Journal of Electrocardiology 73 (2022) 113–119

Contents lists available at ScienceDirect

Journal of Electrocardiology

journal homepage: www.jecgonline.com

The S1S2S3 electrocardiographic pattern — Prevalence and relation to cardiovascular and pulmonary diseases in the general population

Joonas Nurminen, BM [a], Andrés Ricardo Pérez-Riera, MD [b], Antonio Bayés de Luna, MD [c], Kjell Nikus [a,d,*], Leo-Pekka Lyytikäinen [a,d], Heini Huhtala [e], Markku Eskola [a,d], Mika Kähönen [a,f], Antti Jula [g], Terho Lehtimäki [a,h], Jussi Hernesniemi [a,d]

[a] Faculty of Medicine and Health Technology, Tampere University and Finnish Cardiovascular Research Center, Tampere, Finland
[b] Laboratório de Metodologia de Pesquisa e Escrita Científica, Faculdade de Medicina do ABC, Santo André, São Paulo, Brazil
[c] Cardiovascular Research Foundation. Cardiovascular ICCC- Program, Research Institute Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau, Barcelona, Spain
[d] Heart Center, Department of Cardiology, Tampere University Hospital, Finland
[e] Faculty of Social Sciences, Tampere University, Finland
[f] Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland
[g] National Institute for Health and Welfare, Helsinki, Finland
[h] Department of Clinical Chemistry, Fimlab Laboratories, Finland

ARTICLE INFO

Keywords:
ECG
S1S2S3
QRS axis
General population
Normal variant

ABSTRACT

Background: There is lack of studies exploring the incidence and association with diseases of the S1S2S3 electrocardiogram (ECG) pattern in the general population.
Subjects and methods: This population study included 6299 individuals aged 30+, and explored the prevalence and association between S1S2S3 and cardiovascular and pulmonary diseases. Criteria for the S1S2S3-I and S1S2S3-II ECG pattern were fulfilled when there was an S wave in the leads I, II and III, and the S-wave amplitude was greater than the R-wave amplitude in one or two of the leads, respectively.
Results: The S1S2S3-I ECG pattern was found in 2332 subjects (36.9%). After age adjustment, hypertension was associated with S1S2S3-I (Odds ratio [OR] 1.25, 95% CI 1.12–1.41, $p < 0.001$). This age-adjusted association was statistically significant among men but not among women (OR 1.37, 1.16–1.62, $p < 0.001$ and OR 1.13, 0.97–1.33, $p = 0.126$, respectively). The S1S2S3-II ECG pattern was present in 193 subjects (3.1%). After age adjustment, heart failure proved to be associated with S1S2S3-II (OR 1.85, 1.18–2.90, $p = 0.007$). Dividing the population by sex, resulted in a statistically significant age-adjusted association for men but not for women (OR 2.30, 1.22–4.33, $p = 0.010$ and OR 1.59, 0.83–3.03, $p = 0.159$, respectively). Interactions with sex were statistically non-significant.
Conclusion: In the general adult population, the prevalence of the S1S2S3 ECG pattern is markedly affected by the diagnostic ECG criteria. The S1S2S3-I pattern was associated with hypertension, while S1S2S3-II was associated with heart failure, and both associations were enhanced in men. The associations with other studied cardiovascular and pulmonary diseases were minor and not clinically useful for risk stratification.

Introduction

When the final electrical forces of the QRS complex in the 12-lead electrocardiogram (ECG) are oriented superiorly and to the right, S waves appear in the leads I, II and III [1,2]. Various definitions for the S1S2S3 ECG pattern exist. Some clinicians and scientists apply this term to all cases with an S wave in each of the standard leads I, II and III, regardless of magnitude, while others restrict the term to ECGs, where the amplitude of the S wave in these leads equals or exceeds the amplitude of the R wave in one or more of the leads [3].

The S1S2S3 sign has been associated with pulmonary embolism, chronic obstructive pulmonary disease (COPD), and obstructive sleep apnea and with right ventricular hypertrophy in children with congenital heart disease [1,4–7]. However, other authors found no clear association between the S1S2S3 pattern and pulmonary embolism or COPD [8–11]. However, the S1S2S3 ECG pattern has also been considered as

* Corresponding author at: Faculty of Medicine and Health Technology, Tampere University, Arvo Ylpön katu 34, 33520 Tampere, Finland.
E-mail address: kjell.nikus@tuni.fi (K. Nikus).

https://doi.org/10.1016/j.jelectrocard.2022.07.003

Available online 8 July 2022
0022-0736/© 2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

representing minor normal variation of intraventricular conduction [12].

The aim of this study was to explore the prevalence and association with cardiovascular and pulmonary disease and diabetes of the S1S2S3 ECG morphology in the general population using different pre-specified S1S2S3 ECG criteria.

Material and methods

Study population

This study was based on the Health 2000 Study, which is a major Finnish health examination survey carried out in 2000–2001, representing a stratified random cluster sample of the adult Finnish population. For the population aged ≥80 years, the sampling probability was twice as high as among those <80 years. The implementation of the survey has been described in detail elsewhere [13].

The Health 2000 sample comprised 8028 individuals (3637 men and 4391 women) aged 30+, of whom 79% (6354 individuals, 2876 men and 3478 women) participated in the health examination. The National Hospital Discharge Register and the national register on rights to reimbursements for medication costs were linked to the Health 2000 Survey data. The study protocol of the Health 2000 survey was approved by the Epidemiology Ethics Committee of the Helsinki and Uusimaa Hospital District. The participants in the survey signed an informed consent both before the health interview and at the beginning of the health examination.

ECG registration and analysis

Standard 12-lead resting ECGs were obtained in supine position by using MAC 5000 electrocardiographs (Marquette Hellige, Freiburg, Germany and Milwaukee, WI, USA). ECGs were recorded at a paper speed of 50 mm/s using 150 Hz filter. For further analysis, the study ECGs were sent to the Social Insurance Institution's research center in Turku and Minnesota coding was performed at the Institute of Cardiology, Kaunas Medical Academy, Lithuania, by two investigators. At each stage of the ECG analysis, researchers were blinded to the clinical data of the participants. Magellan software program (Marquette Electronics Inc., Milwaukee, WI, USA) was used for ECG analysis. The repeatability of the Minnesota coding was confirmed by 200 repetitions. We excluded 55 participants of the survey from our study because of missing ECG.

For this study, special emphasis was put on the analysis of the limb leads I, II, III and precordial lead V1. Variables for the different analyzes were generated using the amplitudes of the S and R waves, the duration of the QRS complex and the QRS morphology in lead V1. Based on the automatic ECG measurements, the ECGs were divided into separate categories, which are described in detail in Table 1 and shown as ECG examples in Fig. 1-2. We also combined the four different S1S2S3 morphologies defined in Table 1 (S waves in 0–3 of the leads I, II and III) with additional ECG criteria; these were: S1S2S3–150 (S-wave amplitude ≥1.5 mm in all the leads I, II, III), S2 ≥ S3 (the S wave in lead II greater than or equal to the S wave in lead III, QRS duration ≥120 ms and R-prime in lead V1.

Table 1
The titles, definitions and prevalence of the ECG categories.

Title of ECG pattern	Definition of ECG criteria	Prevalence $n = 6299$ n	%
S1S2S3–0	S < R in all the leads I, II and III[a]	4294	68.2
S1S2S3-I	S > R in one of the leads I, II, III[a]	2332	36.9
S1S2S3-II	S > R in two of the leads I, II, III[a]	193	3.1
S1S2S3-III	S > R in all the leads I, II, III[a]	1	0.0
S1S2S3–150	S-wave amplitude ≥1.5 mm in all the leads I, II, III[a]	423	6.7
S2 ≥ S3	S wave in lead II greater than or equal to the S wave in lead III	1475	23.4
R prime	Existence of a second R wave in lead V1	488	7.7

[a] The definition includes existence of an S wave in all the leads I, II and III.

Definition of diseases

Classification of coronary heart disease (CHD) required at least one of the following: diagnosed angina pectoris, myocardial infarction, percutaneous coronary intervention (PCI) or bypass surgery by examining physician; diagnosed PCI or bypass surgery in the health interview; ICD-codes 410–414 (ICD8/9) or I20-I25 (ICD10) in the Care Register for Health Care before the reference date of the study; the right for drug reimbursements for CHD. Classification of myocardial infarction required either a diagnosis of a history of a myocardial infarction by the examining physician, large Q waves in the resting ECG or a history of myocardial infarction in the Care Register for Health Care, ICD-codes 410 (ICD 8/9) or I21-I22 (ICD10). LVH was defined by Minnesota code criteria 3–1, 3–3 or 3–4 [14].

Cerebrovascular disease was defined as a documented history of ischemic or hemorrhagic stroke, or transient ischemic attack, including a stroke diagnosis confirmed by a physician at the health examination. Peripheral arterial disease was defined as a documented history of atherosclerosis of the lower extremities or typical symptoms of claudication. Chronic heart failure was defined as a documented history of congestive heart failure or a positive response to the medication for heart failure. The definition of arrhythmias included both supraventricular and ventricular arrhythmias. The category "Other cardiac disease" was not specified. Evidently, valvular diseases and cardiomyopathies were included.

For the diagnosis of COPD, asthma, chronic bronchitis and "Other pulmonary disease", information gathered during the health interview was used.

Diabetes diagnosis required a serum fasting glucose level ≥ 7.0 mmol/l or use of oral hypoglycemic agents or insulin.

Height, weight and waist circumference were measured and body mass index (BMI) was calculated. Blood pressure was measured with mercury manometer (Mercuro 300, Speidel & Keller, Juningen, Germany) after patient rested for 5 min in sitting position. The cuff was attached to the right upper arm and two measurements were taken. The second measurement was taken two min after the first one and the measurements were averaged. Hypertension was defined as systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg and/or use of antihypertensive drug.

Serum triclycerides, total cholesterol, high-density lipoprotein cholesterol (HDL—C), low-density lipoprotein cholesterol (LDL-C) and plasma glucose concentrations were determined using enzymatic method. Serum γ-glutamyltransferase (GT) was determined using the kinetic method.

Statistical analysis

Statistical analyses were performed using SPSS statistics version 25. Baseline study characteristics were compared by presence and absence of the 'particular' S1S2S3 pattern using the *t*-test for continuous variables and the chi square for categorical variables.

Logistic regression model was used for age-adjusted analyzes. The analyses were done separately for both sexes. The ECG parameters described in Table 1 were used to generate variables for the ECG patterns. A *p*-value of <0.05 was considered as statistically significant. Unadjusted and age adjusted logistic regression analysis was used to study the association between main ECG features (outcome variables) and prevalent medical conditions at baseline (outlined in Table 2). The analyses were also repeated after sex stratification.

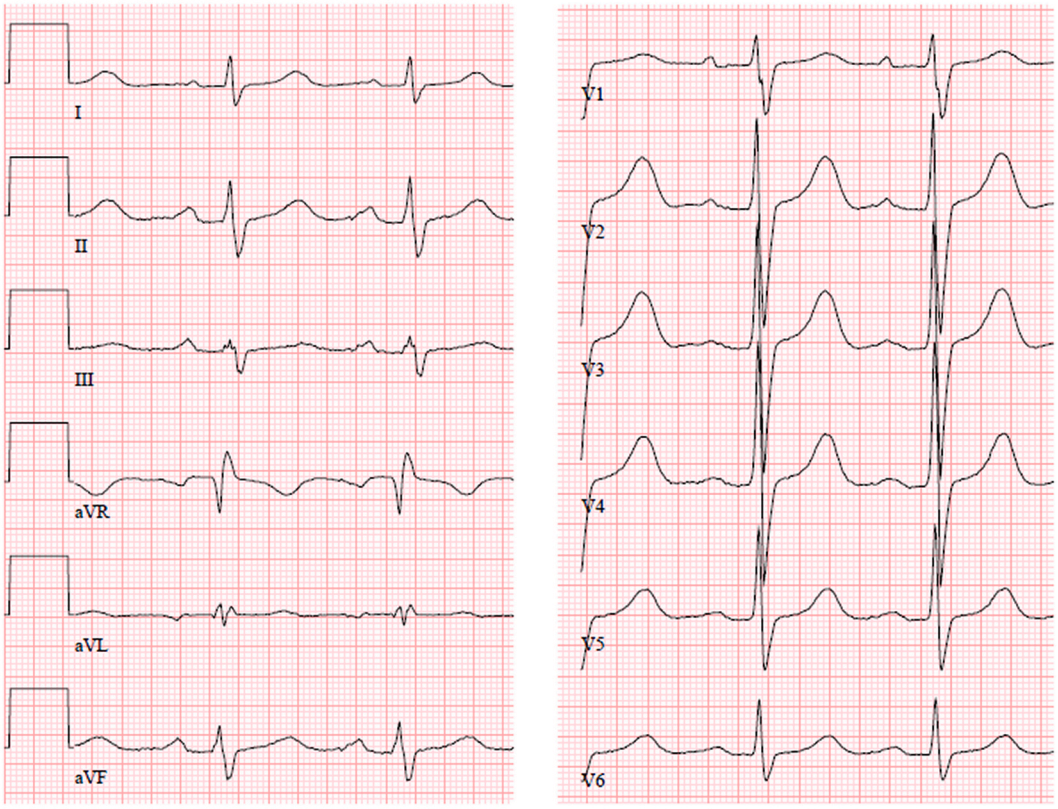

Fig. 1. The ECG (50 mms/s) of a 40-year-old man with no known cardiovascular disease. The S-wave amplitude is greater than the R-wave amplitude in lead III but not in leads I and II. Thereby, the criteria for S1S2S3-I are fulfilled. The frontal QRS axis is +4° and the QRS duration 96 ms according to automatic measurement.

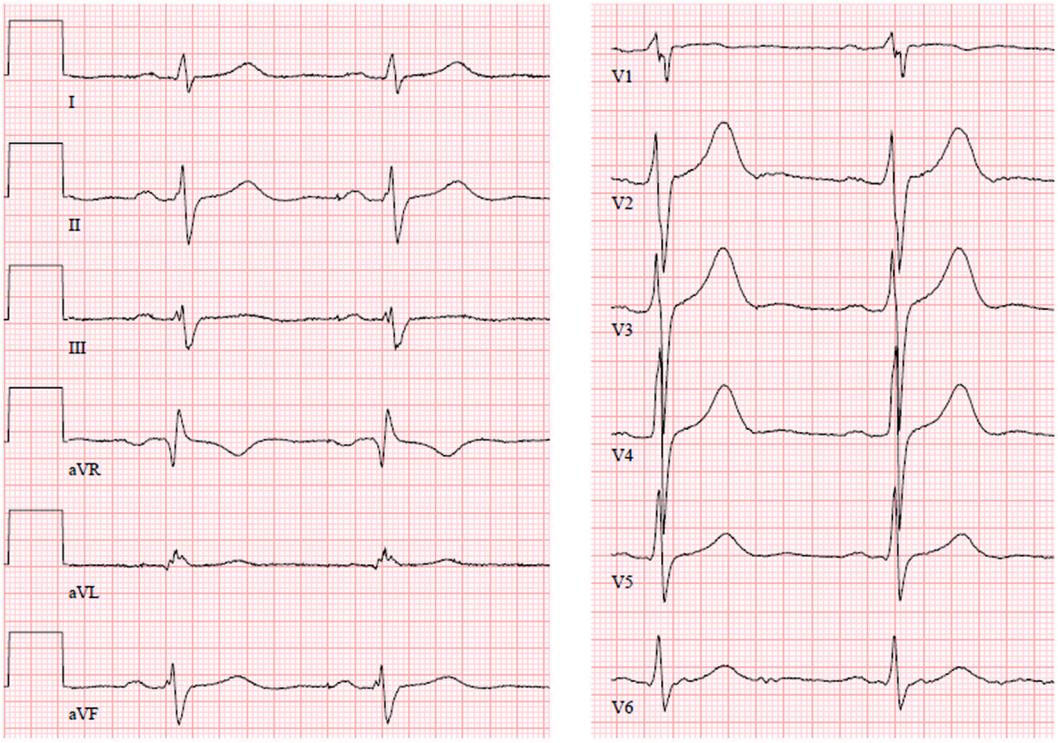

Fig. 2. The 12-lead ECG (50 mm/s) of a 36-year old man with no known cardiovascular disease. The criteria for S1S2S3-II are fulfilled: the S-wave amplitude is larger than the R-wave amplitude in leads II and III but not in lead I. The frontal QRS axis is −67° and QRS duration 104 ms in automatic measurement. There is fragmentation of the S wave in lead V1 and a rather prominent S wave in lead V6 possibly indicating incomplete right bundle branch block. The criteria for left anterior fascicular block are not fulfilled, because the S wave in lead II is deeper than the S wave in lead III.

Table 2
The baseline characteristics and association with diseases for the whole study population ($n = 6299$).

	Mean/n	SD/%
Age	52.8	14.9
Height (cm)	168.2	9.8
Weight (kg)	76.4	15.5
Body mass index (kg/m2)	26.9	4.7
Waist circumference (cm)	92.7	13.3
Glucose (mmol/l)	5.6	1.2
Total cholesterol (mmol/l)	5.94	1.12
HDL-cholesterol (mmol/l)	1.33	0.38
LDL-cholesterol (mmol/l)	3.71	1.06
Triglycerides (mmol/l)	1.6	1.0
C-reactive protein (mg/l)	2.3	6.3
γ-glutamyltransferase (U/l)	36.2	47.0
Uric acid (mol/l)	301.8	81.7
Asthma	570	9.1
COPD	83	1.3
Chronic bronchitis	308	4.9
Other lung disease	604	9.6
Myocardial infarction	247	3.9
Angina pectoris	405	6.5
Heart failure	267	4.3
Arrhythmia	931	14.8
Other cardiac disease	284	4.5
Hypertension	1929	30.7
Stroke	154	2.5
Peripherial arterial disease	113	1.8
Diabetes	350	5.6

COPD, chronic obstructive pulmonary disease.

Results

The study population consisted of 6299 individuals, of which 3442 (54.6%) were women and 2857 (45.4%) men. Table 1 shows the prevalence of the different ECG categories. Table 2 shows the baseline characteristics and association with diseases for the whole study population. The most frequent diseases were hypertension (30.7%), arrhythmia (14.8%) and asthma (9.1%).

The S1S2S3–0 morphology proved to be a very common ECG finding present in 4294 individuals 68.2%. As S1S2S3–0 is a normal finding, this ECG pattern was not included in the statistical analyses. The S1S2S3-III pattern also had to be excluded from further analysis, because only one individual proved to have S > R in all the leads I, II and III.

S1S2S3-I ECG pattern analyses

The S1S2S3-I pattern was found in 2332 subjects (36.9%). As shown in Table 3, individuals with the S1S2S3-I were older, heavier, and they had a higher BMI and waist circumference. They also had higher levels of total cholesterol, LDL-cholesterol, triglycerides and GT, compared to those without this ECG finding.

After age adjustment, hypertension was the only disease category associated with the ECG S1S2S3-I pattern with an odds ratio (OR) of 1.25 (95% confidence interval [CI] 1.12–1.41, $p < 0.001$) (Table 4). When dividing the population by sex, there was an association for men (OR 1.37, 1.16–1.62, p < 0.001), but not for women (OR 1.13, 0.97–1.33, $p = 0.126$). Interaction with sex was statistically non-significant.

In the S1S2S3-I category, broad QRS (≥120 ms) was found in 97 individuals (1.5%), R-prime in lead V1 in 180 subjects (2.8%), and the S2 ≥ S3 finding in 228 subjects (3.6%); the percentages are of the whole study population. Due to the small number of individuals remaining, when S1S2S3-I was combined with any of these additional criteria, statistical analyses were not considered meaningful.

Table 3
The baseline characteristics and association with diseases for the S1S2S3-I criteria.

	S1S2S3-I +		S1S2S3-I -		
	Mean/n	SD/%	Mean/n	SD/%	p-value
Age	55.4	14.9	51.3	14.7	<0.001
Height (cm)	168.5	10.0	168.1	9.8	0.124
Weight (kg)	79.8	15.8	74.3	14.9	<0.001
Body mass index (kg/m^2)	28.1	4.6	26.3	4.6	<0.001
Waist circumference (cm)	96.3	12.9	90.6	13.1	<0.001
Glucose (mmol/)	5.7	1.4	5.5	1.2	<0.001
Total cholesterol (mmol/l)	6.06	1.13	5.87	1.11	<0.001
HDL-cholesterol (mmol/l)	1.29	0.36	1.36	0.38	<0.001
LDL-cholesterol (mmol/l)	3.84	1.06	3.64	1.05	<0.001
Triglycerides (mmol/l)	1.7	1.1	1.5	1.0	<0.001
C-reactive protein (mg/l)	2.3	5.2	2.2	6.9	0.600
γ-Glutamyltransferase (U/l)	39.2	48.3	34.5	46.1	<0.001
Uric acid (μmol/l)	315.3	81.1	293.8	81.0	<0.001
Asthma	232	10.0	338	8.6	0.061
COPD	32	1.4	51	1.3	0.783
Chronic bronchitis	131	5.6	177	4.5	0.043
Other lung disease	235	10.1	369	9.4	0.336
Myocardial infarction	112	4.8	135	3.4	0.006
Angina pectoris	172	7.4	233	5.9	0.022
Heart failure	117	5.0	150	3.8	0.020
Arrhythmia	372	16.0	559	14.2	0.050
Other cardiac disease	116	5.0	168	4.3	0.180
Hypertension	830	35.7	1099	27.8	<0.001
Stroke	67	2.9	87	2.2	0.096
Peripheral arterial disease	44	1.9	69	1.7	0.679
Diabetes	136	5.8	214	5.4	0.473

SD, standard deviation; COPD, chronic obstructive pulmonary disease.

Table 4
Age-adjusted logistic regression analysis for the association between the S1S2S3-I ECG pattern and prevalent medical conditions at baseline.

S1S2S3-I	OR (95% CI)	p-value
Asthma	1.09 (0.92–1.31)	0.326
COPD	0.88 (0.56–1.38)	0.569
Chronic bronchitis	1.11 (0.88–1.41)	0.380
Other lung disease	0.95 (0.80–1.13)	0.566
Myocardial infarction	1.02 (0.79–1.34)	0.859
Angina pectoris	0.87 (0.70–1.08)	0.213
Heart failure	0.89 (0.69–1.16)	0.395
Arrhythmia	0.98 (0.85–1.14)	0.795
Other cardiac disease	1.06 (0.83–1.35)	0.648
Hypertension	1.25 (1.12–1.41)	<0.001
Stroke	0.98 (0.70–1.36)	0.879
Peripheral arterial disease	0.83 (0.56–1.22)	0.335
Diabetes	0.87 (0.69–1.09)	0.230

S1S2S3-II ECG pattern analyses

The S1S2S3-II pattern was distinctly less frequent then the S1S2S3-I pattern ($n = 193$, 3.1%). Table 5 shows the baseline characteristics and association with the diseases for the S1S2S3-II criteria. The subjects with the S1S2S3-II pattern were clearly older than those without the ECG pattern. Accordingly, age adjustment had major effect on the results: only heart failure proved to be associated with the ECG pattern (OR 1.85, 95% CI 1.18–2.90, $p = 0.007$) (Table 6). This was also the case when analyzing separately for men (OR 2.30, 1.22–4.33, $p = 0.010$), but not for women (OR 1.59, 0.83–3.03, $p = 0.159$). Interaction with sex was statistically non-significant.

In the S1S2S3-II category, prolonged QRS was found in 28 (0.4%) and R-prime in lead V1 in 24 subjects (0.4%), and S2 ≥ S3 in 24 individuals (0.4%) (% of the whole study population). Thereby, statistical analysis for combined criteria were not considered meaningful.

Table 5
The baseline characteristics and association with disease for the S1S2S3-II criteria.

	S1S2S3-II +		S1S2S3-II -		
	Mean/n	SD/%	Mean/n	SD/%	p-value
Age	64.1	14.2	52.4	14.8	<0.001
Height (cm)	168.2	10.0	168.2	9.8	0.983
Weight (kg)	76.6	15.7	76.4	15.5	0.825
Body mass index (kg/m^2)	27.0	4.5	26.9	4.7	0.827
Waist circumference (cm)	95.6	12.6	92.6	13.3	0.002
Glucose (mmol/l)	5.9	1.5	5.6	1.2	0.002
Total cholesterol (mmol/l)	6.02	1.19	5.94	1.12	0.300
HDL-cholesterol (mmol/l)	1.24	0.35	1.33	0.38	0.001
LDL-cholesterol (mmol/l)	3.80	1.12	3.7	1.06	0.260
Triglycerides (mmol/l)	1.8	1.2	1.6	1.0	0.001
C-reactive protein (mg/l)	2.8	5.7	2.2	6.3	0.199
γ-glutamyltransferase (u/l)	45.5	65.7	35.9	46.2	0.005
Uric acid (μmol/l)	331.5	89.9	300.8	81.3	<0.001
Asthma	21	10.9	549	9.0	0.362
COPD	3	1.6	80	1.3	0.742
Chronic bronchitis	13	6.8	295	4.8	0.225
Other lung disease	27	14.1	577	9.5	0.035
Myocardial infarction	17	8.9	230	3.8	<0.001
Angina pectoris	24	12.5	381	6.3	0.001
Heart failure	29	15.1	238	3.9	<0.001
Arrhythmia	42	21.9	889	14.6	0.005
Other cardiac disease	15	7.8	269	4.4	0.027
Hypertension	75	39.1	1854	30.5	0.011
Stroke	14	7.3	140	2.3	<0.001
Peripheral arterial disease	6	3.1	107	1.8	0.159
Diabetes	17	8.9	333	5.5	0.044

SD, standard deviation; COPD, chronic obstructive pulmonary disease.

Table 6
Age-adjusted logistic regression analysis for the association between the S1S2S3-II ECG pattern and prevalent medical conditions at baseline.

S1S2S3-II	OR (95% CI)	p-value
Asthma	1.00 (0.63–1.59)	0.995
COPD	0.78 (0.24–2.50)	0.670
Chronic bronchitis	1.03 (0.58–1.85)	0.912
Other lung disease	1.13 (0.74–1.72)	0.583
Myocardial infarction	1.17 (0.69–1.99)	0.567
Angina pectoris	0.95 (0.60–1.51)	0.836
Heart failure	1.85 (1.18–2.90)	0.007
Arrhythmia	1.11 (0.77–1.58)	0.584
Other cardiac disease	1.36 (0.78–2.36)	0.278
Hypertension	1.03 (0.76–1.39)	0.855
Stroke	1.70 (0.95–3.06)	0.076
Peripheral arterial disease	0.98 (0.42–2.29)	0.967
Diabetes	1.01 (0.60–1.70)	0.980

S1S2S3–150 ECG pattern analyses

The S1S2S3–150 pattern — an S wave in all the three leads I, II and III with an amplitude of at least 1.5 mm — was found in 423 subjects (6.7%). Of these, 80 subjects (18.9%) had an associated S2 ≥ S3 pattern. After age adjustment, the S1S2S3–150 pattern was associated with Other cardiac disease (OR 1.68, 95% CI 1.13–2.49, $p = 0.010$), but the association with Other lung disease was negative (OR 0.61, 0.41–0.91), $p = 0.015$).

Discussion

In the present study, we explored the prevalence of the S1S2S3 ECG pattern and its association with cardiovascular and pulmonary disease and diabetes in a nation-wide Finnish population aged 30+. We used different criteria for the S1S2S3 ECG pattern. We found that an ECG pattern with S waves in all the three leads I, II and III, and a larger amplitude of the S wave than the R wave in one of the three leads (S2S2S3-I pattern), was present in about one third of the study cohort (36.9%, $n = 2332$). Using the requirement of S > R in two of the leads I, II and III (S1S2S3-II), the prevalence dropped dramatically to 3.1% ($n = 193$) of the subjects. Also, adding an amplitude requirement to the criteria (S1S2S3–150, S-wave amplitude ≥1.5 mm in all the leads I, II and III) also resulted in a small sub-cohort of 423 subjects (6.7%). Only one subject fulfilled the criteria for the S1S2S3-III pattern. These numbers and rates meant that despite the rather large cohort of studied individuals, it was not possible to perform meaningful statistical analyses using all the chosen definitions of the S1S2S3 criteria; this was especially the case when QRS ≥120 ms, S2 ≥ S3 or R-prime in lead V1 was added to the S1S2S3 criteria.

Previous investigators considered the existence of an S wave in all the three leads I, II and III as a frequent finding in the normal population [3]. Our study showed that more than two thirds (68.2%) of the general Finnish population aged 30+ fulfill these ECG criteria. We can conclude that this is a normal ECG finding.

In a large study of adult male individuals from the United States, Hiss et al. reported a 24% prevalence of the S1S2S3 pattern [12]. They considered this finding as representing minor normal variation of intraventricular conduction, but the definition of the ECG manifestation was not reported. Burch and de Pasquale defined S1S2S3 as S waves in the leads I-III with S2 > S3 [15]. In our study, only 252 individuals had S2 ≥ S3 and either S1S2S3-I or S1S2S3-II. The S1S2S3 pattern is not a typical finding of left anterior fascicular block, where, by definition, the S wave in lead III is deeper than the S wave in lead II, and typically, there is no S wave in lead I [16]. In men without apparent heart disease, the development of marked left axis deviation was a risk marker for the development of ischemic heart disease, but the S1S2S3 pattern was considered as a low-risk ECG category [17].

We found a positive association between the S1S2S3-I pattern and hypertension. This association proved to be even stronger among men when the analysis was stratified by sex. Among women, the association showed similar but weaker tendency and the observed associations were not statistically significant. Individuals with the S1S2S3-II pattern had a higher rate of known heart failure, and this association was found only in male subjects. The S1S2S3–150 ECG phenomenon was associated with the category Other cardiac diseases. This category included other diagnoses than coronary heart disease and heart failure, such as cardiomyopathies and valvular heart disease.

Theoretically, the S1S2S3 pattern can be explained by variation in the position of the heart within the thoracic cavity, such as posterior location of the ventricular apex and with diseases in the basal regions of the heart, where the electrical activation appears late [2]. The supraventricular crest is one of the last structures to be depolarized in the human heart [18]. Hypertrophy and alterations of the Purkinje network of the supraventricular crest were associated with the S1S2S3 pattern [2,15,19,20]. The findings seem to be supported by data from body surface potential mapping, where activation delay in the right ventricular outflow tract was reported [21]. Results from experimental studies indicated that localized defects in the peripheral conduction system, especially of the right bundle branch, affects the last portion of the QRS complex [22]. This in turn could results in the S1S2S3 pattern and R prime in lead V1.

S waves appear in the leads I, II and III when the final electrical forces of the QRS complex are oriented superiorly and to the right, opposed to the electrical forces of the left ventricular free wall [1,2]. This phenomenon is typical for diseases affecting the right side of the heart. In pediatric patients, prominent S waves in all the three standard leads were associated with congenital heart disease, especially those with manifestations of right ventricular hypertrophy and pulmonary hypertension [4].

In chronic cor pulmonale, a state with pulmonary hypertension, the S1S2S3 sign was a strong predictor of death, and most of the studied patients with the ECG manifestation had radiological signs of hyperinflation of the lungs [23]. The authors did not report the definition for the S1S2S3 diagnosis in the study. In patients with a suspicion of acute

pulmonary embolism, S1S2S3 was more frequent in patients, where the diagnosis was verified with computerized tomographic pulmonary angiography, but the difference was only borderline significant (26.5% vs. 8.8%, $p = 0.056$), possible due to the low incidence of the ECG finding (24/136 patients) [9]. Other studies found no association between S1S2S3 and pulmonary embolism [8,24,25]. S1S2S3 was also reported as a temporary finding in pneumonia and has also been associated with sleep apnea [7,26].

In patients with COPD, the spatial orientation of the heart and the insulating effect of the over-aerated lungs induce a late QRS vector oriented superiorly and to the right, resulting in a prominent S wave in leads I, II, III and V4-V6 [27]. Also other studies reported an association between the S1S2S3 pattern and chronic lung disease [1]. In the present study, we found no clear association between obstructive lung disease and the S1S2S3 pattern. There was an unexpected negative association with the category "Other lung disease". We have no detailed data on the composition of this disease category, but it excludes a diagnosis of asthma, COPD and chronic bronchitis.

In a study by Diaz-Gonzalez et al., the crista supraventricularis ECG pattern, defined as QRS duration ≤100 ms, S wave <40 ms in lead I or V6 and an RSR'pattern in lead V1, was found in 13.3% of 6401 young athletes, aged 5–16 y [28]. The proportion of athletes showing the S1S2S3 pattern was higher in those with the crista supraventricularis pattern compared with the other QRS morphologies, including incomplete right bundle branch block. The authors considered late crista supraventricularis activation and posterior/rightward orientation of the apex of the heart as contributing to the ECG pattern. In the present study, R prime in lead V1 associated with S1S2S3 was a rather infrequent finding, and no firm conclusions could be drawn regarding association with diseases.

The associations between S1S2S3 and diseases in the present study concerned hypertension, heart failure and other cardiac diseases. We have no definite explanations for these associations. All of these diseases may be related to left ventricular remodeling and to some part also to secondary right ventricular remodeling. Regarding the association with hypertension, left ventricular hypertrophy expressed as R-wave voltage increase in lead aVL shifts the frontal QRS axis to the left, but may also result in deepening of the S waves in leads II and III. However, it should not result in an S wave in lead I, except if there is some additional factor affecting the axis of the heart.

Future studies should deal with the prognostic value of the S1S2S3 pattern. It would also be important to establish the clinically most relevant diagnostic criteria for the ECG pattern: is the number of leads with S > R the critical issue or is the amplitude of the S wave more important? The diagnostic value and prognostic significance of the ECG pattern needs to be explored both in the general population and in patients with cardiovascular or pulmonary disease.

Study limitations

The study has clear limitations; it is a population study with no imaging data, which could have given more insight into possible association between the ECG findings and diseases. However, this is a rather large population study with standardized ECG recording and detailed ECG analyses. Only one ECG was available for each study participant. Follow-up ECGs might have given more insight into the studied topics. Follow-up data on morbidity and mortality were not collected.

Conclusions

The prevalence and association with diseases of S1S2S3 ECG pattern are markedly affected by the criteria used to detect the ECG finding in the general population. The S1S2S3-I ECG pattern was associated with hypertension, while S1S2S3-II was associated for heart failure and these both associations were enhanced in men. The associations with other studied cardiovascular and pulmonary diseases were minor and thus not clinically useful for risk stratification.

Author contributions

Joonas Nurminen: formal analysis, investigation, methodology, validation.

Andrés Ricardo Pérez-Riera, investigation, methodology, supervision.

Antonio Bayés de Luna, methodology, supervision.

Kjell Nikus: conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation.

Leo-Pekka Lyytikäinen: funding acquisition, methodology, supervision.

Heini Huhtala: formal analysis, investigation, methodology, supervision, validation.

Markku Eskola: conceptualization, funding acquisition, methodology, project administration, resources, supervision, validation.

Mika Kähönen: conceptualization, methodology, project administration, resources, supervision, validation.

Antti Jula: conceptualization, investigation, methodology, resources.

Terho Lehtimäki: funding acquisition, project administration, resources, supervision, validation.

Jussi Hernesniemi: formal analysis, investigation, methodology, project administration, supervision, validation.

In addition:

The following authors have contributed to the conception and design of the study: Nurminen, Pérez-Riera, Bayés de Luna, Nikus, Eskola, Kähönen.

The following authors have contributed to the acquisition of data: Nurminen, Nikus, Eskola, Kähönen.

All authors have contributed to the analysis and interpretation of the data.

All authors have contributed to the drafting of the article or revising it critically for important intellectual content.

All authors have approved the final version of the manuscript to be submitted.

Acknowledgements

The study has been financially supported by the Competitive Research Funding of the Tampere University Hospital (for TL, MK, JH), the Finnish Foundation for Cardiovascular Research (TL), the Emil Aaltonen Foundation, Finland, the Tampere Tuberculosis Foundation, EU Horizon 2020 (grant 755320 for TAXINOMISIS and grant 848146 for To Aition), and the Academy of Finland grant 322098.

References

[1] Schaeffer JW, Pryor R. Pseudo left axis deviation and the S1S2S3 syndrome in chronic airway obstruction. Chest. 1977 Apr;71(4):453–5.
[2] Bayés de Luna A, Carrió I, Subirana MT, Torner P, Cosín J, Sagués F, et al. Electrophysiological mechanisms of the SI SII SIII electrocardiographic morphology. J Electrocardiol 1987 Jan;20(1):38–44.
[3] Surawicz B, Knilans TK, editors. Chou's electrocardiography in clinical practice. 6th ed. Philadelphia, Pa: Saunders Elsevier; 2008. page 23.
[4] Moller JH, White RD, Anderson RC, Adams Jr P. Significance of the S1S2S3 electrocardiographic pattern in children. Am J Cardiol 1965 Oct;16(4):524–33.
[5] Javanshir E, Ghaffari S, Hajizadeh R, Sakha H, Ghodratizadeh S, Kavandi H. Comparison between negative T waves characteristics in acute coronary syndrome and pulmonary embolism. J Electrocardiol 2018 Sep-Oct;51(5):870–3.
[6] Kamper D, Chou TC, Fowler NO, Witt RL, Bloomfield S. The reliability of electrocardiographic criteria of chronic obstructive lung disease. Am Heart J 1970 Oct;80(4):445–52.
[7] Khalil MM, Rifaie OA. Electrocardiographic changes in obstructive sleep apnoea syndrome. Respir Med 1998 Jan;92(1):25–7.
[8] Çağdaş M, Karakoyun S, Rencüzoğulları İ, Karabağ Y, Artaç İ, İliş D, et al. Diagnostic value of QRS and S wave variation in patients with suspicion of acute pulmonary embolism. Am J Emerg Med 2018 Dec;36(12):2197–202.

[9] Rencuzogullari I, Çağdaş M, Karabağ Y, Karakoyun S, Çiftçi H, Gürsoy MO, et al. A novel ECG parameter for diagnosis of acute pulmonary embolism: RS time: RS time in acute pulmonary embolism. Am J Emerg Med 2019 Jul;37(7):1230–6.
[10] Rodger M, Makropoulos D, Turek M, Quevillon J, Raymond F, Rasuli P, et al. Diagnostic value of the electrocardiogram in suspected pulmonary embolism. Am J Cardiol 2000 Oct 1;86(7). 807–9, A10.
[11] Lazović B, Svenda MZ, Mazić S, Stajić Z, Delić M. Analysis of electrocardiogram in chronic obstructive pulmonary disease patients. Med Pregl 2013 Mar-Apr;66(3–4): 126–9.
[12] Hiss RG, Lamb LE, Allen MF. Electrocardiographic findings in 67,375 asymptomatic subjects. X Normal values Am J Cardiol 1960 Jul;6:200–31.
[13] Kattainen A, Salomaa V, Härkänen T, Jula A, Kaaja R, Kesäniemi YA, et al. Coronary heart disease: from a disease of middle-aged men in the late 1970s to a disease of elderly women in the 2000s. Eur Heart J 2006 Feb;27(3):296–301.
[14] Prineas RJ, Crow RS, Blackburn HW. The Minnesota Code Manual of Electrocardiographic Findings. Littleton, MA: John Wright-PSG, Inc; June, 1982.
[15] Burch GE, Depasquale NP. The electrocardiographic diagnosis of pulmonary heart disease. Am J Cardiol 1963 May;11:622–38.
[16] Elizari MV, Acunzo RS, Ferreiro M. Hemiblocks revisited. Circulation. 2007 Mar 6; 115(9):1154–63.
[17] Rabkin SW, Mathewson FA, Tate RB. The relationship of marked left axis deviation to the risk of ischemic heart disease. Int J Cardiol 1981;1(2):169–78.
[18] Durrer D, van Dam RT, Freud GE, Janse MJ, Meijler FL, Arzbaecher RC. Total excitation of the isolated human heart. Circulation. 1970 Jun;41(6):899–912.
[19] De Almeida MC, Araujo M, Duque M, Vilhena V. Crista Supraventricularis Purkinje network and its relation to Intraseptal Purkinje network. Anat Rec (Hoboken) 2017 Oct;300(10):1793–801.
[20] Delise P, Piccolo E, D'Este D, De Piccoli B, Raviele A, Di Pede F, et al. Electrogenesis of the S1S2S3 electrocardiographic pattern. A study in humans based on body surface potential and right ventricular endocardial mapping. J Electrocardiol 1990 Jan;23(1):23–31.
[21] Piccolo E, Delise P, Raviele A, D'Este D, Totaro G, De Piccoli B, et al. The anterior displacement of the QRS loop as a right ventricular conduction disturbance. Electrophysiologic and vectorcardiographic study in man. J Electrocardiol 1980;13 (3):267–74.
[22] Uhley HN, Rivkin L. Electrocardiographic patterns following interruption of main and peripheral branches of the canine right bundle of His. Am J Cardiol 1961 Jun; 7:810–6.
[23] Incalzi RA, Fuso L, De Rosa M, Di Napoli A, Basso S, Pagliari G, et al. Electrocardiographic signs of chronic cor pulmonale: a negative prognostic finding in chronic obstructive pulmonary disease. Circulation. 1999 Mar 30;99(12): 1600–5.
[24] Jankowski K, Kostrubiec M, Ozdowska P, Milanowska-Puncewicz B, Pacho S, Pedowska-Włoszek J, et al. Electrocardiographic differentiation between acute pulmonary embolism and non-ST elevation acute coronary syndromes at the bedside. Ann Noninvasive Electrocardiol 2010 Apr;15(2):145–50.
[25] Kosuge M, Kimura K, Ishikawa T, Ebina T, Hibi K, Kusama I, et al. Electrocardiographic differentiation between acute pulmonary embolism and acute coronary syndromes on the basis of negative T waves. Am J Cardiol 2007 Mar 15; 99(6):817–21.
[26] Stein PD, Matta F, Ekkah M, Saleh T, Janjua M, Patel YR, et al. Electrocardiogram in pneumonia. Am J Cardiol 2012 Dec 15;110(12):1836–40.
[27] Selvester RH, Rubin HB. New criteria for the electrocardiographic diagnosis of emphysema and cor pulmonale. Am Heart J 1965 Apr;69:437–47.
[28] Diaz-Gonzalez L, Bruña V, Velásquez-Rodriguez J, Valenzuela PL, Valero-Masa MJ, González-Saldívar H, et al. Young athletes' ECG: incomplete right bundle branch block vs crista supraventricularis pattern. Scand J Med Sci Sports 2020 Oct;30(10): 1992–8.