Prehypertension, Obesity, and Risk of Kidney Disease: 20-Year Follow-up of the HUNT I Study in Norway

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Background: The combined effect of blood pressure (BP) and body weight on risk of kidney disease has not been previously studied. To improve risk stratification in prehypertensive individuals (ie, BP, 120 to 139/80 to 89 mm Hg), we examined the interaction between BP and body weight on the risk of end-stage renal disease or chronic kidney disease (CKD)-related death.

Study Design: Retrospective cohort study.

Setting & Participants: 74,986 adults participating in the first Health Study in Nord-Trøndelag (88% participation rate) were linked to the Norwegian Renal Registry and Cause of Death Registry.

Predictors: BP and body weight were measured by using standard procedures, and other relevant covariates were obtained from an extensive questionnaire.

Outcome & Measurements: Hazard ratios for treated end-stage renal disease and CKD-related death were calculated.

Results: Mean systolic BP and body mass index (BMI) were 136.8 ± 23.3 (SD) mm Hg and 25.2 ± 3.9 kg/m^2, whereas 12.9% had treated hypertension at baseline, respectively. During a median follow-up of 21 years (1,345,882 person-years), 507 men (1.4%) and 319 women (0.8%) initiated renal replacement therapy (n = 157) or died of CKD (n = 669). Multiadjusted risk of these kidney outcomes increased continuously with no lower threshold for BP. The risk associated with body weight started to increase from a BMI of 25.0 kg/m^2. In participants with BP less than 120/80 mm Hg, risk did not increase with increasing BMI. In prehypertensive participants, multivariate adjusted hazard ratios in the BMI categories 18.5 to 24.9, 25.0 to 29.9, 30.0 to 34.9, and 35.0 kg/m^2 or greater were 1.21 (95% confidence interval [CI], 0.67 to 2.17), 1.10 (95% CI, 59 to 2.00), 2.66 (95% CI, 1.28 to 5.53), and 5.94 (95% CI, 1.94 to 18.20) compared with BP less than 120/80 mm Hg and BMI of 18.5 to 24.9 kg/m^2, respectively ($P = 0.02$ for trend). Corresponding risks in hypertensive participants were 2.13 (95% CI, 1.23 to 3.70), 2.40 (95% CI, 1.40 to 4.15), 3.32 (95% CI, 1.89 to 5.81), and 5.53 (95% CI, 3.01 to 10.20), respectively ($P < 0.001$ for trend).

Limitations: Baseline creatinine measurements were not available; hence, a secondary analysis was performed that excluded all individuals who experienced outcomes in the 5 years after the study start.

Conclusions: Participants with prehypertension are not at increased risk of serious kidney outcomes if BMI is less than 30.0 kg/m^2. However, the risk of kidney disease increases substantially if prehypertension is present in obese participants.

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INDEX WORDS: Adult; blood pressure; body mass index; chronic/epidemiology/mortality; kidney failure; diseases/mortality; prehypertension; retrospective cohort studies/follow-up studies.

Blood pressure (BP) and body weight are important and potentially modifiable risk factors for end-stage renal disease (ESRD),[1-4] but their combined effect previously was not studied, although they often occur together. In 2003, the Seventh Report of the Joint National Committee on High Blood Pressure (JNC-7)[5] introduced the concept of prehypertension, defined as systolic BP of 120 to 139 mm Hg or diastolic BP of 80 to 89 mm Hg. In the last decade, there has been increased focus on what should be defined as normal and the levels at which pharmacological and nonpharmacological treatment should be initiated.[6,7]

Established hypertension is a well-known cause of ESRD.[8] Population-based studies from the United States[3,4] and Asia[9-12] have indicated that the risk extends to prehypertensive individuals. Current guidelines recommend that individuals with diabetes mellitus and chronic kidney disease (CKD) aim for a lower BP goal to prevent kidney disease progression.[5] However, treatment

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of all individuals with prehypertension would have enormous implications because more than 30% of the US and European populations are in this BP category.[13,14] Excess weight also has been identified as a strong and independent risk factor for ESRD[15,16] and cardiovascular and all-cause mortality.[17,18] Obesity is known to lead to ESRD and death from CKD through diabetes and hypertension; however, additional hemodynamic, metabolic, mechanical, and inflammatory mechanisms also may be contributing factors.[19,20] Increased risk of ESRD has been observed in patients with a body mass index (BMI) of 25.0 kg/m^2 and greater.[1] Whether patients with prehypertension should be considered for treatment if they have other traditional cardiovascular risk factors, such as abdominal obesity, has been discussed.[7,21]

To the extent of our knowledge, no study has evaluated the relationship between BP, body weight, and risk of kidney disease. Using almost 75,000 participants from the first Health Study in Nord-Trøndelag (HUNT I), we aim to determine the effect of the interaction between BP and body weight on risk of treated ESRD or CKD-related death to improve risk stratification in prehypertensive study participants.

METHODS

Study Population

The HUNT I Study was conducted between 1984 and 1986.[22] All inhabitants 20 years and older in the county of Nord-Trøndelag, Norway, were invited to participate, and 74,986 (88.2%) accepted the invitation. The population is ethnically homogeneous (>97% white). The study included an extensive questionnaire and brief clinical examination. The clinical examination was organized by 2 mobile "survey teams" from the National Health Screening Service and carried out at community halls and schools. Neither blood nor urine samples were collected. All participants gave informed consent before the examination. The study and morbidity and mortality follow-up were approved by the Regional Committee of Ethics in Medical Research and the Norwegian Data Inspectorate.

Data Collection

BP was measured by using a mercury sphygmomanometer by trained nurses or technicians using a standard cuff size after the patient had been sitting for 5 minutes. Two measurements were performed with a 1-minute interval on a single occasion. Korotkoff phases 1 and 5 indicated systolic and diastolic BP, respectively. The last measurement was prevailing.[22] BP was categorized according to the JNC-7 as normal (systolic BP $<$ 120 mm Hg and diastolic BP $<$ 80 mm Hg), prehypertensive (systolic BP, 120 to 139 mm Hg, or diastolic BP, 80 to 89 mm Hg), and hypertensive (systolic BP $\geq$ 140 mm Hg or diastolic BP $\geq$ 90 mm Hg or treated with antihypertensive medication).[5] Height was measured to the nearest 1 cm, and weight was measured to the nearest 0.5 kg with participants wearing light clothes and no shoes. BMI was calculated as weight/height^2 (kg/m^2), and 4 categories were computed[23,24]: normal weight (BMI, 18.5 to 24.9 kg/m^2), overweight (BMI, 25.0 to 29.9 kg/m^2), class I obesity (BMI, 30.0 to 34.9 kg/m^2), and class II obesity and higher (BMI $\geq$ 35.0 kg/m^2).

From the questionnaire, we obtained information about the occurrence of cardiovascular disease (CVD; angina pectoris, myocardial infarction, and stroke), diabetes mellitus, and use of BP medication in participants. High socioeconomic status was defined by college or university degree, an academic or senior position, or self-employed profession. Leisure-time physical activity was categorized into low, moderate, and high levels based on frequency, duration, and intensity. A frequency of less than once a week was categorized as low. For those with a frequency of once a week or more, a score was calculated by summarizing the ordinal values of frequency, intensity, and duration. Participants then were divided into moderate and high physical activity by dichotomizing at the median value. Cigarette smoking was classified as never, former, or current.

Outcome Assessment

The principal outcome was treated ESRD (dialysis or transplantation) or CKD-related death.

Since 1980, data from all patients in Norway with ESRD have been entered into the Norwegian Renal Registry (www.nephro.no/nnr.html), which is greater than 99.9% complete regarding cases of ESRD (T. Leivestad, Registry director, personal communication, May 2008). The Nordic cause of death registries have been found to be reasonable valid,[25,26] and since 1951, the Cause of Death Registry in Norway has included vitality status for all Norwegian citizens residing in Norway. Cause of death was available for 99.7% of the HUNT I participants (www.ssb.no/dodsarsak). Both registers have a mandatory reporting system, and the unique 11-digit personal number of every Norwegian citizen enabled linkage between all study participants and the registers. This also has been useful in other studies.[27-29] Death was defined as CKD related if any of the following *International Classification of Diseases, Ninth Revision*[30] or *Tenth Revision*[31] codes were listed on the death certificate as the underlying cause of death or were in the direct causal pathway leading to the death: CKD (581 to 583, 585 to 589; N03 to N09, N11 to N16, and N18 to N19), hypertensive kidney disease (403 and I12), hypertensive heart and kidney disease (404 and I13), diabetes with kidney manifestations (250.4, E10.2, E11.2, E13.2, E14.2, and N08.3), and cystic kidney disease (753.1 and Q61). Codes indicating acute kidney failure were not included.

Statistical Analyses

Data were analyzed in a cohort design with BP and BMI as main exposure variables and treated ESRD or CKD-related death as outcome variables by using Stata software,

version 10 (StataCorp, College Station, TX). Observational time was calculated as person-years elapsed from the date of attendance to the health survey (1984 to 1986) until the date of starting renal replacement therapy, date of death, or end of follow-up (December 31, 2006), whichever occurred first. Cox proportional hazards models were used to calculate multiadjusted hazard ratio (HRs) for treated ESRD or CKD-related death. We a priori identified all relevant available covariates and adjusted for these in multivariable analyses. We explored the continuous association with increasing BP and BMI by using restricted cubic splines. A potential interaction between BP and obesity was explored as departure from the additivity of effects according to Rothman et al.[32] Relative excess risk due to additive interaction (RERI) was calculated: RERI = HR(ab) − HR($\bar{a}b$) − HR($a\bar{b}$) + 1, where HR(ab) denotes relative risk in those exposed to both factors and HR($\bar{a}\bar{b}$) is used as a reference category (HR = 1.0). Ninety-five percent confidence intervals (CIs) were calculated as proposed by Hosmer and Lemeshow.[33] We also present the attributable proportion caused by interaction. To minimize the possibility of reverse causation (ie, the possibility that preexisting CKD at baseline would have modified exposure to the studied risk factors), all analyses were repeated after excluding individuals who experienced outcomes in the 5 years after the study start.

In general, most variables had few missing data (<2%; Table 1). However, we found 17% to 25% of data missing for the variables smoking status, physical activity, and socioeconomic status. In a case-wise deletion multiadjusted analysis, this would have resulted in decreased study power because 18,606 participants and 316 cases of treated ESRD and CKD-related death would have been excluded, and systematic bias could have been introduced. We addressed these problems by using multiple imputation, now considered the standard method for handling missing data.[34,35] Multiple imputation estimates the mean and uncertainty of the missing data from the observed values by using a simulation-based approach. Each missing value is replaced by m > 1 simulated values. The resulting m complete data sets then can be analyzed by using a standard complete-data method, and results are combined to produce inferential statements (eg, interval estimates or P values) that incorporate missing data uncertainty. We used m = 20 imputations to achieve maximum accuracy.[34]

RESULTS

Of 74,986 participants (49% men) in the HUNT I study, there were 826 cases of treated ESRD or CKD-related death during a median follow-up of 21 years (1,345,882 person-years of observation), which is equal to a rate of 61.4 cases/100,000 person-years). We included 157

Table 1. Baseline Characteristics of the HUNT I Population (1984-1986)

		BMI Categories (kg/m^2)				
	All (n = 73,925)	18.5-24.9 (n = 39,251)	25.0-29.9 (n = 26,650)	30.0-34.9 (n = 6,443)	≥35.0 (n = 1,581)	No. of Missing Values
Mean BMI (kg/m^2)	25.2 ± 3.9	22.5 ± 1.6	27.0 ± 1.4	31.8 ± 1.3	38.1 ± 3.1	699
Age (y)	49.6 ± 17.6	45.2 ± 17.4	53.7 ± 16.7	57.8 ± 15.8	57.8 ± 14.5	0
Men (%)	49.0	46.9	57.1	39.3	20.0	0
High socioeconomic status (%)	18.8	20.4	18.4	13.7	9.9	12,477
Cigarette smoking history (%)						18,223
Never	40.8	38.1	42.1	50.3	58.2	
Former	23.0	20.1	26.7	24.7	21.5	
Current	36.2	41.4	31.3	25.1	20.3	
Physical activity (%)						15,174
High	20.0	22.5	19.3	12.3	8.3	
Moderate	37.7	37.6	37.8	37.8	35.4	
Low	42.3	39.9	42.9	49.9	56.3	
Diabetes mellitus (%)	2.8	1.9	3.2	6.2	7.6	46
History of CVD (%)	7.2	5.2	9.2	11.2	10.6	238
Mean systolic BP (mm Hg)	136.9 ± 23.7	131.0 ± 21.2	141.7 ± 22.9	149.5 ± 24.0	156.0 ± 24.8	124
Mean diastolic BP (mm Hg)	84.0 ± 11.7	80.7 ± 10.9	86.8 ± 11.2	91.1 ± 11.3	94.5 ± 11.7	124
BP category (%)						124
<120/80	15.8	23.2	8.0	3.1	1.1	
120-139/80-89	35.1	41.4	31.4	18.5	10.4	
>140/90 or treated	49.1	35.4	60.6	78.5	88.5	

Note: Values expressed as mean ± SD or valid percentage within BMI categories.

Abbreviations: BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HUNT I, first Health Study in Nord-Trøndelag.

Table 2. Underlying Cause of Death in Participants With and Without CKD-Related Death

Diagnosis	All	With Diagnosed Kidney Disease	Without Diagnosed Kidney Disease
Kidney disease	254 (1.1)	254 (38)	0 (0)
Chronic glomerulonephritis/nephrotic syndrome	16 (0.1)	16 (2.4)	0 (0)
CKD, unspecified	171 (0.7)	171 (25.6)	0 (0)
Hypertensive kidney disease	67 (0.3)	67 (10.0)	0 (0)
Cardiovascular diseases	11,075 (47.5)	303 (45.3)	10,772 (47.6)
Ischemic heart diseases	4,432 (19.0)	82 (12.3)	4,350 (19.2)
Heart failure	912 (3.9)	58 (8.7)	854 (3.8)
Cerebrovascular diseases	2,588 (11.1)	51 (7.6)	2,537 (11.2)
Other cardiovascular diseases	3,143 (13.5)	112 (16.7)	3,031 (13.4)
Diabetes mellitus	356 (1.5)	42 (6.3)	314 (1.4)
Obstructive urological cancer	378 (1.6)	31 (4.6)	347 (1.5)
Other causes	11,287 (48.3)	39 (5.8)	11,248 (49.5)
In all	23,350 (100)	669 (100)	22,681 (100)

Note: Values expressed as number (valid percentage) with the diagnosis as an underlying cause of death.
Abbreviation: CKD, chronic kidney disease.

patients who initiated renal replacement therapy and 669 with CKD-related death. Baseline characteristics of the study population stratified by categories of BMI are listed in Table 1. Underlying causes of death in participants with and without CKD-related death are listed in Table 2.

Age, male sex, hypertension, smoking, low physical activity, diabetes, history of CVD, and BMI of 30.0 kg/m^2 or greater were significantly associated with treated ESRD or CKD-related death in a multiadjusted model (Table 3). There was no significant association between this study outcome and socioeconomic status, moderate physical activity, prehypertension, or BMI ranging from 25.0 to 29.9 kg/m^2.

Systolic BP and BMI showed a strong and graded association with treated ESRD or CKD-related death (Fig 1). The multiadjusted HR increased approximately linearly with increasing BP with no lower threshold (Fig 1A). Compared with participants with systolic BP of 120 mm Hg, multiadjusted HRs were 1.5 (95% CI, 1.2 to 1.8; $P < 0.001$) and 3.2 (95%, CI 2.4 to 4.2; $P < 0.001$) for those with systolic BP of 140 and 200 mm Hg, respectively. Multiadjusted HRs for BMI curve tended to be flat at less than 25 kg/m^2 and increased gradually more steeply at greater than 25 kg/m^2, especially in the obese range (Fig 1B). Compared with participants with BMI of 23.0 kg/m^2, multiadjusted HRs were 1.7 (95% CI, 1.4 to 1.9; $P < 0.001$) and 4.1 (95% CI, 3.1 to 5.8; $P < 0.001$) for BMIs of 30.0 and 40.0 kg/m^2, respectively. Because hypertension, CVD, and diabetes are intermediate variables rather than confounders in the causal pathway between BMI and kidney failure, we did not adjust for these covariates in Fig 1B. Correspondingly, we did not adjust for CVD in Fig 1A. However, we performed a secondary analysis including these covariates. Resulting HRs for systolic BPs of 140 and 200 mm Hg were 1.4 (95% CI, 1.1 to 1.7; $P < 0.001$) and 3.1 (95% CI, 2.3 to 4.2; $P < 0.001$), respectively. Corresponding HRs for BMIs of 30.0 and 40.0 kg/m^2 were 1.3 (95% CI, 1.1 to 1.5; $P < 0.001$) and 2.5 (95% CI, 1.8 to 3.5; $P < 0.001$), respectively.

An additive interaction between BP and BMI, defined as departure from the additivity of their effects, was explored. Participants with BMI of 25.0 kg/m^2 or greater and BP of 120/80 mm Hg or greater had crude and multiadjusted RERIs of 5.93 (95% CI, 2.78 to 9.10; $P < 0.001$) and 0.56 (95% CI, −0.20 to 1.33; $P = 0.1$), respectively. Because an RERI of 0 means no interaction, an RERI of 5.93 indicates that the HR is 5.93 greater than expected based on the addition of the 2 risk factors. Crude and multiadjusted attributable proportions due to interaction were 0.45 (95% CI, 0.31 to 0.59; $P < 0.001$) and 0.25 (95% CI, −0.15 to 0.66; $P = 0.2$), respectively. An attributable proportion caused by interaction of 0.45 means that 45% of the risk in participants with both increased BP and BMI is caused by the interaction between these 2 risk factors.

Participants with normal BP had no increased risk of treated ESRD or CKD-related death with

Table 3. Age- and Multiadjusted HRs for Treated ESRD or CKD-Related Death

	Treated ESRD (n = 157)		CKD-Related Death (n = 669)		Treated ESRD or CKD-Related Death (n = 826)	
	Age-Adjusted HR	Multiadjusted HR*	Age-Adjusted HR	Multiadjusted HR*	Age-Adjusted HR	Multiadjusted HR*
Age (/1 y)	1.04 (1.03-1.05)	1.02 (1.01-1.03)	1.15 (1.14-1.16)	1.15 (1.14-1.16)	1.11 (1.11-1.12)	1.11 (1.10-1.12)
Male sex	2.22 (1.60-3.10)	2.10 (1.44-3.05)	2.47 (2.12-2.90)	2.56 (2.14-3.08)	2.37 (2.06-2.73)	2.47 (2.10-2.91)
Low socioeconomic status	1.64 (0.97-2.76)	1.36 (0.80-2.31)	1.84 (1.44-2.37)	1.08 (0.84-1.38)	1.80 (1.43-2.26)	1.14 (0.90-1.44)
Cigarette smoking history†						
Former	1.39 (0.89-2.18)	1.12 (0.70-1.80)	1.88 (1.53-2.32)	1.31 (1.04-1.66)	1.72 (1.43-2.09)	1.23 (1.00-1.52)
Current	1.18 (0.75-1.85)	1.14 (0.71-1.82)	1.74 (1.39-2.16)	1.51 (1.19-1.91)	1.56 (1.27-1.92)	1.37 (1.10-1.71)
Physical activity‡						
Moderate	1.15 (0.67-1.95)	1.30 (0.75-2.23)	1.01 (0.79-1.30)	1.17 (0.91-1.51)	1.03 (0.82-1.29)	1.19 (0.94-1.49)
Low	1.42 (0.83-2.45)	1.45 (0.83-2.52)	1.23 (0.96-1.58)	1.34 (1.04-1.73)	1.28 (1.01-1.61)	1.37 (1.08-1.73)
Diabetes mellitus	8.87 (5.26-14.98)	5.18 (3.01-8.89)	3.39 (2.65-4.34)	3.07 (2.40-3.94)	9.62 (7.71-12.00)	3.30 (2.63-4.13)
History of CVD	1.91 (1.10-3.32)	0.98 (0.53-1.78)	1.80 (1.49-2.16)	1.56 (1.29-1.89)	4.09 (3.49-4.79)	1.47 (1.23-1.77)
Blood pressure§						
120-139/80-89	1.86 (0.76-4.53)	1.44 (0.59-3.53)	1.38 (0.81-2.34)	1.23 (0.72-2.09)	1.47 (0.93-2.32)	1.23 (0.78-1.95)
≥140/90 or treated	6.52 (2.81-15.14)	4.45 (1.89-10.50)	2.39 (1.45-3.96)	2.03 (1.23-3.35)	2.87 (1.86-4.42)	2.26 (1.47-3.49)
Body mass index‖						
25.0-29.9	1.63 (1.14-2.33)	1.24 (0.86-1.78)	1.14 (0.95-1.36)	1.09 (0.91-1.31)	1.19 (1.01-1.39)	1.08 (0.92-1.27)
≥30.0	1.94 (1.20-3.11)	1.40 (0.86-2.28)	1.78 (1.45-2.18)	1.94 (1.56-2.41)	1.77 (1.46-2.13)	1.78 (1.46-2.16)

Note: Values expressed as HR (95% confidence interval). Cox proportional hazards models using all 74,986 participants of the HUNT 1 study.

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease; HR, hazard ratio; HUNT I, first Health Study in Nord-Trøndelag.

*Multiadjusted models were adjusted for all other available covariates, eg, sex is adjusted for age, socioeconomic status (high, low), smoking status (never, former, current), physical activity (low, medium, high), diabetes, history of CVD, hypertensive status, and body mass index status.

†Reference category is no smoking history.

‡Reference category is high physical activity.

§Reference category is blood pressure less than 120/80 mm Hg.

‖Reference category is body mass index of 18.5 to 24.9 kg/m^2.

increasing BMI compared with those with normal weight and normal BP (Table 4). However, HRs in prehypertensive and hypertensive participants increased substantially with BMI, particularly for those with BMI of 30.0 kg/m^2 or greater. For example, HRs in prehypertensive participants increased from 1.21 (95% CI, 0.67 to 2.17; $P = 0.5$) if normal weight to 5.94 (95% CI, 1.94 to 18.20; $P = 0.002$) in the BMI category of 35.0 kg/m^2 or greater compared with normal weight and normal BP. The test for linear trend in BMI was not significant for the normal BP category ($P = 0.9$), but was significant for the prehypertensive and hypertensive categories ($P = 0.02$ and $P < 0.001$, respectively).

Finally, we repeated all analyses after excluding all cases with study outcomes occurring in the 5 years after the start of the study (n = 143). However, this had only minimal influence on results. For example, the HR in prehypertensive participants with BMI of 35.0 kg/m^2 or greater changed from 5.94 (95% CI, 1.94 to 18.20; $P = 0.002$) to 6.19 (95% CI, 2.00 to 19.15; $P = 0.002$).

DISCUSSION

In this large European population-based study, we examined the combined effects of BP and body weight on treated ESRD or CKD-related death, with special emphasis on the near-normal range. We found a strong, independent, and continuous association with both BP and body weight. No lower threshold existed for BP, whereas the risk started to increase from a BMI of 25.0 kg/m^2 for body weight. A synergistic effect of BP and BMI tended toward significance, implying increased information when used together. Prehypertensive participants increased their risk of treated ESRD or CKD-related death only if BMI was 30.0 kg/m^2 or greater.

Previous population-based studies from the United States[1,3,4] and Asia[9-11] have reported the

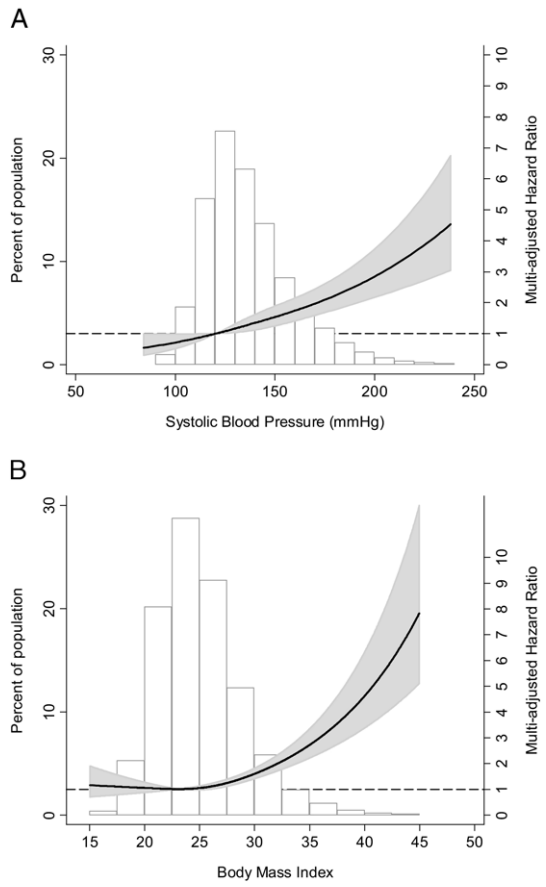

Figure 1. Multiadjusted hazard ratio for treated end-stage renal disease or chronic kidney disease–related death by (A) systolic blood pressure (BP) and (B) body mass index (BMI). The restricted cubic spline regression analysis with 95% confidence interval (shaded area) was adjusted for (A) age, sex, BMI, diabetes, smoking status, physical activity, and socioeconomic status and (B) age, sex, smoking status, physical activity, and socioeconomic status. Distributions of (A) systolic BP and (B) BMI in the study population are shown.

risk of severe kidney outcomes in all ranges of BP and BMI, respectively. In a study from Hsu et al,[3] US participants with BP of 120 to 129/80 to 84 and 130 to139/85 to 89 mm Hg were 62% and 98% more likely to develop ESRD compared with those with normal BP, respectively. In a corresponding study from Reynolds et al,[11] pre-hypertensive participants in China were 30% more likely to develop ESRD or die of CKD. Hsu et al[1] also reported relative risks for ESRD of 1.9 and 7.1 for overweight and class III obesity participants compared with those of normal weight, respectively.

It is debated which anthropometric measurement best reflects obesity status. Both BMI and waist circumference have been reported to be proper markers of obesity in the setting of kidney disease.[36,37] Recent studies have found waist circumference to be a better marker of central obesity than BMI for risk of cardiovascular events, CKD, and all-cause mortality.[38-40] In our study, this measurement was not available. However, we showed a strong, independent, and positive association between BMI and risk of treated ESRD or CKD-related death from a BMI of 25 kg/m^2. The steepest increase in HR was observed in those with BMI of 30 kg/m^2 or greater (Fig 1B). We also observed a continuous and positive association between systolic BP and the study outcome starting from less than 120 mm Hg, the level considered normal (Fig 1A). The latter observation extends previous research from Lewington et al[41] that suggested an association between BP and cardiovascular mortality at a lower threshold of at least 115/75 mm Hg. For years, lowering the BP level for treatment initiation has been discussed, and by introducing the concept of prehypertension, the JNC reports have further emphasized this topic.[5]

A complex and close association between BP and body weight exists, but the combined effects on kidney failure have not been studied previously. Data from the Framingham Study suggest that 65% to 75% of the risk of hypertension can be attributable to obesity.[42] It therefore is discussed whether hypertension is an intermediate factor rather than a confounder in the causal pathway between obesity and kidney failure.[1] We found that hypertension, diabetes, and previous CVD modified the effect of BMI on kidney failure when these covariates also were adjusted for.[37,39] However, a substantial residual effect remained. In obesity, activation of sympaticus and the renin-angiotensin-aldosterone system is increased, which causes increased tubular reabsorption of sodium and impaired pressure natriuresis. Both HT and obesity lead to renal hyperperfusion and glomerular hyperfiltration, which, in turn, cause albuminuria and focal segmental glomerulosclerosis.[19,20,43] Furthermore, it is suggested that leptin produced from adipose tissue may lead directly to renal fibrosis.[44] Ribstein et al[45] found that overweight clearly enhanced the influence of BP on albumin excretion when evalu-

Table 4. Multiadjusted HRs for Treated ESRD or CKD-Related Death by BP and BMI Categories

	BMI (kg/m^2)				Test for Trend BMI (*P*)*
	18.5-24.9	25.0-29.9	30.0-34.9	≥35.0	
BP < 120/80 mm Hg					
Treated ESRD or CKD-related death (no.)	14	6	2	0	
Person-years	187,696	42,935	3,868	250	
HR (95% CI)	1.00 (reference)	0.80 (0.32-2.20)	3.20 (0.72-14.20)	NA	0.9
BP 120-139/80-89 mm Hg					
Treated ESRD or CKD-related death (no.)	60	43	15	4	
Person-years	323,901	162,221	22,380	3,151	
HR (95% CI)	1.21 (0.67-2.17)	1.10 (0.59-2.00)	2.66 (1.28-5.53)	5.94 (1.94-18.20)	0.02
BP ≥140/90 mm Hg					
Treated ESRD or CKD-related death (no.)	195	312	126	47	
Person-years	224,022	256,944	78,455	22,397	
HR (95% CI)	2.13 (1.23-3.70)	2.40 (1.40-4.15)	3.32 (1.89-5.81)	5.53 (3.01-10.20)	<0.001
Test for trend BP (*P*)*	<0.001	<0.001	0.5	0.9	

Note: Cox proportional hazards models using all 74,986 participants of the HUNT I study. HRs for treated ESRD or CKD-related death were adjusted for age, sex, diabetes, smoking status (never, former, current), history of cardiovascular disease, physical activity (low, medium, high), socioeconomic status (high, low).

Abbreviations: BP, blood pressure; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; HR, hazard ratio; HUNT I, first Health Study in Nord-Trøndelag; NA, not applicable (no estimates were assessable due to absence of study outcome).

*Test for trend in BMI within BP less than 120/80 mm Hg was performed by using the BMI category as ordinal covariate in a multiadjusted Cox regression including only participants with BP less than 120/80 mm Hg. Corresponding tests for trend were performed in the other BP categories and in the BMI categories.

ating nondiabetic normotensive and hypertensive participants separately. Evaluating the combined effects of increased BP and overweight on risk of kidney disease, we found the crude relative risk to be significantly greater than expected (RERI, 5.93; 95% CI, 2.78 to 9.10; $P < 0.001$). Adjusting for covariates, we still found an excess risk of 0.56, and the effect tended toward significance. However, the CI limits of the interaction estimate should be interpreted with caution when adjusting for multiple covariates.[46]

Cardiovascular risk factors have a tendency to cluster, and risk stratification schemes are developed to access the total risk.[21] Our results for the joint effect of BP and BMI on kidney dysfunction might have important clinical implications regarding the debate about treatment of people with increased risk of kidney disease. Future risk of treated ESRD or CKD-related death increased substantially for participants with near-normal BP with increasing body weight (Table 4). This information can be important for guiding the treatment plan for people with prehypertension, a condition with high prevalence (>30%) in both the United States and Europe.[13,14] We suggest that obese prehypertensive individuals should be considered for a stricter BP goal, as for patients with diabetes mellitus and CKD (1.8% of the adult population). However, randomized controlled trials are needed to quantify the extent of any potential benefits before pharmacological treatment may be recommended.[7] Until then, such nonpharmacological interventions as weight reduction and physical activity should be strongly suggested for this group.[2]

The strength of this study is the long follow-up of 2 decades. Furthermore, we have a large homogenous general population with a participation rate of almost 90%, which is unique, and the compulsory identification number given to all Norwegian citizens at birth enabled us to identify all cases of treated ESRD and CKD-related death.

However, several limitations need to be discussed. As in other corresponding studies, BP was measured on only a single occasion,[1,3,4,11] and misclassification of BP therefore is possible. In contrast to current recommendations, in this study each participant's BP measurement was

based on only 2 readings. Second, no baseline measurements of urinary protein excretion or serum creatinine values were available. Thus, undetected preexisting kidney injury may bias our results because of the effect of reverse causation. However, our results were minimally affected when participants with treated ESRD and CKD-related death in the subsequent 5 years after baseline were excluded. The latter finding also was reported by Stengel et al.[47] In addition, they excluded all patients with CKD stages 3 to 5 at baseline, which also did not affect results.[47] Third, the original cohort was studied several years before the study outcome without follow-up visits. Hence, misclassification for medical history, including the use of BP medication, is inevitable and might bias our results. Finally, missing data always imply loss of study power and potential bias in a study such as this. However, by using multiple imputation, these effects were minimized.

In conclusion, the multiadjusted HR for treated ESRD or CKD-related death continuously increased at BP levels less than the prevailing guidelines for intervention. The combined assessment of BP and body weight for risk of kidney disease provides increased information. Participants with prehypertension were not at increased risk of serious kidney outcomes if they were of normal body weight. However, HRs increased steeply in participants with BMI greater than 30 kg/m^2.

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