	5,647	8.4%	7,779	11%	< 0.001
HbA1c	13,397	6.72±1.78	5,632	6.70±1.72	7,765	6.73±1.83	0.270
Current smoker	17,991	13%	7,331	10.9%	10,660	15%	< 0.001
Current alcohol use	2,017	1.5%	360	0.5%	1,657	2.3%	< 0.001
REGICOR score	54,685	4.33±4.03	28,732	3.12±3.12	25,953	5.66±4.48	< 0.001
Cardiovascular disease	9,979	7.2%	3,828	5.7%	6,151	8.7%	< 0.001
Heart Failure							
Ischaemic Heart Disease	4,116	3.0%	1,696	2.5%	2,420	3.4%	<0.001
Ischaemic Stroke	4,062	2.9%	1,188	1.8%	2,874	4.0%	< 0.001
Peripheral Artery Disease	2,396	1.7%	1,074	1.5%	1,382	1.9%	< 0.001
Atrial Fibrillation	1,404	1.0%	478	0.7%	926	1.3%	< 0.001
	4,691	3.4%	1,952	2.9%	2,739	3.9%	< 0.001
CHADsVA(S)	2,023	3.03±1.51	858	3.58±1.4	1,165	2.62±1.46	< 0.001
Chronic Kidney Disease	6,998	5.1%	3,279	4.9%	3,719	5.2%	< 0.001
e-GFR	93,485	91.21±21.44	50,305	92.48±21.40	43,180	89.73±21.34	< 0.001

Cognitive Impairment	1,764	1.3%	1,102	1.6%	662	0.9%	< 0.001
Pfeiffer score	6,133	2.71±3.06	3,436	3.06±3.12	2,697	2.27±2.92	< 0.001
Barthel score	5,399	69.9±29.94	2,952	66.9±30.0	2,447	73.42±29.47	< 0.001
AMG	134,175	2.21±1.23	65,828	2.31±1.24	68,347	2.12±1.21	< 0.001
PCC	4,494	3.2%	2,428	3.6%	2,066	2.9%	< 0.001
MACA	598	0.4%	279	0.4%	319	0.4%	0.306
Exitus	1,432	1.0%	562	0.8%	870	1.2%	< 0.001

Table 2. Sex-specific and emerging cardiovascular risk-factors in women/men with Cardiovascular disease.

	All (N %) Women	Women (n ₁) With CVD	Women OR (CI95%)	All Men	Men (n ₂) With CVD	Men OR (CI95%)
Reproductive risk factors	67,512	6,822		70,995	9,457	
History of endometriosis	812 (1.3%)	28 (0.4%)	0.31 (0.22-0.46)	-	-	-
High-risk pregnancy	196 (0.3%)	-	-	-	-	-
Pregnancy Diabetes mellitus	114 (0.6%)	1 (0.0%)	0.08 (0.01-0.56)	-	-	-
Polycystic Ovarian Syndrome	1,127 (1.7%)	26 (0.4%)	0.21 (0.14-0.31)	-	-	-
Early Menopause	1,586 (2.3%)	58 (0.8%)	0.33 (0.26-0.43)	-	-	-
Hormone Replacement	8 (0.1%)	-	-	-	-	-
Breast Cancer	1,864 (2.8%)	379 (5.5%)	2.35 (2.09-2.63)	-	-	-
Autoimmune Diseases						
Hypothyroidism/Hyperthyroidism	6,225 (9.22%)	1,082 (15.7%)	2.04 (1.90-2.20)	1,538 (2.2%)	497 (5.2%)	3.22 (2.9-3.60)
Lupus Erythematosus	159 (0.2%)	44 (0.6%)	3.42 (2.41-4.84)	39 (0.1%)	7 (0.1%)	1.42 (0.63-3.23)
Anti-phospholipid Syndrome	58 (0.1%)	17 (0.44%)	3.70 (2.10-6.51)	30 (0.0%)	14 (0.1%)	5.70 (2.78-11.68)
Rheumatoid Arthritis	264 (0.4%)	50 (0.7%)	2.09 (1.53-2.84)	127 (2.06%)	49 (0.5%)	4.10 (2.87-5.87)
Sjogren Syndrome	452 (0.7%)	107 (1.6%)	2.79 (2.24-3.47)	69 (1.12%)	24 (0.3%)	3.48 (2.12-5.71)
Psychosocial Risk Factors						
Depression diagnosis	8,924 (13.2%)	1,754 (25.5%)	2.58 (2.43-2.74)	4,239 (6%)	1,109 (11.7%)	2.48 (2.31-2.66)
Anxiety	18,169 (26.9%)	2,127 (30.9%)	1.26 (1.19-1.33)	9,720 (13.7%)	1,499 (15.9%)	1.22 (1.15-1.30)
Recorded Gender Violence	226 (0.33%)	6 (0.15%)	0.24 (0.11-0.54)	-	-	-
Active Psychotropic medication ≥ 3 months	3,997 (5.9%)	979 (25.57%)	3.20 (2.96-3.46)	1,981 (2.8%)	574 (6.06%)	2.76 (2.50-3.05)
Social Health Factors						
Employment	14 (0.02%)	1 (0.02%)	0.68 (0.09-5.23)	12 (0.0%)	-	-
Socio-economic and housing						

instability	42 (0.06%)	6 (0.15%)	1.48 (0.62-3.52)	47 (0.1%)	15 (0.2%)	3.05 (1.65-5.64)
Caregiver burden GMA	152 (0.2%)	31 (0.5%)	2.29 (1.54-3.4)	43 (0.1%)	19 (0.2%)	5.16 (2.83-9.42)

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