Stage 1 hypertension, sex, and acute coronary syndromes during midlife: the Hordaland Health Study

Ester Kringeland [1]*, **Grethe S. Tell**[2,3], **Helga Midtbø**[4], **Jannicke Igland**[2], **Teresa R. Haugsgjerd**[2], and **Eva Gerdts**[1,4]

[1]Department of Clinical Science, University of Bergen, PO Box 7804, 5020 Bergen, Norway; [2]Department of Global Public Health and Primary Care, University of Bergen, PO Box 7804, 5020 Bergen, Norway; [3]Division of Mental and Physical Health, Norwegian Institute of Public Health, PO Box 973 Sentrum, 5808 Bergen, Norway; and [4]Department of Heart Disease, Haukeland University Hospital, Jonas Lies vei 65, 5021 Bergen, Norway

Aims	Hypertension has been suggested as a stronger risk factor for acute coronary syndromes (ACS) in women than men. Whether this also applies to stage 1 hypertension [blood pressure (BP) 130–139/80–89 mmHg] is not known.
Methods and results	We tested associations of stage 1 hypertension with ACS in 12 329 participants in the Hordaland Health Study (mean baseline age 41 years, 52% women). Participants were grouped by baseline BP category: Normotension (BP < 130/80 mmHg), stage 1 and stage 2 hypertension (BP ≥140/90 mmHg). ACS was defined as hospitalization or death due to myocardial infarction or unstable angina pectoris during 16 years of follow-up. At baseline, a lower proportion of women than men had stage 1 and 2 hypertension, respectively (25 vs. 35% and 14 vs. 31%, *P* < 0.001). During follow-up, 1.4% of women and 5.7% of men experienced incident ACS (*P* < 0.001). Adjusted for diabetes, smoking, body mass index, cholesterol, and physical activity, stage 1 hypertension was associated with higher risk of ACS in women [hazard ratio (HR) 2.18, 95% confidence interval (CI) 1.32–3.60], while the association was non-significant in men (HR 1.30, 95% CI 0.98–1.71). After additional adjustment for systolic and diastolic BP, respectively, stage 1 diastolic hypertension was associated with ACS in women *(HR 2.79 [95% CI 1.62-4.82]),* but not in men *(HR 1.24 [95% CI 0.95-1.62]),* while stage 1 systolic hypertension was not associated with ACS in either sex.
Conclusion	Among subjects in their early 40s, stage 1 hypertension was a stronger risk factor for ACS during midlife in women than in men.
Keywords	Stage 1 hypertension • Acute coronary syndromes • Myocardial infarction • Hypertension • Sex

Introduction

Acute coronary syndromes (ACS), including myocardial infarction (MI) and unstable angina pectoris, are major causes of morbidity and mortality worldwide.[1] While overall incidence rates and ACS mortality rates have decreased in Western countries over the last decades, these favourable trends do not appear to include younger women.[2–5]

In fact, an increase in hospitalizations for ACS in young and middle-aged women has been observed in several countries.[2,3,6–8]

Emerging evidence suggests that hypertension may be a particularly important risk factor for ACS in women.[9] In the Norwegian Tromsø study, the associations between higher systolic and diastolic blood pressure (BP) and risk of MI were stronger for women aged 35–94 years than for men.[9,10] Similarly, in the UK Biobank study, stage 1 and 2 hypertension

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were both associated with higher hazard ratios (HRs) for MI in women with a mean age of 56 years at baseline than in their male counterparts.[10] However, these studies did not focus on younger women.

Healthy women in their 40s have significantly lower BP and prevalence of hypertension compared to men.[11,12] In contrast, young women with MI are more likely than their male counterparts to have hypertension.[2] In an analysis based upon four large US cohorts, Ji *et al.*[11] demonstrated that women have a steeper increase in BP measures during the life course compared to men that begins already in the third decade. Their findings suggest that certain arterial changes develop earlier and progress faster in women, including small artery remodelling, which in turn has been associated with coronary microvascular dysfunction and increased risk of ACS.[13,14] Taken together, it may be hypothesized that even mildly elevated BP in young women may contribute more strongly as a risk factor for ACS than in men. The current study therefore aimed to test whether mildly elevated BP in the early 40s carried a different risk of ACS during midlife for women than for men.

Methods

Study population

The population-based Hordaland Health Study was initiated in Hordaland County in Western Norway as a collaboration between the national health screening services, local health authorities, and the University of Bergen in 1992 (https://husk-en.w.uib.no/ (15 March 2021)).[15] All residents in the county born in 1950–52 were identified in the National Population Registry and invited to attend the first survey in 1992–1993. Overall acceptance rate was 73% and 12 597 persons participated. For the present analysis, participants with incomplete BP (*n* = 28), body mass index (BMI) (*n* = 19) or serum cholesterol measurements (*n* = 2), a history of MI (*n* = 28) or medically treated hypertension (*n* = 191) were excluded, leaving 6381 women and 5948 men for analyses. The study was performed according to the declaration of Helsinki. All participants provided written, informed consent and the study protocol was approved by the Regional Committee for Medical and Health Research Ethics (2017/294). The dataset used in this study contains potentially sensitive patient information. The Regional committee for medical and health research ethics does not allow for public deposition of the data. Application for access to the data can be done on the Hordaland Health Study website: https://husk-en.w.uib.no/how-to-apply-for-data-access/. (15 March 2021).

Baseline examinations

The baseline visit was performed during 1992–93. Attended brachial BP was measured in triples with 1 min intervals by trained healthcare workers after the participant had been seated for at least 10 min, using calibrated sphygmomanometers (Dinamap 845 XT, Criticon, Tampa, USA).[16] The average of the two last measurements was used for analyses. BP categories were identified in accordance with the 2017 ACC/AHA hypertension guidelines: Normotension was defined as systolic BP <130 mmHg and diastolic BP <80 mmHg, stage 1 hypertension as systolic BP 130–139 mmHg and/or diastolic BP 80–89 mmHg and stage 2 hypertension as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg.[17] Height was measured without shoes to the nearest centimetre, and weight was measured with light clothing to the nearest half-kilogram on a calibrated scale. BMI was calculated as weight in kg/height in metres.[2] Information about physical activity, smoking, use of antihypertensive drugs and medical history including diabetes mellitus was collected in self-reported questionnaires. Physical activity was categorized as sedentary (sedentary or no regular physical activity), light (walking, cycling, or other moderate physical activity for at least 4 h per week), moderate (exercise, gardening with physical exertion, or similar degree of physical activity for at least 4 h per week) or hard (heavy training or competitive sports several times per week). Smoking was defined as daily smoking. Non-fasting blood samples were analysed for serum total cholesterol.

Outcome

The present study assessed incident ACS, defined as hospitalization or death with an acute MI or unstable angina pectoris diagnosis during 16 years of follow-up. Data from the Hordaland Health Study survey in 1992–93 were linked with outcome data from the CardioVascular Disease in NORway (CVDNOR) project and the Cause of Death Registry for the period 1 January 1994 to 31 December 2009. The CVDNOR project includes information about all hospitalizations with a cardiovascular (CV) disease-related diagnosis in Norway for the period 1994–2009 (https://cvdnor.w.uib.no/ (15 March 2021)).[3] The Cause of Death Registry is a national registry including information on date and underlying cause of death in Norway. For the present study data on incident ACS, defined as hospitalization or death with an acute MI or unstable angina pectoris diagnosis [International Classification of Diseases (ICD)-9 codes 410, 411 and ICD-10 codes I20.0, I21 and I22], was taken from these sources.

Statistical analyses

Statistical analyses were done using STATA, version 16 (StataCorp LP, College Station, TX, USA). Continuous variables are expressed as means and standard deviations and categorical variables as proportions. Participants were grouped into three BP categories: normotension, stage 1, and stage 2 hypertension. Comparisons of characteristics between BP categories were done in sex-specific analyses, using linear or logistic regression analyses with BP category as an independent variable, followed by a test for linear trend using the contrast command in Stata. Kaplan–Meier cumulative plots were constructed separately for women and men stratified by BP category. Associations between BP categories and incident ACS were tested in Cox regression analyses adjusted for diabetes, smoking, BMI, serum total cholesterol, and physical activity (model 1). In a secondary analysis, use of contraceptive pills was added to model 1 in women. Normotension was used as the reference group. Separate analyses were performed for women and men. Results are presented as HR, 95% confidence intervals (CIs), and *P*-values. Linear trend over BP categories were tested using linear contrast after Cox regression analyses. To test for interactions between BP category and sex, we compared a model with and without an interaction term using the likelihood-ratio test. In further analyses, the cohort was grouped according to systolic BP categories (systolic normotension, stage 1 and stage 2 systolic hypertension) and diastolic BP categories (diastolic normotension, stage 1 and stage 2 diastolic hypertension), respectively. Associations between systolic BP category and ACS were tested in Cox regression multivariable model 1, using systolic normotension as the reference group. In a second multivariable model, additional adjustment for diastolic BP as a continuous variable was included (model 2). Similar models were tested for diastolic BP categories with adjustment for systolic BP as a continuous variable in model 2. A two-tailed *P*-value of <0.05 was considered statistically significant in all analyses.

Results

Baseline characteristics

A lower proportion of women than men had hypertension at baseline (25% vs. 35% for stage 1 and 14% vs. 31% for stage 2

Table 1 Baseline characteristics of the study population according to blood pressure category: the Hordaland Health Study

	Women (n = 6381)				Men (n = 5948)			
	Normotension (n = 3894)	Stage 1 HT (n = 1604)	Stage 2 HT (n = 883)	P for trend	Normotension (n = 2029)	Stage 1 HT (n = 2079)	Stage 2 HT (n = 1840)	P for trend
Age (years)	41 ± 0.9	41 ± 0.9	41 ± 0.9	0.04	41 ± 0.9	41 ± 0.9	41 ± 0.9	0.48
Systolic BP (mmHg)	116 ± 8	129 ± 7	147 ± 12	<0.01	121 ± 6	132 ± 5	149 ± 11	<0.01
Diastolic BP (mmHg)	71 ± 6	81 ± 5	91 ± 8	<0.01	72 ± 5	80 ± 5	90 ± 9	<0.01
Systolic BP category				<0.01				<0.01
Normal systolic BP	100%	42%	4%		100%	24%	1%	
Stage 1 systolic HT	0%	58%	15%		0%	76%	9%	
Stage 2 systolic HT	0%	0%	81%		0%	0%	89%	
Diastolic BP category				<0.01				<0.01
Normal diastolic BP	100%	25%	9%		100%	36%	14%	
Stage 1 diastolic BP	0%	75%	29%		0%	64%	36%	
Stage 2 diastolic BP	0%	0%	62%		0%	0%	50%	
BMI (kg/m²)	23.4 ± 3.2	24.5 ± 3.9	25.6 ± 4.7	<0.01	24.4 ± 2.8	25.3 ± 2.9	26.1 ± 3.1	<0.01
Total serum cholesterol (mmol/L)	5.3 ± 1.0	5.5 ± 1.0	5.7 ± 1.0	<0.01	5.6 ± 1.0	5.7 ± 1.0	5.9 ± 1.1	<0.01
Diabetes mellitus (%)	0.21%	0.31%	1.02%	<0.01	0.34%	0.67%	0.76%	0.09
Daily smoker (%)	38%	41%	36%	0.27	44%	41%	39%	<0.01
Physical activity				0.03				0.06
Sedentary	17%	16%	18%		17%	18%	17%	
Light	71%	73%	72%		51%	53%	55%	
Moderate	11%	11%	10%		28%	28%	26%	
Hard	1%	0.5%	0.2%		3%	2%	2%	

Continuous variables are expressed as means ± standard deviations and categorical variables as proportions.
BMI, body mass index; BP, blood pressure; HT, hypertension.

hypertension, respectively) (*P* < 0.01 for difference between sexes) (Table 1). Among subjects with hypertension, a lower proportion of women than men had isolated systolic hypertension (25% vs. 36% in stage 1 and 38% vs. 50% in stage 2 hypertension, respectively), while a higher proportion of women than men had isolated diastolic hypertension (42% vs. 24% in stage 1 and 19% vs. 11% in stage 2 hypertension, respectively) (both *P* < 0.01 for difference between sexes).

Compared to men, women had lower BMI and serum total cholesterol (both *P* < 0.001) and a lower proportion of women than men reported daily smoking (*P* = 0.002) (Table 1). Across the different BP categories, stepwise higher BMI and serum cholesterol levels were found with higher BP category for both women and men (all *P* < 0.01 for linear trend). Likewise, a stepwise higher prevalence of diabetes was found with higher BP category (*P* < 0.01 in women and *P* = 0.09 in men).

Hypertension stage and sex-specific risk of ACS

During a median of 16 years of follow-up (interquartile range 16–16 years), (in total 192 251 person years), 89 women (1.4%) and 341 men (5.7%) were hospitalized with or died from ACS (*P* < 0.001 between sexes).

Women with stage 1 hypertension had twice the risk of ACS compared to normotensive women (Table 2). In women with stage 2 hypertension, the risk of ACS was tripled compared to normotensive women (Table 2). These results remained statistically significant after adjustments for diabetes, smoking, BMI, serum total cholesterol, and physical activity (Table 2). Additional adjustment for use of contraceptive pills did not alter the results (HR 2.09, 95% CI 1.21–3.61 for stage 1 hypertension and HR 2.72, 95% CI 1.47–5.05 for stage 2 hypertension, respectively).

Men with stage 1 and stage 2 hypertension had an about 40% and 70% higher risk of ACS, respectively, compared to normotensive men (Table 2). In adjusted models, the association between stage 1 hypertension and ACS in men became statistically non-significant, while the association between stage 2 hypertension and ACS remained significant (Table 2).

A significant interaction between BP category and sex was found in the model on ACS both in univariate and adjusted analyses (*P* = 0.03 and 0.01, respectively) (Figure 1) (Table 2), confirming that hypertension stage 1 and stage 2 affected the risk of ACS in a sex-specific manner.

Systolic BP and sex-specific risk of ACS

The risk of ACS increased with increasing systolic BP category, both in women and men (Table 2) (both *P* < 0.01 for linear trend).

Compared to women with normal systolic BP, the risk of ACS was about 80% higher in women with stage 1 systolic hypertension and two-fold higher in women with stage 2 systolic hypertension in unadjusted and adjusted analyses (model 1, Table 2). After additional adjustment for diastolic BP, there was no significant association between systolic BP category and ACS in women (model 2, Table 2).

Compared to normotensive men, men with stage 1 systolic hypertension did not have an increased risk of ACS, while men with stage 2 systolic hypertension had an about 50% higher risk of ACS in unadjusted analyses (Table 2). In adjusted analyses, stage 2 systolic hypertension was not associated with significantly increased risk of ACS in men (Table 2).

There was no significant sex-interaction between systolic BP category and risk of ACS (Table 2).

Diastolic BP and sex-specific risk of ACS

With increasing diastolic BP category the risk for ACS increased in both sexes (both *P* < 0.001 for linear trend) (Table 2).

Compared to women with normal diastolic BP, women with stage 1 diastolic hypertension had an almost three-fold and women with stage 2 diastolic hypertension a five-fold increased risk of ACS both in unadjusted and adjusted analyses (Table 2).

Compared to men with normal diastolic BP, men with stage 1 diastolic hypertension had an almost 50% higher, and men with stage 2 diastolic hypertension a two-fold higher risk of ACS in unadjusted analysis (Table 2). In adjusted analyses in men, these results remained significant (model 1, Table 2), but after additional adjustment for baseline systolic BP, only stage 2 diastolic hypertension was associated with higher risk of ACS (model 2) (Table 2).

There was a highly significant sex-interaction on the association of diastolic BP category and risk of ACS both in univariate and adjusted analyses (Table 2).

Discussion

This study adds important information on sex-differences in the BP mediated risk of ACS in midlife. Having BP 130–139/80–89 mmHg (stage 1 hypertension by American guidelines) in the early 40s doubled the risk of ACS during midlife in women, while the association was non-significant in men when adjusted for confounding CV risk factors. Diastolic hypertension was a stronger indicator of risk than systolic hypertension.

Hypertension stage and sex-specific risk of ACS

In the Interheart Study, self-reported hypertension, defined as BP ≥ 140/90 mmHg, was a stronger risk factor for MI in women than in men.[18] However, few studies have so far explored sex-specific associations between stage 1 hypertension and ACS.[10,19,20] In the UK Biobank study, including 471 998 participants (56% women, mean age 56 years) with no history of CV disease, both stage 1 and 2 hypertension were associated with a 40% higher risk of combined fatal and non-fatal MI over 8 years in women than in men.[10] In a subsequent publication by Li *et al.*[19] based upon the same cohort, having isolated diastolic hypertension was associated with higher risk of combined MI, stroke, and CV death in women than men younger than 60 years of age, but not in older subjects. However, their analysis did not separate between stage 1 and stage 2 isolated diastolic hypertension, and results from sex interaction analysis were not presented. In contrast, in a pooled analysis grouping three prospective Chinese studies, including 154 407 participants aged 40–80 years, both stage 1 and stage 2 hypertension were associated with higher risk of CV death both in women and men. In stratified analysis, the results were stronger in subjects younger than 65 years and in those without pre-existing CV disease, while no difference between sexes was found.[20] Similarly, stage 1 isolated diastolic hypertension was associated with a comparable increased risk of CV disease (combined hospitalization for MI, stroke, and heart failure) in a Korean study following 30 years

Table 2 Associations between baseline blood pressure and fatal and non-fatal acute coronary syndromes: the Hordaland Health Study

	ACS/no. at risk	Unadjusted			Multivariable model 1			Multivariable model 2		
		HR (95% CI)	P-value	I	HR (95% CI)	P-value	I	HR (95% CI)	P-value	I
ACS by BP category				0.03			0.01			0.24
Women										
Normotension	32/3894	Ref			Ref					
Stage 1 hypertension	31/1604	2.34 (1.43–3.84)	0.001		2.18 (1.32–3.60)	0.002				
Stage 2 hypertension	26/883	3.59 (2.14–6.03)	<0.001		3.09 (1.80–5.31)	<0.001				
Men										
Normotension	87/2029	Ref			Ref					
Stage 1 hypertension	123/2079	1.39 (1.05–1.82)	0.020		1.30 (0.98–1.71)	0.064				
Stage 2 hypertension	131/1840	1.70 (1.29–2.23)	<0.001		1.40 (1.06–1.85)	0.018				
ACS by systolic BP category				0.10			0.16			
Women	50/4607									
Normal systolic BP		Ref			Ref			Ref		
Stage 1 systolic hypertension	21/1061	1.81 (1.09–3.02)	0.022		1.74 (1.04–2.90)	0.035		1.01 (0.57–1.78)	0.975	
Stage 2 systolic hypertension	18/713	2.32 (1.35–3.98)	0.002		1.97 (1.12–3.49)	0.019		0.66 (0.30–1.44)	0.296	
Men	121/2561									
Normal systolic BP		Ref			Ref			Ref		
Stage 1 systolic hypertension	106/1745	1.29 (0.99–1.67)	0.059		1.21 (0.93–1.58)	0.151		1.01 (0.76–1.33)	0.955	
Stage 2 systolic hypertension	114/1642	1.50 (1.16–1.94)	0.002		1.27 (0.98–1.65)	0.075		0.84 (0.60–1.19)	0.327	
ACS by diastolic BP category				0.006			0.002			0.002
Women	34/4369									
Normal diastolic BP		Ref			Ref			Ref		
Stage 1 diastolic hypertension	32/1464	2.82 (1.74–4.56)	<0.001		2.54 (1.56–4.15)	<0.001		2.79 (1.62–4.82)	<0.001	
Stage 2 diastolic hypertension	23/548	5.49 (3.23–9.32)	<0.001		4.64 (2.69–8.00)	<0.001		5.74 (2.66–12.4)	<0.001	
Men	131/3035									
Normal diastolic BP		Ref			Ref			Ref		
Stage 1 diastolic hypertension	124/1988	1.46 (1.14–1.86)	0.003		1.29 (1.00–1.65)	0.047		1.24 (0.95–1.62)	0.107	
Stage 2 diastolic hypertension	86/925	2.25 (1.71–2.95)	<0.001		1.71 (1.28–2.27)	<0.001		1.57 (1.09–2.26)	0.017	

ACS, acute coronary syndromes; BP, blood pressure; CI, confidence interval; HR, hazard ratio; I, P-value interaction test between blood pressure category and sex.
Multivariable model 1: Adjusted for diabetes, smoking, total serum cholesterol, body mass index and physical activity.
Multivariable model 2: Adjusted for model 1 variables and additionally for diastolic blood pressure (as a continuous variable) in the model for systolic BP category and systolic blood pressure (as a continuous variable) in the model for diastolic BP category.
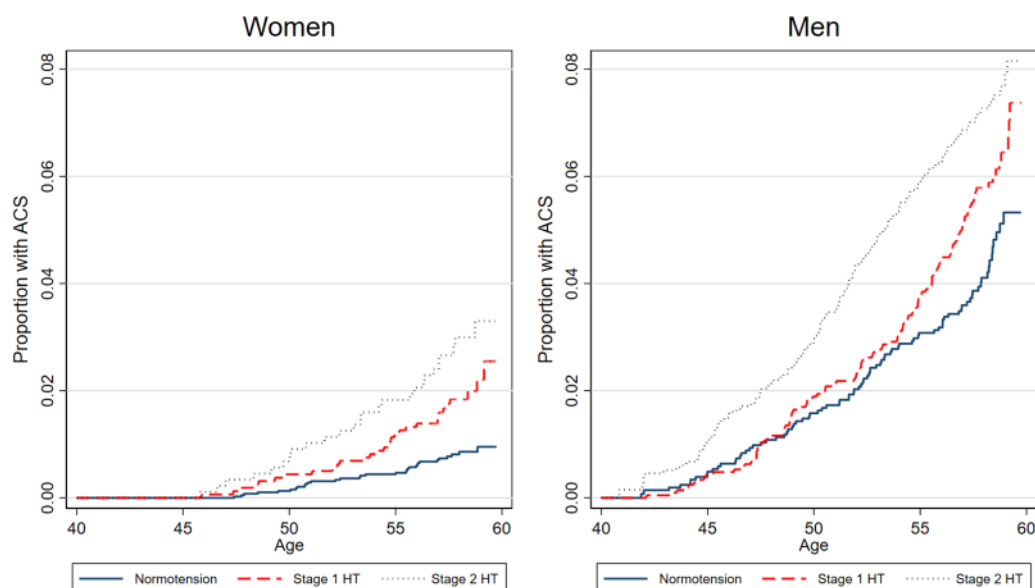
Figure 1 Kaplan–Meier analyses of acute coronary syndromes by age in baseline blood pressure categories in women and men during 16 years of follow-up. Stage 1 and stage 2 hypertension affected the risk of acute coronary syndromes in a sex-specific manner, confirmed by a significant interaction test (*P* = 0.03). ACS, acute coronary syndromes; BP, blood pressure; HT, hypertension.

old women and men for 13 years.[21] In this study, both stage 1 isolated systolic hypertension and stage 1 combined systolic and diastolic hypertension were associated with a 16–22% higher risk in women. However, sex-specific results for the association of BP categories with MI were not reported. Thus, the present study adds important new knowledge by demonstrating that having BP 130–139/80–89 mmHg in the early 40s was particularly associated with increased risk of ACS during midlife in women, and that diastolic stage 1 hypertension was the strongest indicator of risk. These findings were not explained by higher burden of traditional CV disease risk factors in women or use of contraceptive pills. Our results support the growing evidence indicating that hypertension has particularly unfavourable effects on womens' heart.[22,23]

Systolic and diastolic BP and risk of ACS

In former studies, which BP component that best identifies risk for CV disease has varied by age and by the type of CV disease assessed.[24,25] In the Framingham Heart Study, diastolic BP was a stronger indicator of incident coronary heart disease in women and men younger than 50 years, whereas systolic BP and pulse pressure were stronger predictors after the age of 60 years.[24] In the Norwegian Tromsø study including 33 859 subjects, 35–94 years of age, the associations between higher systolic and diastolic BP and risk of MI were both stronger for women than for men.[9] Likewise, in a meta-analysis of 61 studies by Lewington *et al.*,[26] a slightly stronger association between systolic BP and ischaemic heart disease mortality was reported for women than for men, especially in the age group 40–50 years. Importantly, no sex interaction analysis was presented. Finally, in the Atherosclerosis Risk in Communities study, systolic BP was a stronger predictor of peripheral artery disease (PAD) than diastolic BP in subjects with an initial age of 45–64 years followed for

more than 25 years, and the association between higher BP and PAD was a particularly strong in women.[25] In contrast, a Finnish study including 14 786 subjects aged 25–64 years found comparable associations between systolic BP and risk of coronary heart disease in women and men.[27] Furthermore, a meta-analysis and systematic review by Peters *et al.*[28] including data from 56 cohorts, found no sex difference in the relationship between systolic BP and the risk of ischaemic heart disease. However, this meta-analysis included a broad age spectrum (19–104 years), and as reported, there was heterogeneity across studies that could not be fully adjusted for. The present study adds to this previous knowledge by demonstrating that among subjects in their early 40s, diastolic BP was the strongest indicator of ACS risk during midlife, and more strongly for women than for men.

The current sex-specific findings probably reflect differences in vascular biology between young women and men.[11] In particular, changes in small artery compliance and remodelling related to elevated diastolic BP have also been linked to impaired coronary flow reserve and coronary microvascular dysfunction which disproportionally causes ACS in women.[13,29–31] Still, current American and European guidelines do not provide sex-specific definitions and recommendations for management of hypertension, and antihypertensive drug treatment of BP <140/90 mmHg is not recommended in subjects without CV disease, diabetes or renal failure.[17,32] Thus, whether antihypertensive treatment may reduce the demonstrated BP effects in women is not known.

Study limitations

Some limitations in our study should be outlined. The Hordaland Health Study included primarily Caucasians living in a small geographic area in Western Norway. Generalization of results to other ethnic groups should be done with caution. We did not have information

about hypertensive disorders during pregnancy. BP classes were derived from baseline BP measured in triplets at a single visit, and the prevalence of hypertension at baseline may therefore have been overestimated. We did not have information on BP or antihypertensive treatment during follow-up. Some subjects with stage 2 hypertension may have initiated antihypertensive treatment. However, the powerful, independent information on ACS risk during midlife from a standardized BP measurement in young subjects in their early 40s is clearly demonstrated. Fasting blood sugar was not measured, and the prevalence of diabetes may therefore have been underreported. Still, study participants were in their early 40s and obesity was rare in our cohort, reducing the probability of type 2 diabetes. Finally, we did not have information regarding LDL and HDL cholesterol levels or use of cholesterol lowering drugs. The relatively large study sample, prospective design and high participation rate are all strengths of the study.

Conclusion

In the Hordaland Health Study, BP 130–139/80–89 mmHg (stage 1 hypertension by American guidelines) in the early 40s doubled the risk of ACS during midlife in women, while the association was non-significant in men when adjusted for confounding CV risk factors. Stage 1 diastolic BP was a stronger indicator of ACS risk than stage 1 systolic BP. Our results may contribute to explain why ACS incidence rates have declined less in young and middle-aged women than in their male counterparts.

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