



# Serial blood pressure measurements, left ventricular remodelling and cardiovascular outcomes

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## Abstract

**Background:** Hypertension is a risk factor for the development of cardiovascular disease. Whether serial blood pressure (BP) measurements are more closely associated with subclinical left ventricular (LV) remodelling and better predict risk of cardiovascular events over individual BP measurements are not known.

**Methods:** We assessed systolic BP, diastolic BP and pulse pressure at several time points during adulthood in 1333 women and 1211 men participating in the Akershus Cardiac Examination 1950 Study. We defined serial BP measurements as the sum of averaged BPs from adjacent consecutive visits indexed to total exposure time between measurements. We assessed the associations between serial and individual BP measurements and (1) LV structure, function and volumes and (2) incident myocardial infarction, ischemic stroke, heart failure and cardiovascular death.

**Results:** All indices of higher serial BP measurements were associated with increased indexed LV mass, and the associations were stronger than those of individual BP measurements. Serial diastolic BP pressure was strongly and inversely associated with LV systolic function, while higher serial systolic BP was primarily associated with higher LV volumes. Both serial systolic (incidence rate ratio [IRR] 1.10, 95% CI 1.03 to 1.17) and diastolic BPs (IRR 1.14, 95% CI 1.02 to 1.27) were associated with increased incidence of clinical events.

**Conclusion:** In healthy community dwellers without established cardiovascular disease, different serial BP indices associate strongly with LV remodelling and cardiovascular outcomes. Whether the use of serial BP indices for guiding treatment is superior to individual measurements should be explored in additional prospective studies.

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**KEYWORDS**

echocardiography, epidemiology, heart failure, hypertension, longitudinal population-based cohorts

## 1 | INTRODUCTION

Arterial hypertension is one of the strongest risk factors for cardiovascular disease, especially pertaining to the development of myocardial infarction, ischemic stroke and heart failure.<sup>1</sup> Most established cardiovascular risk prediction tools incorporate systolic blood pressure (BP) in their algorithms, including the most recent European Systematic COronary Risk Evaluation (SCORE) model.<sup>2</sup> Diastolic BP may complement systolic BP in cardiovascular risk prediction but is more challenging to interpret due to its nonlinear association with outcomes.<sup>3</sup> The derived BP variable pulse pressure<sup>4</sup> associates with cardiovascular risk, but the results are more conflicting compared to systolic BP. In addition, current cardiovascular risk models only use information from BP measurements taken at a single time point, despite most subjects commonly having repeated BP measurements.

Apart from hypertensive emergencies, high BP is a chronic condition that, over time, can have detrimental effects on organ structure and function, including the heart.<sup>5</sup> Repeated BP measurements, quantified together as serial BP measurements, may better incorporate total risk and therefore associate more closely with end-organ damage than individual BP measurements. One important parameter for subclinical cardiovascular disease is left ventricular (LV) hypertrophy, and only population studies with serial, validated BP measurements and detailed cardiac imaging can provide information on the value of serial BP measurements prior to the development of symptomatic cardiovascular disease. In addition, long follow-up time is required, as the progression from subclinical cardiovascular disease to symptomatic conditions, such as myocardial infarction and heart failure,<sup>6</sup> takes many years. Accordingly, in this study we hypothesized that serial BP measurements are more closely associated with subclinical LV remodelling and incident cardiovascular events than individual BP measurements. We tested this hypothesis in a large prospective, population-based cohort with BP measurements for up to 40 years, detailed echocardiography of all participants at age 62–65 years, and with longitudinal follow-up for clinical outcomes. Results from such a detailed investigation on the interplay between chronic pressure overload, cardiac remodelling and risk of detrimental cardiovascular outcomes could lay the foundation for novel clinical trials aimed at tailoring preventive therapies according to serial BP profiles.

## 2 | METHODS

### 2.1 | Study overview

The Akershus Cardiac Examination (ACE) 1950 Study is a prospective, population-based age cohort that invited all community dwellers born in 1950 from Akershus County, Norway, to participate ( $n = 5827$ ). Study baseline examination was performed from September 2012 to May 2015, and 3706 individuals (63.6%) accepted the study invitation and were included. The study was conducted at the two hospitals of Akershus County, Norway: Akershus University Hospital and Bærum Hospital/Vestre Viken Hospital Trust. Study design has been reported previously.<sup>7</sup> The study complies with the Declaration of Helsinki and is approved by the Regional Committees for Medical Research Ethics – South East Norway (reference REC 2011/1475). All participants provided informed written consent before study commencement.

### 2.2 | Study population

A subset of the ACE 1950 Study participants had participated in the Age 40 Program, a national population-based cardiovascular screening study carried out in 40-year-olds between 1985 and 1999 by the National Health Screening Service. For a subset of the male study participants of the ACE 1950 Study, military screening data was available from conscription records attained at age 18–19 years (Figure S1).<sup>8</sup>

### 2.3 | Covariates

At military screening, BP was assumed to be measured using a manual sphygmomanometer. At the Age 40 Program, BP was measured using an automated device (DINAMAP, Criticon). At the ACE 1950 Study, BP was measured using an automated device (Carescape V100, GE Healthcare). For the two latter, three readings were performed while seated, and systolic BP and diastolic BP were calculated as the mean of the second and third readings. Pulse pressure was calculated as the difference between systolic BP and diastolic BP. More detailed description of the BP measurements has previously been published.<sup>8,9</sup>

Demographics, medical history, current medication, and alcohol and tobacco consumption are self-reported. Clinical examination with assessment of height and weight was performed at the ACE 1950 Study. Resting heart rate was acquired from electrocardiograms. Coronary artery disease was defined as self-reported history of myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention. Diabetes was defined as self-reported diabetes, the use of anti-diabetic medication, or the presence of elevated concentrations of HbA1c ( $\geq 6.5\%$ ) and fasting blood glucose ( $\geq 7.0$  mmol/L) on the ACE 1950 Study baseline examination. Participants with known coronary artery disease at baseline were excluded from the analyses. Use of antihypertensive therapy was recorded at the Age 40 Program and the ACE 1950 Study. No information on antihypertensive therapy was available from military screening, and all study participants were assumed not to be on antihypertensive therapy at the age of 18–19 years.

## 2.4 | Echocardiography

Transthoracic echocardiography was performed using GE Vivid E9 (GE Healthcare) with the M5S probe according to a predefined protocol. Two echocardiography technicians and four trained fellows acquired the echocardiograms. Four cardiac cycles were recorded during breath hold at end expiration from the following views: Parasternal long- and short-axis, and apical four-chamber, two-chamber and long-axis. Standard two-dimensional images, M-mode, tissue velocity imaging, pulsed and continuous Doppler were recorded, and the images were analysed with EchoPAC 201 (GE Healthcare).

Indexed LV mass, diastolic (E/e' ratio and E/A ratio) and systolic (global longitudinal strain [GLS] and LV ejection fraction [LVEF]) function, and LV volumes (indexed LV end-diastolic volume [LVEDVI] and indexed LV end-systolic volume [LVESVI]) were assessed by echocardiography at the ACE 1950 Study. Detailed description of echocardiography in the ACE 1950 Study has recently been published.<sup>10</sup> We used absolute values of GLS in all analyses, that is higher absolute values denoting better LV systolic function.

## 2.5 | Outcomes

Data on cardiovascular death (International Statistical Classification of Diseases [ICD], 10th Revision codes for underlying cause of death; I00–I99 and R96) were obtained from the Norwegian Cause of Death Registry. Data on all registered inpatient hospitalizations with myocardial

infarction (codes I21.x), ischemic stroke (codes I63.x) or heart failure (codes I50.x) as main diagnosis were obtained from the Norwegian Patient Registry. All events were obtained from the date of ACE 1950 Study baseline examination through December 31, 2020.

## 2.6 | Serial blood pressure measurements

We defined serial BP measurements as the sum of averaged BPs from adjacent consecutive visits (military screening – Age 40 Program – ACE 1950 Study), indexed to total exposure time between measurements (Figure S2A). For example, a study participant with systolic BP of 118 mmHg at military screening, 145 mmHg at the Age 40 Program and 130 mmHg at the ACE 1950 Study, and 19 years between military screening and the Age 40 Program and 25 years between the Age 40 Program and the ACE 1950 Study would have a serial systolic BP of 135 mmHg (Figure S2B).

## 2.7 | Statistical methods

Baseline data are reported as absolute numbers (proportion) or median (interquartile range) unless otherwise stated. Continuous variables were analysed with the Mann–Whitney *U* test or Kruskal–Wallis *H* test, and categorical variables were analysed with the Fisher exact test or chi-squared test, as appropriate. Linear regression analyses were used to assess associations between BPs and echocardiography. Coefficients from the regression models were compared using a Hausman test of equality. Nonlinear associations were assessed by restricted cubic splines with knots placed at the 5th, 27.5th, 50th, 72.5th and 95th sample percentiles. We compared overall model fit of the linear and nonlinear models by the likelihood-ratio test. For prognosis, we assessed the associations of BPs with all admissions with myocardial infarction, ischemic stroke or heart failure, or cardiovascular mortality. Follow-up was censored at the time of death, or for survivors, on December 31, 2020. We registered all events during follow-up and used a Poisson regression model to test the relationship between BPs and recurrent event data. Subjects with missing covariate data were excluded from the multivariable regression analyses. All models were adjusted for sex, age, study site, history of diabetes mellitus, current smoking, body mass index and antihypertensive therapy, all from the ACE 1950 Study baseline. We also adjusted for antihypertensive therapy at the Age 40 Program. The Poisson regression models were additionally adjusted for length of follow-up. Sensitivity analyses were performed by (1) excluding subjects with LVEF  $\leq 40\%$  or moderate to severe aortic valve regurgitation, aortic valve

stenosis, or mitral valve regurgitation, or by (2) including only subjects with measurement of BP at military screening. As our study was primarily hypothesis-generating, we did not adjust for multiplicity.<sup>11</sup> Statistical significance was assumed at  $p < .05$ . The analyses were performed with STATA 16 (StataCorp LP).

### 3 | RESULTS

#### 3.1 | Baseline characteristics

Of the 3706 subjects from the ACE 1950 Study, 2722 study participants had valid BP measurements at the Age 40 Program and the ACE 1950 Study. After excluding 178 study participants with established coronary artery disease, 1333 women and 1211 men were included in the following analyses. Of these, 691 men had valid BP measurements at military screening (Figure S1). Serial BP measurements from military screening to the ACE 1950 Study are demonstrated in Figure 1. Baseline characteristics of the ACE 1950 Study according to serial systolic BP are detailed in Table 1. Study participants with higher serial systolic BP were older and more frequently men, with higher body mass index and heart rate. They were more often on antihypertensive and lipid-lowering therapy, exhibited a more unfavourable biochemical profile, had higher indexed LV mass, LVEDVI, LVESVI, and E/e', and lower GLS and E/A ratio. Baseline characteristics of the ACE 1950 Study according to baseline systolic BP are detailed in Table S1, with patterns of demographics, medical therapy, biochemistry, and echocardiography less pronounced but comparable to those of serial systolic BP.

#### 3.2 | Associations between BPs and left ventricular remodelling

Table 2 demonstrates the associations of systolic and diastolic BPs with echocardiography at the ACE 1950 Study; linear models were appropriate for all associations ( $p$  for nonlinearity  $> .05$  for all, Figures S3–S9). Serial systolic and diastolic BPs were associated with indexed LV mass, and stronger than individual BP measurements at the Age 40 Program and the ACE 1950 Study. Generally, the associations between LV remodelling measures and BPs assessed at the Age 40 Program were weaker than those of BP assessed at the ACE 1950 Study and serial BP measurements. For LVEF and GLS, the associations of BPs at the ACE 1950 Study and serial BP measurements were comparable, and superior to the associations of BPs at age 40. These differences were also apparent for pulse pressure, especially regarding indexed LV mass and LV volumes (Table S2).

#### 3.3 | Associations between BPs and long-term cardiovascular outcomes

During a median follow-up of 2340 (2207–2570) days, 106 study participants experienced one or more clinical events (admission for myocardial infarction, ischemic stroke or heart failure, or cardiovascular death). We registered a total of 166 clinical events, and Figure 2 shows number of clinical events per study participant. Study participants who experienced one or more clinical events on follow-up had higher serial systolic and diastolic BPs, but similar pulse pressure, compared to event-free study participants

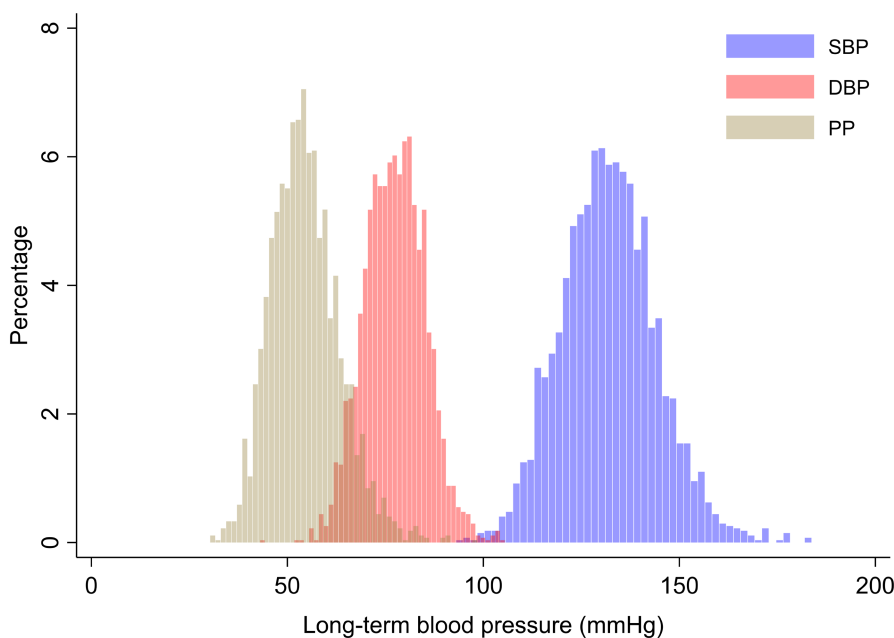


FIGURE 1 Distribution of serial blood pressure measurements. DBP, serial diastolic blood pressure; PP, serial pulse pressure; SBP, serial systolic blood pressure

**TABLE 1** Baseline characteristics at ACE 1950 Study according to quartiles of serial systolic blood pressure

	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-value
N	2544	703	642	615	584	
Serial systolic blood pressure, mmHg (range)		93–124	125–132	133–140	141–184	
Study site Akershus University Hospital, n (%)	1738 (68.3%)	436 (62.0%)	425 (66.2%)	437 (71.1%)	440 (75.3%)	<.001
<b>Demographics</b>						
Age, years	63.9 (63.4–64.4)	63.8 (63.4–64.4)	63.9 (63.4–64.4)	63.9 (63.4–64.5)	64.0 (63.4–64.5)	.036
Male sex, n (%)	1211 (47.6%)	225 (32.0%)	333 (51.9%)	348 (56.6%)	305 (52.2%)	<.001
Current smoker, n (%)	355 (14.1%)	122 (17.5%)	101 (15.9%)	77 (12.6%)	55 (9.5%)	<.001
Alcohol consumption, units/2 weeks	6 (2–11)	5 (2–10)	6 (2–10)	6 (3–12)	5 (2–12)	.001
<b>Clinical examination</b>						
Body mass index, kg/m <sup>2</sup>	26.5 (23.9–29.3)	25.1 (22.9–27.9)	26.4 (23.9–29.1)	27.0 (24.5–30.0)	27.6 (25.1–30.2)	<.001
Waist-to-hip ratio	0.91 (0.84–0.98)	0.87 (0.81–0.93)	0.92 (0.85–0.98)	0.93 (0.85–1.00)	0.92 (0.85–0.99)	<.001
Heart rate, beats/min	62 (56–69)	61 (55–68)	62 (56–68)	62 (57–69)	64 (57–70)	<.001
Systolic blood pressure, mmHg	136 (125–149)	119 (113–126)	134 (127–140)	144 (136–151)	157 (148–167)	<.001
Diastolic blood pressure, mmHg	77 (70–83)	69 (64–75)	76 (71–81)	79 (74–85)	83 (77–90)	<.001
<b>Medical history</b>						
Diabetes mellitus, n (%)	185 (7.3%)	29 (4.1%)	37 (5.8%)	63 (10.2%)	56 (9.6%)	<.001
Atrial fibrillation, n (%)	91 (3.6%)	27 (3.8%)	17 (2.6%)	18 (2.9%)	29 (5.0%)	.13
<b>Medication</b>						
Diuretics, n (%)	69 (2.7%)	12 (1.7%)	17 (2.6%)	18 (2.9%)	22 (3.8%)	.15
β blockers, n (%)	234 (9.2%)	41 (5.8%)	39 (6.1%)	55 (8.9%)	99 (17.0%)	<.001
Calcium antagonists, n (%)	177 (7.0%)	19 (2.7%)	32 (5.0%)	57 (9.3%)	69 (11.8%)	<.001
ACE-I/ARB, n (%)	610 (24.0%)	66 (9.4%)	140 (21.8%)	186 (30.2%)	218 (37.3%)	<.001
Statins, n (%)	541 (21.3%)	113 (16.1%)	127 (19.8%)	147 (23.9%)	154 (26.4%)	<.001
<b>Clinical chemistry</b>						
CRP ≥3 mg/L, n (%)	523 (20.6%)	121 (17.2%)	141 (22.0%)	125 (20.3%)	136 (23.3%)	.038
HbA1c, %	5.7 (5.5–5.9)	5.6 (5.5–5.9)	5.6 (5.4–5.9)	5.7 (5.5–6.0)	5.7 (5.5–6.0)	<.001
Total cholesterol, mg/dl	213 (186–240)	213 (190–244)	217 (186–236)	209 (182–232)	217 (190–244)	.010
HDL cholesterol, mg/dl	58 (46–70)	62 (50–73)	58 (46–70)	58 (46–70)	58 (46–70)	<.001
Triglycerides, mg/dl	97 (71–142)	89 (71–124)	106 (80–142)	97 (71–151)	115 (80–159)	<.001
eGFR, ml/min/1.73m <sup>2</sup>	84.6 (75.0–92.5)	85.7 (76.7–93.0)	84.6 (75.3–92.4)	83.7 (73.9–92.1)	83.6 (74.3–92.1)	.012
<b>Echocardiography</b>						
Indexed LV mass, g/m <sup>2</sup>	72.9 (63.5–85.8)	69.2 (61.0–79.7)	72.1 (62.8–84.4)	76.0 (65.9–88.9)	76.1 (66.0–90.4)	<.001
LV ejection fraction, %	56.0 (52.4–59.7)	56.2 (53.0–60.0)	56.0 (52.3–59.4)	55.8 (52.3–59.1)	55.7 (52.0–59.8)	.13
Global longitudinal strain, %	20.3 (18.7–21.9)	20.6 (19.1–22.2)	20.2 (18.7–21.8)	20.3 (18.4–21.9)	20.0 (18.4–21.7)	.004
E/e'	8.5 (7.2–10.1)	8.1 (7.0–9.6)	8.1 (6.9–9.7)	8.8 (7.5–10.4)	9.2 (7.8–10.7)	<.001
E/A ratio	0.99 (0.88–1.21)	1.06 (0.92–1.32)	0.99 (0.88–1.20)	0.98 (0.88–1.17)	0.96 (0.85–1.17)	<.001
Indexed LV end-diastolic volume, ml/m <sup>2</sup>	67.7 (58.7–78.3)	65.4 (58.1–75.3)	67.6 (58.2–77.8)	70.0 (60.0–80.2)	68.0 (58.3–80.0)	<.001
Indexed LV end-systolic volume, ml/m <sup>2</sup>	29.7 (24.5–35.2)	28.6 (24.2–33.4)	29.7 (24.5–34.8)	30.9 (25.8–36.2)	29.7 (24.3–36.2)	<.001

Abbreviations: ACE, Akershus Cardiac Examination; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LV, left ventricular.



TABLE 2 Associations between systolic and diastolic blood pressures and echocardiography

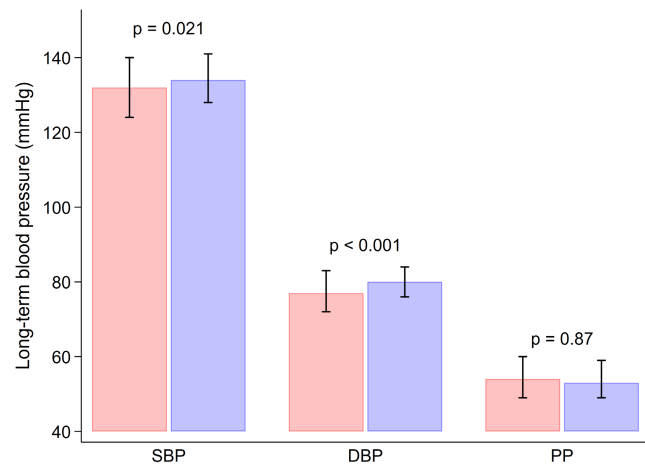
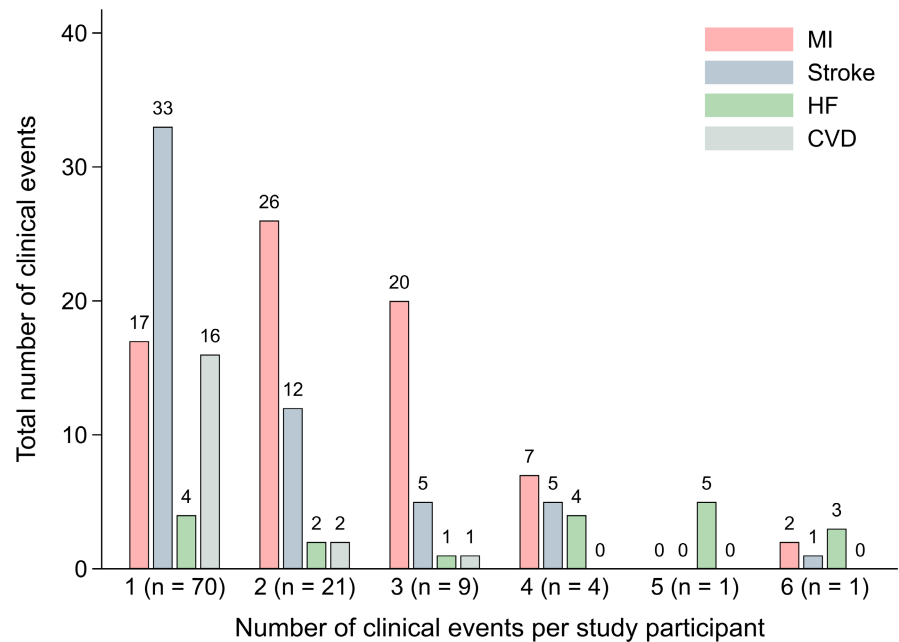
	B (95% CI)					
	Systolic blood pressure			Diastolic blood pressure		
	Age 40 Program	ACE 1950	Serial	Age 40 Program	ACE 1950	Serial
Indexed LV mass ( <i>n</i> = 2479)	0.32 (0.05 to 0.60) <sup>c</sup>	0.59 (0.35 to 0.71) <sup>a</sup>	0.73 (0.45 to 1.01)	0.15 (−0.23 to 0.53) <sup>b</sup>	0.63 (0.28 to 0.98)	0.62 (0.16 to 1.09)
LV ejection fraction ( <i>n</i> = 2411)	0.04 (−0.05 to 0.13) <sup>b</sup>	−0.07 (−0.13 to −0.01)	−0.07 (−0.16 to 0.02)	−0.08 (−0.20 to 0.05) <sup>c</sup>	−0.34 (−0.46 to −0.23)	−0.34 (−0.49 to −0.18)
Global longitudinal strain ( <i>n</i> = 1789)	0.01 (−0.04 to 0.05) <sup>a</sup>	−0.03 (−0.06 to −0.002)	−0.03 (−0.08 to 0.02)	−0.06 (−0.12 to 0.01) <sup>c</sup>	−0.18 (−0.23 to −0.12)	−0.18 (−0.26 to −0.10)
E/e' ( <i>n</i> = 2437)	0.10 (0.06 to 0.14) <sup>b</sup>	0.09 (0.06 to 0.12) <sup>c</sup>	0.15 (0.10 to 0.19)	0.11 (0.05 to 0.16)	0.05 (0.002 to 0.10) <sup>b</sup>	0.12 (0.05 to 0.19)
E/A ratio ( <i>n</i> = 2438)	−0.01 (−0.01 to −0.004) <sup>a</sup>	−0.01 (−0.01 to −0.005) <sup>c</sup>	−0.01 (−0.02 to −0.01)	−0.02 (−0.03 to −0.02) <sup>c</sup>	−0.02 (−0.03 to −0.02) <sup>c</sup>	−0.04 (−0.04 to −0.03)
Indexed LV end-diastolic volume ( <i>n</i> = 2415)	0.11 (−0.13 to 0.34) <sup>b</sup>	0.27 (0.11 to 0.42)	0.34 (0.10 to 0.58)	−0.38 (−0.70 to −0.05)	−0.08 (−0.37 to 0.22) <sup>a</sup>	−0.34 (−0.74 to 0.05)
Indexed LV end-systolic volume ( <i>n</i> = 2412)	0.03 (−0.10 to 0.16) <sup>c</sup>	0.18 (0.09 to 0.26)	0.21 (0.08 to 0.34)	−0.11 (−0.29 to 0.07) <sup>b</sup>	0.21 (0.05 to 0.37)	0.09 (−0.13 to 0.31)

Note: All coefficients adjusted for sex, age, study site, history of diabetes mellitus, current smoking, body mass index, and antihypertensive therapy at both the ACE 1950 Study and at the Age 40 Program. Coefficients reported per 5 mmHg.

Abbreviations: ACE, Akershus Cardiac Examination; LV, left ventricular.

*p* Compared to serial blood pressure measurements: <sup>a</sup> <.05, <sup>b</sup> <.01, <sup>c</sup> <.001.

**FIGURE 2** Number of clinical events per study participant. CVD, cardiovascular death; HF, heart failure; MI, myocardial infarction. Total number of study subjects in parenthesis



**FIGURE 3** Serial blood pressure measurements in study participants who did (blue) and did not (pink) experience clinical events on follow-up. Data presented as medians (bars) with interquartile ranges (whiskers). DBP, serial diastolic blood pressure; PP, serial pulse pressure; SBP, serial systolic blood pressure

(Figure 3). The associations of BPs with clinical events are demonstrated in Table 3. The associations were predominantly comparable for serial BP measurements and individual BPs measured at the Age 40 Program but were weaker for individual systolic and diastolic BP measured at the ACE 1950 Study.

### 3.4 | Sensitivity analysis

We performed additional sensitivity analyses excluding study participants with LVEF  $\leq 40\%$  ( $n = 22$ ), moderate ( $n = 19$ ) to severe ( $n = 0$ ) aortic valve regurgitation,

**TABLE 3** Associations of blood pressures with clinical events (admissions for myocardial infarction, ischemic stroke or heart failure, or cardiovascular death)

	Incidence rate ratio (95% CI)
<b>Systolic blood pressure</b>	
Age 40 Program	1.14 (1.07 to 1.21)
ACE 1950	1.02 (0.98 to 1.07) <sup>a</sup>
Serial	1.10 (1.03 to 1.17)
<b>Diastolic blood pressure</b>	
Age 40 Program	1.18 (1.09 to 1.28)
ACE 1950	0.97 (0.89 to 1.05) <sup>b</sup>
Serial	1.14 (1.02 to 1.27)
<b>Pulse pressure</b>	
Age 40 Program	1.08 (0.99 to 1.17)
ACE 1950	1.06 (1.00 to 1.12)
Serial	1.08 (0.99 to 1.18)

Note: Coefficients reported per 5 mmHg. All coefficients adjusted for sex, age, study site, history of diabetes mellitus, current smoking, body mass index, length of follow-up, and antihypertensive therapy at both the ACE 1950 Study and at the Age 40 Program. Nineteen study participants had missing data for covariates and were excluded from the analyses.

Abbreviation: ACE, Akershus Cardiac Examination.

<sup>a</sup> Compared to serial blood pressure measurements: <sup>a</sup><.05, <sup>b</sup><.01.

moderate ( $n = 5$ ) to severe ( $n = 3$ ) aortic valve stenosis, or moderate ( $n = 10$ ) to severe ( $n = 1$ ) mitral valve regurgitation. In general, the results were not different from those reported for the entire cohort. The associations of serial BP measurements with echocardiography at the ACE 1950 Study were slightly diminished, but the overall patterns between serial BPs were unchanged (Tables S3 and

S4). Concerning prognosis, the associations of serial systolic BP with clinical outcomes were weaker, but the associations of serial diastolic BP were stronger (Table S5). Analyses limited to only subjects with measurement of BPs at military screening ( $n = 691$ ) are presented in Tables S6–S9. Compared with the total cohort, the associations of serial systolic BP with indexed LV mass and clinical outcomes were stronger, but apart from these differences, the overall patterns of association were similar.

## 4 | DISCUSSION

The key findings of the current study are that long-term exposure to higher BPs is associated with alterations in LV structure, function, and volumes and further associate with burden of long-term cardiovascular outcomes. The associations with echocardiography were predominantly linear in fashion, and we found especially strong associations of serial BP measurements with indexed LV mass, which was stronger than the corresponding associations between indexed LV mass and individual BP measurements at the Age 40 Program and the ACE 1950 Study.

Increased BP and established hypertension are some of the strongest modifiable risk factors for cardiovascular disease, especially pertaining to the incidence of atherosclerotic heart disease,<sup>12</sup> heart failure,<sup>13</sup> and cardiovascular death.<sup>14</sup> In line with this model, antihypertensive therapies have proven efficient in concomitantly reducing BP and cardiovascular risk.<sup>15</sup> Single office measurement of BP may quantify individual cardiovascular risk, commonly by risk scores derived from European<sup>2</sup> and US<sup>16</sup> cohorts. Repeated BP measurements over time allow assessment of longitudinal BP exposure and may improve prognostic precision for BP-derived risk prediction.<sup>17</sup> In the Atherosclerosis Risk in Communities Study, averaged systolic BP over 25 years was associated with worse LV structure and LV systolic and diastolic function on follow-up. Further, averaged systolic BP is associated with incident heart failure, particularly with heart failure with preserved ejection fraction.<sup>18</sup> These findings are in line with the current investigation results, where serial systolic and diastolic BP are both associated with LV structure, and serial BP measurements are associated stronger than individual BP measurements. We further demonstrate inverse associations of serial BP measurements with LV function. The associations of serial diastolic BP with LV function are corroborated by seminal work from the Framingham Heart Study, where diastolic BP was the strongest predictor for atherosclerotic heart disease in study participants in middle age.<sup>19</sup> In the current study, we excluded study participants with overt coronary artery disease, largely limiting the effect of significant ischemic coronary disease on LV function. Both low-grade coronary ischemia and

increased diastolic BP per se may contribute to the development of myocardial fibrosis<sup>20</sup> and subsequently increased risk of subtle disturbances in LV function. Higher systolic BP trajectories in young adulthood further associate with subclinical atherosclerosis in mid-life,<sup>21</sup> possibly contributing to subclinical alterations in LV structure and function.

Previous reports have documented associations of temporal BP trajectories<sup>22,23</sup> and serial BPs<sup>24</sup> with cardiovascular outcomes, but the analyses have predominantly focused on systolic BP. We extend these previous findings by detailed analyses of both serial systolic and diastolic BPs, as well as pulse pressure. Serial systolic and diastolic BPs provided strong prognostic information on incident cardiovascular morbidity and death, with 10%–15% higher incidence rates for every 5 mmHg of long-term BPs. This finding is in line with one of the largest meta-analyses on pharmacological BP lowering, where a 5 mmHg reduction in systolic BP was associated with an overall reduction in cardiovascular risk by 10%.<sup>15</sup>

In the sensitivity analyses, we excluded study participants with clinically relevant reductions in LV function consistent with heart failure with reduced ejection fraction and moderate to severe valvular heart disease. Increased BP and, more intriguingly, genetically increased BP associate with incident heart failure<sup>25</sup> and major valvular heart disease.<sup>26</sup> Heart failure and major valvular heart disease are associated with pathological alterations in LV structure and function and ultimately increased cardiovascular risk. In our analyses, the risks associated with serial BP measurements were similar after excluding these study participants, suggesting that long-term BP exposure conveys significant cardiovascular risk in the absence of objective evidence of cardiac pathology. This further underlines the importance of BP control also in community dwellers who have not yet developed overt end-organ damage. When we limited the analyses to subjects with measurement of BPs at military screening, we found stronger associations of serial systolic BP with indexed LV mass and clinical outcomes. This finding is not entirely surprising, as this subgroup had the longest follow-up for BP measurements and putatively the most accurate assessment of chronic pressure overload over time. This should in turn translate to stronger and more precise prediction of LV remodelling and risk of outcomes.

### 4.1 | Strengths and limitations

Strengths of the current study include long-term follow-up of BP, with more than 40 years in study participants with measurement of BP at military screening. We investigated both systolic BP and diastolic BP and the derived variable pulse pressure, enabling comparisons previously



not performed in similar studies. All participants were subjected to a uniform echocardiography protocol performed by dedicated study personnel, increasing the internal validity of these examinations. Limitations include relatively fewer follow-up points of BP measurement than comparable epidemiological studies. Data from the ACE 1950 Study were retrospectively linked to data from the Age 40 Program and military screening data, and the BP measurements were accordingly not performed uniformly at all time points. The time between the three study time points was considerable, and we cannot exclude that in-between unmeasured BP variability may have biased our results towards the null. As we do not have data on home BP, white coat hypertension could be an additional source of BP measurement bias. For a large proportion of the study subjects, we measured BP at only two visits at age 40 and 62–65. Whether the result would have been different with home measurements or with additional measurements in the period will have to be assessed in additional studies. The number of clinical events was moderate, limiting the statistical power of the survival analysis. The ACE 1950 Study has approval from the Regional Committees for Medical Research Ethics for follow-up until 2050, and we will explore clinical outcomes with longer follow-up in future studies. Lastly, as the data from the current investigation are observational and partly retrospective, we cannot rule out residual confounding influencing our results.

## 5 | CONCLUSIONS

In healthy community dwellers without established cardiovascular disease, long-term exposure to higher BPs associates with LV remodelling and risk of long-term cardiovascular outcomes. Lifestyle and pharmacological interventions lowering BP remain important measures to reduce overall cardiovascular risk. Our data support a model that serial BP measurements may be superior to individual BP measurements for risk stratification, but whether guiding therapy after serial BP indices may improve clinical outcomes over individual BP measurements will need to be explored in additional cohorts.

### AUTHOR CONTRIBUTION

MNL, BK and HR conceived and designed the study. MNL, BK, TB, MOP, ENA and HR collected, analysed and interpreted the data. MNL, BK and HR drafted the manuscript. MNL, BK, TB, MOP, ENA, IA, TO, AT, KS and HR critically revised the manuscript. TO, AT, KS and HR provided overall study supervision. MNL is responsible for the overall content and serves as guarantor. All authors read and approved the final manuscript.

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### CONFLICT OF INTEREST

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### REFERENCES

1. Kjeldsen SE. Hypertension and cardiovascular risk: general aspects. *Pharmacol Res.* 2018;129:95-99.
2. Hageman S, Pennells L, Ojeda F, et al. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J.* 2021;42:2439-2454.
3. Flint AC, Conell C, Ren X, et al. Effect of systolic and diastolic blood pressure on cardiovascular outcomes. *N Engl J Med.* 2019;381:243-251.
4. Domanski M, Mitchell G, Pfeffer M, et al. Pulse pressure and cardiovascular disease-related mortality: follow-up study of the multiple risk factor intervention trial (MRFIT). *JAMA.* 2002;287:2677-2683.
5. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J.* 2018;39:3021-3104.
6. Gradman AH, Alfayoumi F. From left ventricular hypertrophy to congestive heart failure: management of hypertensive heart disease. *Prog Cardiovasc Dis.* 2006;48:326-341.
7. Berge T, Vigen T, Pervez MO, et al. Heart and brain interactions—the Akershus cardiac examination (ACE) 1950 study design. *Scand Cardiovasc J.* 2015;49:308-315.
8. Fadum EA, Strand LA, Rudvin I, Haereid ML, Borud EK. The Norwegian armed forces health registry conscription board health examinations 1968–2018. *Scand J Public Health.* 2022;50:153-160.

9. Vigen T, Ihle-Hansen H, Lyngbakken MN, et al. Blood pressure at age 40 predicts carotid atherosclerosis two decades later: data from the Akershus cardiac examination 1950 study. *J Hypertens*. 2019;37:1982-1990.
10. Aagaard EN, Kvisvik B, Pervez MO, et al. Left ventricular mechanical dispersion in a general population: data from the Akershus cardiac examination 1950 study. *Eur Heart J Cardiovasc Imaging*. 2020;21:183-190.
11. Ranstam J. Hypothesis-generating and confirmatory studies, Bonferroni correction, and pre-specification of trial endpoints. *Acta Orthop*. 2019;90:297.
12. Escobar E. Hypertension and coronary heart disease. *J Hum Hypertens*. 2002;16(Suppl 1):S61-S63.
13. Messerli FH, Rimoldi SF, Bangalore S. The transition from hypertension to heart failure: contemporary update. *JACC Heart Fail*. 2017;5:543-551.
14. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903-1913.
15. Rahimi K, Treatment BPL. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *Lancet*. 2021;397:1625-1636.
16. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation*. 2014;129:S49-S73.
17. Allen NB, Khan SS. Blood pressure trajectories across the life course. *Am J Hypertens*. 2021;34:234-241.
18. Teramoto K, Nadruz Junior W, Matsushita K, et al. Mid- to late-life time-averaged cumulative blood pressure and late-life cardiac structure, function, and heart failure. *Hypertension*. 2020;76:808-818.
19. Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation*. 2001;103:1245-1249.
20. Jellis C, Martin J, Narula J, Marwick TH. Assessment of non-ischemic myocardial fibrosis. *J Am Coll Cardiol*. 2010;56:89-97.
21. Allen NB, Siddique J, Wilkins JT, et al. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. *JAMA*. 2014;311:490-497.
22. Tielemans SM, Geleijnse JM, Menotti A, et al. Ten-year blood pressure trajectories, cardiovascular mortality, and life years lost in 2 extinction cohorts: the Minnesota business and professional men study and the Zutphen study. *J Am Heart Assoc*. 2015;4:e001378.
23. Xu Y, Moller J, Wang R, Liang Y. Life-course blood pressure trajectories and cardiovascular diseases: a population-based cohort study in China. *PLoS ONE*. 2020;15:e0240804.
24. Reges O, Ning H, Wilkins JT, et al. Association of Cumulative Systolic Blood Pressure with Long-Term Risk of cardiovascular disease and healthy longevity: findings from the lifetime risk pooling project cohorts. *Hypertension*. 2021;77:347-356.
25. Wan EYF, Fung WT, Schooling CM, et al. Blood pressure and risk of cardiovascular disease in UK biobank: a mendelian randomization study. *Hypertension*. 2021;77:367-375.
26. Nazarzadeh M, Pinho-Gomes AC, Smith Byrne K, et al. Systolic blood pressure and risk of valvular heart disease: a mendelian randomization study. *JAMA Cardiol*. 2019;4:788-795.

## SUPPORTING INFORMATION

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

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