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Clinical and biological determinants of P-wave duration: Cross-sectional data from the population-based CoLaus/PsyColaus-study

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ABSTRACT

Objectives: P-wave duration (PWD) is associated with the development of atrial arrhythmias, cardiovascular (CV) and all-cause mortality. With this study, we aimed to assess the distribution and determinants of PWD in the general population.

Design: Cross-sectional study using data collected between 2014 and 2016.

Setting: In the population-based cohort CoLaus/PsyColaus, Lausanne, Switzerland, we used 12-lead electrocardiograms (ECGs) to measure PWD. Potential demographic, clinical and biological determinants of PWD were collected by questionnaire, anthropometry, blood pressure measurement and biological assays.

Participants: Data from 3459 participants (55% women, 62±10 years, 93% Caucasian) were included. Participants were excluded if they presented 1) atrial fibrillation/atrial flutter on the study ECG or Wolf-Parkinson-White ECG pattern; 2) missing or non-interpretable ECG and 3) missing phenotypic data.

Primary outcome measure: Determine 1) the PWD distribution and 2) the demographic, clinical and biological determinants of PWD in a large population-based cohort.

Results: Median and interquartile range of PWD was 112 [102-120] ms. In the multivariable analyses, PWD was significantly associated with age ($p<0.001$) and height ($p<0.001$), with an adjusted regression coefficient (95% CI) of 0.29 ms/y (0.22-0.36) and 0.31 ms/cm (0.27-0.36), respectively. PWD, given thereafter in ms with adjusted mean ± standard error, was significantly ($p<0.05$) associated with (a) gender (woman 110.0±0.4; man 112.1±0.4), (b) BMI (normal 110.1±0.4; overweight 110.9±0.4; obese 112.9±0.5), (c) abdominal obesity (no 110.5±0.3; yes 111.7±0.4), (d) hypertension (no 110.4±0.3; yes 111.6±0.4) and (e) use of antiarrhythmic medications (no 110.7±0.2; yes 113.0±0.8).

Conclusion: PWD is positively associated with age, height, male gender, obesity markers, hypertension and antiarrhythmic medications. Clinical interpretation of PWD should take these factors into consideration.

Keywords: Epidemiology; cross-sectional; P-wave duration; obesity; risk factors.

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This study evaluated the association between P-wave duration (PWD) and demographic, clinical or biological variables in a general population setting.
- A large number of covariates possibly associated with the PWD were analyzed.
- The study was conducted in a population-based sample allowing for the generalization of the results to similar Caucasian populations.
- Not having a published consensus about the measurement of PWD represents a limit of this study.

INTRODUCTION

P-wave duration (PWD) has received increasing attention during the past decades because of its association with the development of atrial arrhythmias (e.g. atrial fibrillation and flutter),(1) as well as cardiovascular (CV) and all-cause mortality.(2) A prolonged PWD may reflect the presence of structural cardiac abnormalities (atrial inflammation, fibrosis), which lead to impairment in conduction.(2) Therefore, PWD measured on a baseline electrocardiogram (ECG), a non-invasive and easily obtained tool, can be considered as a marker of structural changes affecting the atrial tissue.(3)

Many studies associated PWD with aging(3–5) and male gender.(3) Moreover, hypertension and obesity cause left ventricular hypertrophy, subsequent ventricular diastolic dysfunction and atrial enlargement, and have been linked to prolonged PWD.(2, 6) Finally, diabetes is also associated with atrial structural changes, such as fibrosis and dysregulation of connexin protein expression, both affecting PWD.(4) Hence, the identification of the demographic, clinical and biological factors associated with a prolonged PWD could be used to detect people at risk of arrhythmia and adverse CV outcomes. Such a detection offers the chance to reduce the risk of stroke and heart failure and

possibly to lower mortality rates.(7) Yet, limited information is available on the influence of each determinant on the prolongation of PWD and, importantly, no standard value of PWD has been defined in an unselected population. We used data from CoLaus/PsyColaus cohort to determine 1) the PWD distribution and 2) the demographic, clinical and biological determinants of PWD.

METHODS

Study population and design

The CoLaus/PsyColaus study is a population-based study investigating the clinical, biological and genetic determinants of CV diseases in the population of Lausanne, Switzerland. The sampling strategy and its aims have been described in details elsewhere.(8) The following inclusion criteria were applied: a) written informed consent; b) willingness to take part in the examination and to provide blood samples. The baseline study was conducted between 2003 and 2006, the first follow-up visit between April 2009 and September 2012 and the second follow-up visit between May 2014 and April 2017. Median follow-up time was 10.7 (average 10.9, range 8.8-13.6) years for the second follow-up. As ECG data was only collected during the second follow-up visit, the analysis was restricted to this period.

Examination and electrocardiography

Standard 12-lead ECGs were recorded in resting supine position at 10 mm/mV calibration and paper speed of 25 mm/s on a Cardiovit MS-2015 electrocardiograph (Schiller AG, Baar, Switzerland). PWD values in milliseconds were calculated using SEMA (V3.5, Schiller AG, Baar, Switzerland) as previously described.(9) A former work demonstrated a good concordance between PWD calculated by Schiller's algorithm and manually measured PWD.(10) Therefore, calculated PWD values were used as references for this study, with two exceptions requiring a manual determination of PWD. The first one included ECGs for which the algorithm was unable to provide a PWD value (e.g. artefacted ECGs). The second one pertained to extreme values of automatically calculated PWD (< 80 ms (< 2 standard deviation) or > 150 ms (> 2 standard deviation)), as it has been shown that such

extreme values are often inaccurate.(10) When required, PWD was manually calculated by two investigators (FB and EP). PWD was measured from the beginning of the P-wave defined as the point where the first atrial deflection departs from the isoelectric line and the end of the P-wave defined as the point where the atrial deflection returns to the isoelectric line. The two investigators identified the ECG lead where the measure would be the most accurate and the average PWD value from the two investigators was used.

Covariates

Lifestyle and socio-demographic data were collected using self-filled questionnaires. Participants were separated into two ethnic groups: Caucasian and other. Smoking status was defined as never, former, and current smokers. Alcohol consumption was categorized into non-drinkers, low risk (1-13 units/week), medium risk (14-27 units/week) and high risk (> 28 units/week). Personal and family history of CV diseases (myocardial infarction, angina pectoris, percutaneous revascularization or coronary bypass grafting, stroke or transient ischemic attack), the use of chronotropic medications (class I, II, III and IV antiarrhythmics and digitalis antiarrhythmic) or tricyclic antidepressants were also collected in the questionnaire. Details on anthropometric, blood pressure, and biological measures are described in the Appendix 1.

Exclusion criteria

Participants were excluded from the analysis if they presented 1) atrial fibrillation/atrial flutter on the study ECG or Wolf-Parkinson-White ECG pattern (present on the digital or manual analysis); 2) missing or non-interpretable ECG and 3) missing phenotypic data.

Patient and public involvement

No patients or public were involved in this study design, conduct or analysis.

Statistical analyses

Statistical analyses were performed using Stata version 15.1 for windows (Stata Corporation, College Station, Texas, USA). Results were expressed as number of participants (percentage) for

categorical data and average ± standard deviation or percentiles (10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th}) for continuous data.

The bivariate associations between PWD and continuous variables were assessed through simple linear regression. The bivariate associations between PWD and categorical variables were assessed using Kruskal-Wallis test.

Variables significantly associated with PWD in the bivariate analysis were then carried forward for multivariable analysis. The multivariable analysis was conducted using analysis of variance, and two models were applied. Model 1 was applied for each variable significantly associated with PWD in the bivariate analysis and adjusted for age, height and gender. Model 2 included all variables significantly associated with PWD in Model 1, including age, height and gender. As BMI and abdominal obesity categories were closely related, analyses were conducted separately for each marker (Models 2A and 2B for BMI and waist, respectively). Results were expressed as multivariable-adjusted mean ± standard error for categorical values and as adjusted regression coefficient for continuous variables. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Selection procedure and characteristics of participants

Of the initial 4881 participants at the second follow-up, 3459 (70.9%) were included. The selection procedure is summarized in Figure 1 and the baseline characteristics of the study sample are shown in Table 1. The majority of participants were Caucasian and 55% were women. Mean (±SD) age and BMI were 62±10 years and 26.4±4.6 kg/m^2, respectively. One fifth of the participants smoked, two-thirds had dyslipidaemia, 45% had hypertension and 8.5% were diabetic. One quarter presented with metabolic syndrome and one out of 13 reported a previous history of CV disease.

The characteristics of the excluded population are shown in Table 1 for comparison. Significant differences between both populations were observed for age, BMI categories, alcohol

use, personal and family history of CV diseases, hypertension, dyslipidemia, diabetes, renal failure, use of antiarrhythmic medications, as well as for blood levels of troponin, CRP and NT-pro-BNP.

Table 1. Baseline characteristics of the study population, CoLaus/PsyColaus study, Lausanne, Switzerland, 2014-2016.

	Included	Excluded	P-value
All	3459	1422	
Age in years (mean; SD)	62 ±10	65 ±11	<0.001
Gender			
Men	1543 (44.6)	649 (45.6)	
Women	1916 (55.4)	773 (54.4)	
Race/ethnicity			
Caucasian	3202 (92.6)	1313 (92.3)	
Other	257 (7.4)	109 (7.7)	
BMI categories			0.005
Normal	1405 (40.6)	452 (44.2)	
Overweight	1415 (40.9)	360 (35.2)	
Obese	639 (18.5)	210 (20.6)	
Abdominal obesity	1298 (37.5)	395 (38.5)	0.562
Smoking			0.952
Never	1455 (42.1)	431 (41.6)	
Former	1349 (39.0)	405 (39.1)	
Current	655 (18.9)	200 (19.3)	
Alcohol use			<0.001
Non drinker	908 (26.3)	267 (34.2)	
Low risk	2076 (60.0)	412 (52.8)	
Medium risk	386 (11.2)	87 (11.1)	
High risk	89 (2.6)	15 (1.9)	
Personal history of CVD	309 (8.9)	209 (14.7)	<0.001
Family history of CVD	1344 (38.9)	421 (29.6)	<0.001
Hypertension	1544 (44.6)	719 (58.6)	<0.001
Dyslipidaemia	2444 (70.7)	1064 (74.8)	0.003
Diabetes	294 (8.5)	188 (17.1)	<0.001
Metabolic syndrome	955 (27.6)	304 (30.6)	0.065
Renal failure	373 (10.8)	163 (15.5)	<0.001
Antiarrhythmic medications	342 (9.9)	215 (15.1)	<0.001
Antidepressant medications	35 (1.0)	15 (1.1)	0.892
Troponin T > 14 ng/l	226 (8.9)	156 (19.3)	<0.001
CRP ≥ 5 mg/L	285 (8.2)	111 (15.0)	<0.001

NT-proBNP > 125 pg/ml	702 (32.6)	365 (51.3)	<0.001

Abbreviations: BMI, Body Mass Index; CVD, cardiovascular disease; Please refer to the methods and Appendix 1 for the definition of each characteristic. In column excluded, totals might not add to 1422 due to missing data. Results are expressed as mean standard deviation for continuous variables and as number of participants (column percentage) for categorical variables. Between-group comparisons performed using t-test for continuous variables and chi-square for categorical variables.

PWD measure and distribution

A total of 351 ECG (10.1%) needed a manual determination of PWD according to the previously mentioned criteria. The PWD distribution in the overall sample is illustrated in Figure 2; median and [interquartile range] of PWD were 112 [102-120] ms.

Association of PWD with demographic, clinical and biological markers

The bivariate associations between PWD and the demographic, clinical, biological markers of interest are summarized in Table 2 (categorical variables only). Longer PWD were found in men; in participants with increased BMI or waist circumference; in former smokers; in participants with increased alcohol consumption, hypertension, dyslipidemia, diabetes, metabolic syndrome or renal failure; in participants with a personal history of CV disease; in participants on antiarrhythmic medications, with higher levels of troponin or NT-proBNP. Figures 3A and 3B illustrate the linear association of PWD with age and height, respectively.

Table 2. Bivariate associations between P-wave duration and different demographic, clinical and biological markers, CoLaus/PsyColaus study, Lausanne, Switzerland, 2014-2016.

		P-wave duration (ms)					p-value
	N	**10%**	**25%**	**50%**	**75%**	**90%**	
All	3459	94	102	112	120	128	
Gender							<0.001
Men	1543	98	106	114	122	132	
Women	1916	90	100	110	118	124	
Race/ethnicity							0.155
Other	257	92	102	110	118	126	
Caucasian	3202	94	102	112	120	128	
BMI categories							<0.001

Normal	1405	92	102	110	118	126	
Overweight	1415	94	104	112	120	128	
Obese	639	94	104	114	122	130	
Abdominal obesity							<0.001
No	2160	94	102	110	118	126	
Yes	1298	92	104	112	122	130	
Smoking							0.004
Never	1455	92	102	110	120	128	
Former	1349	94	104	112	120	130	
Current	655	94	102	110	118	126	
Alcohol use							<0.001
Non drinker	908	90	100	110	120	128	
Low risk	2076	94	102	112	120	128	
Medium risk	386	98	104	114	122	130	
High risk	89	98	106	116	122	130	
Personal history of CVD							0.003
No	3150	94	102	112	120	128	
Yes	309	94	104	112	124	132	
Family history for CVD							0.119
No	2115	94	104	112	120	128	
Yes	1344	92	102	110	120	128	
Hypertension							<0.001
No	1915	92	102	110	118	124	
Yes	1544	96	106	114	122	130	
Dyslipidaemia							0.004
No	1015	92	102	110	120	126	
Yes	2444	94	104	112	120	128	
Diabetes							0.012
No	3160	94	102	112	120	128	
Yes	294	94	104	112	122	132	
Metabolic syndrome							<0.001
No	2503	94	102	110	120	126	
Yes	955	94	104	112	122	132	
Renal failure							0.006
No	3086	94	102	112	120	128	
Yes	373	94	104	112	122	130	
Antiarrhythmic medications							<0.001
No	3117	94	102	110	120	126	
Yes	342	96	106	116	126	134	
Antidepressant medications							0.860
No	3424	94	102	112	120	128	
Yes	35	92	100	112	120	126	
Troponin ≥14 ng/L							<0.001

No	2311	94	104	112	120	130	
Yes	226	94	106	118	126	136	
CRP ≥5 mg/L							0.354
No	3174	94	102	112	120	128	
Yes	285	96	104	112	120	126	
NT-proBNP ≥125 ng/L							<0.001
No	1450	92	102	110	118	126	
Yes	702	92	104	112	122	132	

Abbreviations: ms, milliseconds; BMI, Body Mass Index; CVD, cardiovascular disease. Please refer to the methods and Appendix 1 for the definition of each characteristic.

The multivariable associations of PWD with the demographic, clinical and biological markers are summarized in Table 3. After adjusting for age, height and gender in the Model 1, only BMI categories, abdominal obesity, hypertension and antiarrhythmic medications remained significantly associated with PWD. Inclusion of all variables in the Model 2 showed age, height, gender, obesity markers (BMI or abdominal obesity) and antiarrhythmic medications to be significantly associated with PWD, while the association with hypertension was only found in the Model 2B that included abdominal obesity.

Table 3. Multivariable associations between P-wave duration and different demographic, clinical and biological markers, CoLaus/PsyColaus study, Lausanne, Switzerland, 2014-2016.

Characteristics	Model 1	P-value	Model 2A	P-value	Model 2B	P-value
Age (continuous)	-		0.29 (0.22 - 0.36)	<0.001	0.30 (0.25 - 0.35)	<0.001
Height (continuous)	-		0.31 (0.27 - 0.36)	<0.001	0.27 (0.20 - 0.34)	<0.001
Gender				<0.001		<0.001
Woman	-		110.0 ± 0.4		109.8 ± 0.4	
Man	-		112.1 ± 0.4		112.4 ± 0.4	
BMI categories		<0.001		<0.001		
Normal	109.9 ± 0.4		110.1 ± 0.4			
Overweight	110.9 ± 0.3		110.9 ± 0.4			
Obese	113.2 ± 0.5		112.9 ± 0.5			
Abdominal obesity		<0.001				0.022
No	110.4 ± 0.3				110.5 ± 0.3	
Yes	112.0 ± 0.4				111.7 ± 0.4	
Smoking		0.628				
Never	111.0 ± 0.3		-		-	
Former	111.1 ± 0.4		-		-	
Current	110.5 ± 0.5		-		-	
Alcohol use		0.859				
Non drinker	110.7 ± 0.4		-		-	
Low risk	110.9 ± 0.3		-		-	
Medium risk	111.4 ± 0.7		-		-	
High risk	111.6 ± 1.4		-		-	
Personal history of CVD		0.925				
No	110.9 ± 0.2		-		-	

Yes	111.0 ± 0.8		-		-	
Hypertension		<0.001		0.065		0.020
No	110.1 ± 0.3		110.5 ± 0.3		110.4 ± 0.3	
Yes	112.0 ± 0.3		111.5 ± 0.4		111.6 ± 0.4	
Dyslipidaemia		0.318				
No	110.6 ± 0.4		-		-	
Yes	111.1 ± 0.3		-		-	
Diabetes		0.548				
No	111.0 ± 0.2		-		-	
Yes	110.5 ± 0.8		-		-	
Metabolic syndrome		0.113				
No	110.7 ± 0.3		-		-	
Yes	111.5 ± 0.4		-		-	
Renal failure		0.866				
No	111.0 ± 0.2		-		-	
Yes	110.8 ± 0.7		-		-	
Antiarrhythmic medications		< 0.001		0.006		0.004
No	110.6 ± 0.2		110.7 ± 0.2		110.7 ± 0.2	
Yes	113.7 ± 0.7		113.0 ± 0.8		113.1 ± 0.8	
Troponin ≥14 ng/L		0.920				
No	112.4 ± 0.3		-		-	
Yes	112.5 ± 1.0		-		-	
NT-proBNP ≥125 ng/L		0.310				
No	110.5 ± 0.4		-		-	
Yes	111.2 ± 0.5		-		-	

-, not included in the model. BMI, Body Mass Index; CVD, cardiovascular disease. Results are expressed as adjusted coefficient (95% confidence interval) for continuous variables and as average ± standard error for categorical variables. Model 1: adjusted for age (continuous), height (continuous) and gender. Full model (2A and 2B): including all variables indicated. Please refer to the methods and Appendix 1 for the definition of each characteristic.

DISCUSSION

To our knowledge, this is the first study assessing the PWD and its demographic, clinical and biological determinants in the Swiss population. On a study sample of 3459 participants, we found that age, height, gender, obesity markers, hypertension and use of antiarrhythmic medications were associated with PWD.

PWD and age

We found that aging was associated with prolonged PWD, a finding also reported by others in several studies.(2, 3, 5) Electrophysiologic studies and electroanatomic mapping of the atria demonstrated abnormal conduction in older subjects,(2) which appeared to be related to atrial structural changes and to interstitial fibrosis in particular.(11) Collagenous septa separate small groups of muscular fibres, causing electrical uncoupling.(11) In addition, aging is also associated with atrial dilatation, which contributes to prolonged PWD.(12)

PWD and height

Height has been associated with electrocardiographic modifications, particularly with the prolongation of PR interval and QRS duration.(13) Still, little is known regarding the association between height and PWD. In our study, we observed that tall individuals had longer PWD. This finding fits with the literature showing that height is a strong determinant of left atrial size, and that left atrial enlargement is associated with mechanical stress responsible for slower atrial conduction.(13)

PWD and gender

Men had longer PWD than women, a finding also reported elsewhere.(2, 3, 5) The multivariable models we used may not account for all the anthropometric differences between men and women.(5) For instance, the heart size has been shown to be greater in men than in women.(12) Other factors may play a role, such as the effect of sex hormones but there is currently a paucity of data regarding the possible effect of sex hormones on PWD.(12)

PWD and obesity markers

BMI categories or abdominal obesity were positively associated with PWD, a finding also reported elsewhere.(2, 3, 14) Interestingly, obesity has well known effects on the heart, an entity known as metabolic cardiomyopathy. Obesity is responsible for structural and functional changes in cardiomyocytes independently of coronary artery disease or hypertension.(14) Regarding the metabolic cardiomyopathy, an important pathophysiological mechanism is the systemic pro-inflammatory status induced by obesity. This eventually induces low-grade inflammation in the heart with dysfunction of subcellular components (mitochondrial dysfunction; oxidative stress and impaired calcium handling), inflammatory cell infiltration and neurohumoral activation.(15) Advanced stages are characterized by apoptosis, adipocytosis, fibrosis and atrial remodelling.(15) A second important pathophysiological mechanism is the fatty acid accumulation in the cardiomyocytes. The normal heart reaches a balance between free fatty acid (FFA) uptake and oxidation. The increased level of circulating FFA observed in obesity eventually results in accumulation of lipid droplets within the cardiomyocytes, impacting cardiac function and promoting apoptosis also known as lipotoxic cardiomyopathy.(15, 16) Studies have shown an association between cardiomyocyte fat content and ECG changes including longer PWD.(14, 17)

PWD and hypertension

Hypertension was positively correlated with PWD after multivariable adjustments in both models (1 and 2B), an association also reported by others.(3, 7) Left ventricular hypertrophy and diastolic dysfunction caused by high blood pressure are responsible for increased atrial strain with subsequent dilatation and fibrosis.(7, 18) These changes have repercussions on electrical conduction and, therefore, PWD.(18)

PWD and antiarrhythmic medications

Antiarrhythmic medications are responsible for several electrocardiographic modifications such as PR interval, QRS or QT prolongation.(19) These medications are used to control cardiac arrhythmias through their effects on cardiomyocytes' ion channels and adrenergic receptors, thereby slowing the conduction time and increasing the refractory period.(19) Little is know about the effects

of antiarrhythmic medications on PWD. While the association between PWD and the use of antiarrhythmic medications was clearly significant in our study, our interpretation is limited because the various Vaughan Williams antiarrhythmic classes were considered as a single group by study design.

STUDY STRENGTHS AND LIMITATIONS

Our study was conducted in a population-based sample allowing for the generalization of the results to similar Caucasian populations. The large sample size of our study population, together with the full set of collected data, allowed us to explore associations between PWD and a number of relevant variables. All the significant associations found in our study can be easily related with underlying (patho)physiological mechanisms.

Our study has also some limitations. First, there is no published consensus about the measurement of PWD. Most studies used automated measurements provided by different softwares. Each software has its own specific algorithm susceptible to give slightly different values.(20) Second, we used the SEMA software to calculate automatically PWD values. A number of studies have included additional markers of atrial electromechanical function (i.e. P-wave indices, such as P-wave terminal force), which were not part of the results provided by the software we used. Another limitation of our study is our inability to correlate PWD with the left atrial size as determined by echocardiography, which was not part of our study design.

FUTURE DIRECTIONS

Considering the metabolic diseases' burden, incidence of cardiovascular events and death will continue to be high. PWD, as an intermediate phenotype reflecting subclinical, structural and functional changes in the atria, can be a useful marker to both assess and monitor the risk of developing AF and worse CV outcomes.(1, 7) Future work could determine if preventive

interventions (e. g. lifestyle and dietary intervention) based on the PWD have positive effects on clinical outcomes.

CONCLUSION

In a cross-sectional study conducted on a large sample of a population-based cohort, PWD was associated with age, height, male gender, obesity markers, hypertension and use of antiarrhythmic medications. Most of these associations could possibly relate to both structural and functional changes affecting the atrial tissue.

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OTHER REQUIRED STATEMENTS

Contributors

FB conducted the literature search, interpreted the results and wrote the manuscript. PM-V performed the statistical analyses and contributed to write a part of the manuscript. DG interpreted the results and thoroughly revised the manuscript for important intellectual content. FB and EP calculated manually, when required, the P-wave duration. PV and GW participated to conceiving the study. All authors have read and approved this version of the manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

The Ethics Committee of Canton Vaud (www.cer-vd.ch) approved the CoLaus/PsyColaus study (reference 16/03); the approval was renewed for the first (reference 33/09) and the second (reference 26/14) follow-ups. The full decisions can be obtained from the authors upon request. The study was performed in agreement with the Helsinki declaration and in accordance with the applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Due to the sensitivity of the data and the lack of consent for online posting, individual data cannot be made accessible. Only metadata will be made available in digital repositories. Metadata requests can also be performed via the study website www.colaus-psycolaus.ch.

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FIGURE LEGENDS

Figure 1. Selection procedure. Percentages were calculated using the baseline sample size as denominator.

Figure 2. Distribution of P-wave duration in the whole sample, CoLaus/PsyColaus study, Lausanne, Switzerland, 2014-2016.

Figure 3. A Association between P-wave duration and age. **B** Association between P-wave duration and height. The green horizontal line represents the sample average; the red line represents the linear regression.

Figure 1

A

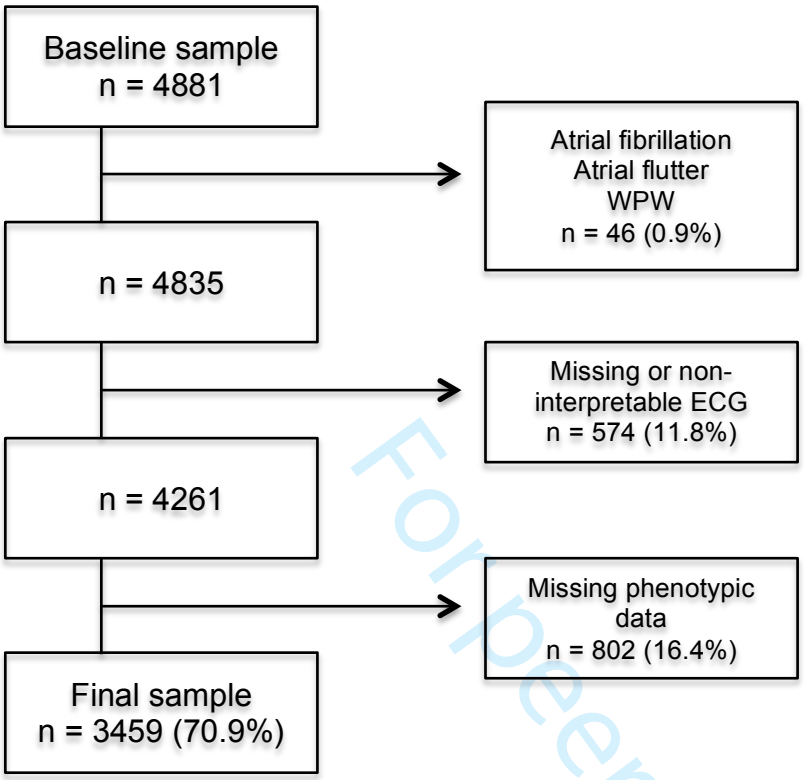


Figure 2

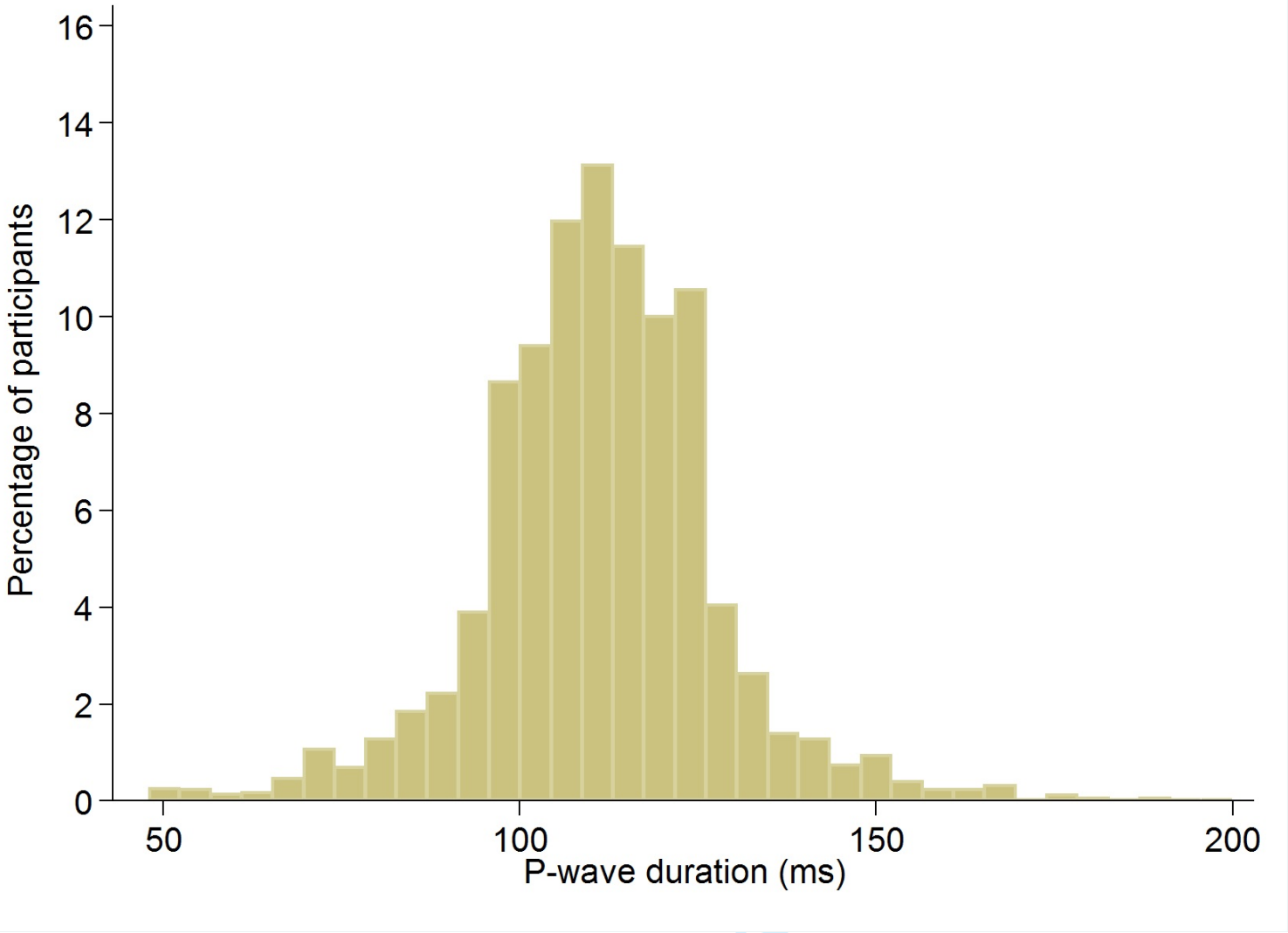
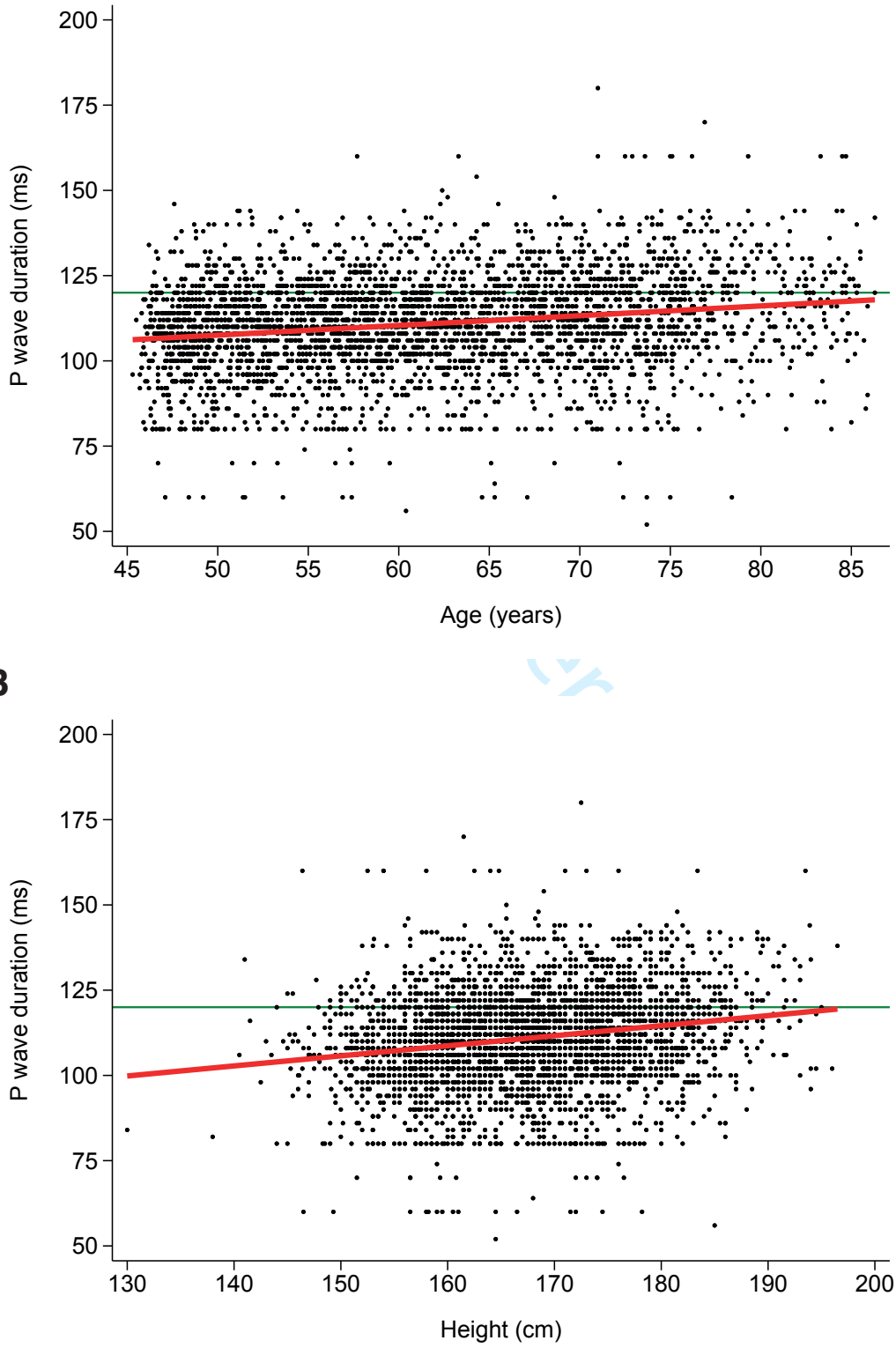


Figure 3


A
P wave duration (ms)
200
175
150
125
100
75
50
45
50
55
60
65
70
75
80
85
Age (years)
B
P wave duration (ms)
200
175
150
125
100
75
50
130
140
150
160
170
180
190
200
Height (cm)

APPENDIX 1

Anthropometric measures and blood pressure measures are described in this Appendix. It also includes a description of the methods used to determine the biological values. A specific set of references is provided for this Appendix.

Body weight and height were measured with participants standing without shoes in light indoor clothing. Weight was measured in kilograms to the nearest 0.1 kg using a Seca™ scale (Seca, Hamburg, Germany). Height was measured to the nearest 5 mm using a Seca™ height gauge (Seca, Hamburg, Germany). Body mass index (BMI) was defined as weight (kg)/height^2 (m^2). Obesity was defined as BMI ≥ 30 kg/m^2, overweight as BMI ≥ 25 and < 30 kg/m^2 and normal as BMI ≤ 25 kg/m^2. Due to the small number of underweight participants (n=55), they were included in the normal category.

Waist circumference was measured mid-way between the lowest rib and the iliac crest and abdominal obesity was defined as waist circumference > 102 cm or > 88 cm for men and women respectively.(1)

Blood pressure (BP) was measured thrice on the left arm after at least 10 minutes rest in the seated position using a clinically validated automated oscillometric device (Omron® HEM-907, Matsusaka, Japan) with a standard cuff, or a large cuff if arm circumference was ≥ 33 cm. The average of the last two measurements was used. Hypertension was defined as mean systolic BP (SBP) ≥ 140 mmHg and/or a mean diastolic BP (DBP) ≥ 90 mmHg and/or use of anti-hypertensive medication.

Venous blood samples (50 mL) were drawn in the fasting state. All biological assays were performed at the clinical laboratory of the Lausanne University Hospital within 2 hours of blood collection on fresh samples. Glycated haemoglobin (HbA1c) was measured by high performance liquid chromatography (Bio-Rad, D-10^{TM}). Subjects were considered to have diabetes if they had a serum HbA1c ≥ 6.5% (≥48 nmol/mmol) and/or were taking anti-diabetic treatment.

Total cholesterol was measured by CHOD-PAP; HDL-cholesterol by CHOD-PAP + PEG + cyclodextrin; triglycerides by GPO-PAP. In our analysis, dyslipidemia was defined as triglycerides ≥ 2 mmol/l and/or LDL ≥ 3 mmol/l and/or lipid lowering treatment.

High sensitivity CRP was assessed by immunoassay (HS latex) and was considered elevated when ≥ 5 mg/l. Serum and urinary creatinine were performed by the Jaffe kinetic compensated method. Renal failure was considered when eGFR was < 60 ml/min/1.73m^2 using CKD-EPI formula. Troponine T hs and NT-proBNP were measured by electrochemiluminescence and considered elevates when ≥ 14 ng/l and 125 ng/l respectively. Biological threshold were defined based on the standard values in our clinical laboratory (Lausanne University Hospital). Since the threshold value for a positive NT-proBNP result usually increased with age, we only considered the lowest threshold value available in our laboratory (i.e. 125 ng/l), as a simple, more sensitive approach to the potential effect of this variable.

The metabolic syndrome was retained in presence of any 3 out of 5 risk factors on the basis of the JIS (Joint Interim Statement) definition. The criteria for clinical diagnosis are: elevated waist circumference (≥ 102 cm for men and ≥ 88 cm for women), elevated triglycerides (≥ 1.7 mmol/l), reduced HDL-C (< 1.0 mmol/l for men and < 1.3 mmol/l for women), elevated BP (systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg), elevated fasting glucose (≥ 5.6 mmol/l).(2)

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Clinical and biological determinants of P-wave duration: Cross-sectional data from the population-based CoLaus|PsyColaus-study

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ABSTRACT

Objectives: P-wave duration (PWD) is associated with the development of atrial arrhythmias, cardiovascular (CV) and all-cause mortality. With this study, we aimed to assess the distribution and determinants of PWD in the general population.

Design: Cross-sectional study using data collected between 2014 and 2016.

Setting: In the population-based cohort CoLaus|PsyColaus, Lausanne, Switzerland, we used 12-lead electrocardiograms (ECGs) to measure PWD. Potential demographic, clinical and biological determinants of PWD were collected by questionnaire, anthropometry, blood pressure measurement and biological assays.

Participants: Data from 3459 participants (55% women, 62±10 years, 93% Caucasian) were included. Participants were excluded if they presented 1) no sinus rhythm or paced rhythm on the study ECG or Wolff-Parkinson-White ECG pattern; 2) missing or non-interpretable ECG and 3) missing phenotypic data.

Primary outcome measure: Determine 1) the PWD distribution and 2) the demographic, clinical and biological determinants of PWD in a large population-based cohort.

Results: Median and interquartile range of PWD was 112 [102-120] ms (milliseconds). In the multivariable analyses, PWD was significantly associated with age ($p<0.001$) and height ($p<0.001$), with an adjusted regression coefficient (95% CI) of 0.29 ms/years (0.23-0.36) and 0.32 ms/cm (0.28-0.37), respectively. PWD, given thereafter in ms with adjusted mean ± standard error, was significantly ($p<0.05$) associated with (a) gender (woman 110.0±0.4; man 112.1±0.4), (b) body mass index (normal 110.1±0.4; overweight 110.9±0.4; obese 113.0±0.5), (c) abdominal obesity (no 110.5±0.3; yes 111.7±0.4) and (d) hypertension (no 110.4±0.3; yes 111.7±0.4).

Conclusion: PWD is positively associated with age, height, male gender, obesity markers and hypertension. Clinical interpretation of PWD should take these factors into consideration.

Keywords: Epidemiology; cross-sectional; P-wave duration; obesity; risk factors.

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This study evaluated the association between P-wave duration (PWD) and demographic, clinical or biological variables in a general population setting.
- A large number of covariates possibly associated with the PWD were analyzed.
- The study was conducted in a population-based sample allowing for the generalization of the results to similar Caucasian populations.
- Not having a published consensus about the measurement of PWD represents a limit of this study.

INTRODUCTION

P-wave duration (PWD) has received increasing attention during the past decades because of its association with the development of atrial arrhythmias (e.g. atrial fibrillation and flutter),(1, 2) as well as cardiovascular (CV) and all-cause mortality.(3) A prolonged PWD may reflect the presence of structural cardiac abnormalities (atrial inflammation, fibrosis), which lead to impairment in atrial conduction and interatrial conduction in particular. The latter may promote the development of an interatrial block, reflecting the conduction delay through specific myocardic fibers connecting both atria and known as the Bachmann bundle.(3–5) Interatrial block is characterized by a PWD ≥ 120 ms and a bimodal morphology; it is a distinct entity from left atrial enlargement, although they can be associated.(2, 4) Therefore, PWD measured on a baseline electrocardiogram (ECG), a non-invasive and easily obtained tool, can be considered as a marker of structural changes affecting the atrial tissue.(6)

Many studies associated PWD with aging(6–8) and male gender.(6) Moreover, hypertension and obesity cause left ventricular hypertrophy, subsequent ventricular diastolic dysfunction and atrial enlargement, and have been linked to prolonged PWD.(3, 9) Finally, diabetes is also associated with atrial structural changes, such as fibrosis and dysregulation of connexin protein expression, both affecting PWD.(7) Hence, the identification of the demographic, clinical and biological factors

associated with a prolonged PWD could be used to detect people at risk of arrhythmia and adverse CV outcomes. Such detection offers the chance to reduce the risk of stroke and heart failure and possibly to lower mortality rates.(10) Yet, limited information is available on the influence of each determinant on the prolongation of PWD. Although PWD cut-offs of 110-120 ms (milliseconds) have been proposed, no standard value of PWD has been defined in an unselected population. We used data from CoLaus|PsyColaus cohort to determine 1) the PWD distribution and 2) the demographic, clinical and biological determinants of PWD.

METHODS

Study population and design

The CoLaus|PsyColaus study is a population-based study investigating the clinical, biological and genetic determinants of CV diseases. The sampling strategy and its aims have been described in details elsewhere.(11) In summary, a non-stratified, representative sample of the population of Lausanne, Switzerland, was recruited between 2003 and 2006, including 6733 participants. The following inclusion criteria were applied: a) aged between 35 and 75 years; b) written informed consent; c) willingness to take part in the examination and to provide blood samples. Participants were invited to attend the Lausanne University Hospital for data collection at baseline and subsequent follow-ups. Each visit included a health questionnaire, a physical examination, and blood tests.

The first follow-up visit was conducted between April 2009 and September 2012 and the second follow-up visit between May 2014 and April 2017. Mean follow-up time was 10.7 (range 8.8-13.6) years for the second follow-up. As ECG data was only collected during the second follow-up, only data collected during the second follow-up was considered.

Electrocardiography

Standard 12-lead ECGs were recorded in resting supine position at 10 mm/mV calibration and paper speed of 25 mm/s on a Cardiovit MS-2015 electrocardiograph (Schiller AG, Baar,

Switzerland). Digital ECGs were stored in an anonymised database of SEMA Data Management System (V3.5, Schiller AG, Baar, Switzerland). ECG measurements, including PWD values, were automatically determined in ms by Schiller AG algorithms based on all 12-leads and the reconstitution of an average beat.(12) A former work demonstrated a good concordance between PWD calculated by Schiller's algorithm and manually measured PWD.(13) Therefore, calculated PWD values were used as references for this study, with two exceptions requiring a manual determination of PWD. The first one included ECGs for which the algorithm was unable to provide a PWD value (e.g. artefacted ECGs, unstable baseline, inverted electrodes). The second one pertained to extreme values of automatically calculated PWD (< 80 ms (< 2 standard deviation) or > 150 ms (> 2 standard deviation)), as it has been shown that such extreme values are often inaccurate.(13) When required, PWD was manually calculated in ms by two investigators (FB and EP). PWD was measured from the beginning of the P-wave defined as the point where the first atrial deflection departs from the isoelectric line and the end of the P-wave defined as the point where the atrial deflection returns to the isoelectric line. The two investigators identified the ECG lead where the measure would be the most accurate and the mean PWD value from the two investigators was used.

Covariates

Lifestyle and socio-demographic data were collected using self-filled questionnaires. Participants were separated into two ethnic groups: Caucasian and other. Smoking status was defined as never, former, and current smokers. Alcohol consumption was categorized into non-drinkers, low risk (1-13 units/week), medium risk (14-27 units/week) and high risk (> 28 units/week). Personal and family history of CV diseases (myocardial infarction, angina pectoris, percutaneous revascularization or coronary bypass grafting, stroke or transient ischemic attack), the use of tricyclic antidepressants were also collected in the questionnaire. Details on anthropometric, blood pressure, and biological measures are described in the Appendix.

Exclusion criteria

Participants were excluded from the analysis if they presented 1) no sinus rhythm or paced rhythm on the study ECG or Wolff-Parkinson-White ECG pattern (present on the digital or manual analysis); 2) missing or non-interpretable ECG (artefacted, unstable baseline, inverted electrodes) and 3) missing phenotypic data.

Patient and public involvement

No patients or public were involved in this study design, conduct or analysis.

Statistical analyses

Statistical analyses were performed using Stata version 15.1 for windows (Stata Corporation, College Station, Texas, USA). Results were expressed as number of participants (percentage) for categorical data and mean ± standard deviation or percentiles (10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th}) for continuous data.

T-test for continuous variables and chi-square for categorical variables were used to compare included and excluded participants as well as participants with a PWD < or ≥ 120 ms. The bivariate associations between PWD and continuous variables were assessed through simple linear regression. The bivariate associations between PWD and categorical variables were assessed using Kruskal-Wallis test.

Variables significantly associated with PWD in the bivariate analysis were then carried forward for multivariable analysis. The multivariable analysis was conducted using analysis of variance, and two models were applied. Model 1 was applied for each individual variable significantly associated with PWD in the bivariate analysis and adjusted for age, height and gender. Model 2 included all variables significantly associated with PWD in Model 1, including age, height and gender. As body mass index (BMI) and abdominal obesity categories were closely related, analyses were conducted separately for each marker (Models 2A and 2B for BMI and waist circumference, respectively). Results were expressed as multivariable-adjusted mean ± standard error for categorical values and as adjusted regression coefficient for continuous variables. As a sensitivity analysis,

multivariable analysis was repeated after exclusion of all the ECGs that required a manual determination of PWD. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Selection procedure and characteristics of participants

Of the initial 4881 participants at the second follow-up, 3459 (70.9%) were included. The selection procedure is summarized in Figure 1. The majority of participants were Caucasian and 55% were women. Mean (±SD) age and BMI were 62±10 years and 26.4±4.6 kg/m^2, respectively. 70% of the participants had dyslipidaemia, 45% had hypertension, 19% smoked and 8.5% were diabetic. 28% presented with metabolic syndrome and 9% reported a previous history of CV disease.

The characteristics of the excluded population and comparison between participants with PWD < 120 and ≥ 120 ms are shown in the Appendix in Supplemental Table 1 and Supplemental Table 2, respectively. Significant differences between both populations were observed for age, BMI categories, alcohol use, personal history of CV diseases, hypertension, dyslipidemia, diabetes, renal failure, as well as for blood levels of troponin and NT-pro-BNP.

PWD measure and distribution

A total of 351 ECGs, i.e. 10% of the ECGs, needed a manual determination of PWD according to the previously mentioned criteria: 101 (29%) for extreme automatically calculated PWD (> or < 2 SD), and 250 (71%) for automatic assessment inability. The PWD distribution in the overall sample is illustrated in Figure 2; median and [interquartile range] of PWD were 112 [102-120] ms. Prevalence of PWD ≥ 120 ms was 21% (confidence interval: 20-23%).

Association of PWD with demographic, clinical and biological markers

The bivariate associations between PWD and the demographic, clinical, biological markers of interest are summarized in Table 1 (categorical and continuous variables). Longer PWD were found in elderly; in men; in participants with increased BMI or waist circumference; in former smokers; in participants with increased alcohol consumption, hypertension, dyslipidemia, diabetes, metabolic

syndrome or renal failure; in participants with a personal history of CV disease; in participants with higher levels of troponin or NT-proBNP. Figures 3a and 3b illustrate the linear and positive association of PWD with age and height, respectively. Supplemental Figure 1 shows mean values of PWD in males and females by age.

Table 1. Baseline characteristics of the study population and bivariate associations between P-wave duration and different demographic, clinical and biological markers, CoLaus|PsyColaus study, Lausanne, Switzerland, 2014-2016.

		P-wave duration (ms)					p-value
	N	10%	25%	50%	75%	90%	
All	3459 (100%)	94	102	112	120	128	
Age group							
40-49	441 (12.7)	88	98	108	116	122	<0.001
50-59	1189 (34.4)	94	102	110	118	124	
60-69	975 (28.2)	96	104	112	120	128	
70-79	704 (20.4)	96	104	114	124	132	
80+	150 (4.3)	101	108	118	126	134	
Gender							<0.001
Men	1543 (44.6)	98	106	114	122	132	
Women	1916 (55.4)	90	100	110	118	124	
Race/ethnicity							0.155
Other	257 (7.4)	92	102	110	118	126	
Caucasian	3202 (92.6)	94	102	112	120	128	
BMI categories							<0.001
Normal	1405 (40.6)	92	102	110	118	126	
Overweight	1415 (40.9)	94	104	112	120	128	
Obese	639 (18.5)	94	104	114	122	130	
Abdominal obesity							<0.001
No	2160 (62.5)	94	102	110	118	126	
Yes	1298 (37.5)	92	104	112	122	130	
Smoking							0.004
Never	1455 (42.1)	92	102	110	120	128	
Former	1349 (39.0)	94	104	112	120	130	
Current	655 (18.9)	94	102	110	118	126	
Alcohol use							<0.001
Non drinker	908 (26.3)	90	100	110	120	128	
Low risk	2076 (60.0)	94	102	112	120	128	
Medium risk	386 (11.2)	98	104	114	122	130	

High risk	89 (2.6)	98	106	116	122	130	
Personal history of CVD							0.003
No	3150 (91.1)	94	102	112	120	128	
Yes	309 (8.9)	94	104	112	124	132	
Family history for CVD							0.119
No	2115 (61.1)	94	104	112	120	128	
Yes	1344 (38.9)	92	102	110	120	128	
Hypertension							<0.001
No	1915 (55.4)	92	102	110	118	124	
Yes	1544 (44.6)	96	106	114	122	130	
Dyslipidaemia							0.004
No	1015 (29.3)	92	102	110	120	126	
Yes	2444 (70.7)	94	104	112	120	128	
Diabetes							0.012
No	3160 (91.5)	94	102	112	120	128	
Yes	294 (8.5)	94	104	112	122	132	
Metabolic syndrome							<0.001
No	2503 (72.4)	94	102	110	120	126	
Yes	955 (27.6)	94	104	112	122	132	
Renal failure							0.006
No	3086 (89.2)	94	102	112	120	128	
Yes	373 (10.8)	94	104	112	122	130	
Antidepressant medications							0.860
No	3424 (99.0)	94	102	112	120	128	
Yes	35 (1.0)	92	100	112	120	126	
Troponin ≥14 ng/L							<0.001
No	2311 (91.1)	94	104	112	120	130	
Yes	226 (8.9)	94	106	118	126	136	
CRP ≥5 mg/L							0.354
No	3174 (91.8)	94	102	112	120	128	
Yes	285 (8.2)	96	104	112	120	126	
NT-proBNP ≥125 ng/L							<0.001
No	1450 (67.4)	92	102	110	118	126	
Yes	702 (32.6)	92	104	112	122	132	

Abbreviations: ms, milliseconds; BMI, Body Mass Index; CVD, cardiovascular disease. Please refer to the methods and Appendix for the definition of each characteristic. Results are expressed as deciles or quartiles. Between-group comparisons performed using non-parametric Kruskal-Wallis test.

The multivariable associations of PWD with the demographic, clinical and biological markers are summarized in Table 2. After adjusting for age, height and gender in the Model 1, only BMI categories, abdominal obesity and hypertension remained significantly associated with PWD. Even

after inclusion of all variables in the Model 2, age, height, gender, obesity markers (BMI or abdominal obesity) and hypertension were significantly associated with PWD. These statistically significant associations were confirmed for both Models even after exclusion of manually analysed ECGs. Results are presented in Supplemental Table 3 of the Appendix.

Table 2. Multivariable associations between P-wave duration and different demographic, clinical and biological markers, CoLaus|PsyColaus study, Lausanne, Switzerland, 2014-2016.

Characteristics	Model 1	P-value	Model 2A	P-value	Model 2B	P-value
Age (continuous)	-		0.32 (0.28 - 0.37)	<0.001	0.31 (0.26 - 0.36)	<0.001
Height (continuous)	-		0.29 (0.23 - 0.36)	<0.001	0.27 (0.21 - 0.34)	<0.001
Gender				<0.001		<0.001
Woman	-		110.0 ± 0.4		109.8 ± 0.4	
Man	-		112.1 ± 0.4		112.4 ± 0.4	
BMI categories		<0.001		<0.001		
Normal	109.9 ± 0.4		110.1 ± 0.4			
Overweight	110.9 ± 0.3		110.9 ± 0.4			
Obese	113.2 ± 0.5		113.0 ± 0.5			
Abdominal obesity		<0.001				0.016
No	110.4 ± 0.3				110.5 ± 0.3	
Yes	112.0 ± 0.4				111.7 ± 0.4	
Smoking		0.628				
Never	111.0 ± 0.3		-		-	
Former	111.1 ± 0.4		-		-	
Current	110.5 ± 0.5		-		-	
Alcohol use		0.859				
Non drinker	110.7 ± 0.4		-		-	
Low risk	110.9 ± 0.3		-		-	
Medium risk	111.4 ± 0.7		-		-	
High risk	111.6 ± 1.4		-		-	
Personal history of CVD		0.925				

No	110.9 ± 0.2		-		-	
Yes	111.0 ± 0.8		-		-	
Hypertension		<0.001		0.010		0.002
No	110.1 ± 0.3		110.4 ± 0.3		110.3 ± 0.3	
Yes	112.0 ± 0.3		111.7 ± 0.4		111.8 ± 0.4	
Dyslipidaemia		0.318				
No	110.6 ± 0.4		-		-	
Yes	111.1 ± 0.3		-		-	
Diabetes		0.548				
No	111.0 ± 0.2		-		-	
Yes	110.5 ± 0.8		-		-	
Metabolic syndrome		0.113				
No	110.7 ± 0.3		-		-	
Yes	111.5 ± 0.4		-		-	
Renal failure		0.866				
No	111.0 ± 0.2		-		-	
Yes	110.8 ± 0.7		-		-	
Troponin ≥14 ng/L		0.920				
No	112.4 ± 0.3		-		-	
Yes	112.5 ± 1.0		-		-	
NT-proBNP ≥125 ng/L		0.310				
No	110.5 ± 0.4		-		-	
Yes	111.2 ± 0.5		-		-	

-, not included in the model. BMI, Body Mass Index; CVD, cardiovascular disease. Please refer to the methods and Appendix for the definition of each characteristic. Results are expressed as adjusted coefficient (95% confidence interval) for continuous variables and as mean ± standard error for categorical variables. Model 1: adjusted for age (continuous), height (continuous) and gender. Full model (2A and 2B): including all variables indicated.

DISCUSSION

To our knowledge, this is the first study assessing the PWD and its demographic, clinical and biological determinants in the Swiss population. On a study sample of 3459 participants, we found that age, height, gender, obesity markers and hypertension were associated with PWD. Moreover, we attested that 21% of the study population had a PWD ≥ 120 ms, possibly reflecting an interatrial block, which is in line with other population-based studies.(1, 2)

PWD and age

We found that aging was associated with prolonged PWD, a finding also reported by others in several studies.(3, 6, 8, 14) Electrophysiologic studies and electroanatomic mapping of the atria demonstrated abnormal conduction in older subjects,(3) which appeared to be related to atrial structural changes and to interstitial fibrosis in particular.(15) Collagenous septa separate small groups of muscular fibres, causing electrical uncoupling.(15) In addition, aging is also associated with atrial dilatation, which contributes to prolonged PWD.(16)

PWD and height

Height has been associated with electrocardiographic modifications, particularly with the prolongation of PR interval and QRS duration.(17) Still, little is known regarding the association between height and PWD. In our study, we observed that tall individuals had longer PWD. This finding fits with the literature showing that height is a strong determinant of left atrial size, and that left atrial enlargement is associated with mechanical stress responsible for slower atrial conduction.(17)

PWD and gender

Men had longer PWD than women, a finding also reported elsewhere.(3, 6, 8, 14) The multivariable models we used may not account for all the anthropometric differences between men and women.(8) For instance, the heart size has been shown to be greater in men than in women.(16) Other factors may play a role, such as the effect of sex hormones but there is currently a paucity of data regarding the possible effect of sex hormones on PWD.(16)

PWD and obesity markers

BMI categories or abdominal obesity were positively associated with PWD, a finding also reported elsewhere.(3, 6, 18) Interestingly, obesity has well known effects on the heart, an entity known as metabolic cardiomyopathy. Obesity is responsible for structural and functional changes in cardiomyocytes independently of coronary artery disease or hypertension.(18) Regarding the metabolic cardiomyopathy, an important pathophysiological mechanism is the systemic pro-inflammatory status induced by obesity. This eventually induces low-grade inflammation in the heart with dysfunction of subcellular components (mitochondrial dysfunction; oxidative stress and impaired calcium handling), inflammatory cell infiltration and neurohumoral activation.(19) Advanced stages are characterized by apoptosis, adipocytosis, fibrosis and atrial remodelling.(19) A second important pathophysiological mechanism is the fatty acid accumulation in the cardiomyocytes. The normal heart reaches a balance between free fatty acid (FFA) uptake and oxidation. The increased level of circulating FFA observed in obesity eventually results in accumulation of lipid droplets within the cardiomyocytes, impacting cardiac function and promoting apoptosis also known as lipotoxic cardiomyopathy.(19, 20) Studies have shown an association between cardiomyocyte fat content and ECG changes including longer PWD.(18, 21)

PWD and hypertension

Hypertension was positively correlated with PWD after multivariable adjustments in both models, an association also reported by others.(6, 10) Left ventricular hypertrophy and diastolic dysfunction caused by high blood pressure are responsible for increased atrial strain with subsequent dilatation and fibrosis.(10, 22) These changes have repercussions on electrical conduction and, therefore, PWD.(22)

STUDY STRENGTHS AND LIMITATIONS

Our study was conducted in a population-based sample allowing for the generalization of the results to similar Caucasian populations. The large sample size of our study population, together with the full set of collected data, allowed us to explore associations between PWD and a number of relevant variables. All the significant associations found in our study can be easily related with underlying (patho)physiological mechanisms.

Our study has also some limitations. First, there is no published consensus about the measurement of PWD. Most studies used automated measurements provided by different softwares. Each software has its own specific algorithm susceptible to give slightly different values.(23) Second, we used the SEMA software to calculate automatically PWD values. A number of studies have included additional markers of atrial electromechanical function (i.e. P-wave indices, such as P-wave terminal force), which were not part of the results provided by the software we used. Third, a significant number of ECG (10%) needed a manual determination of PWD; this might have biased the results. However, even after exclusion of the manually analysed ECGs, associations remained unchanged.

Finally, another limitation of our study is our inability to support causal association between PWD and structural myocardial abnormalities (atrial enlargement, fibro-fatty infiltration) by the lack of anatomo-histological and echocardiographic information, which was not part of our study design.

FUTURE DIRECTIONS

Considering the metabolic syndrome's burden, incidence of CV events and death will continue to be high. PWD, as an intermediate phenotype reflecting subclinical, structural and functional changes in the atria, can be a useful marker to both assess and monitor the risk of developing AF and worse CV outcomes.(1, 2, 10) Based on our results, it would be interesting to know the evolution of the participants according to their PWD. Data from echocardiography or other imaging techniques, as well as post-mortem materials, could be useful to prove the fatty or fibrotic infiltration of the atria or left atrial enlargement. Moreover, future work could determine if preventive interventions (e. g. lifestyle and dietary intervention) based on the PWD have positive effects on clinical outcomes. The ongoing follow-up of the CoLaus|PsyCoLaus cohort would provide some information in the near future.

CONCLUSION

In a cross-sectional study conducted on a large sample of a population-based cohort, PWD was associated with age, height, male gender, obesity markers and hypertension. Most of these associations could possibly relate to both structural and functional changes affecting the atrial tissue.

ACKNOWLEDGEMENTS

Nobody to acknowledge.

OTHER REQUIRED STATEMENTS

Contributors

FB conducted the literature search, interpreted the results and wrote the manuscript. PM-V performed the statistical analyses and contributed to write a part of the manuscript. DG interpreted the results and thoroughly revised the manuscript for important intellectual content. FB and EP calculated manually, when required, the PWD. PV and GW participated to conceiving the study. All authors have read and approved this version of the manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

The Ethics Committee of Canton Vaud (www.cer-vd.ch) approved the CoLaus|PsyColaus study (reference 16/03); the approval was renewed for the first (reference 33/09) and the second (reference 26/14) follow-ups. The full decisions can be obtained from the authors upon request. The study was performed in agreement with the Helsinki declaration and in accordance with the

applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Due to the sensitivity of the data and the lack of consent for online posting, individual data cannot be made accessible. Only metadata will be made available in digital repositories. Metadata requests can also be performed via the study website www.colaus-psycolaus.ch.

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FIGURE LEGENDS

Figure 1. Selection procedure. Percentages were calculated using the baseline sample size as denominator. WPW, Wolff-Parkinson-White; ECG, electrocardiogram.

Figure 2. Distribution of P-wave duration in the whole sample, CoLaus|PsyColaus study, Lausanne, Switzerland, 2014-2016. ms, milliseconds.

Figure 3. Panel A Association between P-wave duration and age. **Panel B** Association between P-wave duration and height. The dashed blue horizontal line represents the sample mean; the red line represents the linear regression. ms, milliseconds; cm, centimetres.

Figure 1

A

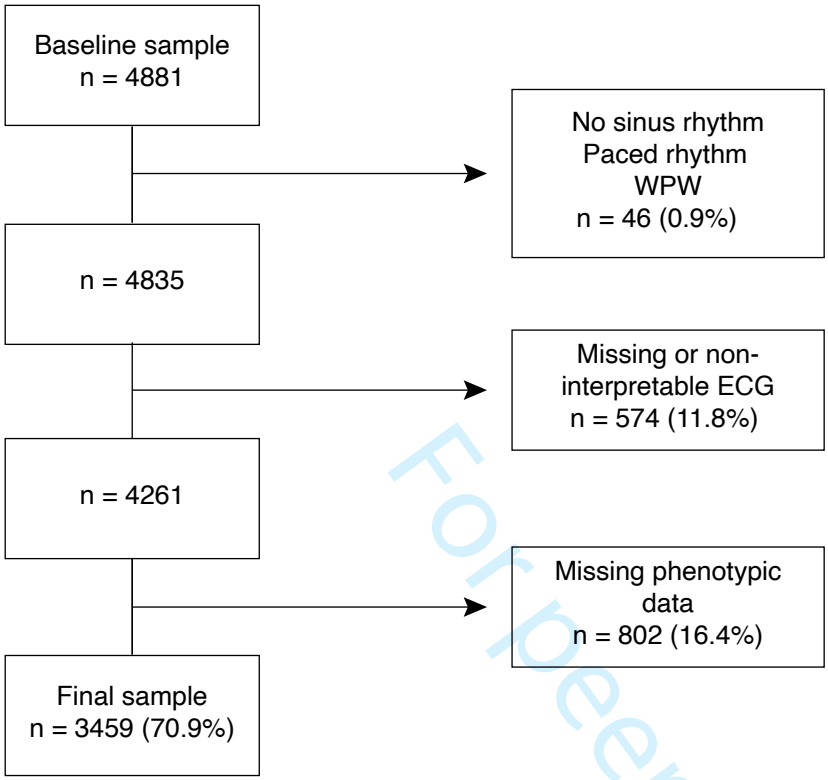


Figure 2

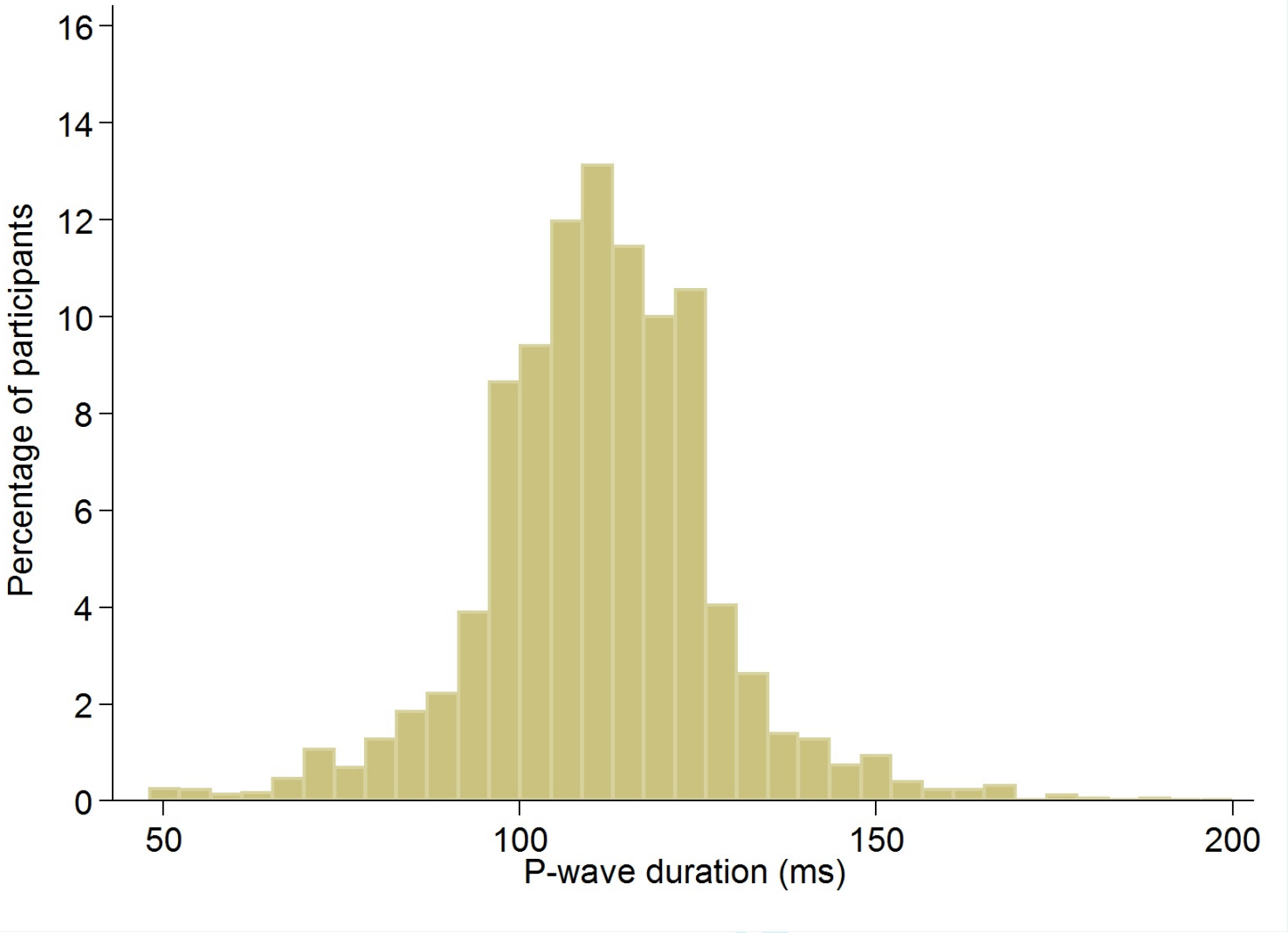
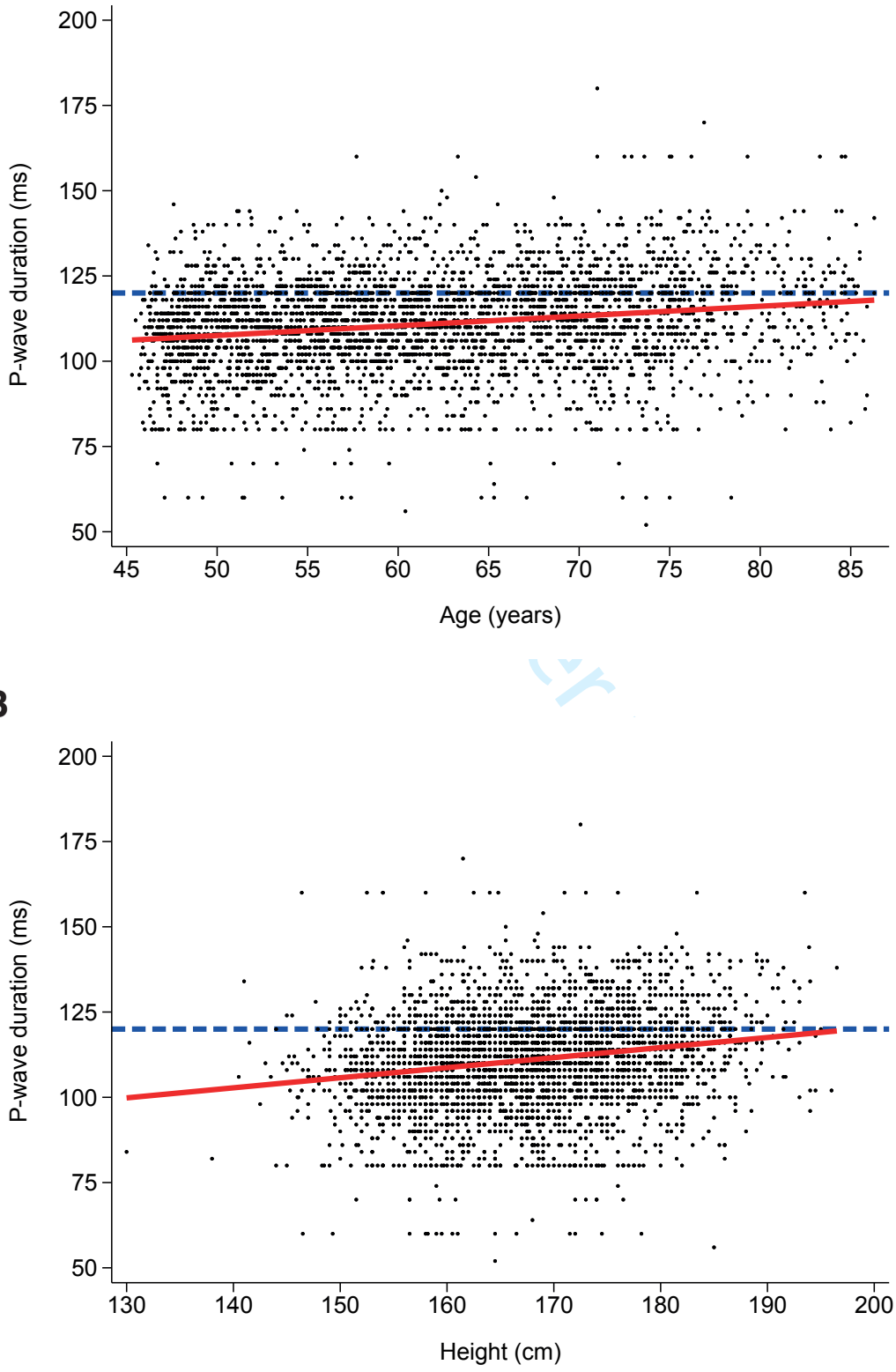
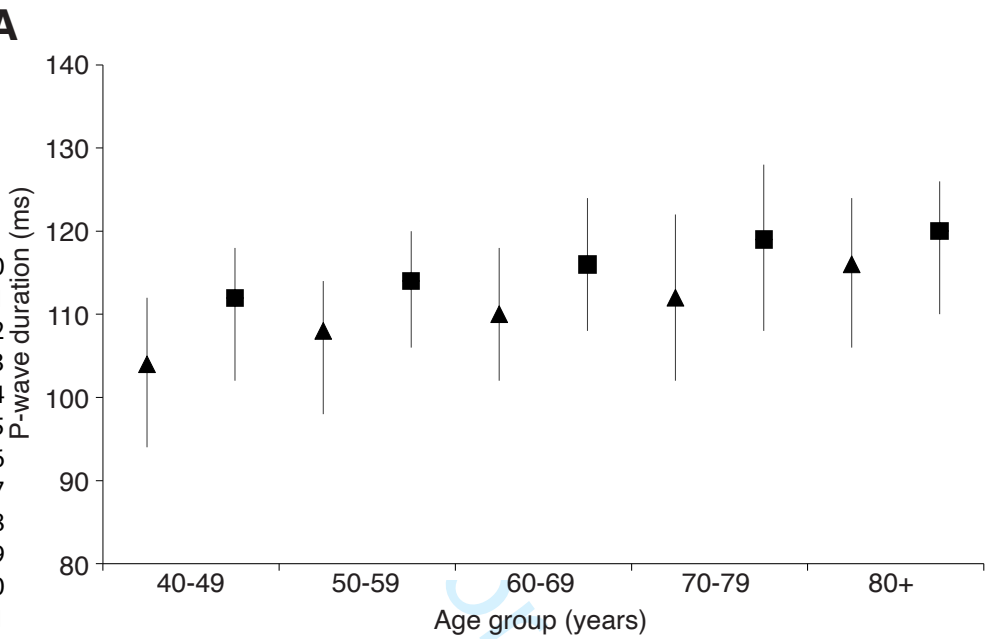


Figure 3


A
P-wave duration (ms)
200
175
150
125
100
75
50
45
50
55
60
65
70
75
80
85
Age (years)
B
P-wave duration (ms)
200
175
150
125
100
75
50
130
140
150
160
170
180
190
200
Height (cm)

Supplemental Figure 1



Supplemental Figure 1. Mean P-wave duration values of males and females by age. ms, milliseconds. Squares represent men and triangles represent women.

APPENDIX

Anthropometric measures and blood pressure measures are described in this Appendix. It also includes a description of the methods used to determine the biological values. A specific set of references is provided for this Appendix.

Body weight and height were measured with participants standing without shoes in light indoor clothing. Weight was measured in kilograms to the nearest 0.1 kg using a Seca™ scale (Seca, Hamburg, Germany). Height was measured to the nearest 5 mm using a Seca™ height gauge (Seca, Hamburg, Germany). Body mass index (BMI) was defined as weight (kg)/height^2 (m^2). Obesity was defined as BMI ≥ 30 kg/m^2, overweight as BMI ≥ 25 and < 30 kg/m^2, normal as BMI ≥ 18.5 and < 25 kg/m^2 and underweight as BMI < 18.5 kg/m^2. Due to the small number of underweight participants (n=55), they were included in the normal category.

Waist circumference was measured mid-way between the lowest rib and the iliac crest and abdominal obesity was defined as waist circumference > 102 cm or > 88 cm for men and women respectively.(1)

Blood pressure (BP) was measured thrice on the left arm after at least 10 minutes rest in the seated position using a clinically validated automated oscillometric device (Omron® HEM-907, Matsusaka, Japan) with a standard cuff, or a large cuff if arm circumference was ≥ 33 cm. The average of the last two measurements was used. Hypertension was defined as mean systolic BP (SBP) ≥ 140 mmHg and/or a mean diastolic BP (DBP) ≥ 90 mmHg and/or use of anti-hypertensive medication.

Venous blood samples (50 mL) were drawn in the fasting state. All biological assays were performed at the clinical laboratory of the Lausanne University Hospital within 2 hours of blood collection on fresh samples. Glycated haemoglobin (HbA1c) was measured by high performance liquid chromatography (Bio-Rad, D-10^{TM}). Subjects were considered to have diabetes if they had a serum HbA1c ≥ 6.5% (≥48 nmol/mmol) and/or were taking anti-diabetic treatment.

Total cholesterol was measured by CHOD-PAP; HDL-cholesterol by CHOD-PAP + PEG + cyclodextrin; triglycerides by GPO-PAP. In our analysis, dyslipidemia was defined as triglycerides ≥ 2 mmol/l and/or LDL ≥ 3 mmol/l and/or lipid lowering treatment.

High sensitivity CRP was assessed by immunoassay (HS latex) and was considered elevated when ≥ 5 mg/l. Serum and urinary creatinine were performed by the Jaffe kinetic compensated method. Renal failure was considered when eGFR was < 60 ml/min/1.73m^2 using CKD-EPI formula. Troponine T hs and NT-proBNP were measured by electrochemiluminescence and considered elevates when ≥ 14 ng/l and 125 ng/l respectively. Biological threshold were defined based on the standard values in our clinical laboratory (Lausanne University Hospital). Since the threshold value for a positive NT-proBNP result usually increased with age, we only considered the lowest threshold value available in our laboratory (i.e. 125 ng/l), as a simple, more sensitive approach to the potential effect of this variable.

The metabolic syndrome was retained in presence of any 3 out of 5 risk factors on the basis of the JIS (Joint Interim Statement) definition. The criteria for clinical diagnosis are: elevated waist circumference (≥ 102 cm for men and ≥ 88 cm for women), elevated triglycerides (≥ 1.7 mmol/l), reduced HDL-C (< 1.0 mmol/l for men and < 1.3 mmol/l for women), elevated BP (systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg), elevated fasting glucose (≥ 5.6 mmol/l).(2)

Supplemental Table 1. Complete baseline characteristics of the study population, CoLaus|PsyColaus study, Lausanne, Switzerland, 2014-2016.

	Included	Excluded	P-value
All	3459	1422	
Age in years (mean; SD)	62 ±10	65 ±11	<0.001
Gender			
Men	1543 (44.6)	649 (45.6)	
Women	1916 (55.4)	773 (54.4)	
Race/ethnicity			
Caucasian	3202 (92.6)	1313 (92.3)	
Other	257 (7.4)	109 (7.7)	
BMI categories			0.005
Normal	1405 (40.6)	452 (44.2)	
Overweight	1415 (40.9)	360 (35.2)	
Obese	639 (18.5)	210 (20.6)	
Abdominal obesity	1298 (37.5)	395 (38.5)	0.562
Smoking			0.952
Never	1455 (42.1)	431 (41.6)	
Former	1349 (39.0)	405 (39.1)	
Current	655 (18.9)	200 (19.3)	
Alcohol use			<0.001
Non drinker	908 (26.3)	267 (34.2)	
Low risk	2076 (60.0)	412 (52.8)	
Medium risk	386 (11.2)	87 (11.1)	
High risk	89 (2.6)	15 (1.9)	
Personal history of CVD	309 (8.9)	209 (14.7)	<0.001
Family history of CVD	1344 (38.9)	421 (29.6)	<0.001
Hypertension	1544 (44.6)	719 (58.6)	<0.001
Dyslipidaemia	2444 (70.7)	1064 (74.8)	0.003
Diabetes	294 (8.5)	188 (17.1)	<0.001
Metabolic syndrome	955 (27.6)	304 (30.6)	0.065
Renal failure	373 (10.8)	163 (15.5)	<0.001
Antidepressant medications	35 (1.0)	15 (1.1)	0.892
Troponin T > 14 ng/l	226 (8.9)	156 (19.3)	<0.001
CRP ≥ 5 mg/L	285 (8.2)	111 (15.0)	<0.001
NT-proBNP > 125 pg/ml	702 (32.6)	365 (51.3)	<0.001

SD, standard deviation; BMI, body mass index; CVD; cardiovascular disease; CRP, C-reactive protein. Please refer to the methods and Appendix for the definition of each characteristic. In column excluded, totals might not add to 1422 due to missing data. Results are expressed as mean ± standard deviation for continuous variables and as number of participants (column percentage) for

categorical variables. Between-group comparisons performed using t-test for continuous variables and chi-square for categorical variables.

Supplemental Table 2. Characteristics of participants with P-wave duration < 120 and ≥ 120 ms, CoLaus|PsyColaus study, Lausanne, Switzerland, 2014-2016.

	PWD < 120 ms	PWD ≥ 120 ms	P-value
All	2718	741	
Age in years (mean; SD)	61 ± 9.6	65.5 ± 10.2	<0.001
Gender			<0.001
Men	1110 (40.8)	433 (58.4)	
Women	1608 (59.2)	308 (41.6)	
Race/ethnicity			0.017
Caucasian	2501 (92.0)	701 (94.6)	
Other	217 (8.0)	40 (5.4)	
BMI categories			<0.001
Normal	1157 (42.6)	248 (33.5)	
Overweight	1106 (40.7)	309 (41.7)	
Obese	455 (16.7)	184 (24.8)	
Abdominal obesity	960 (35.3)	338 (45.6)	<0.001
Smoking			0.005
Never	1159 (42.6)	296 (40)	
Former	1024 (37.7)	325 (43.9)	
Current	535 (19.7)	120 (16.2)	
Alcohol use			0.146
Non drinker	719 (26.5)	189 (25.5)	
Low risk	1645 (60.5)	431 (58.2)	
Medium risk	288 (10.6)	98 (13.2)	
High risk	66 (2.4)	23 (3.1)	
Personal history of CVD	210 (7.7)	99 (13.4)	<0.001
Family history of CVD	1061 (39.0)	283 (38.2)	0.676
Hypertension	1121 (41.2)	423 (57.1)	<0.001
Dyslipidaemia	1899 (69.9)	545 (73.6)	0.051
Diabetes	213 (7.9)	81 (11.0)	0.007
Metabolic syndrome	691 (25.4)	264 (35.6)	<0.001
Renal failure	267 (9.8)	106 (14.3)	<0.001
Antidepressant medications	27 (1.0)	8 (1.1)	0.835
Troponin T > 14 ng/l	140 (7.4)	86 (13.3)	<0.001
CRP ≥ 5 mg/L	219 (8.1)	66 (8.9)	0.456
NT-proBNP > 125 pg/ml	493 (29.4)	209 (44.0)	<0.001

PWD, P-wave duration; ms, milliseconds; SD, standard deviation; BMI, body mass index; CVD; cardiovascular disease; CRP, C-reactive protein. Please refer to the methods and Appendix for the definition of each characteristic. Results are expressed as mean ± standard deviation or as number of participants (column percentage). Between-group comparisons performed using student t-test or chi-square.

Supplemental Table 3. Multivariable associations between P-wave duration and different demographic, clinical and biological markers, CoLaus|PsyColaus study, Lausanne, Switzerland, 2014-2016. Only computer-evaluated ECGs.

Characteristics	Model 1	P-value	Model 2A	P-value	Model 2B	P-value
Age (continuous)	-		0.29 (0.25 - 0.34)	<0.001	0.28 (0.24 - 0.33)	<0.001
Height (continuous)	-		0.27 (0.20 - 0.33)	<0.001	0.24 (0.18 - 0.30)	<0.001
Gender				<0.001		<0.001
Woman	-		110.6 ± 0.3		110.3 ± 0.3	
Man	-		112.5 ± 0.4		112.9 ± 0.4	
BMI categories		<0.001		<0.001		
Normal	110.3 ± 0.3		110.5 ± 0.3			
Overweight	111.7 ± 0.3		111.7 ± 0.3			
Obese	113.2 ± 0.5		113.0 ± 0.5			
Abdominal obesity		<0.001				<0.001
No	110.8 ± 0.3				110.9 ± 0.3	
Yes	112.6 ± 0.3				112.4 ± 0.4	
Smoking		0.716				
Never	111.6 ± 0.3		-		-	
Former	111.5 ± 0.3		-		-	
Current	111.1 ± 0.5		-		-	
Alcohol use		0.875				
Non drinker	111.3 ± 0.4		-		-	
Low risk	111.4 ± 0.3		-		-	
Medium risk	111.9 ± 0.6		-		-	
High risk	111.4 ± 1.3		-		-	
Personal history of CVD		0.632				
No	111.5 ± 0.2		-		-	

Yes	111.1 ± 0.7		-		-	
Hypertension		<0.001		0.011		0.004
No	110.7 ± 0.3		110.9 ± 0.3		110.8 ± 0.3	
Yes	112.4 ± 0.3		112.1 ± 0.3		112.2 ± 0.3	
Dyslipidaemia		0.243				
No	111.1 ± 0.4		-		-	
Yes	111.6 ± 0.2		-		-	
Diabetes		0.146				
No	111.5 ± 0.2		-		-	
Yes	110.4 ± 0.7		-		-	
Metabolic syndrome		0.064				
No	111.2 ± 0.2		-		-	
Yes	112.1 ± 0.4		-		-	
Renal failure		0.732				
No	111.5 ± 0.2		-		-	
Yes	111.2 ± 0.7		-		-	
Troponin ≥14 ng/L		0.707				
No	112.8 ± 0.3		-		-	
Yes	112.5 ± 0.9		-		-	
NT-proBNP ≥125 ng/L		0.933				
No	111.2 ± 0.3		-		-	
Yes	111.3 ± 0.5		-		-	

-, not included in the model. BMI, Body Mass Index; CVD, cardiovascular disease. Please refer to the methods and Appendix for the definition of each characteristic. Results are expressed as adjusted coefficient (95% confidence interval) for continuous variables and as mean ± standard error for categorical variables. Model 1: adjusted for age (continuous), height (continuous) and gender. Full model (2A and 2B): including all variables indicated.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5, Appendix
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5, Appendix
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	6-7
		(*e*) Describe any sensitivity analyses	6-7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7, Figure 1
		(c) Consider use of a flow diagram	7, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, Supplemental Table 1 and 2
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	7-12, Table 1 and 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-12, Table 1 and 2
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplemental Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Clinical and biological determinants of P-wave duration: Cross-sectional data from the population-based CoLaus|PsyColaus-study

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Clinical and biological determinants of P-wave duration: Cross-sectional data from the population-based CoLaus|PsyColaus-study

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ABSTRACT

Objectives: P-wave duration (PWD) is associated with the development of atrial arrhythmias, cardiovascular (CV) and all-cause mortality. With this study, we aimed to assess the distribution and determinants of PWD in the general population.

Design: Cross-sectional study using data collected between 2014 and 2016.

Setting: In the population-based cohort CoLaus|PsyColaus, Lausanne, Switzerland, we used 12-lead electrocardiograms (ECGs) to measure PWD. Potential demographic, clinical and biological determinants of PWD were collected by questionnaire, anthropometry, blood pressure measurement and biological assays.

Participants: Data from 3459 participants (55% women, 62±10 years, 93% Caucasian) were included. Participants were excluded if they presented 1) no sinus rhythm or paced rhythm on the study ECG or Wolff-Parkinson-White ECG pattern; 2) missing or non-interpretable ECG and 3) missing phenotypic data.

Primary outcome measure: Determine 1) the PWD distribution and 2) the demographic, clinical and biological determinants of PWD in a large population-based cohort.

Results: Median and interquartile range of PWD was 112 [102-120] ms (milliseconds). In the multivariable analyses, PWD was significantly associated with age ($p<0.001$) and height ($p<0.001$), with an adjusted regression coefficient (95% CI) of 0.29 ms/years (0.23-0.36) and 0.32 ms/cm (0.28-0.37), respectively. PWD, given thereafter in ms with adjusted mean ± standard error, was significantly ($p<0.05$) associated with (a) gender (woman 110.0±0.4; man 112.1±0.4), (b) body mass index (normal 110.1±0.4; overweight 110.9±0.4; obese 113.0±0.5), (c) abdominal obesity (no 110.5±0.3; yes 111.7±0.4) and (d) hypertension (no 110.4±0.3; yes 111.7±0.4).

Conclusion: PWD is positively associated with age, height, male gender, obesity markers and hypertension. Clinical interpretation of PWD should take these factors into consideration.

Keywords: Epidemiology; cross-sectional; P-wave duration; obesity; risk factors.

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This study evaluated the association between P-wave duration (PWD) and demographic, clinical or biological variables in a general population setting.
- A large number of covariates possibly associated with the PWD were analyzed.
- The study was conducted in a population-based sample allowing for the generalization of the results to similar Caucasian populations.
- Not having a published consensus about the measurement of PWD represents a limit of this study.

INTRODUCTION

P-wave duration (PWD) has received increasing attention during the past decades because of its association with the development of atrial arrhythmias (e.g. atrial fibrillation and flutter),(1–3) as well as cardiovascular (CV) and all-cause mortality.(4) A prolonged PWD may reflect the presence of structural cardiac abnormalities (atrial inflammation, fibrosis), which lead to impairment in atrial conduction and interatrial conduction in particular. The latter may promote the development of an interatrial block, reflecting the conduction delay through specific myocardic fibers connecting both atria and known as the Bachmann bundle.(4–6) Interatrial block is characterized by a PWD ≥ 120 ms and a bimodal morphology; it is a distinct entity from left atrial enlargement, although they can be associated.(2, 5) Therefore, PWD measured on a baseline electrocardiogram (ECG), a non-invasive and easily obtained tool, can be considered as a marker of structural changes affecting the atrial tissue.(7)

Many studies associated PWD with aging(7–9) and male gender.(7) Moreover, hypertension and obesity cause left ventricular hypertrophy, subsequent ventricular diastolic dysfunction and atrial enlargement, and have been linked to prolonged PWD.(4, 10) Finally, diabetes is also associated with atrial structural changes, such as fibrosis and dysregulation of connexin protein expression, both affecting PWD.(8) Hence, the identification of the demographic, clinical and

biological factors associated with a prolonged PWD could be used to detect people at risk of arrhythmia and adverse CV outcomes. Such detection offers the chance to reduce the risk of stroke and heart failure and possibly to lower mortality rates.(11) Yet, limited information is available on the influence of each determinant on the prolongation of PWD. Although PWD cut-offs of 110-120 ms (milliseconds) have been proposed, no standard value of PWD has been defined in an unselected population. We used data from CoLaus|PsyColaus cohort to determine 1) the PWD distribution and 2) the demographic, clinical and biological determinants of PWD.

METHODS

Study population and design

The CoLaus|PsyColaus study is a population-based study investigating the clinical, biological and genetic determinants of CV diseases. The sampling strategy and its aims have been described in details elsewhere.(12) In summary, a non-stratified, representative sample of the population of Lausanne, Switzerland, was recruited between 2003 and 2006, including 6733 participants. The following inclusion criteria were applied: a) aged between 35 and 75 years; b) written informed consent; c) willingness to take part in the examination and to provide blood samples. Participants were invited to attend the Lausanne University Hospital for data collection at baseline and subsequent follow-ups. Each visit included a health questionnaire, a physical examination, and blood tests.

The first follow-up visit was conducted between April 2009 and September 2012 and the second follow-up visit between May 2014 and April 2017. Mean follow-up time was 10.7 (range 8.8-13.6) years for the second follow-up. As ECG data was only collected during the second follow-up, only data collected during the second follow-up was considered.

Electrocardiography

Standard 12-lead ECGs were recorded in resting supine position at 10 mm/mV calibration and paper speed of 25 mm/s on a Cardiovit MS-2015 electrocardiograph (Schiller AG, Baar,

Switzerland). Digital ECGs were stored in an anonymised database of SEMA Data Management System (V3.5, Schiller AG, Baar, Switzerland). ECG measurements, including PWD values, were automatically determined in ms by Schiller AG algorithms based on all 12-leads and the reconstitution of an average beat.(13) A former work demonstrated a good concordance between PWD calculated by Schiller's algorithm and manually measured PWD.(14) Therefore, calculated PWD values were used as references for this study, with two exceptions requiring a manual determination of PWD. The first one included ECGs for which the algorithm was unable to provide a PWD value (e.g. artefacted ECGs, unstable baseline, inverted electrodes). The second one pertained to extreme values of automatically calculated PWD (< 80 ms (< 2 standard deviation) or > 150 ms (> 2 standard deviation)), as it has been shown that such extreme values are often inaccurate.(14) When required, PWD was manually calculated in ms by two investigators (FB and EP). PWD was measured from the beginning of the P-wave defined as the point where the first atrial deflection departs from the isoelectric line and the end of the P-wave defined as the point where the atrial deflection returns to the isoelectric line. The two investigators identified the ECG lead where the measure would be the most accurate and the mean PWD value from the two investigators was used.

Covariates

Lifestyle and socio-demographic data were collected using self-filled questionnaires. Participants were separated into two ethnic groups: Caucasian and other. Smoking status was defined as never, former, and current smokers. Alcohol consumption was categorized into non-drinkers, low risk (1-13 units/week), medium risk (14-27 units/week) and high risk (> 28 units/week). Personal and family history of CV diseases (myocardial infarction, angina pectoris, percutaneous revascularization or coronary bypass grafting, stroke or transient ischemic attack), the use of tricyclic antidepressants were also collected in the questionnaire. Details on anthropometric, blood pressure, and biological measures are described in the Appendix.

Exclusion criteria

Participants were excluded from the analysis if they presented 1) no sinus rhythm or paced rhythm on the study ECG or Wolff-Parkinson-White ECG pattern (present on the digital or manual analysis); 2) missing or non-interpretable ECG (artefacted, unstable baseline, inverted electrodes) and 3) missing phenotypic data.

Patient and public involvement

No patients or public were involved in this study design, conduct or analysis.

Statistical analyses

Statistical analyses were performed using Stata version 15.1 for windows (Stata Corporation, College Station, Texas, USA). Results were expressed as number of participants (percentage) for categorical data and mean ± standard deviation or percentiles (10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th}) for continuous data.

T-test for continuous variables and chi-square for categorical variables were used to compare included and excluded participants as well as participants with a PWD < or ≥ 120 ms. The bivariate associations between PWD and continuous variables were assessed through simple linear regression. The bivariate associations between PWD and categorical variables were assessed using Kruskal-Wallis test.

Variables significantly associated with PWD in the bivariate analysis were then carried forward for multivariable analysis. The multivariable analysis was conducted using analysis of variance, and two models were applied. Model 1 was applied for each individual variable significantly associated with PWD in the bivariate analysis and adjusted for age, height and gender. Model 2 included all variables significantly associated with PWD in Model 1, including age, height and gender. As body mass index (BMI) and abdominal obesity categories were closely related, analyses were conducted separately for each marker (Models 2A and 2B for BMI and waist circumference, respectively). Results were expressed as multivariable-adjusted mean ± standard error for categorical values and as adjusted regression coefficient for continuous variables. As a sensitivity analysis,

multivariable analysis was repeated after exclusion of all the ECGs that required a manual determination of PWD. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Selection procedure and characteristics of participants

Of the initial 4881 participants at the second follow-up, 3459 (70.9%) were included. The selection procedure is summarized in Figure 1. The majority of participants were Caucasian and 55% were women. Mean (±SD) age and BMI were 62±10 years and 26.4±4.6 kg/m^2, respectively. 70% of the participants had dyslipidaemia, 45% had hypertension, 19% smoked and 8.5% were diabetic. 28% presented with metabolic syndrome and 9% reported a previous history of CV disease.

The characteristics of the excluded population and comparison between participants with PWD < 120 and ≥ 120 ms are shown in the Appendix in Supplemental Table 1 and Supplemental Table 2, respectively. Significant differences between both populations were observed for age, BMI categories, alcohol use, personal history of CV diseases, hypertension, dyslipidemia, diabetes, renal failure, as well as for blood levels of troponin and NT-pro-BNP.

PWD measure and distribution

A total of 351 ECGs, i.e. 10% of the ECGs, needed a manual determination of PWD according to the previously mentioned criteria: 101 (29%) for extreme automatically calculated PWD (> or < 2 SD), and 250 (71%) for automatic assessment inability. The PWD distribution in the overall sample is illustrated in Figure 2; median and [interquartile range] of PWD were 112 [102-120] ms. Prevalence of PWD ≥ 120 ms was 21% (confidence interval: 20-23%).

Association of PWD with demographic, clinical and biological markers

The bivariate associations between PWD and the demographic, clinical, biological markers of interest are summarized in Table 1 (categorical and continuous variables). Longer PWD were found in elderly; in men; in participants with increased BMI or waist circumference; in former smokers; in participants with increased alcohol consumption, hypertension, dyslipidemia, diabetes, metabolic

syndrome or renal failure; in participants with a personal history of CV disease; in participants with higher levels of troponin or NT-proBNP. Figures 3a and 3b illustrate the linear and positive association of PWD with age and height, respectively. Supplemental Figure 1 shows mean values of PWD in males and females by age.

Table 1. Baseline characteristics of the study population and bivariate associations between P-wave duration and different demographic, clinical and biological markers, CoLaus|PsyColaus study, Lausanne, Switzerland, 2014-2016.

		P-wave duration (ms)					p-value
	N	10%	25%	50%	75%	90%	
All	3459 (100%)	94	102	112	120	128	
Age group							
40-49	441 (12.7)	88	98	108	116	122	<0.001
50-59	1189 (34.4)	94	102	110	118	124	
60-69	975 (28.2)	96	104	112	120	128	
70-79	704 (20.4)	96	104	114	124	132	
80+	150 (4.3)	101	108	118	126	134	
Gender							<0.001
Men	1543 (44.6)	98	106	114	122	132	
Women	1916 (55.4)	90	100	110	118	124	
Race/ethnicity							0.155
Other	257 (7.4)	92	102	110	118	126	
Caucasian	3202 (92.6)	94	102	112	120	128	
BMI categories							<0.001
Normal	1405 (40.6)	92	102	110	118	126	
Overweight	1415 (40.9)	94	104	112	120	128	
Obese	639 (18.5)	94	104	114	122	130	
Abdominal obesity							<0.001
No	2160 (62.5)	94	102	110	118	126	
Yes	1298 (37.5)	92	104	112	122	130	
Smoking							0.004
Never	1455 (42.1)	92	102	110	120	128	
Former	1349 (39.0)	94	104	112	120	130	
Current	655 (18.9)	94	102	110	118	126	
Alcohol use							<0.001
Non drinker	908 (26.3)	90	100	110	120	128	
Low risk	2076 (60.0)	94	102	112	120	128	
Medium risk	386 (11.2)	98	104	114	122	130	

High risk	89 (2.6)	98	106	116	122	130	
Personal history of CVD							0.003
No	3150 (91.1)	94	102	112	120	128	
Yes	309 (8.9)	94	104	112	124	132	
Family history for CVD							0.119
No	2115 (61.1)	94	104	112	120	128	
Yes	1344 (38.9)	92	102	110	120	128	
Hypertension							<0.001
No	1915 (55.4)	92	102	110	118	124	
Yes	1544 (44.6)	96	106	114	122	130	
Dyslipidaemia							0.004
No	1015 (29.3)	92	102	110	120	126	
Yes	2444 (70.7)	94	104	112	120	128	
Diabetes							0.012
No	3160 (91.5)	94	102	112	120	128	
Yes	294 (8.5)	94	104	112	122	132	
Metabolic syndrome							<0.001
No	2503 (72.4)	94	102	110	120	126	
Yes	955 (27.6)	94	104	112	122	132	
Renal failure							0.006
No	3086 (89.2)	94	102	112	120	128	
Yes	373 (10.8)	94	104	112	122	130	
Antidepressant medications							0.860
No	3424 (99.0)	94	102	112	120	128	
Yes	35 (1.0)	92	100	112	120	126	
Troponin ≥14 ng/L							<0.001
No	2311 (91.1)	94	104	112	120	130	
Yes	226 (8.9)	94	106	118	126	136	
CRP ≥5 mg/L							0.354
No	3174 (91.8)	94	102	112	120	128	
Yes	285 (8.2)	96	104	112	120	126	
NT-proBNP ≥125 ng/L							<0.001
No	1450 (67.4)	92	102	110	118	126	
Yes	702 (32.6)	92	104	112	122	132	

Abbreviations: ms, milliseconds; BMI, Body Mass Index; CVD, cardiovascular disease. Please refer to the methods and Appendix for the definition of each characteristic. Results are expressed as deciles or quartiles. Between-group comparisons performed using non-parametric Kruskal-Wallis test.

The multivariable associations of PWD with the demographic, clinical and biological markers are summarized in Table 2. After adjusting for age, height and gender in the Model 1, only BMI categories, abdominal obesity and hypertension remained significantly associated with PWD. Even

after inclusion of all variables in the Model 2, age, height, gender, obesity markers (BMI or abdominal obesity) and hypertension were significantly associated with PWD. These statistically significant associations were confirmed for both Models even after exclusion of manually analysed ECGs. Results are presented in Supplemental Table 3 of the Appendix.

Table 2. Multivariable associations between P-wave duration and different demographic, clinical and biological markers, CoLaus|PsyColaus study, Lausanne, Switzerland, 2014-2016.

Characteristics	Model 1	P-value	Model 2A	P-value	Model 2B	P-value
Age (continuous)	-		0.32 (0.28 - 0.37)	<0.001	0.31 (0.26 - 0.36)	<0.001
Height (continuous)	-		0.29 (0.23 - 0.36)	<0.001	0.27 (0.21 - 0.34)	<0.001
Gender				<0.001		<0.001
Woman	-		110.0 ± 0.4		109.8 ± 0.4	
Man	-		112.1 ± 0.4		112.4 ± 0.4	
BMI categories		<0.001		<0.001		
Normal	109.9 ± 0.4		110.1 ± 0.4			
Overweight	110.9 ± 0.3		110.9 ± 0.4			
Obese	113.2 ± 0.5		113.0 ± 0.5			
Abdominal obesity		<0.001				0.016
No	110.4 ± 0.3				110.5 ± 0.3	
Yes	112.0 ± 0.4				111.7 ± 0.4	
Smoking		0.628				
Never	111.0 ± 0.3		-		-	
Former	111.1 ± 0.4		-		-	
Current	110.5 ± 0.5		-		-	
Alcohol use		0.859				
Non drinker	110.7 ± 0.4		-		-	
Low risk	110.9 ± 0.3		-		-	
Medium risk	111.4 ± 0.7		-		-	
High risk	111.6 ± 1.4		-		-	
Personal history of CVD		0.925				

No	110.9 ± 0.2		-		-	
Yes	111.0 ± 0.8		-		-	
Hypertension		<0.001		0.010		0.002
No	110.1 ± 0.3		110.4 ± 0.3		110.3 ± 0.3	
Yes	112.0 ± 0.3		111.7 ± 0.4		111.8 ± 0.4	
Dyslipidaemia		0.318				
No	110.6 ± 0.4		-		-	
Yes	111.1 ± 0.3		-		-	
Diabetes		0.548				
No	111.0 ± 0.2		-		-	
Yes	110.5 ± 0.8		-		-	
Metabolic syndrome		0.113				
No	110.7 ± 0.3		-		-	
Yes	111.5 ± 0.4		-		-	
Renal failure		0.866				
No	111.0 ± 0.2		-		-	
Yes	110.8 ± 0.7		-		-	
Troponin ≥14 ng/L		0.920				
No	112.4 ± 0.3		-		-	
Yes	112.5 ± 1.0		-		-	
NT-proBNP ≥125 ng/L		0.310				
No	110.5 ± 0.4		-		-	
Yes	111.2 ± 0.5		-		-	

-, not included in the model. BMI, Body Mass Index; CVD, cardiovascular disease. Please refer to the methods and Appendix for the definition of each characteristic. Results are expressed as adjusted coefficient (95% confidence interval) for continuous variables and as mean ± standard error for categorical variables. Model 1: adjusted for age (continuous), height (continuous) and gender. Full model (2A and 2B): including all variables indicated.

DISCUSSION

To our knowledge, this is the first study assessing the PWD and its demographic, clinical and biological determinants in the Swiss population. On a study sample of 3459 participants, we found that age, height, gender, obesity markers and hypertension were associated with PWD. Moreover, we attested that 21% of the study population had a PWD ≥ 120 ms, possibly reflecting an interatrial block, which is in line with other population-based studies.(1, 2)

PWD and age

We found that aging was associated with prolonged PWD, a finding also reported by others in several studies.(4, 7, 9, 15) Electrophysiologic studies and electroanatomic mapping of the atria demonstrated abnormal conduction in older subjects,(4) which appeared to be related to atrial structural changes and to interstitial fibrosis in particular.(16) Collagenous septa separate small groups of muscular fibres, causing electrical uncoupling.(16) In addition, aging is also associated with atrial dilatation, which contributes to prolonged PWD.(17)

PWD and height

Height has been associated with electrocardiographic modifications, particularly with the prolongation of PR interval and QRS duration.(18) Still, little is known regarding the association between height and PWD. In our study, we observed that tall individuals had longer PWD. This finding fits with the literature showing that height is a strong determinant of left atrial size, and that left atrial enlargement is associated with mechanical stress responsible for slower atrial conduction.(18)

PWD and gender

Men had longer PWD than women, a finding also reported elsewhere.(4, 7, 9, 15) The multivariable models we used may not account for all the anthropometric differences between men and women.(9) For instance, the heart size has been shown to be greater in men than in women.(17) Other factors may play a role, such as the effect of sex hormones but there is currently a paucity of data regarding the possible effect of sex hormones on PWD.(17)

PWD and obesity markers

BMI categories or abdominal obesity were positively associated with PWD, a finding also reported elsewhere.(4, 7, 19) Interestingly, obesity has well known effects on the heart, an entity known as metabolic cardiomyopathy. Obesity is responsible for structural and functional changes in cardiomyocytes independently of coronary artery disease or hypertension.(19) Regarding the metabolic cardiomyopathy, an important pathophysiological mechanism is the systemic pro-inflammatory status induced by obesity. This eventually induces low-grade inflammation in the heart with dysfunction of subcellular components (mitochondrial dysfunction; oxidative stress and impaired calcium handling), inflammatory cell infiltration and neurohumoral activation.(20) Advanced stages are characterized by apoptosis, adipocytosis, fibrosis and atrial remodelling.(20) A second important pathophysiological mechanism is the fatty acid accumulation in the cardiomyocytes. The normal heart reaches a balance between free fatty acid (FFA) uptake and oxidation. The increased level of circulating FFA observed in obesity eventually results in accumulation of lipid droplets within the cardiomyocytes, impacting cardiac function and promoting apoptosis also known as lipotoxic cardiomyopathy.(20, 21) Studies have shown an association between cardiomyocyte fat content and ECG changes including longer PWD.(19, 22)

PWD and hypertension

Hypertension was positively correlated with PWD after multivariable adjustments in both models, an association also reported by others.(7, 11) Left ventricular hypertrophy and diastolic dysfunction caused by high blood pressure are responsible for increased atrial strain with subsequent dilatation and fibrosis.(11, 23) These changes have repercussions on electrical conduction and, therefore, PWD.(23)

STUDY STRENGTHS AND LIMITATIONS

Our study was conducted in a population-based sample allowing for the generalization of the results to similar Caucasian populations. The large sample size of our study population, together with the full set of collected data, allowed us to explore associations between PWD and a number of relevant variables. All the significant associations found in our study can be easily related with underlying (patho)physiological mechanisms.

Our study has also some limitations. First, there is no published consensus about the measurement of PWD. Most studies used automated measurements provided by different softwares. Each software has its own specific algorithm susceptible to give slightly different values.(24) Second, we used the SEMA software to calculate automatically PWD values. A number of studies have included additional markers of atrial electromechanical function (i.e. P-wave indices, such as P-wave terminal force), which were not part of the results provided by the software we used. Third, a significant number of ECG (10%) needed a manual determination of PWD; this might have biased the results. However, even after exclusion of the manually analysed ECGs, associations remained unchanged.

Finally, another limitation of our study is our inability to support causal association between PWD and structural myocardial abnormalities (atrial enlargement, fibro-fatty infiltration) by the lack of anatomo-histological and echocardiographic information, which was not part of our study design.

FUTURE DIRECTIONS

Considering the metabolic syndrome's burden, incidence of CV events and death will continue to be high. PWD, as an intermediate phenotype reflecting subclinical, structural and functional changes in the atria, can be a useful marker to both assess and monitor the risk of developing AF and worse CV outcomes.(1–3, 11) Based on our results, it would be interesting to know the evolution of the participants according to their PWD. Data from echocardiography or other imaging techniques, as well as post-mortem materials, could be useful to prove the fatty or fibrotic infiltration of the atria or left atrial enlargement. Moreover, future work could determine if preventive interventions (e. g. lifestyle and dietary intervention) based on the PWD have positive effects on clinical outcomes. The ongoing follow-up of the CoLaus|PsyCoLaus cohort would provide some information in the near future.

CONCLUSION

In a cross-sectional study conducted on a large sample of a population-based cohort, PWD was associated with age, height, male gender, obesity markers and hypertension. Most of these associations could possibly relate to both structural and functional changes affecting the atrial tissue.

ACKNOWLEDGEMENTS

Nobody to acknowledge.

OTHER REQUIRED STATEMENTS

Contributors

FB conducted the literature search, interpreted the results and wrote the manuscript. PM-V performed the statistical analyses and contributed to write a part of the manuscript. DG interpreted the results and thoroughly revised the manuscript for important intellectual content. FB and EP calculated manually, when required, the PWD. PV and GW participated to conceiving the study. All authors have read and approved this version of the manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

The Ethics Committee of Canton Vaud (www.cer-vd.ch) approved the CoLaus|PsyColaus study (reference 16/03); the approval was renewed for the first (reference 33/09) and the second (reference 26/14) follow-ups. The full decisions can be obtained from the authors upon request. The study was performed in agreement with the Helsinki declaration and in accordance with the

applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Due to the sensitivity of the data and the lack of consent for online posting, individual data cannot be made accessible. Only metadata will be made available in digital repositories. Metadata requests can also be performed via the study website www.colaus-psycolaus.ch.

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FIGURE LEGENDS

Figure 1. Selection procedure. Percentages were calculated using the baseline sample size as denominator. WPW, Wolff-Parkinson-White; ECG, electrocardiogram.

Figure 2. Distribution of P-wave duration in the whole sample, CoLaus|PsyColaus study, Lausanne, Switzerland, 2014-2016. ms, milliseconds.

Figure 3. Panel A Association between P-wave duration and age. **Panel B** Association between P-wave duration and height. The dashed blue horizontal line represents the sample mean; the red line represents the linear regression. ms, milliseconds; cm, centimetres.

Figure 1

A

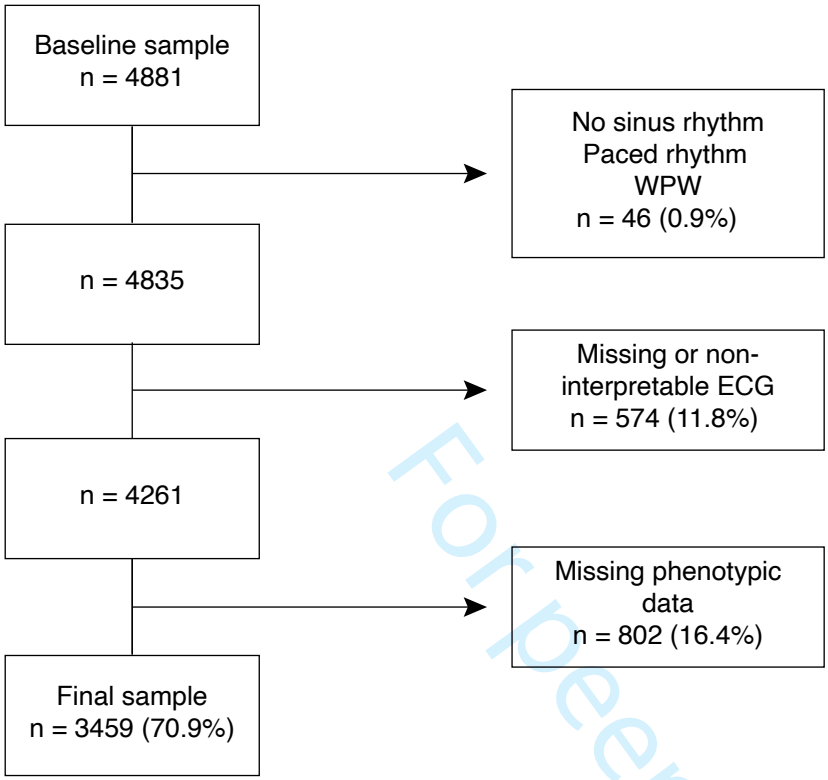


Figure 2

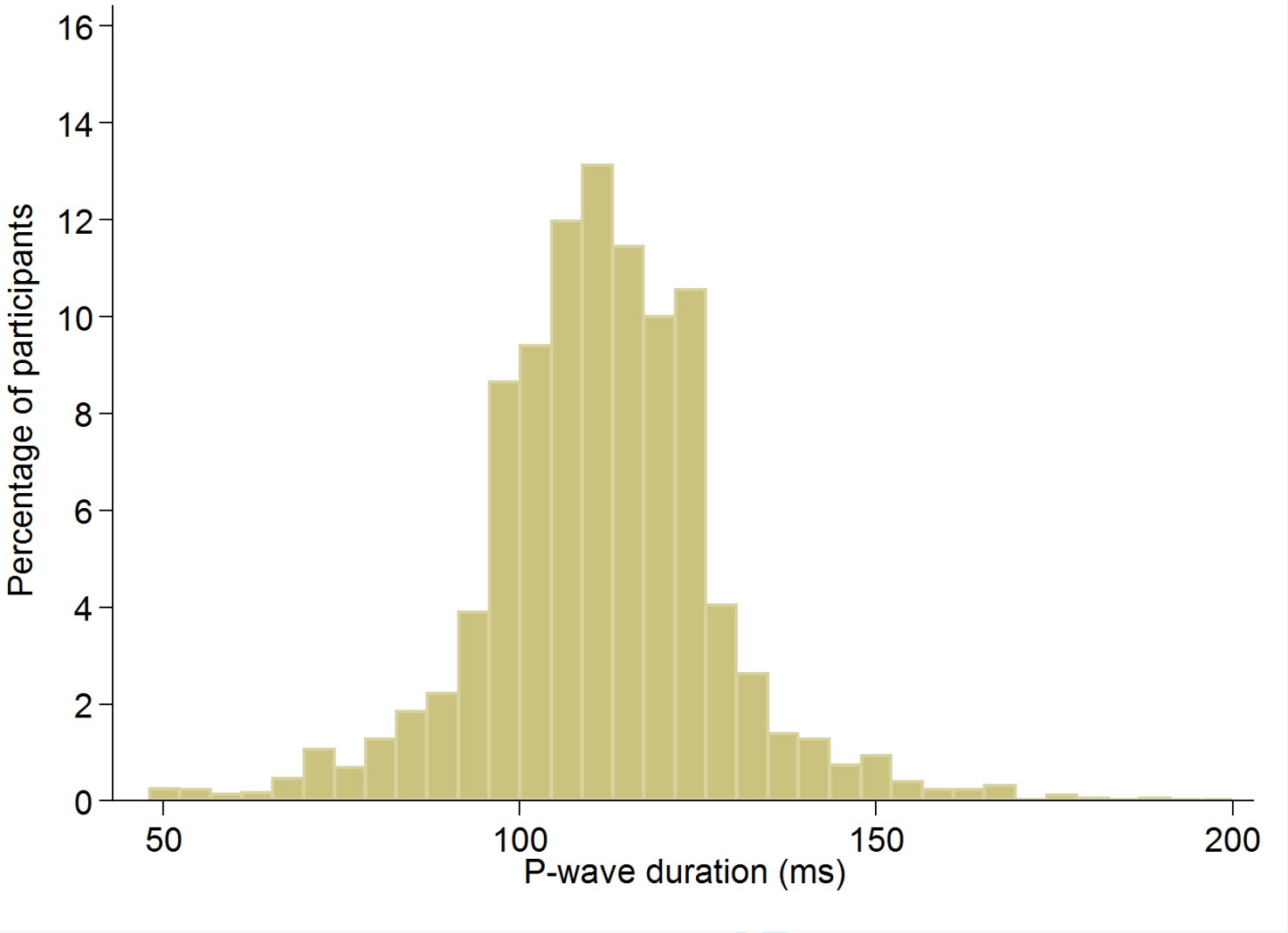
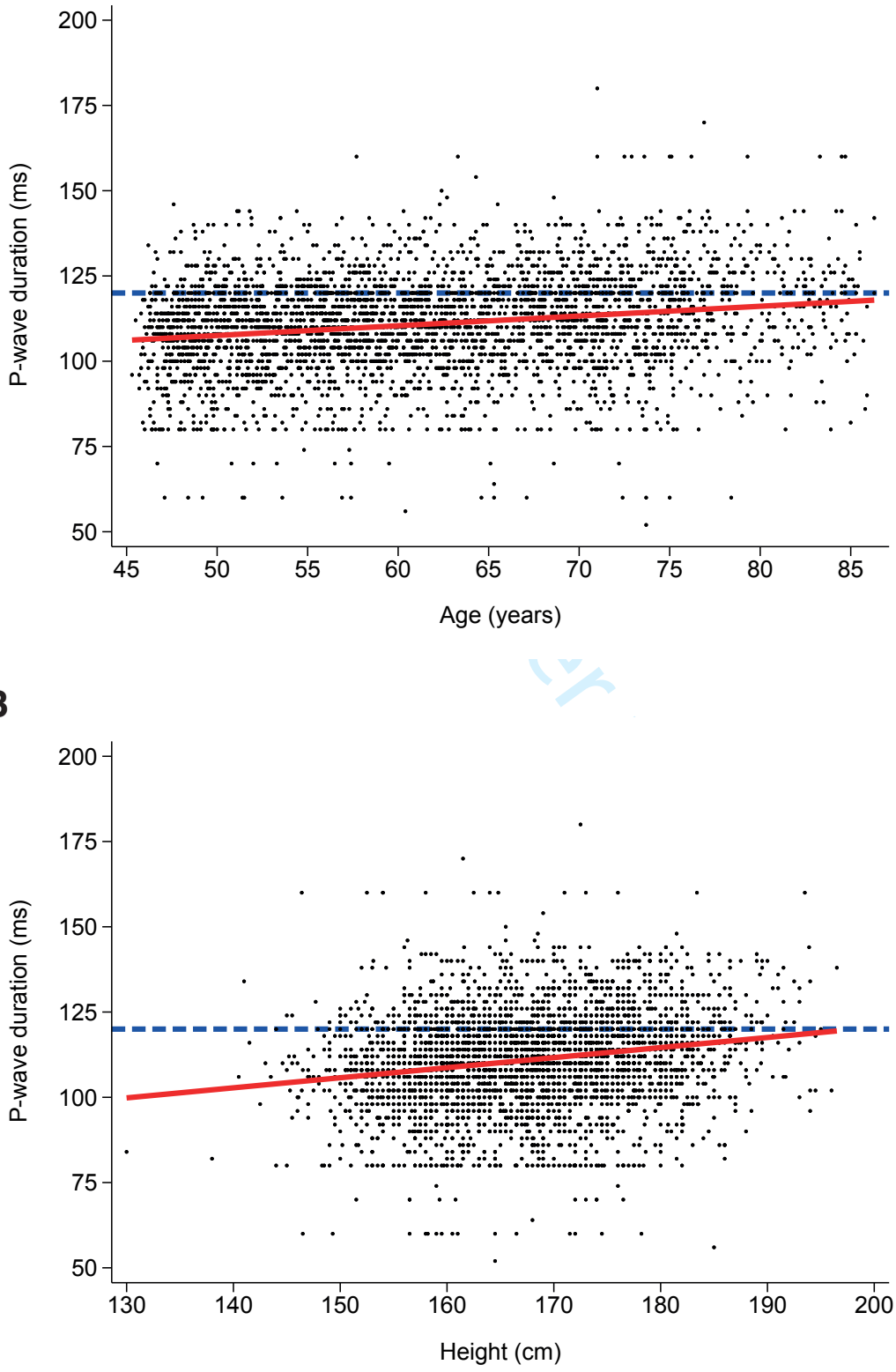
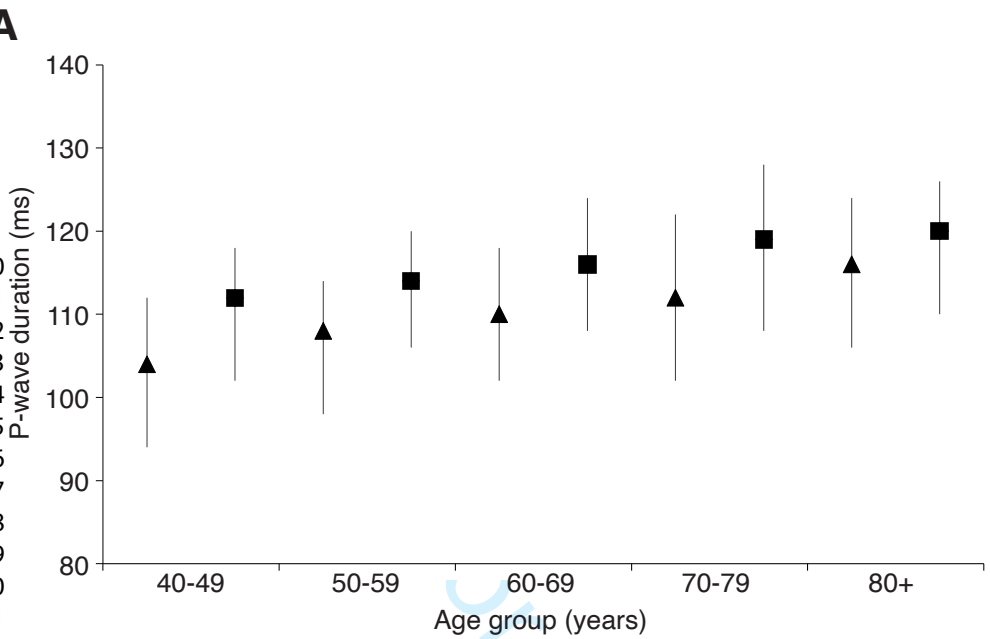


Figure 3


A
P-wave duration (ms)
200
175
150
125
100
75
50
45
50
55
60
65
70
75
80
85
Age (years)
B
P-wave duration (ms)
200
175
150
125
100
75
50
130
140
150
160
170
180
190
200
Height (cm)

Supplemental Figure 1



Supplemental Figure 1. Mean P-wave duration values of males and females by age. ms, milliseconds. Squares represent men and triangles represent women.

APPENDIX

Anthropometric measures and blood pressure measures are described in this Appendix. It also includes a description of the methods used to determine the biological values. A specific set of references is provided for this Appendix.

Body weight and height were measured with participants standing without shoes in light indoor clothing. Weight was measured in kilograms to the nearest 0.1 kg using a Seca™ scale (Seca, Hamburg, Germany). Height was measured to the nearest 5 mm using a Seca™ height gauge (Seca, Hamburg, Germany). Body mass index (BMI) was defined as weight (kg)/height^2 (m^2). Obesity was defined as BMI ≥ 30 kg/m^2, overweight as BMI ≥ 25 and < 30 kg/m^2, normal as BMI ≥ 18.5 and < 25 kg/m^2 and underweight as BMI < 18.5 kg/m^2. Due to the small number of underweight participants (n=55), they were included in the normal category.

Waist circumference was measured mid-way between the lowest rib and the iliac crest and abdominal obesity was defined as waist circumference > 102 cm or > 88 cm for men and women respectively.(1)

Blood pressure (BP) was measured thrice on the left arm after at least 10 minutes rest in the seated position using a clinically validated automated oscillometric device (Omron® HEM-907, Matsusaka, Japan) with a standard cuff, or a large cuff if arm circumference was ≥ 33 cm. The average of the last two measurements was used. Hypertension was defined as mean systolic BP (SBP) ≥ 140 mmHg and/or a mean diastolic BP (DBP) ≥ 90 mmHg and/or use of anti-hypertensive medication.

Venous blood samples (50 mL) were drawn in the fasting state. All biological assays were performed at the clinical laboratory of the Lausanne University Hospital within 2 hours of blood collection on fresh samples. Glycated haemoglobin (HbA1c) was measured by high performance liquid chromatography (Bio-Rad, D-10^{TM}). Subjects were considered to have diabetes if they had a serum HbA1c ≥ 6.5% (≥48 nmol/mmol) and/or were taking anti-diabetic treatment.

Total cholesterol was measured by CHOD-PAP; HDL-cholesterol by CHOD-PAP + PEG + cyclodextrin; triglycerides by GPO-PAP. In our analysis, dyslipidemia was defined as triglycerides ≥ 2 mmol/l and/or LDL ≥ 3 mmol/l and/or lipid lowering treatment.

High sensitivity CRP was assessed by immunoassay (HS latex) and was considered elevated when ≥ 5 mg/l. Serum and urinary creatinine were performed by the Jaffe kinetic compensated method. Renal failure was considered when eGFR was < 60 ml/min/1.73m^2 using CKD-EPI formula. Troponine T hs and NT-proBNP were measured by electrochemiluminescence and considered elevates when ≥ 14 ng/l and 125 ng/l respectively. Biological threshold were defined based on the standard values in our clinical laboratory (Lausanne University Hospital). Since the threshold value for a positive NT-proBNP result usually increased with age, we only considered the lowest threshold value available in our laboratory (i.e. 125 ng/l), as a simple, more sensitive approach to the potential effect of this variable.

The metabolic syndrome was retained in presence of any 3 out of 5 risk factors on the basis of the JIS (Joint Interim Statement) definition. The criteria for clinical diagnosis are: elevated waist circumference (≥ 102 cm for men and ≥ 88 cm for women), elevated triglycerides (≥ 1.7 mmol/l), reduced HDL-C (< 1.0 mmol/l for men and < 1.3 mmol/l for women), elevated BP (systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg), elevated fasting glucose (≥ 5.6 mmol/l).(2)

Supplemental Table 1. Complete baseline characteristics of the study population, CoLaus|PsyColaus study, Lausanne, Switzerland, 2014-2016.

	Included	Excluded	P-value
All	3459	1422	
Age in years (mean; SD)	62 ±10	65 ±11	<0.001
Gender			
Men	1543 (44.6)	649 (45.6)	
Women	1916 (55.4)	773 (54.4)	
Race/ethnicity			
Caucasian	3202 (92.6)	1313 (92.3)	
Other	257 (7.4)	109 (7.7)	
BMI categories			0.005
Normal	1405 (40.6)	452 (44.2)	
Overweight	1415 (40.9)	360 (35.2)	
Obese	639 (18.5)	210 (20.6)	
Abdominal obesity	1298 (37.5)	395 (38.5)	0.562
Smoking			0.952
Never	1455 (42.1)	431 (41.6)	
Former	1349 (39.0)	405 (39.1)	
Current	655 (18.9)	200 (19.3)	
Alcohol use			<0.001
Non drinker	908 (26.3)	267 (34.2)	
Low risk	2076 (60.0)	412 (52.8)	
Medium risk	386 (11.2)	87 (11.1)	
High risk	89 (2.6)	15 (1.9)	
Personal history of CVD	309 (8.9)	209 (14.7)	<0.001
Family history of CVD	1344 (38.9)	421 (29.6)	<0.001
Hypertension	1544 (44.6)	719 (58.6)	<0.001
Dyslipidaemia	2444 (70.7)	1064 (74.8)	0.003
Diabetes	294 (8.5)	188 (17.1)	<0.001
Metabolic syndrome	955 (27.6)	304 (30.6)	0.065
Renal failure	373 (10.8)	163 (15.5)	<0.001
Antidepressant medications	35 (1.0)	15 (1.1)	0.892
Troponin T > 14 ng/l	226 (8.9)	156 (19.3)	<0.001
CRP ≥ 5 mg/L	285 (8.2)	111 (15.0)	<0.001
NT-proBNP > 125 pg/ml	702 (32.6)	365 (51.3)	<0.001

SD, standard deviation; BMI, body mass index; CVD; cardiovascular disease; CRP, C-reactive protein. Please refer to the methods and Appendix for the definition of each characteristic. In column excluded, totals might not add to 1422 due to missing data. Results are expressed as mean ± standard deviation for continuous variables and as number of participants (column percentage) for

categorical variables. Between-group comparisons performed using t-test for continuous variables and chi-square for categorical variables.

Supplemental Table 2. Characteristics of participants with P-wave duration < 120 and ≥ 120 ms, CoLaus|PsyColaus study, Lausanne, Switzerland, 2014-2016.

	PWD < 120 ms	PWD ≥ 120 ms	P-value
All	2718	741	
Age in years (mean; SD)	61 ± 9.6	65.5 ± 10.2	<0.001
Gender			<0.001
Men	1110 (40.8)	433 (58.4)	
Women	1608 (59.2)	308 (41.6)	
Race/ethnicity			0.017
Caucasian	2501 (92.0)	701 (94.6)	
Other	217 (8.0)	40 (5.4)	
BMI categories			<0.001
Normal	1157 (42.6)	248 (33.5)	
Overweight	1106 (40.7)	309 (41.7)	
Obese	455 (16.7)	184 (24.8)	
Abdominal obesity	960 (35.3)	338 (45.6)	<0.001
Smoking			0.005
Never	1159 (42.6)	296 (40)	
Former	1024 (37.7)	325 (43.9)	
Current	535 (19.7)	120 (16.2)	
Alcohol use			0.146
Non drinker	719 (26.5)	189 (25.5)	
Low risk	1645 (60.5)	431 (58.2)	
Medium risk	288 (10.6)	98 (13.2)	
High risk	66 (2.4)	23 (3.1)	
Personal history of CVD	210 (7.7)	99 (13.4)	<0.001
Family history of CVD	1061 (39.0)	283 (38.2)	0.676
Hypertension	1121 (41.2)	423 (57.1)	<0.001
Dyslipidaemia	1899 (69.9)	545 (73.6)	0.051
Diabetes	213 (7.9)	81 (11.0)	0.007
Metabolic syndrome	691 (25.4)	264 (35.6)	<0.001
Renal failure	267 (9.8)	106 (14.3)	<0.001
Antidepressant medications	27 (1.0)	8 (1.1)	0.835
Troponin T > 14 ng/l	140 (7.4)	86 (13.3)	<0.001
CRP ≥ 5 mg/L	219 (8.1)	66 (8.9)	0.456
NT-proBNP > 125 pg/ml	493 (29.4)	209 (44.0)	<0.001

PWD, P-wave duration; ms, milliseconds; SD, standard deviation; BMI, body mass index; CVD; cardiovascular disease; CRP, C-reactive protein. Please refer to the methods and Appendix for the definition of each characteristic. Results are expressed as mean ± standard deviation or as number of participants (column percentage). Between-group comparisons performed using student t-test or chi-square.

Supplemental Table 3. Multivariable associations between P-wave duration and different demographic, clinical and biological markers, CoLaus|PsyColaus study, Lausanne, Switzerland, 2014-2016. Only computer-evaluated ECGs.

Characteristics	Model 1	P-value	Model 2A	P-value	Model 2B	P-value
Age (continuous)	-		0.29 (0.25 - 0.34)	<0.001	0.28 (0.24 - 0.33)	<0.001
Height (continuous)	-		0.27 (0.20 - 0.33)	<0.001	0.24 (0.18 - 0.30)	<0.001
Gender				<0.001		<0.001
Woman	-		110.6 ± 0.3		110.3 ± 0.3	
Man	-		112.5 ± 0.4		112.9 ± 0.4	
BMI categories		<0.001		<0.001		
Normal	110.3 ± 0.3		110.5 ± 0.3			
Overweight	111.7 ± 0.3		111.7 ± 0.3			
Obese	113.2 ± 0.5		113.0 ± 0.5			
Abdominal obesity		<0.001				<0.001
No	110.8 ± 0.3				110.9 ± 0.3	
Yes	112.6 ± 0.3				112.4 ± 0.4	
Smoking		0.716				
Never	111.6 ± 0.3		-		-	
Former	111.5 ± 0.3		-		-	
Current	111.1 ± 0.5		-		-	
Alcohol use		0.875				
Non drinker	111.3 ± 0.4		-		-	
Low risk	111.4 ± 0.3		-		-	
Medium risk	111.9 ± 0.6		-		-	
High risk	111.4 ± 1.3		-		-	
Personal history of CVD		0.632				
No	111.5 ± 0.2		-		-	

Yes	111.1 ± 0.7		-		-	
Hypertension		<0.001		0.011		0.004
No	110.7 ± 0.3		110.9 ± 0.3		110.8 ± 0.3	
Yes	112.4 ± 0.3		112.1 ± 0.3		112.2 ± 0.3	
Dyslipidaemia		0.243				
No	111.1 ± 0.4		-		-	
Yes	111.6 ± 0.2		-		-	
Diabetes		0.146				
No	111.5 ± 0.2		-		-	
Yes	110.4 ± 0.7		-		-	
Metabolic syndrome		0.064				
No	111.2 ± 0.2		-		-	
Yes	112.1 ± 0.4		-		-	
Renal failure		0.732				
No	111.5 ± 0.2		-		-	
Yes	111.2 ± 0.7		-		-	
Troponin ≥14 ng/L		0.707				
No	112.8 ± 0.3		-		-	
Yes	112.5 ± 0.9		-		-	
NT-proBNP ≥125 ng/L		0.933				
No	111.2 ± 0.3		-		-	
Yes	111.3 ± 0.5		-		-	

-, not included in the model. BMI, Body Mass Index; CVD, cardiovascular disease. Please refer to the methods and Appendix for the definition of each characteristic. Results are expressed as adjusted coefficient (95% confidence interval) for continuous variables and as mean ± standard error for categorical variables. Model 1: adjusted for age (continuous), height (continuous) and gender. Full model (2A and 2B): including all variables indicated.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5, Appendix
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5, Appendix
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	6-7
		(*e*) Describe any sensitivity analyses	6-7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7, Figure 1
		(c) Consider use of a flow diagram	7, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, Supplemental Table 1 and 2
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	7-12, Table 1 and 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-12, Table 1 and 2
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplemental Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.