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UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE
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Service de Médecine Interne

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THESE

préparée sous la direction du Professeur Peter Vollenweider
(avec la co-direction du Docteur Jürg Schläpfer)
(avec la collaboration du Professeur Pedro Marques-Vidal)

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Marylène BAY

Médecin diplômée de la Confédération Suisse
Originaire de Silenen (Uri)

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Clinical determinants of electrocardiographic parameters (PR interval duration, intraventricular conduction disturbances) in Swiss middle-aged adults: the CoLausIPsyCoLaus study

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pour Le Doyen
de la Faculté de Biologie et de Médecine

Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

UNIL | Université de Lausanne

Clinical determinants of electrocardiographic parameters (PR interval duration, intraventricular conduction disturbances) in Swiss middle-aged adults: The CoLaus|PsyCoLaus study

Résumé

Contexte : L'intervalle PR prolongé ainsi que les troubles de conduction intraventriculaires sont associés à des outcomes cardiovasculaires négatifs. Toutefois, les données à propos des facteurs cliniques associés au PR prolongé et aux troubles de conduction intraventriculaires sont pauvres. Dans ce contexte, nous avons identifié ces déterminants cliniques dans la population générale.

Méthode : Deux études différentes (la 1ère concernant le PR prolongé, la 2ème concernant les troubles de conduction intraventriculaires) ont été réalisées, dans lesquelles les données de l'étude CoLaus|PsyCoLaus ont été utilisées rétrospectivement. Premièrement, les électrocardiogrammes ont été analysés et le PR a été défini comme normal ou prolongé (>200 ms). Les sous-types des troubles de conduction intra-ventriculaires ont été classifiées comme bloc de branche droit (BBD), bloc de branche gauche (BBG), hémibloc antérieur gauche (HBAG), et trouble de conduction intraventriculaire non-spécifique. Par analyse logistique multivariée, des paramètres cliniques présélectionnés ont été associés à ces différents paramètres électrocardiographiques.

Résultats : Dans la 1ère et dans la 2ème étude, 3655 et 3704 participants ont été inclus respectivement. Parmi les participants de la 1ère étude, 9% présentent un PR prolongé. Dans la 2ème, 5% présentent un trouble de conduction intraventriculaire. Dans la 1ère étude, le sexe masculin (OR 1.41 [1.02-1.97]), l'augmentation de l'âge (65-74 ans: OR 2.29 [1.61-3.24] et de la taille (par 5 cm, OR 1.15 [1.06-1.25]) augmentent la probabilité d'avoir un PR prolongé, alors que l'augmentation de la fréquence cardiaque (≥70 battements/min, OR 0.43 [0.29-0.62]) la diminue. Dans la 2ème, les déterminants diffèrent selon les sous-types de troubles de conduction intra-ventriculaire : le sexe masculin [odds ratio et (95% CI): 2.55 (1.34-4.86)], et l'augmentation de l'âge (p-value pour la tendance <0.001) sont associés au BBD ; l'hypertension artérielle [3.08 (1.20-7.91)] et l'augmentation des NT-proBNP [3.26 (1.43-7.41)] au BBG ; l'augmentation des NT-proBNP [3.14 (1.32-7.46)] à l'HBAG ; et le sexe masculin [5.97 (1.91-18.7)] et l'augmentation de la taille 1.31 (1.06-1.63)] au trouble de conduction intraventriculaire non-spécifique.

Conclusion : Selon si l'on analyse le PR ou les sous-types de troubles de conduction intra-ventriculaires, les déterminants varient. Ces résultats permettent de mieux comprendre la physiopathologie de ces troubles de conduction et d'intégrer ces anomalies électrocardiographiques dans leur contexte clinique.

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CLINICAL INVESTIGATIONS

CLINICAL CARDIOLOGY WILEY

Clinical determinants of the PR interval duration in Swiss middle-aged adults: The CoLaus/PsyCoLaus study

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Abstract

Background: Prolonged PR interval (PRi) is associated with adverse outcomes. However, PRi determinants are poorly known. We aimed to identify the clinical determinants of the PRi duration in the general population.

Hypothesis: Some clinical data are associated with prolonged PRi.

Methods: Cross-sectional study conducted between 2014 and 2017. Electrocardiogram-derived PRi duration was categorized into normal or prolonged (>200 ms). Determinants were identified using stepwise logistic regression, and results were expressed as multivariable-adjusted odds ratio (OR) (95% confidence interval). A further analysis was performed adjusting for antiarrhythmic drugs, P-wave contribution to PRi duration, electrolytes (kalemia, calcemia, and magnesemia), and history of cardiovascular disease.

Results: Overall, 3655 participants with measurable PRi duration were included (55.6% females; mean age 62 ± 10 years), and 330 (9.0%) had prolonged PRi. Stepwise logistic regression identified male sex (OR 1.41 [1.02-1.97]); aging (65-74 years: OR 2.29 [1.61-3.24], and ≥ 75 years: OR 4.21 [2.81-6.31]); increased height (per 5 cm, OR 1.15 [1.06-1.25]); hypertension (OR 1.37 [1.06-1.77]); and hs troponin T (OR 1.67 [1.15-2.43]) as significantly and positively associated, and high resting heart rate (≥70 beats/min, OR 0.43 [0.29-0.62]) as negatively associated with prolonged PRi. After further adjustment, male sex, aging and increased height remained positively, and high resting heart rate negatively associated with prolonged PRi. Hypertension and hs troponin T were no longer associated.

Conclusion: In a sample of the Swiss middle-aged population, male sex, aging and increased height significantly increased the likelihood of a prolonged PRi duration, whereas a high resting heart rate decreased it.

KEYWORDS

adults, cross-sectional, determinants, electrocardiogram, PR interval, Switzerland

1 | INTRODUCTION

The PR interval (PRi) on the electrocardiogram (ECG) measures the conduction time from the beginning of the P-wave to the beginning of the QRS complex. It reflects the conduction through the atria, atrioventricular (AV) node, bundle and its branches, and Purkinje fibers.[1] The normal values range between 120 and 200 millisecond and prolonged PRi or first-degree atrioventricular block are established when the PRi is >200 millisecond. Prolonged PRi is a frequent ECG finding[2] that has long been considered as harmless.[3,4] Yet, one of the studies defining prolonged PRi as benign was based on young and healthy males[4] and it has been hypothesized that elevated vagal tone and decreased sympathetic tone lead to prolonged PRi, as found in well-trained athletes.[5] In 2009, Cheng et al. conducted a study in ambulatory individuals to assess the clinical significance of prolonged PRi. They showed that prolonged PRi was associated with increased risk of atrial fibrillation (AF), all-cause mortality, and pacemaker implantation.[6] Consequently, other studies investigated the association between prolonged PRi and several outcomes, including heart failure, cardiovascular mortality or stroke.[7-10] Contradictory findings were found, some studies reporting a deleterious effect of prolonged PRi on all-cause mortality,[8,10] while others did not.[7,9]

The clinical determinants of prolonged PRi are mostly unknown. Positive associations between the PRi and greater age,[7,10] BMI,[7,11] or genetic markers[12] have been reported. As a prolonged PRi is a frequent finding associated with adverse outcomes, a better identification of the determinants of PRi in an unselected population is recommended. Hence, we aimed to identify the clinical determinants of the PRi duration in the general population.

2 | METHODS

2.1 | Study Cohort

The design of the CoLaus study with the detailed baseline and follow-up methodologies has been reported previously.[13,14] Briefly, CoLaus is a population-based prospective study exploring the biological and clinical determinants of cardiovascular diseases. A non-stratified, representative sample of the population of Lausanne (Switzerland) was recruited between 2003 and 2006, including 6733 participants according to two inclusion criteria: (a) age 35-75 years, (b) written informed consent. The first follow-up occurred between 2009 and 2012 and the second between 2014 and 2017. In this cross-sectional study, all data were collected during the second follow-up by trained field interviewers and were obtained by a questionnaire, an interview, and a physical examination including blood tests and a 12-lead digital ECG recording.

2.2 | Electrocardiography

ECGs were digitally recorded in a resting supine position using a single device (Cardiovit MS-2015, Schiller AG, Baar, Switzerland). In accordance with the local standards, paper speed was 25 mm/second and calibration 10 mV/mm. Digital ECGs were stored in an anonymised database of SEMA Data Management System (V3.5, Schiller AG, Baar, Switzerland).

ECG measurements were determined by Schiller AG algorithms. As automated measurements of ECG intervals significantly vary between manufacturers[15] and the diagnostic accuracy of common ECG algorithms is lower than that of cardiologists,[16] 100 randomly selected ECGs were manually analyzed by M.B. The PRi was defined as the time interval between the earliest detection of atrial depolarization and the earliest detection of ventricular depolarization in any lead. Measurements were performed at a paper speed of 100 mm/second. In case of a > 10 ms disagreement between the automated and the manual values or when diagnoses relative to the PRi (eg, sinus rhythm, AF) were discordant, a senior cardiologist (J.S.) reanalyzed the ECG and measured the PRi. This procedure showed a good agreement between the PRi durations assessed digitally and manually, except for the three following conditions: (a) extreme digital PRi durations (>2 or < 2 SD, respectively >220 ms or < 116 ms); (b) non sinus rhythm or AV conduction abnormality; and (c) missing of PRi duration in presence of sinus rhythm. Hence, in this study, manual analyzes were performed for these three conditions (corresponding to 475 ECGs, ie, 13% of the ECGs). The analyzes were conducted by two investigators (M.B., F.B.) and further confirmed by two senior cardiologists (J.S., E.P.). For the remaining ECGs, digitally determined PRi durations were used. PRis were then categorized into prolonged (>200 ms) or normal (≤200 ms) for analysis.

2.3 | Clinical data

Age was categorized in four 10-year groups (45-54 years, 55-64 years, 65-74 years and > 75 years).

Body weight and height were measured with participants barefoot and in light indoor clothes. Body weight was measured to the nearest 100 g using a Seca scale (Hamburg, Germany) and height was measured to the nearest millimeter using a Seca height gage. Obesity was defined as a body mass index (BMI) ≥30 kg/m^2 and overweight as BMI ≥25 kg/m^2 and < 30 kg/m^2. Waist circumference was measured midway between the lowest rib and the iliac crest using a non-stretchable tape and the average of two measurements was taken. Abdominal obesity was defined as a waist circumference ≥ 102 cm (men) and ≥ 88 cm (women).[17]

Alcohol consumption and smoking status were assessed by self-filled questionnaire. Excessive alcohol consumption was defined as >40 g/day for men and > 20 g/day for women.[18] Participants were considered as current or former smokers when reporting smoking (any type of tobacco combustion), and nonsmoking otherwise.

Cardiovascular risk assessment was evaluated with two risk equations, the European Society of Cardiology SCORE[19] recalibrated for Switzerland[20] and the IAS-arbeitsgruppe lipide und atherosklerose (AGLA) score.[21] The SCORE risk estimates the 10-year risk of death from vascular causes and the AGLA risk estimates the 10-year risk of nonfatal myocardial infarction.

Resting heart rate was obtained on the ECG and defined as high when ≥70 beats per minute.[22] Blood pressure (BP) was measured after at least a 10-minute rest in a seated position using an Omron HEM-907 automated oscillometric sphygmomanometer with an appropriately sized cuff. Three measurements separated by 10-minute intervals were performed and the average of the last two measurements was used. Hypertension was defined by a systolic BP ≥140 mmHg and/or a diastolic BP ≥90 mmHg and/or presence of antihypertensive treatment.

History of cardiovascular disease (CVD) included myocardial infarction, angina pectoris, percutaneous revascularization or bypass grafting, stroke or transient ischemic attack. History of CVD was obtained either based on patient's report (for some of the events occurring before the baseline CoLaus survey) or based on clinical data (obtained during follow-up) validated by an independent adjudication committee including cardiologists and a neurologist.[14]

Participants listed their medications in the self-filled questionnaire. Antiarrhythmic drugs including digoxin, calcium channel blockers (CCBs), amiodarone, and beta-blockers were selected for adjustment because of their impact on the PRi.

2.4 | Biological data

Fasting venous blood samples were processed in the Lausanne University Hospital laboratory. Biological parameters included glucose; HbA1c; total, HDL and LDL-cholesterol; triglycerides; creatinine; NT-proBNP; high-sensitivity cardiac troponin T (hs cTnT), and electrolytes (magnesium, potassium, calcium) for their effect on cardiac conduction.

Diabetes mellitus was defined as fasting plasma glucose ≥7.0 mmoL/L and/or HbA1c ≥48 mmol/mol (≥6.5%) and/or antidiabetic treatment. Renal failure was defined by eGFR <60 mL/min/1.73 m^2 (1 mL/s/m^2) using the CKD-EPI formula. Dyslipidemia was defined either by using the LDL-cholesterol thresholds adapted from the Systematic Coronary Risk Evaluation (SCORE) risk charts (Table S1), and/or by presence of a lipid lowering treatment. Elevated NT-proBNP was considered when ≥125 ng/L and elevated hs cTnT when ≥14 ng/L (≥0.014 μg/L).

2.5 | Exclusion criteria

Exclusion criteria for the current analyzes were as follows: (a) uninterpretable ECG (ie, unstable baseline, missing or inverted electrodes); (b) no sinus rhythm or paced rhythm; (c) Wolff-Parkinson-White syndrome or ≥ second degree AV block; and (d) missing phenotypic data (Figure 1).

2.6 | Statistical analyzes

Statistical analyzes were conducted using STATA version 15.1 for Windows (Stata Corp, College Station, Texas). Concordance between automatic and manual PRi measurements was assessed by Spearman correlation and Lin's concordance coefficients.

Bivariate analysis of the factors associated with prolonged PRi was performed using chi-square for qualitative variables and Student's *t*-test for continuous variables. Results were expressed as number of participants (percentage) or as average ± SD. Multivariable analysis using the PRi duration as dependent variable was performed by stepwise forward logistic regression and findings were further confirmed by stepwise backward logistic regression. Results were expressed as odds ratio (OR) and 95% confidence interval (CI).

Model 1 tested the following covariates: sex; age (45-54, 55-64, 65-74, 75+ years); height (continuous); BMI (normal, overweight, obese); waist (normal, elevated); alcohol intake (none, moderate, excessive); smoking status (never, former, current); 10-year risk of coronary heart disease (CHD) (SCORE and AGLA: low, middle, high, very high); diabetes mellitus (yes/no); hypertension (yes/no); dyslipidemia (yes/no); renal insufficiency (yes/no); resting heart rate (<70, ≥70 bpm); hs cTnT (<14, ≥14 ng/L) and NT-proBNP (<125, ≥125 ng/L). Model 2 tested the same set of variables as model 1, but adjusting for antiarrhythmic drugs; electrolytes (magnesium, potassium, calcium); P-wave contribution to the length of the PRi (P duration/PR duration×100 as suggested by Soliman and et al.[23]) and history of CVD. Model 3 included the same covariates as model 2, but participants under beta-blockers and non-cardioselective CCBs (ATC C08C, C08E, and C08G) were excluded.

Sensitivity analyzes were conducted using inverse probability weighting. Briefly, a logistic model was built including variables significantly different between included and excluded participants, and the probability of inclusion was computed.[24] The inverse of the probability that the observation is included was then used as weight in the different models described above. A second sensitivity analysis was conducted using age and heart rate as continuous variables. Statistical significance was defined by a two-sided *P*-value <.05.

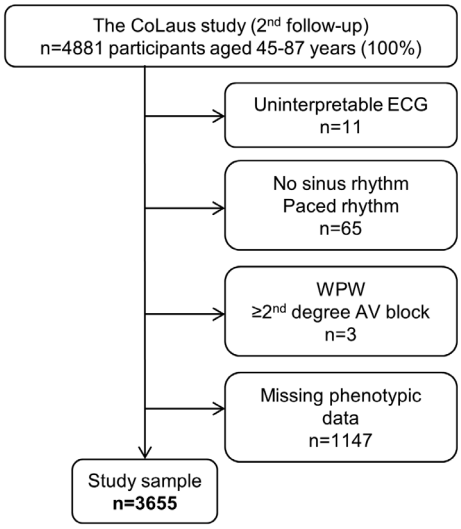

FIGURE 1 Flow diagram: participants selection procedure. AV, atrioventricular; WPW, Wolff-Parkinson-White

2.7 | Ethical statement and consent

The local Institutional Ethics Committee approved the baseline CoLaus study (reference 16/03, decisions of 13 January and 10 February 2003); the approval was renewed for the first (reference 33/09, decision of 23 February 2009) and the second (reference 26/14, decision of 11 March 2014) follow-up. The study was performed in agreement with the Helsinki declaration and the applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

3 | RESULTS

3.1 | Concordance between computerized and manual ECG analyzes

Spearman's rho was 0.95 and concordance correlation coefficient 0.95 (both $P < .001$). The digital algorithm related to the PRi was incorrect for two ECGs: (a) the digital diagnosis was sinus rhythm with an extremely long PRi, while the correct manual diagnosis was AF; (b) the digital diagnosis was an irregular rhythm with no P-wave detected, while the correct manual diagnosis was sinus rhythm. Furthermore, P-wave and PR values were missing in a correctly diagnosed case of sinus bradycardia.

3.2 | Study population

Of the initial 4881 participants, 1226 (25.1%) were excluded. The reasons for exclusion are shown in Figure 1 and the characteristics of excluded and included participants are summarized in Table S2. Excluded participants were older, shorter, with higher BMI, had more abdominal obesity, excessive alcohol intake, diabetes, renal insufficiency, elevated CHD risk scores, dyslipidemia, hypertension, high resting heart rate and elevated hs cTnT and NT-proBNP than included ones.

3.3 | Factors associated with prolonged PRi

Of the 3655 participants with interpretable ECG and measurable PRi duration, 330 (9.0%, 95% CI 8.1 to 10.0%) presented with a prolonged PRi. The clinical characteristics of the participants, overall and according to categories of PRi duration, are presented in Table 1. Participants with prolonged PRi were more frequently male, old, tall and obese. They also had a higher prevalence of renal failure, dyslipidemia, elevated CHD risk scores, hypertension and elevated hs cTnT and NT-proBNP levels. Inversely, they were less prone to smoke and to have high resting heart rate.

Table 2 displays the results of the multivariable stepwise logistic regression assessing the associations between prolonged PRi and clinical characteristics. In model 1, male sex, older age, increased height, hypertension and elevated hs cTnT were significantly and positively associated with prolonged PRi, while high resting heart rate was negatively associated.

After further adjustment according to model 2, male sex, older age, and increased height remained positively, and high resting heart rate negatively associated with prolonged PRi. Conversely, hypertension and hs cTnT were no longer associated. Results were similar after exclusion of participants under beta-blockers and non-cardioselective CCBs (model 3).

3.4 | Sensitivity analysis

The results of the sensitivity analysis using inverse probability weighting are summarized in Table S3. The factors retained were identical to those of the initial analyzes. Similar findings were obtained using age and heart rate as continuous variables (Table S4).

4 | DISCUSSION

In this study, male sex, older age and increased height were significantly and positively associated with prolonged (>200 ms) PRi, while high resting heart rate was negatively associated. These associations were independent of the P-wave contribution to the length of PRi.

4.1 | Agreement between computerized and manual ECG analyzes

The concordance between manual and digital measures of PRi duration and PRi-related diagnoses was good. It has been demonstrated that errors in digital ECG diagnoses are frequently related to arrhythmia and conduction disorders.[16] In our study, there were two incorrect ECG diagnoses by the digital algorithm: one sinus rhythm case misdiagnosed as AF, and one AF case misdiagnosed as an extremely long PRi. In summary, our ECG digital data were reliable for epidemiological studies, but a validation of the algorithm on ECGs sample, and a manual reading is recommended for the following conditions: (a) extreme digital PRi durations (> or < 2 SD); (b) non sinus rhythm or AV conduction abnormality; and (c) absence of PRi duration when sinus rhythm is reported.

4.2 | Prevalence of prolonged PRi

In our sample, approximately one out of 11 (9.0%, 95% CI 8.1-10.0) participants had a prolonged PRi. This is in mid-range of other studies reporting prevalence rates ranging from 1.6% to 18%.[6,7,9,11,23] Several explanations may help to explain these differences. First, by the different characteristics of the studied populations; for example, Holmqvist et al.[11] reported an 18% prevalence rate of prolonged PRi but participants with established coronary artery disease were included, a

TABLE 1 Clinical characteristics of the participants, overall and according to PR interval duration, CoLaus/PsyCoLaus study, Lausanne, Switzerland, 2014-2017

	Overall	PR ≤ 200 ms	PR > 200 ms	*P*-value
No.	3655	3325	330	
Female sex (%)	2032 (55.6)	1900 (57.1)	132 (40.0)	<.001
Age (y)	61.8 ± 9.9	61.3 ± 9.7	66.6 ± 10.6	<.001
Age categories (y) (%)				<.001
45–54	1096 (29.9)	1035 (31.1)	61 (18.5)	
55–64	1201 (32.9)	1128 (33.9)	73 (21.1)	
65–74	944 (25.8)	834 (25.1)	110 (33.3)	
75+	414 (11.3)	328 (9.9)	86 (26.1)	
Height (cm)	167.8 ± 9.5	167.5 ± 9.4	170.1 ± 10.3	<.001
Body mass index (kg/m^2)	26.2 ± 4.6	26.2 ± 4.7	26.8 ± 4.1	.02
Body mass index categories				.03
Normal	1572 (43.0)	1452 (43.7)	120 (36.4)	
Overweight	1445 (39.5)	1302 (39.2)	143 (43.3)	
Obese	638 (17.5)	571 (17.2)	67 (20.3)	
Abdominal obesity (%)	1310 (35.8)	1176 (35.4)	134 (40.6)	.06
Alcohol intake (%)				.34
None	951 (26.0)	858 (25.8)	93 (28.2)	
Moderate	2492 (68.2)	2269 (68.2)	223 (67.6)	
Excessive	212 (5.8)	198 (5.9)	14 (4.2)	
Smoking (%)				.009
Never	1546 (42.3)	1396 (41.9)	150 (45.5)	
Former	1426 (39.0)	1287 (38.7)	139 (42.1)	
Current	683 (18.7)	642 (19.3)	41 (12.4)	
Diabetes mellitus (%)	334 (9.1)	295 (8.9)	39 (11.8)	.08
Renal failure (%)	291 (7.9)	247 (7.4)	44 (13.3)	<.001
10 year risk of CHD (SCORE)				<.001
Low <1%	1124 (30.8)	1066 (32.1)	58 (17.6)	
Medium (≥1 to <5%)	1397 (38.2)	1281 (38.5)	116 (35.2)	
High (≥5 to <10%)	698 (19.1)	599 (18.0)	99 (30.0)	
Very high (≥10%)	436 (11.9)	379 (11.4)	57 (17.3)	
Dyslipidemia (SCORE) (%)	1588 (43.5)	1404 (42.2)	184 (55.8)	<.001
10 year risk of CHD (AGLA)				<.001
Low (<10%)	2582 (70.6)	2385 (71.7)	197 (59.7)	
Middle (10-19%)	142 (3.9)	124 (3.7)	18 (5.5)	
High (≥20%)	83 (2.3)	69 (2.1)	14 (4.2)	
Very high	848 (23.2)	747 (22.5)	101 (30.6)	
Hypertension (%)	1588 (43.5)	1393 (41.9)	195 (59.1)	<.001
Elevated (≥70 bpm) resting heart rate (%)	650 (17.8)	617 (18.6)	33 (10.0)	<.001
Elevated (≥14 ng/L) hs cTnT (%)	236 (6.5)	181 (5.4)	55 (16.7)	<.001
Elevated (≥125 ng/L) NT-proBNP (%)	744 (20.4)	639 (19.2)	105 (31.8)	<.001

Note: Results are expressed as mean ± SD or as number of participants (percentage). Between-group comparisons using chi-square or student *t* test.
Abbreviations: AGLA, Arbeitsgruppe Lipide und Atherosklerose; bpm, beats per minute; CHD, coronary heart disease; hs cTnT, high-sensitivity cardiac troponin T.

condition known to increase the risk of prolonged PRi. Second, by different age; Cheng et al.[6] reported a low (1.6%) prevalence rate in a sample with a mean age of 47 years compared to >60 years in the present study. Conversely, a study reporting prevalence rate of prolonged PRi in a population similar to CoLaus showed a comparable result (8.7%).[23]

TABLE 2 Multivariable associations between prolonged (>200 msec) PR interval and clinical characteristics of participants, CoLaus/PsyCoLaus study, Lausanne, Switzerland, 2014-2017

	Model 1 (n = 3655)		Model 2 (n = 3397)		Model 3 (n = 2991)	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Sex						
Female	1 (ref.)		1 (ref.)		1 (ref.)	
Male	1.41 (1.02-1.97)	.040	1.78 (1.20-2.66)	.005	2.14 (1.36-3.35)	.001
Age (y)						
45-54	1 (ref.)		1 (ref.)		1 (ref.)	
55-64	1.11 (0.77-1.58)	.582	1.21 (0.80-1.82)	.368	1.17 (0.76-1.82)	.47
65-74	2.29 (1.61-3.24)	<.001	2.42 (1.60-3.68)	<.001	2.67 (1.70-4.19)	<.001
75+	4.21 (2.81-6.31)	<.001	5.12 (3.19-8.21)	<.001	5.39 (3.16-9.21)	<.001
P-value for trend	<.001		<.001		<.001	
Height (per 5 cm)	1.15 (1.06-1.25)	.001	1.23 (1.12-1.37)	<.001	1.26 (1.12-1.42)	<.001
Hypertension						
No	1 (ref.)		Not retained		Not retained	
Yes	1.37 (1.06–1.77)	.015				
Resting heart rate						
Normal (<70 bpm)	1 (ref.)		1 (ref.)		1 (ref.)	
Elevated (≥70 bpm)	0.43 (0.29-0.62)	<.001	0.54 (0.34-0.85)	.007	0.44 (0.25-0.77)	.004
Hs cTnT categories						
Normal (<14 ng/L)	1 (ref.)		Not retained		Not retained	
Elevated (≥14 ng/L)	1.67 (1.15-2.43)	.007				

Note: Results are expressed as multivariable-adjusted odds ratio (95% confidence interval). Analysis by stepwise forward logistic regression; results were further confirmed by stepwise backward logistic regression. Model 1 included all variables from Table 1 except for age and BMI as continuous variables. Model 2 tested the same set of variables as model 1, but adjusting for antiarrhythmic drugs; electrolytes (magnesium, potassium, calcium); P-wave contribution to the length of the PR interval (P duration/PR duration×100) and history of CVD. Model 3 included the same covariates as in model 2, but participants under beta-blockers and non-cardioselective CCBs were excluded.

Abbreviations: bpm, beats per minute; CI, confidence interval; Hs cTnT, high-sensitivity cardiac troponin T, OR, odds ratio .

4.3 | Factors associated with prolonged PRi

Older age was positively associated with prolonged PRi, participants aged >75 years having a more than fourfold increase in the likelihood of prolonged PRi compared to the youngest age category. Similar findings were obtained when age was used as a continuous variable. This is a consistent finding in the literature.[7,10,11] A major explanation is that fibrosis increases in the aging heart due to inflammation, haemodynamic factors, cellular senescence and death, and reactive oxygen species[25] and, subsequently, increased fibrosis slows cardiac conduction leading to prolonged PRi.[26]

Male sex was positively associated with prolonged PRi, a finding also reported elsewhere.[7,11] The reasons for this association are not completely understood. It has been proposed that men have a larger heart size, implicating a longer His-Purkinje system and hence a prolonged conduction time.[27] Sex hormones might also be implicated: an animal study has demonstrated that estrogen attenuates the promyofibroblast proliferation effect of angiotensin II,[28] thus reducing cardiac fibrosis. Nevertheless, the reasons why male sex increases the likelihood of prolonged PRi are still speculative and deserve further investigations.

A 5 cm increase in height increased the likelihood of a prolonged PRi by 26%. To our knowledge, height has been seldom associated with ECG characteristics. Nonetheless, both the PRi and height have been linked with AF,[6,29] and Kofler et al.[30] recently observed significant associations of measured and genetically determined height with PRi suggesting that "adult height is a marker of altered cardiac conduction and that these relationships might be causal."[30] Our results support this hypothesis. However, the commonly advanced explanation that tall persons also have a larger heart, which causes PRi prolongation is now debated.[30]

High resting heart rate was the only factor associated with a reduced likelihood of a prolonged PRi, a finding also reported elsewhere.[7] A plausible explanation is that sympathetic activity increases heart rate by shortening the cardiac conduction cycle, partly by accelerating the AV node conduction.[31]

Hypertension and elevated hs cTnT were positively but inconsistently associated with prolonged PRi. A possible explanation for hypertension not being retained in model 2 is linked to the adjustment for medication. As hypertension was defined partly by the presence of antihypertensive drugs (beta-blockers and CCBs included), adjusting for antihypertensive drugs reduced the strength

of the association. Still, hypertension was not retained even after excluding participants on beta-blockers and non-cardioselective CCBs. This echoes the contradictory findings of the literature, where significant[11] or non-significant[7,9] associations between hypertension and PRi duration have been reported. Similarly, hs cTnT was inconsistently associated with PRi duration, possibly because of the adjustment for CVD history. Yet, and despite the inconsistent statistical findings, we believe that hypertension and hs cTnT might be associated with prolonged PRi as both increase the risk of cardiac fibrosis.[25,32]

4.4 | Limitations

This study has several limitations. First, it was limited to an age range of 45 to 86, and might not be applicable in younger or older participants. Second, the sample was mostly restricted to Caucasians and might not be generalizable to other ethnicities. Third, a sizable fraction (one-quarter) of the sample was excluded, and excluded participants differed from the included ones regarding the levels of several determinants of prolonged PRi; this might have biased the associations between potential determinants and prolonged PRi. Still, the results obtained were almost identical when inverse probability weighting was applied. Finally, most PRi durations were digitally measured and errors may have occurred. However, we endeavored to control the reliability of the digital analyzes and optimize the manual reading.

4.5 | Conclusion

In a sample of the Swiss middle-aged population, male sex, older age, and increased height significantly increased the likelihood of a prolonged PRi duration, whereas high resting heart rate decreased it. The effect of hypertension and elevated hs cTnT on the PRi duration needs further investigations.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

M.B., P.M.V., P.V. and J.S. designed the present study; all authors were involved in data collection; M.B. drafted the manuscript; P.V., P.M.V., F.B., E.P and J.S. critically revised the manuscript. All authors gave final approval.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Clinical factors associated with the intraventricular conduction disturbances in Swiss middle-aged adults: The CoLaus|PsyCoLaus study

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ABSTRACT

Background: Intraventricular conduction disturbances are associated with an increased risk of adverse cardiovascular outcomes. However, data about factors associated with intraventricular conduction disturbances are sparse. We aimed to identify the clinical factors associated with intraventricular conduction disturbances in the general population.

Methods: Cross-sectional study in a sample of 3704 participants (age range 45–86 years, 55.2% women). Intraventricular conduction disturbances were defined as QRS > 110 ms on electrocardiograms, and classified into right bundle branch block (RBBB), left bundle branch block (LBBB), left anterior fascicular block (LAFB) and non-specific intraventricular conduction disturbances (NIVCD).

Results: The number of participants, the resulting prevalence (square brackets) and 95% CI (round brackets) of intraventricular conduction disturbances and subtypes (RBBB, LBBB, LAFB and NIVCD) were 187 [5.1% (4.4–5.8%)], 103 [2.9%, (2.3–3.4%)], 29 [0.8% (0.6–1.1%)], 31 (0.9% [0.6–1.2%]), and 47 [1.3% (0.9–1.7)], respectively. Multivariable logistic regression identified male sex [odds ratio and (95% CI): 2.55 (1.34–4.86)] and increasing age (p-value for trend <0.001) as being associated with RBBB; hypertension [3.08 (1.20–7.91)] and elevated NT-proBNP [3.26 (1.43–7.41)] as being associated with LBBB; elevated NT-proBNP [3.14 (1.32–7.46)] as being associated with LFAB; and male sex [5.97 (1.91–18.7)] and increased height [1.31 (1.06–1.63)] as being associated with NIVCD.

Conclusion: In a sample of the Swiss middle-aged population, the clinical factors associated with intraventricular conduction disturbances differed according to the intraventricular conduction disturbances subtype: male sex and ageing for RBBB; hypertension and elevated NT-proBNP for LBBB; elevated NT-proBNP for LAFB; and male sex and increased height for NIVCD.

1. Introduction

In electrocardiography (ECG), the QRS complex evaluates the ventricular depolarization and its duration is considered as normal in adults when <110 ms [1], while higher values indicate intraventricular conduction disturbances. Intraventricular conduction disturbances can be categorized into bundle branch blocks (complete or incomplete bundle branch blocks), left fascicular blocks or non-specific intraventricular conduction disturbances (NIVCD) [2].

Intraventricular conduction disturbances are frequent opportunistic findings in daily practice [3] and have been associated with an increased risk of adverse cardiovascular outcomes such as heart failure, myocardial infarction, pacemaker implantation, cardiovascular and all-cause mortality [3–8]. Management of intraventricular conduction disturbances is not well defined; the clinical benefit of monitoring patients with asymptomatic intraventricular conduction disturbances is unclear and the associated healthcare burden may be considerable as shown for right bundle branch block [2]. Additionally, the interpretation of intraventricular conduction disturbances in the patients' clinical context is uncertain, as the clinical factors associated with intraventricular conduction disturbances are poorly known. Some studies identified male sex, older age, diabetes or hypertension as positively associated with QRS duration [9] or intraventricular conduction disturbances [4,8,10], but relied on a small sample size [9], included a restricted number of clinical characteristics [8] or were limited to one intraventricular

Abbreviations: RBBB, right bundle branch block; LBBB, left bundle branch block; LAFB, left anterior fascicular block;; NIVCD, non-specific intraventricular conduction delay.

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conduction disturbances subtype [4]. Hence, as intraventricular conduction disturbances are frequent ECG findings likely associated with adverse outcomes, solid data about their associated factors should be collected.

In this study, we aimed to identify the clinical factors associated with the intraventricular conduction disturbances in middle-aged adults from a general population sample.

2. Methods

2.1. Study cohort

This study was based on the somatic part (CoLaus) of the CoLaus|PsyCoLaus study, a population-based prospective study exploring the determinants of cardiovascular diseases. The baseline and follow-up methodologies of the CoLaus study have been reported previously [11,12]. The baseline survey occurred between 2003 and 2006, and a representative, non-stratified sample of the Lausanne population (Switzerland) was recruited according to two inclusion criteria: (i) age 35–75 years and (ii) written informed consent. The first follow-up occurred between 2009 and 2012 and the second one between 2014 and 2017.

In this study, we used the data collected during the second follow-up to assess the factors associated with intraventricular conduction disturbances in a cross-sectional setting.

2.2. Electrocardiography

ECGs were digitally recorded in a resting supine position using a single device (Cardiovit MS-2015, Schiller AG, Baar, Switzerland). In accordance with the local standards, paper speed was 25 mm/s and calibration 10 mV/mm. Digital ECGs were stored in an anonymised database of SEMA Data Management System (V3.5, Schiller AG, Baar, Switzerland).

ECG measurements were determined by Schiller AG algorithms [13]. The automated measurements of ECG intervals varying between manufacturers [14] and ECG algorithms having a lower diagnostic accuracy than cardiologists [15], 100 randomly selected ECGs were manually analyzed by one of the researchers (MB). Duration of the QRS complex was measured from the earliest to the latest QRS deflection in any lead at a paper speed of 100 mm/s. When the difference between the automated and the manual values was >10 ms, a senior cardiologist (JS) remeasured the QRS. The Spearman correlation coefficient between the digitally and manually assessed QRS duration was 0.79, and the Lin concordance coefficient was 0.85 (both $p < 0.001$), suggesting a good albeit not perfect agreement. Hence, manual reading of ECG data was performed in the following conditions: i) wide QRS (≥110 ms); ii) very short QRS durations (<2 SD). Overall, 242 ECGs were manually analyzed by MB and values and intraventricular conduction disturbances diagnoses were further confirmed by JS. For the remaining ECGs, digitally determined QRS durations were used.

Intraventricular conduction disturbances were defined as QRS complexes of >110 ms and further classified into bundle blocks [i.e. right and left bundle branch blocks (RBBB, LBBB, respectively)], left anterior and posterior fascicular blocks (LAFB, LPFB, respectively), and NIVCD according to the American Heart Association criteria [1]. Due to small number of cases, complete and incomplete bundle branch blocks were not distinguished.

2.3. Clinical data

Age was categorized in four 10-year groups (45–54 years, 55–64 years, 65–74 years and >75 years).

Body weight and height were measured with participants barefoot and in light indoor clothes. Body weight was measured to the nearest 100 g using a Seca® scale (Hamburg, Germany) and height was measured to the nearest millimeter using a Seca® height gauge. Obesity was defined as a body mass index (BMI) ≥30 kg/m^2 and overweight as BMI ≥25 kg/m^2 and <30 kg/m^2. Waist circumference was measured mid-way between the lowest rib and the iliac crest using a non-stretchable tape and the average of two measurements was taken. Abdominal obesity was defined as a waist circumference ≥102 cm (men) and ≥88 cm (women) [16].

Alcohol consumption and smoking status were assessed by self-filled questionnaire. Excessive alcohol consumption was defined as >40 g/day for men and >20 g/day for women [17]. Smoking status included current and former smoking (any type of tobacco combustion), and non-smoking.

Cardiovascular risk assessment was evaluated with two risk equations, the European Society of Cardiology SCORE [18] recalibrated for Switzerland [19] and the IAS-AGLA score [20]. The SCORE risk estimates the 10-year risk of death from vascular causes and the AGLA risk the 10-year risk of (non)fatal myocardial infarction.

Resting heart rate was obtained on the ECG and defined as high when ≥70 beats per minute [21]. Blood pressure (BP) was measured using an Omron® HEM-907 automated oscillometric sphygmomanometer with an appropriately sized cuff. After a 10-min rest, three measurements separated by 10-min intervals were performed. The average of the last two was used. Hypertension was defined by a systolic BP ≥140 mmHg and/or a diastolic BP ≥90 mmHg and/or presence of antihypertensive treatment.

History of cardiovascular disease (CVD) included myocardial infarction, angina pectoris, percutaneous revascularization or bypass grafting, stroke or transient ischemic attack. History of CVD was obtained either based on patient's report (for some of the events occurring before the baseline CoLaus survey) or on clinical data (obtained during follow-up) validated by an independent adjudication committee including cardiologists and a neurologist [12].

Participants listed their medications in the self-filled questionnaire. Class I and III antiarrhythmic drugs were selected for adjustment because of their impact on the QRS.

2.4. Biological data

Fasting venous blood samples were processed in the Lausanne University Hospital laboratory. Diabetes mellitus was defined as fasting plasma glucose ≥7.0 mmol/l and/or HbA1c ≥48 mmol/mol (≥6.5%) and/or anti-diabetic treatment. Renal failure was defined by eGFR <60 ml/min/1.73 m^2 using the CKD-EPI formula. Dyslipidaemia was defined either by using the LDL-cholesterol thresholds adapted from the Systematic Coronary Risk Evaluation (SCORE) risk charts (Supplementary Table S1), and/or by presence of a lipid lowering treatment. Elevated NT-proBNP was considered when ≥125 ng/l and elevated high-sensitivity cardiac troponin T (hs cTnT) when ≥14 ng/l. Potassium level was included as covariate for its effect on QRS duration.

2.5. Exclusion criteria

Participants were excluded if they had: i) Paced rhythm or Wolff-Parkinson-White syndrome; or ii) Missing phenotypic data.

2.6. Statistical analyses

Statistical analyses were conducted using STATA version 15.1 for Windows (Stata Corp, College Station, Texas, USA). Concordance between automatic and manual QRS measurements was assessed by Spearman correlation and Lin's concordance coefficients.

Results were given as number of participants (percentage) for categorical variables or as average ± standard deviation for continuous variables. Each intraventricular conduction disturbances subtype was compared to participants devoid of intraventricular conduction disturbances. Bivariate analyses were performed using chi-square or Fisher

exact test for categorical variables and student's *t*-test for continuous variables.

Multivariable analyses were performed using logistic regression to identify the factors significantly and independently associated with each type of intraventricular conduction disturbances. Results were expressed as odds ratio (OR) and 95% confidence interval (CI). Three models were used: model 1 included the significant covariates from the bivariate analysis; model 2 tested the same covariates as model 1, further adjusting for antiarrhythmic drugs, potassium levels and history of CVD; model 3 included all the following covariates: sex; age groups (45–54, 55–64, 65–74, 75+ years); height (continuous); BMI categories (normal, overweight, obese); alcohol intake categories (none, moderate, excessive); smoking status (never, former, current); 10-year risk of coronary heart disease (CHD) (SCORE: low, middle, high, very high); diabetes mellitus (yes/no); hypertension (yes/no); dyslipidaemia (yes/no); renal insufficiency (yes/no); resting heart rate (<70, ≥70 bpm); hs cTnT (<14, ≥14 ng/l) and NT-proBNP (<125, ≥125 ng/l).

Sensitivity analyses were conducted using inverse probability weighting. Briefly, a logistic model was built including variables significantly different between included and excluded participants, and the probability of inclusion was computed [22]. The inverse of the probability that the observation is included was then used as weight in the different models described above. Finally, given the small prevalence levels for some subtypes of intraventricular conduction disturbances and the large number of candidate variables, a more parsimonious analysis was conducted by applying stepwise forward logistic regression with a probability for entry of 0.05 and a probability of removal of 0.10, using the significant covariates from the bivariate analysis. This last analysis allowed the identification of the sole variables significantly associated with intraventricular conduction disturbances.

Statistical significance was defined by a two-sided test with *p*-value <0.05.

2.7. Ethical statement and consent

The local Institutional Ethics Committee approved the baseline CoLaus study (reference 16/03, decisions of January 13 and February 10, 2003); the approval was renewed for the first (reference 33/09, decision of February 23, 2009) and the second (reference 26/14, decision of March 11, 2014) follow-up. The study was performed in agreement with the Helsinki declaration and the applicable Swiss legislation. All participants gave their signed informed consent.

Table 1
Clinical characteristics of the participants with no conduction block, and according to each intraventricular conduction disturbances subtype, CoLaus|PsyCoLaus study, Lausanne, Switzerland, 2014–2017.

	No block	RBBB	*p*-value	LBBB	*p*-value	LAFB	*p*-value	NIVCD	*p*-value
N	3517	103		29		31		47	
Female sex (%)	1994 (66.7)	27 (26.2)	<0.001	16 (55.2)	0.869	13 (41.9)	0.099	5 (10.6)	<0.001
Age (years)	61.5 ± 9.8	69.0 ± 9.9	<0.001	66.6 ± 8.5	0.006	71.6 ± 11.2	<0.001	69.4 ± 11.0	<0.001
Age categories (years) (%)			<0.001		0.039		<0.001		<0.001
45–54	1079 (38.7)	8 (7.8)		3 (10.3)		3 (9.7)		7 (14.9)	
55–64	1166 (33.15)	26 (25.2)		9 (32.0)		4 (12.9)		8 (17.0)	
65–74	898 (25.5)	35 (33.9)		13 (44.8)		9 (29.0)		16 (34.0)	
75+	374 (10.6)	34 (33.0)		4 (13.8)		15 (48.4)		16 (34.0)	
Height (cm)	167.6 ± 9.5	170.7 ± 8.8	0.003	169.6 ± 10.9	0.267	167.2 ± 9.5	0.788	174.4 ± 8.4	<0.001
BMI categories (%)			0.531		0.630		0.070		0.011
Normal	1524 (43.3)	40 (38.8)		10 (34.5)		9 (29.0)		12 (25.5)	
Overweight	1380 (39.2)	46 (44.7)		13 (44.8)		12 (38.7)		20 (42.6)	
Obese	613 (17.4)	17 (16.5)		6 (20.7)		10 (32.3)		15 (31.9)	
Abdominal obesity (%)	1258 (35.8)	36 (34.9)	0.864	15 (51.7)	0.074	15 (48.4)	0.145	24 (51.1)	0.030
Alcohol intake (%)			0.051		0.420		0.034		0.197
None	923 (26.2)	18 (17.5)		8 (27.6)		12 (38.7)		8 (17.0)	
Moderate	2391 (67.9)	75 (72.8)		18 (62.1)		15 (48.4)		38 (80.9)	
Excessive	203 (5.8)	10 (9.7)		3 (10.3)		4 (12.9)		1 (2.1)	
Smoking (%)			0.001		0.519		0.547		0.170
Never	1500 (42.7)	25 (24.3)		13 (44.8)		11 (35.5)		21 (44.7)	
Former	1363 (38.8)	50 (48.5)		13 (44.8)		15 (48.4)		22 (46.8)	
Current	654 (18.6)	28 (27.2)		3 (10.3)		5 (16.1)		4 (8.5)	
10-year risk of CHD (SCORE)			<0.001		0.002		<0.001		<0.001
Low <1%	1111 (31.6)	8 (7.8)		4 (13.8)		3 (9.7)		4 (8.5)	
Medium (≥1 to <5%)	1356 (38.6)	28 (27.2)		9 (31.0)		5 (16.1)		12 (25.5)	
High (≥5 to <10%)	648 (18.4)	35 (33.9)		14 (48.3)		14 (45.2)		19 (40.4)	
Very high (≥10%)	402 (11.4)	32 (31.1)		2 (6.9)		9 (29.0)		12 (25.5)	
10-year risk of CHD (AGLA)			<0.001		0.252		<0.001		<0.001
Low (<10%)	2523 (71.7)	45 (43.7)		17 (58.6)		11 (35.5)		12 (25.5)	
Middle (10–19%)	133 (3.8)	5 (4.9)		1 (3.45)		2 (6.5)		4 (8.5)	
High (≥20%)	76 (2.2)	3 (2.9)		1 (3.45)		1 (3.2)		5 (10.6)	
Very high	785 (22.3)	50 (48.5)		10 (34.5)		17 (54.8)		26 (55.3)	
Diabetes mellitus (%)	313 (8.9)	17 (16.5)	0.008	2 (6.9)	1.000	8 (25.8)	0.001	8 (17.0)	0.053
Renal failure (%)	260 (7.4)	20 (19.4)	<0.001	7 (24.1)	0.001	7 (22.6)	0.001	15 (31.9)	<0.001
Dyslipidaemia (SCORE) (%)	1498 (42.6)	68 (66.0)	<0.001	17 (58.6)	0.082	21 (67.7)	0.005	34 (72.3)	<0.001
Hypertension (%)	1502 (42.7)	61 (59.2)	0.001	22 (75.9)	<0.001	21 (67.7)	0.005	37 (78.7)	<0.001
Elevated (≥70 bpm) RHR (%)	635 (18.1)	28 (27.2)	0.018	6 (20.7)	0.714	11 (35.5)	0.012	12 (25.5)	0.187
Elevated (≥14 ng/l) hs cTnT (%)	208 (5.9)	26 (25.2)	<0.001	4 (13.8)	0.091	9 (29.0)	<0.001	15 (31.9)	<0.001
Elevated (≥125 ng/l) NT-proBNP (%)	703 (19.9)	39 (37.9)	<0.001	15 (51.7)	<0.001	20 (64.5)	<0.001	21 (44.7)	<0.001

RBBB, right bundle branch block; LBBB, left bundle branch block; LAFB, left anterior fascicular block; NIVCD, non-specific intraventricular conduction delay; AGLA, Arbeitsgruppe Lipide und Atherosklerose; RHR; resting heart rate; bpm, beats per minute; BMI, body mass index; CHD, coronary heart disease; hs cTnT, high-sensitivity cardiac troponin T. Results are expressed as mean ± SD or as number of participants (percentage). Results are expressed as mean ± SD or as number of participants (percentage). Between-group comparisons using chi-square, Fisher exact test, or student t-test.

3. Results

3.1. Study population

From the initial 4881 participants, 1177 (24.1%) were excluded. Supplementary Fig. S1 displays the exclusion procedure and Supplementary Table S2 summarizes the characteristics of excluded and included participants. Excluded participants were older, shorter, and had higher BMI, more abdominal obesity, excessive alcohol intake, diabetes mellitus, renal failure, elevated CHD risk scores, dyslipidaemia, hypertension, high resting heart rate and elevated hs cTNT and NT-proBNP than included ones.

3.2. Prevalence and clinical factors associated with intraventricular conduction disturbances

Among the 3704 participants, 187 (5.1%, 95% CI: 4.4–5.8%) had at least one intraventricular conduction disturbances subtype: 103 (2.9%, 95% CI: 2.3–3.4%) had RBBB; 29 (0.8%, 95% CI: 0.6–1.1%) LBBB; 31 (0.9%, 95% CI: 0.6–1.2%) LAFB, and 47 (1.3%, 95% CI: 0.9–1.7) NIVCD. Twenty-three participants (0.06%) had both RBBB and LAFB. There was no left posterior fascicular block.

RBBB was associated with sex, age, smoking, diabetes mellitus, renal failure, 10-year risk of CHD (SCORE and AGLA), dyslipidaemia, hypertension, elevated resting heart rate, hs cTnT and NT-proBNP on bivariate analysis (Table 1). On multivariable analysis, the associations with male sex and older age persisted (Tables 2, 3, 4), whereas the associations with diabetes mellitus and current smoking were inconsistent between the models (Tables 2, 3, 4).

LBBB was associated with age, renal failure, 10-year risk of CHD (SCORE), hypertension and elevated NT-proBNP on bivariate analysis (Table 1). On multivariable analysis, the associations with hypertension and elevated NT-proBNP persisted (Tables 2, 3, 4), while height was positively associated only in model 3 (Table 4).

LAFB was associated with age, alcohol intake, diabetes mellitus, renal failure, 10-year risk of CHD (SCORE and AGLA), dyslipidaemia, hypertension, elevated resting heart rate, hs cTnT and NT-proBNP on bivariate analysis (Table 1). On multivariable analysis, the positive association with elevated NT-proBNP persisted (Tables 2, 3, 4).

NIVCD was associated with all parameters except alcohol intake, diabetes mellitus, and elevated resting heart rate on bivariate analysis (Table 1). On multivariable analysis, the associations with male sex and increased height persisted, while renal failure and hypertension were inconsistently associated (Tables 2, 3 and Supplementary Table S2).

Table 2
Multivariable associations between intraventricular conduction disturbances subtypes with clinical characteristics of participants according to model 1, CoLaus|PsyCoLaus study, Lausanne, Switzerland, 2014–2017.

	RBBB (tot. = 3620)		LBBB (tot. = 3546)		LAFB (tot. = 3548)		NIVCD (tot. = 3564)	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Man vs. woman	2.55 (1.34–4.86)	**0.004**	NI		NI		5.97 (1.91–18.7)	**0.002**
Age categories (years)								
45–54	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
55–64	3.14 (1.25–7.88)	**0.015**	2.12 (0.49–9.26)	0.317	1.04 (0.18–5.92)	0.968	1.00 (0.29–3.39)	0.997
65–74	5.28 (1.87–14.9)	**0.002**	1.75 (0.32–9.42)	0.516	1.69 (0.26–11.0)	0.583	2.43 (0.66–8.94)	0.183
75+	8.91 (2.82–28.2)	**<0.001**	0.72 (0.10–5.26)	0.749	3.55 (0.50–25.3)	0.207	3.61 (0.85–15.4)	0.083
p-value (trend)		**<0.001**		0.721		0.192		0.051
Height (per 5 cm increase)	1.14 (0.98–1.32)	0.088	NI		NI		1.31 (1.06–1.63)	**0.014**
BMI categories	NI		NI		NI			
Normal							1 (ref.)	
Overweight							0.98 (0.46–2.09)	0.949
Obese							1.52 (0.66–3.48)	0.322
p-value (trend)								0.322
Alcohol intake (%)	NI		NI				NI	
None					1 (ref.)			
Moderate					0.65 (0.30–1.43)	0.283		
Excessive					1.92 (0.58–6.33)	0.284		
p-value (trend)						0.284		
Smoking			NI		NI		NI	
Never	1 (ref.)							
Former	1.68 (1.01–2.77)	**0.044**						
Current	2.57 (1.42–4.63)	**0.002**						
p-value (trend)		**0.002**						
10-year risk of CHD (SCORE)								
Low <1%	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Medium (≥1 to <5%)	0.90 (0.34–2.39)	0.828	0.94 (0.23–3.80)	0.930	0.93 (0.15–5.84)	0.942	0.79 (0.19–3.34)	0.754
High (≥5 to <10%)	1.06 (0.30–3.82)	0.926	1.83 (0.34–9.86)	0.481	2.24 (0.26–19.2)	0.464	0.33 (0.05–2.25)	0.256
Very high (≥10%)	1.93 (0.50–7.47)	0.339	0.45 (0.06–3.38)	0.441	1.96 (0.19–19.9)	0.569	0.51 (0.08–3.29)	0.481
p-value (trend)		0.347		0.601		0.457		0.359
Clinical conditions (yes vs. no)								
Diabetes mellitus	0.68 (0.36–1.30)	0.250	NI		1.59 (0.58–4.40)	0.368	NI	
Renal failure	1.49 (0.72–3.09)	0.287	1.39 (0.47–4.08)	0.551	0.72 (0.24–2.21)	0.568	3.74 (1.30–10.8)	**0.015**
Dyslipidaemia	0.94 (0.53–1.66)	0.821	NI		0.71 (0.26–1.96)	0.509	1.73 (0.74–4.03)	0.206
Hypertension	0.79 (0.49–1.27)	0.330	3.08 (1.20–7.91)	**0.019**	1.13 (0.46–2.78)	0.794	2.37 (1.05–5.34)	**0.038**
Elevated resting HR	1.37 (0.86–2.20)	0.186	NI		1.83 (0.84–3.99)	0.131	NI	
Elevated hs cTnT	1.56 (0.87–2.80)	0.139	NI		1.71 (0.66–4.41)	0.266	1.39 (0.63–3.10)	0.416
Elevated NT-proBNP	1.40 (0.85–2.31)	0.192	3.26 (1.43–7.41)	**0.005**	3.14 (1.32–7.46)	**0.010**	1.84 (0.88–3.86)	0.106

RBBB, right bundle branch block; LBBB, left bundle branch block; LAFB, left anterior fascicular block; NIVCD, non-specific intraventricular conduction delay; tot., total number of participants included in the analysis; NI, Not included; bpm, beats per minute; BMI, body mass index; CHD, coronary heart disease; hs cTnT, high-sensitivity cardiac troponin T; HR; heart rate. Results are expressed as multivariable-adjusted odds ratio (95% confidence interval). Analysis using logistic regression. Model 1 included the significant covariates from the bivariate analysis. Significant values are indicated in bold.

3.3. Sensitivity analyses

Sensitivity analyses using inverse probability weighting to account for exclusions led to similar results, except that age was significantly associated with LAFB in the model 3 (Supplementary Tables S3, S4, S5). After stepwise analysis, the significant associations found in other models remained, except for increased height, which was no longer associated with NIVCD.

4. Discussion

This is one of the few studies assessing the clinical factors associated with intraventricular conduction disturbances subtypes in a sample of community-dwelling adults. Our results show that the clinical factors associated with intraventricular conduction disturbances differ according to each subtype: male sex and ageing for RBBB; hypertension and elevated NT-proBNP for LBBB; elevated NT-proBNP for LAFB; and male sex and increased height for NIVCD.

4.1. Prevalence of intraventricular conduction disturbances

Intraventricular conduction disturbances were found in one out of 20 participants (5.1%), a value in mid-range of other studies (3.1% and 9.6%) [10,23] and similar to the one found by Rasmussen et al. (4.4%) [3]. Those variations may be due to the definitions of intraventricular conduction disturbances subtypes used or to the characteristics of the samples studied [e.g. the study by Monin et al. was based on a young and healthy population [23]].

4.2. Clinical factors associated with right bundle branch block

RBBB was positively and consistently associated with ageing and male sex, as also reported by Bussink et al. [4]. A plausible explanation is that ageing is associated with increased cardiac fibrosis [24], a condition known to disturb cardiac conduction [25]. Moreover, the ovarian hormone 17β-estradiol has a role in reducing cardiac fibrosis [26], which may explain the higher prevalence of RBBB in males relative to females.

RBBB was additionally positively associated with current smoking in the first model but not in models 2 or 3. A previous study by Bussink et al. also found no association between RBBB and smoking [4]. A possible explanation might be the adjustment for history of CVD, as participants with a positive history of CVD are more frequently smokers. Still, smoking is a strong determinant of lung disease, and lung disease has been associated with RBBB [4]. Hence, our results suggest that smoking could be involved in RBBB via lung disease, although our analyses cannot exclude that participants with RBBB are more likely to smoke. Similarly, RBBB was inconsistently associated with diabetes

Table 3
Multivariable associations between intraventricular conduction disturbances subtypes with clinical characteristics of participants according to model 2, CoLaus|PsyCoLaus study, Lausanne, Switzerland, 2014–2017.

	RBBB (tot. = 3364)		LBBB (tot. = 3295)		LAFB (tot. = 3299)		NIVCD (tot. = 3313)	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Man vs. woman	2.31 (1.18–4.50)	**0.014**	NI		NI		4.95 (1.54–15.9)	**0.007**
Age categories (years)								
45–54	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
55–64	2.65 (1.04–6.79)	**0.042**	2.00 (0.44–9.01)	0.367	0.99 (0.17–5.75)	0.989	1.05 (0.31–3.53)	0.940
65–74	3.73 (1.28–10.8)	**0.016**	1.36 (0.23–7.91)	0.732	1.44 (0.21–9.74)	0.708	2.40 (0.64–9.02)	0.196
75+	5.74 (1.74–18.9)	**0.004**	0.64 (0.08–4.95)	0.666	3.37 (0.46–25.0)	0.234	3.86 (0.85–17.5)	0.080
p-value (trend)		**0.005**		0.609		0.229		0.053
Height (per 5 cm increase)	1.13 (0.97–1.32)	0.110	NI		NI		1.32 (1.06–1.65)	**0.015**
BMI categories	NI		NI		NI			
Normal							1 (ref.)	
Overweight							1.21 (0.54–2.72)	0.643
Obese							1.89 (0.78–4.58)	0.158
p-value (trend)								0.159
Alcohol intake (%)	NI		NI				NI	
None					1 (ref.)			
Moderate					0.68 (0.30–1.53)	0.356		
Excessive					1.98 (0.58–6.78)	0.277		
p-value (trend)						0.277		
Smoking			NI		NI		NI	
Never	1 (ref.)							
Former	1.59 (0.95–2.65)	0.077						
Current	1.87 (1.00–30.5)	0.051						
p-value (trend)		0.051						
10-year risk of CHD (SCORE)								
Low <1%	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Medium (≥1 to <5%)	0.91 (0.33–2.47)	0.845	0.78 (0.18–3.37)	0.744	0.92 (0.14–5.84)	0.930	0.87 (0.21–3.64)	0.849
High (≥5 to <10%)	1.33 (0.36–4.95)	0.675	1.93 (0.33–11.1)	0.464	1.94 (0.21–17.7)	0.558	0.36 (0.05–2.59)	0.312
Very high (≥10%)	2.96 (0.71–12.3)	0.135	0.44 (0.05–3.65)	0.447	2.43 (0.22–26.3)	0.465	0.37 (0.05–2.56)	0.316
p-value (trend)		0.131		0.647		0.395		0.241
Clinical conditions (yes. vs no)								
Diabetes mellitus	0.47 (0.24–0.96)	**0.038**	NI		1.17 (0.39–3.49)	0.776	NI	
Renal failure	1.27 (0.60–2.67)	0.536	1.43 (0.45–4.60)	0.544	0.84 (0.27–2.63)	0.761	2.93 (0.90–9.57)	0.075
Dyslipidaemia	0.88 (0.48–1.61)	0.674	NI		0.66 (0.24–1.86)	0.435	1.63 (0.68–3.88)	0.273
Hypertension	0.91 (0.55–1.52)	0.731	3.13 (1.12–8.76)	**0.030**	1.46 (0.57–3.70)	0.431	2.12 (0.92–4.86)	0.077
Elevated resting HR	1.44 (0.88–2.35)	0.146	NI		2.02 (0.91–4.48)	0.084	1.32 (0.55–3.14)	0.534
Elevated hs cTnT	1.49 (0.80–2.77)	0.205	NI		1.40 (0.52–3.74)	0.505	1.42 (0.62–3.23)	0.402
Elevated NT-proBNP	1.44 (0.85–2.43)	0.177	2.88 (1.20–6.92)	**0.018**	3.65 (1.50–8.87)	**0.004**	1.44 (0.62–3.33)	0.392

RBBB, right bundle branch block; LBBB, left bundle branch block; LAFB, left anterior fascicular block; NIVCD, non-specific intraventricular conduction delay; tot., total number of participants included in the analysis; NI, Not included; bpm, beats per minute; BMI, body mass index; CHD, coronary heart disease; hs cTnT, high-sensitivity cardiac troponin T; HR; heart rate. Results are expressed as multivariable-adjusted odds ratio (95% confidence interval). Analysis using logistic regression. Model 2 tested the same covariates as model 1, further adjusting for antiarrhythmic drugs, potassium levels and history of cardiovascular disease. Significant values are indicated in bold.

Table 4
Multivariable associations between intraventricular conduction disturbances subtypes with clinical characteristics of participants according to model 3, CoLaus|PsyCoLaus study, Lausanne, Switzerland, 2014–2017.

	RBBB (tot. = 3364)		LBBB (tot. = 3295)		LAFB (tot. = 3299)		NIVCD (tot. = 3313)	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Man vs. woman	2.26 (1.15–4.43)	**0.018**	0.51 (0.15–1.77)	0.287	2.87 (0.91–9.10)	0.072	4.71 (1.46–15.2)	**0.010**
Age categories (years)								
45–54	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
55–64	2.64 (1.03–6.76)	**0.043**	2.32 (0.49–10.9)	0.286	1.37 (0.23–8.30)	0.729	0.96 (0.28–3.30)	0.953
65–74	3.72 (1.28–10.8)	**0.016**	1.62 (0.25–10.7)	0.614	2.59 (0.35–19.2)	0.353	1.96 (0.51–7.59)	0.328
75+	5.67 (1.72–18.7)	**0.004**	0.85 (0.09–7.74)	0.889	7.86 (0.89–69.7)	0.064	2.62 (0.55–12.4)	0.225
p-value (trend)		**0.005**		0.821		0.062		0.166
Height (per 5 cm increase)	1.13 (0.97–1.32)	0.129	1.43 (1.08–1.91)	**0.014**	0.96 (0.73–1.26)	0.754	1.33 (1.06–1.66)	**0.014**
BMI categories								
Normal	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Overweight	1.06 (0.65–1.74)	0.803	1.60 (0.61–4.21)	0.341	1.12 (0.44–2.85)	0.812	1.28 (0.57–2.89)	0.545
Obese	0.95 (0.49–1.84)	0.882	1.61 (0.50–5.17)	0.424	2.29 (0.81–6.43)	0.117	2.04 (0.82–5.05)	0.123
p-value (trend)		0.883		0.424		0.117		0.123
Alcohol intake (%)								
None	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Moderate	1.32 (0.74–2.33)	0.347	0.65 (0.26–1.62)	0.353	0.54 (0.23–1.26)	0.154	1.47 (0.61–3.55)	0.392
Excessive	1.90 (0.79–4.58)	0.153	2.01 (0.48–8.46)	0.341	1.85 (0.53–6.54)	0.337	0.90 (0.10–7.95)	0.927
p-value (trend)		0.153		0.341		0.338		0.927
Smoking								
Never	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Former	1.56 (0.93–2.60)	0.091	0.72 (0.30–1.73)	0.464	1.27 (0.55–2.93)	0.579	0.77 (0.39–1.49)	0.434
Current	1.75 (0.92–3.33)	0.087	0.57 (0.15–2.20)	0.417	1.57 (0.48–5.13)	0.458	0.34 (0.10–1.23)	0.101
p-value (trend)		0.087		0.417		0.458		0.102
10-year risk of CHD (SCORE)								
Low <1%	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Medium (≥1 to <5%)	0.90 (0.33–2.45)	0.834	0.77 (0.16–3.79)	0.745	0.53 (0.08–3.59)	0.512	1.04 (0.24–4.48)	0.955
High (≥5 to <10%)	1.31 (0.35–4.89)	0.692	1.99 (0.23–17.3)	0.531	0.85 (0.08–9.01)	0.892	0.51 (0.07–3.88)	0.519
Very high (≥10%)	2.96 (0.71–12.3)	0.135	0.63 (0.05–8.53)	0.726	0.96 (0.07–12.6)	0.972	0.74 (0.10–5.64)	0.770
p-value (trend)		0.131		0.918		0.938		0.636
Clinical conditions (yes vs. no)								
Diabetes mellitus	0.49 (0.24–1.00)	**0.049**	0.56 (0.10–3.16)	0.509	0.93 (0.31–2.83)	0.898	0.52 (0.19–1.42)	0.202
Renal failure	1.32 (0.62–2.79)	0.470	1.69 (0.49–5.89)	0.408	0.83 (0.25–2.75)	0.754	3.44 (1.04–11.4)	**0.043**
Dyslipidaemia	0.86 (0.47–1.58)	0.625	1.03 (0.34–3.09)	0.958	0.70 (0.24–1.98)	0.497	1.58 (0.66–3.81)	0.306
Hypertension	0.92 (0.55–1.55)	0.762	2.93 (1.02–8.39)	**0.045**	1.28 (0.49–3.33)	0.607	2.14 (0.93–4.92)	0.073
Elevated resting HR	1.45 (0.88–2.37)	0.143	0.94 (0.34–2.65)	0.914	1.86 (0.82–4.22)	0.136	1.06 (0.50–2.27)	0.874
Elevated hs cTnT	1.51 (0.81–2.80)	0.191	0.76 (0.18–3.27)	0.717	1.02 (0.36–2.90)	0.971	1.49 (0.62–3.58)	0.368
Elevated NT-proBNP	1.44 (0.85–2.43)	0.177	3.11 (1.24–7.80)	**0.015**	4.43 (1.78–11.0)	**0.001**	1.42 (0.62–3.27)	0.412

RBBB, right bundle branch block; LBBB, left bundle branch block; LAFB, left anterior fascicular block; NIVCD, non-specific intraventricular conduction delay; tot., total number of participants included in the analysis; bpm, beats per minute; BMI, body mass index; CHD, coronary heart disease; hs cTnT, high-sensitivity cardiac troponin T; HR; heart rate. Results are expressed as multivariable-adjusted odds ratio (95% confidence interval). Sensitivity analysis using logistic regression. Model 3 included all covariates, but adjusting for antiarrhythmic drugs, potassium levels and history of cardiovascular disease. Significant values are indicated in bold.

mellitus; those findings are partly in agreement with Bussink et al., who found no association between RBBB and diabetes mellitus [4]. Still, the role of diabetes mellitus cannot be completely ruled out: diabetes mellitus has been shown to increase cardiac fibrosis [27] and inversely, participants with RBBB tend to have more diabetes mellitus, possibly because RBBB has been suggested to increase heart failure [3], thus decreasing physical activity tolerance and consequently increasing the risk of diabetes mellitus.

Overall, the factors associated with RBBB may reflect a right ventricular degenerative evolutive process as already suggested in an older study [28], although larger population studies are needed to confirm this hypothesis.

4.3. Clinical factors associated with left bundle branch block

LBBB was positively associated with hypertension and elevated NT-proBNP. The association with hypertension is in line with a previous study that found a higher prevalence of hypertension in the LBBB group compared to the no conduction defects group [3]. A possible explanation is that hypertension increases left ventricular afterload, thus favouring left bundle branch stretching. This is supported by an older study which showed that left ventricular hypertrophy (often found in patients with hypertension) was more frequently seen in participants who developed LBBB than in the one who did not [29]. On the other way, participants with LBBB are more likely to have elevated NT-proBNP, which has been associated with higher risk of developing hypertension [30]. The association between LBBB and elevated NT-proBNP, a biomarker of cardiac dysfunction and heart failure, is in accordance with Rasmussen et al., who observed that LBBB was predictive of heart failure [3]. Interestingly, these results suggest that LBBB could be the expression of an underlying or emerging cardiomyopathy.

4.4. Clinical factors associated with left anterior fascicular block

LAFB was positively associated with elevated NT-proBNP. To our knowledge, this association has not been described before. Still, it is in accordance with the conclusions of Mandyam and al., who found in an older population of patients that LAFB was associated with an increased risk of atrial fibrillation, congestive heart failure and death [7].

4.5. Clinical factors associated with non-specific intraventricular conduction disturbances

NIVCD is a complex entity that is not yet clinically and pathophysiologically fully understood [31]. In this study, NIVCD was positively and consistently associated with male sex and height. Male participants had approximately a fivefold increase in the likelihood of NIVCD, which might be explained by hormonal differences, similarly to RBBB.

Interestingly, few studies have assessed the association between height and ECG anomalies. Kofler and al. found that genetically determined height was positively associated with QRS duration [32]. A plausible explanation is that tall people could have longer conduction pathways, which would be more prone to slowing of the electric signal, even in the absence of a specific conduction block (bundle branches of fascicles) [31]. However, the association disappeared after stepwise analysis. Hence, the effect of height should be further tested.

NIVCD was positively associated with renal failure in two out of three models. The positive association is in line with a review showing that interstitial cells in heart and kidney have common communication systems upregulating fibrosis [33]. NIVCD was also positively associated with hypertension, although this association did not reach statistical significance in all models. Hypertension was also associated with LBBB; hence, hypertension may impact either specifically the left bundle branch, or non-specifically the ventricular conduction pathways. Inversely, both NIVCD and LBBB might increase the risk of hypertension.

4.6. Study limitations

This study presents several limitations. First, excluded participants presented with higher levels of variables significantly associated with intraventricular conduction disturbances, leading to a possible underestimation of the true prevalence of the intraventricular conduction disturbances subtypes. However, sensitivity analysis using inverse probability weighting and parsimonious analysis led to similar results. Second, the sample included mostly Caucasians aged between 45 and 86 years and results may not be applicable in other ethnicities or other age groups. Third, the number of participants with LBBB and LAFB was small (<35), thus leading to a relatively low statistical power. Still, this is a limitation of most studies on this topic [10] and it would be interesting to perform a meta-analysis of the results of each study to better identify the factors associated with each intraventricular conduction disturbances subtypes. Fourth, the overall sample size (3704) was relatively small, but the number of candidate associated factors was large, which was not the case for bigger studies [3,4,10]. Last, as a cross-sectional study, no causal inference could be deducted; the ongoing CoLaus|PsyCoLaus follow-up will help obtaining this information.

4.7. Conclusion

Our results show that, in a sample of the Swiss middle-aged population, the clinical factors associated with intraventricular conduction disturbances differ according to each subtype: male sex and ageing for RBBB; hypertension and elevated NT-proBNP for LBBB; elevated NT-proBNP for LAFB; and male sex and increased height for NIVCD. These results will help understand the pathophysiological mechanisms of intraventricular conduction disturbances and better interpret these abnormalities in the clinical context.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.12.012.

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