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Prevalence of interarm blood pressure difference is notably higher in women; the Viborg population-based screening program (VISP)

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Abstract

Background Bilateral blood pressure (BP) measurement is important in cardiovascular prevention for identifying systolic interarm BP difference (IAD) and hypertension. We investigated sex-stratified IAD prevalence and its associations and coexistence with screen-detected peripheral atherosclerosis and hypertension. Furthermore, we determined the proportion misclassified as non-hypertensive when using the lower versus the higher reading arm.

Methods This sub-study formed part of the Viborg Screening Program (VISP), a cross-sectorial population-based cardiovascular screening programme targeting 67-year-old Danes. VISP includes screening for peripheral atherosclerosis (lower extremity arterial disease and carotid plaque), abdominal aortic aneurysm, hypertension, diabetes mellitus, and cardiac disease. Self-reported comorbidities, risk factors, and medication use were also collected. Among 4,602 attendees, 4,517 (82.1%) had eligible bilateral and repeated BP measurements. IAD was defined as a systolic BP difference ≥ 10 mmHg. IAD-associated factors (screening results and risk factors) were estimated by logistic regression; proportional coexistence was displayed by Venn diagrams (screening results).

Results We included 2,220 women (49.2%) and 2,297 men (50.8%). IAD was more predominant in women (26.8%) than men (21.0%) ($p < 0.001$). This disparity persisted after adjustment [odds ratio (OR) 1.53; 95% confidence interval (CI) 1.32–1.77]. No other association was recorded with the conditions screened for, barring potential hypertension: BP 140–159/90–99 mmHg (OR 1.68, 95% CI 1.44–1.97) and BP $\geq 160/100$ mmHg (OR 1.82, 95% CI 1.49–2.23). Overall, IAD and BP $\geq 160/100$ mmHg coexistence was 4% in women and 5% in men; for BP $\geq 140/90$ mmHg, 13% and 14%, respectively. Among those recording a mean BP $\geq 140/90$ mmHg in the higher reading arm, 14.5% of women and 15.3% of men would be misclassified as non-hypertensive compared with the lowest reading arm.

Conclusion Female sex was an independent factor of IAD prevalence but not associated with other arterial lesions. Approximately 15% needed reclassification according to BP $\geq 140/90$ mmHg when the lower rather than the higher reading arm was used; verifying bilateral BP measurements improved detection of potential hypertension. In future,

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the predictive value of sex-stratified IAD should be assessed for cardiovascular events and death to verify its potential as a screening tool in population-based cardiovascular screening.

Trial registration for VISP NCT03395509:10/12/2018.

Keywords Systolic blood pressure difference, Interarm measurement, Cardiovascular disease, Cardiovascular risk assessment, Sex

Background

In cardiovascular prevention, identifying at-risk individuals is crucial to address modifiable cardiovascular risk factors. Prophylactic treatment and lifestyle modifications reduce the risk of fatal and non-fatal major adverse cardiovascular events (MACE) associated with high blood pressure (BP) [1]. Individual-level data from 1.5 mill. persons in 112 cohorts showed that the ten-year incidence of cardiovascular disease (CVD) was higher among individuals with raised systolic BP than among individuals with other modifiable risk factors (e.g., smoking and diabetes), particularly in women (29.3%), slightly less in men (21.6%) [2].

International guidelines stress the importance of measuring BP in both arms to diagnose and manage hypertension accurately. Monitoring is recommended on the higher reading arm when a difference is detected [3–5]. Bilateral BP measurements are also important in detecting systolic interarm blood pressure difference (IAD). In a recent meta-analysis with 53,827 individuals, Clark et al. reported that $IAD \geq 10$ mmHg was associated with increased MACE and all-cause mortality [6]. Moreover, in a second meta-analysis by Clark et al., BP measured in the higher versus the lower reading arm was superior in predicting MACE and avoiding misclassification of BP [7]. Thus, bilateral BP readings are of clinical relevance and substantial interest for preventive purposes. Despite this, bilateral BP measurements are infrequently obtained [8].

In the Danish “Viborg Screening Program” (VISP) [9], a population-based screening programme monitoring multiple cardiovascular conditions in 67-year-olds, bilateral BP readings are the standard procedure for identifying the arm with the higher reading for subsequent BP readings. Those with a verified $BP \geq 160/100$ mmHg initiate antihypertensive medication treatment according to the global International Society of Hypertension Global Hypertension Practice Guidelines [3]. In VISP, $BP \geq 160/100$ mmHg was observed in 13.8% of women and 17.1% of men [10]. However, the sex-stratified IAD prevalence, its associations and coexistence with other conditions and the relevance of using the higher versus the lower reading arm remain unclarified in population-based screening. Thus, we aimed to describe (1) the sex-stratified prevalence of systolic $IAD \geq 10$ mmHg in the VISP cohort and (2) determine its association and

coexistence with associated screen-detected conditions while (3) reporting the proportion misclassified as non-hypertensive when using the lower versus the higher reading arm.

Methods

Study population and setting

This Danish study was a non-predefined sub-study adopting a cross-sectional design using data from VISP, previously reported in detail [9]. Briefly, screening participants were invited on their 67th birthday without exclusions, and the programme included examinations for peripheral atherosclerosis (lower extremity arterial disease (LEAD) and carotid plaque (CP)), abdominal aortic aneurysm (AAA), hypertension, cardiac arrhythmia or ischaemia, and diabetes mellitus. Diagnostic criteria and follow-up in VISP are presented in Table 1. In addition to the clinical examinations, participants self-reported risk factors, morbidity and prescribed medicine were collected. The Viborg Healthcare Centre hosts VISP within a collaborative setting, including primary and secondary healthcare. The first participants were enrolled in August 2014, and enrolment is still ongoing. During the initial five years, 5,505 participants were invited, 4,602 of whom participated and subsequently constituted the study population. For further details, please refer to the study protocol [9].

Data sources

Self-reported data

In this study, selected information from the questionnaire attached to the VISP invitation letter was used to obtain data on lifestyle factors (smoking, alcohol consumption and physical activity), weight and height used to calculate Body Mass Index (BMI, kg/m^2), and medication use. Smoking habits were collected in three categories: never, former or current smokers. Alcohol consumption was categorised according to the recommendation of the Danish Health Authority at the time into low risk (women < 7 units/week and men < 14 units/week) and high risk (women > 14 units/week and men > 21 units/week). Level of physical activity was grouped as low (sedentary recreational activities like reading and watching television), moderate (low-intensity physical activity, at least 4 h a week), high (high-intensity activity, at least 4 h a week) and very high (competitive sports regularly) during the past year, in accordance with the Danish

Table 1 Diagnostic criteria and follow-up in the Viborg Screening Program (VISP)

Diagnostic criteria		Follow-Up, in case of positive screening result
Carotid plaque	Focal structure protruding into the lumen ≥ 0.5 mm or $\geq 50\%$ of the vessel diameter.	Recommendation of lipid-lowering and antiplatelet therapy along with lifestyle modification counselling.
Lower extremity arterial disease	Ankle-brachial index < 0.9 or ≥ 1.4 .	Recommendation of lipid-lowering and antiplatelet therapy along with lifestyle modification counselling.
Aortic ectasia or aneurysm	Aortic diameter of ≥ 25 mm and ≥ 30 mm as measured by B-mode ultrasonography.	Participants with ectasia were offered a re-screening after 5 years. Participants with aneurysm were recommended lipid-lowering and antiplatelet therapy, lifestyle modification counselling and follow-up imaging according to size: 30–49 mm: annual ultrasound scan. ≥ 50 mm: CT scan and vascular surgical consultation.
Hypertension	BP $\geq 160/100$ mmHg in the higher reading arm.	Recommendation of three-day home BP measurement for verification of hypertension including follow-up in VISP or by their general practitioner.
Arrhythmia and ischaemia	Significant changes in a single 12-lead electrocardiogram, assessed by an expert cardiologist.	Referred for follow-up by an expert cardiologist.
Diabetes	HbA1c ≥ 48 mmol/mol.	Participants without previously known diabetes and HbA1c ≥ 48 mmol/mol were referred for follow-up by their general practitioner.

Abbreviations: BP, blood pressure; CT, computer tomography; HbA1c, glycated haemoglobin

Regional Health Survey [11]. BMI was subdivided into three groups: BMI < 25 , 25–29 and ≥ 30 . Use of medicine was divided into four groups: lipid-lowering agents, antiplatelet (aspirin, clopidogrel), antihypertensive (angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, calcium channel blockers, thiazides) and antidiabetic agents (insulin and oral antidiabetic agents). The questionnaire developed for VISP is available in Supplementary Material 1; which also includes the EuroQoL five-dimension instrument and the Walking Impairment Questionnaire.

Information on sex

Information about sex was generated from the participants' unique 10-digit civil registration number (CPR)

provided by the Central Office of Civil Registration System [12].

Blood pressure measurement

BP was measured three times in total per screening participant, all in supine position, using the oscillometric method with appropriate cuff size as recommended for use in clinical practice [5, 13]. The Microlife BP A6 PC devices were used with a grade A/A accuracy upon validation in accordance with the protocol of the British and Irish Hypertension Society. First, BP was measured simultaneously and bilaterally immediately after cuff placement, a durable approach in accordance with the Best Rest Trial [14], with identical monitors on the left and right arm. The second and third measurements were made in connection with an ankle-brachial index (ABI) assessment with the participant in a supine position; these two measurements were obtained unilaterally on the arm recording the highest systolic BP at the first measurement.

IAD was calculated from the first BP measurement by subtracting the lowest from the highest systolic BP. IAD was defined as an interarm BP difference ≥ 10 mmHg and sub-grouped into IAD ≥ 10 to 19 mmHg, ≥ 20 to 29 mmHg and ≥ 30 mmHg.

BP misclassification was based on the lower versus the higher reading arm upon the first BP measurement using the thresholds recommended in the International Society of Hypertension guideline; 140–159/90–99 mmHg and $\geq 160/100$ mmHg [3]. In Venn diagrams, BP was categorised by means as BP $\geq 140/90$ mmHg and BP $\geq 160/100$ mmHg. Mean BP was calculated as the mean of the second and third BP measurements; the highest systolic or diastolic value of the mean measurement determined the BP categorisation.

Bilateral brachial BP was used to calculate the ABI; by dividing the mean of the systolic BPs in the tibialis posterior and dorsalis pedis arteries by the higher of the two systolic brachial BPs.

Statistical analysis

Baseline characteristics, medication and screening results were stratified by IAD status (< 10 mmHg or ≥ 10 mmHg) and presented as categorical variables with absolute numbers, proportion and related 95% confidence intervals (CI). Furthermore, sex-stratified results were reported for those with IAD > 10 mmHg. In sub-analysis, IAD was expressed as mean \pm standard deviation (SD). Categorical and continuous variables were analysed by Pearson's chi-squared test and Student's *t*-test, respectively.

Unadjusted and adjusted logistic regression analyses were used to investigate factors associated with IAD ≥ 10 mmHg, reported as odds ratio (OR) with 95% CI. Analyses included observations with complete data. In the

adjusted analyses, we entered variables with an unadjusted p -value of <0.1 and smoking as smoking may constitute a clinically relevant risk factor for IAD [15, 16]. To finally indicate statistical significance, a $p < 0.05$ was used.

Venn diagrams were applied to display the proportional coexistence of IAD with other screening conditions, but only for screening results positively associated with IAD in adjusted logistic regression analyses.

In accordance with the General Data Protection Regulation, the web-based Research Electronic Data Capture (REDCap) system hosted at Open Patient Data Explorative Network, Odense University Hospital, Denmark, was used for storage and processing of all data. STATA version 18.0 (StataCorp, College Station, TX, USA) was used to perform the statistical analyses.

Results

During the first five years of enrolment, 5,505 men and women were invited to participate in VISP. In total, 83.6% ($n=4,602$) accepted the invitation with no sex difference in participation rates. A total of 1.8% of the participants were excluded due to a lack of bilateral ($n=78$) and repeated BP measurements ($n=7$), leaving 82.1% ($n=4,517$) of the participants eligible for the study (Fig. 1).

Lifestyle habits like smoking and alcohol consumption were similar for participants with and without $IAD \geq 10$ mmHg, whereas the level of physical exercise tended to be different ($p=0.058$). Among participants with an $IAD \geq 10$ mmHg, a significantly higher proportion of participants were obese; 29.6% versus 19.7% among those with an $IAD < 10$ mmHg ($p < 0.001$) (Table 2).

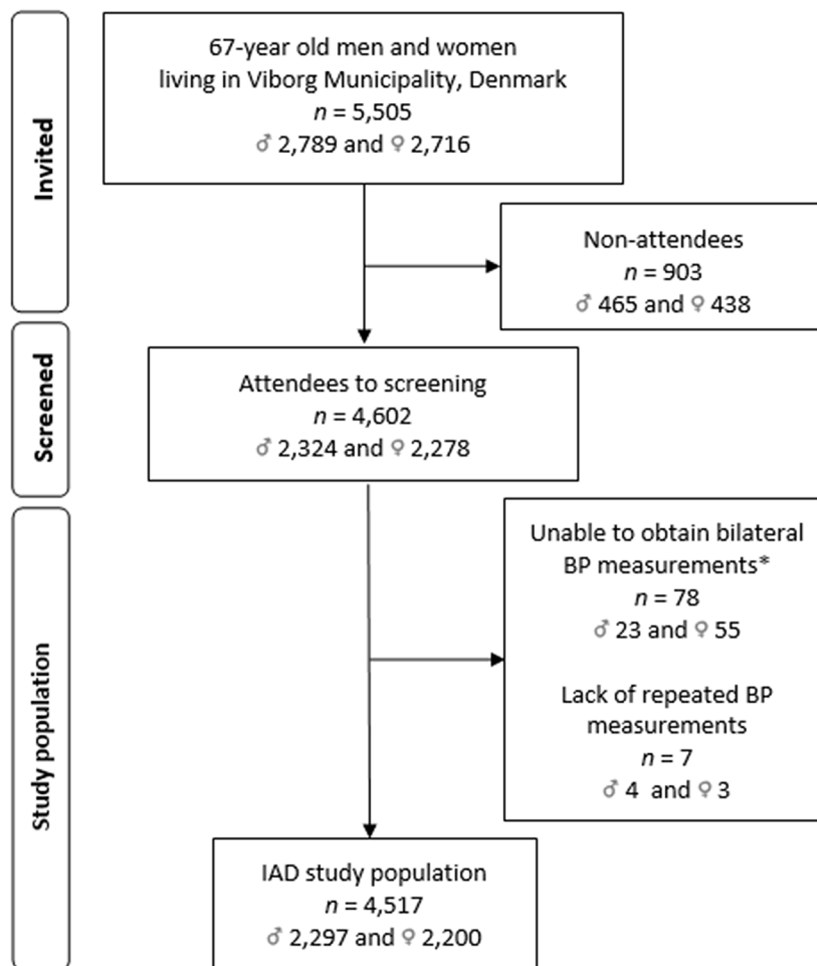


Fig. 1 Flow diagram of the study population. Abbreviation: IAD, interarm blood pressure difference. *Causes of lacking bilateral BP measurement: discomfort or abstained from bilateral BP measurement due to previous breast cancer and surgical mastectomy leaving the affected side inappropriate for BP readings

Table 2 Characteristics of participants by IAD status ($n=4,517$)

IAD, mmHg	Missing, <i>n</i>	Total, <i>n</i>	IAD < 10 mmHg		IAD ≥ 10 mmHg	
			<i>n</i> = 3,440	95% CI	<i>n</i> = 1,077	95% CI
Sex	0					
Women		2,220 (49.2)	1,625 (47.2)	45.57–48.91	595 (55.3)	52.26–58.19
Men		2,297 (50.8)	1,815 (52.8)	51.09–54.43	482 (44.8)	41.81–47.74
Lifestyle habits						
Smoking	26					
Never		1,855 (41.3)	1,419 (41.5)	39.85–43.15	436 (40.7)	37.80–43.15
Current		737 (16.4)	560 (16.4)	15.17–17.65	177 (16.5)	14.42–18.87
Former		1,899 (42.3)	1,441 (42.1)	40.49–43.80	458 (42.8)	39.83–45.75
Alcohol , units/week	227					
♀: <7, ♂: <14		3,422 (79.8)	2,585 (79.4)	77.97–80.75	837 (81.0)	78.44–83.23
♀: 7–14, ♂: 14–21		595 (13.9)	454 (13.9)	12.80–15.18	141 (13.6)	11.68–15.87
♀: ≥14, ♂: ≥21		273 (6.3)	217 (6.7)	5.86–7.57	56 (5.4)	4.19–6.97
Level of exercise*	45					
Low		418 (9.4)	301 (8.8)	7.93–9.84	117 (11.0)	9.23–13.00
Moderate		2,832 (63.3)	2,142 (62.9)	61.25–64.50	690 (64.7)	61.81–67.54
High		1,153 (25.8)	909 (26.7)	25.23–28.20	244 (22.9)	20.46–25.51
Very high		69 (1.5)	54 (1.6)	1.22–2.06	15 (1.4)	0.85–2.32
BMI , kg/ m ²	57					
< 25		1,698 (38.1)	1,370 (40.3)	38.67–41.97	328 (30.9)	28.20–33.76
25–30		1,780 (39.9)	1,361 (40.0)	38.41–41.70	419 (39.5)	36.59–42.47
≥ 30		982 (22.0)	668 (19.7)	18.35–21.02	314 (29.6)	26.92–32.41
Medications						
Lipid-lowering	25	1,380 (30.7)	1,050 (30.7)	29.16–32.25	330 (30.8)	28.14–33.68
Antiplatelet	25	834 (18.6)	644 (18.8)	17.54–20.16	190 (17.8)	15.58–20.16
Antihypertensive	25	1,855 (41.3)	1,410 (41.2)	39.56–42.86	445 (41.6)	38.67–44.57
Antidiabetic	25	345 (7.7)	257 (7.5)	6.67–8.44	88 (8.2)	6.72–10.03
Screening results						
Peripheral atherosclerosis	8	1,802 (40.0)	1,346 (39.2)	37.55–40.82	456 (42.5)	39.57–45.48
Carotid plaque	n/a**	1,735 (38.4)	1,296 (37.7)	36.07–39.31	439 (40.8)	37.90–43.77
LEAD	7	249 (5.5)	176 (5.1)	4.43–5.91	73 (6.8)	5.44–8.47
BP 140–159/90–99 mmHg	0	1,463 (32.4)	1,047 (30.4)	28.92–32.00	416 (38.6)	35.76–41.57
BP ≥ 160/100, mmHg	0	660 (14.6)	458 (13.3)	12.22–14.49	202 (18.8)	16.53–21.20
HbA1c ≥ 48, mmol/mol	n/a**	404 (8.9)	296 (8.6)	7.72–9.60	108 (10.0)	8.37–11.97

Abbreviations: BMI, Body Mass Index; BP, blood pressure; CI, confidence interval; HbA1c, glycated haemoglobin; IAD, interarm blood pressure difference; LEAD, lower extremity arterial disease

* Level of physical activity was grouped into: low (sedentary recreational activities like reading and watching television), moderate (low-intensity physical activity, at least 4 h a week), high (activity of high intensity, at least 4 h a week) and very high (competitive sports on a regular basis) during the past year

** To protect anonymity, we are not allowed to report numbers ≤ 3

Systolic interarm blood pressure difference

In total, 1,077 (23.8%) of the 4,517 participants had an IAD ≥ 10 mmHg (95% CI 22.61–25.11), with a higher frequency being recorded in women (26.8%) than men (21.0%) ($p < 0.001$). This female preponderance was observed in all IAD subgroups (Figure S1, Supplementary Material 2). In participants with IAD < 10 mmHg, the mean IAD was 3.98 (2.63) compared with 15.22 (5.86) in those with IAD ≥ 10 mmHg. No BP difference was observed in 5.4%. Among those with an IAD ≥ 10 mmHg, BP was most frequently lowest in the left arm (59.0% versus 41.0%) ($p < 0.001$).

Among the positive screening results, hypertension was significantly more frequent in those with IAD ≥ 10

mmHg (BP 140–159/90–99, 38.6%; BP ≥ 160/100, 18.8%) than in those with IAD < 10 mmHg (BP 140–159/90–99, 30.4%; BP ≥ 160/100, 13.3%) ($p < 0.001$) (Table 2).

Table 3 presents the characteristics of participants with IAD ≥ 10 mmHg stratified by sex. The table shows a significantly higher rate of peripheral atherosclerosis (LEAD and CP) in men (49.7%) than in women (36.7%) ($p < 0.001$). Table 3 also shows that approximately 30% were taking lipid-lowering medication before participating in VISP (no gender-specific difference), whereas only 16.6% of women and 19.2% of men were in antiplatelet therapy. Use of antihypertensive medication was frequent in both men and women, with IAD ≥ 10, 40.6% and 42.8%, respectively.

Table 3 Characteristics of participants with an IAD ≥ 10 mmHg, by sex ($n = 1,077$)

Sex	Missing	Total, <i>n</i>	Women		Men	
	0		<i>n</i> = 595	95% CI	<i>n</i> = 482	95% CI
Lifestyle habits						
Smoking						
Never	6	436 (40.7)	264 (44.7)	40.70–48.71	172 (35.8)	31.66–40.23
Current		177 (16.5)	91 (15.4)	12.70–18.54	86 (17.9)	14.73–21.61
Former		458 (42.8)	236 (39.9)	36.05–43.94	222 (46.3)	41.83–50.73
Alcohol, units/week						
♀: <7, ♂: <14	43	837 (81.0)	470 (82.5)	79.11–85.37	367 (79.1)	75.15–82.56
♀: 7–14, ♂: 14–21		141 (13.6)	81 (14.2)	11.57–17.33	60 (12.9)	10.17–16.31
♀: ≥ 14 , ♂: ≥ 21		56 (5.4)	19 (3.3)	2.13–5.17	37 (8.0)	5.83–10.82
Level of exercise*						
Low	11	117 (11.0)	60 (10.2)	8.00–12.93	57 (11.9)	9.31–15.15
Moderate		690 (64.7)	405 (68.9)	65.01–72.50	285 (59.6)	55.15–63.94
High		244 (22.9)	119 (20.2)	17.18–23.68	125 (26.2)	22.40–30.28
Very high		15 (1.4)	4 (0.7)	0.26–1.80	11 (2.3)	1.28–4.11
BMI, kg/m²						
< 25	16	328 (30.9)	204 (35.1)	31.28–39.02	124 (25.9)	22.16–30.00
25–30		419 (39.5)	206 (35.4)	31.61–39.37	213 (44.5)	40.07–48.96
≥ 30		314 (29.6)	172 (29.5)	25.98–33.39	142 (29.6)	25.72–33.90
Medications						
Lipid-lowering	7	330 (30.8)	185 (31.3)	27.69–35.16	145 (30.3)	26.32–34.54
Antiplatelet	7	190 (17.8)	98 (16.6)	13.79–19.81	92 (19.2)	15.92–22.99
Antihypertensive	7	445 (41.6)	240 (40.6)	36.71–44.63	205 (42.8)	38.43–47.28
Antidiabetic	7	88 (8.2)	50 (8.5)	6.47–10.99	38 (7.9)	5.82–10.72
Screening results						
Peripheral atherosclerosis**	4	456 (42.5)	217 (36.7)	32.86–40.62	239 (49.7)	45.23–54.15
BP 140–159/90–99 mmHg	0	416 (38.6)	196 (32.9)	29.28–36.83	220 (45.6)	41.24–50.12
BP $\geq 160/100$, mmHg	0	202 (18.8)	95 (16.0)	13.23–19.14	107 (22.2)	18.71–26.13
HbA1c ≥ 48 , mmol/mol	0	108 (10.0)	61 (10.3)	8.06–12.96	47 (9.8)	7.40–12.74

Abbreviations: BMI, Body Mass Index; BP, blood pressure; CI, confidence interval; HbA1c, glycated haemoglobin; IAD, interarm blood pressure difference

* Level of physical activity was grouped into: low (sedentary recreational activities like reading and watching television), moderate (low-intensity physical activity, at least 4 h a week), high (activity of high intensity, at least 4 h a week) and very high (competitive sports on a regular basis) during the past year

** Peripheral atherosclerosis constitutes lower extremity arterial disease and carotid plaque

Table 4 displays factors associated with an IAD ≥ 10 mmHg. After adjusting for smoking habits, level of exercise, BMI and screening results, the predominant female findings of IAD ≥ 10 mmHg persisted (OR 1.53, 95% CI 1.32–1.77, $p < 0.001$). Furthermore, BMI was associated with IAD ≥ 10 mmHg; BMI ≥ 25 –29 (OR 1.32, 95% CI 1.11–1.56, $p = 0.001$) and BMI ≥ 30 (OR 1.88, 95% CI 1.55–2.27, $p < 0.001$) when using BMI < 25 as a reference. Among positive screening results, only raised BP was associated with IAD ≥ 10 mmHg; BP 140–159/90–99 (OR 1.68, 95% CI 1.43–1.97, $p < 0.001$) and BP $\geq 160/100$ (OR 1.82, 95% CI 1.49–2.23, $p < 0.001$) (Table 4), leaving no associations with diabetes or peripheral atherosclerosis such as CP and LEAD.

Coexistence of IAD and screen-detected hypertension

In the entire screening cohort, the coexistence of IAD ≥ 10 mmHg and BP $\geq 140/90$ mmHg was observed in 13% of all women. A similar tendency was seen in all men

(14%). Coexistence of IAD and BP $\geq 160/100$ mmHg was 4% in women and 5% in men (Fig. 2).

In the participants with IAD ≥ 10 mmHg or/and BP $\geq 140/90$ mmHg, coexistence of IAD increased to 23% in women and 24% in men. At a BP threshold of at least 160/100 mmHg, coexistence of IAD decreased to 12% in women and 15% in men (Figure S2, Supplementary Material 2).

Higher versus lower reading arm for classification of hypertension

For both sexes, differences in the proportions of high BP were found when comparing the higher and lower reading arm (Table 5). At the 140–159/90–99 mmHg BP threshold, 6.2% of women and 5.3% of men would have been misclassified when using the lower rather than the higher readings (women: 32.4% minus 26.2% and men: 38.4% minus 33.1%). For BP $\geq 160/100$ mmHg, misclassification rates were 8.3% in women (22.6 minus 14.3) and

Table 4 Factors associated with an IAD ≥ 10 mmHg

	Unadjusted			Adjusted*		
	OR	95% CI	P-value	OR	95% CI	P-value
Sex						
Men	<i>ref</i>			<i>ref</i>		
Women	1.38	1.20–1.58	<0.001	1.53	1.32–1.77	<0.001
Lifestyle habits						
Smoking						
Never	<i>ref</i>			<i>ref</i>		
Current	1.03	0.84–1.26	0.782	1.10	0.89–1.36	0.388
Former	1.03	0.89–1.20	0.695	1.05	0.90–1.23	0.31
Alcohol , units/week						
♀: <7, ♂: <14	<i>ref</i>					
♀: 7–14, ♂: 14–21	0.96	0.78–1.18	0.686	-		
♀: ≥ 14 , ♂: ≥ 21	0.80	0.59–1.08	0.143	-		
Level of exercise						
Low	<i>ref</i>			<i>ref</i>		
Moderate	0.83	0.66–1.04	0.110	0.90	0.71–1.14	0.386
High	0.69	0.53–0.89	0.005	0.84	0.64–1.11	0.221
Very high	0.71	0.39–1.32	0.281	0.97	0.52–1.82	0.934
BMI, kg/m²						
< 25	<i>ref</i>			<i>ref</i>		
25–30	1.29	1.09–1.51	0.002	1.32	1.11–1.56	0.001
≥ 30	1.96	1.64–2.35	<0.001	1.88	1.55–2.27	<0.001
Lipid-lowering						
Not using	<i>ref</i>					
Using	1.00	0.87–1.17	0.922	-		
Antiplatelet						
Not using	<i>ref</i>					
Using	0.93	0.78–1.11	0.435	-		
Antihypertensive						
Not using	<i>ref</i>					
Using	1.02	0.88–1.17	0.823	-		
Antidiabetic						
Not using	<i>ref</i>					
Using	1.10	0.86–1.42	0.444	-		
Peripheral atherosclerosis **						
Not found	<i>ref</i>			<i>ref</i>		
Found	1.15	1.00–1.32	0.052	1.11	0.95–1.28	0.191
BP $\geq 160/100$, mmHg ***						
Not found	<i>ref</i>			<i>ref</i>		
140–159/90–99	1.68	1.44–1.95	<0.001	1.68	1.44–1.97	<0.001
$\geq 160/100$ mmHg	1.86	1.53–2.26	<0.001	1.82	1.49–2.23	<0.001
HbA1c ≥ 48, mmol/mol						
Not found	<i>ref</i>					
Found	1.18	0.94–1.49	0.156	-		

Abbreviations: BMI, Body Mass Index; BP, blood pressure; CI, confidence interval; HbA1c, glycated haemoglobin; IAD, interarm blood pressure difference. OR, odds ratio

* In the adjusted analyses, we entered variables with an unadjusted p value of <0.1 and smoking; as smoking may constitute a clinically relevant risk factor for interarm difference

** Peripheral atherosclerosis constitutes lower extremity arterial disease and carotid plaque

*** Blood pressure is the mean of the second and third blood pressure measurements in accordance with guidelines

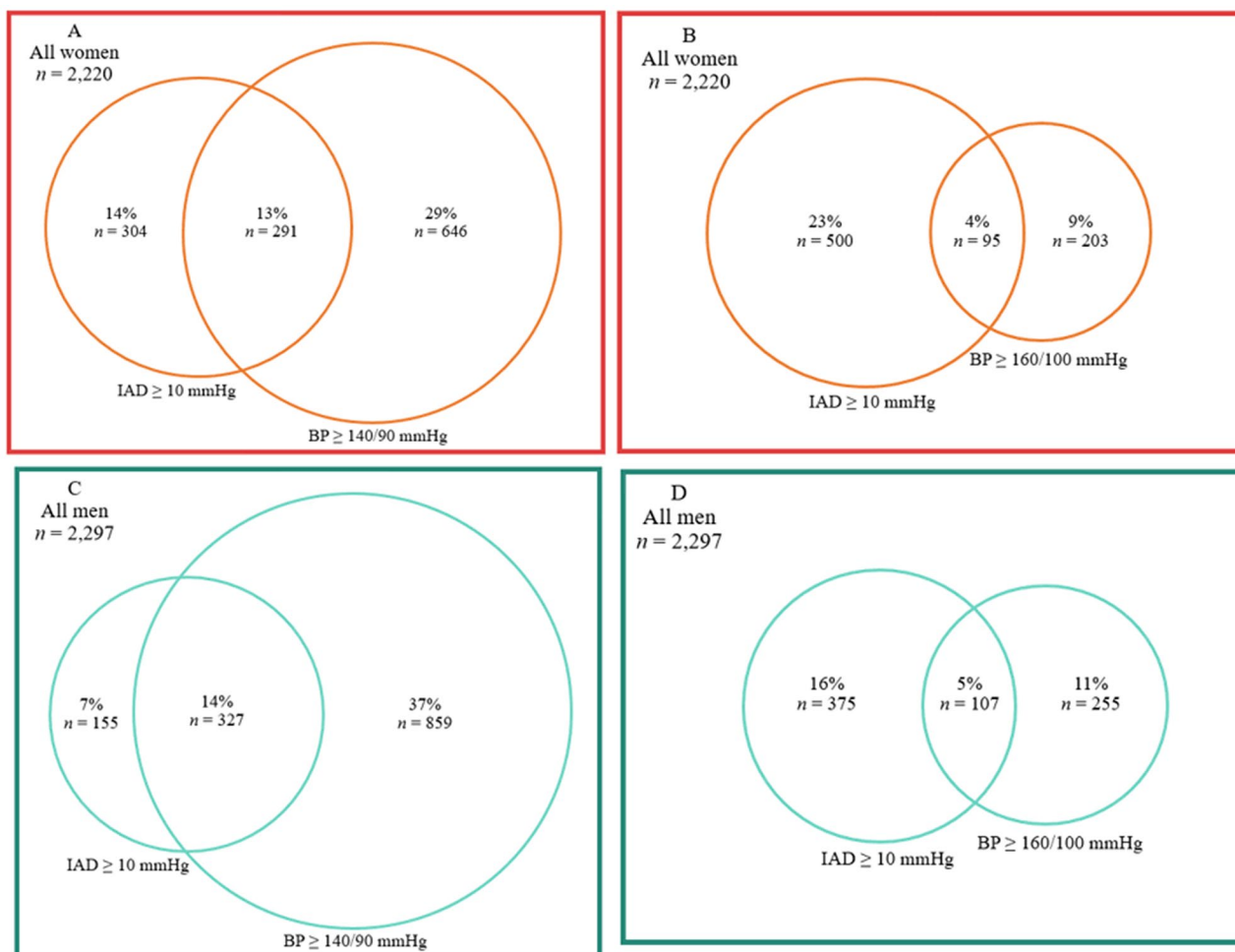


Fig. 2 Venn diagram displaying coexistence of IAD ≥ 10 mmHg and BP at 140/90 mmHg or 160/100 mmHg thresholds, stratified by sex. Abbreviations: BP, blood pressure; IAD, interarm blood pressure difference. Percentages are for all women (**A** and **B**) or men (**C** and **D**), respectively

10.0% in men (27.0 minus 17.0%), resulting in a total misclassification of 14.5% in women and 15.3% in men.

A comparison of the first BP measurements showed similar proportions classified as hypertensive, regardless of whether their systolic reading alone or both their systolic and diastolic readings were considered (Table 5).

Discussion

In this population-based cross-sectional study of 4,517 Danes aged 67 years, we investigated sex differences in IAD prevalence and its associations and coexistence with screen-detected cardiovascular conditions. Finally, we studied the magnitude of hypertension misclassification. Overall, we found a 23.8% prevalence of IAD ≥ 10 mmHg. The prevalence of systolic IAD is reported to fluctuate with age, ethnicity and cohort comorbidity. A meta-analysis by Clark et al. found a pooled 11.2% prevalence of IAD ≥ 10 mmHg in patients from primary care populations [17]. However, in cross-sectional studies, IAD prevalences reached up to 19% among primary care patients

with hypertension (mean age 69.6 years) [18] and up to 27% among 18–60-year-old healthy male Indians [19]. Among 3,350 asymptomatic men and women with elevated CVD risk (mean age 61.9 years) enrolled in a randomised trial within primary care, IAD was observed in 38% [20]. In secondary care, IAD prevalence was observed in up to 48% of patients with coronary artery disease [21]. Among Danes referred to a vascular laboratory for potential LEAD, of whom 46.8% were diagnosed with LEAD, 27% had IAD ≥ 10 mmHg at three repeated simultaneous BP measurements [22].

Previous studies have shown that conducting multiple measurements generates fewer individuals with an IAD [23, 24]. Our observation of IAD prevalence in a general population may be attributed to initially using only a single simultaneous bilateral BP reading to calculate IAD. In contrast, our approach involved simultaneously measured BP, which is a favourable approach for identifying IAD compared with sequential bilateral BP [17].

Table 5 Prevalence of screen-detected hypertension, stratified by sex

BP, mmHg	Total, n	Women n = 2,220		Men n = 2,297	
		n (%)	95% CI	n (%)	95% CI
First systolic BP reading*					
Higher reading arm					
< 140	1,896 (42.0)	1,036 (46.7)	44.60–48.75	860 (37.4)	35.48–39.44
140–159	1,548 (34.3)	692 (31.2)	29.28–33.13	856 (37.3)	35.31–39.26
≥ 160	1,073 (23.7)	492 (22.1)	20.48–23.94	581 (25.3)	23.56–27.11
Lower reading arm					
< 140	2,550 (56.5)	1,351 (60.9)	58.81–62.87	1,199 (52.2)	50.15–54.24
140–159	1,280 (28.3)	556 (25.0)	23.29–26.89	724 (31.5)	29.65–33.45
≥ 160	687 (15.2)	313 (14.1)	12.71–15.61	374 (16.3)	14.83–17.85
First systolic and/or diastolic BP reading*					
Higher reading arm					
< 140 / 90	1,793 (39.7)	998 (45.0)	42.90–47.03	795 (34.6)	32.69–36.58
140–159 / 90–99	1,600 (35.4)	719 (32.4)	30.47–34.36	881 (38.4)	36.39–40.36
≥ 160 and/or ≥ 100	1,124 (24.9)	503 (22.6)	20.96–24.45	621 (27.0)	25.26–28.89
Lower reading arm					
< 140 / 90	2,466 (54.6)	1,320 (59.5)	57.40–61.48	1,146 (49.9)	47.85–51.94
140–159 / 90–99	1,343 (29.7)	582 (26.2)	24.43–28.09	761 (33.1)	31.23–35.08
≥ 160 / 100	708 (15.7)	318 (14.3)	12.93–15.84	39 (17.0)	15.50–18.57
Second and third systolic and/or diastolic BPs in higher reading arm*					
Mean					
< 140 / 90	2,394 (53.0)	1,283 (57.8)	55.73–59.83	1,111 (48.4)	46.33–50.41
140–159 / 90–99	1,463 (32.4)	639 (28.8)	26.94–30.70	824 (35.9)	33.94–37.86
≥ 160 / 100	660 (14.6)	298 (13.4)	12.07–14.91	362 (15.7)	14.33–17.31

Abbreviations: BP, blood pressure; CI, confidence interval

* Missing, n=0

We found that IAD reflected a significant female preponderance, a trend reflected in all IAD subgroups. This sex-related difference persisted after adjustment for relevant available cardiovascular risk factors and screening results. In contrast, no sex differences in IAD prevalence were reported in an Indian population (men 42.9%;

women 44.2%) [25] or an African population (men 19%; women 20%) [26]. Moreover, in a study of 484 Finnish participants (mean age 49.7 years), a similar IAD prevalence was observed in men (12.1%) and women (8.3%) ($p=0.16$) [27]. Thus, further investigation into sex-stratified prevalence and potential causality is warranted in a large-scale, elderly Caucasian population.

In the present study, screen-detected raised BP was the only medical condition positively associated with IAD. In contrast, other studies have reported IAD to be related to the presence of co-occurring cardiovascular conditions, e.g., LEAD, hypertension, diabetes mellitus, carotid stenosis and abdominal aortic dissection [28–30]. We chose not to report OR for LEAD separately as the sensitivity of IAD in identifying LEAD is low (15%), albeit its specificity is high (96%) [30]. These diverse findings may partly be explained by the composition of the VISP cohort, which comprises a general population of all 67-year-old persons in a restricted geographical area with a low prevalence of, e.g., LEAD (5.5%), and as we report carotid plaque and not carotid stenosis. Similarly, no association between IAD and the presence of carotid plaque was observed in a cross-sectoral study among 1,426 individuals in primary care [31]. When assessing IAD as a screening tool, we believe that data from populations with a low-to-moderate CVD risk are important. Such populations will mirror those seen in general practice.

Coexistence of IAD and BP at a threshold of $\geq 140/90$ mmHg was seen in 13% of women and 14% of men. This coexistence was lower at a BP threshold of at least 160/100 mmHg, indicating that IAD was an isolated screening result. This result is novel and unexplored in the literature.

Systolic IAD has been associated with an increased risk of MACE and all-cause mortality [6]. In a sub-analysis of the Cardiovascular Outcomes for People Using Anti-coagulation Strategies (COMPASS) trial, consisting of patients with chronic LEAD or coronary artery disease, a similar risk was observed when comparing those with and without IAD in terms of the composite endpoint of MACE, except for stroke [32]. Thus, IAD may constitute a risk marker in advanced risk assessment, mainly in primary prevention. A systematic Cochrane review found that frequently used cardiovascular risk scores for primary cardiovascular prevention had an uncertain effect [33]. Emerging evidence suggests that IAD may supplement existing risk prediction scores, such as Framingham and QRISK2 [6], substantiating the need for further evaluation of new CVD assessment methods. Nevertheless, in cardiovascular screening initiatives like VISP, it is important to research and investigate the additional value of including IAD as a risk marker, especially considering a gender-specific perspective. International hypertension management guidelines recognise IAD

as a marker in atherosclerotic disease associated with increased CVD risk at a threshold of IAD ≥ 15 mmHg (class I, level A [5] and class I, level C [4]). However, these guidelines have not taken into account the meta-analysis by INTERPRESS-IPD (the Interarm Blood Pressure Difference Individual Patient Data Collaboration) headed by Clark, in which a threshold of IAD ≥ 10 mmHg is recommended [6]. This new evidence served as the rationale for our decision on the IAD threshold. As of now, cardiovascular prophylaxis with antiplatelet and lipid-lowering agents is not recommended for IAD. Noteworthy, identification of IAD may hold prophylactic potential in the general population. We found that only a third of the VISP participants with IAD ≥ 10 mmHg received lipid-lowering therapy before screening, and less than 20% received antiplatelet therapy. Further research is warranted to clarify the rationale for initiating such prophylactic medication upon IAD.

When adopting a mean BP threshold of $\geq 140/90$ mmHg in the higher versus the lower reading arm, we found that 14.5% of women and 15.3% of men needed reclassification. Our results aligned with the results from a secondary meta-analysis by Clark et al. with multinational participation ($n=53,173$); overall, 12% of men and women required reclassification from non-hypertensive to hypertensive when using the higher rather than the lower reading arm to diagnose hypertension at a systolic BP of 130 and 140 mmHg [7]. Moreover, Clark et al. found that utilising a higher rather than a lower reading arm is superior in predicting MACE and all-cause mortality [7]. These findings emphasise the significance of considering BP readings from both arms and favouring the measurement from the higher arm in clinical practice.

Strengths and limitations

The main strengths of our study are its population-based design and high participation rate with a complete dataset (82.1%). Moreover, including both sexes is a strength as women continue to be underrepresented in cardiovascular research [34]. Another strength is that we used simultaneous BP measurements as sequential have been reported to overestimate IAD threefold compared with simultaneous BP measurements [17].

The limitations of our study are related to the fact that we only obtained one simultaneous BP measurement. Thus, our study cannot contribute to clarifying the reproducibility of IAD or its coexistence with CVD conditions. The Multi-Ethnic Study of Atherosclerosis (MESA) found that high systolic IAD was not persistent across three exams conducted throughout a 9.5-year follow-up period. Nevertheless, Duprez et al. found that at least one maximum absolute IAD ≥ 15 mmHg had a graded association with incident stroke and LEAD [35]. Furthermore,

the review by Clark et al. suggested that a threshold for systolic IAD ≥ 10 mmHg was sufficient based on a single pair of sequential BP measurements [6]. In the VISP set-up, BP measurements were obtained as part of non-automatic ABI measurements and based on three consecutive measurements conducted during the same visit. Ideally, the reproducibility of misclassification should be assessed at separate visits. However, performing separate BP measurements jeopardises the feasibility of VISP. Additionally, it would have been preferable to perform BP measurements without the screening nurses being present to avoid any white-coat effect. On the other hand, in a review, Clark et al. concluded that white-coat hypertension is less frequently diagnosed when BP measurements are made by nurses than by doctors [36]. The white-coat effect occurs at all grades of hypertension but is greatest for grade 1 hypertension. This supports our threshold for action of BP $\geq 160/100$ mmHg [4] to limit the risk of false positives. Finally, using self-reported information carries a risk of social desirability bias.

Conclusion

This study highlighted the importance of bilateral BP measurements in identifying IAD and enhancing the diagnostic accuracy of hypertension. Female sex and raised BP emerged as an independent factor for IAD prevalence, whereas IAD showed no association with diabetes or other arterial lesions such as LEAD or CP. The coexistence of IAD and raised BP was observed in up to 14% of participants, with a decreasing tendency at a higher BP threshold, indicating that IAD may be an isolated factor in the general population. Using the lower reading arm resulted in approximately 15% of women and men being misclassified as non-hypertensive at a threshold of BP $\geq 140/90$ mmHg due to false negatives.

In future studies, the predictive value of sex-stratified IAD should be assessed for cardiovascular events and death to verify its potential as a screening tool in population-based CVD screening.

Abbreviations

AAA	Abdominal aortic aneurysm
ABI	Ankle-brachial index
ACE	Angiotensin-converting enzyme
BP	Blood pressure
BMI	Body Mass Index
CP	Carotid plaque
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
CPR	Civil registration number
CT	Computed tomography
CVD	Cardiovascular disease
HbA1c	Glycated haemoglobin
IAD	Interarm blood pressure difference
LEAD	Lower extremity arterial disease
MACE	Major adverse cardiovascular events
REDCap	Research Electronic Data Capture
VISP	Viborg Screening Program

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12889-024-19388-8>.

Supplementary Material 1

Supplementary Material 2

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Author contributions

JL and MD designed VISP. JL, AH and MD are members of the VISP steering committee. MD and JWA analysed the data. MD drafted the main body of the manuscript. JWA, JL, NTK, BB, NU, and AH provided valuable criticisms of the revised sequential versions of the manuscript and approved the final version for publication.

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Data availability

In accordance with Danish law and for data protection purposes, the datasets analysed for this study are not publicly available. However, the datasets are available from the corresponding author on reasonable request, pending data transfer approval by the Danish Data Protection Agency.

Declarations

Ethics approval and consent to participate

VISP is a preventive initiative launched by the public administration of Viborg Municipality, Denmark. Therefore, no ethical approval was required from the Central Denmark Region Committees on Health Research Ethics (1-10-72-163-19); only approval from the Danish Data Protection Agency was required (1-16-02-232-15). All participants provided verbal informed consent. Verbal and written information is given to all screening participants, informing them about the collection and usage of their self-reported information and screening results for research and evaluation, among others. This procedure is endorsed due to no requirement of ethical approval as stated by The Central Denmark Region Committees on Health Research Ethics.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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