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The importance of pulse pressure on cardiovascular risk and total mortality in the general population: Is sex relevant?

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The aim of the present study is to investigate the predictive value of pulse pressure (PP) on cardiovascular events in the general population and in both sexes, separately. The study involved 2045 participants from the PAMELA study who underwent 24-hour ambulatory blood pressure (BP) monitoring. The participants were followed from the initial medical visit for a time interval of 137 ± 23 months. It was found that office, home, and 24-hour blood pressures were significantly higher in the individuals who experienced cardiovascular (CV) events. Office, 24-hour, and daytime PP were independent predictors of CV events after adjustment for main demographic and clinical parameters in the whole study population. Nighttime PP was an additional independent predictor in men. In conclusion, PP represents an important predictor of cardiovascular events in the general population, particularly among men. Daytime and 24-hour PP have greater predictive importance than nighttime PP in the general population.

1 | INTRODUCTION

Pulse pressure (PP) is calculated as the difference between systolic and diastolic blood pressure (BP) and it represents a surrogate parameter of arterial stiffness.[1,2] Its increment is associated with increased systolic BP, decreased diastolic BP, or a combination of both. Previous investigations showed that PP was associated with cardio- and cerebrovascular risk,[3-6] cardiovascular and all-cause mortality,[7,8] and subclinical cardiovascular disease[9] in the normotensive and hypertensive population. Additionally, PP was shown to be related with left ventricular diastolic dysfunction, hypertrophy, and impaired mechanics.[10-12] It should be emphasized that the same studies reported that other BP components such as systolic, diastolic, or mean BP were also associated with cardiac remodeling and increased morbidity and mortality.

Whether or not sex affects the impact of PP on cardiovascular morbidity and all-cause mortality has not been established yet. Previous studies showed that PP was associated with cardiovascular morbidity and mortality and all-cause mortality in the global and hypertensive population independently of age and sex.[3-8] A limited number of studies reported risk of morbidity and mortality in females and males, separately.[12-14]

To the best of our knowledge, this is the first study that provides the data regarding the prognostic value of PP determined during office, home, and 24-hour ambulatory monitoring measurements. The aim of the present study was to show the predictive value of PP assessed by different techniques on cardiovascular morbidity/mortality and all-cause mortality in the global population and in both sexes, separately.

2 | METHODOLOGY

2.1 | Study population

The PAMELA study started in 1990-1991 and included individuals aged between 25 and 74, randomly selected from the residents in Monza, Italy, to be representative of its population, using the criteria of the World Health Organization Monitoring Diseases (WHO-MONICA) project performed in the same geographic area.[15]

2.2 | Entry data

Methods used in the PAMELA study have been previously explained in detail.[16] All study participants underwent a comprehensive clinical examination at the outpatient clinic of the S. Gerardo University Hospital of Monza. All participants signed an informed consent. The data taken from the study participants included full medical history, blood samples, physical examination, antihypertensive medications, and 3 sphygmomanometric BP measurements in the sitting position. Glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease Study equation and GFR < 60 mL/min/1.73 m² was considered as decreased renal function. Body weight was recorded to the nearest 0.1 kg using a calibrated electronic scale with participants wearing indoor clothing without shoes. Height was recorded to the nearest 0.5 cm using a standardized wall-mounted height board.

On the same day when physical examination was performed all participants underwent 24-hour ambulatory BP monitoring with an adequate ambulatory BP monitoring device (Spacelabs 90207, Spacelabs Healthcare, Issaquah, WA, USA) set to obtain automated BP and heart rate oscillometric readings every 20 minutes over 24 hours. The participants were asked to follow their usual activities during the monitoring period and to hold the arm still during BP measurement. In most of the participants (79.6%) the time of going to bed and waking up was taken from the patients' diary. However, when this was not available, daytime was calculated from 7:00 AM to 11:00 PM. The rest was observed as nighttime. All ambulatory BP recordings were analyzed to obtain 24-hour daytime and nighttime average systolic and diastolic (SBP and DBP), after being edited for artifacts based on preselected criteria.[17] Each individual was given a validated semiautomatic BP measuring device (Philips, model HP 5331) for taking BP at home at 7:00 AM and 7:00 PM. Office BP and 24-hour BP monitoring were measured on the same arm. Home BP was measured on the other arm because it was the only arm that the participant could use.

2.3 | Follow-up

All the participants were followed from the time of the initial medical visit (from 1990 to 1993) for a total time interval of 137 ± 23 months (median 144). Only 8 out of 2051 participants of the PAMELA study were lost during follow-up (0.39%). The data regarding death outcome were retrieved from the National Institute of Statistics database and coded using the International Classification of Diseases and Causes of Death, 10th revision (ICI-10).[18] ICD-10 codes from I-0 to I-99 were considered as cardiovascular deaths. Nonfatal CV events were identified by the hospital discharge list. Myocardial ischemia and stroke and cardiovascular deaths were further validated by the MONICA criteria,[19] whereas heart failure was validated by the Framingham criteria[20] by checking medical records, which was done by an independent investigator. Only the first adverse event was registered.

2.4 | Data analysis

In each participant, 3 office and 2 home BP as well as HR values collected over 24 hours were separately averaged. All ambulatory BP recordings were analyzed to obtain 24-hour, daytime, and nighttime average systolic and diastolic BP (SBP and DBP), as well as mean BP, after being edited for artifacts, based on preselected criteria.[17] Pulse pressure (PP) was calculated as the difference between SBP and DBP.

The values were expressed as means ± standard deviation or percentages. The means were compared by Student's *t* test for independent samples and chi-square test or Fisher's exact test for categorical data. The normal distribution was tested for all continuous variables. In case of nonnormal distribution logarithmic transformation was used and *t* test was applied. Two types of *t* test were used: (1) pooled method in case of equal variances and (2) Satterthwaite method in case of unequal variances.

Adjusted hazard ratios (HR), for 1 standard deviation increase, of fatal and nonfatal cardiovascular events were calculated by Cox's proportional hazard model. The data were adjusted for PP, sex, age, cholesterol, glycemia, body mass index (BMI), and previous antihypertensive drugs. Statistical analysis was performed by SAS System (version 9.4; SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Cardiovascular events

During the follow-up of 12 years 170 out of 2045 participants experienced a cardiovascular event (infarction, stroke, heart failure). The participants who experienced a CV event were significantly older with higher BMI, glucose, cholesterol, and creatinine levels than the participants who were free of a CV event (Table 1). Hypertension and diabetes were significantly more prevalent among the participants who had a CV event (Table 1). The prevalence of renal impairment (GFR < 60 mL/min/1.73 m^2) was significantly higher among the participants who suffered a CV event (Table 1). Office, home, and 24-hour blood pressures (SBP, DBP, mean BP, and PP) were significantly higher in the individuals with a CV event in comparison with those without a CV event (Table 1). Additionally, prevalence of antihypertensive therapy and previous CV events was significantly higher in the participants who had a CV event (Table 1). Beta-blockers were used in 125 participants (32.8%), calcium channel blockers in 88 (23.1%), diuretics in 204 (53.5%), angiotensin converting enzyme inhibitors in 123 (32.3%), vasodilators in 27 (7.1%), and other medications in 19 (5%). For 8 participants therapy was unknown. One medication was used by 212 (55.6%) patients, 2 medications were used by 137 (35.9%), 3 drugs were used by 28 (7.4%) patients, and 4 medications were used by 4 (1.05%) individuals. There was no statistically significant difference in smoking habits between the participants with and without CV event (Table 1).

TABLE 1 Cardiovascular (CV) events in the whole study population

	No CV event	CV event	*P* value
N	1875	170	
Age (y)	49.8 ± 13.5	63.4 ± 8.7	< .001
Men (%)	906 (48.3)	126 (74.1)	< .001
BMI (kg/m^2)	25.4 ± 4.2	27.3 ± 4.2	< .001
Cholesterol (mg/dL)	223.1 ± 42.6	234.8 ± 43.4	< .001
Glucose (mg/dL)	89.5 ± 18.5	103.7 ± 34.7	< .001
Diabetes (%)	28 (1.5)	15 (8.8)	< .001
Creatinine (mg/dL)	0.9 ± 0.2	1.0 ± 0.3	< .001
GFR ≤ 60 mL/min/1.73 m^2 (%)	70 (3.7)	18 (10.7)	< .001
Office SBP (mm Hg)	131.2 ± 20.5	151.1 ± 22.1	< .001
Office DBP (mm Hg)	83.4 ± 10.6	88.5 ± 10.2	< .001
Office mean BP (mm Hg)	99.4 ± 13	109.4 ± 12.4	< .001
Office PP (mm Hg)	47.6 ± 14	62.2 ± 18.3	< .001
Hypertension (%)	803 (42.8)	142 (83.5)	< .001
Home SBP (mm Hg)	123.1 ± 18.5	141.6 ± 20.2	< .001
Home DBP (mm Hg)	76 ± 10.4	82.1 ± 11.2	< .001
Home mean BP (mm Hg)	91.7 ± 12.1	101.9 ± 12.3	< .001
Home PP (mm Hg)	47.1 ± 13.7	59.6 ± 17.3	< .001
24 h SBP (mm Hg)	119.4 ± 11.3	130 ± 14.5	< .001
24 h DBP (mm Hg)	74.1 ± 7.4	77.6 ± 8.5	< .001
24 h mean BP (mm Hg)	89.2 ± 8.3	95.1 ± 9.7	< .001
24 h PP (mm Hg)	45.3 ± 6.9	52.4 ± 10.4	< .001
Daytime SBP (mm Hg)	124.4 ± 11.8	134.6 ± 15.2	< .001
Daytime DBP (mm Hg)	78.9 ± 7.9	81.7 ± 8.9	< .001
Daytime mean BP (mm Hg)	94.1 ± 8.7	99.3 ± 10.2	< .001
Daytime PP (mm Hg)	45.6 ± 7.2	52.9 ± 10.9	< .001
Nighttime SBP (mm Hg)	109.3 ± 12.3	120.8 ± 15.5	< .001
Nighttime DBP (mm Hg)	64.6 ± 8.1	69.4 ± 9.1	< .001
Nighttime mean BP (mm Hg)	79.5 ± 9	86.6 ± 10.5	< .001
Nighttime PP (mm Hg)	44.7 ± 7.3	51.4 ± 10.4	< .001
Antihypertensive therapy (%)	318 (17)	80 (47.1)	< .001
Smoking (%)	506 (27)	57 (33.5)	.067
Previous CV event (%)	49 (2.6)	37 (21.8)	< .001

BMI, body mass index; BP, blood pressure; CV, cardiovascular; DBP, diastolic blood pressure; GFR, glomerular filtration rate; PP, pulse pressure; SBP, systolic blood pressure.

TABLE 2 Risk for CV events and total mortality during follow-up in the whole population

CV events risk				
	HR	95% CI		*P* value
Unadjusted				
Office PP	1.975	1.780	2.193	**< .001**
Home PP	1.782	1.607	1.976	**< .001**
24 h PP	1.919	1.733	2.125	**< .001**
Daytime PP	1.862	1.688	2.055	**< .001**
Nighttime PP	1.850	1.661	2.061	**< .001**
Adjusted for corresponding mean BP, sex, and age				
Office PP	1.314	1.095	1.576	**0.003**
Home PP	1.121	0.955	1.316	.161
24 h PP	1.298	1.123	1.500	**< .001**
Daytime PP	1.304	1.135	1.499	< .001
Nighttime PP	1.255	1.077	1.461	.004
Adjusted for corresponding mean BP, sex, age, cholesterol, glycemia, BMI, previous antihypertensive medication				
Office PP	1.258	1.047	1.511	**.014**
Home PP	1.141	0.968	1.345	.115
24 h PP	1.186	1.018	1.382	**.029**
Daytime PP	1.213	1.046	1.407	**.012**
Nighttime PP	1.139	0.975	1.331	.101
Adjusted for corresponding mean BP, sex, age, cholesterol, glycemia, BMI, previous antihypertensive medication, and creatinine				
Office PP	1.257	1.045	1.512	**.015**
Home PP	1.136	0.964	1.340	.128
24 h PP	1.201	1.024	1.409	**.025**
Daytime PP	1.228	1.052	1.433	**.009**
Nighttime PP	1.149	0.980	1.347	.086

BMI, body mass index; BP, blood pressure; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; PP, pulse pressure.

3.2 | Cardiovascular risk in the whole population

Office, home, 24-hour, daytime, and nighttime PP were predictors of adverse cardiovascular events (Table 2). Home PP lost its predictive value after adjustment for age, sex, and mean PP. After adjustment for mean BP, age, cholesterol, glycemia, BMI, and previous antihypertensive medication, only office, 24-hour, and daytime PP were independent predictors of cardiovascular events (Table 2). The results remained the same even after introduction of creatinine level in the model (Table 2).

3.3 | Cardiovascular risk in both sexes

All types of PP that were measured in this study (office, home, 24-hour, daytime, and nighttime PP) were statistically important predictors of CV and mortality risk in both sexes (Tables 3 and 4). However, after adjustment for demographic and clinical parameters, in females all PPs

TABLE 3 Risk for CV events and total mortality during follow-up in females

CV events risk				
	HR	95% CI		*P* value
Unadjusted				
Office PP	2.097	1.725	2.550	**< .001**
Home PP	1.847	1.473	2.317	**< .001**
24 h PP	1.937	1.591	2.359	**< 0.001**
Daytime PP	1.946	1.592	2.379	**< .001**
Nighttime PP	1.789	1.47	2.178	**< .001**
Adjusted for corresponding mean BP and age				
Office PP	1.133	0.789	1.628	.498
Home PP	1.107	0.788	1.555	.559
24 h PP	1.102	0.809	1.501	.539
Daytime PP	1.191	0.883	1.605	.252
Nighttime PP	0.977	0.724	1.317	.878
Adjusted for corresponding mean BP, age, cholesterol, glycemia, BMI, previous antihypertensive medication				
Office PP	0.943	0.653	1.362	.753
Home PP	0.898	0.637	1.266	.539
24 h PP	0.896	0.643	1.247	.514
Daytime PP	0.962	0.699	1.324	.811
Nighttime PP	0.865	0.642	1.167	.343
Adjusted for corresponding mean BP, age, cholesterol, glycemia, BMI, previous antihypertensive medication, and creatinine				
Office PP	1.012	0.695	1.474	.951
Home PP	0.916	0.654	1.284	.612
24 h PP	0.969	0.693	1.355	.853
Daytime PP	1.021	0.739	1.409	.901
Nighttime PP	0.918	0.675	1.248	.584

BMI, body mass index; BP, blood pressure; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; PP, pulse pressure.

TABLE 4 Risk for CV events and total mortality during follow-up in males

CV events risk				
	HR	95% CI		*P* value
Unadjusted				
Office PP	1.947	1.72	2.204	**< .001**
Home PP	1.649	1.465	1.855	**< .001**
24 h PP	1.871	1.662	2.107	**< .001**
Daytime PP	1.767	1.581	1.974	**< .0001**
Nighttime PP	1.967	1.710	2.262	**< .0001**
Adjusted for corresponding mean BP, and age				
Office PP	1.366	1.11	1.679	**.003**
Home PP	1.117	0.938	1.331	.215
24 h PP	1.349	1.152	1.581	**< .001**
Daytime PP	1.308	1.140	1.502	**< .001**
Nighttime PP	1.363	1.145	1.622	**< .001**
Adjusted for corresponding mean BP, age, cholesterol, glycemia, BMI, previous antihypertensive medication				
Office PP	1.355	1.102	1.666	**.004**
Home PP	1.179	0.989	1.406	.066
24 h PP	1.295	1.095	1.532	**.003**
Daytime PP	1.310	1.111	1.545	**.001**
Nighttime PP	1.270	1.065	1.515	**.008**
Adjusted for corresponding mean BP, age, cholesterol, glycemia, BMI, previous antihypertensive medication, and creatinine				
Office PP	1.365	1.107	1.684	**.004**
Home PP	1.175	0.985	1.403	.073
24 h PP	1.351	1.129	1.616	**.001**
Daytime PP	1.355	1.138	1.614	**.001**
Nighttime PP	1.313	1.092	1.579	**.004**

BMI, body mass index; BP, blood pressure; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; PP, pulse pressure.

lost statistical significance. In males all PPs, except home PP, turned out to be independent predictors of CV risk, also including age, and mean PP in the statistical model (Table 4). The same results were confirmed after further adjustment for glycemia, BMI, serum cholesterol, creatinine level, and use of antihypertensive drugs (Table 4).

4 | DISCUSSION

Our study revealed that PP was associated with CV events. However, it seems that influence of PP is limited to male participants. Interestingly, PP measured in office and during 24-hour ambulatory BP monitoring were good predictors of CV events, whereas home BP showed borderline statistical significance. Furthermore, in men PP evaluated in office or during 24-hour ambulatory BP monitoring (24-hour, daytime, and nighttime) was a predictor of CV events independent of demographic and clinical parameters in general population.

Recently published results from the REACH trial, which included 45 087 participants with clinical atherothrombotic disease or risk factors for its development, showed that PP was independent of demographic and clinical parameters associated with all outcomes (nonfatal myocardial infarction, all myocardial infarction, cardiovascular hospitalization, and a combined outcome) except stroke and cardiovascular death during the 4-year follow-up.[21] This largely agrees with our results regarding increased CV events (myocardial infarction, stroke, heart failure). Similar findings were reported by the previous investigation.[8,9,22]

Data regarding sex influence the relationship between PP and CV morbidity/mortality. Miura and colleagues[14] showed that all components of BP including PP were associated with 25-year mortality risks from coronary heart disease or CV disease in men and women. However, after adjustment for demographic and main clinical parameters and diastolic BP, PP remained an independent predictor of mortality only in men between 60 and 74 years of age.

Benetos and colleagues[13] reported that PP was an independent predictor of CV mortality only in men (normotensive and hypertensive) but not in women, during the follow-up of almost 20 years. Stroke and coronary artery induced mortality was not associated with PP in both sexes. PP was an independent predictor of all-cause mortality only in hypertensive men.[13]

Our findings showed that PP obtained by office measurements, as well as with 24-hour ambulatory BP monitoring, were independent predictors of CV events in the general population and in men but not in women. Interestingly, PP derived from home BP measurement was not an independent predictor of CV events in any of the observed groups. The advantage of the present study over the aforementioned investigations was the use of several possible methods in determination of PP. We succeeded in showing that office, home, 24-hour, daytime, and nighttime PP do not have the same importance. Office, 24-hour, and daytime PP were independent predictors of CV events in the general population. Nighttime PP, besides previously mentioned PP, was an additional independent predictor of CV events in the male population. One should be aware of the difference between oscillometric and auscultatory measurements. The mercury manometer technique results in consistently greater BP values than do oscillometric devices.[23]Recently, Liu and colleagues[24] showed that oscillometric measurement is more accurate when pulse pressure is < 50 mm Hg than if PP is > 50 mm Hg. However, our results showed that both methods for PP assessment were independent predictors of CV events. Considering the fact that PP showed significantly smaller variation in comparison with SBP and DBP, it might be a reasonable explanation why PP was a good predictor of CV morbidity in our study.

Two important topics that deserve further discussion are (1) greater predictive importance of PP in men and (2) value of 24-hour ambulatory BP monitoring in assessment of PP.

PP represents a surrogate for arterial stiffness and therefore is influenced by different factors that determine aortic wall structure, wave reflection, and central hemodynamics. The arterial stiffening is a complex pathophysiological process affected by many different factors such as age and sex hormones.[25] Aging provokes arterial remodeling—excessive degradation of elastin and replacement with collagen fibers, which leads to stiffening of the arterial wall.[26] Estrogen directly affects arterial wall remodeling by changing the activation of matrix metalloproteinases, increasing elastin production, and decreasing collagen deposition in human arteries.[27] The aorta has estrogen and progesterone receptors in both sexes, but women have more estrogen receptors than men.[28,29] These are the reasons for positive effects of estrogen on vascular function in women of reproductive age. However, in menopause arterial compliance is significantly decreased because of aging and lack of estrogen.[30,31] On the other hand, low testosterone is also associated with aortic stiffening.[32] The interaction between sex and genetic factors, which has already been described in the PAMELA study, could also be responsible for the different importance of PP in men and women.[33] In our study the average age of females indicates that most of them were in perimenopause or in early postmenopause, which is why arterial stiffness was intermediate—worse than in young women but still slightly better than in men. Considering the results of previous studies regarding the testosterone level in the population of similar age,[32] it is reasonable to hypothesize that the testosterone level among our male participants was decreased. These are all potential sex hormone-related reasons for greater importance of arterial stiffness and its surrogate PP in men than in women in the PAMELA population.

The superiority of 24-hour ambulatory BP monitoring over office and home BP measuring has been shown many times.[34,35] However, the latest study showed that the 10-year predictions obtained from ambulatory BP measurement were similar to the predictions from office BP.[36] Furthermore, nighttime BP was not shown to improve the 10-year predictions obtained from daytime measurements.[36] Kao and colleagues[37] reported that PP obtained by 24-hour ambulatory BP monitoring had greater predictive value than office PP for long-term outcomes. The authors showed that 24-hour, daytime, and nighttime PP were independent predictors for all-cause, CV, and non-CV mortality but not for stroke, CV, and coronary heart disease.[37] However, after adjustment for systolic BP, only 24-hour and daytime PP remained independent predictors of all-cause mortality. Our findings emphasized the importance of PP evaluation in office and during 24-hour ambulatory BP monitoring because office, daytime, and 24-hour PP showed a great predictive value in the general population. Nighttime PP was an additional independent predictor in men.

4.1 | Limitations

Our study has several limitations that need to be discussed. First, our findings are limited to the middle-aged population with low prevalence of obesity and diabetes, which is why they could not be automatically extrapolated to other populations. Second, hormonal status of the study participants was not determined and there are no data regarding the prevalence of menopause among the females. Third, parameters such as physical activity and alcohol consumption are not available and therefore not included in our analysis. Fourth, the lack of additional visits and BP measurements during the follow-up represents an additional limitation. Fifth, the data about the therapy during the follow-up were not available, which could also be considered as a limitation. Sixth, a limited number of events among women could be the reason for the lack of independent relationship between PPs and CV events.

5 | CONCLUSION

The present findings showed that pulse pressure represents an important predictor of cardiovascular events in the general population, particularly among men. There is no difference in prognostic value between PP determined by office or 24-hour ambulatory blood pressure monitoring, which is very important for clinical practice. Daytime and 24-hour PP has greater predictive importance than

nighttime PP. The importance of PP is greater in men than in women for prediction of cardiovascular events. The mechanisms behind the adverse prognostic value of a pulse pressure remain to be clarified.

CONFLICT OF INTEREST

None.

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