Sex differences in blood pressure in midlife: associations with risk factors and acute coronary syndromes in the Hordaland Health Studies

Ester Anne Kringeland

Thesis for the degree of Philosophiae Doctor (PhD)
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Name: Ester Anne Kringeland

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1. Abbreviations

ACC	American College of Cardiologists
ACS	acute coronary syndromes
AHA	the American Heart Association
BMI	body mass index
BP	blood pressure
CI	confidence interval
CVD	cardiovascular disease
CVDNOR	Cardiovascular Disease in Norway Project
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HUSK	The Hordaland Health Study
hs-CRP	high-sensitive C-reactive protein
ICD	International Classification of Diseases
KTR	kynurenine tryptophan ratio
MINOCA	myocardial infarction with nonobstructive coronary arteries
PAr	pyroxic acid ratio
PAD	peripheral artery disease
RAAS	renin-angiotensin-aldosterone system

2. Scientific environment

The current research project was carried out within the Bergen Hypertension and Cardiac Dynamics group and at the Centre for research on Cardiac Disease in Women, both at the Department of Clinical Science, Medical Faculty, University of Bergen. The Bergen Hypertension and Cardiac Dynamic group consists of Chair Professor Eva Gerdts, one senior researcher, Helga Midtbø, one assistant professor, 1 post-doctoral fellow, 8 PhD candidates, 1 research-medical student, 1 research nurse and 1 engineer. The group has non-invasive cardiac imaging including echocardiography and MRI as their main research tools, and core fields of interest include valvular heart disease, hypertensive heart disease and sex differences in cardiovascular disease (CVD). Centre for Research on Cardiac disease in Women was established in 2020. The Centre organises network activities for researchers and groups focusing on cardiac disease in women and has research and building of competence on cardiac disease in women as its focus.

The project was based on data from the Hordaland Health Study (HUSK) and the Cardiovascular Disease in Norway Project 1994-2009 (CVDNOR). The research group for Lifestyle Epidemiology, Department of Global Public Health and Primary Care, University of Bergen was the main collaborating partner. During this work the research group for Lifestyle Epidemiology was chaired by Professor Grethe Tell, who was also the leader of HUSK. Grethe Tell provided access to HUSK and CVDNOR and Jannicke Igland and Kari Juul contributed with statistical and data managing support, respectively.

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4. Sammendrag

Bakgrunn: Blant unge voksne har friske kvinner vanligvis lavere blodtrykk (BT) enn menn. Men allerede fra 20-årene har kvinner en brattere stigning i BT enn menn på samme alder. Målet med dette arbeidet var å identifisere faktorer assosiert med BT og BT-endring i 40 årene og sammenhengen mellom BT tidlig i 40 årene og risiko for sykehusinnleggelse eller død av akutt koronarsyndrom (AKS) i løpet av 16 års oppfølging hos kvinner og menn.

Materiale og metode: Arbeidet er basert på data fra den befolkningsbaserte Helseundersøkelsen i Hordaland (HUSK) og «Cardiovascular Disease in Norway Project 1994-2009» (CVDNOR). CVDNOR inneholder informasjon om alle sykehusinnleggelser og dødsfall i Norge med en hjertekar- eller diabetesdiagnose i perioden 1994-2009. Studiedeltagerne i HUSK fikk utført standardiserte BT-målinger og det ble samlet inn informasjon om kardiovaskulære risikofaktorer da de var gjennomsnittlig 41 år gamle i HUSK1 (baseline) og 6 år senere i HUSK2. Informasjon om sykehusinnleggelser eller død av AKS i løpet av 16 års oppfølgingstid ble hentet fra CVDNOR. Inflammasjonsmarkører, inkludert høysensitivt C-reaktivt protein (hs-CRP), neopterin og pyridoksal syre ratio (PAr), ble målt i HUSK2.

Resultat: I studie 1 var høyere BT og kroppsmasse indeks (KMI) målt ved baseline, og stigning i KMI, kolesterol og triglyserider fra HUSK1 til HUSK 2 de viktigste faktorene assosiert med stigning i BT eller nyoppstått hypertensjon ved HUSK2 hos både kvinner og menn. I Studie 2 økte risiko for AKS med høyere BT hos begge kjønn. Kvinner som hadde et lett forhøyet BT (systolisk BT 130-139 mmHg og /eller diastolisk BT 80-89 mmHg) tidlig i 40 årene hadde doblet risiko for AKS i løpet av 16 års oppfølgingstid sammenlignet med kvinner som hadde normalt BT også etter justering for andre kardiovaskulære risikofaktorer. Tilsvarende assosiasjon fant vi ikke hos menn. Forskjellen ble dokumentert med signifikant interaksjonstest mellom BT og kjønn. I Studie 3 var hs-CRP signifikant assosiert med høyere systolisk og diastolisk BT i HUSK2, samt med nyoppstått hypertensjon de siste 6 år hos kvinner, men ikke hos menn. I tillegg var høyere serum neopterin assosiert med høyere

diastolisk BT kun hos kvinner, mens høyere PAr indeks var assosiert med høyere systolisk og diastolisk BT hos menn. Disse kjønnsforskjellene ble bekreftet med signifikante interaksjonstester mellom BT og kjønn i modellen for AKS, mellom hs-CRP og kjønn i modellene for systolisk og diastolisk BT og nyoppstått hypertensjon, og mellom neopterin og kjønn i modellen for diastolisk BT.

Konklusjon:

Høyere baseline KMI, vektoppgang og stigning i serum lipider var de viktigste faktorene assosiert med stigning i BT og nyoppstått hypertensjon hos både kvinner og menn i 40 årene. Sammenhengen mellom inflammasjon og BT var sterkere hos kvinner enn hos menn. Å ha et lett forhøyet BT tidlig i 40 årene var en sterkere risikofaktor for AKS før fylte 60 år hos kvinner enn hos menn. Resultatene peker på et behov for kjønnsspesifikke anbefalinger for diagnostisering og forebygging av hypertensjon.

5. Abstract

Background: Among healthy young adults, women have lower blood pressure (BP) compared to their male counterparts. Then, from the third decade onwards, women have a steeper increase in BP than men. The aim of the current project was to explore factors associated with BP and BP change among women and men in their forties and to test sex-specific associations between BP in the early forties and risk of ACS over 16 years follow-up.

Materials and methods: This work was performed using data from the community-based Hordaland Health Study (HUSK) and the "Cardiovascular Disease in Norway Project 1994-2009" (CVDNOR). The latter includes information about all hospital stays and deaths in Norway with a cardiovascular disease (CVD) or diabetes diagnosis in the period 1994-2009. BP was measured and information about CVD risk factors collected when participants were 41±1 years old in HUSK1 and 6 years later in HUSK2. Information about hospitalizations or death from an ACS over 16 years follow-up was obtained from the CVDNOR project. Plasma markers of inflammation, including high-sensitive C-reactive protein (hs-CRP), neopterin, and the pyridoxic acid ratio (PAr), were measured in HUSK2.

Results: In study 1, initial BP, higher body mass index (BMI), weight-gain and increases in serum cholesterol and serum triglycerides were the main factors associated with increase in BP and incident hypertension from HUSK1 to HUSK2 both in women and men. In study 2, having a mildly elevated BP (systolic BP 130-139 mmHg and/or diastolic BP 80-89 mmHg) in the early forties doubled the risk of ACS over 16 years follow-up in women, compared to women with a normal BP, after adjustment for other CVD risk factors. The same association was not found in men. In study 3, after adjustment for BMI, higher levels of hs-CRP in the forties were associated with higher BP and new onset hypertension during the last 6 years in women, but not in men. Furthermore, higher levels of plasma neopterin was associated with higher diastolic BP only in women, while higher PAr was associated with higher systolic and diastolic BP in men. These sex differences were confirmed by significant interactions between BP and sex in the model on ACS, between hs-

CRP and sex in the models on systolic and diastolic BP and incident hypertension, and between neopterin and sex in the model on diastolic BP.

Conclusion: Among women and men in their early forties, initial BP, BMI, weight gain and increases in serum lipids were the main factors associated with increases in BP and new onset hypertension. Plasma markers of inflammation were particularly associated with higher BP level in women. Finally, having a mildly elevated BP in the early forties was a stronger risk factor for ACS before the age of 60 years in women than in men. Taken together our results suggest a need for sex-specific recommendations and actions for diagnosis and prevention of hypertension.

6. List of Publications

Kringeland E, Tell GS, Midtbø H, Haugsgjerd TR, Igland J, Gerdts E. Factors associated with increase in blood pressure and incident hypertension in early midlife: the Hordaland Health Study. Blood Press. 2020;29(5):267-275.

Kringeland E, Tell GS, Midtbø H, Igland J, Haugsgjerd TR, Gerdts E. Stage 1 hypertension, sex, and acute coronary syndromes during midlife: the Hordaland Health Study. Eur J Prev Cardiol. 2022;29(1):147-154.

Kringeland E, Gerdts E, Ulvik A, Tell GS, Igland J, Haugsgjerd TR, Ueland PM, Midtbø H. Inflammation, sex, blood pressure changes and hypertension in midlife: The Hordaland Health Study. J Hum Hypertens 2022; Submitted

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8. Introduction

8.1 Blood pressure as a global health problem

High blood pressure (hypertension) is a leading risk factor for cardiovascular disease (CVD) and mortality.[1] Worldwide, the age standardized prevalence of hypertension (defined as systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg) was 32% in women and 34% in men aged 30-79 years in 2019.[2] Systolic hypertension was the number 1 risk factor for death in women and accounted for 20% of all deaths in 2019 according to the Global burden of disease study. Among men, systolic hypertension was the number 2 CVD risk factor after smoking, and accounted for 18% of all deaths in 2019.[3] Before the age of 40 years, hypertension is uncommon, but a higher proportion of men than women in this age-range has hypertension.[4] After the age of 60 years, hypertension is found in more than 60% of the population, and a higher proportion of women than men has hypertension.[4] The global hypertension prevalence has been virtually unchanged over the past 20 years, reflecting that the reduction in hypertension prevalence in high-income countries is matched by a similar increase in prevalence in low and middle-income countries. Despite a stable global prevalence, the absolute number of subjects with hypertension has nearly doubled during this period due to population growth and aging.[2] Thus, hypertension remains a major cause of CVD morbidity and mortality, and better strategies for prevention of hypertension are called for.

8.2 Sex differences in BP development in midlife

Age-associated BP development differs by sex.[5] Healthy, young adult women have lower BP compared to men of the same age.[4, 5] Then, from the 3rd decade onwards women have a steeper increase in all BP measures.[5] A particular sharp increase in BP is observed in women compared to men during midlife, i.e. 40-60 years of age. However, underlying mechanisms of the observed sex difference in BP development in midlife are not fully understood. While increases in diastolic BP probably reflects increased peripheral resistance and small artery remodelling in young adults, increases

in systolic BP and pulse pressure seen from the age of 40 years are markers of central arterial stiffening.[6] In invasive hemodynamic studies, hypertensive men aged 18-30 years had higher cardiac output due to increased heart rate, compared to age matched normotensive controls, suggesting increased sympathetic nervous system activity.[6] In further studies, age associated increases in systolic and diastolic BP in hypertensive men were associated with an increase in total peripheral resistance and reductions in cardiac output and stroke volume, particularly during exercise.[6] In two small studies among subjects with hypertension, young women aged 18-45 years had less, while postmenopausal women had more autonomic dysfunction, compared to their male counterparts.[7, 8] Autonomic function parameters including baroreceptor-sensitivity and heart rate variability were especially impaired in postmenopausal women with hypertension, compared to both women with normotension and men with hypertension of the same age.[8] Furthermore, in women, profound changes in sex hormone production takes place during midlife.[9] In particular, both the oestrogen-associated inhibition of the renin-angiotensin-aldosterone system (RAAS) and the progesterone-associated inhibition of aldosterone decline during midlife in women, predisposing women to BP increase and sodium retension.[10] Finally, hypertensive pregnancy disorders including chronic hypertension, gestational hypertension and pre-eclampsia affect 5-10% of all pregnancies and increase the risk of future hypertension and CVD in these women.[11, 12]

Increasing body mass index (BMI) and obesity have been proposed as a major cause of the age-associated increase in BP in midlife, but sex-specific data is limited. In 2016 11% of men and 15% of women were obese, according to the World Health Organization.[13] Body fat distribution differs by sex, and there are known sex differences in mechanisms of hypertension in obesity.[14] Aldosterone levels increase more with increasing BMI in women compared to men.[14] Women have greater body fat mass and a larger proportion of body fat is stored subcutaneously in women compared to their male counterparts. Men, on the other hand, have a greater propensity to store fat around the internal organs, referred to as visceral obesity. Obesity is associated with chronic low-grade inflammation in adipose tissue.[15] Furthermore,

adipose tissue secrets all components of RAAS and in particular visceral adiposity is associated with activation of RAAS.[15] Likewise, visceral adipose tissue is more susceptible to adipose tissue inflammation compared to subcutaneous adipose tissue.[15] Among 50 years old participants in the Framingham Heart Study, visceral fat was more strongly associated with higher BP and hypertension in women compared to men.[16] Furthermore, in the community-based Tromsø study, higher BMI was a stronger predictor for systolic and diastolic BP increase in women aged 20-56 years than in 20-62 year old men.[17]

Obesity is associated with unfavourable changes in glucose and lipid metabolism.[18] Clustering of metabolic risk factors like dyslipidaemia, obesity, impaired glucose metabolism and hypertension, often referred to as the metabolic syndrome, is common in subjects with hypertension.[19] Glucose and lipid metabolism are also modulated by oestrogen and testosterone.[18] After menopause, oestrogen deficiency promotes insulin resistance and higher serum levels of total cholesterol and lipoprotein a, predisposing to a more atherogenic lipid profile in postmenopausal women.[11] While the metabolic syndrome is more common in men, the prevalence increases considerably after menopause in women.[20] Furthermore, in the Women's Health Study, higher serum triglycerides level was associated with higher risk of CVD, particularly in young women.[21] It is unclear whether BMI and other metabolic risk factors carry a different risk of BP increase and incident hypertension among women than men in early midlife (i.e. in 40-50 years old subjects).

8.3 Cardiovascular inflammation in hypertension

Hypertension is an inflammatory state, characterized by immune activation and dysregulation, and microvascular remodelling.[22] In hypertension, immune cells, including T cells, accumulate in perivascular fat tissue and the end-organs (kidneys, brain and heart) and promote chronic cardiovascular inflammation leading to endothelial dysfunction, capillary rarefication, arterial remodelling, and arterial stiffening.[23] Although most experimental research on inflammation in hypertension has been performed in male animals, there are known sex differences in immune

mechanisms, in particular in the role of T cells.[23, 24] Activated T cells secrete cytokines including interferon-γ that stimulates production of neopterin in macrophages.[25] Likewise, higher levels of interferon-γ increases the catabolism of the essential amino acid tryptophan to kynurenine through the kynurenic pathway, thereby increasing the kynurenine tryptophan (KTR) ratio.[26] Thus, in humans, the degree of T cell activation may be assessed from measurement of neopterin and KTR.

High-sensitive C-reactive protein (hs-CRP) and pyridoxic acid ratio (PAr) are more general markers of inflammation.[27, 28] Vitamin B6 homeostasis is altered in inflammation. The active vitamin B6 metabolite pyridoxal-5' phosphate is decreased in acute and chronic disease and inversely associated with hs-CRP. As a result, the PAr index, which reflects the ratio between the vitamin B6 metabolites plasma 4-pyridoxic acid: (pyridoxal + pyridoxal-5′-phosphate), has been developed as a marker of inflammation.[27] In former analyses from the Hordaland Health Study (HUSK), higher levels of neopterin, KTR and the PAr index were all associated with increased risk of CVD.[29, 30] Among 27 939 women in the Women's Health Study there was a strong association between higher levels of hs-CRP and risk of CVD.[31] Furthermore, higher levels of hs-CRP, neopterin, KTR and PAr have been found in subjects with hypertension compared to normotensive subjects.[29, 32, 33] Little is known about whether sex differences in these prognostically validated markers of inflammation may contribute to sex differences in BP development in midlife.

8.4 Blood pressure and risk of acute coronary syndromes in women and men

Acute coronary syndromes (ACS), including myocardial infarction and unstable angina pectoris, are the leading cause of death in women and men worldwide.[34] Despite the overall decrease in ACS incidence and mortality rates in Western countries during the last decades, several studies have reported an increase in hospitalizations for ACS in young and middle-aged women.[3, 35-37] Among young adults presenting with ACS, women have a higher comorbidity burden, including higher prevalence of hypertension compared to men.[36] Accumulating evidence over the past 20 years indicates that

hypertension defined as a systolic BP ≥140 mmHg and/or a diastolic BP ≥90 mmHg may be a stronger risk factor for ACS in women compared to their male counterparts.[38, 39] In The Interheart Study, a case control study including 30 000 participants from 52 countries, hypertension was a stronger risk factor for myocardial infarction in women than in men.[40] In this study, median age was 65 years in women vs. 56 years in men. In a meta-analysis of 61 prospective studies, a slightly stronger association between systolic BP and coronary heart disease mortality was found in women, especially in the age group 40-50 years, corresponding to early midlife.[38] Among 35-94 years old participants in the Tromsø study, the relative risk of myocardial infarction increased more with increasing systolic and diastolic BP level in women compared to men.[39] However, the incidence of myocardial infarction remained higher in men than women even among subjects above the age of 75 years in the Tromsø study.[41] Taken together, hypertension seemed to be a stronger risk factor for myocardial infarction in women than men.

In 2017, the American College of Cardiology (ACC)/ the American Heart Association (AHA) Guideline for the Prevention, Detection, Evaluation and management of High Blood Pressure in Adults lowered the threshold for diagnosis of hypertension and defined AHA/ACC Stage 1 hypertension as systolic BP 130-139 mmHg and/or diastolic BP 80-89 mmHg in both sexes.[42] However, whether having a mildly elevated BP, defined as AHA/ACC Stage 1 hypertension in early midlife carries a different risk for ACS in women compared to men remains unclear.

9. Hypothesis and study aims

9.1 Hypothesis

We hypothesized that CVD risk factors and inflammation are associated with BP development in a sex-specific manner in early midlife, and that the association of BP with risk of ACS differs by sex

9.2 Objectives

1. Identify the impact of lifestyle and other CVD risk factors on change in BP and incident hypertension over a 6-year period for women and men in early midlife
2. Explore the association of BP in early midlife with hospitalization and death from ACS over 16 years follow-up in women and men
3. Explore the association of markers of inflammation with BP development and new onset hypertension in women and men in early midlife

10. Materials and methods

10.1 Data sources

This thesis is based on data from HUSK and the "Cardiovascular Disease in Norway Project 1994-2009" (CVDNOR). **Studies 1 and 3** are based on data from the first and second survey of HUSK performed in 1992-1993 (HUSK1) and in 1997-1999 (HUSK2) (Table 2). **In study 2**, data from HUSK1 was linked with data from CVDNOR and the Cause of Death Registry.

Table 1. Participants, study design, exposure, and outcome in studies 1-3

	Study 1	**Study 2**	**Study 3**
Data sources	HUSK1 1992-1993 HUSK2 1997-1999	HUSK1 1992-1993 CVDNOR 1994-2009	HUSK1 1992-1993 HUSK2 1997-1999
Study participants	2008 women and 1610 men born 1950 -1951	6381 women and 5948 men born 1950-1952	1829 women and 1451 men born 1950-1951
Study design	Prospective cohort study	Prospective cohort study	Prospective cohort study
Follow-up	6 years	16 years	6 years
Exposure	Lifestyle and metabolic risk factors	Blood pressure categories	Plasma markers of inflammation
Outcome	BP change, Incident hypertension	ACS	BP, BP change, Incident hypertension

10.2 The Hordaland Health Study

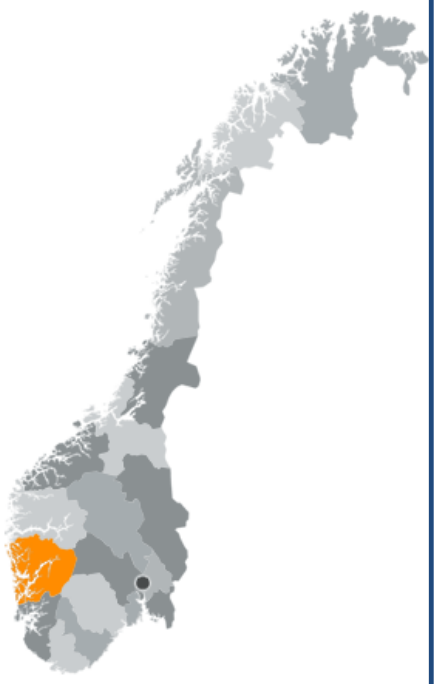

Figure 1: The Hordaland Health Study was performed in Hordaland County on the western coast of Norway, marked in orange. Hordaland County is now a part of Vestland County.

HUSK (HUSK-english – The Hordaland Health Studies (uib.no)) is a community-based health study that was initiated in Hordaland County in Western Norway (Figure 1) in 1992 as a collaboration between the University of Bergen, the Norwegian Health Screening Services (now a part of the Norwegian Institute of Public Health) and local health services.[43, 44] Eligible subjects were identified from the National Population Registry based on year of birth and site of residence. In 1992-93, all residents in Hordaland County born in 1950-52 were invited to the HUSK1 survey, which included 17 303 subjects and an acceptance rate of 73% (Figure 2). (HUSK1 was initially named the Hordaland Homocysteine study). Cohort members born in 1950-51, residing in Bergen or the neighbouring suburban municipalities who participated in HUSK1 were reinvited to participate in HUSK2 in 1997-99 (n=4849, acceptance rate 77%).

Study population in the current project

In **Studies 1 and 3** the study population consisted of women and men born in 1950 - 1951 who were examined in HUSK1 (baseline) and 6 years later in HUSK2 (follow-up) (Figure 2) (Table 1). The study population in **Study 2** consisted of women and men born in 1950-1952 examined in HUSK1 (Figure 2) (Table 1). In **study 2** BP measurements and other data from HUSK1 were coupled with outcome data from CVDNOR and the Cause of Death Registry for the period 1 January 1994 to 31

December 2009. Participants taking antihypertensive medication at baseline were excluded in **Studies 1 and 2** (n=50 and n=191).

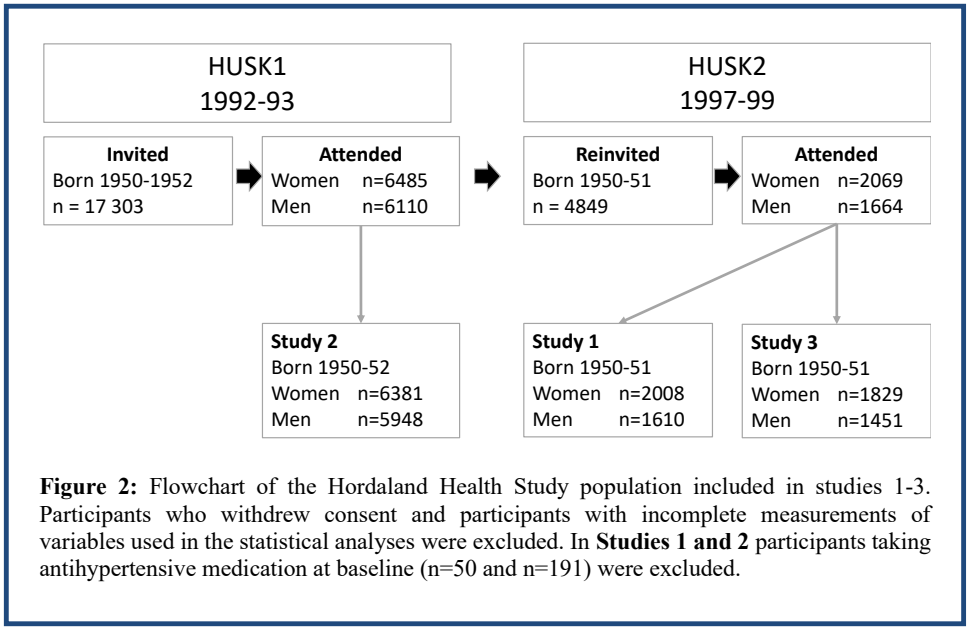

Figure 2: Flowchart of the Hordaland Health Study population included in studies 1-3. Participants who withdrew consent and participants with incomplete measurements of variables used in the statistical analyses were excluded. In **Studies 1 and 2** participants taking antihypertensive medication at baseline (n=50 and n=191) were excluded.

10.3 The Cardiovascular Disease in Norway (CVDNOR) Project 1994-2009

The CVDNOR project includes information about all hospitalizations and deaths with diabetes or a cardiovascular disease diagnosis in Norway during 1994-2009 (CVDNOR – Cardiovascular Disease in Norway 1994-2014 (uib.no)). The project was initiated as a collaboration between the University of Bergen and the Norwegian Knowledge Centre for the Health Services (now part of the Norwegian Institute of Public Health). For the period 1994 through 2009, CVDNOR retrospectively retrieved data from the electronic Patient Administrative Systems in all hospitals in Norway. All hospital stays with cardiovascular disease (International Classification of Disease (ICD) -9: 390-459, ICD-10: I00-I99, G45), congenital malformations of the circulatory system (ICD-9: 745-747, ICD-10: Q20-Q28) or diabetes (ICD-9: 250, ICD-10: E10-E14) as a primary or secondary diagnosis were included in the database. Information regarding cause of death originated from the Cause of Death Registry, a national registry that includes

information on date, underlying and contributing causes of all deaths in Norway (https://cvdnor.w.uib.no). Each patient was assigned a unique identification number that enables linkage to other data sources. In **study 2**, ACS was defined as hospitalization or death from an acute myocardial infarction or unstable angina pectoris diagnosis (ICD-9 codes 410, 411 and ICD-10 codes I20.0, I21 and I22).

10.4 Cardiovascular risk factor assessment in the Hordaland Health Study

Participants were examined by trained health care workers following standardized protocols.

10.4.1 Measurement of BP

Attended brachial BP and heart rate were measured three times with 1-minute intervals in the seated position. Attended BP measurement was performed with an appropriately sized cuff and calibrated sphygmomanometers (Dinamap 845 XT or Dinamap 8100 Criticon, Tampa, FL, USA) after a minimum of 10 minutes (HUSK 1) or 2 minutes rest (HUSK2).[45] The average of the two last measurements was taken as the clinic BP in each survey and is used in the analyses included herein.

10.4.2 Definitions of BP classes and hypertension

Current guidelines do not have sex-specific definitions or treatment recommendations for hypertension, except for recommendations related to pregnant women.[42, 46] Both the World Health organization and the 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) Guidelines for the management of arterial hypertension define hypertension as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg in both women and men (Table 2).[46] The 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation and management of High Blood Pressure in Adults lowered the diagnostic threshold for hypertension to a systolic BP ≥130 mmHg and/or diastolic BP ≥80 mmHg (Table 1).[42] An overview of BP classification by the current ACC/AHA and ESC/ESH guidelines is provided in Table 2. In **Study 1**, BP classes were defined in accordance with the ESC/ESH guidelines.[46] High-normal BP

was defined as a systolic BP 130-139 mmHg and/or diastolic BP 85-89 mmHg. Hypertension was defined as a systolic BP ≥140 mmHg and/or a diastolic BP ≥90mmHg, and/or self-reported use of antihypertensive medication.[46] In **Study 2**, BP classes were defined in accordance with the ACC/AHA guideline.[42] Normotension was defined as a systolic BP <130 mmHg and a diastolic BP <80 mmHg. Stage 1 hypertension as a systolic BP 130-139 mmHg and/or a diastolic BP 80-89 mmHg and Stage 2 hypertension as systolic BP ≥140 mmHg and/or a diastolic BP ≥90 mmHg (Table 2). **In study 3**, new onset hypertension was defined in accordance with the ACC/AHA guideline as a systolic BP ≥130 mmHg and/or a diastolic BP ≥80mmHg and/or self-reported use of antihypertensive medication.[42]

Table 2. American and European guideline definitions of BP classification.

ACC/AHA Guideline 2017				ESC/ESH Guidelines 2018			
Category	Systolic (mmHg)		Diastolic (mmHg)	Category	Systolic (mmHg)		Diastolic (mmHg)
Normal	<120	And	<80	Optimal	<120	and	<80
Elevated	120-129	and/or	<80	Normal	120-129	and/or	80-84
Stage 1 HT	130-139	and/or	80-89	High normal	130-139	and/or	85-89
Stage 2 HT	≥140	and/or	≥90	HT	≥140	and/or	≥90
Isolated systolic HT	≥130	and	<80	Isolated systolic HT	≥140	and	<90
Isolated diastolic HT	<130	and	≥80	Isolated diastolic HT	<140	and	≥90

ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; ESH, European Society of Hypertension; BP, blood pressure; HT, Hypertension

10.4.3 Anthropometric measurements

Height was measured to the nearest centimetre without shoes, and weight was measured to the nearest half kilogram with light clothing. BMI was calculated as weight in kg/height in meters^2. Overweight was classified as BMI 25-29.9 kg/m^2 and obesity as BMI ≥30.0 kg/m^2, according to the World Health Organization definitions.[47]

10.4.4 Self reported health

Information about education, physical activity and medical history including smoking and diabetes, was collected in self-reported questionnaires. In HUSK1, questionnaires collected information regarding antihypertensive medication, use of contraceptive pills, hormone replacement therapy and menopausal status. In HUSK2 participants reported the medications they had been taking the previous day, up to a maximum number of 20. Education was classified as primary education/lower secondary school (1), upper secondary school (2) and higher education (3) based on data from HUSK1 and HUSK2.

10.4.5 Physical activity

In HUSK1 **(studies 1 and 2)**, physical activity was categorized as *sedentary* if participants reported sedentary or no regular physical activity in the questionnaire, *light* if participants reported walking, cycling, or other moderate physical activity for at least 4 hours per week, *moderate* if participants reported exercise, gardening with physical exertion, or similar degree of physical activity for at least 4 hours per week, and *hard* if participants reported heavy training or competitive sports several times per week. In HUSK 2 **(study 3)**, physical activity was categorized as none, <1 hour, 1-2 hours or ≥3 hours of vigorous physical activity per week resulting in sweating/shortness of breath.

10.4.6 Smoking

Smoking was defined as self-reported daily smoking in HUSK1 and as self-reported daily smoking or a serum cotinine ≥85 nmol/L in HUSK2. Cotinine is a nicotine degradation product, and cotinine level measured in blood can be used to objectively identify tobacco users.[48]

10.4.7 Diabetes

In HUSK1, diabetes was identified as self-reported diabetes. In HUSK2, diabetes was identified by any of the following: self-reported diabetes, a serum glucose level ≥11.1 mmol/L in participants who had eaten during the last 8 hours, a serum glucose level ≥7.0 mmol/L in participants who had been fasting for at least 8 hours, or self-reported use of antidiabetic medication.[49]

10.4.8 Biochemical analyses

Non fasting blood samples were collected, kept on ice before centrifugation and stored at –80°C before analysis. In HUSK1 and 2 blood samples were analysed for serum triglycerides and serum total cholesterol. In HUSK2 analyses also included high density (HDL) cholesterol, serum glucose and serum creatinine.

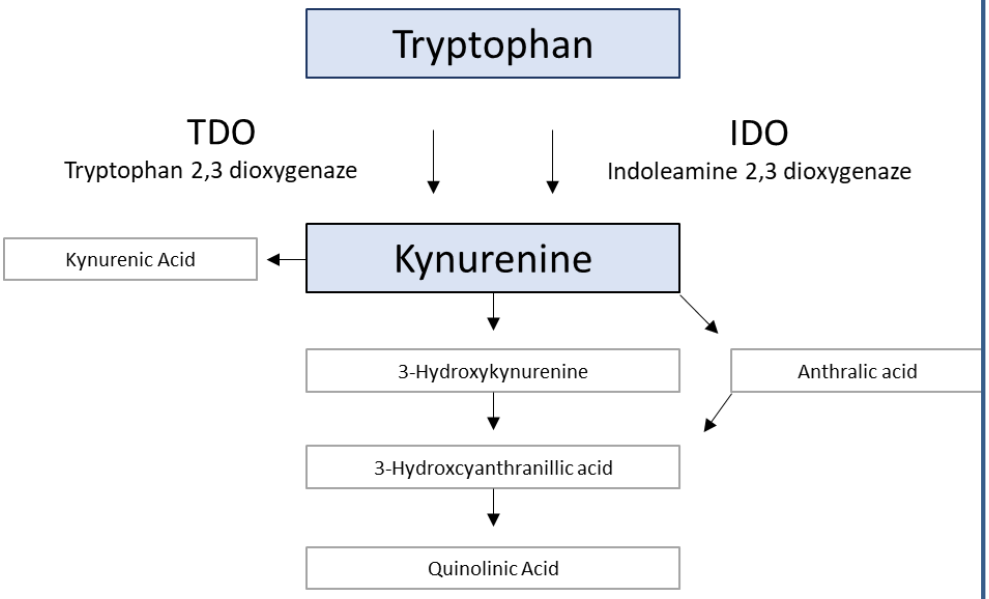

Figure 3: Kynurenine pathway: In the kynurenine pathway the essential amino acid tryptophan is metabolized to kynurenine by two enzymes; IDO and TDO. IDO is upregulated by different cytokines, in particular interferon-γ. Therefore, the kynurenine/tryptophan ratio (KTR) is a marker of interferon-γ, and T cell mediated immune response.

10.4.9 Measurements of inflammatory biomarkers in biobank samples

In HUSK2 plasma concentrations of neopterin, kynurenines, tryptophan, 4-pyridoxic acid, pyridoxal 5'-phosphate and pyridoxal were quantified by LC-tandem MS at Bevital, Bergen, Norway. (www.bevital.no). Furthermore, in HUSK2 an immuno-Matrix-Assisted Laser Desorption/Ionization-based assay was used to measure hs-CRP. 90% of tryptophan metabolism is directed through the kynurenic pathway, producing numerous metabolites, collectively named kynurenines as depicted in Figure 3. KTR was defined as the ratio plasma kynurenine (nmol/L): tryptophan (mmol/L),

and the PAr index was defined as the ratio plasma 4-pyridoxic acid: (pyridoxal + pyridoxal-5'-phosphate). [27]

10.5 Statistical methods and data analyses

Statistical analyses were performed using STATA, versions 15-17 (StataCorp, LP, College Station, TX, USA). Continuous variables are expressed as means and standard deviations for normally distributed variables, and medians and interquartile ranges for non-normally distributed variables (serum triglycerides, hs-CRP, neopterin, KTR and PAr). Categorical variables are expressed as numbers and percentages. Comparisons between groups were done using the Student's t-test or the Chi square test, as appropriate. For non-normally distributed variables comparisons between groups were done using quantile regression. Multivariable adjusted cubic spline plots and linear spline plots with one knot were used to visualize the associations between explanatory variables and changes in systolic and diastolic BP. Factors associated with BP and change in BP were identified in univariable and multivariable linear regression analyses. Results are reported as standardized β-coefficients and p-values. For the analyses of incident hypertension in HUSK2, participants with hypertension in HUSK1 were excluded (n=695 in **Study** 1 and n=1599 in **Study** 3). Factors associated with incident hypertension were tested in logistic regression analyses. Results are reported as odds ratios (OR), 95 % confidence intervals (CI) and p-values.

In **study 2**, participants were grouped into three BP categories: normotension (BP <130/80 mmHg), stage 1 hypertension (BP 130-139/80-89 mmHg) and stage 2 hypertension (BP ≥140/90 mmHg). Kaplan-Meyer cumulative plots were constructed stratified by BP category, in women and men. Associations between BP categories and incident ACS were tested in Cox regression analyses, with normotension as the reference category.

In all studies, separate analyses were performed for women and men. To test for interactions between explanatory variables and sex (effect modification), we compared

the model with and without the interaction term, using the likelihood-ratio test. A two tailed p-value of <0.05 was considered statistically significant in all analyses.

11. Ethics

Written informed consent was retrieved from all participants. The study was performed according to the declaration of Helsinki and the study protocol was approved by the Regional Committee for Medical and Health Research Ethics (2017/294).

12. Results

12.1 Study 1: Factors associated with increase in blood pressure and incident hypertension in early midlife: The Hordaland Health Study

A total of 2 008 women and 1 610 men, mean age 42±1 years at baseline, were followed for 6 years. At baseline, average BP was lower in women compared to men (122/75 mmHg, vs. 132/80 mmHg, respectively (both $p<0.05$)). Women also had lower baseline BMI than men (23.7 kg/m^2 vs. 25.1 kg/m^2, $p<0.001$), while the prevalence of obesity did not differ by sex (5.0% in women vs. 5.2% in men, $p=0.81$). On average during follow-up, women had an increase in systolic BP and a decrease in diastolic BP to 124/72 mmHg, while on average decreases in both systolic and diastolic BP to 130/78 mmHg were found in men (all $p<0.05$).

Results from linear regression analysis are presented as standardized β-coefficients. In multivariable analyses in women, higher baseline BMI (β=0.11), heart rate (β=0.06), and increases in BMI (β=0.20), serum cholesterol (β=0.09), and serum triglycerides (β=0.08) were associated with a larger increase in systolic BP during follow-up. Increases in BMI (β=0.13), serum cholesterol (β=0.12) and serum triglycerides (β=0.07) were associated with a larger increase in diastolic BP in women. Using linear spline plots, positive associations between baseline BMI and systolic (β=0.13) and diastolic (β=0.06) BP were found in women with a BMI ≥21 kg/m^2 (Figure 4, panel 1 and 3). In women with a BMI below 21 kg/m^2, there was no significant associations between baseline BMI and BP change (both $p>0.05$).

In men, higher baseline BMI (β=0.10), heart rate (β=0.08) and serum cholesterol (β=0.05) and increases in BMI (β=0.18), serum cholesterol (standardized β=0.11) and serum triglycerides (β=0.09) were associated with increases in systolic BP during follow-up (all $p<0.05$). Baseline BMI (β=0.075) and increases in BMI (β=0.14), serum cholesterol (β=0.14) and serum triglycerides (β=0.07) were positively associated with increase in diastolic BP in men (all $p<0.001$).

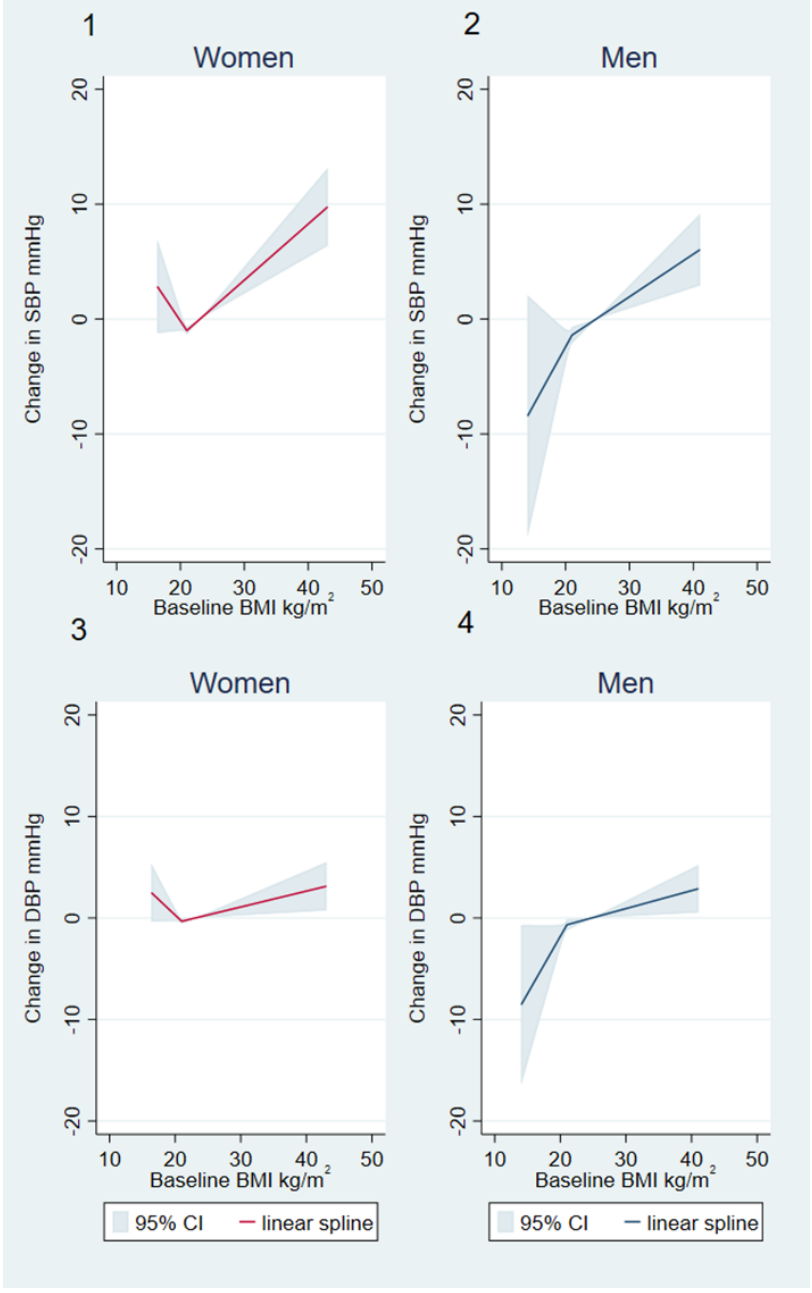

Figure 4: Linear spline plots. Changes in systolic and diastolic BP over 6 years associated with baseline BMI in women and men in early midlife. The model is adjusted for baseline BP and education. BP, blood pressure; BMI, body mass index.

There were close to linear relationships between baseline BMI and systolic and diastolic BP change during follow-up in men (Figure 4, panel 2 and 4)).

Among 2 323 participants with normotension (a systolic BP <140 mmHg and diastolic BP <90 mmHg) at baseline, a lower proportion of women (11%) than men (14%) developed incident hypertension ($p<0.01$). In women, having high-normal BP (OR 5.45, 95% CI 3.94-7.54) and higher BMI (OR 1.11, 95% CI 1.06-1.16) at baseline, and increases in BMI (OR 1.24, 95% CI 1.13-1.25), serum cholesterol (OR 1.32, 95% CI 1.04-1.68) and serum triglycerides (OR 1.30, 95% CI 1.07-1.58) during follow-up was associated with incident hypertension in multivariable logistic regression analyses. Also in men, high-normal BP (OR 3.94, 95% CI 2.74-5.64) and higher BMI (OR 1.10, 95% CI 1.03-1.16) at baseline, as well as increases in BMI (OR 1.41, 95% CI 1.24-1.60) and serum triglycerides (OR 1.21, 95% CI 1.01-1.44) during follow-up were associated with incident hypertension 6 years later. Having serum triglycerides in the highest compared to the lowest quartile at baseline was associated with incident hypertension in women (OR 1.87, 95% CI 1.13-3.09), but not in men (OR 0.92, 95% CI 0.54-1.56). This sex difference was confirmed by a significant interaction between serum triglyceride level and sex in the model on incident hypertension ($p<0.05$).

12.2 Study 2: Stage 1 hypertension, sex and acute coronary syndromes during midlife: The Hordaland Health Study

A total of 6 381 women and 5 948 men, mean age 41±1 years were followed for a median of 16 years. During follow-up, 1.4% of women and 5.7% of men were hospitalized with or died from an ACS ($p<0.001$).

In Cox regression analysis adjusted for diabetes, smoking, total serum cholesterol, BMI and physical activity, women with stage 1 hypertension had a double risk of ACS over 16 years follow-up, compared to normotensive women (model 1) (HR 2.18, 95% CI 1.32-3.6) (Figure 5). After adjustment for the same CVD risk factors, men with stage 1 hypertension did not have increased risk of ACS (HR 1.30, 95% CI 0.98-1.71) (Figure 5). Having stage 2 hypertension in the early forties increased the HR of ACS during

follow-up in both sexes, but more in women (HR 3.09 95% CI 1.80-5.31) than in men (HR 1.40 95% CI 1.40-5.31). These sex differences were confirmed by a significant interaction between BP category and sex in the model on ACS (p=0.01).

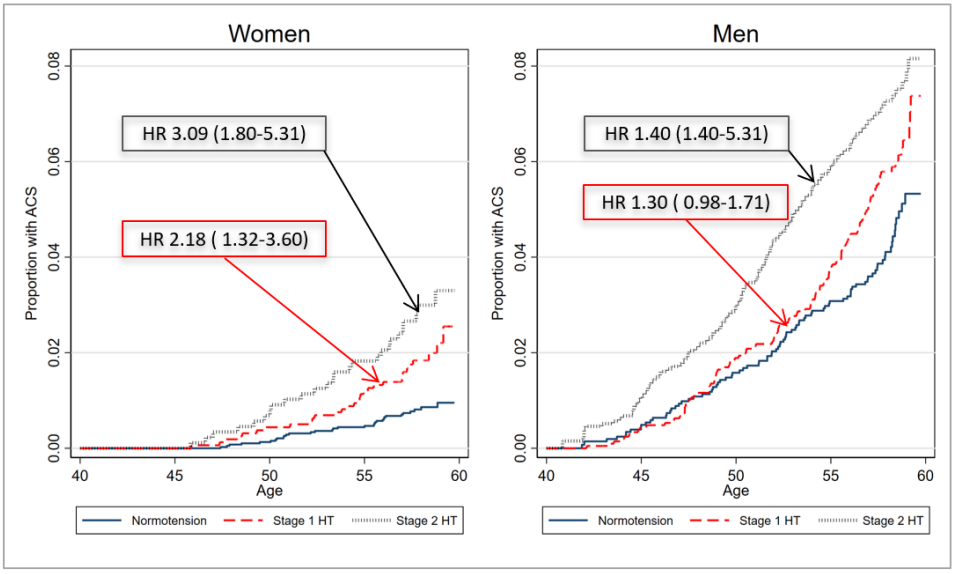

Figure 5: Kaplan Meyer curves of ACS by baseline BP category over 16 years follow-up in women and men. The boxes represent results from sex-specific multivariable Cox regression analyses on associations between baseline BP category and subsequent ACS. In Cox regression analyses multivariable models are adjusted for diabetes, smoking, total serum cholesterol, BMI and physical activity. Results are presented as HR and 95% CI. Red curves and boxes represent stage 1 hypertension and black curves and boxes stage 2 hypertension. Normotension was the reference category. The Figure is adapted with permission from "Kringeland E, Tell GS, Midtbø H, Igland J, Haugsgjerd TR, Gerdts E. Stage 1 hypertension, sex, and acute coronary syndromes during midlife: the Hordaland Health Study. Eur J Prev Cardiol. 2022;29(1):147-154."

ACS, acute coronary syndromes; HR, hazard ratio; HT: hypertension

The risk of ACS increased with increasing systolic and diastolic BP category in both women and men (both p for trend <0.01). Stage 1 and 2 systolic hypertension was not

associated with ACS compared to systolic normotension in either sex in Cox regression analyses adjusted for model 1 and diastolic BP (all p>0.05).

Stage 1 diastolic hypertension was significantly associated with increased risk of 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) in Cox regression analysis adjusted for model 1 and systolic BP. Stage 2 diastolic hypertension was associated with increased risk of ACS in both sexes, but the association was particularly strong in women (HR 5.74, 95% CI 2.66-12.4 in women and HR 1.57, 95% CI 1.09-2.26 in men). The sex-specific association between diastolic BP category and ACS was confirmed by a highly significant diastolic BP category-sex interaction in the model on ACS (p=0.002).

12.3 Study 3: Inflammation, sex, blood pressure changes and hypertension in midlife: The Hordaland Health Study.

Among 1 829 women and 1 451 men with a mean age of 48±1 years who were re-examined in the HUSK2 survey, average BP was lower in women (124/72 mmHg) compared to men (130/78 mmHg) (p<0.01). Women had lower plasma levels of hs-CRP than men, while plasma neopterin and PAr levels were higher in men than in women (all p<0.05).

All regression coefficients are standardized β-coefficients. In women, higher plasma levels of hs-CPR were associated with systolic (β=0.09) and diastolic BP (β=0.10) and increases in systolic (β=0.08) and diastolic BP (β=0.09) during the past 6 years (all p<0.01) in multivariable analyses. Likewise, compared to hs-CRP <1 mg/L, higher levels of hs-CRP (hs-CRP >1-3 mg/L and hs-CRP ≥3 mg/L, respectively) were both associated with a nearly 2-fold higher incidence of new-onset hypertension over the past 6 years in women (OR 1.81, 95% CI 1.25-2.61 and OR 1.94, 95% CI 1.26-3.01) (Figure 6). Furthermore, higher level of plasma neopterin was associated with higher diastolic BP in women (β= 0.08 p<0.01), while KTR and PAr were not associated with BP development (follow-up systolic or diastolic BP, systolic or diastolic BP change, or new onset hypertension) in women (all p>0.05).

In men, there were no significant associations between hs-CRP and systolic (β=0.04) or diastolic (β=0.05) BP, or systolic (β=0.02) or diastolic BP change (β=0.01) in multivariable adjusted analyses (all p>0.05). Compared to hs-CRP <1 mg/L, higher levels of hs-CRP >1-3 mg/L and hs-CRP ≥3 mg/L were not associated with higher incidence of new onset hypertension in men (OR 1.24, 95% CI 0.80-1.92 and OR 0.85, 95% CI 0.49-1.51). Higher PAr was associated with higher systolic (β=0.07) and diastolic (β=0.09) BP in men (both p<0.05). There were no significant associations between neopterin and KTR with BP development (follow-up systolic or diastolic BP, systolic or diastolic BP change, or new onset hypertension) in men (all p>0.05).

Sex differences were confirmed by significant interactions between hs-CRP and sex in models on new onset hypertension (p<0.05) and between neopterin and sex in models on diastolic BP (p<0.05).

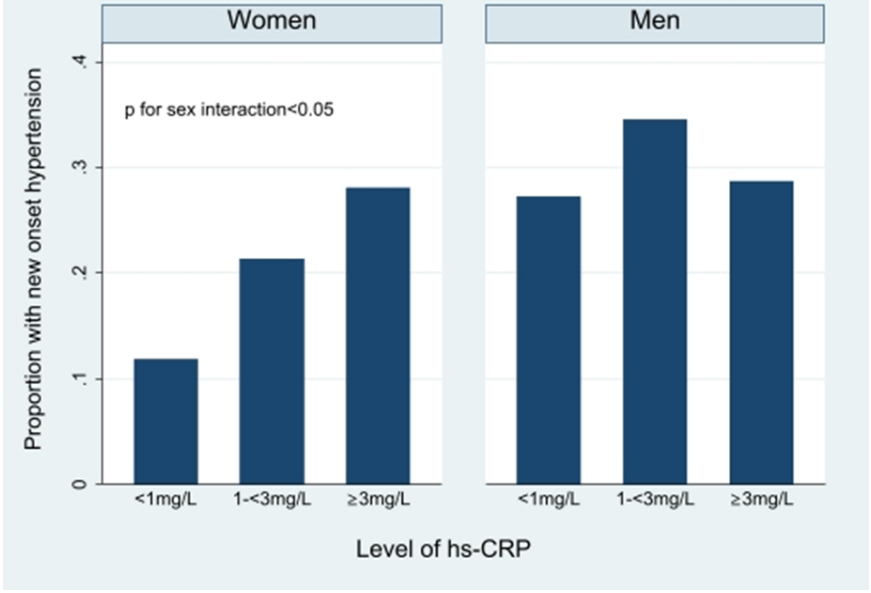

Figure 6: Proportion of women and men with new onset hypertension defined as a systolic BP ≥130 mmHg and/or a diastolic BP ≥80 mmHg or use of antihypertensive medication in different levels of hs-CRP at the follow-up visit. X axis demonstrates level of hs-CRP, and Y-axis demonstrates proportion (%) of participants with new onset hypertension. There was a significant interaction between level of hs-CRP and sex in the model on incident hypertension ($p<0.05$).

hs-CRP , high-sensitive C-reactive protein

13. Discussion

The current project focused on factors associated with BP and BP change among women and men in early midlife, participating in the Hordaland Health Study. Furthermore, we assessed sex-specific associations between BP in early midlife and risk of ACS over 16 years follow-up. The main findings of the project are: Firstly, the main factors associated with increase in BP and new onset hypertension during early midlife were baseline BP, higher BMI, weight gain and increases in serum lipids both among women and men. Secondly, having mildly elevated BP (ACC/AHA stage 1 hypertension) in the early forties was independently associated with a doubled risk for ACS over 16 years among women, while this association was non-significant among men in adjusted analyses. Thirdly, circulating inflammatory markers were associated with BP and new onset hypertension in a sex-specific manner.

13.1 Metabolic factors associated with BP and new onset hypertension in women and men

13.1.1 BMI, obesity and risk of hypertension

The HUSK population was relatively lean. At 42 years of age, mean BMI was 23.7 kg/m^2 in women vs. 25.1 kg/m^2 in men and only 5% of the population was obese. Still, we found a strong association between higher baseline BMI and increase in BMI with both BP increase and new onset hypertension in women and men. This is an important finding, indicating that level of BMI and BMI change, even within the normal range, is associated with BP change and risk of hypertension in both women and men in early midlife. These results add to previous reports from the Framingham Heart Study and the Strong Heart Study.[50, 51] Among 8 244 on average overweight participants aged 35-64 years in the Framingham Heart study, a 5% weight gain was associated with 20-30% increased odds of hypertension.[50] Among mostly overweight or obese American Indians aged 54±7 years in the Strong Heart Study, obesity and diabetes were the main factors associated with new onset hypertension during 8 years follow-up.[51] However, in these reports, sex-specific results were not presented. In line with our findings, higher BMI and increase in BMI were associated with increases in BP among 18-30

year old both women and men with a mean BMI of 24 kg/m^2 in the CARDIA Study.[52] In contrast, in the community-based Tromsø study, higher BMI was associated with systolic and diastolic BP increase in women aged 20-56 years, but not in 20-62 year old men.[17] Also in the Tromsø study, increase in BMI was associated with increases in BP in both sexes.

Some former studies have suggested a stronger association between obesity and BP in women than in men.[16, 17, 53, 54] In a population of Israelian young adults aged 25-45 years, the association between obesity and hypertension was stronger in women than in their male counterparts.[53] In this cross-sectional study, the association was particularly strong in young obese women with a BMI ≥35 kg/m^2, who had a prevalence of hypertension comparable to that found in obese young men. In a Japanese study including 6 803 men and 22 800 women, obesity was a stronger risk factor for hypertension in women than in men.[54] Furthermore, in the Framingham Heart Study, obesity was associated with a slightly higher relative risk (RR) for hypertension during follow-up in 35-65 year old women compared to men (RR 2.63 in women vs 2.23 in men), but no test for sex-interaction was presented.[55] Because of the low prevalence of obesity in our study, we do not have power to draw conclusions about sex-specific associations between obesity and BP in early midlife.

In **Study 1**, spline plots revealed a J shaped relationship between BMI and BP change in women, with a positive association between baseline BMI and increase in BP in subjects with a BMI ≥21 kg/m^2 (Figure 4). Women with a BMI <21kg/m^2 did not have a significant association between baseline BMI and BP change as opposed to men who had a close to linear relationship between baseline BMI and BP change (Figure 4). This may be caused by differences in body fat distribution between women and men. Women with a BMI below 21 kg/m^2 probably store fat subcutaneously, and therefore have less metabolic activity in their adipose tissue compared to men who typically have a higher proportion of visceral fat than women.[14, 15] Furthermore, adipose tissue produce oestrogen, and underweight women may have higher BP due to lower oestrogen levels.[56]

13.1.2 Serum lipids and risk of hypertension

In **study 1** we found an association between higher serum total cholesterol level and increase in systolic BP in early midlife in men. Furthermore, we found an association between increase in serum-total-cholesterol with increases in systolic and diastolic BP in both sexes and with new onset hypertension in women. These findings are in line with results from the Women's Health Study and the Physicians' Health Study.[57, 58] In the Women's Health Study higher levels of serum-total-cholesterol and lower levels of HDL cholesterol were associated with increased risk of hypertension among 16 300 women.[57] Likewise, in the Physicians' Health Study, higher serum total cholesterol levels were associated with increased risk of hypertension among 3 110 men. Still, cholesterol lowering statin treatment did not lower BP in a meta-analysis of 18 randomized clinical trials.[59] In the Tromsø study higher serum cholesterol level was a stronger risk factor for myocardial infarction in men compared to women.[39] In contrast, there are no convincing sex-differences in the association between serum cholesterol level and risk of hypertension.

In our **Study 1**, having baseline serum triglycerides in the highest compared to the lowest quartile almost doubled the risk of new onset hypertension during follow-up in women**.** Increases in serum triglycerides from baseline to follow-up was associated with increases in BP and new onset hypertension in both sexes. In contrast, in a Finnish study including men only, there was a significant association between higher serum triglyceride level and new onset hypertension during 7 years follow-up.[60] In the Framingham Offspring Study, baseline triglycerides and increase in serum triglycerides were associated with an increase in mean arterial pressure, but sex-specific results were not presented.[61] In line with our results, in the Cohort Norway study including 140 790 Norwegians, non-fasting serum triglycerides level was a stronger risk factor for myocardial infarction in women compared to men.[62] Furthermore, serum triglyceride level is a marker of increased risk of diabetes, and diabetes is a stronger risk factor for myocardial infarction in women than in men.[62-64] In the Women's Health Study, the association of serum triglycerides with risk of myocardial infarction was particularly strong in younger age groups.[21] Taken together,

serum triglyceride level may be a particularly important marker of unfavourable metabolic profile in women. However, more research is necessary to clarify this.

13.2 Associations between inflammation and BP in women and men

13.2.1 Hs-CRP

In **Study 3,** after adjustment for BMI, hs-CRP was associated with BP, increases in BP and new onset hypertension in women, but not in men. These findings are supported by results from former studies.[32, 65, 66] Among 20 525 women aged 45 years or older in the Women's Health Study, higher levels of hs-CRP increased the risk of new onset hypertension during 8 years follow-up.[32] In contrast, after adjustment for BMI there was no significant association between baseline hs-CRP level and risk of developing hypertension during 14 years follow-up among male physicians older than 40 years, in the Physicians' Health Study.[65] In line with this, in a meta-analysis including 142 640 participants, higher levels of hs-CRP was associated with higher risk of hypertension in women compared to men.[66] However, in this meta-analysis, sex-specific results adjusted for BMI were not presented.

13.2.2 Neopterin and KTR

In **Study 3**, neopterin was associated with higher diastolic BP and diastolic BP increase in women but not in men. On the other hand, KTR, that also reflects T cell activation and interferon-γ mediated inflammation, was not associated with systolic or diastolic BP in women, nor in men. In former analyses from HUSK, higher levels of both neopterin and KTR have been associated with increased risk of future ACS and CVD death.[29, 67] In a Chinese study, among both hypertensive persons and healthy controls, higher levels of neopterin was associated with reduced endothelial function.[68] Neopterin levels are also elevated in pregnant women with preeclampsia, compared to pregnant women without preeclampsia.[29, 68, 69] Equivalent to hypertension, preeclampsia is characterised by endothelial dysfunction and cardiovascular inflammation.[11, 12] Finally, neopterin has been found in coronary atherosclerotic lesions.[70] Taken together, increase in diastolic BP in early midlife may be particularly

associated with vascular inflammation in women. This adds to the results from **study 2,** where diastolic BP was the strongest predictor of ACS risk, and a particular strong risk factor among women.

PAr, reflecting vitamin B6 metabolism, is suggested as a maker of both acute phase reaction and cellular inflammation.[27, 33] In former analyses from HUSK, higher levels of PAr were associated with all-cause mortality among both men and women with known CVD , and with increased risk of stroke in the general population.[30, 67] In **study 3**, higher levels of PAr were associated with higher systolic and diastolic BP in men.

The sex-specific findings in **Study 3** suggest a sex-specific interaction between inflammation and BP in midlife. Cardiovascular inflammation may be potentiated by autoimmune disorders and concomitant obesity. Women are more prone to develop autoimmune disorders compared to men. Also more women than men develop obesity worldwide, but the prevalence of obesity did not differ by sex in HUSK.[71] It is well documented in several large studies that higher levels of CRP is associated with higher risk of CVD.[31] Still, assessment of CRP is not routinely used in clinical practice for CVD risk assessment.[72] [73] This is because CRP has little effect on reclassification of patients when added to established CVD risk scores, reflecting that most individual CVD risk factors are associated with inflammation.[73] It is therefore unlikely that inflammatory markers will be useful as a screening tool to identify individuals at high risk of hypertension.

13.3 CVD risk factors in women and men

The decrease in ischemic heart disease morbidity and mortality in western countries during the last decades is caused by improvements in CVD prevention, and by improved treatment of ACS. It is unclear why this favourable trend is less pronounced in young women.[35, 74-76] Sex differences in CVD risk factors are not well incorporated in current CVD risk scores. Women and men share many traditional CVD risk factors, including hypertension, dyslipidaemia, diabetes, obesity, sedentary lifestyle and

smoking.[77] Particularly diabetes and hypertension are stronger risk factors for ischemic heart disease in women compared to men.[40] In addition to these established CVD risk factors, premature menopause, gestational diabetes, hypertensive disorders of pregnancy, preterm delivery and polycystic ovarian syndrome increase the risk of CVD in women.[77] Finally, migraine, autoimmune disorders, chronic anxiety, and depression are CVD risk factors that disproportionally affects women.[77] In men, androgenic hair loss and erectile dysfunction are associated with increased risk for ischemic heart disease.[78] The lack of communication about sex differences in CVD risk factors, may contribute to underestimation of CVD risk in women both by health care providers and by women themselves.[40, 77] Among all CVD risk factors, elevated BP and hypertension are leading risk factors for CVD morbidity and death. According to The Lancet women and cardiovascular disease commission report 2021, hypertension is the most substantial and neglected health burden in women.[77]

13.4 Associations between BP and ACS in women and men

13.4.1 Hypertension and ACS in women and men

At present, the definition of hypertension differs between international guidelines (Table 2). [42, 46] While the ESC/ESH 2018 guidelines defines hypertension as systolic BP ≥140 mmHg and/or a diastolic BP ≥90 mmHg, the ACC/AHA 2017 guideline lowered the threshold, and defined ACC/AHA stage 1 hypertension as systolic BP ≥130-139 mmHg and/or a diastolic BP ≥80-89 mmHg.[42, 46] Despite known sex-differences in adult BP development, current guidelines do not have sex-specific definitions of hypertension. As first demonstrated in the Interheart study, hypertension, defined as a systolic BP ≥140 mmHg and/or a diastolic BP ≥90 mmHg, has emerged as a stronger risk factor for ACS in women than in men.[40] In HUSK, having a mildly elevated BP (ACC/AHA stage 1 hypertension) in early midlife was associated with a doubled risk of ACS during 16 years follow-up in women, even after adjustment for other CVD risk factors (**Study 2**). In contrast, in adjusted analysis there was no significant association between having ACC/AHA stage 1 hypertension and risk of ACS in men. Few former studies have explored sex-specific associations between

ACC/AHA stage 1 hypertension and ACS.[79, 80] In the UK Biobank study, following 471 988 participants, mean age 56 years, for 7 years, ACC/AHA stage 1 hypertension was associated with a 40% higher risk of myocardial infarction in women than in men.[79] In another publication based on the same cohort, ACC/AHA isolated diastolic hypertension (systolic BP <130 mmHg and diastolic BP ≥80mmHg) was associated with higher risk of combined myocardial infarction, stroke and CVD death in women and subjects younger than 60 years, but not in men and older subjects.[80] Two Korean studies have reported sex-specific associations between ACC/AHA stage 1 hypertension and CVD, defined as hospitalization for myocardial infarction, stroke and heart failure.[81 82] In a nationwide cohort including more than 15 million Koreans aged 20-94 years, ACC/AHA stage 1 hypertension was associated with CVD in both women and men.[83] Among subjects below 65 years of age, ACC/AHA stage 1 hypertension had higher HR for CVD in women compared to men, but no test for sex interaction was reported. In a population-based study following 6 424 090 Korean subjects with a mean age of 30 years, ACC/AHA stage 1 isolated diastolic hypertension was associated with a comparable increased risk of CVD in women and men over 13 years follow-up. In the same study, ACC/AHA stage 1 isolated systolic and stage 1 combined systolic and diastolic hypertension were associated with a 6-22 % higher risk of CVD in women compared to men. In contrast, a pooled analysis based on three Chinese cohorts found a comparable association between AHA/ACC stage 1 hypertension and CVD death in women and men during approximately 12 years follow-up.[81]

13.4.2 Systolic and diastolic BP and ACS in women and men

In **Study 2**, diastolic BP was a stronger indicator of ACS risk compared to systolic BP in early midlife. In line with our results, diastolic BP was a stronger predictor of coronary heart disease risk before the age of 50 years among both women and men in the Framingham Heart Study.[84] In the same report, systolic BP and pulse pressure were better indicators of coronary heart disease risk after the age of 60 years. On the other hand, systolic BP was a stronger predictor of peripheral artery disease (PAD) risk than diastolic BP in subjects with an initial age of 45-64 years, and the association between BP and PAD was particularly strong in women.[85] Taken together, which BP component that best identifies CVD risk varies by age and type of CVD assessed.

Furthermore, in **Study 2**, diastolic BP was a stronger indicator of ACS risk in women in early midlife, compared to their male counterparts. Few former studies have reported sex-specific associations between diastolic BP and risk of ACS.[39] Among 33 859 subjects aged 35-94 years in the community-based Tromsø study both systolic and diastolic BP were stronger risk factors for myocardial infarction in women compared to men.[39] In a meta-analysis on 61 prospective studies published in Lancet in 2002, higher levels of BP was associated with increased risk of coronary heart disease mortality, without any evidence of a threshold down to at least 115/75 mmHg.[38] In this large meta-analysis, a slightly stronger association between systolic BP and coronary heart disease was found in 40-50 year old women compared to their male counterparts. Unfortunately, sex-interaction analyses were not presented. In contrast, a meta-analysis and systematic review including participants between 19-104 years of age found comparable associations between systolic BP and risk of coronary heart disease in women and men.[86] In this last analysis, the authors did however report heterogeneity across studies that could not be fully adjusted for. A Finnish study with participants aged 25-64 years also failed to demonstrate any sex difference in the association between systolic BP and risk of coronary heart disease.[87]

13.4.3 Absolute vs relative risk of myocardial infarction

In **Study 2**, a higher proportion of men than women (5.7% vs 1.4%) developed ACS over 16 years follow-up, and the incidence of ACS per 10 000 person years was 8.8 for women and 35.6 for men. In both sexes, the incidence of myocardial infarction increases with increasing age.[41] In women, myocardial infarctions occur on average approximately 9 years later in life than in men.[40] Still, at all ages men have a higher incidence of myocardial infarctions.[40, 41, 79] Among 33 997 35–102-year-old individuals followed for 17.6 years in the Tromsø study, men had roughly twice the risk of myocardial infarction compared to women. The sex difference in risk of MI was highest in the age group 35-65 years and then diminished with increasing age. To sum up, although the relative risk of myocardial infarction increases more with increasing BP category in women, the absolute risk of myocardial infarction is higher in men, at all ages. Likewise, the relative risk of myocardial infarction increases more with

increasing BP category in younger compared to older persons, but the absolute risk of myocardial infarction is higher in older individuals.[79, 80, 88]

13.4.4 Potential mechanisms for the stronger associations between BP in midlife and ACS in women than in men

Sex differences in arterial function in hypertension

In early midlife, healthy women have lower BP compared to men.[5] Thus, among individuals with ACC/AHA stage 1 hypertension in early midlife, women have had a relatively larger increase in BP, compared to men. In the Enigma Study, including 18–40-year-old individuals, cardiovascular phenotypes in hypertension differed markedly between sexes.[89] Among subjects with ACC/AHA stage 1 hypertension cardiac output was increased in both sexes, whereas peripheral vascular resistance was increased only in women. These results suggest that young adult women with ACC/AHA stage 1 hypertension have more advanced BP associated arterial changes compared to their male counterparts.

Sex differences in coronary heart disease

Hypertension is associated with small artery remodeling, including remodeling in the coronary arteries.[90] Furthermore, hypertension and small artery remodeling have been particularly associated with reduced coronary flow reserve and coronary microvascular dysfunction in women.[90-93] In ACS, women have less extensive and less obstructive coronary artery disease than men on angiograms and a larger proportion of women than men with ACS have myocardial infarction in the absence of obstructive coronary arteries (MINOCA).[94, 95] In addition, relative to men, women have smaller epicardial coronary arteries and higher baseline blood flow.[94]

Pregnancy complications

Hypertensive pregnancy disorders increase the risk of maternal CVD, even after adjustment for other CVD risk factors, including hypertension.[96] Most pregnancy disorders, including preeclampsia, fetal growth restriction, and spontaneous preterm birth are associated with placenta dysfunction, characterized by endothelial dysfunction. Furthermore, it has been suggested that pregnancy complications lead to inflammation and damage in the arterial wall that persists after birth.[97] Among 45-55

years old women, 60% of women with former preeclampsia had hypertension, compared to 26% in the control group.[98] In the same publication, 30% of women with former preeclampsia had signs of coronary atherosclerosis on cardiac computer tomography angiography, compared to 18% of women from the control group. In women, pregnancy complications are important risk factors for both hypertension and coronary artery disease in midlife.[12, 96, 98] This may be one of the reasons why hypertension is a particularly strong risk factor for ACS in young women.

Sex differences in hypertensive heart disease and arterial stiffening

Hypertension leads to structural and functional damages in the heart, collectively named hypertensive heart disease. Left ventricular hypertrophy (LVH), defined as an abnormal increase in the left ventricular mass, is the hallmark of hypertensive heart disease. Previous epidemiologic studies and clinical trials have demonstrated that both middle aged and older women have higher prevalence of hypertensive heart disease than men with hypertension at similar age.[99-103] Also, among patients hospitalized for ischemic heart disease, LVH was more often found in women than in men.[78] With increasing age, hypertension is also associated with arterial stiffening, which leads to augmentation of systolic BP and pulse pressure.[46] Women have a steeper increase in arterial stiffness with aging and hypertension compared to men.[89] Further, both LVH and increased arterial stiffness are associated with increased risk of CVD in hypertension. The higher propensity to develop LVH and increased arterial stiffness, may contribute to explain why hypertension is a particularly strong risk factor for ACS in women.

13.5 Methodological considerations- strenghts and limitations

13.5.1 Study design

Studies 1-3 were prospective cohort studies, considered to be the strongest observational study design. In prospective studies, within person variability of a risk factor may cause underestimation of the association between the risk factor and disease because of regression dilution bias.[104] In **Study** 2 participants were examined only once, before they were followed until censoring or end of follow-up. We do not

have information about BP or CVD risk factors between these timepoints, which may have caused weakening of associations. Still, our **Study 2** clearly demonstrated the association between a standardized BP measurement in early midlife and risk of ACS over 16 years follow-up. Furthermore, inflammatory markers were measured only at follow-up in **Study 3**. Therefore, associations between inflammatory markers and subsequent BP development could not be tested.

13.5.2 Precision

Precision, the relative lack of random error in a study, can be improved by increasing the study population or improving the study design.[105] Although our study population was relatively large, only 89 women experienced an ACS in **Study 2,** and therefore the confidence intervals in women were relatively wide. In **Studies 1-3**, the precision could have been improved by measuring 24-hours BP. 24-hours BP is a more precise measurement of BP compared to office BP measurements.[46] On the other hand, standardized office BP measurements have high prognostic value are widely used in the clinic.[46] Our results are therefore of great clinical importance.

13.5.3 Validity

Internal validity is the degree to which a study is free from systematic error.[105] Possible systematic errors include selection bias, information bias and confounding.

Selection bias

Participants in health screenings are usually healthier and have higher health awareness than non-participants.[106] However, self-selection in cohort studies mainly affect prevalence of estimates, rather than associations between exposure and outcome.[107] Because **Studies 1-3** are all prospective cohort studies, we do not think that self-selection into HUSK have caused important bias.

Information bias

Information bias is a flaw in measuring variables that results in different accuracy of information between comparison groups.[105]

Self-reported health

Women and men may report health variables differently, which could have been a source of information bias in this work.[77] Medical history, including information regarding physical activity, smoking and diabetes was collected in self-reported questionnaires in HUSK 1 and 2. However, adjustment for these self-reported health variables (physical activity, smoking and diabetes) did not alter the main results in **Studies 1-3**. Thus, we do not think that use of self-reported health variables has caused important bias in this work.

Definition of ACS

Study 2, ACS was defined as hospitalization or death with acute myocardial infarction or unstable angina pectoris. There was a change in the definition of myocardial infarction in Norway from the 1979 WHO criteria to the 2000 ESC/ACC criteria during follow-up.[108] Implementation of the 2000 ESC/ACC criteria and measurements of troponins have probably caused a larger proportion of myocardial infarctions to be diagnosed after year 2000.[108] Coding for cause of death may have been more unreliable in persons dying outside hospitals. Because these possible classification errors are not related to the exposure (BP measured in midlife), we think that the probability of systematic bias is low.

Confounding

Confounding is what happens when the effect for the exposure is mixed with the effect of another variable.[105] Confounding can be defined as "the distortion of the measure of the effect of an exposure on an outcome due to the association of the exposure with other factors that influence the occurrence of the outcome".[105] In our studies we tried to minimize the effect of confounding by adjusting for known risk factors for hypertension in studies 1 and 3, and for known ACS risk factors in study 2. In all studies we adjusted for education as a marker of socioeconomic status. Unfortunately, we did not have information regarding creatinine, LDL and HDL

cholesterol levels or use of cholesterol lowering drugs at baseline. Furthermore, sex hormones were not measured in HUSK. Sex hormones affect BP development through several mechanisms, and women experience a transition in sex hormones during midlife.[9] However, mean age at baseline was 41 years, 10 years younger than average menopausal age in Norwegian women.[109] Also, we did not have information regarding pregnancy complications.[77] Finally, in epidemiological studies there is always a risk of residual confounding, i.e., confounding that persist after adjustment for recognized confounders.[105]

External validity; Generalizability of results

Use of the unique Norwegian personal identification number to identify all habitants within a geographic area and the high attendance rate above 70%, are strengths in the studies reported herein. The study sample is relatively large, HUSK is a community-based study, and the participants were not invited based on specific criteria. Still, HUSK included relatively lean, primarily Caucasian participants in early midlife, living in a small geographical area on the western coast of Norway. Generalizability of results to other ethnic groups, age groups and obese populations should be done with caution. On the other hand, this work adds important knowledge regarding community dwelling women and men in early midlife with a large potential for prevention of future CVD.

Effect modification

Effect modification, also referred to as an interaction between factors, means that the association of an independent variable with a dependent variable varies with the value of a third variable.[105] In this work this could mean that the associations between metabolic risk factors and BP, between BP and ACS or between inflammatory markers and BP vary in different strata of a third variable, for example sex. In **Studies 1-3** analyses stratified by sex combined with interaction analyses revealed effect modification by sex for several explanatory variables. These findings support our hypothesis: Inflammation is associated with BP development in a sex-specific manner in early midlife, and the association of BP with risk of ACS differs by sex.

13.5.4 Classification of hypertension

At present, international guidelines differ in their definition of hypertension.[42, 46] In **Study 1** we chose to use the ESC/ESH definition of hypertension. In **Study 2**, our aim was to assess sex specific associations between having a mildly elevated BP in early midlife and risk of ACS in women and men. To increase power, we chose to use ACC/AHA stage 1 hypertension instead of the ESC/ESH high normal BP (Table 2). Then finally, in **Study 3** we continued to define hypertension according to the ACC/AHA guideline.

13.5.5 Inflammatory markers

Previous exploration of the association of inflammatory markers with CVD within the Hordaland Health Study has focused on neopterin, KTR, hs-CRP and PAr.[30, 67] Because these are all prognostically validated, we chose to include neopterin, KTR, hs-CRP and PAr as markers of inflammation in **Study 3**.

13.6 Other limitations

Echocardiography and measurement of arterial stiffness was not performed in HUSK1/HUSK2. We were therefore not able to assess the associations between mildly elevated BP and hypertensive heart disease or arterial stiffness in the current project. In HUSK1, fasting blood glucose was not measured, and prevalence of diabetes may therefore have been underreported. Because the questionnaires were different in HUSK 1 and 2, classification of physical activity was different in **Study 3** compared to **Studies 1-2**

14. Conclusions

We hypothesized that CVD risk factors and inflammation are associated with BP development in a sex-specific manner in early midlife, and that the association of BP with risk of ACS differs by sex.

In Study 1 the aim was to identify the impact of lifestyle and other CVD risk factors on change in BP and incident hypertension over a 6-year period for women and men in early midlife.
We found that higher BMI, weight gain and increases in serum lipids were the main factors associated with increases in systolic and diastolic BP, and incident hypertension in both women and men in early midlife.

In Study 2 the aim was to explore the association of BP in early midlife with hospitalization and death from ACS over 16 years follow-up in women and men.
We found that among women in early midlife, having a mildly elevated BP (systolic BP 130-139 mmHg and/or diastolic BP 80-89 mmHg) was associated with a doubled risk of ACS over 16 years follow-up in adjusted analysis, compared to normotension. In adjusted analysis in men, there was no significant association between having a mildly elevated BP and risk of ACS.

In Study 3 the aim was to explore the association of markers of inflammation with BP development and new onset hypertension in women and men in early midlife.
We found that in early midlife, associations between plasma markers on inflammation and both BP and new onset hypertension differed between women and men. After adjustment for BMI, higher hs-CRP was associated with higher BP and with new onset hypertension only in women. Likewise, higher plasma neopterin was associated with higher diastolic BP only in women. In contrast, higher PAr index was associated with higher systolic and diastolic BP in men.

15. Future perspectives

The sex-specific mechanisms contributing to the multifactorial pathogenesis and varying consequences of hypertension in women and men are not well understood. **There is a need for increased knowledge on BP and associated cardiac disease in women.**

Early detection and management of CVD risk factors is of great importance to improve cardiovascular health. Not only physicians, but also women themselves underestimate CVD risk in women. Furthermore, sex differences in CVD risk factors are not well incorporated in current CVD risk scores. **Increased awareness on BP and cardiac health in women is necessary**.

Hypertension is particularly deleterious for the female heart. Still, current guidelines do not have sex-specific definitions or treatment recommendations for hypertension, except for recommendations related to pregnancy in women.[42, 46] The findings of this thesis indicates that the risk of ACS starts at a lower BP level in women compared to men, and having ACC/AHA stage 1 hypertension in early midlife doubles the risk of ACS in women. Whether antihypertensive treatment may reduce the risk of CVD in ACC/AHA stage 1 hypertension in women is not known, because adequately powered prospective clinical studies are lacking. Future CVD treatment trials need to both include young women and present sex-specific results. Based on current knowledge, **sex-specific recommendations for diagnosis and treatment of hypertension in women should be developed.**

Source of data

1. WHO. Hypertension. Vol 20222021.

2. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet.* 2021;398:957-980.

3. GBD2019RiskFactorCollaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* 2020;396:1223-1249.

4. Fryar CD, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Hypertension Prevalence and Control Among Adults: United States, 2015-2016. *NCHS Data Brief.* 2017:1-8.

5. Ji H, Kim A, Ebinger JE, et al. Sex Differences in Blood Pressure Trajectories Over the Life Course. *JAMA Cardiol.* 2020;5:19-26.

6. Omvik P, Lund-Johansen P. Hemodynamic patterns in hypertension. In: Mancia G, Grassi G, Tsioufis C, Dominiczak A, Rosei EA, eds. *Manual of Hypertension of the EUropean Society of Hypertension*2019.

7. Philbois SV, Facioli TP, Gastaldi AC, et al. Important differences between hypertensive middle-aged women and men in cardiovascular autonomic control-a critical appraisal. *Biol. Sex Differ.* 2021;12:11.

8. Sevre K, Lefrandt JD, Nordby G, et al. Autonomic function in hypertensive and normotensive subjects: the importance of gender. *Hypertension.* 2001;37:1351-1356.

9. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N. Engl. J. Med.* 1999;340:1801-1811.

10. Mallareddy M, Hanes V, White WB. Drospirenone, a new progestogen, for postmenopausal women with hypertension. *Drugs Aging.* 2007;24:453-466.

11. Maas A, Rosano G, Cifkova R, et al. Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists. *Eur. Heart J.* 2021;42:967-984.

12. Magee LA, Nicolaides KH, von Dadelszen P. Preeclampsia. *N. Engl. J. Med.* 2022;386:1817-1832.

13. WHO. Obesity and overweight fact sheet. Vol 20222021.

14. Faulkner JL, Belin de Chantemèle EJ. Sex Differences in Mechanisms of Hypertension Associated With Obesity. *Hypertension* 2018;71:15-21.

15. Koenen M, Hill MA, Cohen P, Sowers JR. Obesity, Adipose Tissue and Vascular Dysfunction. *Circ. Res.* 2021;128:951-968.

16. Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation.* 2007;116:39-48.

17. Wilsgaard T, Schirmer H, Arnesen E. Impact of body weight on blood pressure with a focus on sex differences: the Tromso Study, 1986-1995. *Arch. Intern. Med.* 2000;160:2847-2853.

18. Regitz-Zagrosek V, Lehmkuhl E, Mahmoodzadeh S. Gender aspects of the role of the metabolic syndrome as a risk factor for cardiovascular disease. *Gend. Med.* 2007;4 Suppl B:S162-177.

19. Gerdts E, Regitz-Zagrosek V. Sex differences in cardiometabolic disorders. *Nat. Med.* 2019;25:1657-1666.

20. Group CCS, EUGenMed T, Oertelt-Prigione S, et al. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *Eur. Heart J.* 2015;37:24-34.

21. Dugani SB, Moorthy MV, Li C, et al. Association of Lipid, Inflammatory, and Metabolic Biomarkers With Age at Onset for Incident Coronary Heart Disease in Women. *JAMA Cardiol.* 2021;6:437-447.

22. Rizzoni D, De Ciuceis C, Szczepaniak P, Paradis P, Schiffrin EL, Guzik TJ. Immune System and Microvascular Remodeling in Humans. *Hypertension.* 2022;79:691-705.

23. Drummond GR, Vinh A, Guzik TJ, Sobey CG. Immune mechanisms of hypertension. *Nat. Rev. Immunol.* 2019;19:517-532.

24. Sandberg K, Ji H, Hay M. Sex-specific immune modulation of primary hypertension. *Cell. Immunol.* 2015;294:95-101.

25. Huber C, Batchelor JR, Fuchs D, et al. Immune response-associated production of neopterin. Release from macrophages primarily under control of interferon-gamma. *J. Exp. Med.* 1984;160:310-316.

26. Taylor MW, Feng GS. Relationship between interferon-gamma, indoleamine 2,3-dioxygenase, and tryptophan catabolism. *FASEB J.* 1991;5:2516-2522.

27. Ulvik A, Midttun Ø, Pedersen ER, Eussen SJ, Nygård O, Ueland PM. Evidence for increased catabolism of vitamin B-6 during systemic inflammation. *Am. J. Clin. Nutr.* 2014;100:250-255.

28. Schröcksnadel K, Wirleitner B, Winkler C, Fuchs D. Monitoring tryptophan metabolism in chronic immune activation. *Clin. Chim. Acta.* 2006;364:82-90.

29. Sulo G, Vollset SE, Nygård O, et al. Neopterin and kynurenine-tryptophan ratio as predictors of coronary events in older adults, the Hordaland Health Study. *Int. J. Cardiol.* 2013;168:1435-1440.

30. Zuo H, Tell GS, Ueland PM, et al. The PAr index, an indicator reflecting altered vitamin B-6 homeostasis, is associated with long-term risk of stroke in the general population: the Hordaland Health Study (HUSK). *Am. J. Clin. Nutr.* 2018;107:105-112.

31. Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk Scores. *Circulation.* 2004;109:1955-1959.

32. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. *JAMA.* 2003;290:2945-2951.

33. Ulvik A, Pedersen ER, Svingen GF, et al. Vitamin B-6 catabolism and long-term mortality risk in patients with coronary artery disease. *Am. J. Clin. Nutr.* 2016;103:1417-1425.

34. Study GBoD. Global Burden of Disease Study. Vol 20222019.

35. Sulo G, Igland J, Nygard O, Vollset SE, Ebbing M, Tell GS. Favourable trends in incidence of AMI in Norway during 2001-2009 do not include younger adults: a CVDNOR project. *Eur J Prev Cardiol.* 2014;21:1358-1364.

36. Arora S, Stouffer GA, Kucharska-Newton AM, et al. Twenty Year Trends and Sex Differences in Young Adults Hospitalized With Acute Myocardial Infarction. *Circulation.* 2019;139:1047-1056.

37. Gabet A, Danchin N, Juillière Y, Olié V. Acute coronary syndrome in women: rising hospitalizations in middle-aged French women, 2004-14. *Eur. Heart J.* 2017;38:1060-1065.

38. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. 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.

39. Albrektsen G, Heuch I, Lochen ML, et al. Risk of incident myocardial infarction by gender: Interactions with serum lipids, blood pressure and smoking. The Tromso Study 1979-2012. *Atherosclerosis.* 2017;261:52-59.

40. Salim Y, Hawken S, Ôunpuu S, Dans T, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364:937-952.

41. Albrektsen G, Heuch I, Løchen ML, et al. Lifelong Gender Gap in Risk of Incident Myocardial Infarction: The Tromsø Study. *JAMA Intern Med.* 2016;176:1673-1679.

42. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71:e13-e115.

43. Refsum H, Nurk E, Smith AD, et al. The Hordaland Homocysteine Study: A Community-Based Study of Homocysteine, Its Determinants, and Associations with Disease. *J. Nutr.* 2006;136:1731S-1740S.

44. Ueland PM, Nygård O, Vollset SE, Refsum HJL. The Hordaland Homocysteine Studies. *Lipids.* 2001;36:S33-S39.

45. Nygård O, Vollset S, Refsum H, et al. Total plasma homocysteine and cardiovascular risk profile: The hordaland homocysteine study. *JAMA.* 1995;274:1526-1533.

46. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J. Hypertens.* 2018;36:1953-2041.

47. WHO. Obesity and overweight. Vol 20192018.

48. Jarvis MJ, Tunstall-Pedoe H, Feyerabend C, Vesey C, Saloojee Y. Comparison of tests used to distinguish smokers from nonsmokers. *Am. J. Public Health.* 1987;77:1435-1438.

49. Association AD. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2014;37 Suppl 1:S81-90.

50. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. *Lancet.* 2001;358:1682-1686.

51. de Simone G, Devereux RB, Chinali M, et al. Risk factors for arterial hypertension in adults with initial optimal blood pressure: the Strong Heart Study. *Hypertension.* 2006;47:162-167.

52. Liu K, Ruth KJ, Flack JM, et al. Blood pressure in young blacks and whites: relevance of obesity and lifestyle factors in determining differences. The CARDIA Study. Coronary Artery Risk Development in Young Adults. *Circulation.* 1996;93:60-66.

53. Sharabi Y, Grotto I, Huerta M, Grossman E. Susceptibility of the influence of weight on blood pressure in men versus women: lessons from a large-scale study of young adults. *Am. J. Hypertens.* 2004;17:404-408.

54. Fujita M, Hata A. Sex and age differences in the effect of obesity on incidence of hypertension in the Japanese population: A large historical cohort study. *J. Am. Soc. Hypertens.* 2014;8:64-70.

55. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch. Intern. Med.* 2002;162:1867-1872.

56. Hetemäki N, Mikkola TS, Tikkanen MJ, et al. Adipose tissue estrogen production and metabolism in premenopausal women. *J. Steroid Biochem. Mol. Biol.* 2021;209:105849.

57. Sesso HD, Buring JE, Chown MJ, Ridker PM, Gaziano JM. A prospective study of plasma lipid levels and hypertension in women. *Arch. Intern. Med.* 2005;165:2420-2427.

58. Halperin RO, Sesso HD, Ma J, Buring JE, Stampfer MJ, Gaziano JM. Dyslipidemia and the risk of incident hypertension in men. *Hypertension.* 2006;47:45-50.

59. Banach M, Nikfar S, Rahimi R, et al. The effects of statins on blood pressure in normotensive or hypertensive subjects--a meta-analysis of randomized controlled trials. *Int. J. Cardiol.* 2013;168:2816-2824.

60. Laaksonen DE, Niskanen L, Nyyssonen K, Lakka TA, Laukkanen JA, Salonen JT. Dyslipidaemia as a predictor of hypertension in middle-aged men. *Eur. Heart J.* 2008;29:2561-2568.

61. Zachariah JP, Rong J, Larson MG, et al. Metabolic Predictors of Change in Vascular Function: Prospective Associations From a Community-Based Cohort. *Hypertension.* 2018;71:237-242.

62. Egeland GM, Igland J, Sulo G, Nygard O, Ebbing M, Tell GS. Non-fasting triglycerides predict incident acute myocardial infarction among those with favourable HDL-cholesterol: Cohort Norway. *Eur J Prev Cardiol.* 2015;22:872-881.

63. Preis SR, Pencina MJ, Mann DM, D'Agostino RB, Sr., Savage PJ, Fox CS. Early-adulthood cardiovascular disease risk factor profiles among individuals

with and without diabetes in the Framingham Heart Study. *Diabetes Care.* 2013;36:1590-1596.

64. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. *Diabetologia.* 2014;57:1542-1551.

65. Sesso HD, Jiménez MC, Wang L, Ridker PM, Buring JE, Gaziano JM. Plasma Inflammatory Markers and the Risk of Developing Hypertension in Men. *J Am Heart Assoc.* 2015;4:e001802.

66. Jayedi A, Rahimi K, Bautista LE, Nazarzadeh M, Zargar MS, Shab-Bidar S. Inflammation markers and risk of developing hypertension: a meta-analysis of cohort studies. *Heart.* 2019;105:686-692.

67. Zuo H, Ueland PM, Ulvik A, et al. Plasma Biomarkers of Inflammation, the Kynurenine Pathway, and Risks of All-Cause, Cancer, and Cardiovascular Disease Mortality: The Hordaland Health Study. *Am. J. Epidemiol.* 2016;183:249-258.

68. Zhang YY, Tong XZ, Xia WH, et al. Increased plasma neopterin levels are associated with reduced endothelial function and arterial elasticity in hypertension. *J. Hum. Hypertens.* 2016;30:436-441.

69. Pergialiotis V, Karampetsou N, Zoumpourlis P, Papantoniou N, Thomakos N, Daskalakis G. Serum neopterin levels in women with preeclampsia: a systematic review. *Hypertens. Pregnancy.* 2018;37:220-226.

70. Shirai R, Sato K, Yamashita T, et al. Neopterin Counters Vascular Inflammation and Atherosclerosis. *J Am Heart Assoc.* 2018;7.

71. WHO. Obesity and overweight. Vol 20222021.

72. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur. Heart J.* 2016;37:2315-2381.

73. Kaptoge S, Di Angelantonio E, Pennells L, et al. C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N. Engl. J. Med.* 2012;367:1310-1320.

74. Wilmot KA, O'Flaherty M, Capewell S, Ford ES, Vaccarino V. Coronary Heart Disease Mortality Declines in the United States From 1979 Through 2011: Evidence for Stagnation in Young Adults, Especially Women. *Circulation.* 2015;132:997-1002.

75. Okoth K, Crowe F, Marshall T, Thomas GN, Nirantharakumar K, Adderley NJ. Sex-specific temporal trends in the incidence and prevalence of cardiovascular disease in young adults: a population-based study using UK primary care data. *Eur J Prev Cardiol.* 2022;29:1387-1395.

76. Sulo G, Igland J, Vollset SE, et al. Trends in incident acute myocardial infarction in Norway: An updated analysis to 2014 using national data from the CVDNOR project. *Eur J Prev Cardiol.* 2018;25:1031-1039.

77. Vogel B, Acevedo M, Appelman Y, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. *Lancet.* 2021;397:2385-2438.

78. Perrino C, Ferdinandy P, Bøtker HE, et al. Improving translational research in sex-specific effects of comorbidities and risk factors in ischaemic heart disease and cardioprotection: position paper and recommendations of the ESC Working Group on Cellular Biology of the Heart. *Cardiovasc. Res.* 2021;117:367-385.

79. Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. *BMJ.* 2018;363:k4247.

80. Li FR, He Y, Yang HL, et al. Isolated systolic and diastolic hypertension by the 2017 American College of Cardiology/American Heart Association guidelines and risk of cardiovascular disease: a large prospective cohort study. *J. Hypertens.* 2021;39:1594-1601.

81. Liu N, Yang JJ, Meng R, et al. Associations of blood pressure categories defined by 2017 ACC/AHA guidelines with mortality in China: Pooled results from three prospective cohorts. *Eur J Prev Cardiol.* 2020;27:345-354.

82. Lee H, Yano Y, Cho SMJ, et al. Cardiovascular Risk of Isolated Systolic or Diastolic Hypertension in Young Adults. *Circulation.* 2020;141:1778-1786.

83. Lee H, Cho SMJ, Park JH, Park S, Kim HC. 2017 ACC/AHA Blood Pressure Classification and Cardiovascular Disease in 15 Million Adults of Age 20-94 Years. *J Clin Med.* 2019;8.

84. 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.

85. Lu Y, Ballew SH, Tanaka H, et al. 2017 ACC/AHA blood pressure classification and incident peripheral artery disease: The Atherosclerosis Risk in Communities (ARIC) Study. *Eur J Prev Cardiol.* 2020;27:51-59.

86. Peters SA, Huxley RR, Woodward M. Comparison of the sex-specific associations between systolic blood pressure and the risk of cardiovascular disease: a systematic review and meta-analysis of 124 cohort studies, including 1.2 million individuals. *Stroke.* 2013;44:2394-2401.

87. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland. *Circulation.* 1999;99:1165-1172.

88. Wang Y. Stage 1 hypertension and risk of cardiovascular disease mortality in United States adults with or without diabetes. *J. Hypertens.* 2022;40:794-803.

89. Nardin C, Maki-Petaja KM, Miles KL, et al. Cardiovascular Phenotype of Elevated Blood Pressure Differs Markedly Between Young Males and Females: The Enigma Study. *Hypertension.* 2018;72:1277-1284.

90. Dean J, Cruz SD, Mehta PK, Merz CN. Coronary microvascular dysfunction: sex-specific risk, diagnosis, and therapy. *Nat. Rev. Cardiol.* 2015;12:406-414.

91. Rizzoni D, Palombo C, Porteri E, et al. Relationships between coronary flow vasodilator capacity and small artery remodelling in hypertensive patients. *J. Hypertens.* 2003;21:625-631.

92. Mygind ND, Michelsen MM, Pena A, et al. Coronary Microvascular Function and Cardiovascular Risk Factors in Women With Angina Pectoris and No Obstructive Coronary Artery Disease: The iPOWER Study. *J Am Heart Assoc.* 2016;5:e003064.

93. Vaccarino V, Badimon L, Corti R, et al. Ischaemic heart disease in women: are there sex differences in pathophysiology and risk factors? Position paper from the working group on coronary pathophysiology and microcirculation of the European Society of Cardiology. *Cardiovasc. Res.* 2011;90:9-17.

94. Clayton JA, Gaugh MD. Sex as a Biological Variable in Cardiovascular Diseases: JACC Focus Seminar 1/7. *J. Am. Coll. Cardiol.* 2022;79:1388-1397.

95. Mehilli J, Presbitero P. Coronary artery disease and acute coronary syndrome in women. *Heart.* 2020;106:487-492.

96. Riise HKR, Sulo G, Tell GS, et al. Hypertensive pregnancy disorders increase the risk of maternal cardiovascular disease after adjustment for cardiovascular risk factors. *Int. J. Cardiol.* 2019;282:81-87.

97. Staff AC, Redman CWG. IFPA Award in Placentology Lecture: Preeclampsia, the decidual battleground and future maternal cardiovascular disease. *Placenta.* 2014;35:S26-S31.

98. Zoet GA, Benschop L, Boersma E, et al. Prevalence of Subclinical Coronary Artery Disease Assessed by Coronary Computed Tomography Angiography in 45- to 55-Year-Old Women With a History of Preeclampsia. *Circulation.* 2018;137:877-879.

99. Gerdts E, Izzo R, Mancusi C, et al. Left ventricular hypertrophy offsets the sex difference in cardiovascular risk (the Campania Salute Network). *Int. J. Cardiol.* 2018;258:257-261.

100. Izzo R, Losi, M. A, Stabile, E, Lonnebakken, M T, Canciello, G, Esposito, G, Barbato, E, De Luca, N, Trimarco, B, de Simone, G. Development of Left Ventricular Hypertrophy in Treated Hypertensive Outpatients: The Campania Salute Network. *Hypertension.* 2017;69:136-142.

101. Gerdts E, Okin PM, de Simone G, et al. Gender differences in left ventricular structure and function during antihypertensive treatment: the Losartan Intervention for Endpoint Reduction in Hypertension Study. *Hypertension.* 2008;51:1109-1114.

102. Os I, Franco V, Kjeldsen SE, et al. Effects of losartan in women with hypertension and left ventricular hypertrophy: results from the Losartan Intervention for Endpoint Reduction in Hypertension Study. *Hypertension.* 2008;51:1103-1108.

103. de Simone G, Devereux RB, Izzo R, et al. Lack of reduction of left ventricular mass in treated hypertension: the strong heart study. *J Am Heart Assoc.* 2013;2:e000144.

104. Clarke R, Shipley M, Lewington S, et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am. J. Epidemiol.* 1999;150:341-353.

105. Porta M. *A dicionary of epidemiology*. United States of America: Oxford University Press; 2014.

106. Knudsen AK, Hotopf M, Skogen JC, Overland S, Mykletun A. The health status of nonparticipants in a population-based health study: the Hordaland Health Study. *Am. J. Epidemiol.* 2010;172:1306-1314.

107. Nilsen RM, Surén P, Gunnes N, et al. Analysis of self-selection bias in a population-based cohort study of autism spectrum disorders. *Paediatr. Perinat. Epidemiol.* 2013;27:553-563.

108. Langørgen J, Ebbing M, Igland J, et al. Implications of changing definitions of myocardial infarction on number of events and all-cause mortality: the WHO 1979, ESC/ACC 2000, AHA 2003, and Universal 2007 definitions revisited. *Eur J Prev Cardiol.* 2014;21:1349-1357.

109. Gottschalk MS, Eskild A, Hofvind S, Gran JM, Bjelland EK. Temporal trends in age at menarche and age at menopause: a population study of 312 656 women in Norway. *Hum. Reprod.* 2020;35:464-471.

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Factors associated with increase in blood pressure and incident hypertension in early midlife: the Hordaland Health Study

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ORIGINAL ARTICLE

Factors associated with increase in blood pressure and incident hypertension in early midlife: the Hordaland Health Study

Ester Kringeland[a], Grethe S. Tell[b,c], Helga Midtbø[d], Teresa R. Haugsgjerd[b], Jannicke Igland[b] and Eva Gerdts[a,d]

[a]Department of Clinical Science, University of Bergen, Bergen, Norway; [b]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway; [c]Division of Mental and Physical Health, Norwegian Institute of Public Health, Bergen, Norway; [d]Department of Heart Disease, Haukeland University Hospital, Bergen, Norway

ABSTRACT

Purpose: We aimed to identify sex-specific factors associated with increase in blood pressure (BP) and incident hypertension in early midlife.

Materials and methods: 2,008 women and 1,610 men aged 40-43 years were followed for six years in the Hordaland Health Study. Participants taking antihypertensive medication at baseline were excluded. High-normal BP was defined as baseline BP 130-139/85-89 mmHg, and incident hypertension as BP≥140/90 mmHg or use of antihypertensive medication at follow-up.

Results: During follow-up, an increase in systolic (SBP) and diastolic (DBP) BP was observed in 54% and 30% of women vs. 44% and 41% of men, respectively (both $p<0.001$). In both sexes higher baseline body mass index (BMI) and increases in BMI and serum lipids were associated with increases in SBP and DBP during follow-up (all $p<0.05$). Incident hypertension was more common in men (14 vs.11%, $p<0.01$), and predicted by higher BMI and high-normal BP at baseline in both sexes, and by higher serum triglyceride level in women (all $p<0.01$).

Conclusion: In the Hordaland Health Study, BP development differed between women and men in early midlife. The main factors associated with BP increase in both sexes were higher BMI, weight gain and increases in serum lipids.

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Introduction

The World Health Organization has defined hypertension as the leading risk factor for cardiovascular (CV) disease (CVD), and currently, 1 in 4 men and 1 in 5 women have hypertension worldwide [1]. The global obesity epidemic has been identified as a major driver for the increasing incidence and prevalence of hypertension [2,3]. As demonstrated both in the Framingham Study and the Strong Heart Study, the main risk factors for incident hypertension in 50-year-old subjects were obesity and diabetes [2,3]. However, sex-specific results were not presented. In contrast, in the Tromsø Study, high body mass index (BMI) was a more important predictor of blood pressure (BP) increase in women than in men [4].

Although the prevalence of hypertension rises with increasing age in both sexes, there is a striking difference in BP changes between women and men [5,6]. While the rate of increase in BP attenuates in men after 40 years, the rates of increase in both systolic BP (SBP) and diastolic BP (DBP) remain constant with ageing in women [6]. As a consequence, hypertension is more common in men than in women before the age of 40 years, while after the age of 60 years more women have hypertension [5,7]. Even in the very elderly above 90 years of age, a larger proportion of women than men have hypertension [8]. Thus, there is a need for further sex-specific knowledge on factors associated with BP increase and incident hypertension, in particular in early midlife. The aim of the current study was to identify sex-specific factors associated with increases in SBP, DBP and incident hypertension in women and men in their forties, using data from the community-based Hordaland Health study in Western Norway.

Methods

Study population

The Hordaland Health study is a community-based study in Hordaland County in Western Norway,

CONTACT Ester Kringeland ester.kringeland@uib.no

initiated as a collaboration between the National Health Screening Service, the University of Bergen and local health services in 1992 (https://husk-en.w.uib.no/) [9,10]. Eligible subjects were identified from the National Population Registry based on year of birth and site of residence. The current study focused on the 2050 women and 1650 men, born 1950–1951 who had participated at both the 1992–1993 (baseline) and 1997–1999 (follow-up) surveys [9]. Participants who lacked data on BP ($n = 6$), BMI ($n = 7$), serum lipids ($n = 3$), salt intake ($n = 2$) and level of education ($n = 14$) were excluded, as well as participants that used antihypertensive treatment at baseline ($n = 50$), leaving 2,008 women and 1,610 men eligible for the present analysis. For the analysis of incident hypertension, 254 women and 441 men who had SBP $\geq$140 mmHg and/or DBP $\geq$90 mmHg at baseline, were excluded. All participants provided written informed consent. The present study was performed according to the declaration of Helsinki, and the study protocol was approved by the Regional Committee for Medical and Health Research Ethics (2017/294).

Blood pressure measurement

Heart rate, SBP and DBP were measured by trained health workers after at least 2 min of rest in the sitting position using calibrated sphygmomanometers (Dinamap 845 XT or Dinamap 8100, Criticon, Tampa, FL) [10]. Brachial BP was measured at the heart level on the right arm. The BP was measured in triplets with one-minute intervals during staff attendance, and the average of the two last measurements was taken as the clinic BP and used for the analyses. High-normal BP was defined as SBP 130–139 mmHg and/or DBP 85–89 mmHg in accordance with European guidelines [11]. Hypertension was defined as BP $\geq$140/90 mmHg. Incident hypertension was defined as a reported use of antihypertensive medication or hypertension at the follow-up examination.

Other cardiovascular risk factors

Height and weight were measured without shoes, height to the nearest centimeter, and weight with light clothing to the nearest half-kilogram on a calibrated scale. BMI was calculated as weight in kg/height^2. Overweight was defined as BMI 25.0–29.9 kg/m^2 and obesity as BMI $\geq$30.0 kg/m^2 [12]. Information about medical history, CV risk factors including smoking, alcohol intake, use of extra table salt on food, education, menopausal status, contraceptive pills, hormone replacement therapy, antihypertensive medication and time since last meal was collected in self-reported questionnaires at both surveys. Smoking was defined as current daily smoking and education was classified as (1) primary education/lower secondary school, (2) upper secondary school and (3) higher education. Non-fasting blood samples were analyzed for serum triglycerides and total cholesterol.

Outcome

The following outcomes were assessed (1) change in SBP during follow up, (2) change in DBP during follow up and (3) incident hypertension, defined as recorded BP $\geq$140 mmHg systolic and/or 90 mmHg diastolic or reported use of antihypertensive medication at the follow-up examination.

Statistical analyses

Statistical analyses were done using STATA, version 15 (StataCorp LP, College Station, TX). Continuous variables are expressed as means and standard deviations (SD) or medians and interquartile ranges (IQR) and categorical variables as numbers and percentages. Comparisons between groups were done using the Student's *t*-test or the Chi-square test. For non-normally distributed variables (serum triglycerides) comparison between groups was done by quantile regression. Factors associated with changes in SBP and DBP from baseline to the follow-up survey were identified in uni- and multivariable linear regression analyses. Results are reported as standardized β-coefficients and *p*-values. Factors associated with incident hypertension were identified using uni- and multivariable logistic regression analyses. Results are presented as odds ratios (OR), 95% confidence intervals (CI) and *p*-values. Cubic spline plots with multivariable adjustments were performed to visualize the association between continuous independent variables and changes in SBP or DBP. Non-linear associations detected in cubic spline plots were further tested in a linear spline plot. Linear spline plots with one knot (the point at which the linear slope changed) and multivariable adjustments were performed for the association between baseline BMI and change in SBP and DBP. The knot was placed based on a visual assessment of the cubic spline plot. All multivariable models were adjusted for baseline BP (SBP, DBP or presence of high-normal BP, respectively), BMI and education. Adjustment for time since last meal at

baseline was done in models on serum triglycerides, while adjustment for time since last meal at baseline and follow-up was done in models on change in triglycerides. Adjustment for change in BMI was done in models on change in serum cholesterol and serum triglycerides. Additional adjustment for baseline serum cholesterol and triglycerides was done in models on change in serum cholesterol and triglycerides, respectively. Separate analyses were performed for women and men. Covariates of incident hypertension were explored also in the total study population. To test for interactions between explanatory variables and sex in the total study population, we compared a model with an interaction term with a model without an interaction term using the likelihood-ratio test. A two-tailed p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

At baseline, SBP and DBP were lower in women than in men, and high-normal BP and hypertension were both less prevalent in women (all $p < 0.001$) (Table 1). Compared to men, women also had a lower baseline BMI, serum total cholesterol and triglycerides, and lower prevalence of overweight (all $p < 0.001$) (Table 1). Obesity was rare, found in 5.0% in women and 5.2% in men ($p = 0.81$) (Table 1). Alcohol intake was lower in women than in men 1.8 vs. 4.1 units per week ($p < 0.01$). The use of contraceptive pills and hormone replacement therapy was reported by 48 (2.5%) and 57 (2.8%) women, respectively. Only 1.1% of women were postmenopausal at baseline.

When tested by the likelihood-ratio test we found significant interactions between baseline SBP and DPB with sex and changes in SBP and DBP, respectively. Similarly, there were significant interactions between quartiles of serum triglycerides and change in serum cholesterol with sex in the model on incident hypertension.

Factors associated with BP development in women during follow-up

On average women had a significant increase in SBP and a decrease in average DBP during follow-up (all $p < 0.001$) (Table 1). An increase in SBP and DBP was seen in 54% and 30% of women, respectively.

Higher BMI was associated with a larger increase in SBP both in uni- and multivariable linear regression analysis ($p < 0.001$) (Table 2). A J-shaped relationship between baseline BMI and change in SBP was demonstrated in a cubic spline plot (Figure 1a). Using linear spline plot, a positive association between baseline BMI and increase in SBP was demonstrated in women with BMI $>21\,kg/m^2$ ($\beta = 0.13$, $p < 0.001$), while no significant association between baseline BMI and change in SBP was found in women with lower BMI ($\beta = -0.04$, $p = 0.07$). The baseline heart rate was positively associated with a change in SBP in multivariable linear regression analysis ($p = 0.014$) (Table 2). During follow-up, larger increases in BMI, serum cholesterol, and triglycerides were all associated with a larger increase in SBP (all $p < 0.001$) (Table 2). Adding the use of contraceptive pills and hormone replacement therapy to the multivariable model did not alter the positive association between increase in serum triglycerides and increase in SBP in women ($\beta = 0.086$, $p < 0.001$).

A J-shaped relationship was also found between baseline BMI and change in DBP (Figure 1b). In linear spline plot, baseline BMI was associated with an increase in DBP in women with BMI above $21\,kg/m^2$ ($\beta = 0.060$, $p = 0.01$), while no significant association was found in those with lower baseline BMI. Increases in BMI, serum cholesterol and triglycerides during follow-up were all associated with an increase in DBP (all $p < 0.01$) (Table 3) (Figure 2b). Adding the use of contraceptive pills and hormone replacement therapy to the multivariable model did not alter the positive association between increase in serum triglycerides and increase in DBP in women ($\beta = 0.071$, 0.003).

Factors associated with BP development in men during follow-up

On average both SBP and DBP decreased from baseline to follow-up in men (both $p < 0.001$) (Table 1). However, an increase in SBP and DBP was seen in 44 and 41% of men, respectively. Thus, an increase in SBP was more common in women, while an increase in DBP was more common in men (both $p < 0.001$ between sexes).

Higher BMI, heart rate and serum cholesterol at baseline were identified as predictors of SBP increase in men in multivariable linear regression analyses (all $p < 0.05$) (Table 2). There was a close to the linear relationship between baseline BMI and change in SBP in men in the cubic spline plot (Figure 1c). Furthermore, increases in BMI, serum

Table 1. Characteristics of the study population at baseline and follow-up.

	Baseline 1992–93			Follow-up 1997–99			Change		
Variables	Women ($n = 2,008$)	Men ($n = 1,610$)	p*	Women ($n = 2,008$)	Men ($n = 1,610$)	p*	Women	Men	p*
Age, years	42 ± 1	42 ± 1	0.311	48 ± 1	48 ± 1	0.084	6.0 ± 1	6.0 ± 1	0.414
SBP, mmHg	122 ± 14	132 ± 13	<0.001	124 ± 16	130 ± 14	<0.001	1.8 ± 12	−1.2 ± 11	<0.001
DBP, mmHg	75 ± 10	80 ± 9	<0.001	72 ± 11	78 ± 10	<0.001	−3.7 ± 8	−1.5 ± 8	<0.001
Hypertension, *n* (%)	254 (13)	441 (27)	<0.001	300 (15)	391 (24)	<0.001			
High-normal BP, *n* (%)	319 (16)	446 (28)	<0.001	330 (16)	411 (26)	<0.001			
Heart rate, beats per minute	75 ± 13	70 ± 13	<0.001						
BMI, kg/m^2	23.7 ± 3.4	25.1 ± 2.9	<0.001	24.8 ± 4.0	26.1 ± 3.2	<0.001	1.1 ± 1.7	1.0 ± 1.4	0.078
Overweight, *n* (%)	438 (22)	669 (42)	<0.001	603 (30)	814 (51)	<0.001			
Obesity, *n* (%)	100 (5.0)	83 (5.2)	0.811	185 (9.2)	179 (11)	0.058			
Serum cholesterol, mmol/L	5.4 ± 1.0	5.7 ± 1.0	<0.001	5.7 ± 1.0	5.8 ± 1.0	<0.001	0.3 ± 0.8	0.1 ± 0.8	<0.001
Serum triglycerides, mmol/L	1.0 (0.7-1.4)	1.6 (1.1-2.4)	<0.001	1.2 (0.9–1.7)	1.8 (1.2–2.5)	<0.001	0.21 (−0.1 to 0.5)	0.12 (−0.4 to 0.7)	<0.001
Mean time since last meal, hours	3.0 ± 1.8	3.1 ± 2.0	0.31	2.6 ± 1.7	2.8 ± 2.1	0.003			
Extra table salt on food, *n* (%)	540 (27)	593 (37)	<0.001						
Alcohol intake, units/week	1.8 ± 2.7	4.1 ± 1.4	<0.001						
Diabetes mellitus, *n* (%)	6 (0.3)	9 (0.6)	0.226	9 (0.5)	20 (1.2)	0.015			
Daily smoker, *n* (%)	743(37)	604(37)	0.751	687 (34)	550 (34)	0.646			
Cardiovascular disease, *n* (%)	4 (0.20)	2 (0.12)	0.58	5 (0.25)	18 (1.1)	0.001			
Thyroid disease, *n* (%)	51 (3.0)	8 (0.59)	<0.001						
Kidney disease, *n* (%)	63 (3.1)	31 (1.93)	0.023						
Education, *n* (%)			<0.001						
Primary/lower secondary school	534 (27)	290 (18)							
Upper secondary school	862 (43)	674 (42)							
Higher education	612 (30)	646 (40)							

SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: blood pressure; BMI: body mass index; Overweight: BMI 25.0–29.9 kg/m^2; Obesity: BMI ≥30.0 kg/m^2; Cardiovascular disease: self-reported stroke or myocardial infarction.
Data are given as median (IQR) for serum triglycerides, as mean ± SD for other continuous variables and as n (%) for categorical variables.
*p-Values for differences between women and men.

Table 2. Factors associated with change in systolic blood pressure over 6 years in midlife.

	Women				Men			
	Univariate		Multivariable		Univariate		Multivariable	
Variable	β	p	β	p	β	p	β	p
Baseline								
Baseline SBP, mmHg	−0.273	<0.001	**−0.298**	<0.001	−0.353	<0.001	**−0.373**	<0.001
Baseline BMI, kg/m^2	0.052	0.021	**0.109**	<0.001	0.014	0.562	**0.104**	<0.001
Baseline heart rate beats/minute	−0.035	0.120	**0.055**	0.014	−0.0003	0.991	**0.082**	0.001
Serum cholesterol, mmol/L	−0.027	0.232	−0.014	0.537	0.017	0.508	**0.049**	0.040
Serum triglycerides, mmol/L	−0.013	0.566	−0.013[a]	0.582	−0.010	0.675	0.022[a]	0.390
Smoking	0.003	0.909	−0.007	0.739	−0.007	0.784	−0.007	0.782
Diabetes	0.024	0.290	0.017	0.430	0.014	0.566	0.019	0.410
Adding table salt on food	0.024	0.285	0.021	0.325	0.059	0.017	0.039	0.094
Education								
Primary/lower secondary school	(ref)		(ref)		(ref)		(ref)	
Upper secondary school	0.064	0.018	0.058	0.026	−0.013	0.716	−0.016	0.621
Higher education	0.010	0.712	−0.018	0.498	0.055	0.110	0.023	0.482
Changes during follow-up								
Δ BMI, kg/m^2	0.208	<0.001	**0.199**	<0.001	0.172	<0.001	**0.176**	<0.001
Δ Serum cholesterol, mmol/L	0.116	<0.001	**0.094**[a]	<0.001	0.094	<0.001	**0.106**[a]	<0.001
Δ Serum triglycerides, mmol/L	0.114	<0.001	**0.084**[a]	<0.001	0.095	<0.001	**0.090**[a]	0.001

SBP: systolic blood pressure; BMI: body mass index.
β: coefficients for factors significantly associated with increase in SBP in multivariable analysis are written in bold.
Distinct multivariable models were built for each explanatory variable. All multivariable models were adjusted for baseline systolic BP, education and baseline BMI.
[a]Adjustment for time since last meal at baseline was done in models on serum triglycerides, while adjustment for time since last meal at baseline and follow up was done in models on change in triglycerides. Adjustment for change in BMI was done in models on change in serum cholesterol and serum triglycerides. Additional adjustment for baseline serum cholesterol or triglycerides was done in models on change in serum cholesterol or triglycerides, respectively.

cholesterol, and triglycerides in men during follow-up were all associated with an increase in SBP (all $p < 0.01$) (Table 2).

There was a close to the linear relationship between baseline BMI and change in DBP in men (Figure 1d). Higher baseline BMI and larger increases

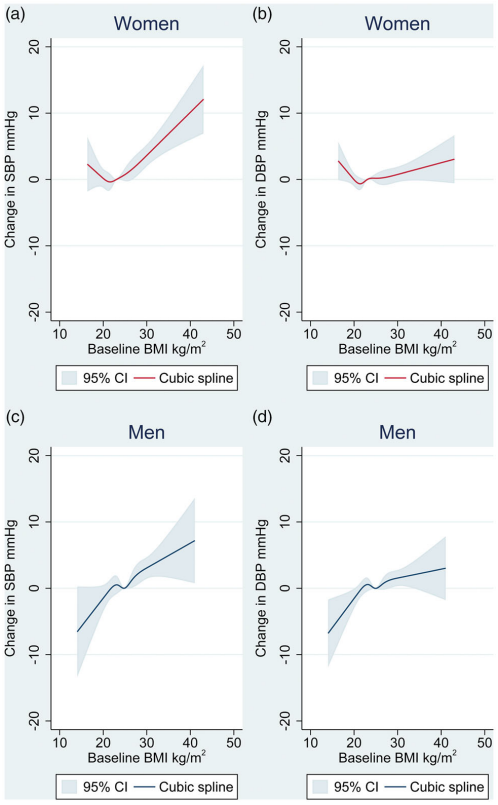

Figure 1. (a–d) Change in SBP and DBP over 6 years associated with baseline BMI in women and men in their forties. Median BMI at baseline is the reference point. The model is adjusted for baseline blood pressure and education. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure

in BMI, serum cholesterol and triglycerides during follow-up were all positively associated with an increase in DBP in men (all $p < 0.01$) (Table 3) (Figure 2d).

Incident hypertension during follow-up

Among the 1754 women and 1169 men who were normotensive at baseline, a lower proportion of women than men developed incident hypertension during 6 years follow-up (185 [11%] vs. 161 [14%], respectively, $p < 0.01$). Among these, 51 (15%) subjects were classified as having incident hypertension based upon antihypertensive drug use alone. In a univariate analysis in the total study population, women were less prone to develop incident hypertension compared to men (OR 0.74, 95% CI: 0.59–0.93, $p = 0.008$). After multivariable adjustments for baseline high-normal BP, BMI and education, women had a comparable risk of incident hypertension to that observed in men (OR 1.20, 95% CI: 0.93–1.52, $p = 0.17$). If baseline high-normal BP was replaced by baseline SBP in this model, women had a higher risk of incident hypertension than men (OR 1.42, 95% CI: 1.11–1.82, $p = 0.005$).

Factors associated with incident hypertension in women

In women, higher BMI and high-normal BP at baseline predicted a higher incidence of hypertension (Table 4). In addition, increases in BMI, serum cholesterol and triglycerides during follow-up, were all associated with a higher risk for incident hypertension in multivariable logistic regression analysis (all $p < 0.05$) (Table 4). Women in the highest quartile of serum triglycerides had a higher risk of incident hypertension compared to women in the lowest quartile ($p = 0.016$) (Table 4). Additional adjustment for use of contraceptive pills and hormone replacement therapy in the multivariable analyses did not alter the association between having serum triglycerides in the highest compared to the lowest quartile with incident hypertension in women (OR 1.87, 95% CI: 1.14–3.10, $p = 0.014$), nor the association between increase in serum triglycerides and incident hypertension in women (OR 1.30, 95% CI: 1.07–1.58, $p = 0.009$).

Factors associated with incident hypertension in men

Also in men, higher BMI and high-normal BP at baseline predicted incident hypertension at follow-up (Table 4). In multivariable logistic regression analysis, the presence of high-normal BP and higher BMI at baseline, and larger increases in BMI and serum triglycerides during follow-up, were all associated with a higher risk of incident hypertension (all $p < 0.05$) (Table 4). Having serum triglycerides in the highest compared to the lowest quartile was not associated with incident hypertension in men.

Discussion

It has been demonstrated that BP trajectories differ between women and men [6]. While rates of increase in SBP and DBP decline in men from 40 years and onward, rates of SBP and DBP increase remain

Table 3. Factors associated with change in diastolic blood pressure over 6 years in midlife.

	Women				Men			
	Univariate		Multivariable		Univariate		Multivariable	
Variable	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Baseline								
Baseline DBP, mmHg	−0.303	<0.001	**−0.308**	<0.001	−0.396	<0.001	**−0.411**	<0.001
Baseline BMI, kg/m^2	−0.026	0.249	0.038	0.083	−0.019	0.453	**0.075**	0.001
Baseline heart rate beats/minute	−0.143	<0.001	−0.030	0.197	−0.136	<0.001	0.004	0.886
Serum cholesterol, mmol/L	−0.097	<0.001	**−0.051**	0.019	−0.045	0.074	0.012	0.600
Triglycerides, mmol/L	−0.045	0.043	−0.006 [a]	0.807	−0.046	0.062	−0.005 [a]	0.843
Smoking	−0.026	0.244	−0.010	0.637	−0.014	0.578	−0.011	0.646
Diabetes	−0.009	0.690	−0.003	0.873	−0.039	0.118	−0.022	0.345
Adding table salt on food	0.037	0.097	0.032	0.133	0.032	0.201	0.027	0.240
Education								
Primary/lower secondary school	(ref)		(ref)		(ref)		(ref)	
Upper secondary school	0.028	0.312	0.021	0.421	−0.006	0.869	0.005	0.869
Higher education	0.067	0.014	0.030	0.246	0.038	0.271	0.029	0.363
Changes during follow-up								
Δ BMI, kg/m^2	0.118	<0.001	**0.125**	<0.001	0.123	<0.001	**0.138**	<0.001
Δ Serum cholesterol, mmol/L	0.154	<0.001	**0.119**[a]	<0.001	0.153	<0.001	**0.136**[a]	<0.001
Δ Serum triglycerides, mmol/L	0.065	0.003	**0.068**[a]	0.004	0.049	0.050	**0.067**[a]	0.011

DBP: diastolic blood pressure; BMI: body mass index.
β: coefficients for factors significantly associated with increase in DBP in multivariable analysis are written in bold.
Distinct multivariable models were built for each explanatory variable. All multivariable models were adjusted for baseline DBP, education and baseline BMI.
[a]Adjustment for time since last meal at baseline was done in models on serum triglycerides, while adjustment for time since last meal at baseline and follow up was done in models on change in triglycerides. Adjustment for change in BMI was done in models on change in serum cholesterol and serum triglycerides. Additional adjustment for baseline serum cholesterol or triglycerides was done in models on change in serum cholesterol or triglycerides, respectively.

constant with increasing age in women [6]. The present analysis from the Hordaland Health study aimed at identifying factors associated with an increase in BP and incident hypertension over 6 years in women and men in their forties. We found that although BP development significantly differed between women and men in early midlife, higher BMI, weight gain and increases in serum lipids were the main factors associated with an increase in BP in both sexes. As expected, a lower proportion of women than men developed incident hypertension during 6 years follow-up. However, after adjustments for baseline BP category, BMI and education, the risk of incident hypertension was similar in women and men. The presence of high-normal BP at baseline was an important predictor of incident hypertension in both sexes.

Our sex-specific analysis expands previous results from the population-based Framingham Heart Study and Strong Heart Study that both were based upon on average overweight subjects with a mean age of around 50 years, and that did not present sex-specific results [2,3]. In the Framingham Heart Study, the presence of high-normal BP was associated with a 12-fold higher risk of incident hypertension over 4 years compared to those with optimal initial BP. Furthermore, a 5% weight gain was associated with an additional 20–30% increased risk of incident hypertension during follow-up [2]. In a sub-study of 967 mostly obese North-American Indians with initial optimal BP in the Strong Heart Study, higher SBP and waist circumference at baseline and increases in these factors were associated with incident hypertension after 8 years follow-up [3].

It is of particular interest that an association between baseline BMI and increases in SBP and DBP was evident in both sexes in our population that mostly included non-obese subjects. Our results indicate that level of BMI, even within the normal range is associated with a change in BP in early midlife. While a positive association between baseline BMI and change in SBP and DBP was evident over the whole BMI spectrum in men, the association between baseline BMI and increase in BP was J-shaped in women. The lowest increase in BP was seen in women with a BMI of around 21 kg/m^2. Previous studies on the association of BMI with BP change have reported diverging results [4,13,14]. In a study by Liu K et al., including both black and white young adults, similar associations between higher baseline BMI and BMI increase with increases in SBP and DBP were found in both sexes [15]. In contrast, in the community-based Tromsø study, higher baseline BMI was associated with larger increases in SBP and DBP over 8 years in women than men in a population with an initial mean age of 39 years [4]. However, in the Tromsø study, adjustment for baseline BP was not performed, although the initial SBP was

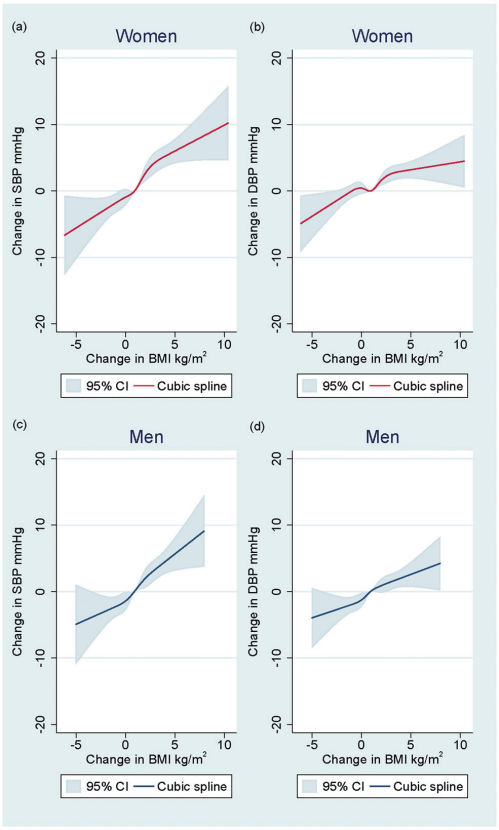

Figure 2. (a–d) Change in SBP and DBP over 6 years in midlife associated with change in BMI in women and men in their forties. Median change in BMI is the reference point. The model is adjusted for baseline blood pressure, BMI and education. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure

10 mmHg lower in women than in men. Also in a Japanese cohort study including 6803 men and 22,800 women aged 40–79 years, incident hypertension was more strongly associated with obesity in women than in men [14].

Resting heart rate has been suggested as a marker of sympathetic activity [16]. In a Chinese study, higher resting heart rate was associated with a higher risk of incident hypertension, however, separate analyses in women and men were not presented [17]. In the present sex-specific analysis, we found a positive association between higher resting heart rate and increase in SBP in women and men, but not with incident hypertension.

Our results suggest a stronger association of elevated serum triglycerides with incident hypertension in women than in men. In contrast, elevated serum triglycerides predicted development of hypertension during 7 years follow-up in 311 Finnish men [18]. In the Framingham offspring study, baseline BMI, serum triglycerides, and increase in these factors were associated with an increase in mean BP over 6 years follow-up, but sex-specific results were not reported [19]. The Copenhagen city study recently demonstrated a positive association between higher levels of non-fasting serum triglycerides and plasma C-reactive protein (CRP) levels, suggesting that elevated serum triglycerides is a marker of inflammation [20]. It has been proposed that the presence of elevated serum triglycerides may identify those at risk for diabetes development [21,22]. Diabetes mellitus is a stronger risk factor for coronary heart disease in women than men [21,23]. Likewise, higher serum triglyceride levels appear to be a more important risk factor for ischaemic heart disease in women than in men [21,23]. Because of the low prevalence of diabetes, we were not able to test the association between diabetes and incident hypertension in the present cohort.

We demonstrated an independent association of an increase in serum cholesterol during follow-up with increases in SBP and DPB in both sexes, and with incident hypertension particularly in women. These findings are in line with results in the Women's Health Study [24]. Furthermore, similar findings were reported for men in the Physicians' Health Study and a Japanese cohort study of 14,215 male workers [25,26]. Despite these findings, a meta-analysis of 18 randomized clinical trials assessing the effect of cholesterol-lowering treatment on BP reduction found no evidence of substantial BP-lowering effect of statin treatment [27].

Some study limitations should be outlined. The Hordaland Health Study was performed in a small region in Western Norway in an ethnically homogenous study sample with a very low prevalence of obesity. Thus, our results add to previous observations in overweight and obese cohorts. However, the generalisation of results should be done with caution. The relatively large study sample and prospective design are major strengths of this study. Furthermore, participation rates were high, above 70% both at the baseline and the follow-up survey [9]. Out of office BP measurements were not included in the Hordaland Health Study. Although only 51 (15%) study participants were classified as having incident hypertension at follow-up based solely on

Table 4. Factors associated with incident hypertension in women and men over 6 years in midlife.

	Women				Men			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
Variable	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Baseline								
High-normal BP	5.85 (4.24–8.06)	<0.001	**5.45 (3.94-7.54)**	<0.001	4.17 (2.93–5.95)	<0.001	**3.94 (2.74–5.64)**	<0.001
Baseline BMI, kg/m^2	1.13 (1.08–1.17)	<0.001	**1.11 (1.06–1.16)**	<0.001	1.12 (1.06–1.19)	<0.001	**1.10 (1.03–1.16)**	0.003
Baseline heart rate beats/min	1.02 (1.00–1.03)	0.012	1.01 (0.99–1.02)	0.422	1.01 (0.99–1.02)	0.281	1.00 (0.99–1.02)	0.749
Serum cholesterol, mmol/L	1.13 (0.97–1.32)	0.116	1.01 (0.86–1.20)	0.866	1.24 (1.05–1.45)	0.009	1.18 (1.00–1.39)	0.054
Serum triglycerides, mmol/L	1.42 (1.19–1.70)	<0.001	1.14 (0.92–1.41)	0.224	1.17 (1.02–1.33)	0.022	1.02 (0.87–1.18)	0.838
Quartiles serum triglycerides								
Q1	ref		ref		ref		ref	
Q2	1.55 (0.95–2.53)	0.077	1.61 (0.97–2.67)	0.065	0.90 (0.53–1.51)	0.689	0.70 (0.40–1.21)	0.200
Q3	1.63 (1.00–2.65)	0.051	1.37 (0.82–2.29)	0.228	1.63 (1.02–2.61)	0.041	1.35 (0.82–2.21)	0.242
Q4	2.66 (1.68–4.20)	<0.001	**1.87 (1.13–3.09)**	0.014	1.50 (0.93–2.41)	0.093	0.92 (0.54–1.56)	0.760
Changes during follow-up								
ΔBMI, kg/m^2	1.27 (1.17–1.38)	<0.001	**1.24 (1.13–1.35)**	<0.001	1.36 (1.20–1.53)	<0.001	**1.41 (1.24–1.60)**	<0.001
Δ serum cholesterol, mmol/L	1.28 (1.03–1.57)	0.023	**1.32[a](1.04–1.68)**	0.022	0.94 (0.76–1.15)	0.540	0.95[a](0.75–1.21)	0.679
Δ serum triglycerides, mmol/L	1.49 (1.24–1.78)	<0.001	**1.30[a](1.07–1.58)**	0.009	1.19 (1.02–1.39)	0.025	**1.21[a](1.01–1.44)**	0.036

OR: odds ratio; CI: confidence interval; BP: blood pressure; BMI: body mass index; Q: quartile.
ORs for factors significantly associated with incident hypertension in multivariable analysis are written in bold.
Distinct multivariable models were built for each explanatory variable. All multivariable models were adjusted for baseline high-normal BP, education and BMI.
[a]Adjustment for time since last meal at baseline was done in models on serum triglycerides, while adjustment for time since last meal at baseline and follow up was done in models on change in triglycerides. Adjustment for change in BMI was done in models on change in serum cholesterol and serum triglycerides. Additional adjustment for baseline serum cholesterol or triglycerides was done in models on change in serum cholesterol or triglycerides, respectively.

antihypertensive drug use, we cannot exclude that some of these participants may have had another indication for use of these drugs, and therefore were misclassified. Information on the use of steroid hormones and statin treatment was not included in the baseline survey in 1992–1993. Serum triglycerides were measured in non-fasting blood samples. Non-fasting serum triglycerides probably have an even stronger association with CVD than fasting triglycerides level [28,29]. Finally, serum glucose, creatinine, and thyroid hormones were not measured at baseline in the present cohort. Medical history was collected in self-reported questionnaires. Prevalent diabetes, CVD, thyroid, and kidney disease may therefore be underreported.

Conclusion

In the Hordaland Health Study, BP development differed between women and men in early midlife. Higher BMI, weight gain, and increases in serum lipids were the main factors associated with increases in SBP and DBP and incident hypertension during 6 years follow-up both in women and men in their forties. As initial blood pressure was lower in women than in men, women were less prone to develop hypertension during follow-up. The presence of high-normal BP at baseline was an important predictor of incident hypertension in both sexes.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

[1] WHO [Internet]. Geneva (Switzerland): World Health Organization. Hypertension; 2019 [cited 2020 January 03]. Available from: https://www.who.int/news-room/fact-sheets/detail/hypertension.
[2] Vasan RS, Larson MG, Leip EP, et al. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. Lancet. 2001;358(9294):1682–1686.
[3] de Simone G, Devereux RB, Chinali M, et al. Risk factors for arterial hypertension in adults with initial optimal blood pressure: the Strong Heart Study. Hypertension. 2006;47(2):162–167.
[4] Wilsgaard T, Schirmer H, Arnesen E. Impact of body weight on blood pressure with a focus on sex differences: the Tromso Study, 1986–1995. Arch Intern Med. 2000;160(18):2847–2853.
[5] Fryar CD, Ostchega Y, Hales CM, et al. Hypertension prevalence and control among adults: United States, 2015. NCHS Data Brief. 2016; 2017(289):1–8.
[6] Scuteri A, Morrell CH, Orru M, et al. Longitudinal perspective on the conundrum of central arterial

stiffness, blood pressure, and aging. Hypertension. 2014;64(6):1219–1227.
[7] Hasselstrom J, Zarrinkoub R, Holmquist C, et al. The Swedish primary care cardiovascular database (SPCCD): 74 751 hypertensive primary care patients. Blood Press. 2014;23(2):116–125.
[8] Wallentin F, Wettermark B, Kahan T. Current antihypertensive drug therapy in 12,436 Swedish patients, 90 years and above, in relation to sex and comorbidity. Blood Press. 2019;26:1–7.
[9] Refsum H, Nurk E, Smith AD, et al. The Hordaland Homocysteine Study: a community-based study of homocysteine, its determinants, and associations with disease. J Nutr. 2006;136(6):1731S–1740S.
[10] Nygård O, Vollset S, Refsum H, et al. Total plasma homocysteine and cardiovascular risk profile: the Hordaland Homocysteine Study. JAMA. 1995; 274(19):1526–1533.
[11] Williams B, Mancia G, Spiering W, et al. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. Blood Pressure. 2018;27(6):314–340.
[12] WHO [Internet]. Geneva (Switzerland): World Health Organization. Obesity and overweight; 2018 [updated 16 February 2018; cited 2019 May 13th]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
[13] Sharabi Y, Grotto I, Huerta M, et al. Susceptibility of the influence of weight on blood pressure in men versus women: lessons from a large-scale study of young adults. Am J Hypertens. 2004;17(5):404–408.
[14] Fujita M, Hata A. Sex and age differences in the effect of obesity on incidence of hypertension in the Japanese population: a large historical cohort study. J Am Soc Hypertens. 2014;8(1):64–70.
[15] Liu K, Ruth KJ, Flack JM, et al. Blood pressure in young blacks and whites: relevance of obesity and lifestyle factors in determining differences. The CARDIA Study. Coronary Artery Risk Development in Young Adults. Circulation. 1996;93(1):60–66.
[16] Grassi G, Vailati S, Bertinieri G, et al. Heart rate as marker of sympathetic activity. J Hypertens. 1998; 16(11):1635–1639.
[17] Wang A, Liu X, Guo X, et al. Resting heart rate and risk of hypertension: results of the Kailuan cohort study. J Hypertens. 2014;32(8):1600–1605.
[18] Laaksonen DE, Niskanen L, Nyyssonen K, et al. Dyslipidaemia as a predictor of hypertension in middle-aged men. Eur Heart J. 2008;29(20):2561–2568.
[19] Zachariah JP, Rong J, Larson MG, et al. Metabolic predictors of change in vascular function: prospective associations from a community-based cohort. Hypertension. 2018;71(2):237–242.
[20] Hansen SEJ, Madsen CM, Varbo A, et al. Low-grade inflammation in the association between mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis: a study of more than 115000 individuals from the general population. Clin Chem. 2019;65(2): 321–332.
[21] Egeland GM, Igland J, Sulo G, et al. Non-fasting triglycerides predict incident acute myocardial infarction among those with favourable HDL-cholesterol: Cohort Norway. Eur J Prev Cardiolog. 2015;22(7): 872–881.
[22] Preis SR, Pencina MJ, Mann DM, et al. Early-adulthood cardiovascular disease risk factor profiles among individuals with and without diabetes in the Framingham Heart Study. Diabetes Care. 2013;36(6): 1590–1596.
[23] Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia. 2014;57(8):1542–1551.
[24] Sesso HD, Buring JE, Chown MJ, et al. A prospective study of plasma lipid levels and hypertension in women. Arch Intern Med. 2005;165(20):2420–2427.
[25] Halperin RO, Sesso HD, Ma J, et al. Dyslipidemia and the risk of incident hypertension in men. Hypertension. 2006;47(1):45–50.
[26] Otsuka T, Takada H, Nishiyama Y, et al. Dyslipidemia and the risk of developing hypertension in a working-age male population. J Am Heart Assoc. 2016;5(3):e003053.
[27] Banach M, Nikfar S, Rahimi R, et al. The effects of statins on blood pressure in normotensive or hypertensive subjects–a meta-analysis of randomized controlled trials. Int J Cardiol. 2013;168(3):2816–2824.
[28] Bansal S, Buring JE, Rifai N, et al. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA. 2007;298(3):309–316.
[29] Nordestgaard BG, Benn M, Schnohr P, et al. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA. 2007;298(3):299–308.

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FULL RESEARCH PAPER
Blood pressure

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

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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

* Corresponding author. Tel: +47 93098296, Email: ester.kringeland@uib.no

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 ($n = 6381$)			*P* for trend	Men ($n = 5948$)			*P* for trend
	Normotension ($n = 3894$)	Stage 1 HT ($n = 1604$)	Stage 2 HT ($n = 883$)		Normotension ($n = 2029$)	Stage 1 HT ($n = 2079$)	Stage 2 HT ($n = 1840$)	
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/m^2)	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**

			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		ACS/no. at risk			0.03			0.01			
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		ACS/no. at risk			0.10			0.16			0.24
Women	Normal systolic BP	50/4607	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	Normal systolic BP	121/2561	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		ACS/no. at risk			0.006			0.002			0.002
Women	Normal diastolic BP	34/4369	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	Normal diastolic BP	131/3035	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.

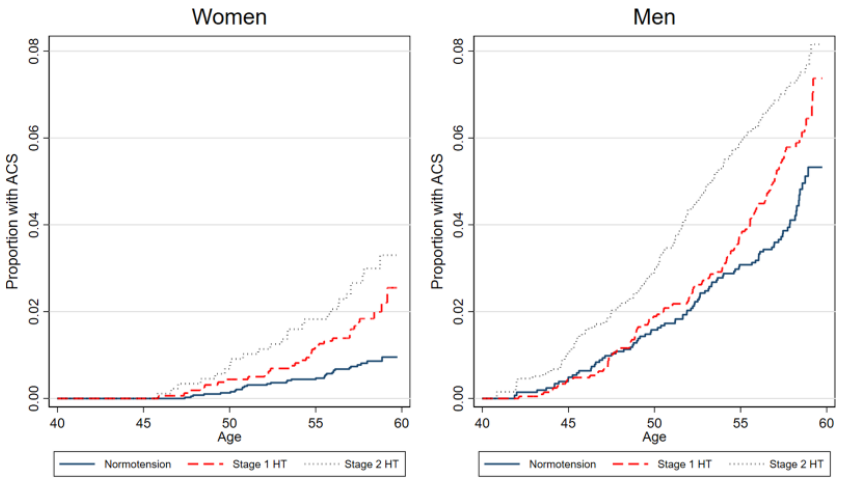

Figure 1 Kaplan–Meier analyses of acute coronary syndromes by age in baseline blood pressure categories in women and men during 16 years of follow-up. Stage 1 and stage 2 hypertension affected the risk of acute coronary syndromes in a sex-specific manner, confirmed by a significant interaction test ($P = 0.03$). 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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Disclaimer

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Conflict of interest: The Authors declare that there is no conflict of interest.

References

1. WHO. Cardiovascular diseases 2017. https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (10 January 2021).
2. Arora S, Stouffer GA, Kucharska-Newton AM, Qamar A, Vaduganathan M, Pandey A, Porterfield D, Blankstein R, Rosamond WD, Bhatt DL, Caughey MC. Twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction. *Circulation* 2019;**139**:1047–1056.
3. Sulo G, Igland J, Nygard O, Vollset SE, Ebbing M, Tell GS. Favourable trends in incidence of AMI in Norway during 2001-2009 do not include younger adults: a CVDNOR project. *Eur J Prev Cardiol* 2014;**21**:1358–1364.
4. Sulo G, Igland J, Vollset SE, Ebbing M, Egeland GM, Ariansen I, Tell GS. Trends in incident acute myocardial infarction in Norway: an updated analysis to 2014 using national data from the CVDNOR project. *Eur J Prev Cardiol* 2018;**25**: 1031–1039.
5. Wilmot KA, O'Flaherty M, Capewell S, Ford ES, Vaccarino V. Coronary heart disease mortality declines in the United States from 1979 through 2011: evidence for stagnation in young adults, especially women. *Circulation* 2015;**132**: 997–1002.
6. Nedkoff LJ, Briffa TG, Preen DB, Sanfilippo FM, Hung J, Ridout SC, Knuiman M, Hobbs M. Age- and sex-specific trends in the incidence of hospitalized acute coronary syndromes in Western Australia. *Circ Cardiovasc Qual Outcomes* 2011;**4**: 557–564.
7. Gabet A, Danchin N, Juillière Y, Olié V. Acute coronary syndrome in women: rising hospitalizations in middle-aged French women, 2004-14. *Eur Heart J* 2017; **38**:1060–1065.
8. Sörensen NA, Neumann JT, Ojeda F, Schäfer S, Magnussen C, Keller T, Lackner KJ, Zeller T, Karakas M, Münzel T, Blankenberg S, Westermann D, Schnabel RB. Relations of sex to diagnosis and outcomes in acute coronary syndrome. *J Am Heart Assoc* 2018;**7**:007297.
9. Albrektsen G, Heuch I, Lochen ML, Thelle DS, Wilsgaard T, Njolstad I, Bønaa KH. Risk of incident myocardial infarction by gender: Interactions with serum lipids, blood pressure and smoking. The Tromso Study 1979-2012. *Atherosclerosis* 2017;**261**:52–59.
10. Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. *BMJ* 2018;**7;363**: k4247.
11. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Bairey MC, Cheng S. Sex differences in blood pressure trajectories over the life course. *JAMA Cardiol* 2020; **5**:19–26.
12. Kringeland E, Tell GS, Midtbø H, Haugsgjerd TR, Igland J, Gerdts E. Factors associated with increase in blood pressure and incident hypertension in early midlife: the Hordaland Health Study. *Blood Press* 2020;**29**:267–275.
13. Rizzoni D, Palombo C, Porteri E, Muiesan ML, Kozàkovà M, La Canna G, Nardi M, Guelfi D, Salvetti M, Morizzo C, Vittone F, Rosei EA. Relationships between coronary flow vasodilator capacity and small artery remodelling in hypertensive patients. *J Hypertens* 2003;**21**:625–631.
14. Rizzoni D, Porteri E, Boari GE, De CC, Sleiman I, Muiesan ML, Castellano M, Miclini M, Agabiti-Rosei E. Prognostic significance of small-artery structure in hypertension. *Circulation* 2003;**108**:2230–2235.
15. Refsum H, Nurk E, Smith AD, Ueland PM, Gjesdal CG, Bjelland I, Tverdal A, Tell GS, Nygård O, Vollset SE. The Hordaland Homocysteine Study: a community-based study of homocysteine, its determinants, and associations with disease. *J Nutr* 2006;**136**:1731S–1740S.
16. Nygård O, Vollset S, Refsum H, Stensvold I, Tverdal A, Nordrehaug JE, Ueland M, Kvåle G. Total plasma homocysteine and cardiovascular risk profile: the Hordaland Homocysteine Study. *JAMA* 1995;**274**:1526–1533.
17. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison HC, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;**71**:e13–e115.
18. Salim Y, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**: 937–952.
19. Li FR, He Y, Yang HL, Liu HM, Zhou R, Chen GC, Wu XX, Zou MC, Wang JY, Wu XB. Isolated systolic and diastolic hypertension by the 2017 American College of Cardiology/American Heart Association guidelines and risk of cardiovascular disease: a large prospective cohort study. *J Hypertens* 2021;**3**: 0000000000002805.
20. Liu N, Yang JJ, Meng R, Pan XF, Zhang X, He M, Li H, Gao YT, Xiang YB, Shu XO, Zheng W, Wu T, Yu D, Pan A. Associations of blood pressure categories defined by 2017 ACC/AHA guidelines with mortality in China: pooled results from three prospective cohorts. *Eur J Prev Cardiol* 2020;**27**:345–354.
21. Lee H, Yano Y, Cho SMJ, Park JH, Park S, Lloyd-Jones DM, Kim HC. Cardiovascular risk of isolated systolic or diastolic hypertension in young adults. *Circulation* 2020;**141**:1778–1786.
22. Izzo R, Losi MA, Stabile E, Lonnebakken MT, Canciello G, Esposito G, Barbato E, De Luca N, Trimarco B, de Simone G. Development of left ventricular

hypertrophy in treated hypertensive outpatients: the Campania Salute Network. *Hypertension* 2017;**69**:136–142.
23. Gerdts E, Izzo R, Mancusi C, Losi MA, Manzi MV, Canciello G, De Luca N, Trimarco B, de Simone G. Left ventricular hypertrophy offsets the sex difference in cardiovascular risk (the Campania Salute Network). *Int J Cardiol* 2018;**258**: 257–261.
24. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, Levy D. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation* 2001;**103**:1245–1249.
25. Lu Y, Ballew SH, Tanaka H, Szklo M, Heiss G, Coresh J, Matsushita K. 2017 ACC/AHA blood pressure classification and incident peripheral artery disease: the Atherosclerosis Risk in Communities (ARIC) Study. *Eur J Prev Cardiol* 2020; **27**:51–59.
26. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. 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.
27. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland. *Circulation* 1999;**99**:1165–1172.
28. Peters SA, Huxley RR, Woodward M. Comparison of the sex-specific associations between systolic blood pressure and the risk of cardiovascular disease: a systematic review and meta-analysis of 124 cohort studies, including 1.2 million individuals. *Stroke* 2013;**44**:2394–2401.
29. McEniery CM, Yasmin Wallace S, Maki-Petaja K, McDonnell B, Sharman JE, Retallick C, Franklin SS, Brown MJ, Lloyd RC, Cockcroft JR, Wilkinson IB; ENIGMA Study Investigators. Increased stroke volume and aortic stiffness contribute to isolated systolic hypertension in young adults. *Hypertension* 2005;**46**: 221–226.
30. Schiffrin EL, Deng LY. Relationship between small-artery structure and systolic, diastolic and pulse pressure in essential hypertension. *J Hypertens* 1999;**17**: 381–387.
31. Taqueti VR, Shaw LJ, Cook NR, Murthy VL, Shah NR, Foster CR, Hainer J, Blankstein R, Dorbala S, Di Carli MF. Excess cardiovascular risk in women relative to men referred for coronary angiography is associated with severely impaired coronary flow reserve, not obstructive disease. *Circulation* 2017;**135**: 566–577.
32. Williams B, Mancia G, Spiering W, Agabiti RE, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I; Authors/Task Force Members. 2018 ESC/ESH Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018;**36**:1953–2041.

III

Inflammation, sex, blood pressure changes and hypertension in midlife: The Hordaland Health Study

Ester Kringeland MD[a]

Eva Gerdts MD PhD[a]

Arve Ulvik MSc PhD[b]

Grethe S. Tell MPH PhD[c]

Jannicke Igland PhD[c]

Teresa R. Haugsgjerd MSc PhD[a]

Per Magne Ueland MD PhD[b]

Helga Midtbø MD PhD[a,d]

[a]Department of Clinical Science, University of Bergen, Bergen, Norway

[b]BEVITAL, Bergen, Norway

[c]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

[d] Department of Heart Disease, Haukeland University Hospital, Bergen, Norway

Corresponding author: Ester Anne Kringeland MD,
Department of Clinical Science
University of Bergen
P.O. Box 7804
5020 Bergen,
Phone: +4793098296
E-mail: ester.kringeland@uib.no

Summary table

What is known about the topic

- Age-associated blood pressure (BP) development differs between women and men. Among young adults, women have lower BP than men. Then, starting from the 3rd decade, women have a steeper increase in BP than men.
- BP is a stronger risk factor for coronary heart disease in women than men, and this risk initiates at a lower BP level in women than men.
- Inflammation is associated with higher risk of hypertension.

What this study adds

- Among 48-year-old participants in the Hordaland Health study, higher markers of vascular inflammation were associated with higher BP and new-onset hypertension in a sex-specific manner.
- Higher levels of plasma CRP and neopterin were associated with new onset hypertension and higher BP only in women. Our results suggest a sex-specific interaction between BP and vascular inflammation in midlife.

Abstract:

Aim: To test sex-specific associations of markers of inflammation with blood pressure (BP) and incident hypertension in midlife.

Methods: Participants in the Hordaland Health study, (n=3280, 56% women, mean age 48 years) were examined at baseline and followed for 6 years. Circulating levels of inflammatory markers including high-sensitive C-reactive protein (hs-CRP), neopterin, and pyridoxic acid ratio (PAr) index were measured at follow-up. The associations with systolic/diastolic BP and incident hypertension were tested in sex-specific linear- or logistic- regression analyses adjusted for body mass index, total- and high-density lipoprotein cholesterol, triglycerides, creatinine, physical activity, smoking and diabetes.

Results: At follow-up, women had lower mean BP than men (124/72 vs. 130/78 mmHg, $p<0.001$). Higher hs-CRP was significantly associated with greater systolic and diastolic BP (standardized $\beta=0.09$ and $\beta=0.10$, both $p<0.01$) in women, but not in men. Higher neopterin was associated with higher diastolic BP only in women (standardized $\beta=0.08$) and higher PAr index was associated with higher BP in men (all $p<0.01$). Compared to hs-CRP <1 mg/L, higher levels of hs-CRP 1-<3 mg/L and hs-CRP ≥3 mg/L were associated with new-onset hypertension in women (odds ratio (OR) 1.81, 95% CI 1.25-2.61 and OR 1.94, 95% CI 1.26-3.01), but not in men. Sex-interactions were found for hs-CRP and neopterin in models on incident hypertension and diastolic BP, respectively (both $p<0.05$).

Conclusion: Higher plasma levels of inflammatory markers were associated with higher BP and incident hypertension in a sex-specific manner. Our results suggest a sex-specific interaction between cardiovascular inflammation and BP in midlife.

Introduction

Elevated blood pressure (BP) is the leading risk factor for cardiovascular disease and mortality.(1) Sex differences in BP development over the life course have been identified, where women have a steeper increase in BP with aging, starting already in the third decade of life.(2) Further, we recently reported that the risk for acute coronary syndromes increased at a lower BP level in women than in men participating in the community-based Hordaland Health Study.(3) The underlying causes for these sex-differences in BP development have not been established; however, evidence from experimental studies indicates that sex-specific activation of the immune system may contribute.(4)(5) In particular, vascular activation of T cells in response to stimuli like angiotensin 2 and high salt intake seems to be central for BP development in animal studies.(4) These activated T cells may modulate the BP response through production of pro-inflammatory cytokines such as interferon gamma (IFN-γ) that stimulates production of neopterin by activated macrophages, and activates metabolism of the essential amino acid tryptophan through the kynurenine pathway.(6)(7) The degree of T cell activation may be assessed through measurement of neopterin and the kynurenine-tryptophan ratio (KTR).(8)

Previous studies in community-based cohorts have documented that elevated high-sensitive C-reactive protein (hs-CRP), neopterin, KTR and the pyridoxic acid ratio (PAr index), the latter reflecting altered vitamin B6 catabolism during inflammation, are associated with high BP.(9)(10)(11)(12)(13)(14) Furthermore, elevated plasma levels of these inflammatory markers have been reported to be associated with risk of cardiovascular disease.(11)(12)(15)(16)(14) However, there is a paucity of clinical information on the sex-specific associations between these prognostic inflammatory markers and BP development. In the present analysis, we explored the sex-specific associations of prognostically validated

markers of inflammation with systolic and diastolic BP and new onset hypertension over the past 6 years in middle-aged women and men participating in the Hordaland Health Study.(17)

Methods

Study population

The community-based Hordaland Health Study was initiated in Hordaland County in Western Norway as a collaboration between the National Health Screening Service, the University of Bergen and local health services in 1992 (https://husk-en.w.uib.no/). Eligible subjects were identified from the National Population Registry based on year of birth and site of residence. The cohort used in the present analysis includes 3 700 women and men born in 1950-51 participating in the 1st and 2nd Hordaland Health Survey in 1992-93 and 1997-99, respectively.(17) Participation rate was above 70 % in both surveys. We excluded participants with missing data on BP (n=6), biomarkers of inflammation (n=264) body mass index (BMI) (n=4), serum creatinine (n=1) and physical activity (n=164), leaving 1 829 women and 1 451 men eligible for the present study. The study was performed according to the declaration of Helsinki, and the study protocol was approved by the Regional Committee for Medical and Health Research Ethics (2017/294).

Blood pressure measurement

Study participants were examined following standardized protocols in 1992-93 and 1997-99. Attended brachial BP was measured in seated position after a minimum of 2 minutes rest with calibrated sphygmomanometers (Dinamap 845 XT or Dinamap 8100, Criticon, Tampa, FL, USA). BP was measured three times by trained health care workers, and the average of the two last measurements was used for analyses. Hypertension was defined as BP≥130/80 mmHg or self-reported use of antihypertensive drugs. (18)

Other cardiovascular disease risk factors

Information about use of antihypertensive medication in 1992-93 (baseline) was collected in self-reported questionnaires. Likewise, information about physical activity, smoking, medical history and use of medication in 1997-99 (follow-up) was collected in self-reported questionnaires. Physical activity was categorized as none, <1 hour, 1-2 hours or ≥3 hours per week of vigorous physical activity resulting in sweating or shortness of breath. Smoking was defined as self-reported daily smoking or serum cotinine ≥85 nmol/L.(19) Diabetes was defined as self-reported diabetes, use of antidiabetic medication, a serum glucose level ≥11.1 mmol/L in participants who had eaten during the last 8 hours and/or a serum glucose level ≥7.0 mmol/L in participants who had been fasting for at least 8 hours. Weight was measured with light clothing to the nearest half-kilogram, and height was measured without shoes to the nearest centimeter. Body mass index (BMI) was calculated as weight in kg/height in meters^2 and obesity was defined as BMI ≥30 kg/m^2.

Biochemical analyses

Non-fasting blood samples were collected at follow-up, kept on ice before centrifugation (for less than 3 hours), and stored at –80°C before analysis. Plasma concentrations of tryptophan, kynurenine, neopterin, 4-pyridoxic acid, pyridoxal 5'-phosphate, pyridoxal, cotinine, and creatinine were quantified by LC-tandem MS at Bevital, Bergen, Norway (www.bevital.no).(20) Plasma hs-CRP was measured with an immuno-Matrix-Assisted Laser Desorption/Ionization–based assay.(21) KTR was calculated by dividing the plasma concentration of kynurenine (nmol/L) by the concentration of tryptophan (mmol/L), and the PAr index was defined as the ratio plasma 4-pyridoxic acid: (pyridoxal + pyridoxal-5'-phosphate).(10)

Statistical analyses

Statistical analyses were done using STATA, version 17 (Stata Corp LP, College Station, TX, USA). Continuous variables are expressed as means and standard deviations (SD) or medians

and interquartile ranges (IQR) for variables (CRP, neopterin, KTR and PAr) not normally distributed. Categorical variables are presented as numbers and percentages. Comparisons between groups were done using the Student's *t*-test or the Chi-square test. For non-normally distributed variables comparisons of medians between groups were done using quantile regression. Cross-sectional associations between inflammatory markers and systolic and diastolic BP measured at follow-up were tested in univariable and multivariable linear regression analyses. Likewise, associations between inflammatory markers measured at follow-up with changes in systolic and diastolic BP during the past 6 years were tested by linear regression analyses. Results are reported as standardized β-coefficients and *p*-values. For the analysis of new onset hypertension at follow-up, participants with hypertension at baseline were excluded (n=1599). Associations between inflammatory markers and new onset hypertension at follow-up were tested by logistic regression analyses. Results are reported as odds ratios (OR), 95% confidence intervals (CI) and *p*-values. The inflammatory markers were all non-normally distributed and log-transformed before inclusion in linear or logistic regression analyses. Separate analyses were performed for women and men. To test for interactions with sex in the associations between biomarkers of inflammation and blood pressure/hypertension, we compared a model with and without an interaction term, using the likelihood-ratio test. Multivariable model 1 was adjusted for BMI. Model 2 was adjusted for BMI, serum creatinine, physical activity, daily smoking, and diabetes. In addition, multivariable models on changes in systolic and diastolic BP were adjusted for systolic or diastolic BP measured at baseline, respectively. We performed sensitivity analyses after exclusion of participants taking antihypertensive medication at baseline (n=169) and of participants with prior myocardial infarction and stroke (n=32).

Results

Characteristics of the study population in the Hordaland Health Study

At follow-up, women had lower systolic and diastolic BP and lower prevalence of hypertension compared to men (all $p<0.001$) (Table 1). In participants with hypertension, 13% of women and 9% of men were taking antihypertensive medication ($p=0.03$). Women had lower hs-CRP and higher neopterin and PAr levels than men (all $p<0.05$), while KTR did not differ according to gender ($p<0.05$) (Table 1). Women also had lower BMI and serum creatinine (both $p<0.001$) (Table 1).

Association of BP with markers of inflammation in women and men

Women

Higher hs-CRP was significantly associated with higher systolic and diastolic BP both in univariable analyses (Figure 1 and 2), after adjustments for BMI (Table 2, model 1), and after further adjustment for creatinine, physical activity, daily smoking, and diabetes (Table 2, model 2) ($\beta=0.17$, $\beta=0.08$ and $\beta=0.09$ for systolic, and $\beta=0.17$, $\beta= 0.10$ and $\beta=0.10$ for diastolic BP, respectively, all models $p<0.01$). In adjusted analysis, higher plasma neopterin was associated with higher diastolic BP ($\beta=0.08$, $p<0.01$) (Table 2, model 2), while no significant association with systolic BP ($\beta=-0.01$, $p=0.66$) was found. No significant associations between KTR and systolic ($\beta =-0.04$) or diastolic ($\beta=0.008$) BP was found (both $p>0.05$) (Table 2). Likewise, there were no associations between PAr index and systolic ($\beta=0.002$) or diastolic ($\beta=0.04$) BP in women (both $p>0.05$).

Men

Higher hs-CRP was associated with higher systolic ($\beta=0.10$) and diastolic ($\beta=0.09$) BP in univariable analysis (both $p<0.01$) (Figure 1 and 2), but not in adjusted analyses ($\beta=0.04$ and $\beta=0.05$, respectively, both $p>0.05$) (Table 2, model 2). A higher plasma PAr index was associated with higher systolic ($\beta=0.07$) and diastolic ($\beta=0.09$) BP in adjusted analyses (both

p<0.01) (Table 2). There were no significant associations between plasma neopterin with systolic (β=-0.05) or diastolic (β=-0.004) BP (both p>0.05) (Table 2, model 2). Further, there were no associations between KTR with systolic (β=-0.04) or diastolic (β= 0.009) BP in men (both p>0.05) (Table 2, model 2).

Significant interactions between plasma hs-CRP and sex were found in univariable analyses for systolic and diastolic BP (both p<0.05). A significant sex-interaction with neopterin was found in the model on diastolic BP (p=0.01) (Table 2), indicating that neopterin has a significantly stronger association with diastolic BP in women compared to men.

Association of BP changes over the prior 6 years with markers of inflammation in women and men

Over 6 years follow-up, women had an increase in systolic BP and a decrease in diastolic BP, while men had decreases in both systolic and diastolic BP (both p<0.01 for sex-difference) (Table 1).

Women

Univariable results are presented in Table 3. In adjusted analysis, higher hs-CRP at follow-up was associated with larger increases in systolic (β=0.08) and diastolic (β=0.09) BP over the prior 6 years (both p<0.01) (Table 3, model 2). Higher plasma neopterin was associated with a larger increase in diastolic BP (β=0.07) over the prior 6 years (p<0.01) (Table 3). Neither PAr index nor KTR ratio were associated with changes in systolic or diastolic BP over the prior 6 years (all p>0.05).

Men

Univariable results are presented in Table 3. In contrast to findings in women, hs-CRP was not associated with increases in systolic (β=0.02) or diastolic (β=0.008) BP over the prior 6 years in men (p>0.05) (Table 3, model 2). Neopterin was also not associated with prior

increases in systolic (β=0.008) or diastolic (β=0.02) BP. After multivariable adjustments in model 2, higher PAr index was associated with a larger increase in diastolic BP (β=0.07) over the prior 6 years, while higher KTR was associated with a decrease in systolic BP (β=-0.05) (both $p<0.05$) (Table 3).

A significant sex-interaction with hs-CRP was found in univariable analyses for changes in systolic and diastolic BP (both $p<0.05$).

Associations of new onset hypertension with markers of vascular inflammation in women and men

Among 1 155 women and 526 men who were normotensive and free from antihypertensive medication at baseline, 17% of women and 30% of men developed new-onset hypertension during 6 years follow-up ($p<0.01$). Among women, new-onset hypertension was associated with higher serum hs-CRP (OR 1.20 95 % CI 1.06-1.35) (Model 2, Table 4). Both women with hs-CRP >1-3 mg/L (OR 1.81, 95% CI 1.25-2.61) and hs-CRP >3 mg/L (OR 1.94, 95% CI 1.26-3.01) had an increased risk of new-onset hypertension compared to women having hs-CRP <1 mg/L (Model 2, Table 4). Neopterin, KTR or the PAr index were not associated with new onset hypertension in women. Among men, neither hs-CRP, neopterin, KTR nor the PAr index were associated with new onset hypertension (all $p>0.05$) (Table 4). A significant interaction between hs-CRP and sex was found in models on incident hypertension, confirming a sex-specific association between hs-CRP and hypertension (all $p<0.05$).

Sensitivity analysis

In sensitivity analysis excluding participants with previous myocardial infarction or stroke and participants taking antihypertensive medication, the associations between hs-CRP and neopterin with BP, BP change and new-onset hypertension did not change significantly.

In sensitivity analysis excluding participants with previous myocardial infarction or stroke, higher KTR was associated with lower systolic BP in women (β -0.050, p=0.03) after multivariable adjustments as in model 2. Likewise, when excluding participants taking antihypertensive medication, higher KTR was associated with lower systolic BP in women (β -0.053, p=0.03), while higher PAr index was associated with higher diastolic BP in women (β 0.048, p=0.046).

Discussion

The present study adds novel information on sex-specific associations between prognostically validated markers of inflammation and BP in early midlife. Among women, higher hs-CRP levels were independently associated with higher BP, larger 6-year BP increase and new-onset hypertension in early midlife. Likewise, higher neopterin, a marker of T cell activation, was associated with both higher diastolic BP and higher 6-year increase in diastolic BP in women. In contrast, a higher PAr index was associated with higher systolic and diastolic BP in men.

The role of inflammation in BP development has been reported in experimental studies.(22)(5) Common hypertensive stimuli like angiotensin II and high dietary salt intake activate pro-inflammatory T cells which infiltrate the arterial wall and promote peripheral arterial dysfunction, resulting in increased vascular resistance which contributes to BP elevation.(22)(23) However, there is a paucity of clinical studies of this topic, in particular of studies using a sex-specific approach. Although healthy young women have lower average systolic and diastolic BP than their male counterparts,(24) with increasing age, women have a steeper increase in BP than men, starting already in the third decade.(2) Our study expands earlier findings by demonstrating that markers of inflammation are associated with BP and BP change in early midlife in a sex-specific manner. Taken together these results suggests a sex-specific interaction between inflammation, vascular injury, and BP increase.

Chronic low grade cardiovascular inflammation is a hallmark of obesity.(25) Obesity is a common co-morbidity in hypertension, particularly in women.(26) It is therefore of special interest that the associations of higher hs-CRP with BP-increase and new onset hypertension in early midlife were independent of BMI and only found in women in the present study. These results add to knowledge from previous studies.(27)(28) In the Women's Health Study, higher levels of CRP was associated with incident hypertension in 20 525 women aged 45 years or older.(29) However, in the Physician's Health Study performed in men only, CRP was not associated with a higher risk of hypertension among individuals age 40-84 years.(28) Taken together these findings are in line with results from the present study, where the association between hs-CRP and systolic and diastolic BP in men was explained by higher BMI. In contrast, the association between hs-CRP and systolic and diastolic BP was independent of BMI in women.

Higher plasma neopterin was associated with higher diastolic BP, and increase in diastolic BP in women only, suggesting that T-cell-mediated inflammation may be involved in diastolic BP increase in middle-aged women. Increased levels of plasma neopterin have been associated with vascular dysfunction and atherosclerosis.(30) In a small study by Zhang et al.in 24 middle-aged subjects with hypertension, higher neopterin was associated with endothelial dysfunction and higher arterial stiffness.(31) Furthermore, in 121 patients with diabetes type 2, higher serum neopterin concentrations were associated with higher prevalence of carotid plaques.(32) In the Hordaland Health study, we recently demonstrated a strong association between stage 1 diastolic hypertension in early midlife and risk of acute coronary syndromes during 16 years follow-up in women.(3) In line with this, in the UK biobank study, isolated diastolic hypertension was associated with increased risk of myocardial infarction and CVD death in women, but not in men.(33) Taken together, these

results indicate that vascular inflammation may contribute to increased risk for acute coronary events through diastolic BP elevation in middle aged women.(3)

Systemic inflammation leads to altered metabolism of vitamin B6.(10) The newly developed PAr index reflects impaired vitamin B6 metabolism and is both a marker of acute phase reaction and cellular inflammation.(10) This marker has been associated with increased risk of stroke and all-cause mortality in community based cohorts.(11)(34)(35) In the present study, the PAr index was positively associated with both systolic and diastolic BP in men, contrasting our findings related to neopterin, and pointing to a sex-specific activation of the adaptive immune system in human hypertension.

Limitations and strengths

Our study has some important limitations. Sex hormones influence BP development and regulation through a number of mechanisms. In midlife, women experience a transition in female sex hormones. Sex hormones were not measured in our study cohort. However, the average age was 41 years at baseline, 14 years less than the average menopausal age in Norwegian women. Furthermore, inflammatory markers were only measured at the end of the 6 years follow-up. Thus, the prospective associations between circulating levels of inflammatory markers and subsequent BP development could not be tested. The strengths of the study include the wide selection of inflammatory markers, the relatively large and unselected community-based study population and the sex-specific analysis approach.

Conclusion

In the Hordaland Health study, higher plasma levels of markers of inflammation, including hs-CRP, neopterin and the PAr index, were associated with higher BP, BP change and new onset hypertension in a sex-specific manner. After adjustment for BMI, higher hs-CRP was associated with higher BP and new onset hypertension only in women. Neopterin was

associated with diastolic BP in women, while PAr was particularly associated with BP in men. Our results suggest that there is a sex-specific interaction between vascular inflammation and BP in midlife.

Data Availability Statement

The dataset used in this study contains potentially sensitive 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 HUSK website: https://husk-en.w.uib.no/how-to-apply-for-data-access/

Author Contributions

EK, GST, HM, EG, AU and PMU contributed to the conception or design of the work. EK, GST, HM, JI, TRH and EG contributed to the acquisition, analysis, or interpretation of data for the work. EK drafted the manuscript. All authors critically revised and gave final approval to the manuscript.

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Competing interests:

None**.**

References:

1. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020; 396:1223–49.
2. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Bairey Merz CN, et al. Sex Differences in Blood Pressure Trajectories Over the Life Course. JAMA Cardiol. 2020;5:19–26.
3. Kringeland E, Tell GS, Midtbø H, Igland J, Haugsgjerd TR, Gerdts E. Stage 1 hypertension, sex, and acute coronary syndromes during midlife: the Hordaland Health Study. Eur J Prev Cardiol. 2022;29:147-154.
4. Sylvester MA, Brooks HL. Sex-Specific Mechanisms in Inflammation and Hypertension. Curr Hypertens Rep. 2019;21:53.
5. Mikolajczyk TP, Guzik TJ. Adaptive Immunity in Hypertension. Curr Hypertens Rep. 2019;2:68.
6. Huber C, Batchelor JR, Fuchs D, Hausen A, Lang A, Niederwieser D, et al. Immune response-associated production of neopterin. Release from macrophages primarily under control of interferon-gamma. J Exp Med. 1984;160:310-6.
7. Taylor MW, Feng G. Relationship between interferon-γ, indoleamine 2,3-dioxygenase, and tryptophan catabolism. FASEB J. 1991;5:2516–22.
8. Schröcksnadel K, Wirleitner B, Winkler C, Fuchs D. Monitoring tryptophan metabolism in chronic immune activation. Clin Chim Acta. 2006;364:82–90.
9. Miller M, Zhan M, Havas S. High Attributable Risk of Elevated C-Reactive Protein Level to Conventional Coronary Heart Disease Risk Factors: The Third National Health and Nutrition Examination Survey. Arch Intern Med. 2005;165:2063–8.
10. Ulvik A, Midttun Ø, Pedersen ER, Eussen SJPM, Nygård O, Ueland PM. Evidence for increased catabolism of vitamin B-6 during systemic inflammation. Am J Clin Nutr. 2014;100:250–5.
11. Zuo H, Tell GS, Ueland PM, Nygard O, Vollset SE, Midttun O, et al. The PAr index, an indicator reflecting altered Vitamin B-6 homeostasis, is associated with long-term risk of stroke in the general population: The Hordaland Health Study (HUSK). Am J Clin Nutr. 2018;107:105–12.
12. Sulo G, Vollset SE, Nygard O, Midttun O, Ueland PM, Eussen SJPM, et al. Neopterin and kynurenine-tryptophan ratio as predictors of coronary events in older adults, the Hordaland Health Study. Int J Cardiol. 2013;168:1435–40.
13. Ueland M, Ulvik A, Rios-Avila L, Midttun Ø, Gregory JF. Direct and Functional Biomarkers of Vitamin B6 Status. 2015;35:33-70.
14. Ulvik A, Pedersen ER, Svingen GFT, McCann A, Midttun Ø, Nygård O, et al. Vitamin B-6 catabolism and long-term mortality risk in patients with coronary artery disease. Am J Clin Nutr. 2016;103:1417–25.
15. Blake GJ, Rifai N, Buring JE, Ridker PM. Blood Pressure, C-Reactive Protein, and Risk of Future Cardiovascular Events. Circulation. 2003;108:2993–9.
16. Zuo H, Ueland PM, Ulvik A, Eussen SJPM, Vollset SE, Nygård O, et al. Plasma Biomarkers of Inflammation, the Kynurenine Pathway, and Risks of All-Cause, Cancer, and Cardiovascular Disease Mortality: The Hordaland Health Study. Am J Epidemiol. 2016;183:249–58.
17. Refsum H, Nurk E, Smith AD, Ueland PM, Gjesdal CG, Bjelland I, et al. The Hordaland Homocysteine Study: a community-based study of homocysteine, its determinants, and associations with disease. J Nutr. 2006;136:1731S-1740S.
18. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C,

et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018; 71:1269-1324. e139
19. Jarvis MJ, Tunstall-Pedoe H, Feyerabend C, Vesey C, Saloojee Y. Comparison of tests used to distinguish smokers from nonsmokers. Am J Public Health. 1987;77:1435.
20. Midttun O, Hustad S, Ueland PM. Quantitative profiling of biomarkers related to B-vitamin status, tryptophan metabolism and inflammation in human plasma by liquid chromatography/tandem mass spectrometry. Rapid Commun Mass Spectrom. 2009;23:1371–9.
21. Gao J, Meyer K, Borucki K, Ueland PM. Multiplex Immuno-MALDI-TOF MS for Targeted Quantification of Protein Biomarkers and Their Proteoforms Related to Inflammation and Renal Dysfunction. Anal Chem. 2018;90:3366–73.
22. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, et al. Role of the T cell in the genesis of angiotensin II-induced hypertension and vascular dysfunction. J Exp Med. 2007;204:2449–60.
23. Rizzoni D, De Ciuceis C, Szczepaniak P, Paradis P, Schiffrin EL, Guzik TJ. Immune System and Microvascular Remodeling in Humans. Hypertension. 2022;79:691–705.
24. Kringeland E, Tell GS, Midtbø H, Haugsgjerd TR, Igland J, Gerdts E. Factors associated with increase in blood pressure and incident hypertension in early midlife: the Hordaland Health Study. Blood Press. 2020;29:267–75.
25. Hall JE, Mouton AJ, Da Silva AA, Omoto ACM, Wang Z, Li X, et al. Obesity, kidney dysfunction, and inflammation: interactions in hypertension. Cardiovasc Res. 2021;117:1859–76.
26. Sharabi Y, Grotto I, Huerta M, Grossman E. Susceptibility of the influence of weight on blood pressure in men versus women: lessons from a large-scale study of young adults. Am J Hypertens. 2004;17:404–8.
27. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-Reactive Protein and the Risk of Developing Hypertension. JAMA. 2003;290:2945–51.
28. Sesso HD, Jiméenez MC, Wang L, Ridker PM, Buring JE, Michael Gaziano J. Plasma inflammatory markers and the risk of developing hypertension in men. J Am Heart Assoc. 2015;4:1–9.
29. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-Reactive Protein and the Risk of Developing Hypertension. J Am Med Assoc. 2003;290:2945–51.
30. Zhang Y-Y, Tong X-Z, Xia W-H, Xie W-L, Yu B-B, Zhang B, et al. Increased plasma neopterin levels are associated with reduced endothelial function and arterial elasticity in hypertension. J Hum Hypertens. 2016;30:436–41.
31. Zhang MA, Rego D, Moshkova M, Kebir H, Chruscinski A, Nguyen HK, et al. Peroxisome proliferator-activated receptor (PPAR)α and -γ regulate IFNγ and IL-17A production by human T cells in a sex-specific way. Proc Natl Acad Sci U S A. 2012 Jun 12;109:9505–10.
32. Wan RH, Yuan Y, Hao W, Zheng LY, Lu J. Relationship Between Serum Neopterin Level and Peripheral Arterial Plaque in Patients with Type 2 Diabetes. Diabetes Metab Syndr Obes. 2021;14:2871–8.
33. Li FR, He Y, Yang HL, Liu HM, Zhou R, Chen GC, et al. Isolated systolic and diastolic hypertension by the 2017 American College of Cardiology/American Heart Association guidelines and risk of cardiovascular disease: a large prospective cohort study. J Hypertens. 2021;39:1594–601.
34. Dugué P-A, Hodge AM, Ulvik A, Ueland PM, Midttun Ø, Rinaldi S, et al. Association

of Markers of Inflammation, the Kynurenine Pathway and B Vitamins with Age and Mortality, and a Signature of Inflammaging. J Gerontol A Biol Sci Med Sci. 2022;77:826–36.
35. Ulvik A, Pedersen ER, Svingen GF, McCann A, Midttun Ø, Nygård O, et al. Vitamin B-6 catabolism and long-term mortality risk in patients with coronary artery disease. Am J Clin Nutr. 2016;103:1417–25.

Figure 1. GAM plots demonstrating univariable associations of hs-CRP with systolic and diastolic blood pressure in 46-49 years old women and men in the Hordaland Health Study. The solid lines indicate blood pressure and the shaded areas 95% confidence intervals. Density plots indicate distributions, and the vertical white lines indicate the 5th, 20th, 50th, 80th and 95th percentiles of hs-CRP. CRP, high sensitive C-reaktive protein.

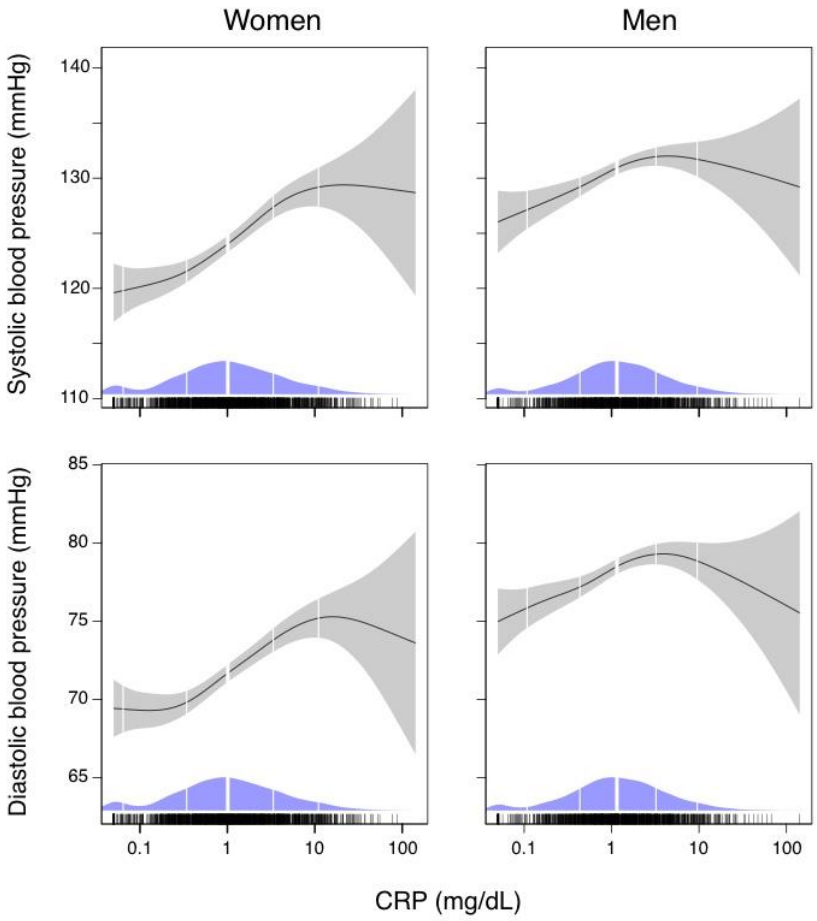

Figure 2. Associations of 4 markers of inflammation (hs:CRP, neopterin, PAr index and KTR) with systolic and diastolic blood pressure in 46-49 years old women and men in the Hordaland Health Study. Red (women) and blue (men) diamonds indicate standardized beta coefficients and lines 95% confidence intervals from univariable linear regression analysis, respectively.

p, p for interaction between biomarker and sex; CRP, high-sensitive C-reactive protein; PAr, the ratio plasma 4-pyridoxic acid: (pyridoxal + pyridoxal-5'-phosphate); KTR, kynurenine:tryptophan ratio

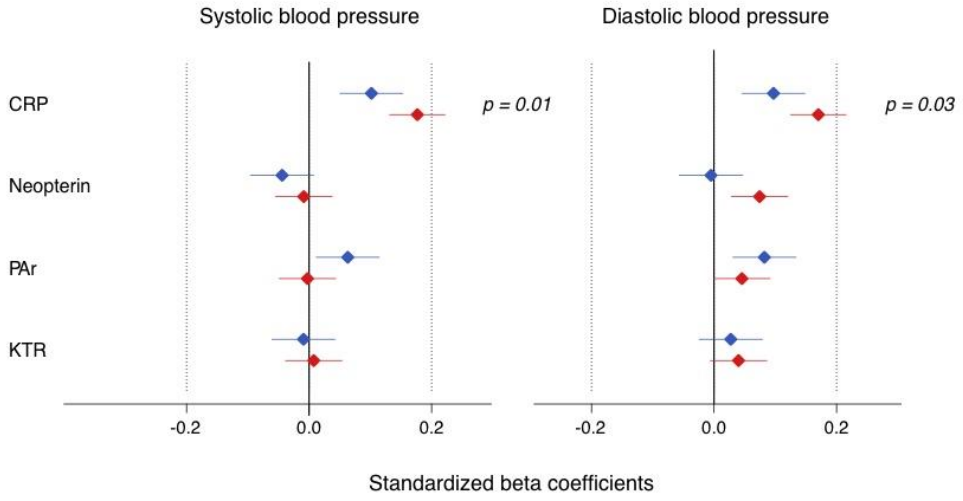

Table 1. Characteristics of the study population at follow-up in 1997-1999: The Hordaland Health Study

	Women n= 1,829	Men n= 1,451	P for sex difference
Age, years	48±1	48±1	0.36
Systolic BP, mmHg	124±16	130±14	<0.01
Diastolic BP, mmHg	72±11	78±10	<0.01
Δ systolic BP during 6 years follow-up	1.8±12	-1.3±11	<0.01
Δ diastolic BP during 6 years follow-up	-3.8±8.4	-1.7±8.6	<0.01
Hypertension, n (%)	670 (37)	836 (58)	<0.01
Patients with treated hypertension, n (%)	85 (13)	77 (9)	0.03
Body mass index, kg/m^2	24.8±4.0	26.1±3.1	<0.01
Obesity, n (%)	195 (10)	184 (11)	0.13
Creatinine, mmol/L	82±9	95±11	<0.01
Smoking, n (%)	673 (37)	552 (38)	0.46
Diabetes, n (%)	10 (0.55)	26 (1.8)	<0.01
Physical activity, n (%)			<0.01
None	554 (30)	336 (23)	
<1 hour/week	480 (26)	443 (31)	
1-2 hours/week	580 (32)	425 (29)	
≥3 hours/week	215 (12)	247 (17)	
Myocardial infarction, n (%)	1 (0.06)	16 (1.11)	<0.01
Stroke, n (%)	10 (0.55)	5 (0.34)	0.56
hs-CRP, median (IQR) mg/L	1.01 (0.43-2.56)	1.15 (0.53-2.62)	0.02
Neopterin, median (IQR) nmol/L	7.07 (6.02-8.36)	6.69 (5.72-7.86)	<0.01
Kynurenine, median (IQR) µmol/L	1.39 (1.23-1.57)	1.53 (1.36-1.71)	<0.01
Tryptophan, median (IQR) µmol/L	68.2 (60.8-76.6)	75.8 (67.5-84.1)	<0.01
KTR, median (IQR) nmol/µmol	20.1 (18.0-22.6)	20.3 (18.0-22.5)	0.38
PAr, median (IQR)	0.36 (0.28-0.47)	0.31 (0.25-0.41)	<0.01

Values are given as means (SD) unless otherwise indicated

BP, blood pressure; Hypertension, BP ≥130/80 mmHg or use of antihypertensive medication; hs-CRP, high-sensitive C-reactive protein; KTR, kynurenine:tryptophan ratio; PAr index: ratio 4-pyridoxic acid / (pyridoxal 5'-phosphate + pyridoxal); SD, standard deviation; IQR, interquartile range

Table 2. Association of systolic and diastolic BP with plasma levels of markers of inflammation in 46-49 years old women and men: The Hordaland Health study

	Women						Men						Interaction biomarker and sex	
Variable	Univariable		Model 1		Model 2		Univariable		Model 1		Model 2		Univariable	Model 2
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	*p*	*P*
Systolic BP														
hs-CRP	**0.172**	**<0.01**	**0.081**	**<0.01**	**0.089**	**<0.01**	**0.102**	**<0.01**	0.036	0.17	0.044	0.11	**0.03**	0.45
Neopterin	-0.001	0.98	0.001	0.97	-0.01	0.66	-0.039	0.13	-0.037	0.14	-0.050	0.06	0.30	0.24
KTR	0.013	0.58	-0.032	0.16	-0.043	0.07	-0.009	0.72	-0.025	0.32	-0.038	0.16	0.53	0.79
PAR index	-0.002	0.95	0.004	0.87	0.002	0.93	**0.065**	**0.01**	**0.065**	**<0.01**	**0.073**	**<0.01**	0.07	0.08
Diastolic BP														
hs-CRP	**0.165**	**<0.01**	**0.101**	**<0.01**	**0.104**	**<0.01**	**0.094**	**<0.01**	0.04	0.13	0.047	0.09	**0.04**	0.17
Neopterin	**0.084**	**<0.01**	**0.085**	**<0.01**	**0.081**	**<0.01**	-0.004	0.87	-0.002	0.93	-0.004	0.89	**0.01**	**0.01**
KTR	**0.049**	**0.04**	0.015	0.51	0.008	0.74	0.023	0.38	0.010	0.70	0.009	0.75	0.41	0.98
PAR index	0.045	0.06	**0.049**	**0.03**	0.044	0.06	**0.079**	**<0.01**	**0.084**	**<0.01**	**0.088**	**<0.01**	0.34	0.37

BP, blood pressure; hs-CRP, high-sensitive C-reactive protein; PAr index: ratio: 4-pyridoxic acid / (pyridoxal 5'-phosphate + pyridoxal); KTR, kynurenin:tryptophan ratio

Model 1 is adjusted for BMI

Model 2 is in addition adjusted for serum creatinine, physical activity, daily smoking, and diabetes.

Table 3. Association of changes in systolic and diastolic BP over the prior 6 years with plasma levels of markers of inflammation in 46-49 years old women and men: The Hordaland Health Study

	Women						Men						Interaction biomarker and sex	
Variable	Univariable		Model 1		Model 2		Univariable		Model 1		Model 2		Univariable	Model 2
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	*p*	*P*
Δ systolic BP														
hs-CRP	**0.102**	**<0.01**	**0.067**	**<0.01**	**0.083**	**<0.01**	0.016	0.54	-0.005	0.87	0.019	0.47	**0.01**	0.09
Neopterin	0.023	0.32	0.024	0.30	0.018	0.38	-0.012	0.64	-0.011	0.66	0.008	0.73	0.32	0.19
KTR	-0.006	0.81	-0.026	0.27	-0.045	0.05	-0.039	0.14	-0.044	0.093	**-0.050**	**0.046**	0.38	0.73
PAR index	0.012	0.60	0.015	0.53	0.007	0.74	0.024	0.36	0.026	0.33	0.046	0.06	0.76	0.77
Δ diastolic BP														
hs-CRP	**0.054**	**0.02**	**0.058**	**0.02**	**0.087**	**<0.01**	-0.023	0.38	-0.029	0.28	0.008	0.76	**0.03**	0.08
Neopterin	**0.065**	**<0.01**	**0.065**	**<0.01**	**0.071**	**<0.01**	0.026	0.33	0.026	0.32	0.017	0.48	0.30	0.06
KTR	0.006	0.81	0.004	0.88	-0.002	0.94	0.001	0.98	-0.0004	0.99	0.044	0.86	0.89	0.82
PAR index	0.014	0.54	0.014	0.54	0.024	0.28	0.039	0.14	0.039	0.14	**0.071**	**<0.01**	0.45	0.31

β, standardized B coefficient; BP, blood pressure; hs-CRP, high-sensitive C-reactive protein; PAr index: ratio: 4-pyridoxic acid / (pyridoxal 5'-phosphate + pyridoxal); KTR, kynurenin:tryptophan ratio. Model 1 is adjusted for body mass index. Model 2 is adjusted for body mass index, serum creatinine, physical activity, daily smoking and diabetes. In addition, model 2 is adjusted systolic or diastolic BP at baseline in the models on change in systolic and diastolic BP, respectively.

Table 4. Association of new onset hypertension with plasma levels of markers of inflammation in 46-49 years old women and men: The Hordaland Health Study

	Women n=1155				Men n=526				Interaction biomarker and sex	
Variable	Univariable		Model 2		Univariable		Model 2		Univariable	Model 2
	OR 95% CI	P	OR 95% CI	P	OR 95% CI	P	OR 95% CI	P	P	P
hs-CRP[a]	**1.34 (1.20-1.50)**	**<0.01**	**1.20 (1.06-1.35)**	**<0.01**	1.04 (0.91-1.18)	<0.61	0.97 (0.84-1.13)	0.85	**<0.01**	**0.04**
hs-CRP										
<1 mg/L	**Ref**		**Ref**		Ref		Ref		**<0.01**	**0.03**
1-<3 mg/L	**2.02 (1.41-2.90)**	**<0.01**	**1.81(1.25-2.61)**	**<0.01**	1.40 (0.93-2.14)	0.11	1.24 (0.80-1.92)	0.35		
≥3 mg/L	**2.91 (1.98-4.29)**	**<0.01**	**1.94 (1.26-3.01)**	**<0.01**	1.08 (0.65-1.79)	0.78	0.85 (0.49-1.51)	0.59		
Neopterin[a]	1.06 (0.61-1.84)	0.83	0.99 (0.56-1.76)	0.97	0.90 (0.45-1.82)	0.77	0.80 (0.38-1.68)	0.85	0.71	0.65
KTR[a]	1.92 (0.85-4.32)	0.11	0.99 (0.41-2.40)	0.99	0.90 (0.32-2.49)	0.83	0.68 (0.23-2.00)	0.48	0.25	0.60
PAr index[a]	1.34 (0.93-1.93)	0.11	1.27 (0.88-1.85)	0.21	0.99 (0.60-1.63)	0.97	0.98 (0.59-1.65)	0.87	0.34	0.42

Hypertension, BP ≥130/80 mmHg or use of antihypertensive medication; OR, odds ratio; CI, confidence interval; hs-CRP, high-sensitive C-reactive protein; PAr index: ratio: 4-pyridoxic acid / (pyridoxal 5'-phosphate + pyridoxal); KTR, kynurenin:tryptophan ratio

Model 2 is adjusted for BMI, creatinine, physical activity, daily smoking, and diabetes.

[a]: OR per 1 unit increase on log-transformed scale for each inflammation marker

For this analysis participants with hypertension at baseline were excluded.

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