Received: 21 November 2025 | Accepted: 12 January 2026

DOI: 10.1111/eci.70179

ORIGINAL ARTICLE

WILEY

Increased levels of serum surfactant protein D are associated with cardiovascular disease incidence in the Spanish adult population: Di@bet.es study

Wasima Oualla-Bachiri[1,2,3] | **Ana Lago-Sampedro**[1,2,3] | **Eva García-Escobar**[1,2] | **Cristina Maldonado-Araque**[1,2] | **Elías Delgado**[4,5] | **Felipe J. Chaves**[1,6] | **Luis Castaño**[1,7] | **Alfonso Calle-Pascual**[1,8] | **Josep Franch-Nadal**[1,9] | **Gabriel Olveira**[1,2,3] | **Gemma Rojo-Martínez**[1,2] | **Viyey Doulatram-Gamgaram**[1,2] | **Sergio Valdés**[1,2]

[1]Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III, Madrid, Spain

[2]Servicio de Endocrinología y Nutrición, Hospital Regional Universitario de Málaga, IBIMA Plataforma BIONAND, Málaga, Spain

[3]Facultad de Medicina, Universidad de Málaga, Andalucía Tech, Campus de Teatinos s/n, Málaga, Spain

[4]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto De Salud Carlos III, Madrid, Spain

[5]Department of Endocrinology and Nutrition, Central University Hospital of Asturias, Health Research Institute of the Principality of Asturias (ISPA), University of Oviedo, Oviedo, Spain

[6]Genomic and Genetic Diagnosis Unit, INCLIVA Biomedical Research Institute, Valencia, Spain

[7]Cruces University Hospital, Bio-Bizkaia, Department of Pediatrics, University of the Basque Country (UPV/EHU), European Reference Network on Rare Endocrine Conditions (Endo-ERN), Barakaldo, Spain

[8]Department of Endocrinology and Nutrition, San Carlos University Hospital of Madrid, Madrid, Spain

[9]EAP Raval Sud, Catalan Institute of Health, GEDAPS Network, Primary Care, Research Support Unit (IDIAP-Jordi Gol Foundation, Barcelona, Spain

Correspondence
Wasima Oualla-Bachiri, Plaza del Hospital Civil s/n. Pabellón 5 sótano. 29009, Málaga, Spain.
Email: wasimaouallabachiri@gmail.com, wasimaouallabachiri@uma.es

Eva García-Escobar, Plaza del Hospital Civil s/n. Pabellón 5 sótano. 29009, Málaga, Spain.
Email: eyring@gmail.com, eva.garcia@ciberdem.org

Funding information
Consejería de Salud y Consumo, Junta

Abstract

Aims: Cardiovascular disease (CVD) remains the leading cause of mortality. New biomarkers are needed to improve CVD risk prediction. Several studies have reported associations between surfactant protein D (SP-D), an innate immune system component, and CVD; however, general population studies remain scarce. The main aim of this study was to investigate the association between SP-D and CVD events incidence in the Spanish general adult population.

Methods: Socio-demographic, lifestyle (including smoking status) and clinical data from 1707 participants of the di@bet.es cohort without previous CVD events were collected and analysed. CVD events (including both morbidity and

Wasima Oualla-Bachiri and Ana Lago-Sampedro contributed equally to this study.

Viyey Doulatram-Gamgaram and Sergio Valdés contributed equally to this work and are both senior researchers.

de Andalucía, Grant/Award Number: C-0060-2012; Instituto de Salud Carlos III, Grant/Award Number: FI21/0040, PI17/02136, PI20/01322, PI23/00347 and MV23/00104

mortality) were reported at baseline and after 7.5 years of follow-up. SP-D serum levels were measured by ELISA and categorized in quartiles.

Results: SP-D categories are associated with CVD events incidence, independently from other strong risk factors such as cardiovascular risk scores (SCORE2 and SCORE2-OP), BMI, hs-CRP, or eGFR. Although SP-D has been linked to smoking, SP-D categories predicted CVD events incidence even among non-smokers. The addition of SP-D to multivariate models improved performance in the assessment, predicting 83% of the events with a specificity of 74% and a sensitivity of 84% in the overall population.

Conclusions: SP-D may be considered as a promising biomarker of CVD events in combination with other well established factors in clinical practice.

KEYWORDS

biomarkers, cardiovascular diseases, heart disease risk factors, incidence, pulmonary surfactant-associated protein D, smoking

1 | INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide. More than half a billion people are affected by cardiovascular diseases, which accounted for 20.5 million deaths in 2021.[1] Projections for the period 2025–2050,[2] suggest that the prevalence will likely continue to be unchanged, atherosclerosis being the major cause of CVD.

In this context, several approaches have been considered to predict and estimate the cardiovascular risk. Cardiovascular risk scores – such as the Framingham Risk Score[3] or the Systematic Coronary Risk Evaluation (SCORE2 and its variants)[4] – are essential tools widely used in clinical practice to estimate 10-year cardiovascular disease risk. Recent advances have enabled the development of polygenic risk scores.[5] and Artificial Intelligence (AI) has shown potential to accelerate CVD diagnosis.[6]

Also, biomarkers play a crucial role in the early detection and risk stratification of CVD. Classical biomarkers for atherosclerotic cardiovascular risk include total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. High sensitivity C reactive protein (hs-CRP) has been widely considered in the context of CVD due to its implications in vascular inflammation.[7] Lower estimated glomerular filtration rates (eGFR) have also been associated with CVD mortality.[8]

Detecting new biomarkers for predicting CVD remains necessary to reduce disease prevalence and consequently, mortality. Surfactant protein D (SP-D), a component of the innate immune system secreted as part of pulmonary surfactant, has attracted attention in CVD. The sources of circulating SP-D have not yet been fully elucidated. Although SP-D migrates from the alveolar tissue to the bloodstream after lung damage, evidence shows that SP-D is also expressed in vascular tissue and influences vascular inflammation.[9] From a clinical perspective, elevated circulating SP-D levels have been consistently associated with a higher risk of CVD and death.[10]

We hypothesized that increased serum SP-D levels are related to an atherosclerotic environment that leads to higher CVD events incidence. The aim of this work was to assess whether SP-D could be used as a predictive biomarker of CVD events in the spanish adult general population.

Key Messages

Surfactant protein D (SP-D), an innate immune system component, is associated with cardiovascular disease (CVD) events incidence in Spanish adult general population

- Higher SP-D categories were linked to a greater risk of developing CVD, even among non-smokers, despite the increase in SP-D levels having been traditionally related to smoking.
- The addition of SP-D categories to well-known risk factors for CVD such as SCORE2 risk score, BMI, hs-CRP, and eGFR improved accuracy of risk prediction models, highlighting its potential value as a biomarker for CVD.

2 | METHODS

2.1 | Study population

The study population was based on Di@bet.es study. Detailed information and participant flow chart have been previously described.[11,12] Briefly, Di@bet.es study was a cohort study conducted between 2008 and 2010, with a re-evaluation between 2016 and 2017 (average follow-up time of 7.5 ± 0.6 years). The primary goal of this study was to assess the prevalence and incidence of T2DM in Spain. Participants older than 18 years were selected using a cluster sampling design from the National Health System registries. Exclusion criteria included institutionalized subjects, pregnancy or nursing, serious disease or surgery that prevented them from participating in the study or not signing the informed consent. Di@bet.es baseline sample resulted in 5072 individuals and a total of 2408 subjects participated in the follow-up. For our sub-study, only followed-up participants with no CVD events at baseline, no missing data on serum SP-D levels and tobacco use were selected, resulting in a final population of 1707 followed-up participants at risk of CVD.

Written informed consent was obtained from all the participants. The study was approved by the Ethics and Clinical Investigation Committee of the Hospital Regional Universitario de Malaga (Malaga, Spain) in addition to other regional ethics and clinical investigation committees all over Spain. The research was carried out in accordance with the Declaration of Helsinki of the World Medical Association.

2.2 | Variables and procedures

Clinical, lifestyle and sociodemographic data were collected through an interviewer-administered structured questionnaire. Phisical examinations, followed by blood sample collection, were performed. Blood samples, obtained under overnight fasting conditions, were centrifuged and serum was frozen at −80°C until analysis. Serum SP-D levels were measured by ELISA (Human SP-D ELISA Kit EH3809; FineTest, Biolake (China)). Serum samples were diluted 1:2. The assay had a sensitivity of 0.938 ng/mL, and a range of 1.563–100 ng/mL. Values outside this range were excluded.

The following variables were considered for this study: age, sex, weight, height, fasting plasma glucose, cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, systolic and diastolic blood pressure, creatinine and hs-CRP. Sex was defined as men/women (self-reported in the questionnaire). BMI was calculated as weight/height^2 (kg/m^2). Insulin resistance was estimated by the homeostasis model assessment (HOMA)[13]; estimated GFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[14] Regarding exposure variables, smoking status was defined as current smokers versus former/never been smokers. Presence of type 2 diabetes (T2D) at baseline was defined as patients requiring oral antidiabetic drugs/insulin therapy and diagnosed prior to admission. Pulmonary diseases recorded included chronic obstructive pulmonary disease (COPD), asthma and bronchitis and were self-reported. Cardiovascular disease events at baseline included non-fatal cardiovascular events before the recruitment such as coronary artery disease (CAD), cerebrovascular disease or peripheral artery disease (PAD) and were self-reported in a questionnaire. Cardiovascular Risk Score (classified as low, moderate and high risk) was calculated using the *RiskScorecvd* package in Rstudio, applying SCORE2 (general) and SCORE2-OP (for older population) algorithms according to the European Cardiovascular Guidelines 2021.[4] Data regarding age, sex, smoking status, systolic blood pressure, total cholesterol, HDL-cholesterol and diabetes were used for the calculation. CVD events at follow-up included non-fatal and fatal cardiovascular events to assess the incidence of both CVD morbidity and mortality, respectively. Non-fatal cardiovascular events were collected at follow-up with a self-reported questionnaire and included CAD, cerebrovascular disease and PAD. Fatal cardiovascular events were collected through a query to the National Institute of Statistics (INE) with a censoring date of December 2016.

2.3 | Statistical analysis

Descriptive results are expressed as median (interquartile range) or N (percentage of subjects). Normal distribution of the variables was evaluated with Lilliefors test, Q-Q plots and histograms. Non-normal variables were normalized with the *Bestnormalize* package. Homogeneity of the variances was tested with Levene's test. Adjusted ANOVA or χ^2-square Pearson test were performed to assess the differences between variables. Incident CVD events were evaluated by using generalized regression models adjusted for potential confounders. The ability of SP-D to predict the risk of CVD events was evaluated through using receiver operating characteristic (ROC) curve analysis. Area Under the Curve (AUC), specificity and sensitivity of the models were calculated with the *pROC* package. Differences between the AUC of models were studied by using DeLong test. The predictive accuracy of the model was determined by calculating the Integrated Discrimination Improvement (IDI) and the continuous Net Reclassification Improvement (NRI). Post-hoc analysis for statistical power was performed

TABLE 1 Baseline characteristics of the study population at risk of CVD regarding SP-D categories.

Variable	SP-D Q_1 ($n=457$)	SP-D Q_2 ($n=449$)	SP-D Q_3 ($n=407$)	SP-D Q_4 ($n=394$)	*p*
Age, years	48.00 (38.00–59.00)	48.00 (38.00–61.00)	50.00 (40.00–62.00)	52.00 (41.00–64.00)	**<0.001**
Sex					**<0.001**
Men	152 (33.3%)	185 (41.2%)	186 (45.7%)	182 (46.2%)	
Women	305 (66.7%)	264 (58.8%)	221 (54.3%)	212 (53.8%)	
BMI, kg/m^2	27.45 (24.61–30.44)	27.18 (24.25–30.75)	27.43 (24.60–31.01)	27.80 (24.91–30.55)	0.73
Glycemia, mg/dL	92.52 (84.42–101.16)	93.78 (86.04–102.42)	94.14 (86.04–104.13)	94.32 (86.67–104.04)	**0.03**
HOMA index	1.68 (1.19–2.57)	1.79 (1.18–2.71)	1.77 (1.20–2.72)	1.76 (1.20–2.51)	0.27
Cholesterol, mg/dL	197.22 (169.76–226.99)	196.06 (170.92–221.19)	197.41 (173.63–224.28)	202.24 (175.37–227.38)	0.59
LDL, mg/dL	104.22 (85.07–127.22)	104.02 (84.69–123.36)	106.54 (85.85–125.29)	110.60 (87.39–131.48)	0.31
HDL, mg/dL	52.98 (45.24–60.32)	51.04 (44.08–59.55)	51.43 (43.89–60.71)	50.66 (42.15–58.00)	**<0.01**
Triglycerides, mg/dL	99.20 (70.86–139.06)	100.97 (74.40–143.49)	99.20 (75.73–133.75)	108.06 (78.39–148.80)	**<0.01**
Systolic Blood Pressure, mmHg	125.50 (113.33–140.00)	130.00 (116.50–141.00)	130.00 (117.00–145.67)	130.00 (119.00–145.50)	**<0.001**
Diastolic Blood Pressure, mmHg	74.50 (69.00–82.33)	76.50 (70.00–83.50)	77.00 (71.00–83.50)	77.50 (70.00–85.00)	**<0.01**
hs-CRP, mg/mL	1.59 (0.71–3.44)	1.72 (0.83–3.25)	1.44 (0.67–3.29)	1.78 (0.94–3.61)	0.15
eGFR, $ml/min/1.73\,m^2$	102.17 (94.06–111.81)	101.15 (91.46–110.94)	99.21 (89.82–109.73)	98.21 (87.43–110.01)	**<0.001**
Smoking habit	60 (13.1%)	100 (22.3%)	97 (23.8%)	151 (38.3%)	**<0.001**
SCORE2 CVD risk score					**<0.001**
Low risk	319 (72.3%)	280 (64.5%)	242 (61.1%)	189 (49.2%)	
Moderate risk	96 (21.8%)	116 (26.7%)	106 (26.8%)	127 (33.1%)	
High risk	26 (5.9%)	38 (8.8%)	48 (12.1%)	68 (17.7%)	
Baseline T2DM	38 (8.3%)	50 (11.1%)	54 (13.3%)	60 (15.2%)	**0.01**
Pulmonary diseases	20 (4.38%)	28 (6.27%)	32 (7.86%)	26 (6.60%)	0.19
Incident CVD event	13 (2.84%)	22 (4.90%)	32 (7.86%)	41 (10.41%)	**<0.001**

Note: Differences across SP-D categories were measured by ANOVA adjusted by age, sex and/or BMI as appropriate, or chi-square test. SCORE2 algorithm estimates 10-year cardiovascular risk and incorporates age, sex, smoking status, systolic blood pressure, total cholesterol, HDL-cholesterol and diabetes.

with WebPower package. Multicollinearity was assessed by using correlation matrices, Variance Inflation Factor (VIF) and Tolerance (TOL) values. All statistical analysis were performed by using R Statistical Software (version 4.3.3) for Windows.

3 | RESULTS

3.1 | Baseline characteristics of the population at risk of CVD according to SP-D categories

Study sample included 1707 individuals with a mean age of 50 years (age range 18–89 years), of whom 58.7% were women. SP-D quartiles were calculated and used to define the categories Q1 to Q4 (Q1: 1.69–6.92 ng/mL, $n=457$; Q2: 6.92–9.60 ng/mL, $n=449$; Q3: 9.60–13.92 ng/mL, $n=407$; Q4: 13.92–95.86 ng/mL, $n=394$).

Differences in baseline characteristics of the subjects at risk of CVD according to the SP-D categories are presented in Table 1. Those subjects in the higher SP-D category presented higher median age, triglycerides levels, systolic and diastolic blood pressure values. There were differences in the fasting plasma glucose levels across categories. HDL-cholesterol levels significantly decreased across SP-D categories, as well as estimated GFR. There were statistically significant differences in sex distribution across categories. The percentage of smokers was higher in the highest SP-D category and increased across SP-D categories (Q1: 13.1%,

TABLE 2 Likelihood of incident CVD after 7.5 years across SP-D categories regarding smoking status.

	Overall Population (*N* = 1707,108 CVD events)		Non-smokers (*N* = 1299, 91 CVD events)		Smokers (*N* = 408, 17 CVD events)	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Model 1						
SP-D Q_2 versus Q_1	1.26 (0.60–2.64)	0.55	1.41 (0.64–3.09)	0.39	1.00 (0.09–11.29)	0.99
SP-D Q_3 versus Q_1	2.10 (1.05–4.21)	0.04	2.51 (1.21–5.21)	0.01	1.26 (0.11–14.08)	0.85
SP-D Q_4 versus Q_1	2.35 (1.20–4.61)	0.01	3.07 (1.48–6.35)	< 0.01	2.18 (0.24–20.06)	0.49
SCORE2						
Moder. versus low	3.99 (2.21–7.19)	< 0.001	4.68 (2.51–8.73)	< 0.001	4.81 (0.54–42.68)	0.15
High versus low	17.73 (9.94–31.65)	< 0.001	19.11 (10.29–35.50)	< 0.001	27.38 (3.28–228.95)	< 0.01
BMI	1.06 (1.02–1.11)	< 0.01	1.04 (0.99–1.09)	0.11	1.13 (1.02–1.26)	0.02
Model 2						
SP-D Q_2 versus Q_1	1.29 (0.61–2.73)	0.50	1.44 (0.65–3.17)	0.37	1.14 (0.10–13.21)	0.92
SP-D Q_3 versus Q_1	2.16 (1.08–4.35)	0.03	2.55 (1.23–5.31)	0.01	1.25 (0.11–14.20)	0.86
SP-D Q_4 versus Q_1	2.38 (1.20–4.69)	0.01	2.97 (1.43–6.19)	*p* < 0.01	2.22 (0.23–21.13)	0.49
SCORE2						
Moder. versus low	3.39 (1.87–6.14)	< 0.001	3.81 (2.00–7.23)	< 0.001	5.04 (0.56–45.01)	0.15
High versus low	11.27 (5.98–21.23)	< 0.001	12.10 (5.98–24.50)	< 0.001	31.35 (3.36–292.09)	< 0.01
BMI	1.06 (1.01–1.11)	< 0.01	1.04 (0.99–1.10)	0.13	1.15 (1.02–1.29)	0.02
hs-CRP	1.01 (0.97–1.04)	0.72	1.01 (0.98–1.04)	0.62	0.97 (0.87–1.08)	0.55
eGFR	0.98 (0.96–0.99)	< 0.01	0.98 (0.97–0.99)	0.02	1.01 (0.96–1.05)	0.78

Note: Model 1 was adjusted by SCORE2 and BMI. Model 2 was adjusted by SCORE2, BMI, hs-CRP and eGFR. SCORE2: Systematic Coronary Risk Estimation 2 (includes age, sex, smoking status, systolic blood pressure, total cholesterol, HDL-cholesterol and diabetes).

Q2: 22.3%, Q3: 23.8%, Q4: 38.3%). Baseline prevalence of T2D increased progressively across SP-D quartiles. In Q1, 8.3% of participants had T2D at baseline, compared with 11.1% in Q2, 13.3% in Q3, and 15.2% in Q4 ($p = 0.01$). SCORE2-based classification indicated that low CVD risk was more frequent in Q1, whereas moderate/high CVD risk was more common in Q4. No associations were found in our study population between SP-D categories and BMI, insulinoresistance, total cholesterol, LDL-cholesterol or hs-CRP levels. Interestingly, no significant differences were found between SP-D categories and the presence of pulmonary diseases in our study population. Otherwise, correlation analyses between SP-D and our study variables were conducted, with results available in Table S1.

3.2 | CVD incidence after 7.5 years according to SP-D categories

In our study population, 108 incident cases of CVD events were reported after follow-up. We identified 39 cases of coronary artery disease (36.11%), 28 cases of cerebrovascular disease (25.93%), 13 cases of peripheral artery disease (12.04%) and 33 deaths related to cardiovascular causes (30.55%). In addition, the proportions of participants who developed CVD events according to SP-D categories were studied. Among the subjects who developed CVD events, 13 (2.84%) had SP-D levels ranged in Q1, 22 (4.89%) in Q2, 32 (7.88%) in Q3, 41 (10.41%) in Q4, what reveals an increase in the incidence across categories ($p < 0.001$) (Table 1). This increase was maintained in the sex-stratified analyses for both sexes (men; $p = 0.01$, women; $p = 0.01$) (Table S2).

We evaluated the association between SP-D levels and CVD event likelihood (Table 2). Multivariate analyses showed that those subjects who were in higher SP-D category had a higher likelihood of developing CVD event after 7.5 years of follow-up. Particularly, when adjusting for SCORE2 and BMI (Model 1), those participants who had SP-D levels ranged in Q4 had 2.35-fold higher likelihood of developing CVD event than those who had SP-D levels ranged in Q1. When stratified analyses were performed regarding smoking status, non-smokers with SP-D levels ranged in Q4 had 3.07 times more likelihood of CVD event, while in smokers we did not detect a significant association, due to limited statistical power confirmed with post-hoc power analyses. In the fully adjusted model (Model 2, adjusted for SCORE2, BMI, hs-CRP and eGFR) the associations remained consistent: Q3 and Q4 were associated with

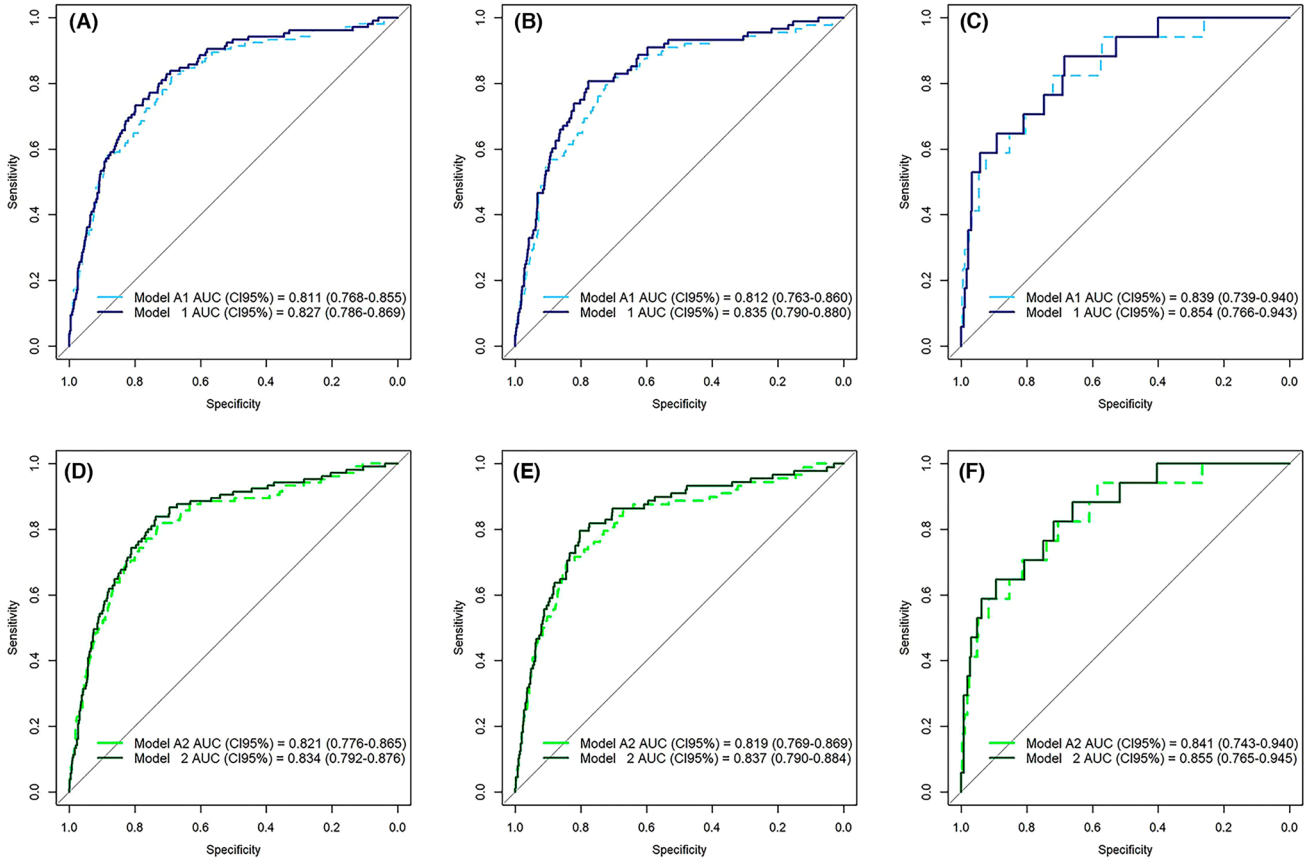

FIGURE 1 ROC curve for the predictive value of serum levels of SP-D in estimating CVD event incidence for Model A1 versus Model 1 in overall population (A), non-smokers (B), and smokers (C), and for Model A2 versus Model 2 in overall population (D), non-smokers (E), and smokers (F). In light blue, model A1: SCORE2 + BMI; in dark blue, model 1: SCORE2 + BMI + SP-D categories; in light green, model A2: SCORE2 + BMI + hs-CRP + eGFR; in dark green, model 2: SCORE2 + BMI + hs-CRP + eGFR + SP-D categories. CVD: Cardiovascular disease; SCORE2: Systematic Coronary Risk Estimation 2 (includes age, sex, smoking status, systolic blood pressure, total cholesterol, HDL-cholesterol and diabetes); hs-CRP: Ultrasensitive C Reactive Protein. eGFR: Estimated Glomerular Filtration Rate. AUC, Area Under the Curve; 95% CI, 95% Confidence Interval; ROC, Receiver Operating Characteristic.

ORs of 2.16 ($p=0.03$) and 2.38 ($p=0.01$), respectively, in overall population, and with ORs of 2.55 ($p=0.01$) and 2.97 ($p<0.01$) in non-smokers, with no detectable significant associations in smokers. Estimated GFR showed an inverse association with CVD risk in overall population (OR = 0.98; $p<0.01$) and in non-smokers (OR = 0.98; $p=0.02$), whereas hs-CRP was not significant in any subgroup. Likelihood of incident CVD regarding sex was reported in Table S3. Multicollinearity among independent variables was assessed using Variance Inflation Factor (VIF), Tolerance (Tol) values, and correlation matrixes, revealing no evidence of multicollinearity (all VIF<5, Tol>0.2 and $|r|<0.7$).

3.3 | Predictive value of SP-D on the risk of CVD incidence

We also aimed to assess whether incorporation of SP-D into logistic regression models containing established CVD-related variables could improve the prediction of cardiovascular events both in overall population and after stratification by smoking status. For that, two basic predictive models, were evaluated: Model A1, which included SCORE2 and BMI and Model A2, comprising SCORE2, BMI, hs-CRP, and estimated GFR. Extended models (Model 1 and Model 2) were constructed by adding SP-D categories to Model A1 and Model A2 respectively. AUC for these models and CI95% for each one are represented in Figure 1. Specificity and sensitivity of the models were calculated and shown in Table 3. The predictive value of the models was evaluated and results for the DeLong test, IDI and NRI are reported in Table 4.

In overall population, the inclusion of SP-D categories in the model comprising SCORE2 and BMI (Model 1 vs. Model A1) resulted in a modest increase in specificity (0.69 to 0.70) while maintaining sensitivity at 0.83. This was accompanied by a significant AUC improvement (from 0.811 to 0.827; DeLong $p=0.025$) and (continuous

TABLE 3 Comparison between predictive models for CVD incidence in overall population and across smoking categories.

	Overall population		Non-smokers		Smokers	
	Spec.	**Sens.**	**Spec.**	**Sens.**	**Spec.**	**Sens.**
Mod. A1 (SCORE2 + BMI)	0.69	0.83	0.73	0.80	0.72	0.82
Mod. 1 (SCORE2 + BMI + SP-D)	0.70	0.83	0.78	0.81	0.69	0.88
Mod. A2 (SCORE2 + BMI + hs-CRP + eGFR)	0.73	0.81	0.84	0.70	0.70	0.82
Mod. 2 (SCORE2 + BMI + hs-CRP + eGFR + SP-D)	0.74	0.84	0.80	0.80	0.66	0.88

Note: Area Under the Curve (AUC) was calculated from Receiver Operating Curve (ROC) and showed with 95% confidence interval. Specifity (Spec.) and Sensitivity (Sens.) Model A1: SCORE2 + BMI; Model 1: SCORE2 + BMI + SP-D categories; Model A2: SCORE2 + BMI + hs-CRP + eGFR, Model 2: SCORE2 + BMI + hs-CRP + eGFR+SP-D categories.

NRI = 0.459; 95%CI 0.266–0.652; $p < 0.001$), although the integrated discrimination index (IDI) was not statistically significant ($p = 0.105$). A similar pattern was observed when SP-D was added to the model that included SCORE2, BMI, hs-CRP and eGFR (Model 2 vs. Model A2), with specificity increasing from 0.73 to 0.74, sensitivity increasing from 0.81 to 0.84, significant AUC improvement (from 0.821 to 0.834; DeLong $p = 0.036$), and significant NRI (0.459; 95% CI 0.266–0.652; $p < 0.001$), but no significant IDI change ($p = 0.208$). The addition of SP-D suggest an improvement in the prediction; however, a higher sample size would be needed to assess the improvement of discrimination with certainty.

When analyses were stratified by smoking status, the improvement in the predictive value after the inclusion of SP-D in the models remained significant in non-smokers. Adding SP-D (Model 1 vs. Model A1) increased specificity from 0.73 to 0.78 and sensitivity from 0.80 to 0.81, with significant AUC gain (from 0.812 to 0.835; $p = 0.022$), significant IDI improvement (0.015; $p = 0.031$), and significative reclassification accuracy (continuous NRI = 0.519; 95% CI 0.310–0.725; $p < 0.001$). In the extended model for non-smokers, SP-D also improved AUC (from 0.819 to 0.837; $p = 0.022$) and NRI (0.519; 95% CI 0.310–0.725; $p < 0.001$), while IDI showed a non-significant trend ($p = 0.071$). No statistically significant improvements in the predictive value of the models were detected among smokers, also attributable to limited statistical power in this subgroup.

4 | DISCUSSION

Despite ongoing efforts to prevent CVD, risk prediction remains imprecise and incidence rates of cardiovascular events are still high. This highlights the urgent need to identify new strategies to improve CVD prediction. In this study, we evaluated for the first time the role of SP-D as a potential biomarker for incident CVD events after 7.5 years in a representative cohort of the Spanish adult general population. Our findings provide evidence that higher SP-D categories are associated with higher risk of developing CVD, independent of from strong well-established risk factors for CVD such as SCORE2, BMI, hs-CRP and eGFR.

Clinical cross-sectional studies examining the association between SP-D and CVD in different health conditions have been reported. A positive association between levels of circulating SP-D, carotid intima-media thickness and coronary artery calcification, both established markers of atherosclerosis, was found in patients on long-term haemodialysis.[15] Elevated serum SP-D levels have also been observed in patients with heart failure[16] and were associated with cardiovascular events among individuals with coronary heart disease and heart failure.[17] In contrast, only one cross-sectional study whose population was over 60 years old reported that there was no significant association between plasma SP-D and subclinical atherosclerosis.[18]

The relationship between circulating SP-D and incident CVD events or mortality, particularly from cardiovascular causes has been also evaluated, with several studies supporting its independent association beyond other traditional risk factors,[10,19–21] most of them focused on subjects with previous cardiovascular related conditions. For example, Hill et al. reported that serum SP-D is a good predictor of cardiovascular morbidity and mortality.[10] Similarly, Xu et al. revealed that plasma SP-D levels may independently predict cardiovascular events after a mean follow-up of 28 months in patients with coronary artery disease.[19] Furthermore, SP-D levels have been linked to

TABLE 4 Statistical comparison of the predictive models for CVD incidence using DeLong's test, integrated discrimination improvement (IDI), and continuous Net reclassification improvement (NRI).

	Overall Population			Non-smokers			Smokers		
	DeLong *p* value	IDI (CI95%), *p* value	Cont. NRI (CI 95%), *p* value	DeLong *p* value	IDI, *p* value	Cont. NRI (CI 95%), *p* value	DeLong *p* value	IDI, *p* value	Cont. NRI (CI 95%), *p* value
Mod. 1 versus Mod. A1	0.025	0.008 (−0.017, 0.002), $p = 0.105$	0.459 (0.266–0.652), $p < 0.001$	0.022	0.015 (−0.029, −0.001), $p = 0.031$	0.519 (0.310–0.725), $p < 0.001$	0.257	0.003 (−0.028, 0.022), $p = 0.822$	0.461 (−0.063–0.948), $p = 0.070$
Mod. 2 versus Mod. A2	0.036	0.006 (−0.016, 0.004), $p = 0.208$	0.459 (0.266–0.652), $p < 0.001$	0.032	0.013 (−0.027,0.001), p = 0.071	0.519 (0.310–0.725), $p < 0.001$	0.315	0.003 (−0.027,0.019), $p = 0.725$	0.455 (−0.065–0.942), $p = 0.076$

Note: Results are shown for overall population and stratified by smoking status (non-smokers and smokers). Model A1: SCORE2 + BMI; Model 1: SCORE2 + BMI + SP-D categories; Model A2: SCORE2 + BMI + hs-CRP + eGFR, Model 2: SCORE2 + BMI + hs-CRP + eGFR+SP-D categories. SCORE2: Systematic Coronary Risk Estimation 2 (includes age, sex, smoking status, systolic blood pressure, total cholesterol, HDL-cholesterol and diabetes).

CVD outcomes in patients with peripheral arterial disease.[20] Increased circulating SP-D has been associated with total mortality in elderly population.[21] However, data regarding the association between higher serum SP-D levels and incident CVD as well as cardiovascular related death in the general population are scarce. As far as we know, only a study evaluated the relationship between SP-D and mortality in general population[21]; however, the study population was elderly (>70 years) and mortality cause was not assessed. In our case, participants aged 18–89 were selected, what comprises a broad range from adult population, and only CVD related mortality was assessed, in contrast to the mentioned study.[21] Additionally, non-fatal and fatal CVD events were studied as a single outcome in order to capture all cardiovascular related events, which is similar to the strategy performed by Otaki et al[20] Furthermore, our study population included 1707 participants without previously reported CVD, providing evidence in a representative cohort free of prior CVD, which is a distinctive aspect compared to previously discussed studies.[10,19,20] Finally, no previous studies assessed the role of smoking habit in the analyses. Despite the differences, our results would be in line with previous literature reporting association between SP-D and CVD events.

In this context, chronic lung inflammation has been suggested to be related with increased risk of cardiovascular and total mortality[22]; however, there are no universally accepted biomarkers that could predict these events. Among the candidates, surfactant protein D (SP-D) has been studied in the context of pulmonary diseases, as its circulating levels rise in response to increased translocation from the lungs into the systemic circulation.[23] In our study, the presence of pulmonary diseases at baseline was found to be unrelated to SP-D categories and did not substantially affect the associations between SP-D and CVD risk in our fully adjusted model (results not shown). Importantly, it is well established that circulating SP-D increases with smoking, being nearly 40% higher in active smokers compared with non-smokers.[24] In our study population, this relationship was clearly reflected: the proportion of smokers increased progressively across SP-D categories, reaching its highest value in the fourth quartile. However, despite the strong association between smoking and SP-D levels, our findings demonstrate that elevated SP-D significantly increases 3 times the likelihood of CVD incidence even among non-smokers subjects, reinforcing the detrimental effects of increased serum SP-D levels on health outcomes suggested by Sorensen et al. and revealing that SP-D serves as more than just a marker for smoking in the context of mortality risk.[21] This provides insights into alternative sources of circulating SP-D beyond tobacco exposure, which is consistent with reports describing SP-D secretion by various tissues.[9]

Regarding SP-D associations with CVD events in smokers, we did not detect a significant association, likely due to limited statistical power, although the size of the effect showed an increase tendence across SP-D categories. The sample size of smoking participants who develop CVD events ($n = 17$) in our study limits the statistical power to assess differences. Post-hoc power analysis indicated that this subgroup was markedly underpowered, and a higher sample size would be needed to achieve higher statistical power. Therefore, these results should be interpreted cautiously, and the absence of significance likely reflects limited statistical power rather than the absence of a biological effect.

Sex-stratified analyses of CVD incidence across SP-D categories should also be considered as it has been reported that there are sex differences regarding SP-D levels.[25] Baseline characteristics of our study population showed a higher proportion of men in the highest SP-D category, whereas women where more frequently represented in the lowest SP-D category. However, sex-based analyses performed were also limited by statistical power. While the incidence of CVD events increased across SP-D categories in both sexes, suggesting an association independent of sex, no significant differences were found between CVD events incidence between men and women within each quartile (Supplementary Material). Further analyses and larger sample size is needed to clarify sex-related effects.

Remarkably, our results reveal that SP-D categories were significantly associated with CVD events incidence even considering that the models contained strong CVD-related variables such as validated risk scores (SCORE2 and SCORE2-OP), BMI, hs-CRP and eGFR. Interestingly, despite being a well-recognized inflammatory biomarker,[7] hs-CRP was not a significant predictor in our models, despite showing an association in univariate analysis, whereas SP-D categories emerged as a more relevant predictor in our study population. Several factors may explain the lack of association between hs-CRP and CVD risk in our models. First, hs-CRP measured at a single time point may not accurately reflect chronic inflammation, which has been shown to be more predictive of CVD when cumulative or longitudinal measures are used.[26,27] Second, prior research indicates that the predictive value of hs-CRP may vary by specific outcomes, being stronger for coronary heart disease and non-fatal myocardial infarction than for other events or insufficient evidence for stroke[7]—while our study grouped all cardiovascular outcomes, potentially diluting such associations. Third, hs-CRP's incremental value over established risk factors is known to be modest and sometimes inconsistent,[28] which may explain the attenuation of its signal in fully adjusted models. Finally, large population-based[29] and Mendelian randomization studies[30] have not confirmed a causal relationship between hs-CRP and atherosclerosis. Thus, its influence on cardiovascular events may involve non-atherosclerotic pathways. In contrast, SP-D could reflect alternative mechanistic pathways involved in atherosclerosis, providing a complementary perspective on cardiovascular risk.

Otherwise, the predictive capability of the models improved when SP-D categories were added, both in overall population and non-smokers. Taken together, these results suggest that SP-D is independently associated with CVD events and adds information to traditional risk prediction algorithms.

The molecular mechanisms underlying the association of SP-D and CVD are still under investigation. Some studies have suggested that SP-D plays a dual role in the development of atherosclerosis. In general, SP-D exerts anti-inflammatory properties, and dampens local inflammation in the vessel, as well as systemic inflammation. However, SP-D can also exert a pro-inflammatory role, as it stimulates C-C chemokine receptor 2 inflammatory blood monocytes to secrete tumour necrosis-factor α and increases secretion of interferon-γ from natural killer cells.[31] SP-D binding to OSCAR receptors induced TNF-α secretion from CCR2+ inflammatory monocytes.[32] The explanation for that could be that human SP-D has different isoforms and a shift in SP-D isoforms can lead to changes in its pro- or anti-inflammatory role.[9] Sorensen et al. also reported that SP-D, particularly in vessel walls have pro-inflammatory effects, which enhance the risk of atherosclerosis.[9] In vitro studies in human coronary artery smooth muscle cells revealed that inflammatory mediators upregulate the expression of SP-D and functions as an anti-inflammatory protein by reducing IL-8 release.[33] In vivo studies examining the role of SP-D in the development of atherosclerosis agree that SP-D plays a proatherogenic role, with SP-D knockout mice having smaller atherosclerotic plaque areas, which might be caused by a decreased systemic inflammation.[34] Other study revealed that SP-D deficiency in mice reduces atherosclerosis by decreasing the accumulation and proliferation of macrophages and systematically reduced IL-6 levels.[35]

Mixed approaches that combine biomarkers, CVD risk scores and artificial intelligence are the road to achieve personalized prevention. Together, our results support the utility of SP-D as a promising biomarker for cardiovascular risk prediction, with potential for integration into clinical practice.

The main strength of this research is that data were obtained from a sizable nationwide cohort, with a considerable follow-up duration and a substantial number

of events (108 incident cases). Analyses were stratified by smoking status, which revealed significant associations of SP-D even in non-smokers, which has not been previously assessed. Additionally, we provide evidence on the predictive role of SP-D for CVD events in the general population without prior CVD related conditions, an area with limited existing research. Finally, this study evaluates representatively the predictive capability of SP-D in the general population from a nationwide perspective, which enables broader extrapolation of our results and increases their implications for the public health system, potentially leading to important repercussions for CVD prevention strategies in Spain.

However, our study also presents some limitations. It is not possible to know what portion of total serum SP-D levels comes from lungs and what portion comes from other tissues, since it has been reported that many tissues secrete SP-D. Reference values for serum SP-D have not been established yet and the measurement of its levels has not been standardized or implemented in clinical practice. Other limitations of our study include its observational nature, which prevents us from establishing causal associations or fully excluding residual confounding in the relation between SP-D levels and CVD events. Additionally, we could not assess the effect of SP-D over different subtypes of CVD events as all CVD-related events were studied together due to sample size and also to avoid self-report bias in the classification of CVD events. Moreover, because CVD status was based on self-report, "no prior CVD" group could be a mixed population containing both genuinely healthy individuals and those with unrecognized disease, as only those participants who reported previously diagnosed CVD were excluded, leading to an underestimation of subclinical atherosclerosis that may partially account for the observed associations. Finally, despite the presence of pulmonary disease being considered in this study, self-reporting may lead to the possibility of underdiagnosis of lung disease because of a lack of objective measures to assess the presence of pulmonary disease such as spirometry. Nevertheless, our findings can be the basis for future studies with a proper design that include standardized assessments for cardiovascular and pulmonary diseases diagnosis for the detection of subclinical cases.

In conclusion, our study demonstrates that high SP-D levels are associated with CVD event incidence, including both morbidity and mortality. This association has been confirmed even in non-smokers, despite SP-D has been linked with smoking. In smokers, we did not detect significant associations due to limited statistical power. SP-D could be considered as a potential biomarker for CVD event incidence in combination with other risk factors. Further investigations with larger cohorts and long-term follow-up are needed to validate these findings before its implementation in clinical practice.

AUTHOR CONTRIBUTIONS

Conceptualization, G.R.M., V.D.G., and S.V.; methodology, G.R.M., E.G.E and S.V.; software, E.G.E and W.O.B.; formal analysis, W.O.B., E.G.E. and G.R.M.; investigation, W.O.B., A.L.S., C.M.A.,V.D.G., E.D., F.J.C., L.C., A.C.P., J.F.N., G.O; Resources, G.R.M. and S.V.; data curation, G.R.M., W.O.B, A.L.S., and E.G.E.; writing—original draft preparation, W.O.B., A.L.S., and E.G.E.; writing—review and editing, all authors; supervision, G.R.M., G.O., V.D.G., and E.G.E.; project administration, G.R.M.; funding acquisition, G.R.M. and S.V. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGEMENTS

This study has been funded by Instituto de Salud Carlos III (ISCIII) through CIBERDEM and the projects PI17/02136, PI20/01322 and PI23/00347 and co-funded by the European Union. Gemma Rojo-Martinez belongs to the Nicolás Monardes research program of the Consejería de Salud (C-0060-2012; Junta de Andalucía, Spain). Wasima Oualla-Bachiri is the recipient of a "PFIS" predoctoral research contract (FI21/0040, Instituto de Salud Carlos III). Funding for open access charge: Universidad de Málaga/CBUA. We express our deepest gratitude and sincere thanks to the di@bet.es Study Group. Our profound appreciation goes to Isabel Ramis for her help at all times in the organization of the study, the primary care managers and personnel of the participating health centers. To all the field workers, nurses, and technicians, without whose work the study would not have been possible. More information about the working group of the di@bet.es study can be found at https://www.ciberdem.org/programas-de-investigacion/proyectos/otros-proyectos/estudio-di-betes (accessed on 20 October 2025) and https://www.sediabetes.org/cientifico-y-asistencial/proyectos-de-investigacion/estudio-dibet-es/ (accessed on 20 October 2025). LifeScan España (Madrid, Spain) kindly donated the glucometers and test strips for capillary glucose measurements. We are indebted to the staff of the UGC of Laboratories of the Hospital Regional Universitario of Malaga for their invaluable technical assistance. We wish to acknowledge the kind collaboration of the Spanish Diabetes Society. We are indebted to the Biobank of the Hospital Regional Universitario of Malaga-IBIMA and CIBERDEM Biorepository (IDIBAPS Biobank), integrated in the Spanish National Biobank Network, for the samples management.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

ORCID

Wasima Oualla-Bachiri https://orcid.org/0000-0002-9760-0883
Cristina Maldonado-Araque https://orcid.org/0000-0002-3452-3489
Gemma Rojo-Martínez https://orcid.org/0000-0003-2179-2134
Viyey Doulatram-Gamgaram https://orcid.org/0000-0002-0178-0040
Sergio Valdés https://orcid.org/0000-0001-8623-4331

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How to cite this article: Oualla-Bachiri W, Lago-Sampedro A, García-Escobar E, et al. Increased levels of serum surfactant protein D are associated with cardiovascular disease incidence in the Spanish adult population: Di@bet.es study. *Eur J Clin Invest*. 2026;56:e70179. doi:10.1111/eci.70179